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**Editorial**

**Science and Pseudo-science**

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The Journal of the Science of Healing Outcomes, State College, Pennsylvania, USA and Mangalore, India*  
Manipal University, Manipal, India**  
The Middlesex Medical School, University of London, UK#  
Northern Colorado University, USA##

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##Affiliate Professor of Human Health

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Much is made out of the word “science” and many would want to equate science with truth! Some pig-headed, the latter with lot of bloating inside, want to call anything that they do not think is science as pseudoscience. What is real science then? Harry Collins and Peter Trevor, two physicists in their book, *The Golem*, describe science thus: “science is fallible and untidy, a matter of craft than logic”. To do that, they have examined a series of experiments, some famous like the proof of the relativity theory, and some not so famous. However, in each case it shows that scientific certainties do not necessarily always come from experimental method, but many times from the way ambiguous results were interpreted! This book also shows the fallibility even in the so-called crucial experiments.

The real personality of science is neither all good nor all bad; it is neither a chivalrous knight nor a pitiless juggernaut. They show that science is a Golem. The latter is a creature of Jewish mythology: a humanoid made by man from clay and water, with incantations and spells. It is powerful and grows powerful by the day. It will follow your orders and protect you, but it is clumsy and dangerous. Without control, the golem may destroy its masters with its flailing vigour. Different traditions have different connotations of the golem.

In fact, science and religion are not poles apart as we think they are. They are the two faces of the same coin. Scientists are not Gods, neither are they charlatans. They are just experts like your plumber, for example. If your plumber could make mistakes, so could your scientist! Science, therefore, could only be as good as your scientists are. Society should safeguard science by seeing that the best brains get there to make less mistakes. The common man also must have the right attitude towards science, not to expect too much from it. If one reads this book by Harry Collins and Trevor Pinch, one would not use the word pseudoscience any more. Instead, anyone who thinks that the science the other man refers to is not to his/her liking, they call it as fringe science. If a man on the street needs to know more science, then more science things become clearer. Young men and women who study in prestigious institutions in India run by the tax payers’ money should not think that they own science, but should try and understand science instead.

The other area where science touches human lives is in the field of forensic science. Scientific evidence in the court of law should be understood in the light of what is written above about science and not to be accepted as sacrosanct. However, the law demands science as witness. Very strange indeed! The westerners who wanted to control us through science seem to have mostly succeeded, as most of us believe that science is the be-all and end-all of all wisdom, forgetting that it is just simple knowledge which is far removed from wisdom. Another problem is that all experiments in science cannot be totally under our control, and that is where experimenter’s regress comes in. Science could be as good as our experiments are and not better.

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Review Article

The promising role of percutaneous hepatic perfusion in unresectable hepatic malignancies

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ABSTRACT

Hepatic malignancies are a major cause of morbidity and mortality worldwide. Patients with unresectable primary or secondary liver malignancies have limited therapeutic options. Thus, treatment of such malignancies is challenging, and the demand for effective treatment remains high, even in the presence of systemic chemotherapy. Loco regional chemotherapy is a minimally invasive technique that allows the delivery of high dose chemotherapy with minimal extra-hepatic toxicity. Surgical isolated hepatic perfusion has been shown to be effective in patients with unresectable hepatic malignancies; however, its complexity, high complication rates and non-repeatability limit its global acceptance.

Percutaneous hepatic perfusion is a novel method of delivering regional chemotherapy in a selective fashion to the liver. In addition, it is relatively less invasive and has a low rate of complications. This review article will illustrate the technique of percutaneous hepatic perfusion and will provide an overview about its safety and potential complications, then discussing the results of the selected relevant articles.

INTRODUCTION

Liver tumor is considered the most frequent site of overall malignancies, and is a common culprit of worldwide morbidity and mortality[1]. Primary and secondary unresectable liver malignancies have a poor prognosis with few therapeutic options; as a result, they are an irrefutable therapeutic challenge for most clinicians[1]. Although surgical resection is the optimal treatment for these malignancies, few patients are eligible for the operation due to either advanced disease or deranged hepatic function[1]. Despite advances in systemic chemotherapy, the prognosis for such malignancies is still poor[1].

Blood supply of the liver is unique, in which more than two-thirds of the supply of the normal hepatic tissue is derived from the portal vein (PV), whereas the hepatic artery (HA) is the predominate feeder for the hepatic neoplastic tissue. Therefore, this peculiar dual blood supply provides the basics for loco-regional chemotherapy[2,3].

Surgical isolated hepatic perfusion (IHP) is a loco-regional therapy which is done through a transient exclusion of the hepatic circulation from the systemic one, thereby limiting systemic chemotoxicity. IHP was first tested on a canine model in 1961, followed by trials on patients with different liver malignancies[4,5]. IHP is a complex surgical procedure in which both the inferior vena cava (IVC) and the PV should be temporarily clamped to isolate hepatic circulation, then a high dose of chemotherapeutic agent is injected via the HA[6,7]. During the last two decades, several studies have been performed in the United States and Europe to evaluate the safety and efficacy of IHP for the management of inoperable liver malignancies[8-10]. The outcome of these studies was not highly satisfactory worldwide because of potential high rate of morbidity and mortality[11-13].

Percutaneous hepatic perfusion (PHP) is an endovascular procedure that has replaced IHP due to its minimal invasiveness and repeatability, as well as

KEY WORDS: chemosaturation, isolated liver perfusion, liver secondaries

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its low rate of morbidity and mortality compared to IHP\cite{14}. This review illustrates the technique of PHP, and provides an overview about the safety and the potential complications of the procedure, then will discuss the results of the selected articles.

METHODS AND HISTORY
Evidence acquisition
Eight key articles discussing the efficacy, applications, and potential complications of PHP were outlined in Table 1\cite{15-22}. These articles were sourced through PubMed, Scopus, Ovid Medline, Clinical trials, Cochrane library and Google Scholar. Several keywords and subject headings were used including percutaneous hepatic perfusion, chemosaturation, liver malignancies, hepatic tumors, chemotherapy, cancer and regional perfusion.

Due to the presence of different PHP techniques, only studies using Melphalan-PHP for treatment of unresectable liver malignancies were included. Articles published in languages other than English were excluded. Studies dealing with isolated hepatic surgical perfusion as well as non-human trials were also excluded.

One recent randomized control trial- phase III (RCT) is found\cite{15} along with other studies, such as prospective (n = 4)\cite{16,19-21}, retrospective (n = 2)\cite{17,18}, and one case-series study\cite{22}.

The last date of this search was on 15th of January, 2018.

PHP procedure
PHP is a minimally invasive procedure which is usually performed under general anesthesia by an experienced anesthesiologist, interventional radiologist and an extracorporeal perfusionist (Figure 1). Currently, two techniques of PHP have been used. The first one entails three catheters; the first 16F double...
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study</th>
<th>Hepatic cancer</th>
<th>No. patients/ (No. PHPs)</th>
<th>Endpoint</th>
<th>ORR% (n)</th>
<th>hPFS median</th>
<th>OS, median</th>
<th>Complications</th>
</tr>
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<tbody>
<tr>
<td>Hughes et al, 2016</td>
<td>RCT</td>
<td>Melanoma</td>
<td>93 (max 6 per pt)</td>
<td>Response (primary: hPFS)</td>
<td>27.30% (vs 4.1% in control)</td>
<td>7.0 months</td>
<td>10.6 months</td>
<td>Low WBC (85.7%), low platelets (80%), low hemoglobin (62.9%), transient hyperbilirubinemia (14.3%), cardiac toxicity (12.9%), brain ischemia (1.2%), death (3.2%)</td>
</tr>
<tr>
<td>De Leede et al, 2017</td>
<td>Prospective, clinical and pharmacological study</td>
<td>Melanoma (n = 4) CRC (n = 4)</td>
<td>7 (10)</td>
<td>Analyzed the pharmacokinetics and toxicity of PHP</td>
<td>n.r</td>
<td>n.r</td>
<td>n.r</td>
<td>Hematological (low hemoglobin, WBC, platelets) Hepatic (elevated liver enzymes and bilirubin)</td>
</tr>
<tr>
<td>Vogl et al, 2014</td>
<td>Retrospective</td>
<td>Melanoma</td>
<td>14 (18)</td>
<td>Response and toxicity</td>
<td>50 (7)</td>
<td>n.r</td>
<td>n.r</td>
<td>Myelosuppression; death (7.1%), retroperitoneal hemorrhage</td>
</tr>
<tr>
<td>Forster et al, 2013</td>
<td>Retrospective</td>
<td>Melanoma (n = 9) sarcoma (n = 1)</td>
<td>10 (27)</td>
<td>Response and toxicity</td>
<td>50 (5)</td>
<td>7.9 months</td>
<td>n.r.</td>
<td>Myelosuppression, mild increase serum troponin (70%)</td>
</tr>
<tr>
<td>Pingpank et al, 2005</td>
<td>Phase I</td>
<td>melanoma (n = 13), NET (n = 4), CRC (n = 2), HCC (n = 3), RCC (n = 2), AdrC/Breast/CA (n = 2), PaAd (n = 1), sarcoma (n = 1)</td>
<td>28 (74)</td>
<td>MTD, toxicity, pharmacokinetics</td>
<td>29.6 (8)</td>
<td>n.r.</td>
<td>n.r.</td>
<td>Neutropenia (73.6%), thrombocytopenia (36.8%), anemia (21.1%)</td>
</tr>
<tr>
<td>Pingpank et al, 2011</td>
<td>Phase II</td>
<td>NET (n = 23)</td>
<td>23 (68)</td>
<td>Response (ORR)</td>
<td>79</td>
<td>39 months</td>
<td>n.r.</td>
<td>Acute elevated liver enzymes (22%), neutropenia (47%), thrombocytopenia (29%) anemia (15%), mortality (0.04%) due to cholangitis</td>
</tr>
<tr>
<td>Miao et al, 2008</td>
<td>Prospective</td>
<td>melanoma (n = 16), NET (n = 12), CRC (n = 7), HCC (n = 5), RCC (n = 4), AdrC/Breast/CA (n = 2)</td>
<td>51 (136)</td>
<td>Hemodynamics and metabolic changes</td>
<td>n.r</td>
<td>n.r</td>
<td>n.r.</td>
<td>Self-limiting hypotension, metabolic acidosis, nausea/vomiting (10%)</td>
</tr>
<tr>
<td>Fitzpatrick et al, 2014</td>
<td>Case series</td>
<td>Melanoma</td>
<td>5 (15)</td>
<td>Feasibility and toxicity</td>
<td>n.r</td>
<td>n.r</td>
<td>n.r.</td>
<td>Self-limiting mild hypothermia, metabolic acidosis</td>
</tr>
</tbody>
</table>

OS: overall survival; RCT: randomized control trial; hPFS: hepatic progression-free survival; WBC: white blood cells; CRC: colorectal carcinoma; PHP: percutaneous hepatic perfusion; n.r: not reported; NET: neuroendocrine tumor; HCC: hepatocellular carcinoma; RCC: renal cell carcinoma; AdrC: adrenocortical carcinoma; PaAd: periampullary adenoma; MTD: maximum tolerated dose; ORR: objective response rate (complete plus partial response)
balloon catheter (Chemosaturation Hepatic Delivery System, Delcath Systems Inc, New York, USA) is placed in the right common femoral vein (RCFV) and advanced to the IVC via 18F sheath catheter, the cranial and the caudal balloons of 16F catheter are inflated at the supra and infra hepatic caval levels, respectively (Figure 2). The second 10F sheath catheter is inserted in the right internal jugular vein (RIJV) to return the filtered blood to systemic circulation. The third 5F catheter is placed in the HA through the left common femoral artery (LCFA) for melphalan infusion.

Only two catheters are used for the second technique; the first catheter is a double balloon catheter with a charcoal hemoperfusion (4-lumen/2-balloon Fuji System Co. Ltd, Tokyo, Japan; DHP-1; Kuraray Co., Ltd., Osaka, Japan) which is inserted from the RCFV and is positioned in the IVC. The second catheter is placed in the LCFA and then advanced to the HA. In the second technique, adriamycin or doxorubicin chemotherapeutic drugs have been used instead of melphalan.

Melphalan is superior to other chemotherapeutic agents in terms of easy administration, low hepatic toxicity, high hepatic excretion rate and short half-life with rapid effect on tumor cells. In this review, studies using the first technique have solely been selected.

After placing all these lines and sheaths, 300 U/kg of heparin is infused to achieve the activated clotting time above 400 s during the entire procedure.

A hepatic venous angiogram is done through the 16F double balloon catheter (Figure 2). Aspiration of effluent blood through the fenestrated part of the catheter is pumped to the extracorporeal circulation system which consists of a centrifugal pump and two drug filtration activated carbon filters. The filtered blood is returned to the RIJV via 10F catheter at a flow rate not exceeding 0.8 L/min and pre-pump pressures not exceeding -250 mmHg to avoid collapsing or kinking the IVC catheter. Meanwhile, hepatic arteriogram mapping is done before and during the procedure via the 5F HA sheath catheter to ensure a satisfactory hepatic arterial flow pattern. Continuous hemofiltration of effluent hepatic blood usually lasted 30 minutes “washout period” to achieve maximal clearance of chemotherapeutics.

At the end of the procedure, protamine sulfate is injected to correct the coagulation status. A vascular closure device may be placed at the arterial puncture site to prevent hematoma formation.

LITERATURE REVIEW

PHP is a relatively safe procedure as compared to IHP. There are some potential effects associated with PHP including hypotension, hypothermia and myelosuppression. Hypotension may occur initially because of transient IVC occlusion by the balloons or due to hemodilution by the extracorporeal blood diversion and it can be controlled by intravenous fluids or norepinephrine (or phenylephrine) infusion; in addition, the activated carbon may filter 67 - 95% of the sympathomimetics present in the diverted blood, which can lead to a second phase of hypotension that could
be corrected by a high infusion rate of norepinephrine (0.2 – 1.5 μg/kg/min) and phenylephrine (0.4 – 3.0 μg/kg/min)[21].

Apart from hypotension, mild transient hypothermia is commonly encountered during PHP due to flowing blood in a non-heated extracorporeal system which could be corrected by using an air-warming system[21].

Although myelosuppression (neutropenia, thrombocytopenia or anemia) is the main side effect of systemic exposure to melphalan, the mortality related to bone marrow failure is not significant[15]. This chemotoxicity may be a result of an incomplete filtration of melphalan, an insufficient sealing of balloons, collateral pathways between the IVC and the systemic venous circulation (azygos, hemizygous) and/or a delayed release of retained melphalan from the hepatobiliary system[16,17,21]. Leakage of the chemotherapeutic agent to systemic circulation can be measured accurately during IHP by injecting human serum albumin or erythrocytes labeled with iodine-131 or technetium-99m[27,28]. This method cannot be applied to PHP because the type of perfusion in PHP is a closed circuit; therefore, a quantitative laboratory measurement of plasma melphalan levels is the only mean used to estimate the leakage. However, this measurement is impractical because it is not real-time, complex and time-consuming[28].

There are several precautions to PHP which include extensive extrahepatic disease, severe cardiopulmonary comorbidity, insufficient liver function and during menstruation[21]. Contraindications to heparin infusion and severe portal hypertension are other precautions[23].

In this review, eight articles were recruited to evaluate the efficacy of PHP in terms of survival rate and tumor response. In general, all these articles agree that PHP has a promising role in treating unresectable isolated liver malignancies as demonstrated in Table 1. The search strategy was developed in accordance with the Consolidated Standards of Reporting Trials (CONSORT)[29].

DISCUSSION
The recently published RCT-phase III, sample size of 93 patients at nine centers in the United States, which compared PHP with the best alternative care (BAC) in patients with hepatic metastases from melanoma, seems the most relevant in our search[15]. For this RCT, the CONSORT 2010 check list and the SPIRIT statement 2013 have been followed to appraise the trial[29,30]. After randomly allocating the patients to a melphalan-PHP group (n = 44) or BAC group (n = 49), they were followed up every six months for the first two years and then yearly thereafter to assess survival and hepatic disease progression[15]. The result of this RCT showed that objective response rate (ORR) was significant (p = 0.003) between the groups[20]. In addition, the hepatic progression-free survival (hpPFS) was statistically significant (p <0.0001). Conversely, there was no significant difference in the overall survival between the two groups (p >0.05) due to the cross-over group (n = 28) who shifted to the melphalan-PHP group during the trial[15]. This RCT has several strengths according to the CONSORT and SPIRIT check lists, including the sample size selection which has 80% power for four months hpPFS, random allocation sequence, blinding technique and effective statistical method to compare the results. This trial is the only RCT that studied the role of PHP; however, its results are encouraging for further clinical trials.

According to De Leede et al, the filtration rate of the generation 2 hemofiltration system performs better than the first-generation[16]. In regards to the clinical outcome of this small sample size study, a partial response was observed in all patients with liver metastases due to ocular melanoma with the mean time to progression (TTP) of 15.5 months (range: 9 – 28 months), and the partial response of patients with colorectal cancer was noticed in one patient (33.3%) and the mean TTP of this patient was 4.3 months (range: 1 – 5 months)[16].

In the retrospective study described by Vogl et al, a small sample size of 14 patients with unresectable hepatic metastases from different primary solid tumors, who underwent chemosaturation-PHP with melphalan at two centers[17]. The ORR was 50% in total, in which one patient got complete response and other six patients developed partial response. The ORR observed in this study was higher than Hughes et al[15], possibly due to smaller sample size and fewer number of centers.

In the cohort study performed by Forster et al, a small sample size of 10 patients with unresectable melanomatous or sarcomatous hepatic metastasis were treated with PHP and retrospectively reviewed in one center from 2008 to 2013[18]. The median survival rate was 7.9 months and the median regression of hepatic tumor volume was 33.3%[18].

Pingpank et al conducted phase I and phase II clinical studies to assess the feasibility, maximum tolerated dose and dose-limiting toxicity of melphalan in PHP[19,20]. In phase I study, a total of 74 PHPs were performed in 28 patients with different solid metastatic liver malignancies[19]. The observed ORR was 50% among 10 patients with ocular melanoma including two complete responses, and 30% ORR was observed in all treated patients[19]. The maximum safe tolerated dose of melphalan administered was 3 mg/kg[19]. A standard Response Evaluation Criteria in Solid Tumors criterion was used to assess radiological...
In the phase II study, a sample size of 23 patients with hepatic secondaries related to neuroendocrine tumor (NET) underwent 68 PHPs, and the reported hPFS was 39 months and ORR was 79%[20]. This high figure in the response rate might be due to pathological differences in the hepatic malignancies.

In the prospective study depicted by Miao et al, a sample size of 51 patients with NET, melanoma, and different metastatic tumors underwent 136 PHPs[21]. This study did not assess the survival or response rate; nevertheless, hemodynamic and metabolic changes along with anesthetic data were analyzed, and the reported complications of PHP were transient hypotension and metabolic acidosis[21].

In the case-series study presented by Fitzpatrick et al to find out the feasibility and toxicity of PHP, only five patients with metastatic melanoma to the liver underwent 15 PHPs[22]. Transient mild hypothermia and metabolic acidosis were noted[22].

As a limitation to our review, the number of relevant articles was not large enough.

CONCLUSION
Percutaneous hepatic perfusion is a minimally invasive liver-directed chemotherapy with a reasonably high response rate, and tolerable morbidity and mortality. Furthermore, it has a predictable and manageable systemic toxicity profile. Therefore, more clinical trials in this field are essential to assess and to confirm its pivotal therapeutic role.

ACKNOWLEDGMENT
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Conflict of interest: The authors declare that no conflict of interest exists.

REFERENCES

The promising role of percutaneous hepatic perfusion in unresectable hepatic malignancies


Original Article

Comparison of the radiologic tumour size with the pathologic tumour size in renal cell carcinoma

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ABSTRACT

Objective: This study aims to compare the radiologic tumour size (RTS) as measured by preoperative computerised tomography (CT) with the pathologic tumour size (PTS) as measured in a pathology specimen during the postoperative period for patients operated on due to renal tumours.

Design: Retrospective study

Setting: Samsun Training and Research Hospital, University of Health Sciences, Samsun, Turkey

Subjects: One hundred and four patients who were operated on at our clinic due to renal tumours

Intervention: The RTS is measured preoperatively using CT to determine the tumour’s longest diameter, while the PTS is measured in a pathology specimen based on its longest diameter.

Main outcome measure: The RTS and the PTS are compared in all the patients according to their histologic subtype and T stage.

Results: For the 104 patients included in the study, the median RTS is 57.5 mm (range: 18 – 280 mm) and the median PTS is 52.5 mm (range: 12 – 280 mm), which is statistically significant (p = 0.009). According to the pathological staging for T1a tumours, the median RTS of 38 mm (range: 21 – 90 mm) and the median PTS of 30 mm (range: 12 – 40 mm) are determined to be statistically significant (p <0.001).

Conclusions: The preoperative CT measurement of the renal tumour is significantly higher than that of the pathology specimen, which may result in differences between clinical staging and pathological staging. It should be noted that a discrepancy between the RTS and PTS values can affect treatment selection for the patient.

INTRODUCTION

Renal cell carcinoma (RCC) represents 2 – 3% of all cancer cases[1]. The incidence of RCC has increased by approximately 2% worldwide during the last two decades[2]. In the European Union in 2012, approximately 84,400 new RCC cases were reported, while the number of deaths due to RCC was calculated as 34,700[3]. In the United States in 2015, 61,560 new cases and 14,080 deaths occurred due to RCC[4].

Due to the increasingly common usage of computerised tomography (CT) and ultrasonography, there has been an increase in the incidental detection of RCC. The detected tumours are generally small in size and of a lower stage[5-7]. For the diagnosis of renal tumours, CT and magnetic resonance imaging are used. CT is cheap and easily accessible, which means it is used more frequently.

The selection of the appropriate treatment method for renal tumours is made according to the clinical staging. The tumour size is of great importance to the renal tumour staging as well as the prognosis of the disease. Two approaches can be applied in renal tumour surgery: radical nephrectomy (RN) and partial nephrectomy (PN). According to the European Association of Urology (EAU) guide, PN treatment is recommended for T1a stage tumours (tumour size ≤4 cm)[8]. For this reason, during the clinical staging, the correct evaluation of the tumour size is very important to the surgeon’s decision regarding the type of operation to be conducted.

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A search of the literature reveals that a lot of studies have compared the radiologic tumour size (RTS) and the pathologic tumour size (PTS). Our objective is to extend the findings of these studies by detecting the consistency between the tumour size as measured radiologically and the tumour size as measured pathologically, as well as evaluating how this consistency affects the treatment of the patient.

**SUBJECTS AND METHODS**

Some 104 patients who applied to our clinic between March 2012 and October 2016, who underwent PN or RN due to a pre-diagnosis of renal tumour and whose medical records could be accessed are analysed retrospectively. A preoperative intravenous contrast-enhanced abdomen CT is applied to all the patients prior to the operation (7 – 30 days). The RTS of the longest diameter of the tumour is measured using CT by an experienced radiologist, while the PTS of the longest tumour diameter in a pathology specimen is measured by an experienced pathologist. The age, gender, side where the tumour is located, type of surgery, histologic type of the tumour, and tumour’s T stage of all the patients are recorded. The TNM 2012 staging system is used to determine the clinical and pathologic staging, which is evaluated as: T1a = tumour size ≤4 cm; T1b = 4 cm <tumour size ≤7 cm; T2a = 7 cm <tumour size ≤10 cm; and T2b = tumour size >10 cm. The RTS and PTS of all the patients are compared. Moreover, the RTS and PTS are compared by grouping the patients according to their sex, tumour side, histologic subtype and T stage. The decreasing stage and increasing stage of the patients are also evaluated when the RTS and PTS are compared. Approval for this study was obtained from the Samsun Training and Research Hospital, Scientific Researches Assessment Board.

**Statistical analysis**

All data are analysed using IBM SPSS V23 (Chicago, USA). The convenience of the quantitative data to a normal distribution is analysed using the Shapiro-Wilk test. To compare the data that do not fit into a normal distribution, the Wilcoxon test and the Mann-Whitney U test are used. A Cohen Kappa analysis is used to analyse the conformity between the categorical data. The continuous data is presented as the median (min–max), while the discrete data is presented as the frequency (percentage). The significance level is taken as p <0.05.

**RESULTS**

Of the 104 patients included in this study, 60 (57.7%) participants are male, while 44 (42.3%) are female. Their mean age is found to be 57.8 years (range: 23 – 85 years). The clinical data concerning the 104 patients are presented in Table 1. RN is applied to 73 (70.1%) patients, while PN is applied to 31 (29.9%). In the histologic analysis of the removed tumour tissues, the following is reported: clear cell renal carcinoma for 79 (75.9%) patients; renal carcinoma without clear cells for 19 (18.3%) patients; angiomylolipoma for 4 (3.9%) patients; and oncocytoma for 2 (1.9%) patients. The surgical margins were negative in all cases. The distribution of the patients with respect to the pathologic T stage is: 39 (37.5%) patients with T1a tumours; 38 (36.6%) patients with T1b tumours; 19 (18.2%) patients with T2a tumours; and 8 (7.7%) patients with T2b tumours.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (min-max)</td>
<td>57.8 (23 - 85)</td>
</tr>
<tr>
<td>Sex, n(%)</td>
<td>Male 60 (57.7) Female 44 (42.3)</td>
</tr>
<tr>
<td>Tumour side, n(%)</td>
<td>Right 49 (47.1) Left 55 (52.9)</td>
</tr>
<tr>
<td>Surgery type, n(%)</td>
<td>Radical nephrectomy 73 (70.1) Partial nephrectomy 31 (29.9)</td>
</tr>
<tr>
<td>Histology, n(%)</td>
<td>Clear cell 79 (75.9) Papillary 11 (10.6) Chromophobe 4 (3.9) Multilobular cystic 3 (2.9) Unclassified 1 (0.9) Angiomyolipoma 4 (3.9) Oncocytoma 2 (1.9)</td>
</tr>
<tr>
<td>Pathological stage, n(%)</td>
<td>T1a 39 (37.5) T1b 38 (36.6) T2a 19 (18.2) T2b 8 (7.7)</td>
</tr>
</tbody>
</table>

The patients’ median RTS is 57.5 mm (range: 18 – 280 mm), while their median PTS is 52.5 mm (range: 12 – 280 mm), which is statistically significant (p = 0.009). According to the pathological staging, the median RTS is 38 mm (range: 21 – 90 mm) and the median PTS is 30 mm (range: 12 – 40 mm) for the T1a tumours, which is statistically significant (p <0.001). For the T1b tumours, the median RTS is 60 mm (range: 18 – 109 mm) and the median PTS is 60 mm (range: 45 – 70); while for the T2a tumours the median RTS is 83 mm (range: 63 – 115) and the median PTS is 85 mm (range: 75 – 90 mm). For the T2b tumours, the median RTS is 122.5 mm (range: 85 – 280 mm) and the median PTS is 125 mm (range: 110 - 280 mm). The p-values found in the comparison of the T1b, T2a and T2b tumours are 0.298, 0.819 and 0.141, respectively, and no statistically significant difference is detected (Table 2). There were 13 patients with RTS
less than 3 cm. Twelve patients underwent PN (8 open and 4 laparoscopic). In one patient, laparoscopic RN was performed because of the near tumour location to the renal vascular pedicule. The mean RTS and PTS of these patients were 26.03 mm (range: 18 – 29) and 26.92 mm (range: 20 – 38) respectively and there was no statistically significant difference between them (p = 0.764).

When the RTS and PTS of the 104 patients are compared, it can be seen that the tumour stage of eight patients increased, while the tumour stage of 18 patients decreased. There exist differences between the RTS and PTS of the patients who experienced an increase in their tumour stage (p = 0.012). The pathologic sizes are found to be greater than the radiologic sizes. Likewise, there also exist differences between the RTS and PTS of the patients who experienced a decrease in their tumour stage (p <0.0001). The radiologic sizes are found to be greater than the pathologic sizes. A statistically significant difference is determined between the PTS and RTS of the ten patients who changed from stage T1b to stage T1a and the five patients who changed from stage T2a to stage T1b (p = 0.005 and p = 0.068, respectively, Table 3).

When the RTS and PTS are compared according to the histologic subtypes, differences between the median RTS and PTS values are detected in the patients who have histologically clear cell renal carcinoma (p = 0.002). A median RTS of 55 mm (range: 18 – 140 mm) and a median PTS of 50 mm (range: 12 – 140 mm) are found. The patients whose histology is not clear do not exhibit any differences between their median RTS and PTS values (p = 0.981), since a median RTS of 70 mm (range: 24 – 280 mm) and a median PTS of 60 mm (range: 20 – 280 mm) are found.

As a result of the histological examination, a comparison can be made between the patients who have renal cell carcinoma and the patients whose tumours are of a benign character (i.e., oncocytoma and angiomyolipoma). The patients with RCC have a median RTS of 56.5 mm (range: 18 – 280 mm) and a median PTS of 50 mm (range: 12 – 280 mm), and a statistically significant difference is detected between these values (p = 0.007). The patients who do not have RCC have a median RTS of 64 mm (range: 45 – 93 mm) and a median PTS of 67.6 mm (range: 45 – 90 mm), which does not indicate a statistically significant difference (p = 0.893).

**DISCUSSION**

Today, the increasingly common usage of various imaging methods has increased the number of incidentally detected renal tumours. The detection of renal tumours during the early stage and when the tumours are small in size is very important for the patient’s prognosis[9]. CT is most commonly used to evaluate renal tumours. The sensitivity of CT in detecting small renal tumours in the kidney is greater than 90%[10]. In order to evaluate whether the correct measurement of the tumour size is achieved when it is detected radiologically, a number of prior studies have compared the tumour size as measured

### Table 2: Comparison of PTS and RTS

<table>
<thead>
<tr>
<th>Feature</th>
<th>n (%)</th>
<th>RTS (mm)*</th>
<th>PTS (mm)*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>104</td>
<td>57.5 (18 – 280)</td>
<td>52.5 (12 – 280)</td>
<td>0.009</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>60 (57.7)</td>
<td>60 (18 – 280)</td>
<td>52.5 (12 – 280)</td>
<td>0.021</td>
</tr>
<tr>
<td>Female</td>
<td>44 (42.3)</td>
<td>55.5 (22 – 140)</td>
<td>52.5 (25 – 140)</td>
<td>0.216</td>
</tr>
<tr>
<td>Tumour side</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>49 (47.1)</td>
<td>47 (22 – 115)</td>
<td>50 (12 – 130)</td>
<td>0.161</td>
</tr>
<tr>
<td>Left</td>
<td>55 (52.9)</td>
<td>65 (18 – 280)</td>
<td>60 (25 – 280)</td>
<td>0.023</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear cell</td>
<td>79 (75.9)</td>
<td>55 (18 – 140)</td>
<td>50 (12 – 140)</td>
<td>0.002</td>
</tr>
<tr>
<td>Non-clear cell</td>
<td>19 (18.2)</td>
<td>70 (24 – 280)</td>
<td>60 (20 – 280)</td>
<td>0.981</td>
</tr>
<tr>
<td>Having RCC</td>
<td>98 (94.2)</td>
<td>56.5 (18 – 280)</td>
<td>50 (12 – 280)</td>
<td>0.007</td>
</tr>
<tr>
<td>Not having RCC</td>
<td>6 (5.8)</td>
<td>64 (45 – 93)</td>
<td>67.5 (45 – 90)</td>
<td>0.893</td>
</tr>
<tr>
<td>Pathological stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1a</td>
<td>39 (37.5)</td>
<td>38 (21 – 90)</td>
<td>30 (12 – 40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T1b</td>
<td>38 (36.6)</td>
<td>60 (18 – 109)</td>
<td>60 (45 – 70)</td>
<td>0.298</td>
</tr>
<tr>
<td>T2a</td>
<td>19 (18.2)</td>
<td>83 (63 – 115)</td>
<td>85 (75 – 90)</td>
<td>0.816</td>
</tr>
<tr>
<td>T2b</td>
<td>8 (7.7)</td>
<td>122.5 (85 – 280)</td>
<td>125 (110 – 280)</td>
<td>0.141</td>
</tr>
</tbody>
</table>

*Values shown as median (min-max)

### Table 3: Comparison of RTS and PTS by down-staged tumors

<table>
<thead>
<tr>
<th>Down-staged tumors</th>
<th>Radiologic tumour size (mm)</th>
<th>Pathologic tumour size (mm)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1b → T1a</td>
<td>47.5 (41 – 70)</td>
<td>37.5 (25 – 40)</td>
<td>0.005</td>
</tr>
<tr>
<td>T2a → T1b</td>
<td>82.5 (75 – 95)</td>
<td>70 (65 – 70)</td>
<td>0.068</td>
</tr>
<tr>
<td>No change</td>
<td>55 (21-280)</td>
<td>55 (12 – 280)</td>
<td>0.038</td>
</tr>
</tbody>
</table>

*Values shown as median (min-max)
radiologically with the tumour size of a pathology specimen. However, there is no clear consensus on the subject. In many of these prior studies, the RTS is found to be significantly higher when compared with the PTS\textsuperscript{[11-13]} Yet, in other studies, no significant difference is found\textsuperscript{[14-16]}. In our study, while the median RTS of our patients is 57.5 mm (range: 18 – 280 mm), the median PTS is 52.5 mm (range: 12 – 280 mm), which is statistically significant (p = 0.009).

In Choi et al’s patient groups, according to the classification made based on the pathologic T stage, for patients in the T1a and T1b stages, the RTS is statistically significantly higher than the PTS, while for patients in the T2a and T2b stages, there is no statistically significant difference detected between the RTS and PTS\textsuperscript{[16]}. However, Kurta et al found that the RTS is higher than the PTS for patients in the T1b stage\textsuperscript{[11]}. In another study, it is determined that for T1a and T1b stage patients, the RTS is statistically significantly higher than the PTS, while for T2 stage patients, there is no statistically significant difference between the RTS and PTS\textsuperscript{[16]}. In our study, the RTS is found to be higher than the PTS only for T1a stage tumours (p <0.001). No statistically significant difference is detected in the other stages. In order to explain why the PTS is lower, Herr et al determined that following the interruption of the renal artery flow during the operation, secondarily to the decrease in tumour vascularisation, the tumour size decreases\textsuperscript{[17]}. Another reason for shrinkage of the size may be the routine pathologic processing with formalin fixation. This is a process that has been shown to reduce tumour volume\textsuperscript{[18]}. Tumour necrosis is more common in large tumours\textsuperscript{[19]}. Therefore, the tumour blood build up may be decreased, which might explain why there is no difference between the RTS and PTS in larger tumours.

In terms of the histologic subtypes, Lee et al found that the RTS is significantly higher than the PTS in clear cell renal carcinoma\textsuperscript{[20]}. Herr determined that for all the histologic subtypes, the RTS is higher than the PTS, although the ratio is statistically higher in the clear cell subtype when it is compared with the other subtypes (9.7 mm to 3.9 mm)\textsuperscript{[17]}. In two separate studies conducted by Kanofsky and Yaycıoğlu, it is found that for patients with the clear cell subtype, the RTS is statistically higher than the PTS\textsuperscript{[21,22]}. We detected that the RTS is significantly higher in the clear cell subtype when we compared the RTS and PTS values according to the histologic subtypes (p = 0.002), although there is no difference for the other subtypes (p = 0.981). These values might have been effected in the CT imaging due to the clear cell subtype having a greater vascular network when compared to the other subtypes\textsuperscript{[23,24]}.

Inconsistency between the RTS and the PTS may lead to a change in the clinical and pathological stage of the patient. In the study conducted by Karnofsky et al, according to the postoperative pathologic results, a change was identified in the stages of 21 patients out of a total of 198 renal carcinoma patients\textsuperscript{[23]}. Fifteen of these patients’ stage decreased, while six patients’ stage increased. When Jeffery et al evaluated the CT report using the pathology specimens of some 122 T1 and T2 clinical stage renal cell patients prior to operating, they detected that 21 (17.3%) patients’ stage decreased and 14 (11.5%) patients’ stage increased\textsuperscript{[22]}. Ateş et al detected 16 stage changes out of 86 patients. They found lower stages for six patients and higher stages for 13 patients\textsuperscript{[14]}. In our study of 104 patients operated on due to renal carcinoma, according to the pathology results, 26 patients’ stage changed. Eighteen (17.3%) patients experienced a decrease in their stage, while eight (7.7%) experienced an increase.

According to the EAU guide, PN is recommended for patients in the T1a stage (Grade A). PN can even be applied for the tumours in the T1b stage (Grade B)\textsuperscript{[8]}. However, the majority of clinics mostly apply PN for patients in the T1a stage. The patient’s clinical stage is determined based on the CT scan taken prior to the operation. The surgeon chooses the operation type based on the measured tumour size. Therefore, the accuracy of CT tumour size measurement is highly important. Additionally, the tumour size is not only important in terms of the decision regarding the operation type, but also the decision concerning ablative treatments. Previous studies have mentioned that a comparison of the PN and cryoablation methods as applied for tumours smaller than 4 cm shows there to be no difference in terms of either disease free survival, local recurrence or the progression of metastatic disease\textsuperscript{[25,26]}. In relation to ablative methods, it is not possible to correlate the tumour size with pathology, so we should rely on the CT tumour size measurement when making decisions regarding treatment.

CONCLUSION

As a result, with regards to the evaluation of patients with renal tumours, CT plays an important role in urology practice in terms of both clinical staging and treatment decisions. The correct interpretation of CT results by developed devices and experienced radiologists will help to identify a clearer path towards selecting the most appropriate treatment method for the patient. Our study is limited by the fact that it is retrospective, monocentric and does not include many patients. We believe that conducting prospective studies involving a greater number of patients will contribute more to this subject.
ACKNOWLEDGMENT
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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

REFERENCES

Original Article

Effects of 5α-reductase inhibitor therapy with dutasteride on sexual function in patients with benign prostatic hyperplasia

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Kuwait Medical Journal 2019; 51 (2): 140 - 144

ABSTRACT

Objective: To investigate the changes in sexual function and hormonal parameters during a six month follow-up period of dutasteride therapy in patients with benign prostatic hyperplasia (BPH)

Design: Prospective study

Setting: Sakarya University, Sakarya Training and Research Hospital

Subjects: Fifty patients who were administered 0.5 mg dutasteride daily due to BPH

Interventions: All patients were evaluated before and 6 months after the treatment for sexual function, hormonal parameters and also for the bladder outlet obstruction symptoms.

Main outcome measure: Sexual function domain scores of the International Index of Erectile Function (IIEF), total testosterone (TT), free testosterone, estradiol (E2), luteinizing hormone, follicle-stimulating hormone and sex hormone-binding globulin.

Results: There was no significant difference between each pretreatment and posttreatment sexual function domain scores of the IIEF after six months of dutasteride treatment. Dutasteride treatment significantly increased the serum TT and E2 levels compared to pretreatment values.

Conclusion: Six-month therapy of dutasteride in men with BPH did not alter the sexual functions.

INTRODUCTION

Benign prostatic hyperplasia (BPH) is the most common cause of benign prostatic obstruction and subsequent lower urinary tract symptoms (LUTS) in men over the age of 50. LUTS impair quality of life and are frequently accompanied by sexual function disorders in these patients[1]. 5α-reductase inhibitors (5α-RIs) therapy with finasteride or dutasteride and α1- adrenergic receptor blockers are widely used for treatment of LUTS due to BPH[2]. The 5-alpha reductase converts circulating testosterone to the more biologically active dihydrotestosterone (DHT). It was postulated that inhibiting 5-alpha reductase would decrease DHT levels within the prostate cells, leading to a decrease in prostatic volume[3,4]. Evidences from several clinical trials have demonstrated the efficacy of 5α-RIs in the treatment of BPH. Dutasteride is a 5α-RI and inhibits both isozymes of 5α-reductase (types 1 and 2). One of the main concerns with 5α-RI therapy is the adverse effects on sexual function[5–9]. The aim of this study was to investigate the changes in sexual function and hormonal parameters during a six month follow-up period of dutasteride therapy in patients with LUTS associated with BPH.

SUBJECTS AND METHODS

After having obtained approval of Institutional Ethics Committee, we performed a prospective analysis of 50 patients who were administered 0.5 mg dutasteride daily due to BPH, had an enlarged prostate (total volume ≥30 g), had LUTS (International Prostate Symptom Score (IPSS) >10). All patients were evaluated before and 6 months after the treatment for sexual function, hormonal parameters and also for

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bladder outlet obstruction symptoms. Patients with endocrinological disease that could affect the results of blood samples, and those who were administered any drugs which could affect the results, such as androgen replacement therapy or phosphodiesterase 5 inhibitor therapy, were excluded from the study. Patients with post-void residual urine volume >100 ml and prostate-specific antigen (PSA) levels ≥4 ng/ml were also excluded from the study.

After having a signed informed consent form, patient’s body mass index (BMI), IPSS, peak flow rate, post-void residual urine, International Index of Erectile Function (IIEF)-15 scores, and prostate volume by transrectal ultrasonography were achieved before and 6 months after the treatment. Blood samples were analyzed for hemogram and biochemistry parameters with serum PSA levels, total testosterone (TT), free testosterone (fTest), estradiol (E2), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and sex hormone-binding globulin (SHBG) before and 6 months after the treatment. Serum lipid profile including total cholesterol, triglycerides, high density lipoprotein (HDL) and low density lipoprotein (LDL) were also analyzed. Hormone measurements were all analysed on the same assay to reduce variability. Sexual function before and after dutasteride therapy was analyzed by erectile function domain scores (Q1, 2, 3, 4, 5, and 15), sexual intercourse satisfaction scores (Q6, 7, and 8), orgasmic function scores (Q9 and 10), sexual desire scores (Q11 and 12), and overall satisfaction scores (Q13 and 14).

All statistical analyses were performed on Statistical Package for the Social Science, Chicago, USA version 20. Data were expressed as mean ± standard deviation. The normal distribution of variables was determined by the Shapiro-Wilk test. A paired t-test is used to compare before and after observations on the same subjects when the differences of mean were normally distributed, or Wilcoxon Signed Ranks test was used when the population cannot be assumed to be normally distributed. Correlations between changes in IIEF scores and changes in IPSS scores, prostate volume and PSA levels were analyzed by using the Pearson’s correlation test. For all comparisons, p < 0.05 was considered as significant.

**RESULTS**

Seven of the 50 patients lost their follow up and finally 43 patients were included in the study. The mean age of patients was 60.3 ± 5.5 (range: 48 - 74) years. There was no significant difference between each pretreatment and post-treatment sexual function domain scores of the IIEF after six months of dutasteride treatment (Table 1). Dutasteride treatment significantly increased the serum TT and E2 levels compared to pretreatment values. TT and E2 values were increased from 5.4 ± 1.9 ng/ml to 7 ± 2.7 ng/ml (p <0.001) and from 30 ± 10.1 pg/ml to 35 ± 14 pg/ml (p = 0.011), respectively. However, there was no effect of the treatment on serum levels of fTest, LH, FSH or SHBG.

At the end of 6-month administration of the treatment, a statistically significant increase in total cholesterol, LDL cholesterol and also HDL cholesterol was detected (p <0.001). However, the increase in triglyceride was not statistically significant (p = 0.836). In addition, an increase in BMI, weight and waist circumference was also detected (p <0.001) (Table 2).

<table>
<thead>
<tr>
<th>Metabolic parameters</th>
<th>Before treatment (Average ± SD)</th>
<th>After treatment (Average ± SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>188 ± 30.4</td>
<td>202 ± 37</td>
<td>&lt;0.001 *</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>114 ± 23</td>
<td>129 ± 32</td>
<td>&lt;0.001 *</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>40.9 ± 10.3</td>
<td>44.1 ± 9.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>138.9 ± 84.6</td>
<td>140.6 ± 71.8</td>
<td>0.836 6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>83.44 ± 5.5</td>
<td>85.58 ± 13</td>
<td>&lt;0.001  *</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.05 ± 3.7</td>
<td>29.1 ± 3.9</td>
<td>&lt;0.001  *</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>105.6 ± 10.7</td>
<td>111 ± 9.2</td>
<td>&lt;0.001  *</td>
</tr>
</tbody>
</table>

*Wilcoxon signed ranks test, *Paired T test, LDL : low density lipoprotein; HDL : high density lipoprotein; BMI: body mass index

The treatment with dutasteride caused 50% decrease in PSA levels and the mean prostate volume decreased from 53 ± 20.6 cc to 35 ± 17.2 cc at the end of the 6 months (p<0.001). IPSS and uroflowmetric parameters including Qmax, Qaverage, and postvoiding residual volume were significantly improved with the treatment of dutasteride (p<0.001) (Table 3). However, there was
no significant correlation between the change in each sexual function domain scores and those IPSS scores, TT, E2 levels, BMI, weight and waist circumference.

DISCUSSION

Sexual adverse effects such as erectile dysfunction, loss of libido, and ejaculation disorders have been consistent side effects of 5α-RI therapy\(^{[6,9]}\). Many investigators believe that the adverse effects on sexual function affects only a small proportion of treated patients and such adverse effects are thought to resolve with continuing treatment. These adverse effects are seen in a maximum percentage of 15% after 1 year of therapy as reported in the PLESS study\(^{[10]}\). Debruyne \textit{et al} concluded that the onset of drug-related adverse events were reported most frequently at the start of therapy and declined over time in patients receiving dutasteride\(^{[11]}\). Roehrborn \textit{et al} suggested that the majority of the adverse events reported were not drug related in the judgment of the investigators\(^{[9]}\). The authors further stated that the drug-related events were of sexual nature and were the most common and included impotence, decreased libido, ejaculation disorders, and gynecomastia in the course of the 24-month study. More importantly, the authors claimed that most of these effects were transient, and the incidence of new occurrences of each event decreased in the 2\(^{nd}\) year. The MTOPS study represents the longest and largest clinical trial conducted in patients with BPH, which showed similar worsening of the erectile function domain over a 4-year period, when compared with placebo\(^{[12]}\).

Studies of the dual 5α-RI dutasteride also showed short-term effects of sexual dysfunction after treatment in men with BPH. Chi and Kim showed that after 1 month of treatment, dutasteride therapy resulted in a significant reduction in all investigated sexual function domains. The authors noted that partial recovery in sexual function was noted at 3 months, and orgasmic function and sexual desire were restored to baseline levels at 6 months\(^{[13]}\). In one study, Mondaini \textit{et al} have reported a nocebo effect (an adverse side effect that is not a direct result of the specific pharmacological action of the drug) of finasteride. In this study, blinded administration of finasteride was associated with a significantly higher proportion of sexual dysfunction in patients informed on sexual side effects as compared to those in which the same information was omitted\(^{[14]}\). In our study, we informed all the patients before treatment about the sexual side effects of dutasteride, but we did not see any significant difference in erectile function scores before and after six months of dutasteride therapy.

The underlying mechanism of sexual related effects due to 5α-RIs is not known but it may be a result of a decrease in dihydrotestosterone and a reduction in nitric oxide in the corpus cavernosum\(^{[15]}\). It is well accepted that androgens play an important role in sexual function, including libido, erectile function and orgasm, and have central as well as peripheral physiological effects on male sexuality. 5α-RIs play a central role in androgens metabolism. Thus, it is conceivable that inhibition of 5α-RIs may result in sexual adverse effects during the treatment, and even after cessation of the treatment, due to the complex mechanism of these enzyme reactions\(^{[16-18]}\). However, the results of the current study showed that dutasteride treatment did not affect the sexual function domain scores of the IIEF. DHT may be related to libido and appears to regulate both semen volume and viscosity through its action on the development and function of the prostate and seminal vesicles\(^{[19,20]}\). 5α-RIs reduce blood DHT levels by over 70%, but induce a compensatory rise in testosterone level by 20%\(^{[21]}\). In our study, we have also studied the hormonal parameters of the patients before and after the 6-month therapy of dutasteride. Dutasteride treatment resulted in a significant increase in testosterone (T) and E2 levels over the 6 months of treatment. However, there was no alteration of fTest, LH, FSH or SHBG levels with the treatment. These findings are inconsistent with some prior reports in which T levels were shown either to remain unchanged subsequent to 5α-RI therapy or relative increase in T levels were reported with 5α-RI therapy\(^{[22-26]}\). Kacker \textit{et al} did not find any alteration in T levels in men receiving dutasteride treatment; however, there was a clear tendency for a decline in T which did not reach statistical significance\(^{[27]}\).

It should be noted that Hong \textit{et al} and Roehrborn \textit{et al} noted marked increase in T levels in patients with low baseline T and reduced increase in T levels in patients with high baseline T levels\(^{[25,26]}\). It is well known that the increase of testosterone may cause an increase of the serum E2 level, due to the effect of aromatase enzyme which converts testosterone

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**Table 3: Prostate size and uroflowmetry parameters before and after treatment**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Before treatment (Average ± SD)</th>
<th>After treatment (Average ± SD)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate size (cc)</td>
<td>53 ± 20.6</td>
<td>35 ± 17.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Uroflowmetry datas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Qmax (ml/s)</td>
<td>11 ± 2.9</td>
<td>16.1 ± 4.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Qmean (ml/s)</td>
<td>5.7 ± 2.2</td>
<td>7.5 ± 1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Voided volume (ml)</td>
<td>265 ± 82.7</td>
<td>256 ± 106</td>
<td>0.508</td>
</tr>
<tr>
<td>Post voiding residue (ml)</td>
<td>107 ± 37.3</td>
<td>38 ± 29.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sum of IPSS</td>
<td>17.4 ± 5.1</td>
<td>8.8 ± 5.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Paired T test, IPSS: International Prostate Symptom Score
to estradiol[28]. The increase in E2 levels in our study can be due to this conversion. Our data on prostate volume, IPSS score, and PSA levels are consistent with previous studies reported using 5α-RI therapy in men with BPH[30].

The main limitations of this study are relatively small sample size and the lack of control group, although this is a prospective study.

CONCLUSION

The results of this study showed that six-month therapy of dutasteride in men with BPH has not altered the sexual functions. However, further prospective studies with larger sample size are needed on this field.

Competing Interests: The authors declare that they have no competing interests.

REFERENCES

Ovarian cancer management: Experience from Jordan University Hospital

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²Department of Urology, The University of Jordan, Jordan University Hospital, Amman, Jordan
³The University of Jordan, Jordan University Hospital, Amman-Jordan

ABSTRACT

**Objectives:** The aim of the present study was to assess the management protocol and outcome for patients diagnosed with ovarian cancer.

**Design:** Retrospective study

**Setting:** The University of Jordan, School of Medicine, Amman, Jordan

**Subjects:** All patients diagnosed to have epithelial ovarian cancer treated mainly with surgery between July 2008 and July 2014 at Jordan University Hospital were included.

**Intervention:** Surgery mainly

**Main outcome measure:** Presenting features, pathology, stage, operative procedures, residual disease volume and subsequent management steps

**Results:** The presenting symptoms were abdominal swelling in 22 patients (38%), abdominal pain in 12 patients (21%), difficulty in eating in 11 patients (19%), bloating in 7 patients (12%), and abnormal vaginal bleeding in 6 patients (10%). All patients underwent debulking surgeries which can be classified into three groups according to the operative procedures subjected: complete debulking in 27 patients (46.5%); optimal debulking in 16 patients (27.6%), where the sum of the residual tumor was less than 2 cm; and finally suboptimal debulking in 15 patients (25.9%), where more than 2 cm of the residual tumor was not resected.

**Conclusion:** In the course of this study, the team applied the surgical step followed by chemotherapy for all patients included in this study, results of which were satisfactory and achieved the desired targets.

INTRODUCTION

It is commonplace that ovarian cancer is one of the most common malignancies suffered by women. In fact, ovarian cancer sits at second place, high on the list of common gynecological malignancies in the United States, Europe, and Jordan[1-3]. According to epidemiological studies, age is a common risk factor of ovarian cancer because the ovaries of post-menopausal women become smaller and folded[4]. Sadly, a diagnosis of the disease does not occur in up to 80% of the cases until it is at advanced stages[5,6]. Of the causes of death from gynecologic malignancy, ovarian cancer is considered the leading one[7,8]. In terms of probability, the likelihood of being affected by ovarian cancer during lifetime is 1.6% for every woman[2,8]. Said probability is increased in the western part of the world due to environmental factors and modern life style[9]. Given that ovaries are estrogen-dependent organs, the relationship between estrogen and ovarian cancer is inseparable. Therefore, many reproductive, environmental, and lifestyle factors may contribute to the development of ovarian cancer as far as those factors affect estrogen levels[9]. Patients suffering from ovarian cancer are most often treated by applying the debulking surgery coupled with upfront platinum-taxane combination chemotherapy. However, and notwithstanding the aforementioned treatment, it is established that the median survival remains at 18 - 24 months, noting that reoccurrence takes place within the first 5 years in 80% of treated patients[10,11].
Primary surgery aimed at complete resection, followed by platinum and paclitaxel chemotherapy is the core of treatment for advanced ovarian cancer[9,12]. As it stands today, there exist no indicators so as to distinguish between patients that are likely to respond to chemotherapy and be treated with same, from those who are not. Nevertheless, response rates were proven high. However, in light of the evident lack of any reliable selection criteria, all patients currently receive postoperative chemotherapy, which is complementary and part and parcel of the holistic treatment approach. Chemo-sensitivity is the prime factor on which outcome of chemotherapy relies. Currently though, said factor is not subject to any interference by the treating team. Although medical treatment is homogenous, curiously, the outcome of interference by the treating team. Although medical treatment is homogenous, curiously, the outcome of such treatment is heterogeneous.

If compared to chemotherapy, surgical treatment is considered to be of more individualized nature in that, its performance and outcome depends on resectability of the tumor, patient’s tolerance to extensive surgical procedures, and the skill, capability and coordination of the surgical team as well as a well-put, agreed treatment plan between the surgical team and the patient[13,14]. Contrary to chemotherapy, surgical outcome is to a far greater extent subject to variation and amendment by the treating team. In the course of this study, the team applied the surgical step followed by chemotherapy for all patients included in this study, results of which were satisfactory and achieved the desired targets. The aim of the present study was to assess the management protocol and outcome for patients diagnosed with ovarian cancer at our hospital during the period July 2008 to July 2014 at Jordan University Hospital.

SUBJECTS AND METHODS

Prior to conducting the study, ethical approval was obtained according to the Jordan University Hospital regulations.

This is a retrospective study, wherein all patients with epithelial ovarian cancer treated during the study period were included in this study. The detailed information on presenting features, investigations, pathology, stage, operative procedures, volume of residual disease and subsequent management steps were abstracted from the medical records for said patients. After a thorough discussion with the patient about her case, a written consent was obtained. After general anesthesia, the bladder was catheterized, cleaned and draped, then standard operative procedure was applied in all cases. The abdominal wall was opened via a midline incision, fluid for cytology was obtained, systemic palpation for all abdominal organs, and finally the decision for the surgery type was made. All patients were subjected to the standard work up including complete blood count, kidney function tests, and liver function tests.

Deceased cases up to the first of July 2014 were included in the study *inter alia* the follow up duration for each said dead patient. All histopathological reports were reviewed by the authors. Staging was performed by one of the authors (K.F) in accordance with the standards of International Federation of Gynecology and Obstetrics classification and its recommendations thereto which standards were accredited and published in 2009, relying upon the operative note findings, the extent of the surgical procedure, pathology report and the results of all available investigations. The chemotherapy cycles that ensued surgery composed of platinum (cis or carboplatinum) with an alkylating agent (paclitaxel or docetaxel), were summarized and reported. Patients were given a subcutaneous injection of Neupogen to improve the possible suppressed immunity. The chemotherapy cycles when given were monitored by frequently checking the level of the tumor markers and the imaging studies.

RESULTS

In Table 1, we summarized the demographic and clinical characteristics of the study population. The mean age was 56.9 years (range: 32 - 80), the mean gravidity was 4.7 (range: 0 - 13), while the mean parity was 4.4 (range: 0 - 11). The marital status of the population study was: 33 patients (56.9%) were married, 13 patients (22.4%) were widowed or divorced, and the remaining 12 patients (20.7%) were single.

<table>
<thead>
<tr>
<th>Demographic criteria</th>
<th>Range</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>23 - 80</td>
<td>56.9</td>
</tr>
<tr>
<td>Gravidity</td>
<td>0 - 13</td>
<td>4.7</td>
</tr>
<tr>
<td>Parity</td>
<td>0 - 11</td>
<td>4.4</td>
</tr>
<tr>
<td>Marital status, n(%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>33</td>
<td>56.9</td>
</tr>
<tr>
<td>Widow/ Divorce</td>
<td>13</td>
<td>22.4</td>
</tr>
<tr>
<td>Single</td>
<td>12</td>
<td>20.7</td>
</tr>
<tr>
<td>Total</td>
<td>58</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 2 summarized the presenting symptoms, which were abdominal swelling in 22 patients (38%), abdominal pain in 12 patients (21%), dysphagia in 11 patients (19%), bloating in 7 patients (12%), and abnormal vaginal bleeding in six patients (10%). The operative procedures performed were complete debulking in 27 patients (46.5%), optimal debulking (the sum of the residual tumor less than 2 cm) in 16 patients (27.6%), and suboptimal debulking (the sum of the residual tumor more than 2 cm) in 15 patients (25.9%).
Table 2: Presenting symptom/Operative procedure

<table>
<thead>
<tr>
<th>Presenting Symptom</th>
<th>Number</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal swelling</td>
<td>22</td>
<td>38</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>Bloating</td>
<td>07</td>
<td>12</td>
</tr>
<tr>
<td>Abnormal bleeding</td>
<td>06</td>
<td>10</td>
</tr>
<tr>
<td>Operative procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete debulking</td>
<td>27</td>
<td>46.5</td>
</tr>
<tr>
<td>Optimal debulking</td>
<td>16</td>
<td>27.6</td>
</tr>
<tr>
<td>Suboptimal debulking</td>
<td>15</td>
<td>25.9</td>
</tr>
</tbody>
</table>

Table 3: Stages of disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>21</td>
<td>36.21</td>
</tr>
<tr>
<td>II</td>
<td>04</td>
<td>06.90</td>
</tr>
<tr>
<td>III</td>
<td>25</td>
<td>42.10</td>
</tr>
<tr>
<td>IV</td>
<td>08</td>
<td>13.79</td>
</tr>
<tr>
<td>Total</td>
<td>58</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 4: Type of tumor

<table>
<thead>
<tr>
<th>Type of tumor</th>
<th>Number</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary serous carcinoma</td>
<td>31</td>
<td>53.45</td>
</tr>
<tr>
<td>Endometroid carcinoma</td>
<td>12</td>
<td>20.69</td>
</tr>
<tr>
<td>Mucinous carcinoma</td>
<td>04</td>
<td>06.90</td>
</tr>
<tr>
<td>Mixed Mullarian malignant tumor</td>
<td>02</td>
<td>03.45</td>
</tr>
<tr>
<td>Mature Cystadenoma carcinoma</td>
<td>02</td>
<td>03.45</td>
</tr>
<tr>
<td>Clear cell Cystadeno carcinoma</td>
<td>01</td>
<td>01.72</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>01</td>
<td>01.72</td>
</tr>
<tr>
<td>Sertoli cell tumor</td>
<td>01</td>
<td>01.72</td>
</tr>
<tr>
<td>Adenomatoid carcinoma</td>
<td>01</td>
<td>01.72</td>
</tr>
<tr>
<td>Metastatic poorly carcinoma</td>
<td>01</td>
<td>01.72</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>01</td>
<td>01.72</td>
</tr>
<tr>
<td>Fallopian tube carcinoma</td>
<td>01</td>
<td>01.72</td>
</tr>
<tr>
<td>Total</td>
<td>58</td>
<td>100</td>
</tr>
</tbody>
</table>

(36.2%), well differentiated in 19 patients (32.8%), moderately differentiated in 15 patients (25.39%), and unknown in three patients (5.2%). The ovarian cancer presented with advanced disease (stage III or IV) are more likely to have poorly differentiated types. The cytology was positive for malignancy in 34 patients (58.62%). Forty-four patients (75.86%) are alive, eight patients (13.80%) died due to the disease, and four patients (6.90%) fate was unknown. Forty patients (68.97%) were found to have positive lymph nodes for malignancy.

Postoperative platinum based chemotherapy was given to 45 patients (77.6%) with an average of 6.15 cycles/patient (range: 2 - 12), and the time interval between each cycle was the standard three weeks. The median follow-up since time of surgery till last visit was 34 months (range: 6 – 62). Patient’s characteristics and unadjusted survival varied for ovarian cancer patients treated during the study period. The overall five year survival rate for patients treated before five years was about 82%, where a total number of eight patients died, thus representing about 18% and the cause of death is related directly to the cancer situation.

The cases where results were not up to expectation were predominantly due to late stage diagnosis, old age, poor histological differentiation, poor pathologic type, presence of ascites, or a combination of these factors.

DISCUSSION

So as to improve patients’ survival prospects, the authors applied in their plan of management of ovarian cancer patients the surgical staging and optimal tumor debulking followed by platinum based chemotherapy, the results of which have proven to be effective as evidently demonstrated by others[15-17]. It is the authors’ view that the optimal management for patients with ovarian cancer should ideally consist of histopathological diagnosis, accurate surgical staging, debulking surgery and platinum-based chemotherapy[18-22].

The preceding places the fact that treatment of ovarian carcinoma is one of the most challenging tasks for the gynecologic oncologist. Several treatment modalities are integrated into this remedial plan, with surgery and chemotherapy being the most important and frequently used nowadays. Contrary to the other main types of gynecologic cancers, considerable improvements in long-term survival are noted for ovarian carcinoma[23,24]. Since the seventies of the past decade, various random trials proved the role of platinum compounds. Nine of the trials were included in the 1998 meta-analysis, comparing 1704 patients and 1428 deaths[25]. The meta-analysis included both combinations and single agent, with the key outcome of this meta-analysis being that the use of platinum compounds should not be delayed until relapse[26,27].

Notwithstanding the fact that surgery remained controversial till the seventies of the past century, it is now recognized as part and parcel of the ideal treatment in so far as advanced ovarian carcinoma is concerned. The outcomes of our study are confirming the results of previous studies that the
effect of removing tumor extensively provided a better survival even in advanced stage disease, hence the introduction of primary tumor debulking surgery\[28-30\]. Griffith and Fuller\[31\] clarified the theory behind primary debulking surgery and confirmed its value. Latter work illustrated that poor functionality and nutritional troubles like nausea and loss of appetite were improved by debulking surgery\[32,33\]. Primary debulking surgery was also suggested to have the effect of removing tumor cells that are therapy-resistant and at the same time raises the number of proliferated tumor cells (the Gompertzian phenomenon), thus making them more inclined to positively react to subsequent chemotherapy\[32,34\]. Given the availability of further subsequent treatment aimed at controlling unresectable residual disease, debulking surgery is worth considering when it comes to ovarian cancer. Maximum debulking surgery was suggested by Meigs as early as 1934 as being of benefit\[35\]. More than three and a half decades later, ‘maximum surgical effort’ was suggested by Munnell\[36\].

The amount of postoperative residual tumor is a detrimental factor in classifying the surgical outcome of ovarian cancer. In the event that no macroscopically visible tumor is left, a complete resection is considered. Should there remain visible tumor post surgery, the classification is done in accordance with the largest diameter. Where residuals of largest diameter up to 1 cm remained after operations, they were classified as “optimal debulking” as opposed to suboptimal debulking for those resulting in larger residual tumor.

Survival has been shown to increase in cases where debulking surgery was applied, given that it is most effective in debulking a tumor or in best case scenario, the removal of any gross disease. Any increase in debulking by 10% compares to an increase of 5.5% in so far as median survival is concerned. Prospects of success of optimal debulking fall between 20% and 90%\[37\]. Ovarian cancer and the epithelial type in particular has been recognized as one of the most biologically sensitive solid cancers to cytotoxic chemotherapeutic agents, with responses expected in greater than 80% of women who receive standard platinum and paclitaxel-based treatment. In light of the preceding, the standard plan adopted by the authors in the management of patients with such disease was to adhere to ideal debulking surgery, followed by the combined regimen of chemotherapy through the same treating team. The results were satisfactory with 77.6% of patients enrolled in this regimen who had a median follow-up in the realm of 34 months up to the time of collection of this data for publication. The preceding ought to be regarded in view of the fact that in excess of 75% of clinically complete responders do happen to develop recurrent disease\[38\].

The current first line chemotherapy of epithelial ovarian cancer remains paclitaxel + carboplatin (TC). However, this mode of therapy only achieves a 60% to 70% response rate\[39\]. To the exclusion of paclitaxel, the recent use of taxanes in the new regimens resulted in no significant difference of response between docetaxel + carboplatin (DC) therapy using docetaxel and TC in a phase 3 comparative study as shown in the following response ratios: 58.7% to DC therapy and 59.5% to TC therapy\[40\].

Notwithstanding the growth of use of tumor markers in so far as laboratory medicine is concerned, such use remains constrained against accuracy, sensitivity and specificity given the variety and varsity of indications that such markers could provide, thus rendering the use of said markers precluded for the early detection of malignancy\[40\].

Whilst serum CA125 is beneficial in two aspects, the first being the differential diagnosis of ovarian masses, post menopause in particular, and the second being monitoring the response to chemotherapy and follow-up of patients with histologically proven ovarian carcinoma, its role in the screening of malignancy remains contentious, noting that serum CA125 is the most reliable serum marker for ovarian cancer. Fluctuation in the level of CA125 may, subject to various criteria, constitute an indicator for responsiveness or progression, but without a defined role in diagnosis or prognosis\[41\].

Excellent response in all patients was reported in cases where tumor markers were used as an indicator for the steps to be adopted in the management plan. Following surgery, levels of CA125 may still be elevated as a result of tissue damage for two weeks thereafter, which period ought not to give rise to concern. However, upon the passing of said two week period, should plateau levels be above the upper limit of the norm, or a rise is detected, residual disease should then be suspected. It may be many weeks after surgery until CA125 returns to its normal levels, based on a half-life of 6 days of this marker. Therefore, any subsequent fall in the CA125 would be the result of surgery and/or chemotherapy, particularly so where pre-chemotherapy level was the same or higher than that which was taken post surgery\[41\].

Various factors are involved in improving the 5-year survival rate. Mainly, that the patient is seen or initially referred to a gynecologist, being operated on by a gynecologist, having debulking surgery to less than 2 cm residual, and receiving platinum based chemotherapy. These factors sum up the experience at a teaching hospital, where the presence of a multidisciplinary team provides for better service, and hence a better outcome. The aforementioned shares the vision reached by Gillis and his coauthors\[42\].
Notwithstanding the improvement in the management of ovarian cancer, the long-term prognosis for patients with advanced stage of the disease who were treated before the year 1995 remained poor. Little change occurred on the age-adjusted ovarian cancer mortality rates in the US between 1979 and 1995. The year preceding the introduction of paclitaxel witnessed no improvement in the long-term survival for women treated in Norway. The results deduced from our data illustrates that whether the patient presented with an early stage ovarian cancer or an advanced stage of ovarian cancer, the survival rate was overall pro-rata to the stage of the disease acceptable with a median of 34 months, as eight patients died after 5 years, and all said patients underwent optimal care of therapy which consisted of radical surgery, followed by the standard universal platinum-paclitaxel chemotherapy regimen.

Due to both factors of tolerability and activity, the combination of carboplatin and paclitaxel is frequently accepted as the standard course of therapy. In most cases, the aforementioned process resulted in enabling the authors to achieve good results among its study group. The authors’ view stated herein above is strongly supported by Valentina et al as well as the review of current management of epithelial ovarian cancer by Guppy et al.

The second look surgery is not carried out as a standard step in the treatment plan. It is only resorted to as part of the management plan in the event of recurrence. The standard approach for follow up is conducted through regular physical examinations, imaging tools and the tumor markers level. It is only when suspicion of recurrence exists that a second look surgery is warranted, whether it be through laparotomy or laparoscopy. Data deduced from our study showed that women who presented with ovarian cancer and were subjected to our protocol and survive for 6 years post diagnosis and management should have the same survival rate of women of the same age group without the disease.

CONCLUSION

We conclude that surgical debulking has utmost significance that reflects on the prognosis of advanced ovarian cancer. Regardless of the extent of the disease, better survival rates are achieved with the combination of optimal surgery and chemotherapy. Such survival rates are pro rata to the extent of the disease, which also dictates the extent of the debulking.

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REFERENCES


Objective: Several scoring systems and laboratory values are used to predict outcomes in coronary artery bypass graft surgery. The present study investigates the relationship of albumin, creatinine, sodium, and potassium levels with the outcomes of coronary surgery, to determine whether these values together may comprise an easy-to-interpret, high-quality, low-cost indicator.

Design: Retrospective, observational, cross-sectional study

Setting: Department of Anesthesia, Türkiye Yüksek İhtisas Education and Research Hospital

Subjects: 1157 patients undergoing elective, on-pump, coronary artery bypass graft surgery from January 2013 to January 2015

Intervention: Data collection, coronary artery bypass graft surgery, blood tests

Main outcome measures: Postoperative complications were grouped under combined adverse events (CAE) heading: (i) Myocardial infarction; (ii) Cardiac re-operation; (iii) Prolonged mechanical ventilation; (iv) Prolonged hospital stay; (v) Re-hospitalization; and (vi) Mortality classifications were made.

Results: Of the 1157 patients, 76.1% were male with a mean age of 62.3 ± 9.9 years. In 17% of the patients (n = 197), CAE were observed. Univariate logistic regression analysis showed that albumin and sodium were significantly lower in CAE patients. Multivariate logistic regression analysis also showed that hyponatremia and hypoalbuminemia were independent risk factors for CAE. Sodium <136 mmol/L increased the risk of CAE 3.1 fold, and albumin <3.5 g/dl increased the risk of CAE 2.7 fold. Coexistence of hypoalbuminemia and hyponatremia increased the risk of CAE development 5.61 fold.

Conclusions: In coronary artery surgery patients having both hypoalbuminemia and hyponatremia, the risk of CAE development increases 5.61 fold. In such patients, sodium and albumin levels may be used for an easy and quick preoperative risk evaluation. In patients with low levels of these parameters, increased risk should be considered, and thus, both surgery and anesthesia management may be planned more carefully.

KEY WORDS: coronary artery bypass surgery, hypoalbuminemia, hyponatremia, morbidity predictors, mortality predictors

INTRODUCTION

Coronary artery diseases are currently among the leading causes of mortality and morbidity. Atherosclerosis and myocardial infarction pathogenesis of coronary artery are quite complicated and complex. In coronary artery patients, an effective treatment compatible with etiopathogenesis and clinical manifestation substantially increases both quality of life and survival. Coronary arterial bypass grafting (CABG) surgery is one among these options. In patients undergoing bypass surgery, changes in hematological and biochemical parameters may occur depending on preoperative comorbidities and the existing cardiac condition. Cardiac surgeries accompanied with chronic inflammation may pose a risk in terms of possible postoperative complications. By determining the preoperative morbidity and mortality risks of patients, it is possible to optimize
the patients. By postoperative close monitoring, comorbidities are controlled, the surgery method may be modified, intraoperative anesthetic medication is organized, and thus the anticipated risks are avoided. Due to all these reasons, various scoring systems and laboratory parameters are used preoperatively. Some biochemical parameters that are routinely checked during the preparation of the patient for the surgery help with the postoperative risk analysis.

Albumin is a protein with a long half-life and it indicates malnutrition. Diseases, stress, and chronic inflammatory processes may decrease albumin levels[3]. In cardiac surgery patients, postoperative creatinine increases may occur with varying grades within acute kidney injury classifications[3]. Due to chronic diuretic treatment, preoperative electrolyte changes may occur in most of the cardiac surgery patients[4]. There exist several studies in the literature examining the relationship of preoperative albumin, creatinine, sodium, and potassium levels with coronary surgery outcomes. However, to the best of our knowledge, there exist no studies examining all these parameters together. The present study aims to investigate whether these four parameters, which are routinely evaluated preoperatively in coronary surgery, can be used as a high quality, low-cost, quick, and easy-to-interpret outcome predictor in cardiac surgeries.

SUBJECTS AND METHODS

The present study was carried out in our cardiac surgery hospital after obtaining permission from the Hospital Education Planning and Ethics Committee (Date: November 1, 2016, no:01-02-16). The study was registered with the clinical trials system (NCT02765061).

Patients and data acquisition
In this retrospective, observational, cross-sectional study, the data belonging to patients from the time period of 2013 and 2015 were used. The patients who underwent cardiac surgery in this period were evaluated and the data belonging to 1300 patients complying with the protocol of the study were obtained via electronic data system and their files. In total, 143 patients were excluded from the study due to missing data pertaining to intraoperative and intensive care periods, and 1157 patients were included in the study. The study included patients undergoing elective, on-pump, coronary bypass graft surgery. Those who were operated under urgent or semi-urgent conditions, pediatric patients, those who were administered combined procedures, and those undergoing off-pump cardiac surgery were excluded from the study. Demographic data of the patients, preoperative comorbidities, American Society of Anesthesiology scores, and Euroscores were recorded. For preoperative albumin (3.5 - 5.2 g/dl), creatinine (0.66 - 1.09 mg/dl), sodium (Na) (136 - 146 mmol/L) and potassium (K) (3.5 - 5.1 mmol/L) parameters, the normal ranges used at our laboratories were used as cutoff values.

Definitions
Important postoperative complications were grouped as combined adverse events (CAE). Therefore, (i) Myocardial infarction; (ii) Cardiac re-operation; (iii) Prolonged mechanical ventilation (>48 hours); (iv) Prolonged hospital stay; (v) Re-hospitalization; and (vi) Mortality classifications were made and used to define postoperative outcome. Pulmonary complication[5], neurological complication[6], renal complication[7], low cardiac output syndrome (LCOS)[8], sternal wound infection[9], and infective complications were considered as postoperative complications developed independent from CAE. The definitions used are given below:

- Pulmonary complication: pneumonia, pneumothorax, pulmonary emboli, pleural effusion;
- Neurological complication: recently developed cerebrovascular event/transient ischemic attack, stroke;
- Renal complication: acute postoperative renal insufficiency, an increase of serum creatinine over 2.0, 50% or greater increase in creatinine over baseline preoperative value, new requirement for dialysis;
- Infective complication: proven infections occurring in the body (except liver and wound site infections);
- LCOS: low cardiac output syndrome,
- Superficial or deep sternal wound infection.

Postoperative pathologies were recorded based on these definitions.

Statistical analysis
To determine the statistical methods to be utilized, first the Shapiro Wilk normality test was carried out, and because normality hypothesis was not satisfied in at least one of the groups, non-parametric test methods were used. Therefore, the Mann-Whitney U test was used to compare the parameters in two independent groups, and the Chi-square and Fisher’s exact tests were used to observe the relationship in terms of categorical variables or to examine the differences between groups. To determine the risk factors that were considered to have an effect on the occurrence of CAE, univariate logistic regression analyses were carried out, and those variables with 0.25 or less significance were subjected to the multivariate logistic regression model. The variables left out in the model
RESULTS

It was found that, of the 1157 patients undergoing CABG, 76.1% (n = 881) were male and 23.9% (n = 276) were female, and the mean age was 62.3 ± 9.9 years. To categorize the symptoms of the 1157 CABG patients and to establish their relationship with postoperative outcomes, those patients with CAE were grouped separately. Development of CAE was observed in 17% (n = 197) of the patients. When the demographic data were compared between the groups with and without CAE, Euroscore, pulmonary disease, diabetes mellitus, hypertension, and ejection fraction were found to be significant (Table 1). For biochemical parameters, namely Na, K, creatinine, and albumin, the univariate logistic regression analysis was performed and it was found that albumin and sodium parameters were significantly lower in CAE patients (Table 2). For the parameters found significant in univariate analyses, multivariate logistic regression analyses showed that all causes of hyponatremia and hypoalbuminemia were independent risk factors for CAE development. It was found that Na <136 mmol/L increased CAE development by 2.7 fold. In patients with both hypoalbuminemia and hyponatremia, the development by 3.1 fold, and albumin <3.5 g/dl increased CAE development by 4.5 fold. The most frequent postoperative complication in the study (n = 1157) was pulmonary problems (4.7%, n = 55). For the biochemical parameters, OR, 95% CI, and p-values were presented in Table 2. The results of group comparisons are presented as percentage for quantitative variables, and mean ± standard deviation and/or median (min-max) for qualitative variables. SPSS 15.0 was used for statistical analyses of the study, and the significance level was set as p <0.05.

Table 1: Patient’s characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>All cases (n = 1157)</th>
<th>CAE(+) (n = 197,17%)</th>
<th>CAE(-) (n = 960, 83%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n(%)</td>
<td>(95%low-upp)*</td>
<td>n(%)</td>
<td>(95%low-upp)*</td>
</tr>
<tr>
<td>Age</td>
<td>62.27 ± 9.86 †</td>
<td>65.85 ± 9.94 †</td>
<td>64.45 – 67.26 †</td>
<td>61.54 ± 9.69 †</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>881 (76.1)</td>
<td>139 (70.6)</td>
<td>0.63 - 0.76*</td>
<td>742 (77.3)</td>
</tr>
<tr>
<td>Female</td>
<td>276 (23.9)</td>
<td>58 (29.4)</td>
<td>0.23 - 0.36*</td>
<td>218 (22.7)</td>
</tr>
<tr>
<td>ASA scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>481 (41.6)</td>
<td>33 (16.8)</td>
<td>0.12 - 0.22*</td>
<td>448 (46.7)</td>
</tr>
<tr>
<td>3</td>
<td>656 (56.7)</td>
<td>152 (77.2)</td>
<td>0.70 - 0.82*</td>
<td>504 (52.5)</td>
</tr>
<tr>
<td>4</td>
<td>20 (1.7)</td>
<td>12 (6.1)</td>
<td>0.03 - 0.10*</td>
<td>8 (0.8)</td>
</tr>
<tr>
<td>Euroscore(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.22 ± 3.06 †</td>
<td>5.18 ± 4.58 †</td>
<td>4.53 ± 5.82</td>
<td>2.82 ± 2.46 †</td>
<td>2.66 - 2.97*</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>121 (10.5)</td>
<td>41 (20.8)</td>
<td>0.15 - 0.27*</td>
<td>80 (8.3)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>397 (34.3)</td>
<td>82 (41.6)</td>
<td>0.34 - 0.48*</td>
<td>315 (32.8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>589 (50.9)</td>
<td>123 (62.4)</td>
<td>0.55 - 0.68*</td>
<td>466 (48.5)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>30 (2.6)</td>
<td>10 (5.1)</td>
<td>0.02 - 0.09*</td>
<td>20 (2.1)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>393 (34)</td>
<td>70 (35.5)</td>
<td>0.29 - 0.42*</td>
<td>323 (33.6)</td>
</tr>
<tr>
<td>Renal disease</td>
<td>48 (4.1)</td>
<td>26 (13.2)</td>
<td>0.09 - 0.18*</td>
<td>22 (2.3)</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.18 ± 0.54 †</td>
<td>4.01 ± 0.65 †</td>
<td>3.91 - 4.10†</td>
<td>4.22 ± 0.51 †</td>
</tr>
<tr>
<td>Na</td>
<td>140.18 ± 3.24 †</td>
<td>139.76 ± 4.28 †</td>
<td>139.1 - 140.3†</td>
<td>140.26 ± 2.98 †</td>
</tr>
<tr>
<td>Active smoking</td>
<td>166 (14.3)</td>
<td>13 (6.6)</td>
<td>0.03 - 0.10†</td>
<td>153 (15.9)</td>
</tr>
<tr>
<td>Ejection fraction(%)</td>
<td>&gt;50</td>
<td>227 (19.6)</td>
<td>0.07 - 0.16†</td>
<td>204 (21.2)</td>
</tr>
<tr>
<td></td>
<td>50-30</td>
<td>732 (63.3)</td>
<td>0.45 - 0.59†</td>
<td>628 (65.4)</td>
</tr>
<tr>
<td></td>
<td>&lt;30</td>
<td>198 (17.1)</td>
<td>0.29 - 0.42†</td>
<td>128 (13.3)</td>
</tr>
</tbody>
</table>

* indicates 95% Confidence Intervals for means and ratios where appropriate; † values given as mean ± standard deviation
ASA: American Society of Anesthesiologists; CAE: combined adverse events; Na : sodium

and their odds, 95% confidence intervals, and p-values are presented in respective tables. Demographic data and results of group comparisons are presented as percentage for quantitative variables, and mean ± standard deviation and/or median (min-max) for qualitative variables. SPSS 15.0 was used for statistical analyses of the study, and the significance level was set as p <0.05.
45, which was followed by infectious complications (3.1%, n = 36), LCOS (2.9%, n = 33), newly onset atrial fibrillation (2.6%, n = 30), renal complications (1.9%, n = 22), re-admission to ICU (1.9%, n = 22), neurologic complications (1.6%, n = 18), and sternal infection (0.8%, n = 9). All these complications were significantly higher in patients with CAE (p < .0001). Mortality was observed to be 2.9% (n = 34) in all patient groups and 16.2% (n = 32) in the CAE group (p < .0001) (Table 4). In the CAE group, mortality was 25% (n = 8) in hypoalbuminemia patients and 15.6% (n = 5) in hyponatremia patients.

**DISCUSSION**

In this study, we investigated the ability of preoperative sodium, potassium, albumin, and creatinine parameters to predict postoperative outcomes in patients undergoing on-pump coronary surgery. The multivariate logistic regression analysis provides independent distinctive data regarding the relationship between pathology and disease in terms of risk evaluation, and based on this analysis, it was found that hypoalbuminemia and hyponatremia can independently predict the development of CAE. It was observed that hyponatremia increased CAE development by 3.1 fold and hypoalbuminemia increased it by 2.7 fold. It was also observed that using multivariate independent analysis, the concurrent low albumin and sodium levels predicted CAE development better (5.61 fold).

**Sodium**

It is quite probable to observe electrolyte disorders in preoperative cardiac patients. One of the frequently used medications to decrease sodium levels is thiazide diuretics. In addition, medications such as bupropion, escitalopram, carbamazepine, and desmopressin are known to cause hyponatremia even though they are not used frequently[10]. It was shown in postoperative cardiac patients that preoperative hyponatremia increases postoperative complications, hospital stay, and mortality[11]. Hyponatremia frequently occurs in patients with overt heart failure or those with left ventricular dysfunction. Therefore, hyponatremia is an indication of heart failure and the severity of depressed ejection fraction. In such patients, worse outcomes are naturally expected. However, it was shown that in cardiac surgery patients with normal ejection fraction and no depressed ventricle, hyponatremia can still occur, and again it is an indication of negative outcomes. An explanation for this scenario is that whatever the underlying mechanism of hyponatremia is, it leads to neurohormonal activation, which has a deteriorating effect on myocardi[12]. In other studies where hyponatremia concurs with poor outcomes in cardiac surgery, the etiology of the condition was associated with neurohormonal activation and hypoosmolarity. It was also claimed that the severity of the hyponatremia is linearly associated with postoperative negative outcomes in cardiac surgeries[11]. It was asserted that low sodium levels lead to high levels of catecholamine, renin, angiotensin 2 and vasopressin, and therefore, renal and hepatic blood flow decrease and cardiovascular response deteriorates, which eventually leads to end organ damage[13]. Furthermore, it is not definitely known whether hyponatremia can be cured preoperatively, or whether it can positively affect the outcome even if it is cured[14]. Moreover, another negative effect of hyponatremia is that it leads to cell-level edema and dysfunction, which is mostly associated with the brain[15]. Similarly, if this effect is considered to be carried over to edema and cellular dysfunction in myocyte cells, possible global effects of hyponatremia in cardiac patients become more obvious. Due to all these reasons, in cardiac patients diagnosed with preoperative hyponatremia, cardiac anesthetists and surgeons should be aware of the increased risk of CAE.

* indicates 95% Confidence Intervals for ratios of complications, CAE: combined adverse events

<table>
<thead>
<tr>
<th>Complications</th>
<th>All cases (n = 1157)</th>
<th>CAE(+) (n = 197,17%)</th>
<th>CAE(-) (n = 960, 83%)</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>n(%)</td>
<td>(95%low-upp)*</td>
<td>n(%)</td>
<td>(95%low-upp)*</td>
</tr>
<tr>
<td>Pulmonary complication</td>
<td>54 (4.7)</td>
<td>45 (22.8)</td>
<td>0.17 - 0.29*</td>
<td>0.00 - 0.01*</td>
</tr>
<tr>
<td>Readmission to ICU</td>
<td>22 (1.9)</td>
<td>22 (11.2)</td>
<td>0.07 - 0.16*</td>
<td>0.00 - 0.0004*</td>
</tr>
<tr>
<td>Neurological complication</td>
<td>18 (1.6)</td>
<td>13 (6.6)</td>
<td>0.03 - 0.10*</td>
<td>0.00 - 0.01*</td>
</tr>
<tr>
<td>Renal complication</td>
<td>22 (1.9)</td>
<td>17 (8.6)</td>
<td>0.11 - 0.26*</td>
<td>0.00 - 0.01*</td>
</tr>
<tr>
<td>Infective complication</td>
<td>36 (3.1)</td>
<td>28 (14.2)</td>
<td>0.10 - 0.19*</td>
<td>0.00 - 0.01*</td>
</tr>
<tr>
<td>Sternal wound infection</td>
<td>9 (0.8)</td>
<td>5 (2.5)</td>
<td>0.01 - 0.05*</td>
<td>0.00 - 0.01*</td>
</tr>
<tr>
<td>Low Cardiac Output Syndrome</td>
<td>33 (2.9)</td>
<td>29 (14.7)</td>
<td>0.00 - 0.01*</td>
<td>0.00 - 0.01*</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>30 (2.6)</td>
<td>18 (9.1)</td>
<td>0.10 - 0.20*</td>
<td>0.00 - 0.02*</td>
</tr>
<tr>
<td>Mortality</td>
<td>34 (2.9)</td>
<td>32 (16.2)</td>
<td>0.11 - 0.22*</td>
<td>0.00 - 0.007*</td>
</tr>
</tbody>
</table>

Table 4: Postoperative complications
development and mortality (which is 3.1 fold higher in the present study).

**Albumin**

Serum albumin is produced in the liver and comprises 60 - 70% of the total plasma protein. Its fundamental function is to constitute the plasma oncotic pressure. It also binds and transports several elements, such as hormones, molecules, bile salts, iron, free fatty acids, calcium, and medicines. Its half-life is 18 - 20 days. It is an indication of nutrition, inflammation, hepatic function and general catabolic state. In many chronic conditions, hypoalbuminemia co-occurs with poor prognosis, and especially in cardiac surgery patients, it has been well documented that it increases postoperative mortality[16,17].

Hypoalbuminemia is associated with systemic inflammation, sepsis, and infection. Albumin selectively inhibits the TNF alpha-induced vascular cell adhesion protein-1 expression. It leads to the activation of nuclear factor-kappa B in endothelial cells. These two mechanisms are biological processes playing anti-inflammatory role and the decrease in albumin levels deteriorates the anti-inflammation system[18]. Therefore, poor wound healing and more infection risks are possible[19]. Similar to sodium replacement, the preoperative replacement of albumin is also a topic of discussion. This replacement may have a positive effect in the short run; however, it does not have an effect on morbidity and mortality, and it may also transfer the synthetic albumin to the extravascular area[20]. The increase in albumin is not a reason, but a result. Therefore, in the short run, the replacement treatment cannot eliminate the cause of the condition and the long process causing the condition.

**Sodium and albumin**

As mentioned above, it has been well-documented that hypernatremia and hypoalbuminemia have a prognostic value in cardiac surgery, each of which can predict the postoperative outcome. However, there is no study in the literature examining the use of hypernatremia and hypoalbuminemia in predicting CAE development risk in coronary bypass patients. In patients with high hypoalbuminemia and hypernatremia, the risk of CAE development is 5.6 fold higher.

**CONCLUSION**

Therefore, in patients undergoing coronary surgery, biochemical parameters, especially sodium and albumin levels, may be evaluated for a fast and effective risk analysis. Patients with both hypoalbuminemia and hypernatremia are considered to have a high risk, and planning in these patients should be carried out more carefully.

Our study has some limitations. First of all it was a single center, retrospective study. Secondly, we did not receive “preoperative drug reports” from patients, these drugs may actually affect preoperative sodium levels. Also, we did not have any information about the duration of hyponatremia and hypoalbuminemia. Third, we examined hyponatremia, however hypernatremia may also have adverse effects and we did not analyze it. Finally it would be better to do more detailed analysis with more patients.

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The role of torque teno virus (TTV) viremia in sarcoidosis etiology

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Objective: To investigate a possible role of torque teno virus (TTV) in the etiology of sarcoidosis

Design: Controlled prospective study

Setting: Faculty of Meram Medicine, Necmettin Erbakan University, Konya, Turkey

Subjects: This cross-sectional, clinical study included 37 sarcoidosis patients and 9 healthy control patients.

Intervention: TTV DNA quantification was performed by real-time PCR by the hybridization probe system, and viral load was interpreted by means of the crossing point (CP) value in sera of subjects.

Main outcome measures: The prevalence and viral load of TTV

Results: TTV DNA was detected in the majority of both patients and healthy controls. The prevalence was 59.5% in patients and 55.6% in controls. This difference was not statistically significant. However, CP values were statistically different in the patient group from the control group (p <0.001); namely, the viral load of TTV was higher in the patient group than in the healthy control group.

Conclusions: Overall, these findings demonstrate for the first time that TTV plays a role in the etiology of sarcoidosis. It is likely that the role of TTV in the pathogenesis of sarcoidosis is an aberrant immune response, driven by viral antigens.

INTRODUCTION

Sarcoidosis is a multisystemic disorder characterized by non-caseating granulomatous inflammation. Sarcoidosis can affect nearly all organs and tissues. The most commonly involved organs are lymph nodes, lung, skin, and eyes[1,2]. At the present time, the etiology of sarcoidosis has yet to be revealed sufficiently, despite extensive research and great developments. Since the initial description, the infectious etiology has been assumed to be based on the clinical and histological similarity between sarcoidosis and infectious granulomatous diseases such as tuberculosis[3]. Nowadays, the dominant hypothesis is that the pathogenetic mechanism of sarcoidosis is an abnormal immune response, driven by a specific but unexplained antigen (or antigens) in genetically susceptible individuals[4,5].

Torque teno virus (TTV) is an ubiquitous, human, non-enveloped virus with a circular single stranded DNA genome belonging to the Anelloviridae family. TTV was first described as a “transfusion-transmitted virus” in humans by Nishizawa et al[6]. TTV was initially believed to be responsible for non-A-E hepatitis infection, as it was isolated first in sera of Japanese patients with posttransfusion hepatitis[6]; further studies did not confirm to have a causal role in this disease, and actually no concrete disease associations with TTV currently exist[7]. TTV primary infection occurs in the first years of life by horizontal and perinatal route[8,9]; viral transmission in adulthood is
mainly parenteral\textsuperscript{[10,11]}, however, it can also occur with many body samples, including respiratory secretions, saliva, nasal fluids, breast milk, genital secretions and feces\textsuperscript{[12]}. Also, the virus is being readily detectable in nearly all parts of the body\textsuperscript{[13]}. In other words, it causes multisystem involvement as in sarcoidosis. The prevalence of TTV infection is above 80\% in the general population worldwide. However, high prevalence rates have been reported in healthy individuals\textsuperscript{[14]}. On the other hand, direct causal evidence to support the specific clinical manifestations associated with TTV infection has not been demonstrated clearly. In fact, studies have revealed interesting positive correlations between TTV load and severity of some chronic inflammatory diseases such as asthma and rheumatoid arthritis\textsuperscript{[15,16]}. There are a number of studies showing that T-cell response in tissues affected by sarcoidosis is strongly polarized towards a T-helper 1 (Th1) cytokine profile. The immune response to antigenic stimulus is largely determined by the cytokines produced by the active Th1 cells. IFN-$\gamma$, IL-2, IL-12, TNF-$\alpha$, and other related cytokines are expressed by differentiated Th1 cells at locations of inflammation in sarcoidosis\textsuperscript{[17]}. Molecules of innate immunity such as toll-like receptors (TLRs) are mediating the activation of immune cells in the pathogenesis of sarcoidosis\textsuperscript{[18]}. Nowadays, in vitro experimental investigations have demonstrated that TTV can stimulate the secretion of cytokines (IFN-$\gamma$, IL-6, and IL-10), probably interacting with the TLR-9, and potentiating the activity of TLR-9 ligands\textsuperscript{[19]}. We thought a hypothesis inspired by all these information: can persistent TTV infection cause sarcoidosis? To investigate a possible role of TTV in sarcoidosis etiology, TTV presence and viral load were analyzed in sera of sarcoidosis patients and controls. To our knowledge, this study is the first research concerning the relationship between sarcoidosis and TTV.

**SUBJECTS AND METHODS**

### Subjects and specimens

A total of 37 patients with a diagnosis of sarcoidosis according to the established criteria by the American Thoracic Society, European Respiratory Society and World Association of Sarcoidosis and Other Granulomatous Disorders\textsuperscript{[1]} and followed by our tertiary respiratory care clinic, were enrolled in the study. The diagnosis of sarcoidosis was made using a compatible clinical picture, histological demonstration of non-caseating granulomas, and exclusion of other diseases capable of producing a similar histological or clinical picture. Patients with both anti-hepatitis C virus and anti-HIV antibody were not included in the study. Nine healthy controls with voluntary blood donors were required to be in good health, which is defined as the absence of chronic diseases, HIV, hepatitis B and hepatitis C infections. The individuals who made blood transfusion previously were not included in the study.

Written informed consent was obtained from all patients and controls. The study was approved by the Necmettin Erbakan University Medical School Human Research Ethics Committee.

For all the 46 individuals (37 patients and 9 healthy controls), a blood sample was aseptically collected into vacutainer tubes and immediately delivered to the microbiology laboratory of our university hospital. At the end of the clotting time, the tubes were centrifuged at 3000 rpm for 10 min and the obtained serum samples were placed into sterile cryovials for storage at -70 °C until use.

### TTV DNA detection and quantification

In the microbiology laboratory of our university hospital, total DNA was purified from 200 μl of serum using the High Pure Viral Nucleic Acid Kit (Roche Diagnostic, Mannheim, Germany) and the elution volume was set to be a final 50 μl. TTV DNA quantification was carried out with a real time PCR by the hybridization probe system, which consists of two fluorescently labeled oligonucleotides. To amplify most TTV strains, specific oligonucleotide primers were employed derived from the ORF2 as conserved region of TTV. Previously published sequence of TTV genome was utilized for deciding the sequence of oligonucleotides\textsuperscript{[20,21]}. The hybridization probes were labeled with LightCycler (LC) Red 640 at the 5’ end (LC probe, acceptor probe) and with fluorescein at the 3’ end (FL probe, donor probe), for detection of the target sequence (Lightcycler Faststart DNA Master Hybprobe, Roche Diagnostic, Mannheim, Germany). For detection of the internal control, hybridization probe were labeled with LC red 705 at the 5’ end and with fluorescein at the 3’ end. It was decided to forward primer (5’-CCGAATGGCTGAGTTTTCCA-3’, position 103 to 122), reverse primer (5’-TTTTTCAGAGCCCTTGCCCATAG-3’, position 259 to 238), FL probe (5’-CCGAATGGCTGAGTTTTCCA-3’, position 219 to 195) and LC probe (5’-A ACTCACTTTGGCACCCGCCCTC-3’, position 192 to 169) with reference to AB0008394 GenBank accesion ID. On the other hand, V00618 gene locus of *E. coli* was used as hybridization probe for detection of the internal control (Lightcycler Faststart DNA Master Hybprobe, Roche Diagnostic, Mannheim, Germany)\textsuperscript{[22]}. The PCR master mix was prepared to a final volume of 15 μl, and a 5 μl extracted sample was added to the master mix in LC glass capillary, as described by
Koidl et al. Real time PCR was performed on the LC instrument (Roche). The cycling protocol was run as follows: one cycle of 95 °C for 7 minutes, followed by 65 cycles consisting of denaturation for 1 second at 95 °C, annealing for 10 seconds at 64 °C, and elongation for 25 seconds at 72 °C. After the final cycle, the melting curve was started at 50 °C for 1 minute and the thermal chamber temperature was slowly (0.2 °C/s) raised to 85 °C and the fluorescence was measured stepwise. The capillaries were then cooled for 2 seconds at 40 °C. Fluorescence curves were analyzed with the LC software (version 3.5.3), as described by Koidl et al.

The TTV viral load was interpreted through the crossing point (CP) value.

Statistical analysis

Group data were analyzed using SPSS 16.0 statistical software. The descriptive statistics as the mean and standard deviation, and the categorical variables information as frequency were given. Chi-square analysis was used for the relationship between positive and negative categories in terms of TTV DNA. The distribution of variables was analyzed with the Shapiro-Wilk test and Kolmogorov-Smirnov. Dunnett’s C test method was preferred for pairwise comparisons with control group. Probability values of p <0.05 were accepted as significant.

RESULTS

Serum samples from 46 individuals (37 patients and 9 controls) enrolled in the study were tested for TTV DNA by using the universal real-time PCR. Mean age was 47 ± 10.6 years (33 females) in the patients group, and was 34.6 ± 6.7 years (3 females) in the control group. Demographic and clinical characteristics of the subjects are summarized in Table 1. TTV DNA was detected in the majority of both sarcoidosis patients and healthy controls, as the prevalence was 59.5% (22/37) in patients and 55.6% (5/9) in healthy controls. The prevalence of TTV DNA was higher in the sarcoidosis patients, but this difference was not statistically significant (p >0.05). The presence of TTV DNA in both groups is shown in Figure 1. No statistical difference was found as well among sarcoidosis stages in terms of TTV DNA prevalence. Notably, serum prevalence of TTV was similar in both patients with and without treatment (60% vs. 58.8%).

Wide distributions in CP value were observed in sera of healthy controls (range: 32.6 - 35.8), whereas they were constricted in a narrow range in sera of sarcoidosis patients (range: 30.2 - 31.4). Interestingly, mean CP values were lower in the sarcoidosis patients (mean ± SD: 30.8 ± 1.3) compared to healthy controls (mean ± SD: 34.2 ± 1.3, Table 2). Overall, these findings showed that TTV viral load or viremia was significantly higher in sarcoidosis patients (p <0.001). The CP values for PCR positive results in both groups are shown in Figure 2. Notably, no statistical difference was found between patients undergoing treatment (mean: 30.2) and without undergoing treatment (mean: 31.4) in terms of CP value (p >0.05).

DISCUSSION

A consensus statement found in most peer-reviewed literature on sarcoidosis is that the etiology of sarcoidosis is obscure. There is increasing evidence for the role of microbial pathogens in sarcoidosis etiology. Epidemiological studies indirectly support

| Table 1: Patient and healthy subject characteristics |
|---------------------------------------|----------------|----------------|
| Characteristic | Sarcoidosis patients | Healthy subjects |
| N | 37 | 9 |
| Gender | | |
| Female | 33 | 3 |
| Male | 4 | 6 |
| Age in years mean (±SD) | 47.0 (±10.6) | 34.6 (±6.7) |
| Smoking, N (%) | 8 (21.6%) | 3 (33.3%) |
| Chest X-ray, N (%) | | |
| Stage I | 18 (48.6%) | |
| Stage II | 14 (37.8%) | |
| Stage III | 5 (13.5%) | |
| Stage IV | 0 (0%) | |
| Therapy, N (%) | 20 (54.1%) | None |

| Table 2: The CP values for PCR positive results in both groups |
|-------------------------------|-------|-------|--------|--------|
| Group | N | Mean | Std. Deviation | Minimum | Maximum |
| Controls | 5 | 34.20 | 1.304 | 32.62 | 35.81 |
| Patients | 22 | 30.77 | 1.307 | 30.19 | 31.38 |
| Total | 27 | 31.41 | 1.866 | 30.19 | 35.81 |
the infectious etiology of sarcoidosis. Seasonal clustering of sarcoidosis in the springtime, change of prevalence over climate zones, time and space clusters, an increased incidence in health workers, an association of environmental exposure with sarcoidosis or specific sarcoidosis phenotypes, and the transmission or recurrence of sarcoidosis by or in transplants have been observed, and all of these data support the hypothesis that animate agents are involved in the sarcoidosis etiology[24]. An overlapping ingredient in environmental and geographic reports is the likelihood of exposure to microbial agents. Newman et al observed positive associations between sarcoidosis risk and certain occupations, such as agricultural employment, exposure to insecticides, and moldy environments[25].

Based on serological evidence, it has been proposed that several different lymphotropic viruses’ infections such as Epstein-Barr virus, cytomegalovirus, human herpes viruses, human T-lymphotropic virus type 1, and HIV are a possible initiating factor in the sarcoidosis pathogenesis. An important limitation of this hypothesis is that it is not known whether viruses cause typical epitheloid granulomas of sarcoidosis. High titers of antibodies against lymphotropic viruses have been described in patients with sarcoidosis, but there is also a significant proportion of the general population with previous exposure to these organisms[3]. TTV is a human commensally virus[6] that may play a role in sarcoidosis etiology. Some studies showed that TTV concentrations have a positive correlation with inflammatory respiratory disease such as asthma, chronic obstructive pulmonary disease, bronchiectasis, idiopathic pulmonary fibrosis, and the extent of inflammation greatly contributes to clinical severity[15,28-30]. When planning this study, our hypothesis was that TTV might play a role in sarcoidosis by inducing inflammatory mechanism previously identified. TTV virus viremia and viral load could be an important indicator for us. On the other hand, viral load determination was very important, because the prevalence of the virus was high in healthy individuals in many studies. In our study, viral load was interpreted through the CP value. To our knowledge, no other studies have examined the relationship between sarcoidosis and TTV.

Results of our analyses showed that serum prevalence of TTV DNA was detected in the majority of both patients and healthy controls. Serum prevalence of TTV DNA was more frequent among patients with sarcoidosis than the healthy controls, but this difference was not statistically significant. The prevalence of TTV in healthy individuals and variety risk groups has been reported to be above 80%[14]. The TTV prevalence rate in a study conducted in our country has been found to be 47.5% in healthy children[31]. In another study conducted in our country, TTV prevalence was reported in 63% of patients with thalassemia and 54% of control group[32]. In our study, higher prevalence of TTV in both healthy and patient groups is noteworthy. Although, the results of the above studies were obtained by various PCR target region and in different age groups, higher prevalence in this study is an important finding. Nonetheless, this higher prevalence in patients groups may be associated with the presence of sarcoidosis. In order to better understand the causal relationship, we should know “how is the viral load in patients and in healthy individuals?” Thus, the viral load was determined by CP value and exciting results emerged. So much so, the mean values of CP were lower in patients than in healthy individuals, so viral loads were higher in patients. This difference was statistically significant.

TLRs mediate the activation of immune cells in the pathogenesis of sarcoidosis[18]. An increased expression of TLR-2, TLR-4, and TLR-9 and their signal transduction is observed in sarcoidosis[18,33]. Veltkamp et al could not confirm association between TLR-9 polymorphisms and sarcoidosis, although decreased IFN-γ production has been seen in response to TLR-9 stimulation in peripheral blood mononuclear cells of sarcoidosis patients. However, it has been speculated that polymorphisms in the TLR-9 gene might influence the functional capability of TLR-9. Functional deficits
in TLR-9 induced IL-23 production may support that this pathway is involved in the pathogenesis of sarcoidosis[38]. TLRs are also members of the pattern recognition receptors involved in microbial defence. TLR-9 has been localized to the endoplasmic reticulum of macrophages and dendritic cells, suggesting that this TLR may be activated by intracellular microbial pathogens such as viruses[34]. TLR-9 was originally identified as the receptor for unmethylated bacterial CpG DNA. Recently, herpex simplex virus type 1 (HSV-1), HSV-2, and murine cytomegalovirus, all of which contain genomes rich in CpG DNA motifs, were shown to activate inflammatory cytokine and IFN secretion via TLR-9[35]. TTV circular single stranded DNA genome is also rich in unmethylated CpG motifs. Nowadays, in vitro experimental investigations have demonstrated that TTV can stimulate the secretion of cytokines (IFN-γ, IL-6, and IL-10) probably interacting with the TLR-9, and potentiating the activity of TLR-9 ligands[39].

CONCLUSION

Our findings demonstrated for the first time that TTV may be associated with sarcoidosis. In our study, TTV DNA was detected in healthy controls as frequently as in sarcoidosis patients. This calls into question the role of TTV as a true pathogenic organism in sarcoidosis, but interactions may exist between TTV and other factors to promote inflammation in sarcoidosis. Further definitive, reproducible studies allowing clarification of such issues are necessary to understand the role of TTV in etiology of sarcoidosis. We are hopeful that future studies will help uncover the etiology of this mysterious disorder.

REFERENCES

22. Stöcher M, Leb V, Hölzl G, Berg J. A simple approach to the generation of heterologous competitive internal


Predictors of successful weight loss after sleeve gastrectomy: Sex matters

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3Human Genetics Unit, Department of Pathology, Kuwait University, Kuwait

ABSTRACT

Objectives: To investigate if there is a correlation between body mass index (BMI), age and gender before undergoing laparoscopic sleeve gastrectomy (LSG) and the weight outcomes after
Design: A retrospective study was conducted. Absolute and percent excess weight loss (%EWL) were measured and compared across gender, age and pre-operative BMI at one and three years follow up.
Setting: Amiri Hospital, Kuwait
Subjects: Patients who underwent LSG from October 2011 to December 2014
Interventions: Laparoscopic sleeve gastrectomy
Main outcome measures: %EWL post-op as compared to gender, age and BMI
Results: A total of 597 patients were included, of which 139 (23.2%) had reached the three-year follow-up. The mean age was 35.5 ± 10.3 years and 75.2% of patients were female. Mean %EWL was 60.4% at one year and 64.8% at three years. Analysis showed significantly better outcomes in the male population in terms of successful %EWL at both one-year (p = 0.014) and at three years (p <0.005) post-operatively. Both younger age and lower pre-operative BMI were positive predictors of %EWL (p <0.005 and p <0.005 respectively) during the first year, with pre-operative BMI remaining a significant factor at the three-year follow-up (p <0.005).
Conclusion: There is a clear advantage in our population of successful %EWL after LSG for males, patients with lower pre-operative BMI, and younger patients at the time of surgery. The better outcome in males is still not fully understood, and more long term studies are needed to compare the other possible predictors.

INTRODUCTION

The prevalence of severe obesity is rising rapidly, and with it raises its economic burden[1]; the latter directly correlated to the ‘individual’ morbidity associated with being obese[2]. Bariatric surgery has now become considered an effective treatment strategy for morbid obesity in terms of weight loss and improvement of co-morbidities, with laparoscopic sleeve gastrectomy (LSG) becoming the most popularly performed bariatric procedure as of 2014[3,4]. As part of the natural evolution of surgery, the approach to a bariatric patient from a surgical point of view has begun to adopt a more algorithmic/guideline-based approach[5]. However, weight regain post-operatively, a well-known and documented phenomenon, still needs further studies in relation to management.

Weight regain or variability in weight loss after bariatric surgery has been attributed to numerous factors. Pre-operative body mass index (BMI), advanced age, female gender, and consistency in outpatient clinic follow up have all been studied among various authors as some of the factors that may influence the outcome of percent excess weight loss (%EWL) after bariatric surgery[6-8]. In a review of the literature, it was found that the %EWL three months after roux-en-Y gastric bypass accurately predicted patients’ three year outcomes[9]. The goal of this study was to delineate a potential relationship between pre-operative patient factors and variability in weight loss after undergoing LSG. The main variable of interest for our study was gender; a factor that has been interestingly found to favor males with regards to weight loss at our institute,
while showing no correlation in previous studies\textsuperscript{[10-11]}. The ability to reliably predict which patient will be successful and who will fail would help practitioners and patients make appropriate surgical and medical decisions.

**SUBJECTS AND METHODS**

A retrospective study was conducted on patients who underwent LSG at Amiri Hospital in Kuwait from October 2011 to December 2014. The patients’ records were obtained and analyzed for weight loss at one year and three years. Both absolute and %EWL were measured and comparisons across gender, age and pre-operative BMI were made. Successful weight loss was defined as >50% EWL at 12 months. Multiple logistical regression analysis was then used to identify factors that affect weight loss failure at one and three years.

Ethical approval for the study was obtained from the Ministry of Health in Kuwait and the Kuwait Institute for Medical Specialization institutional review boards. Statistical analysis was performed using SPSS computer software (version 23 SPSS Inc, Chicago, IL, USA).

Sleeve gastrectomy technique

LSG was performed in a standard split-leg French position using five laparoscopic ports. Devascularization of the greater curvature of the stomach was carried out starting from 4 - 6 cm from the pylorus and up to the angle of His. A 36-Fr calibrating bougie was then passed through the stomach to the duodenum before creating the gastric sleeve. The sleeve was performed with a linear laparoscopic stapler using green or black cartridges for the antrum and blue cartridges for the body and fundus, aiming for a final gastric pouch size of 100 ml. The calibrating bougie was then pulled proximally and 100 ml of methylene blue was injected through it to assess for leak. No intrabdominal drains were placed.

Statistical analysis

Patients were matched in relation to gender. Statistical analysis of the data was carried out using SPSS software version 22. Results were expressed as the mean ± standard deviation and 95% confidence intervals or as frequencies where appropriate. Student t-test was used in measuring weight outcomes at baseline and at different time points. Multivariate analysis using linear regression was used to evaluate the pre-operative factors affecting %EWL. Statistical significance was set at p-value <0.05. %EWL was calculated using an ideal body weight equivalent to a BMI of 25 kg/m\(^2\).

**RESULTS**

A total of 597 patients were included in this study, all of whom completed a one-year follow-up. Of these patients, 139 (23.2\%) had reached the three-year post-operative follow-up at the time of the study. The mean age was 35.5 ± 10.3 years and 449 (75.2\%) patients were female. Demographic and pre-operative weight characteristics are listed in Table 1. Mean initial weight and BMI were 123.3 ± 25.7 kg and 46.2 ± 8.7 kg/m\(^2\) respectively. Mean %EWL was 60.4\% at one year and 64.8\% at three years. Change in weight, BMI and %EWL at one and three years are illustrated in Table 2.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
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<tr>
<td>All cohort</td>
<td>597</td>
</tr>
<tr>
<td>Age (years)</td>
<td>35.5 ± 10.3</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>449 (75.2)</td>
</tr>
<tr>
<td>Males</td>
<td>148 (24.8)</td>
</tr>
<tr>
<td>Pre-op BMI (kg/m(^2))</td>
<td>46.2 ± 8.7</td>
</tr>
<tr>
<td>Pre-op weight (kg)</td>
<td>123.3 ± 25.7</td>
</tr>
<tr>
<td>3 year follow-up cohort</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>36.4 ± 10.4</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>97 (66.2)</td>
</tr>
<tr>
<td>Male</td>
<td>47 (23.8)</td>
</tr>
<tr>
<td>Pre-op BMI (kg/m(^2))</td>
<td>46.1 ± 9.4</td>
</tr>
<tr>
<td>Pre-op weight (kg)</td>
<td>123.2 ± 27.9</td>
</tr>
</tbody>
</table>

BMI: body mass index

Observing each predictor of %EWL individually, it was found that at the first post-operative year, male sex (B coefficient 5.49, p = 0.014), age (B coefficient -0.40, p <0.005) and pre-operative BMI (B coefficient -0.99, p <0.005) were all significant predictors of successful %EWL (Table 3). However, at the third post-operative year, only male sex (B coefficient 14.9, p <0.005) and pre-operative BMI (B coefficient -0.76, p <0.005) remained factors of significance.

**DISCUSSION**

LSG has now been proven to be a safe procedure with low complication and re-operation rates, and results comparable to laparoscopic roux-en-Y gastric bypass (LRYGB)\textsuperscript{[12-16]}. With the added benefit of its
low cost and learning curve, LSG is becoming more prevalent, and the leading bariatric operation in most centers around the world[17-19]. Nevertheless, even with a procedure as prevalent and novel as the LSG, a recent systematic review showed that there remains insufficient evidence in the literature regarding its long-term outcomes[20].

When it comes to evaluating success post-LSG, most surgeons today quote average %EWL to patients as a guide for expected weight-loss results. In relation to our patient population, average %EWL at 1 and 3 years was shown to be 60.4% and 64.8%, respectively. This proved to be well within the range of published %EWL values at 1 year in previous studies[21-23], and therefore correlate with data for other practices and centers. However, this type of presentation is not individualized and not a significantly realistic guide.

In this study, an attempt was made at observing successful weight loss in relation to pre-operative BMI, age and gender, with greater attention placed on the influence of gender on post-operative outcomes for these bariatric patients. The study at hand represents the largest population comparing gender difference post LSG. This helped control variability in patients presenting demographics and weight loss outcomes, with our results showing significantly better outcomes in the male population in terms of successful %EWL at both one-year (p = 0.014) and at three years (p <0.005) post-operatively.

Long-term studies comparing the outcome between genders in patients undergoing bariatric procedures other than LSG, such as LRYGB and laparoscopic adjustable band, showed either no significant difference in outcome[25-29] or results favoring females[30,31]. In contrast, studies comparing the outcome of successful %EWL between the genders after LSG are scarce, of small patient population, and have shown conflicting results (Table 4).

For example, Lehmann et al found in their series of 72 patients post LSG that gender proved to be an insignificant predictor of %EWL[32], while both Anderson et al and Perrone et al observed that, in terms of percent excess BMI loss (%EBMIL), men significantly outperform women (p = 0.003 and p = 0.003 respectively)[16,33]. In contrast, Cheng et al found in their series of 130 patients post LSG that females had a significantly greater %EWL and reduction in waist/hip ratio (p <0.001 and p = 0.003 respectively)[34]. These discrepancies in previous studies have highlighted the need to evaluate the relationship between gender and weight loss outcomes in patients that have undergone an LSG.

Weight gain and loss between males and females in general has long been studied, but has yet to be fully understood[35-37]. Previous studies have suggested that females have an increased lipolytic status post bariatric surgery as compared to males, which results in better weight loss[38]. It has also been hypothesized that females produce more energy from fat cells, especially during exercise and this proposes another possibility for the gender discrepancy[39]. A recent study comparing sex differences in obesity, energy expenditure and physical activity among mice found that levels of the brain pro-opiomelanocortin peptide neurons play a major role in the ability of a subject to regulate energy balance.[40] The functional heterogeneity of these neurons between the genders favors weight loss among males, and as the authors suggest, shows how males and females are “hardwired” differently in their regulation of energy balance.

In addition to gender, age and pre-operative BMI were also studied in relation to weight loss outcomes post-LSG, and were both determined to be independent predictors of weight loss as well. It was found that both younger age and lower pre-operative BMI were positive predictors of %EWL (p <0.005 and p <0.005 respectively) during the first year post surgery.

Table 3: Pre-operative predictors of weight loss after laparoscopic sleeve gastrectomy

<table>
<thead>
<tr>
<th>Variable</th>
<th>B coefficient (95% CI)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>1 year post LSG</td>
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<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.40 (-0.58, -0.22)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>5.49 (1.11 - 9.87)</td>
<td>0.014</td>
</tr>
<tr>
<td>Pre-BMI</td>
<td>-0.99 (-1.2, -0.77)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>3 years post LSG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.25 (-0.59, -0.096)</td>
<td>0.156</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>14.9 (7.3-22.5)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Pre-BMI</td>
<td>-0.76 (-1.14, -0.37)</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

BMI: body mass index; LSG: laparoscopic sleeve gastrectomy

Table 4: Review of post-laparoscopic sleeve gastrectomy weight loss gender differences

<table>
<thead>
<tr>
<th>Author et al</th>
<th>Year</th>
<th>n</th>
<th>Weight loss</th>
<th>Favoring Males/Females</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perrone F</td>
<td>2015</td>
<td>162</td>
<td>%EBMIL</td>
<td>Males</td>
<td>p = 0.003</td>
</tr>
<tr>
<td>Anderson JR</td>
<td>2014</td>
<td>160</td>
<td>%EBMIL</td>
<td>Males</td>
<td>p = 0.003</td>
</tr>
<tr>
<td>Cheng I</td>
<td>2014</td>
<td>130</td>
<td>%EWL</td>
<td>Females</td>
<td>p &lt;0.001</td>
</tr>
<tr>
<td>Lehmann A</td>
<td>2014</td>
<td>72</td>
<td>%EWL</td>
<td>Same</td>
<td>p &gt;0.05</td>
</tr>
</tbody>
</table>

BMI: body mass index; %EWL: percentage excess weight loss; %EBMIL: percentage excess BMI loss
with pre-operative BMI remaining as a significant factor at three years follow-up (p < 0.005). However, this could be due to the fact that weight loss is expressed in relative terms (%EWL), and therefore, patients with increased BMI need to lose a larger amount of weight to achieve the same percentage of EWL.

This finding is not new, as Perrone et al found in their study that increasing age was negatively associated with %EBMIL in patients post LSG and LRYGB, with more prominence among males. Another study found that when assessing the relationship between age and weight loss after bariatric procedures, patients younger than 45 years had a greater %EBMIL. In addition, Anderson et al found that along with female gender, higher preoperative BMI was a negative predictor of %EBMIL (p = 0.001). A possible hypothesis for this phenomenon is that aging is associated with a progressive decline in quantity and quality of muscular tissue, basal metabolic rates and energy requirements, and therefore, these metabolic parameters could influence the response to bariatric surgery.

Even though this study sheds new light on the influence of gender on %EWL post LSG, a number of potential weaknesses must be highlighted. Firstly, as this study focuses only on gender, age and pre-operative BMI, other possible predictors remain unaccounted for. Such factors could serve to better explain the gender gap as well as rule out any possible confounding. In addition, the lack of a more extensive long-term patient follow-up (>5 years) reduces the ability to draw a final conclusion on these findings.

CONCLUSION

LSG has now been shown to be a safe procedure with comparable outcomes to other bariatric modalities. However, it is of importance to be able to predict weight-loss results for patients on an individual basis pre-operatively so as to inform patients on post-operative outcome expectations. The better outcome in males at both 1 and 3 years post-operatively is still not fully understood. However, more long term studies are needed comparing multiple predictors between males and females, such as presence of co-morbidities, smoking, psychiatric status, physical activity, and eating habits.

ACKNOWLEDGMENT

Compliance with ethical standards

Funding: None

Competing Interests: The authors declare that they have no competing interests.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

REFERENCES


Analysis of maxillofacial traumas in an emergency clinic

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ABSTRACT

Objective: To examine epidemiology, fracture pattern and the relation between fracture pattern and Duke facial trauma severity index in patients admitted for maxillofacial traumas

Design: Retrospective study

Setting: Emergency Department, Ankara Numune Education and Research Hospital, Turkey

Subjects: Four hundred and twenty-eight patients who presented with a diagnosis of maxillofacial trauma

Intervention: Medical treatment of patients with maxillofacial trauma

Main outcome measure: Epidemiology, fracture pattern and the relation between fracture pattern and Duke facial trauma severity index

Results: Of the 428 patients, 185 cases with at least one fracture of the maxillofacial bones were included in the study, 147 (79.5%) males and 38 (20.5%) females. Distribution of gender showed significant difference (p <0.001). Age range was 8 – 90 years and average age was 38.69 ± 14.6 years. The most frequent cause of maxillofacial trauma was violence. The most frequent age range was 21 - 30 years old (28.6%, n = 53). The most frequent cause of maxillofacial trauma was violence in male cases and traffic accidents in female cases. There was a statistically significant relationship between gender and etiology (chi-square test, p <0.003). There were a total of 268 facial fractures in the cases. Nasal bone fractures (21%) were the most common fractures. Violence was the most common cause of nasal bone, orbital floor and medial wall, zygomatic arch and Le-Fort II fractures. Falling was the most common cause of frontal sinus, zygomaticomaxillary complex and maxillary sinus fractures. The most detected fracture was isolated upper midface fractures (51.4%). There was a statistically significant relationship between upper midface fractures and violence (Z test, p <0.001). There was also a statistically significant difference between midface fractures and violence and falling (Z test, p <0.002). Conservative treatment was applied to 66.5% of the cases and surgical treatment was applied to 33.5% of the cases.

Conclusion: Maxillofacial fractures were significantly more common in males in the third decade of life, in the nasal bone, were caused by violence and treated with conservative treatments.

INTRODUCTION

Trauma is the leading cause of death before the 4 th decade of life, as well as the third major cause in patients over 40 years old. Maxillofacial injuries may cause functional and aesthetic bad outcomes, because of the frequency of permanent deficits and potentially disfiguring scars that can dramatically affect patient’s quality of life. These traumas are frequently complicated by traumatic brain injuries or facial substance loss¹. In the worldwide literature, epidemiological data vary according to different geographical areas, e.g. hospitals located in mountain areas of Central-Northern Europe and India report a broader series of cases. Diagnostic accuracy together with type and timing of treatments significantly affect the clinical evolution of such traumas, allowing to improve functional results and limit cosmetic damages²,³.

The aim of our study was to analyze epidemiology, fracture pattern and the relation between fracture pattern and Duke facial trauma severity index in patients admitted for maxillofacial traumas to the Emergency Department of the Ankara Numune Education and Research Hospital.

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MATERIALS AND METHODS

Maxillofacial computed tomography examinations were retrospectively reviewed in 428 patients who presented with a diagnosis of maxillofacial trauma. One hundred and eighty-five cases with at least one fracture of the maxillofacial bones were included in the study.

Computer tomography examination results were reviewed for each case with maxillofacial trauma. Age, gender, etiology of trauma, number and localization of facial fractures were recorded. Duke severity score of facial injuries was calculated. The relation between fractures and Duke severity score of facial injuries were investigated.

Trauma etiology was divided into four groups, namely violence, falling, traffic accidents and firearm injuries. In classifying maxillofacial fractures, the face region is divided into four main units: frontal unit, upper midface unit, lower midface unit and mandibular unit. The fractures in all cases were classified according to the four main units described. At least three of the four units were evaluated as panfacial fractures.

Statistical analysis was performed using SPSS version 15. The relation between etiology-gender and etiology-treatment in maxillofacial trauma was evaluated by chi-square test. The relationship between fracture pattern, fracture number and facial injury severity score was assessed by Kruskal-Wallis multiple comparison test. The level for statistical significance was set at p <0.05.

RESULTS

Among 185 patients, 147 (79.5%) were males and 38 (20.5%) were females. Distribution of gender showed a significant difference (p <0.001). Age range was 8 - 90 years and average age was 38.69 ± 14.6 years.

The most frequent cause of maxillofacial trauma was violence. Distribution of maxillofacial traumas according to etiology is shown in Table 1.

Table 1: Distribution of maxillofacial traumas according to etiology

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Number (n)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Violence</td>
<td>78</td>
<td>42.2</td>
</tr>
<tr>
<td>Falling</td>
<td>55</td>
<td>29.7</td>
</tr>
<tr>
<td>Traffic accidents</td>
<td>44</td>
<td>23.8</td>
</tr>
<tr>
<td>Firearm injuries</td>
<td>8</td>
<td>4.3</td>
</tr>
</tbody>
</table>

The most frequent age range was 21 - 30 years (28.6%, n = 53). Distribution of cases by age range and sex is shown in Table 2.

The most frequent cause of maxillofacial trauma was violence in males. The most frequent cause of maxillofacial trauma was traffic accidents in females.

Table 2: Distribution of maxillofacial traumas by age range and gender

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>Male (n%)</th>
<th>Female (n%)</th>
<th>Total (n%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-10</td>
<td>2 (1.4%)</td>
<td>0 (0)</td>
<td>2 (1.1%)</td>
</tr>
<tr>
<td>11-20</td>
<td>8 (5.4%)</td>
<td>1 (2.6)</td>
<td>9 (4.9)</td>
</tr>
<tr>
<td>21-30</td>
<td>43 (29.3%)</td>
<td>10 (26.3)</td>
<td>53 (28.6%)</td>
</tr>
<tr>
<td>31-40</td>
<td>30 (20.4%)</td>
<td>7 (18.4)</td>
<td>37 (20.5%)</td>
</tr>
<tr>
<td>41-50</td>
<td>36 (24.5%)</td>
<td>7 (18.4)</td>
<td>43 (23.2%)</td>
</tr>
<tr>
<td>51-60</td>
<td>21 (14.3%)</td>
<td>7 (18.4)</td>
<td>28 (15.1%)</td>
</tr>
<tr>
<td>61-70</td>
<td>5 (3.4%)</td>
<td>1 (2.6)</td>
<td>6 (1.4)</td>
</tr>
<tr>
<td>71-80</td>
<td>1 (0.7)</td>
<td>5 (13.2)</td>
<td>6 (1.4)</td>
</tr>
<tr>
<td>81-90</td>
<td>1 (0.7)</td>
<td>0 (0)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Total</td>
<td>147 (100%)</td>
<td>38 (100)</td>
<td>185 (100%)</td>
</tr>
</tbody>
</table>

Distribution of etiology according to gender of cases is shown in Table 3.

Table 3: Distribution of etiology according to gender of cases

<table>
<thead>
<tr>
<th>Gender</th>
<th>Violence (n%)</th>
<th>Falling (n%)</th>
<th>Traffic accidents (n%)</th>
<th>Firearm injuries (n%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>70 (47.6%)</td>
<td>44 (29.9%)</td>
<td>22 (18.4%)</td>
<td>6 (4.1%)</td>
</tr>
<tr>
<td>Female</td>
<td>8 (21.1%)</td>
<td>11 (28.9%)</td>
<td>17 (44.7%)</td>
<td>2 (5.3%)</td>
</tr>
</tbody>
</table>

There was a statistically significant relationship between gender and etiology (chi-square test, p <0.003). Distribution of gender according to etiology is shown in Table 4.

Table 4: Distribution of gender according to etiology

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Male (n%)</th>
<th>Female (n%)</th>
<th>Total (n%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Violence</td>
<td>70 (89.7)</td>
<td>8 (10.3)</td>
<td>78 (100)</td>
</tr>
<tr>
<td>Falling</td>
<td>44 (80)</td>
<td>11 (20)</td>
<td>55 (100)</td>
</tr>
<tr>
<td>Traffic accidents</td>
<td>27 (61.4)</td>
<td>17 (38.6)</td>
<td>44 (100)</td>
</tr>
<tr>
<td>Firearm injuries</td>
<td>6 (75)</td>
<td>2 (25)</td>
<td>8 (100)</td>
</tr>
</tbody>
</table>

There were a total of 268 facial fractures in the cases. Nasal bone fractures (21%) were the most common fractures. The other most common localizations were as follows: orbital floor fractures (12.6%), medial orbital fractures (11.1%), zygomaticomaxillary complex fractures (10.5%), mandibular fractures (7.7%) and maxillary sinus fractures (7.1%).

Violence was the most common cause of nasal bone, orbital floor and medial wall, zygomatic arch and Le-Fort II fractures. Falling was the most common cause of frontal sinus, zygomaticomaxillary complex and maxillary sinus fractures.

When fractures were classified, the most detected fracture was isolated upper mid-facial unit fractures (51.4%). Upper midface and lower midface fractures were 22.2% and lower middle facial unit and panfacial fractures were 6.5%. There was a statistically significant relationship between upper midface fractures and...
violence (Z test, p <0.001). There was also a statistically significant difference between midface fractures and violence and falling (Z test, p <0.002).

The relationship between etiology and facial injury severity score was explored by Kruskal-Wallis multiple comparisons test. Violence-falling and violence-traffic accident were the groups that created the difference in the result of binary comparisons. Falling and traffic accidents caused higher facial injury severity scores than violence cases. The difference between the groups was significant (Table 5).

Table 5: Relationship between etiology and facial injury severity score

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Facial injury severity score</th>
<th>Facial injury severity score</th>
<th>Kruskal-Wallis P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Violence</td>
<td>1.522 ± 0.801</td>
<td>1 (1-4)</td>
<td></td>
</tr>
<tr>
<td>Falling</td>
<td>2.145 ± 1.445</td>
<td>2 (1-7)</td>
<td></td>
</tr>
<tr>
<td>Traffic accident</td>
<td>2.340 ± 1.790</td>
<td>2 (1-9)</td>
<td></td>
</tr>
<tr>
<td>Firewall injury</td>
<td>2.250 ± 1.358</td>
<td>2 (1-5)</td>
<td>0.019</td>
</tr>
<tr>
<td>Total</td>
<td>1.935 ± 1.353</td>
<td>1 (1-9)</td>
<td></td>
</tr>
</tbody>
</table>

* Mean ± standard deviation; † Median (min/max)

Conservative treatment was applied to 66.5% of the cases and surgical treatment was applied to 33.5% of the cases. Of the patients who underwent surgical treatment, 32.3% had traffic accidents; and 49.6% of patients who underwent conservative treatment were involved in violence.

DISCUSSION

Demographic data of maxillofacial fractures in this study showed that they were significantly more prevalent in men and in the third decade of life. These results were similar when compared with data of several studies in various regions of the world[11-13]. The cultural and socioeconomic characteristics of the studied population may affect the rates of facial fractures in women. The possible reason was that males between the ages of 21 years and 30 years are more susceptible to traffic accidents and interpersonal violence because of their higher rate of commuting, consequently leading to higher rates of accidents[14-17].

The most affected age group was 21 to 30 years (28.6%). Many reports of maxillofacial fracture studies have similar results regarding age[17-20]. These findings are similar to the other studies, which indicate that young people suffer more trauma.

The causes of maxillofacial fractures vary depending on the geographic, demographic and socioeconomic characteristics of people. In most countries, traffic accidents are the main cause of maxillofacial injuries[21]. Here, maxillofacial fractures were first due to violence and then due to falling. It is interesting to note that the most recently published studies on maxillofacial fractures also consistently identify interpersonal violence as the most common etiology of maxillofacial fractures in developed countries nowadays[22-24]. Legislative changes and preventive measures involving seat belt and airbag use, as well as the reduction of drinking and driving likely account for the reduced incidence of traffic accident-related facial injuries in some developed countries[25]. High incidence of fall-related maxillofacial fractures in elderly people has also been reported[26].

In our study, the most frequent cause of maxillofacial trauma was violence in males and the most frequent cause of maxillofacial trauma was traffic accidents in female. There was a statistically significant relationship between gender and etiology. The possible reason was that males are more susceptible to interpersonal violence[27].

There were a total of 268 facial fractures in the cases. Nasal bone fractures (21%) were the most common fractures. The other most common localizations were as follows: orbital floor fractures, medial orbital fractures, zygomaticomaxillar complex fracture, mandibular fracture and maxillar sinus fracture. Nasal bone fracture was the most prevalent type of trauma in some studies[28-30]. Mandibular fracture was the most common fracture in some other studies[31-33]. Other studies found that facial fractures in the zygomatic complex were more frequent[34-36]. Differences in the frequency of fractures can be caused by variations in the etiology of fractures in various studies.

Falling and traffic accidents caused higher facial injury severity scores than violence cases. It can be explained that trauma is more severe and complex in traffic accident and falling cases.

Conservative treatment was applied to 66.5% of the cases and surgical treatment was applied to 33.5% of the cases. 32.3% of patients who underwent surgical treatment had traffic accidents and 49.6% of patients who underwent conservative treatment were involved in violence. Innovations, technology, and materials have influenced trauma management in current years[23,24]. More surgeons are using open reduction and plate osteosynthesis instead of closed reduction, leading to early recovery, segment stability, more rapid return of function, and patient comfort[25]. Although treatment of facial fractures varies from surgeon to surgeon, it also depends on available instrumentation at hand. In our study, the treatment method was similar to some surveys[26] and contradictory to some older studies[27].

CONCLUSION

On the basis of the results of this study, maxillofacial fractures were significantly more common in males, in the third decade of life, in the nasal bone caused...
by violence and treated with conservative treatments. Citizen awareness programs should be initiated. Legislation on preventive measures should be enforced and followed by every citizen.

REFERENCES

Original Article

The gender differentiation affects the nutritional status and biochemical characteristics during Ramadan fasting

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ABSTRACT

Objectives: Muslims consume two meals during Ramadan, one each at dawn and sunset. The changing daily rhythm affects metabolism. We examined the response of metabolism to fasting considering the gender differentiation.

Design: Cross-sectional

Setting: Istanbul Medipol University, Turkey

Subjects: Thirty healthy fasting individuals

Intervention: None

Main outcome measures: The demographic, anthropometric and nutritional data were taken using a survey. Biochemical parameters were analyzed. Blood pressures were measured.

Results: Ramadan fasting increased weight, body mass index (BMI) (p <0.05), fat (%) and muscle mass of women while it decreased weight, BMI and fat (p <0.05) in men. The waist circumference/hip circumference ratio decreased in men but stayed the same in women. The energy intake of men increased in the middle and decreased (p >0.05) at the end of Ramadan, however the opposite trend was observed in women (p >0.05). Daily water consumption increased for both women (p >0.05) and men (p <0.05). The difference in consumption of proteins in women and of proteins, saturated fatty acids and monounsaturated fatty acids in men were significant. The serum levels of HbA1c decreased in both genders (p >0.05). The levels of serum creatinine, uric acid, albumin, total cholesterol, high density lipoprotein and low density lipoprotein altered significantly in women, while the only significance was observed in serum glucose level of men. Systolic and diastolic pressures increased in both genders (p <0.05).

Conclusions: Ramadan fasting affects the nutritional status and serum parameters in a different way for women and men.

KEY WORDS: blood pressure, BMI, energy intake, metabolism, serum lipids

INTRODUCTION

Ramadan is the ninth month of the lunar calendar and its duration varies between 29 and 30 days. During this holy month, Muslims are not allowed to eat and drink from dawn to sunset. According to Islam, fasting during Ramadan is obligatory for all healthy Muslims. Sick, travelling, pregnant, breast feeding, menstruating or debilitated individuals are the exceptions. Daily life, especially sleeping and eating periods, can be affected during Ramadan. The lunar calendar is different from Georgian calendar, so that Ramadan occurs 11 days earlier from the previous year. Therefore, the fasting period varies from 11-18 hours at the latitudes between 36° and 42° according to seasons.

Most Muslims typically consume two main meals per day during this month; one after sunset and the other before dawn. Cultural influences, hours of fasting, climatic conditions, physical activity and dietary patterns influence fasting in Ramadan[1-3]. However, the eating habits have changed over the years[4]. It is more common to consume foods that are richer in fat, protein and sugar[5]. Also, sugary foods and drinks are consumed more frequently[6]. The differences in eating habits during Ramadan fasting in comparison with normal days affect body composition. Specifically, distortion in sleeping times in order to eat before dawn and after dusk influences circadian rhythm and results in fatigue, decline in performance, physical
stress and changes in eating behavior. There have been several studies regarding the effect of fasting on various metabolic aspects. However, their results have been conflicting.

In fact, Ramadan fasting was applied to numerous studies as a model of how dietary modifications might affect body composition and serum biochemical parameters. Besides the religious and holistic sides, fasting has recently been popularized by ‘intermittent fasting’ or ‘modified fasting’ patterns, in which a very low-calorie intake is allowed on alternate days. Animal and human studies indicated that intermittent or periodic fasting protected against diabetes, cancers, heart disease, neurodegeneration, obesity, hypertension, asthma, and rheumatoid arthritis. Johnstone proposed that intermittent fasting may be an option for achieving weight loss. In a study by Eshghinia and Mohammadzadeh, it was suggested that short time modified alternate-day fasting helped obese individuals lose weight and decreased some coronary disease risk factors. Moreover, there are several papers to monitor the role of fasting in adaptive cellular responses that optimize energy metabolism and reduce oxidative damage and inflammation. Intermittent fasting decreased glucose and insulin levels and increased insulin sensitivity and lifespan, suggesting a potentially beneficial metabolic effect.

Hunger is an adaptive response to food deprivation. Gotthardt et al demonstrated that intermittent fasting produced alterations in hypothalamic norepinephrine and neuropeptide Y, suggesting that short-term weight loss was associated with an intermittent fasting dietary strategy. Fasting caused dramatic increase in adiponectin level, suggesting roles for adiponectin in the beneficial effects of intermittent fasting on the cardiovascular system. Castello et al showed that alternate-day fasting protects the rat heart against age-induced inflammation and fibrosis by inhibiting oxidative damage and NF-kB activation. Chausse et al revealed that intermittent fasting affected redox balance in a tissue-specific manner, leading to redox imbalance in the liver and brain and protection against oxidative damage in the heart.

Following 12 - 24 hours of fasting, depending on the level of physical activity, serum glucose decreases 20% or greater and metabolism switches on the nonhepatic glucose mode. In this condition, depending on body weight and composition, energy can be obtained by gluconeogenesis, fat-derived ketone bodies, and free fatty acids. Adaptation to new eating pattern for body and brain needs a transition period of 3 - 6 weeks. This metabolic shift stimulates adaptive cellular stress response and repair molecular damage.

This study aimed to assess the impact of fasting during different periods of Ramadan fasting and to evaluate the effect of fasting on nutrition status, anthropometric and biochemical profiles on healthy adults.

SUBJECTS AND METHODS

Study population

The present work was approved by the Ethics and Research Committee of Istanbul Medipol University, Istanbul, Turkey. This cross-sectional study was performed during Ramadan of June-July 2015 in Istanbul. Written informed consent was taken from the subjects. Regular fasting healthy adults (15 women and 15 men) participated in the study. The women declared fasting for the whole month of Ramadan even in their menstruation period. The participants who were not fasting the whole month, had chronic diseases, and were pregnant and lactated were excluded.

Study design

All participants were informed about the study before initiating the study. The volunteers were invited to Vatan Clinic of Istanbul Medipol University to take intravenous blood samples and measure blood pressure at the hours between 10.00 and 11.00 am in the 4 days of beginning (stage I), the middle (14 - 16 days, stage II) and the end of Ramadan (28 - 30 days, stage III). All measurements were done while the participants were fasting. We conducted a questionnaire to determine the demographic characteristics and nutritional status. Daily nutrient intake was recorded using a 24-hour dietary recall questionnaire at hospital attendance.

Measurements and analyses

The age, weight, height, and waist circumference were determined for each participant. Bioelectrical impedance analysis was used for estimating body composition, which was performed using In Body J10 (Biospace, Seoul, Korea). Bioelectrical impedance analysis required the subjects to not consume alcohol and/or participate in sports for 24 hours and avoid consuming tea, coffee, or food for two hours. In Ramadan fasting conditions, since the participants consumed meal at dawn, there was no need for mentioned restrictions in our study. Waist circumferences were measured at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest using an unstretched tape. For measurements, subjects stood with their arms at sides, feet positioned close together, and weight evenly distributed across the feet. Duplicate measurements were taken, and if the difference between measurements exceeded 1 cm, the two measurements were repeated.

Blood samples were taken by health professionals in the morning. The samples were then moved to
the laboratory via an ice bag, centrifuged to separate serum, aliquoted off, and stored at −20 °C, until analysis. Standard analysis methods were used in the biochemistry laboratory at Vatan Clinic of Istanbul Medipol University. HbA1c value was analyzed by the boronate affinity (Primus Diagnostics, a Trinity Biotech Company, Kansas City, USA) HPLC method. Other routine biochemical parameters were analyzed with the use of Vitros-350 System (Ortho-Clinical Diagnosis, Johnson&Johnson Co., Brazil).

An aneroid sphygmomanometer (Erka, Perfect Aneroid Clinic 48, Germany) was used for blood pressure measurements. Participants were asked to rest for five minutes before measurement. Systolic and diastolic blood pressures were taken twice and the mean value was recorded.

### Statistical analyses

Statistical Package for Social Sciences version 22.0 (IBM SPSS, Chicago, IL, USA) was used for all statistical analyses. With large effect size and 5% error, 80% power was achieved with the number of samples available. The values were expressed as means ± SD and percentages for descriptive purposes. The repeated measures ANOVA was used for the comparison of data between the stages of Ramadan fasting for each gender. Pearson coefficient of correlation was used to analyze relationships between numerical variables. Differences were considered statistically significant at the levels of p <0.05, p <0.01 and p <0.001 during the first, second and third stages of Ramadan respectively.

### RESULTS

The mean age of participants was 31.6 ± 10.23 years. The anthropometric parameters of 30 participants (15 women + 15 men) were given in Table 1. During Ramadan, men lost but women gained weight. The mean weight of women increased in the middle and decreased at the end of Ramadan while men’s weight thoroughly decreased from the beginning till the end. From the beginning to the end of Ramadan, the decrease in body mass index (BMI) values of men was not significant. However, the BMI values of women increased in the middle of Ramadan, following a significant decrease at the end of Ramadan. Although the waist circumference (WC) and hip circumference (HC) decreased in both women and men, the ratio of WC/HC had been protected throughout Ramadan in women but decreased in men. The fat percentage of women rose up in the middle and down at the end of Ramadan. However, the value at the end was higher than at the beginning of Ramadan. In men, the body fat percentage did not change at the middle but lowered at the end of Ramadan. The muscle mass slightly increased in both genders in the middle of Ramadan and decreased at the end.

The daily energy and nutrients intake of participants were given in Table 2. The energy intakes in both genders increased in the middle and decreased at the end of Ramadan. However, the only significant decrease was found between the middle and the end of Ramadan for men. Men had higher energy intake than women.
The daily water consumption increased in the middle of Ramadan in women and men (p <0.05) and decreased during the following days till the end for both genders, but it was significant only for men (p <0.05). However, the water intake at the end was much higher than the values at the beginning of Ramadan for both genders.

Daily protein consumption decreased in women between the beginning and the end of Ramadan (p <0.05). However, for men, it increased in the middle and decreased significantly at the end, becoming even less than the beginning level. The MUFA levels increased significantly at the end to the level which was lower than the beginning level. The daily intake of saturated fatty acids (SFA) for men increased in the middle and decreased significantly at the end, becoming even less than the beginning level. The MUFA levels increased significantly at the end to the level which was lower than the beginning level. The dietary restriction due to fasting resulted in lower fiber intake than the daily recommended intake (DRI).

The distribution of fats for women at the beginning and at the end of Ramadan were 21.6 g vs 21.4 g of saturated fatty acids (SFA), 20.4 g vs 19.3 g of monounsaturated fatty acids (MUFA) and 16.1 g and 17.3 g of polyunsaturated fatty acids (PUFA) respectively. In women, SFA consumption stayed at the same level till the middle and decreased at the end of Ramadan. The fiber consumption stayed at the same level till the middle and decreased at the end of Ramadan. The dietary restriction due to fasting resulted in lower fiber intake than the daily recommended intake (DRI).

The daily carbohydrate intake increased during Ramadan for women. However, for men, it increased in the middle and decreased at the end. For both genders, the increase in carbohydrate intake was higher at the end than the level at the beginning. The daily consumed carbohydrate percentage was higher in men in comparison with the women’s intake. The daily fiber intake increased in the middle and decreased at the end of Ramadan in women. The fiber consumption stayed at the same level till the middle and decreased at the end of Ramadan. The dietary restriction due to fasting resulted in lower fiber intake than the daily recommended intake (DRI).
The daily cholesterol intake of women decreased in the first 15 days and was nearly stable till the end of Ramadan. For men, the daily intake of cholesterol increased in the middle and decreased at the end of Ramadan. However, it was still higher than at the beginning of Ramadan.

The serum biochemical profile of participants is shown in Table 3. The HbA1c(%) values decreased at the end of Ramadan. The difference in HbA1c between the middle and the end of Ramadan were significant for women and men. Fasting glucose level increased from the beginning to the end for women, but for men, it increased in the first 15 days (p <0.05) and then dropped down at the end of Ramadan. Urea levels decreased in the middle and increased at the end of Ramadan. The comparison of the levels of urea between the beginning and the end of Ramadan showed that it stabilized at the same level for women and was high in men. Serum creatinine level increased in the middle of Ramadan for women (p <0.05 I-II) and men (p >0.05) following further increase in men but decrease in women (p <0.05 I-III). Serum uric acid level increased throughout Ramadan for women (p <0.05 I-II) and men (p >0.05) following further increase in men but decrease in women (p <0.05 I-III). For men, TG values increased in the first half then decreased to the lowest level at the end. Nonetheless, the levels of HDL decreased in the middle and slightly increased at the end which was lower than the beginning value. The level of serum LDL in women increased significantly throughout Ramadan (p <0.05 I-II; II-III; I-III) in spite of a fluctuation in men; it first increased and then decreased at the end. The very low density lipoprotein (VLDL) levels in both women and men increased in the middle and decreased at the end of Ramadan to come down to the lowest levels in comparison with the beginning levels.

Blood pressures of participants were summarized in Table 4. Systolic and diastolic blood pressures of men were higher than women during Ramadan fasting. The differences in systolic blood pressures between the beginning and the end of Ramadan were significant for both genders (p <0.05). All blood pressure measurements during Ramadan were in the normal range which was described in the range

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Gender</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>DRI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>Women</td>
<td>5.04 ± 0.25</td>
<td>5.09 ± 0.24</td>
<td>5.00 ± 0.24</td>
<td>4-6</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>5.04 ± 0.38</td>
<td>5.08 ± 0.28</td>
<td>4.97 ± 0.34</td>
<td></td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>Women</td>
<td>89.2 ± 7.7</td>
<td>92.2 ± 6.6</td>
<td>93.6 ± 7.5</td>
<td>70-100</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>91.9 ± 6.6</td>
<td>97.8 ± 7.0</td>
<td>97.2 ± 13.6</td>
<td></td>
</tr>
<tr>
<td>Urea (mg/dL)</td>
<td>Women</td>
<td>31.5 ± 7.2</td>
<td>29.7 ± 6.4</td>
<td>31.1 ± 5.6</td>
<td>19-50</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>23.1 ± 7.9</td>
<td>22.4 ± 7.6</td>
<td>25.4 ± 9.3</td>
<td></td>
</tr>
<tr>
<td>Serum creatinin (mg/dL)</td>
<td>Women</td>
<td>0.59 ± 0.09</td>
<td>0.66 ± 0.10</td>
<td>0.64 ± 0.09</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>0.85 ± 0.11</td>
<td>0.86 ± 0.14</td>
<td>0.88 ± 0.11</td>
<td></td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>Women</td>
<td>3.52 ± 1.11</td>
<td>3.77 ± 1.07</td>
<td>3.79 ± 1.07</td>
<td>2.5-6.2</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>5.52 ± 0.96</td>
<td>5.80 ± 1.40</td>
<td>5.70 ± 1.37</td>
<td>3.5-8.5</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>Women</td>
<td>4.10 ± 0.25</td>
<td>4.18 ± 0.28</td>
<td>4.17 ± 0.23</td>
<td>3.5-5.0</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>4.30 ± 0.26</td>
<td>4.34 ± 0.21</td>
<td>4.34 ± 0.24</td>
<td></td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>Women</td>
<td>27.5 ± 32.3</td>
<td>23.4 ± 32.3</td>
<td>24.5 ± 25.9</td>
<td>10-159</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>59.3 ± 42.7</td>
<td>54.8 ± 36.7</td>
<td>52.6 ± 40.9</td>
<td>30-435</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>Women</td>
<td>165.0 ± 28.0</td>
<td>170.4 ± 26.9</td>
<td>180.0 ± 21.6</td>
<td>&lt;200</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>178.8 ± 28.4</td>
<td>186.2 ± 30.0</td>
<td>181.4 ± 26.4</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>Women</td>
<td>72.8 ± 39.5</td>
<td>72.2 ± 23.9</td>
<td>69.8 ± 24.9</td>
<td>&lt;150</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>125.7 ± 111.5</td>
<td>144.8 ± 146.3</td>
<td>107.4 ± 44.6</td>
<td></td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>Women</td>
<td>60.4 ± 16.7</td>
<td>57.6 ± 13.9</td>
<td>56.7 ± 11.4</td>
<td>&gt;40</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>43.1 ± 8.1</td>
<td>42.0 ± 8.4</td>
<td>42.5 ± 11.7</td>
<td></td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>Women</td>
<td>89.9 ± 20.3</td>
<td>97.7 ± 20.2</td>
<td>109.2 ± 18.9</td>
<td>&lt;130</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>114.8 ± 25.4</td>
<td>118.6 ± 26.6</td>
<td>117.4 ± 25.2</td>
<td></td>
</tr>
<tr>
<td>VLDL (mg/dL)</td>
<td>Women</td>
<td>14.6 ± 7.8</td>
<td>14.7 ± 5.4</td>
<td>13.6 ± 4.9</td>
<td>0-35</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>25.1 ± 22.3</td>
<td>28.9 ± 29.5</td>
<td>21.3 ± 8.9</td>
<td></td>
</tr>
</tbody>
</table>

HbA1c: glycated hemoglobin; HDL: high density lipoprotein; LDL: low density lipoprotein; VLDL: very low density lipoprotein.

Statistical significance at p <0.05 level; *: between stages I and II; **: between stages II and III; ***: between stages I and III.
of 120/80 mmHg (systolic/diastolic) by the American Heart Association[31].

**DISCUSSION**

Besides the importance of holistic healing for Muslims, Ramadan is a period giving an opportunity to analyze how fasting affects the body composition, nutritional status and biochemical parameters. In our study, we focused on the outcomes of fasting throughout Ramadan between healthy men and women.

We observed a different adaptation pattern in 30 days fasting in Ramadan for women and men. One of the reasons could be the changing circadian rhythms which oscillate with 24 hour rhythmicity in humans. In a review by Hutchison et al, the influence of circadian rhythm on obesity, glucose metabolism and metabolic health was reported[32]. The fasting period influences the circadian clock maintained by the suprachiasmatic nucleus (SCN) in the brain due to disturbance in sleep/wake cycle and eating times[33,34].

Several studies demonstrated that the daily energy intake in Ramadan changes possibly due to the differences in eating habits. In our study, the daily energy intake decreased in the middle and increased at the end for women and it was opposite in trend for men. Similar to our results, Al-Hourani et al also observed a downward trend in daily energy intake in the middle of Ramadan in comparison to the beginning and an increase after Ramadan for women[35]. The energy intakes at the three stages of Ramadan for both genders were lower than the DRI. Moreover, for both genders, the energy intakes were lower than the beginning of Ramadan. It seems that Ramadan fasting restricts energy intake possibly due to the limited eating period as shown in many other researchers[2,16,36]. On the other hand, several studies demonstrated increased energy intake during Ramadan[37]. In a study by Shalaei et al, the nutritional evaluation of men (n = 119) and women (n = 147) revealed that the energy intake significantly increased for participants less than 35 years old due to high consumption of carbohydrates[38]. Moreover, Norouzy et al showed weight loss and fat–free mass reductions during fasting in Ramadan. However, body composition changed depending on sex and age divided by over 35 and 36 - 70 years[39]. In our study, we did not evaluate the age differences.

We observed that the nutritional attitude of women at the end of Ramadan changed in the way of decreasing proteins and increasing fats and carbohydrates in comparison with the beginning. However, for men, the consumption of protein, fat and carbohydrate (g/day) decreased in the middle and increased at the end of Ramadan. In other words, the only dietary difference was the intake of fat, which increased in women but decreased in men. Serum fasting glucose level increased in both genders, but with significance only for men (p <0.05 I-II). Several studies reported a decline, while some revealed an increase in serum glucose during fasting[39-41]. Although protein and carbohydrate intakes were in normal limits, fat consumption was over the DRI (20 - 25%). In our study, 19.6% of daily energy came from proteins, 38.8% from fats and 41.6% from carbohydrates for women, and 15.5% from proteins, 40% from fats and 44.4% from carbohydrates for men at the beginning of Ramadan. A study by Barkia et al[36] on 19 men and 6 women reported a decrease in the contribution of proteins and fats and an increase of carbohydrates to energy percentages, similar to our results on men. The similarity between the studies was possibly due to the high number of men in the studied population. Norouzy et al also reported no changes in the dietary intake between the beginning and middle of Ramadan excluding the significant decrease (p <0.05) in protein intake of men[39]. Likewise, the gender difference of fasting on caloric intake and body composition was observed in a study by Yeoh et al[42].

Dietary carbohydrates and fats are well known energy suppliers for the body[43]. It was shown that the percentages of energy intake from fat and carbohydrates were reciprocally related. High fat consumers tend to have higher BMI than high sugar consumers[44]. In our study, women gained and men lost weight in comparison with the beginning of Ramadan. This reflected to BMI values which increased in women and decreased in men. The ratio of WC/HC declined in men, but did not change in women. Lowering dietary fat intake of men during Ramadan resulted in a significant decrease in the

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### Table 4: Systolic and diastolic blood pressures of participants

<table>
<thead>
<tr>
<th>Blood pressure (mmHg)</th>
<th>Gender</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic</td>
<td>Women</td>
<td>91.4 ± 11.6</td>
<td>107.3 ± 12.7</td>
<td>104.6 ± 15.5</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>105 ± 17.4</td>
<td>116.6 ± 11.7</td>
<td>118 ± 12</td>
</tr>
<tr>
<td>Diastolic</td>
<td>Women</td>
<td>61.4 ± 9.4</td>
<td>64 ± 10.5</td>
<td>64 ± 11.2</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>67.1 ± 9.1</td>
<td>70.6 ± 7.9</td>
<td>68.6 ± 8.3</td>
</tr>
</tbody>
</table>

Statistical significance at p <0.05 level; a: between stages I and II; b: between stages II and III; c: between stages I and III.

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June 2019
body fat. Similar to our result, Syam et al reported that fasting in Ramadan decreased body fat but not protein mass in an unbalanced proportion of male and female subjects. There are several studies that show a decline, an increase and no change of weight, WC and BMI for both genders between pre- and post-Ramadan during fasting. Fasting or intermittent fasting or calorie restriction causes several modifications in metabolism reflecting, on the body composition. Patterson et al revised the different fasting regimens and concluded that fasting may be a promising approach to lose weight and improve metabolic health for people.

There are controversial results on serum lipid profiles after Ramadan fasting. Ismail and Haron reported a significant decrease in the levels of TG and LDL and an increase in the level of HDL in comparison with the values measured pre-Ramadan on 33 healthy university students. However, the increase in TC was not significant. In our study, we observed significant increase in the level of cholesterol for women, while the increase in men was not significant. Moreover, the decrease in the level of HDL and the increase in the level of LDL were significant for women, but not for men. Shehab et al observed a decrease in the levels of TC, TG and LDL in contrast to an increase in the levels of HDL at the end of Ramadan for both genders. Changes in LDL and HDL were significant. On the contrary, Ziaee et al demonstrated a significant increase in LDL and decrease in HDL during Ramadan. We found that alteration in the level of TG in men and women showed different trends. The decrease of TG in women throughout Ramadan was associated with the decrease in HDL and a significant increase in LDL, indicating the healthy effect of fasting. In men, TC, TG and LDL levels increased in the middle of Ramadan, and then decreased at the end.

Although there are many comparative studies between pre- and post-Ramadan, a limited number of articles have evaluated the body composition, nutritional status and biochemical parameters at different stages of Ramadan fasting. One of those studies came from Maislos et al, who took the data at weeks 1, 2 and 4 of Ramadan, and 4 weeks after Ramadan in Bedouin participants. They reported an increase in plasma HDL at the 4th week and a return to basal level after Ramadan. They also observed that dietary changes did not affect the plasma LDL, VLDL and BMI. These results are not consistent with our data, which showed a decline of HDL at the end of Ramadan for both genders. The other biochemical parameters were affected by fasting in Ramadan possibly due to changing dietary habits. In another study by Mansi, the effects of fasting on serum lipid profile and glucose were investigated on Jordanian students before, during and after Ramadan. TC, LDL and TG decreased and HDL increased at the 4th week of Ramadan in comparison with the values taken before Ramadan. After 2 weeks of Ramadan, TC, HDL and TG were higher and LDL was lower than the levels at pre-Ramadan. It seems that changing dietary habits from varied cultures affected the blood lipid characteristics.

We observed a significant difference of systolic pressure in women (p < 0.05 I-II, I-II) and in men (p < 0.05 I-III), as well as increased diastolic pressure with no significance between the beginning and the end of Ramadan. Habbal et al evaluated the variations of blood pressure during Ramadan and concluded that the variations of blood pressure were minimal and affected by sleep, activity and eating behavior. In a study by Soltani et al on patients with controlled or mild hypertension on antihypertensive therapy revealed that the mean systolic, diastolic, and mean blood pressure, before and during Ramadan were not significantly different. In addition, Mansi showed that systolic/diastolic pressure of healthy male subjects decreased till the end of Ramadan and increased two weeks after Ramadan. However, they were lower than the pressures pre-Ramadan.

CONCLUSION

In conclusion, fasting during Ramadan for healthy women and men affects the body composition, serum biochemistry and blood pressure in different ways. The long non-eating hours, the seasonal air temperature, and disturbed circadian rhythm (mainly the sleeping time) are the major differences of fasting in Ramadan. Therefore, there has been conflicting data in literature, which reported opposite outcomes on body composition, serum biochemistry and blood pressure during fasting in Ramadan. In our study, we observed that the nutritional behavior of men and women were different during Ramadan. Women increased dietary fats and carbohydrates, while men increased carbohydrates. Thus, the BMI values and the body fat were higher in women but lower in men than the beginning of Ramadan.

Limitation

Ramadan is a very special month when Muslims prefer to involv e in other acts of worship besides fasting. We asked our volunteers to come to the hospital 3 times for measurements during Ramadan. Therefore, the number of volunteer participants is limited but in adequate size for power analysis. Although women are not expected to fast in their menstrual period, they accepted to fast for the whole month of Ramadan for the sake of accuracy and...
reliability of the present study. Dietary patterns have not been reported and classified. We did not analyze the daily energy and nutrient intakes in terms of consumed foods.

ACKNOWLEDGMENT

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Original Article

Technology integration into a curriculum using simulation techniques

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ABSTRACT

Objectives: Nowadays, education strives to introduce more practical aspects, including simulation into the curriculum. Technology is meant to facilitate a more practical side of classes as well as to provide a viable testing tool.

Design: We decide to investigate the influence of modern technology used with simulation techniques during one of the courses employing self-reported questionnaire and assessment results. The research is a cohort study. The research reviews the value of the course in terms of acquiring procedural skills using modern technology by medical students before entering a clinical setting.

Setting: The research was led in a newly-developed Centre for Medical Simulation, Medical University of Lublin.

Subjects: The students sample consisted of 299 second year medical students in the Medical University of Lublin.

Intervention: Introduction of a novel course, Basic Clinical Skills using simulation and online resources.

Main outcome measure: Students’ opinions were analysed and compared with assessment outcomes.

Result: 223 participants stated their definite content with the training, grading it 5 out of 5. 237 medical students agreed with the definite importance of its contents considering their future profession. 218 confirmed a definite increase in their knowledge (72.9%) because of that course. Assessment results confirmed the high level of participants’ abilities after course completion.

Conclusions: The research confirms the usefulness of modern technology in the implementation of curricular changes, enabling unification of the procedures in terms of basic clinical skills in further practice.

KEY WORDS: clinical skills, medical education, medical students, simulation, technology

INTRODUCTION

Simulation based learning courses during medical studies have an increased impact, the reason behind it is usually to ensure patients safety and also due to the insufficient number of patients in clinical setting¹-³. Introduction of simulation class based on modern technology enables students to include the practical mode within the study period. Students should be able to familiarize themselves with the equipment and the steps of practiced procedure prior to clinical experience. With experience gained in the simulated environment, the student can access real-time experience connected with the basic medical procedures.

Simulation training ensures repetitiveness of the given procedures and enables mastering of these skills⁴-⁵. Without causing harm or pain to patients, medical students are able to implement a step-by-step basic procedure and familiarize themselves with the equipment and the appropriate method of handling the equipment⁶. So-called low fidelity simulation provides satisfying results as far as the basic procedures are concerned⁷. The procedures chosen for the course implementation were based on the Bill of Polish Health Ministry on education standards for medical students⁸. The research reviews the value of the course in terms of acquiring procedural skills using modern technology by medical students, before entering clinical setting.

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SUBJECTS AND METHODS

Course design

Basic Clinical Skills (BCS) course was introduced as an innovative, facultative course for medical students of Medical University. The course was implemented between February and April 2015 (students’ second year of studies). The Objective Structured Clinical Examination (OSCE) exam took place in May 2015. The lab sessions focused on the practical skills. A division of five blocks were introduced, constituting the basis for proceedings in any medical unit (hospital, general practitioner or specialized practice). They included measurements of basic vital signs, intravenous catheterization, urinary bladder catheterization, intramuscular injections implemented on low-fidelity simulators and task simulators ensuring the repetitiveness of the procedure (Table 1).

Furthermore, students were supported with access to electronic resources, the UpToDate® database, available within an internet learning platform to enable blended learning, which refers to the combination of face-to-face involvement and online resources to increase interaction between teaching staff, students and reliable sources. The website contained resources concerning all the courses lead in the Centre for Medical Simulation. The website contained course descriptions, rules and regulations, teaching aids and the names of the teachers leading the course.

Those resources in opposition to course books could be updated rapidly according to the newest guidelines, as their online version enabled such forms of editing. Additionally, established medical faculty authored those articles. The UpToDate® articles are evidence-based, meant to assist physicians at their everyday decision-making. The class was led and assessed by an interdisciplinary team.

The need for such training was undeniable as the whole year enrolled for the course. Consequently, 299 students of the second year were acquiring the above-mentioned skills between February and May 2015. Each lab session was divided into a 30-minute long theoretical part in the form of lecture and discussion and practical performance of the procedure on low-fidelity simulators as well as task trainers (Table 2 and Figure 1). Additionally, elements of professionalism in the form of students’ appropriate attire and behaviour were implemented during the course, except for medical procedures. Moreover, participants were obliged to pay attention to the communicative side of a given procedure including proper verbal and nonverbal contact with the patient before, during and after completion of the procedure.

Instrument

To assess the training, students were invited to complete a paper self-reported questionnaire containing 14 closed items assessing each element of the training sessions. The survey used the 5-point Likert scale, where students could indicate their opinions: 1 meant ‘complete dissatisfaction’ with the course and 5 meant ‘complete satisfaction’ with the completed training. The questionnaire also collected participants’ socio-demographic data and was concerned with an overall opinion of the course, as well as detailed questions regarding its organization, equipment used and surroundings, topics, and trainers’ attitudes towards participants.

<table>
<thead>
<tr>
<th>Learning outcome</th>
<th>Time</th>
<th>Assessment methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>defines the vital signs and interprets the results of these parameters</td>
<td>3 x 45 minutes</td>
<td>TEST MCQ 25 questions</td>
</tr>
<tr>
<td>measures the heart rate, body temperature, pulse oximetry</td>
<td>3 x 45 minutes</td>
<td>Objective Structured Clinical Examination</td>
</tr>
<tr>
<td>implements asepsis and aseptic practices during medical procedures</td>
<td>3 x 45 minutes</td>
<td></td>
</tr>
<tr>
<td>perform hygienic and surgical hands scrub</td>
<td>3 x 45 minutes</td>
<td></td>
</tr>
<tr>
<td>defines non-invasive blood pressure measurement</td>
<td>3 x 45 minutes</td>
<td></td>
</tr>
<tr>
<td>performs non-invasive blood pressure measurement</td>
<td>3 x 45 minutes</td>
<td></td>
</tr>
<tr>
<td>interprets the results</td>
<td>3 x 45 minutes</td>
<td></td>
</tr>
<tr>
<td>enumerates the major superficial veins of the upper and lower limb</td>
<td>3 x 45 minutes</td>
<td></td>
</tr>
<tr>
<td>defines the indications and contraindications for intravenous catheterisation</td>
<td>3 x 45 minutes</td>
<td></td>
</tr>
<tr>
<td>performs an intravenous catheterisation</td>
<td>3 x 45 minutes</td>
<td></td>
</tr>
<tr>
<td>knows the structure of female and male urinary tract</td>
<td>3 x 45 minutes</td>
<td></td>
</tr>
<tr>
<td>defines the indications and contraindications for urinary catheters</td>
<td>3 x 45 minutes</td>
<td></td>
</tr>
<tr>
<td>performs catheterization of the bladder in men and women</td>
<td>3 x 45 minutes</td>
<td></td>
</tr>
<tr>
<td>knows the structure of injection sides</td>
<td>3 x 45 minutes</td>
<td></td>
</tr>
<tr>
<td>defines the indications and contraindications for intramuscular injection</td>
<td>3 x 45 minutes</td>
<td></td>
</tr>
<tr>
<td>performs intramuscular injection</td>
<td>3 x 45 minutes</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Learning outcomes of the Basic Clinical Skills course based on simulation training.
### Functionality of equipment used in Basic Clinical Skills course

<table>
<thead>
<tr>
<th>The name of the procedure</th>
<th>Manufacturer / Model of the Trainer / Simulator</th>
<th>Functionalities</th>
</tr>
</thead>
</table>
| Auscultation/ Pulse check | Laerdal MegaCode Kelly                         | • The possibility of auscultating heart sounds  
|                            |                                               | • The possibility of lung auscultating  
|                            |                                               | • The possibility of examining the carotid pulse and radial pulse  
|                            |                                               | • Head tilted forward, backward and sideways rotated 90 degrees in any direction  
|                            |                                               | • The manikin allows training of the following actions:  
|                            |                                               | o Introduction of oropharyngeal airway and suction  
|                            |                                               | o Introduction of nasopharyngeal airway and suction  
|                            |                                               | o Introduction of laryngeal airway  
|                            |                                               | o Ventilation using the resuscitation bag (ambu bag)  
| Blood pressure measurement| 3B Scientific W 44068                         | • The possibility of demonstrating 5 Korotkov’s phases  
|                            |                                               | • Adjustable volume  
|                            |                                               | • Ability to set heart rate in the range of 50 to 100 beats per minute  
|                            |                                               | • The possibility of adjusting the pressure (both systolic and diastolic)  
| Peripheral venous cannulation | 3B Scientific P50                         | • The possibility of intravenous injection  
|                            |                                               | • The possibility of puncture of peripheral veins for blood sampling  
|                            |                                               | • The possibility of venepuncture of: basilic, cephalic, cubital median, dorsal venous  
|                            |                                               | • Assembling cannula  
| Catheterization of urinary bladder | Laerdal 375-21001 Catheterization and Enema Trainer | • Convertible male and female genitalia  
|                            |                                               | • Hygiene of the crotch area  
|                            |                                               | • Intravaginal administration of medication  
|                            |                                               | • The possibility of introducing catheter, their care and removal  
| Intramuscular injections | Nasco Life form Intramuscular Injection Simulator LF00961U | • It has a simulated bony structure  
|                            |                                               | • It has a cut-out portion of the buttock, which allows visualization of structures  
|                            |                                               | • Using the simulator, you can practice three types of intramuscular injections  

**Table 2:** Functionality of equipment used in Basic Clinical Skills course

![Fig 1 A-E: The task trainers and mannequins used during Basic Clinical Skills labs.](image-url)
Participants

The students' sample consisted of 299 second year medical students (40.5% male and 59.5% female) of the Medical University. They had no previous experience in simulation-based course embedded into a formal curriculum.

All 299 participants returned completed questionnaires. The observational study included testing the reliability of the BCS course in terms of creating golden standards in case of those five procedures. Reliability was concerned with the extent to which repeated steps in the same procedure lead to the same result, standardizations of the procedure.

In addition to students' subjective assessment, the OSCE was implemented to provide objective assessment of acquired skills.

The stations were equipped with the same low-fidelity mannequins and task-simulators as students used during the labs. The preparation of the exam was divided into three stages. Firstly, coordinators of

Fig 2: Questionnaire items and students' evaluation ratings: mean value (blue circle) ± standard deviation (blue line).
the course and its teaching staff planned the stations, checklists and the schedule. The coordinator of the class as well as the teachers further developed the checklists. Later, medical practitioners verified the checklists. Afterwards, there was a training for the examiners. The recordings of each station were additional novelty providing immediate feedback in case of instructor’s hesitation concerning assigning points to the particular step. The recordings were also made available to the students upon their request.

The assessment was carried out not only by the employees of Medical University, but also by the 5th year medical students, implementing elements of the Peer Assessment Technique included in the training procedures. After meticulous preparation, the examination of the participants took place. The long period of preparation has demanded a lot of time and effort from the coordinators as well as the assessors themselves\(^\text{[10]}\).

**Procedure**

The research was a cohort study. Statistical analysis was performed for the results obtained. Database and statistical calculations were based on computer software STATISTICA 10 (StatSoft Polska). Quantitative parameters were presented using means, median values, and standard deviations; qualitative ones were presented as numbers and percentages. The collected data were statistically analyzed and the test difference between groups was verified with U Mann-Whitney test, taking the level of statistical significance at \(p < 0.05\).

**RESULTS**

The survey results outlined general satisfaction with the simulation-based course of BCS: 223 participants stated their definite content with the training, grading it 5 out of 5 (Fig 2).

Even more medical students (237, 80\%) agreed with the definite importance of its contents in light of their future profession (Fig 2). Next, 218 confirmed a definite increase in their knowledge (72.9\%) because of that course (Fig 2). 214 students confirmed active participation in the simulation-based course (71.6\%, Table 3). 234 of the surveyed confirmed their enjoyment of the novel way of acquiring medical skills (Fig 2). Except for students’ thorough participation, the surveyed confirmed teachers’ involvement during the course (68.2 % scored 5 on this question, Fig 2). Similarly, 260 students (87.6\%) confirmed fairness in case of teachers’ assessment with mean value equalising to 4.8. Additionally, the participants assessed the set learning outcomes as achievable (262, 87.9\% score 5 out of 5) and the course as well-coordinated and well-structured (197, 66.1\% scored 5 on Likert scale). The lowest level of positive responses was obtained in case of question concerning usefulness of the provided learning platform (150 students, 50\%). All in all, students expressed their satisfaction with the course itself with mean value 4.5 and standard deviation ± 0.8.

Furthermore, the lowest discrepancies on the assessment of the course applied to the question about learning outcomes, as the lowest grade given by the students was 3 out of 5 in that case. Additionally, there was no lowest mark (1/5) assigned to the question concerning the course structure as well as the equipment.

Results showed the overall content regarding the course as well as the expectation from the students to include such classes in the future.

In addition to students’ opinion, an OSCE confirmed the high level of participants’ abilities after course completion (Table 4). No correlation was found between the rate of fail/pass and the gender of the respondents.

### Table 3: Median opinions of the respondents according to their gender (± standard deviation) with correlation between gender and positive responses among participants of the BCS course.

<table>
<thead>
<tr>
<th>Questions</th>
<th>Gender</th>
<th><strong>p</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>I am satisfied with Basic Clinical Skills course in general.</td>
<td>Female: 4.79 (0.5)</td>
<td>Male: 4.58 (0.7)</td>
</tr>
<tr>
<td>The contents of that course are important for my future profession.</td>
<td>Female: 4.80 (0.5)</td>
<td>Male: 4.64 (0.7)</td>
</tr>
<tr>
<td>I have learnt a lot during that course.</td>
<td>Female: 4.75 (0.5)</td>
<td>Male: 4.58 (0.7)</td>
</tr>
<tr>
<td>I have actively learnt new procedural skills in that course.</td>
<td>Female: 4.71 (0.6)</td>
<td>Male: 4.58 (0.7)</td>
</tr>
<tr>
<td>I have participated in this course with pleasure.</td>
<td>Female: 4.80 (0.5)</td>
<td>Male: 4.62 (0.7)</td>
</tr>
<tr>
<td>I have worked effectively during the course time.</td>
<td>Female: 4.59 (0.6)</td>
<td>Male: 4.47 (0.7)</td>
</tr>
<tr>
<td>The teachers were interested in the students learning outcome.</td>
<td>Female: 4.60 (0.6)</td>
<td>Male: 4.62 (0.7)</td>
</tr>
<tr>
<td>I have been treated fairly by the teachers.</td>
<td>Female: 4.85 (0.5)</td>
<td>Male: 4.84 (0.4)</td>
</tr>
<tr>
<td>The virtual learning objectives are comprehensive.</td>
<td>Female: 4.88 (0.3)</td>
<td>Male: 4.86 (0.4)</td>
</tr>
<tr>
<td>The course contents are well coordinated and structured well.</td>
<td>Female: 4.62 (0.6)</td>
<td>Male: 4.52 (0.7)</td>
</tr>
<tr>
<td>Premises and equipment of CSM are satisfying.</td>
<td>Female: 4.60 (0.6)</td>
<td>Male: 4.48 (0.7)</td>
</tr>
<tr>
<td>The iMUL Skill Guide helped me significantly with course preparation.</td>
<td>Female: 4.10 (1.2)</td>
<td>Male: 4.14 (1.0)</td>
</tr>
<tr>
<td>The course motivated me to practice my skills regularly.</td>
<td>Female: 4.15 (0.9)</td>
<td>Male: 4.00 (1.0)</td>
</tr>
<tr>
<td>I am content with the organizational handling of the BCS course.</td>
<td>Female: 4.53 (0.8)</td>
<td>Male: 4.49 (0.8)</td>
</tr>
</tbody>
</table>

*: statistically relevant correlation
The only significant correlation (p <0.05) found during the statistical analysis applies to female students being more likely than the male ones to provide positive responses to four questions assessing the course: the overall assessment of the course; the definite importance of its contents in the light of their future profession; the definite increase in their knowledge; and confirmed their enjoyment of the novel way of acquiring medical skills (Table 4).

DISCUSSION

The concept of a novel simulation-based course appealed to the medical students. Participants underlined the value of active participation during the class, as well as introduction of basic skills they can build on. There is a worldwide proven need for practicing invasive skills in a safe environment, ensuring repetitiveness and learning on ones’ own mistakes[13].

Pringle et al confirmed the notion of standardization of procedures in the research concerning low-cost simulation trauma course for physicians[12]. The BCS class was based on that principle by ensuring transparency of the procedures prior to implementing them in the clinical setting.

Another reason for executing simulation-based training was striving for general consistency and unification of performed procedures. The general skills constitute a basis for further medical career; therefore, medical students found them useful[13]. Those procedures are basic, however, still provide countless possibilities for errors or misconducts.

Similarly to our study, Pugh et al’s research included simulation course participants expressing their satisfaction with the laparoscopic ventral hernia course[14]. Additionally, there are widely spread rules of conduct concerning the clinical procedures available in the form of guidelines[15]. Implementing safe, well-established rules also enables the prevention of blood exposure[16]. There is also a verified effectiveness of using basic simulators during introduction into the medical profession[17]. Similar to ours, the study by Kurashima et al proved transferability of skills learnt during low cost simulation based course into the clinical environment[18]. The outcome of the OSCE confirmed its efficacy, meaning successful implementation of the procedure according to the set of objectivised procedures by the majority of participants[19].

The literature concerning simulation courses also confirmed a noticeable increase of confidence when performing procedures in clinical settings, after practicing in the simulated environment. Its structured and dynamic environment enabled students to learn and master the necessary skills in a way that reflected clinical reality, bringing real, practical activity into the educational environment[20]. Faulkner et al proved the rise in confidence in case of participants of a simulation-based course and shortening the time of performing fluoroscopically guided lumbar puncture. The outcome of the simulation course shows an undeniable increase in both knowledge and skill, students appreciate this the most. In addition to the subjective evaluation of the course, OSCE exam proved the usefulness of that course in this matter. Even more, Carr et al have proven simulation utility when introducing procedural skills. Both the faculty members as well as students reported simulation as the primary method of acquiring these skills[21]. However, monitoring further development of the career and the abilities would be an even more useful factor. Additionally, students familiarize themselves with the equipment, the whole procedure as well as its communicative aspect. As a result, they are not overwhelmed by that aspect, nor taken by surprise that there is a need to explain certain aspects of procedures to patients[22]. Heskin et al proved the increase in the procedure implementation confidence among participants of their boot camp employing simulation methods to teach technical and nontechnical skills[23]. The lack of changing, altered conditions/aspects might be shortfalls deteriorating the benefits of low-fidelity simulation; however, they are only an introductory stage being followed by practice in an advanced simulation classroom and moving into the clinical setting. Bloom in his pyramid underlines the necessity of applying a new concept/skill in a typical situation before learning to use it on an atypical medical case. Therefore, a planned application of acquired skills should take place before employing the skill in a complex clinical situation[24]. Kneebone et al developed the issue in their study, proving the

<table>
<thead>
<tr>
<th>The name of the station</th>
<th>Total number of students</th>
<th>First pass</th>
<th>Failed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auscultation of the heart and pulse check</td>
<td>299</td>
<td>118</td>
<td>3</td>
</tr>
<tr>
<td>Non-invasive blood pressure measurement</td>
<td>115</td>
<td>174</td>
<td>6</td>
</tr>
<tr>
<td>Peripheral vein cannulation</td>
<td>167</td>
<td>176</td>
<td>11</td>
</tr>
<tr>
<td>Intramuscular injections</td>
<td>178</td>
<td>180</td>
<td>11</td>
</tr>
<tr>
<td>Urinary bladder catheterization</td>
<td>143</td>
<td>174</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 4: The results of the Objective Structured Clinical Examination including the gender information
successful transfer of skills taught in the simulation room to the clinical setting. Moreover, Woelfel et al. showed that the possibilities of acquiring procedural skills in clinical setting have been decreasing; therefore, a substitutionary form of education needs to be implemented.

The downfall of the course was insufficient information on the supporting website with the BCS. Trainees expect nowadays to find crucial data regarding a course on supporting websites, enabling them to revise previous topics and present them with an adequate reference. This aspect has been taken under consideration when implementing the next BCS course. As a result, students were provided with instructional videos with a full rerun of each procedure; the same materials constitute a base for demonstrating each procedure during the lab. In this sense, the assessment of the course gives us the chance to improve it in the areas where students noticed the need for upgrading. Additionally, learning abilities, consistency and reproducibility became an important factor. The student had the possibility to go back to a particular part of the performance to rehearse it to the point where it is fully mastered. The importance of those issues grows with the decreasing acceptance for making errors on live patients. There is also a need to remember that the benefits of simulations are being uncovered through the process of implementing this teaching method into the academic landscape. The BCS as a course has been implemented into the curriculum as an obligatory subject and moved to the first year, just before the students nursing clerkship. The participants as well as the order of teaching settings implemented by the changes compatible with the Recommendations for Clinical Skills Curricula for Undergraduate Medical Student of the Association of American Medical Colleges proposed the change. The recommendations identify simulation as an immediate predecessor of clinical patient care experience.

Limitations
As our primary objective was to assess students’ perception of the course concept, we did not investigate their knowledge before and after completion of the BCS. However, further investigations addressing students’ short and long-term competence and the transferability of skills into patient care are already being carried out.

CONCLUSIONS
The research demonstrates the beneficial role of technology enhanced course lead in simulation environment as a tool introducing active learning in the preclinical teaching, which was independently confirmed by the high percentage of passes among examined students during the OSCE. Additionally, subjective assessment of the participants underlined their perception of the course contents as being of great importance in light of their future profession.

Furthermore, emphasizing the value of our study, it resulted in an important curricular change within the Faculty of Medicine of the Medical University, making the BCS course obligatory for all first-year students from the spring semester 2016 before their nursing clerkship.

Next, designed frames of the OSCE have become a basis for further assessments, drawing from BCS experience.

ACKNOWLEDGMENT
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ORIGINAL ARTICLE

The comparison of percutaneous and transurethral cystolithotripsy methods simultaneously performed with Transurethral Resection of Prostate in patients with BPH and bladder stone

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ABSTRACT

OBJECTIVE: To compare the efficiency of percutaneous (PCL) and transurethral (TCL) cystolithotripsy simultaneous with transurethral prostatectomy (TUR-P).

Design: Retrospective study

Setting: Sakarya University, School of Medicine, Sakarya, Turkey

Subjects: The data of 79 patients who underwent PCL (n = 33) and TCL (n = 46) simultaneous with TUR-P were evaluated. Preoperatively, physical examination, routine blood tests, prostate-specific antigen, uroflowmetry and ultrasonographic examination were performed. The stone size was calculated as mm². TUR-P was done initially with 26 F continuous-flow resectoscope in the PCL patients. Then the bladder stone lithotripsy was done using pneumatic lithotripter via 30 F Amplatz sheath.

Intervention: Percutaneous and transurethral cystolithotripsy, transurethral prostatectomy

Results: There was no difference between groups in terms of age and co-morbidity. While stone size was 920 ± 193.3 mm² (600 - 1240 mm²) in PCL group, it was calculated as 449 ± 337.6 mm² (96 - 1305 mm²) in TCL group. Stone burden was found to be statistically significantly higher in PCL group (p <0.001). The stone extraction time and total operation time was found to be significantly shorter in PCL group (p = 0.007 and p = 0.017, respectively). Since urethral stricture developed in nine patients during follow-up in TCL group, the patients were re-operated. No urethral stricture developed during follow-up in PCL group.

Conclusion: The use of urethral approach for long periods during TCL increases the risk of urethral stricture in the postoperative period. In patients who are planned to undergo TUR-P and who have an accompanying high stone burden, the combination of TUR-P + PCL seems to be a rational approach.

INTRODUCTION

Bladder stones constitute approximately 5% of all urinary system stones. Bladder outlet obstruction, neurogenic voiding disorders, infections, and foreign bodies are considered as principal etiologic factors[1]. Whereas bladder outlet obstruction is more common in male patients, infections are responsible more frequently in female patients[2,3]. Since the incidence of benign prostatic hyperplasia (BPH) increases with age, bladder stone is a disorder that is met more frequently in elderly men. Taking into consideration the fact that comorbidity increases with age, it seems more rational to prefer minimally invasive methods for treatment of bladder stone and BPH. Today, extracorporeal cystolithotripsy (ESWL), percutaneous cystolithotripsy (PCL), and transurethral cystolithotripsy (TCL) are among the preferred methods. Considering that the effect of ESWL on large and hard bladder stones is limited, PCL and TCL methods are being used more commonly. PCL has been shown to be a faster and more effective treatment method with fewer complications when compared to TCL[4,5]. In patients

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undergoing PCL and transurethral resection of prostate (TUR-P), TUR-P is generally performed initially after removing the stone by PCL. However, TUR-P can be performed before the PCL to avoid requirement for cystostomy catheter postoperatively, which can result in increasing the patient comfort and reducing the risk of urinary system infection. This study aims to present the results of our PCL technique, which is performed in an unconventional method in patients undergoing TUR-P, and to compare these with TCL results.

SUBJECTS AND METHODS
This study has obtained approval from Ethics Committee of Sakarya University School of Medicine. The written informed consent has been obtained from all the participants. Data of 79 patients who had undergone simultaneous bladder stone surgery and TUR-P between February 2009 and December 2014 were analyzed retrospectively. Patients whose medical history revealed prostate cancer, previous prostate surgery, urethral stricture, previous abdominal or pelvic surgery, and neurogenic bladder were excluded from the study. Preoperatively, physical examination, routine blood tests, prostate-specific antigen, uroflowmetry, plain abdominal radiography, and ultrasonographic examination were performed. The stone size was calculated in mm² (multiplication of long edge by short edge). Urine culture (+) patients were operated following sterilization of their urine with appropriate antibiotic treatment. In all patients, preoperative single dose ceftriaxone was administered as antibiotic prophylaxis. In patients having both bladder stone and BPH, the methods to be performed were chosen by the surgeon. The same surgeon performed both operations.

Technique
Following the administration of spinal or general anesthesia, 25F cystoscope (Karl Storz, Germany) were used for the evaluation of urethra, prostate, and bladder. The surgery method (TCL or PCL) depended on the decision of surgeon at the time of operation. In patients undergoing TCL, the bladder stone was disintegrated by pneumatic lithotripter (Elmed, Ankara, Turkey) under 0.9% saline. The stones were extracted using grasping forceps. Then, using mannitol as the irrigation fluid, TUR-P was performed by 26F resectoscope. Following the procedure, a three-way 22F Foley catheter was inserted. The durations for stone extraction by TCL and TUR-P were separately recorded. The patients were discharged 2 - 3 days following the operation in average.

In PCL group, TUR-P was performed initially by using 26F resectoscope and mannitol. Following bleeding control, under cystoscopic vision, 18G Chiba needle was inserted into the bladder suprapubically. A 0.038 mm sensor guide was introduced through the needle. An approximately one cm incision was made adjacent to the guide. 30F Amplatz sheath was introduced into the bladder, following 14-30 F dilation by Amplatz dilators. For controlling the bleeding, 22F three-way Foley catheter was inserted through the urethra and its balloon was inflated at the prostatic lodge. By using 26F nephroscope (Karl Storz, Germany), the stones were fragmented by pneumatic lithotripter (Elmed, Ankara, Turkey) under 0.9% saline infusion. The fragmented stones were extracted using grasping forceps. After removing the stones, the incision was closed with 3.0 Vicryl sutures. The urethral catheter was removed after an average period of three days, and the patient was discharged from the hospital.

Patients were followed-up with control examinations in the 1st, 3rd, and 6th months following the operation within the 1st year, and then with annual control examinations. At the control examinations, the patients were evaluated in terms of BPH complaints, together with residual or recurrent stones.

Statistical analysis
The normality distribution of group data was performed by Shapiro Wilk test. Data showing normal distribution were compared by using t test (test for the difference between two independent groups). Data which were not showing normal distribution were compared by using Mann-Whitney U test. Chi-square test was used for categorical variables. P-value <0.05 was considered significant.

RESULTS
The patients’ data according to groups were summarized in Table 1. There was no difference between groups in terms of age and comorbidity. While stone size was 920 ± 193 mm² (600 – 1240 mm²) in PCL group, it was calculated as 449 ± 337 mm² (96 - 1305 mm²) in TCL group. Stone burden was found to be significantly higher in PCL group (p <0.001). While two patients had non-opaque stones in PCL group, the number of patients having non-opaque stones was eight in TCL group. No statistically significant difference was found between groups in terms of duration of TUR-P procedure. The stone extraction time and total operation times were shorter in PCL group (p = 0.007 and p = 0.017, respectively). Four patients who underwent TCL developed low-grade fever and recovered with symptomatic treatment. In one patient who underwent TCL, retention developed on the 7th postoperative day. In the PCL group, three patients developed low-grade fever which lasted for a short period, and they recovered with symptomatic treatment.
The mean follow-up period of patients was 20.4 ± 15 months (1 - 72 months). Since urethral stricture developed in nine patients during the follow-up in TCL group, these patients were re-operated. While six of these patients underwent internal urethrotomy, meatotomy procedure was performed in three patients. No urethral stricture developed during the follow-up in the PCL group. Stone recurrence was evaluated by plain abdominal radiography and ultrasonography. No residual stone was determined during the follow-up.

**DISCUSSION**

In patients undergoing PCL and TUR-P, TUR-P is generally performed after removing the stone by PCL\([5,6]\). However, in our study, TUR-P was performed first; PCL was performed thereafter. Here, our purpose was two-fold: not to disturb the integrity of the bladder before TUR-P, avoiding extravasation following TUR-P; and also not to let the patient lose his chance for TUR-P, the gold standard surgical method in BPH treatment, in the same session, if we encounter a complication such as converting to open surgery during PCL. The other advantage of this approach was to provide controlled hemostasis by inflating the balloon of three-way Foley catheter at the prostatic lodge, together with establishing proper drainage. Moreover, it also allowed us to avoid requirement for cystostomy catheter used postoperatively for drainage in patients who undergo PCL; therefore, increasing the patient comfort and reducing the risk of urinary system infection.

Since bladder outlet obstruction usually takes first place in the etiology of bladder stone in men, addition of TUR-P to the management plan has become a routine procedure in patients diagnosed with BPH. However, a consensus is not present on this subject. Some authors have emphasized that, with medical treatment, prostate surgery is not required, and stone recurrence has not been observed during the follow-up in patients who underwent stone extraction by PCL under local anesthesia\([7]\). However, in the study conducted by Philippou *et al.*, patients diagnosed with BPH and bladder stone were divided into two groups; in one group, TCL and medical treatment (tamsulosin + finasteride) were performed, in the other group TCL and TUR-P were performed. The authors stated that, in the postoperative period, IPSS and Q max were better in TCL group when compared to medical treatment group. They also stated that in 34% of patients, they were obliged to perform TUR-P after the follow-up period in the medical treatment group\([8]\).

Aron *et al.* compared data of patients in whom TUR-P+PCL and TUR-P+TCL were performed and pneumatic lithotripter was used for stone fragmentation\([9]\). They reported that if the stone burden was higher, the duration for stone extraction was shorter in PCL group. Furthermore, authors preferred to extract the stone initially and perform TUR-P thereafter. They also stated that bleeding from the prostatic tissue might significantly reduce vision quality. Similarly, in our study, the stone burden of patients undergoing PCL was significantly higher and their operation time was significantly shorter. However, we preferred to perform TUR-P first, and we aimed to improve patient comfort and to reduce additional interventions by using a balloon to control bleeding that may originate from the prostatic lodge and by avoiding cystostomy catheter. To avoid extravasation and for healing of the incised bladder wall, we prolonged the catheter withdrawal time in the PCL group. Aron *et al.* identified two cases of urethral stricture in TCL group and no stricture in PCL group.

Similarly, in the study conducted by Tugcu *et al.*, the stone burden was higher and stone extraction time was shorter in the PCL group\([6]\). They reported that while extravasation occurred in one patient in PCL group, three patients in TCL group had residual stones due to bleeding. The stone-free rate was reported as 100% in the PCL group and 92% in the TCL group.

### Table 1: Data of patients

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>PCL(^{1}) (n = 33)</th>
<th>TCL(^{1}) (n = 46)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>70.5 ± 7.2</td>
<td>66.6 ± 10.3</td>
<td>0.063*</td>
</tr>
<tr>
<td>Stone burden (mm(^2))</td>
<td>920 ± 193 (600-1240)</td>
<td>449 ± 337 (96-1305)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Duration of operation (min)</td>
<td>85.7 ± 16.7</td>
<td>90 ± 15.8</td>
<td>0.017*</td>
</tr>
<tr>
<td>Stone extraction period</td>
<td>27.8 ± 10.6 (10-50)</td>
<td>35.7 ± 12.4 (20-80)</td>
<td>0.007*</td>
</tr>
<tr>
<td>TUR-P period</td>
<td>57.8 ± 8.4 (45-70)</td>
<td>55.1 ± 7.9 (40-70)</td>
<td>0.170</td>
</tr>
<tr>
<td>Duration of catheter stay (days)</td>
<td>3.3 ± 1.1</td>
<td>2.6 ± 0.7</td>
<td>0.009*</td>
</tr>
<tr>
<td>Follow-up period (months)</td>
<td>27.2 ± 15.6 (1-72)</td>
<td>15.6 ± 12.6 (3-57)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Urethral stricture</td>
<td>0</td>
<td>9 (19.6%)</td>
<td>0.005(\beta)</td>
</tr>
<tr>
<td>Present</td>
<td>33 (100%)</td>
<td>37 (80.4%)</td>
<td></td>
</tr>
</tbody>
</table>

\*T test aMann Whitney U test, \(\beta\) Chi-Square; PCL: percutaneous cystolithotripsy; TCL: transurethral cystolithotripsy; TUR-P: transurethral resection of prostate; \(^{1}\) Mean ± SD (min-max)
In the followed-up period, three patients in the TCL group were diagnosed with urethral stricture. In our study, while urethral stricture was diagnosed in nine patients in the TCL group, no stricture was present in the PCL group during the follow-up period. Since no complication, which may interrupt the operation, was encountered in both the PCL and TCL groups, all patients were freed from their stones.

The diversity of usable equipment has led to experiencing various treatment methods in TUR-P and bladder stone operations. Ercil et al divided patients who were diagnosed with bladder stone and BPH into two groups and performed the prostate surgery in both groups by PlasmaKinetic. In both groups, the stone extraction procedure was performed by transurethral lithotripsy; however, while they used pneumatic lithotripter for stone fragmentation, in the other group, they preferred Ho:Yag laser\cite{9}. The duration of the operation and stone extraction time were found to be significantly less in the group where Ho:Yag laser was preferred. They reported that no statistically significant difference was found between the two groups in terms of complications. Although Ho:Yag laser reduces the duration of the operation by making short fragmentations, its unavailability in every center together with its high cost are its disadvantages.

Urethral stricture is a bothersome complication, interfering with life comfort of the patients, and it may necessitate disturbing and recurrent operations. In stone fragmentation performed by transurethral methods, bleeding due to prostatic tissue trauma, unavailability of optimal exposure and high urethral injury risk may be considered as disadvantages of the method. Also, the use of urethral approach for long periods during TCL increases the risk of urethral stricture in the postoperative period. On the other hand, in percutaneous approach, wide-diameter instruments can be used for large and multiple stones, and higher stone-free rates (85 - 100%) can be accomplished in shorter periods. The small risk of urethral trauma and enabling removal of more numbers of stones in a shorter period are significant advantages of PCL, and this can decrease the risk of urethral stricture in the postoperative period.

In our cases, urethral stricture developed in nine patients during follow-up in the TCL group, and these patients were re-operated. On the other hand, no urethral stricture developed in the PCL group during the follow-up.

**CONCLUSION**

In BPH patients with high stone burden, the combination of TUR-P and PCL seems to be a rational approach. The use of urethral approach during TCL increases the risk of urethral stricture. TUR-P can be performed before PCL to reduce the risk of complications and to increase patient’s comfort.

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**REFERENCES**

Cervical cancer screening: A 10-year retrospective review in Tertiary Care Hospital in Saudi Arabia and future national perspectives

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ABSTRACT

Objectives: The Papanicolaou screening test (Pap smears) is performed to preemptively identify and treat cervical cancer. This study aims to estimate the frequency of positive cervical Pap smears during the last 10 years in our institution and compare with world literature.

Design: Retrospective chart review

Setting: Tertiary hospital in Riyadh, Saudi Arabia

Subjects: Cervical smears of Saudi women from 2004-2014 were reviewed, abnormal smears identified and correlated with histopathology. The prevalence, mean age and standard deviation for each type of abnormal smear was calculated. Non-Saudi women were excluded from this study. The obtained data was compared with national and international studies.

Interventions: None

Main outcome measure and results: The number of cervical smears reported as abnormal was low (1% in 10 years). About half the abnormal smears were atypical cells of undetermined significance (47.6%), followed by low-grade squamous intraepithelial lesion (23.2%), high-grade squamous intraepithelial lesion (8.5%), squamous cell carcinoma (SCC, 6.1%), atypical glandular cells favor neoplasia (6.1%), adenocarcinoma (AC, 3.3%) and others (5.3%). The mean ages of SCC and AC were 57 and 70 years, respectively.

Conclusion: The proportion of abnormal cervical Pap smears in Saudi Arabian women is low and the women positive for squamous carcinoma are in the relatively older age group. We recommend establishing human papilloma virus (HPV)-DNA testing at all our major centers to guide management. Despite low incidence of cervical carcinoma, adding HPV vaccine to the mandatory list of vaccinations in Saudi Arabia will be useful.

INTRODUCTION

Cervical cancer is the fourth most common cancer in women worldwide[1]. It is estimated that in 2016, there will be 12,990 new cases of cervical cancer and an estimated 4,120 people will die of this disease[2]. Mortality varies 18-fold between different regions of the world, ranging from less than 2 per 100,000 in Western Asia, Western Europe, and Australia/New Zealand to more than 20 per 100,000 in Melanesia (20.6), Central Africa (22.2) and Eastern (27.6) Africa[1].

The data on the incidence and prevalence of cervical cancer in the Middle East is limited; however few previously published local studies have shown that, in contrast to global statistics, the incidence of cervical cancer in Saudi Arabia is low[3-6]. According to the latest published data, cervical cancer in Saudi Arabia ranked as the eighth-most frequent cancer among women between 15 and 44 years of age, with an annual crude incidence of 1.9 per 100,000 population[7]. The reason for this low incidence is unknown, but the conservative nature of the Saudi society in addition to the low rate of human papillomavirus (HPV) infection (an overall prevalence of 9.8%) and the high rate of male circumcision are likely contributing factors[8,9].

The aim of this study was to estimate the frequency of positive cervical Pap smears in a major tertiary
hospital in Riyadh and to study the age distribution in relation to different cervical lesions. A literature review of similar national and international studies is also presented, with a comparison of our findings to the previously published data.

SUBJECTS AND METHODS

This is a retrospective review conducted at a tertiary level hospital in Riyadh, Saudi Arabia. The hospital primarily serves Saudi nationals with approximately 2000 Pap smears performed annually. The data pertaining to all Pap smears performed between January 2004 and December 2014 were obtained. After excluding unsatisfactory specimens and the occasional smears of non-Saudi women, a total of 24,516 satisfactory Pap smears were retrieved and revised. The clinical and demographic data were collected from patients’ medical charts and electronic records. The review was conducted in accordance with the Saudi regulations and an approval was obtained from the Institutional Review Board.

The standard procedure of obtaining cell samples for Pap smears, in which cells are collected from the cervical transformation zone using cytobrushes, is followed by our center and performed by trained gynecologists. The cytobrush is then placed in a liquid-based cytology transport preservative (PreservCyt®) and transferred to the cytology lab where the slides are prepared and screened by cytotechnologists. All slides (negative and positive smears) are revised and verified by board-certified pathologists as per the recommendations of the Bethesda system for reporting cervical cytology, 2001[10].

In this study, all smears with epithelial cell abnormalities were identified and categorized as follows: atypical squamous cells of undetermined significance (ASC-US), atypical cells in which high-grade lesions cannot be excluded (ASC-H), low-grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesions (HSIL), squamous cell carcinoma (SCC), atypical glandular cells (AGC), atypical glandular cells favor neoplastic (AGCFN), endocervical adenocarcinoma in situ, adenocarcinoma and undifferentiated carcinoma. The mean age of incidence for each category was also calculated and recorded.

RESULTS

A total of 24,516 Pap smears from women ranging from 18 years to 99 years of age were included in this study. Out of the 24,516 Pap smears, 246 smears (1%) reported positive for epithelial cell abnormalities. Of these, ASCUS was the most common (47.6%), followed by LSIL (23.2%), HSIL (8.5%), SCC (6.1%), AGCFN (6.1%), AGC (3.7%), endocervical adenocarcinoma (3.3%), ASC-H (1.2%) and undifferentiated carcinoma (0.4%) (Table 1).

The mean age of incidence for ASCUS was around 46 years, 47 years for ASC-H, 41 years for LSIL, 50 years for HSIL and 57 years for SCC. Regarding cervical glandular lesions, the mean age was 53 years for AGC, 51 years for AGCFN, 70 years for endocervical adenocarcinoma, and 99 years for undifferentiated malignancy (Table 1). The clinical presentation of patients with abnormal smears is also summarized (Table 2). The majority of women were asymptomatic (44.7%), followed by women with postmenopausal bleeding (13%), abnormal vaginal discharge (11.4%) and dysfunctional uterine bleeding (7.3%). Other symptoms included post-coital bleeding (6.1%), menorrhagia (4.1%), lower abdominal pain (4.1%) and dyspareunia (0.4%). Also, 2.8% had a history of previously abnormal Pap smear. None of the patients had a history of HPV vaccination.

### Table 1: Distribution of cervical atypical epithelial lesions in our population using the Bethesda reporting system for cervical cytology, 2001

<table>
<thead>
<tr>
<th>Cytological diagnosis (Bethesda category)</th>
<th>Number of cases</th>
<th>Percentage</th>
<th>Age range (years)</th>
<th>Mean age ± SD (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCUS</td>
<td>117</td>
<td>47.6%</td>
<td>18 - 63</td>
<td>46.3 ± 10</td>
</tr>
<tr>
<td>ASC-H</td>
<td>3</td>
<td>1.2%</td>
<td>37 - 59</td>
<td>47.6 ± 11</td>
</tr>
<tr>
<td>LSIL</td>
<td>57</td>
<td>23.2%</td>
<td>21 - 59</td>
<td>41.1 ± 9</td>
</tr>
<tr>
<td>HSIL</td>
<td>21</td>
<td>8.5%</td>
<td>37 - 76</td>
<td>50.7 ± 12</td>
</tr>
<tr>
<td>AGC</td>
<td>9</td>
<td>3.7%</td>
<td>42 - 86</td>
<td>53.2 ± 8</td>
</tr>
<tr>
<td>AGC, favor neoplastic</td>
<td>15</td>
<td>6.1%</td>
<td>30 - 70</td>
<td>51.2 ± 10</td>
</tr>
<tr>
<td>SCC</td>
<td>15</td>
<td>6.1%</td>
<td>46 - 84</td>
<td>57.1 ± 10</td>
</tr>
<tr>
<td>Endocervical adenocarcinoma</td>
<td>15</td>
<td>6.1%</td>
<td>30 - 70</td>
<td>51.2 ± 10</td>
</tr>
<tr>
<td>Other: undifferentiated malignant cells</td>
<td>8</td>
<td>3.3%</td>
<td>60 - 85</td>
<td>70.2 ± 7.6</td>
</tr>
<tr>
<td>Other: malignant cells</td>
<td>1</td>
<td>0.4%</td>
<td>99</td>
<td>99</td>
</tr>
</tbody>
</table>

ASCUS: atypical squamous cells of undetermined significance; ASC-H: atypical squamous intraepithelial lesion; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion; SCC: squamous cell carcinoma.

All patients with ASC-H and HSIL, as well as those with the diagnosis of an invasive carcinoma, underwent colposcopy and colposcopy-directed biopsy, which confirmed the cytological diagnoses of high-grade dysplasia or invasive carcinoma. One Pap smear reported as undifferentiated malignant cells turned out to be a case of carcinosarcoma (malignant mixed mullerian tumor) on a subsequent cervical biopsy.

In the absence of HPV genotyping in our institution, the guidelines on follow up patients with ASCUS and LSIL are yet to be established and...
implemented. Cervical biopsies were performed on some of the patients reported as ASCUS or LSIL and yielded in a range of findings. Two cases, reported as ASCUS, showed squamous cell carcinoma on cervical biopsy and a case of ASCUS and 5 cases of LSIL showed high-grade squamous intraepithelial lesion. Negative adequate cervical biopsies were seen in 16 patients with ASCUS (13.6%) and 10 patients with LSIL (17.5%). Fifty-four patients (46.1%) with ASCUS and 19 patients (33.3%) with LSIL had negative cytology after 3 months follow up without undergoing colposcopy or cervical biopsies. Some patients with the diagnosis of ASCUS (31.6%) and LSIL (31.5%) were lost to follow up.

DISCUSSION

Cervical cancer used to be a major cause of cancer death among females in the United States of America. The introduction and implementation of the Pap screening program has dramatically reduced both the incidence and mortality rates from 1955 to 1992. Currently, the incidence rates of cervical cancer are highest in the sub-Saharan Africa, Melanesia, Latin America, and the Caribbean Islands and are lowest in Western Asia, Australia/New Zealand, and Northern America[11]. This geographic variation reflects differences in the availability of screening and HPV infection prevalence[11]. The prevalence of all types of HPV infection varies widely, being a high 21% in Africa; 16% in Latin America and the Caribbean; 9% in Asia; and a low 5% in Northern America[12].

Several local studies have examined the patterns of abnormal Pap smears in various regions of Saudi Arabia (Table 3). For instance, Jamal et al reviewed 22,089 cases of cervical Pap smears in the Western region of Saudi Arabia over 16 years. They reported a prevalence of 1.7% of positive Pap smears with cervical epithelial lesion, among which cervical SCC was a mere 7.1%. ASCUS including squamous metaplasia with atypia comprised 26.3%, cervical intraepithelial neoplasia (CIN) I including HPV changes 22.5%, CIN II 12.2%, CIN III 7.3%, atypical glandular cells of undetermined significance 9.8%, herpes virus changes 5.4%, HPV changes 5.1%, adenocarcinoma of endometrium 1.4%, adenocarcinoma of endocervix 1.9%, positive for malignant cells 6% and reparative atypia 1.6%;[10]. A recently published study from the Southwestern region of the country reported a 0.33% incidence rate of cervical SCC, with a peak between 50 - 59 years of age[6]. In the Eastern province of Saudi Arabia, the prevalence of Pap smears with atypical epithelial lesions and cervical SCC were 4.95% and 0.34%, respectively[13]. A study from another tertiary center in Riyadh representing the central region of Saudi Arabia, showed a 4.3% prevalence of positive Pap smears for atypical epithelial lesions[14].

In our review, 1% of the study group had abnormal cervical epithelial cells detected on Pap smears. This finding is concordant with the findings from other regions of Saudi Arabia. The proportion of cervical SCC in our study (6.1% of the study group) is higher than the majority of the reported local data. It is also noteworthy that the majority of squamous intraepithelial lesions diagnosed in our population

Table 2: Patient’s history and clinical presentation of patients having abnormal smears and included in this study

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Number of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous abnormal smear</td>
<td>7</td>
<td>2.8</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>110</td>
<td>44.7</td>
</tr>
<tr>
<td>Vaginal discharge</td>
<td>28</td>
<td>11.4</td>
</tr>
<tr>
<td>Lower abdominal pain</td>
<td>10</td>
<td>4.1</td>
</tr>
<tr>
<td>Menorrhea</td>
<td>10</td>
<td>4.1</td>
</tr>
<tr>
<td>Irregular bleeding</td>
<td>18</td>
<td>7.3</td>
</tr>
<tr>
<td>Post-menopausal bleeding</td>
<td>32</td>
<td>13</td>
</tr>
<tr>
<td>Post coital bleeding</td>
<td>15</td>
<td>6.1</td>
</tr>
<tr>
<td>Cervical mass</td>
<td>6</td>
<td>2.4</td>
</tr>
<tr>
<td>Cervical polyp</td>
<td>2</td>
<td>0.8</td>
</tr>
<tr>
<td>Warts</td>
<td>6</td>
<td>2.4</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>Pelvic mass</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>Total</td>
<td>246</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 3: Distribution of Pap smears with abnormal epithelial cells in different regions of Saudi Arabia

<table>
<thead>
<tr>
<th>Region</th>
<th>Study duration</th>
<th>Number of cases</th>
<th>Percentage of Pap smears**</th>
<th>ASCUS*</th>
<th>LSIL*</th>
<th>HSIL*</th>
<th>ASC-H*</th>
<th>SCC*</th>
<th>AGC, favor neoplastic*</th>
<th>AGC/AGUS*</th>
<th>AC*</th>
<th>Positive for malignant cells, NOS</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western1</td>
<td>1984 - 2000</td>
<td>22089</td>
<td>1.7</td>
<td>26.3</td>
<td>22</td>
<td>19.5</td>
<td>0</td>
<td>7.1</td>
<td>0</td>
<td>9.8</td>
<td>3.3</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Southwestern11</td>
<td>1994 - 2003</td>
<td>2100</td>
<td>7.9</td>
<td>34.9</td>
<td>16.3</td>
<td>8.4</td>
<td>2.4</td>
<td>4.2</td>
<td>0</td>
<td>32.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Eastern19</td>
<td>2003 - 2010</td>
<td>1171</td>
<td>4.9</td>
<td>60.3</td>
<td>1.72</td>
<td>13.8</td>
<td>12.1</td>
<td>6.9</td>
<td>0</td>
<td>5.2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Central50</td>
<td>2008 - 2011</td>
<td>19650</td>
<td>4.3</td>
<td>59.1</td>
<td>20.2</td>
<td>5.1</td>
<td>5.8</td>
<td>1</td>
<td>0</td>
<td>6.3</td>
<td>2.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Current study</td>
<td>2004 - 2014</td>
<td>24.516</td>
<td>1</td>
<td>47</td>
<td>23.2</td>
<td>8.5</td>
<td>1.2</td>
<td>6.1</td>
<td>5.7</td>
<td>3.7</td>
<td>3.3</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

ASCUS: atypical squamous cells of undetermined significance; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion; ASC-H: atypical squamous cells, high-grade squamous intraepithelial lesion cannot be excluded; SCC: squamous cell carcinoma; AGC/AGUS: atypical glandular cells atypical glandular cells of undetermined significance; AC: adenocarcinoma; NOS: not otherwise specified; Others: includes endometrial cells, epithelial cells with reparative/ inflammatory/ Herpes virus associated atypia. 

** Percentage of Pap smears with abnormal epithelial cells

* Percentage of the abnormal

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were ASCUS. The ASCUS category represented 47.6% of all positive Pap smears, followed by LSIL at 23.2%. While we acknowledge that most cases of LSIL regress completely, it is important to note that in the absence of routine HPV testing in our institution, the follow up guidelines for ASCUS and LSIL categories are still controversial.

The mean age of incidence of atypical epithelial cells detected by cervical cytology was greater than 40 years in all published studies from Saudi Arabia[3,4,6,13,14]. The mean age of women with cervical SCC was over 50 years[3,4,6,15]. Our findings fall into the same range, with a mean age of incidence of 47.7 years and 57.1 years for cervical atypical epithelial cells and cervical SCC, respectively.

In the United States of America, most women with cervical cancer between 2006 and 2010 were diagnosed before the age of 50, with a median age of 49 years. In 2014, Cuzick et al revised 219,610 Pap smears from women aged 15 - 84 years collected in 2011 in New Mexico, USA[15]. They found that 91.9% of screening tests were negative, 6.6% showed ASCUS or LSIL, and 0.9% exhibited higher grade abnormalities (ASC-H, HSIL, AGC, adenocarcinoma in situ, adenocarcinoma, SCC, or unspecified cancer). Most abnormalities were more common in younger women; ASCUS results were reported in 8.2% of tests for women aged 15 – 20 years, but in only 2.8% of women aged 50 – 65 years. Similarly, LSIL dropped from 8.4% to 0.6% for these age groups and ASC-H dropped from 0.6% to 0.2%. HSIL was highest in the 21 – 29 year age group (0.5%) while AGC peaked in the 40 – 49 year age group (0.4%)[15]. In the United Kingdom, cervical cancer is the 12th most common cancer, with around 3,200 cases diagnosed in 2013 and an age-specific incidence rate peaking in women in their early 30s[16]. Notably, following a gradual reduction in the incidence rate in women in their 40s, the incidence rose again in women in their 70s and 80s. As a result of the robust screening program in the United Kingdom, many cervical cancers were detected in younger women, with around 60% of cases occurring in women aged 25 - 49 years[16]. In the People’s Republic of China, the mean age of patients with cervical cancer between 2000 and 2009 was 44.7 years[17].

The neighboring Gulf countries share the same cultural background as Saudi Arabia. Alzaabi et al reviewed 4593 Pap smears from Abu Dhabi, United Arab of Emirates (between January-December 2013) from both local/national and expatriate/non-national women (smears from non-national women comprised 53.84% in this study)[18]. They documented positive Pap smears in 4.89% of cases and included the following: ASCUS in 114 cases (2.48%), ASC-H in 5 cases (0.10%), LSIL in 72 cases (1.56%), HSIL in 27 cases (0.58%), glandular lesions in 5 cases (0.10%), and SCC in 2 cases (0.04%), with a mean age of 45 years. In an earlier study from Kuwait, the prevalence of cervical atypical epithelial cells and cervical SCC over 13 years was 4.3% and 0.05%, respectively, with a mean age of cervical SCC of 48 years[19]. The differences noticed between these published data and our findings might be attributed to the inclusion of non-national citizens in both of the above-mentioned studies[18,19]. Although the incidence of cervical SCC in Saudi Arabia is one of the lowest in the world, it is anticipated that as the population ages, there will be an increase in the number of affected women[20].

In our study, the majority of the women that presented with invasive cervical cancers either never had a previous Pap test or their last Pap test was done more than 5 years ago. We therefore recommend the implementation and adherence to the screening program guidelines published by the WHO and emphasized by the Saudi guidelines, as regards to the screening frequency and treatment of precancerous cervical lesions[20,21]. As demonstrated in various earlier studies, carcinogenesis usually starts two decades prior to the development of invasive cervical carcinoma, and since the mean age of developing invasive cervical carcinoma (squamous and adenocarcinoma) in Saudi women in our study was 63.6 years, the possibility of revising the starting age of screening in this region should be explored[22]. We suggest that the starting age of screening be delayed by a decade in native Saudi women. This may give considerable respite to the workload and to the financial burden on the Saudi healthcare system.

It is also noteworthy to mention that HPV infection was found in 95.5% of cervical cancer cases in Saudi Arabia[23]. The most common genotype was HPV-16 (63.4%), followed by HPV-18 (11.1%), HPV-45 (4.5%), HPV-33 (3.3%), and HPV-52, 53, 58, 59, and 66 (2.2% each)[21]. For this reason, we highly recommend establishing HPV-DNA testing in all tertiary centers to help identify HPV types and guide further management, especially for the ASCUS and LSIL categories. Several vaccines have been developed to protect against two, four or nine types of HPV. The first HPV vaccine became available in 2006, and by 2014, up to 58 countries have implemented it as part of their routine immunization schedules[24]. The vaccination should ideally be given before individuals become sexually active and are potentially exposed to HPV. The FDA has approved Gardasil for use in females (and males) aged 9 to 26 years and Cervarix for use in females aged 9 to 25 years[25]. Both vaccines are available in Saudi Arabia, but they are not included in the basic vaccination schedules[24].
schedule. In addition, our reporting of Pap smears should be standardized according to the updated 2014 version of the Bethesda System for Reporting Cervical Cytology[20].

CONCLUSION

In summary, the number of abnormal cervical Pap smears in Saudi Arabia is low and women with squamous cell carcinoma are relatively older compared to other countries. Multiple large-scale studies are needed to augment our national data and increase our understanding of the disease trends. The findings in this part of the world may in fact differ from the data published in Western populations. These differences may eventually lead to an adjustment in the starting age for cervical cancer screening in Saudi Arabia. Should the recommended age to start screening for cervical cancer based on our national data be delayed, it will reduce the workload and financial burden on the healthcare system. Even though the rate of cervical carcinoma in this region is low, the HPV vaccine should be incorporated in the list of mandatory vaccinations. We acknowledge that this retrospective review is limited, as it only represents the central region of Saudi Arabia and we encourage the conduction of larger nationwide population-based surveys. We also recommend updating our reporting criteria and management options based on the Bethesda System for Reporting Cervical Cytology, 2014.

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REFERENCES


Original Article

Comparison of the results of 16 to 20 French percutaneous access dilatation of mini-percutaneous nephrolithotomy in pediatric patients

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ABSTRACT

Objective: The aim of the study was to compare the efficiency and complications of minimally invasive percutaneous nephrolithotomy (mini-PCNL) using 16 F and 20 F access sheaths in pediatric population.

Design: Retrospective study

Setting: Faculty of Medicine, Erciyes University, Kayseri, Turkey

Subjects: Data from 122 patients under 13 years of age who underwent mini-PCNL were reviewed retrospectively. The patients were classified into two groups according to the dilatation size of 16 F (group 1) and 20 F (group 2).

Intervention: Mini-PCNL using 16 F and 20 F sheath

Main outcome measures: Comparison of efficiency and complications between two different size access sheaths which are commonly used for mini-PCNL in pediatric population.

Results: Mean ages of both groups were 5.1 ± 3.3 years. The median stone burden was 200 (100 - 400) mm² in group 1 and 225 (120 - 300) mm² in group 2. There was no statistically significant difference between groups' data in terms of stone localization, stone burden, operation time, hemoglobin drop, nephrostomy duration and length of hospital stay. Fluoroscopy time was significantly lower in group 1 than group 2 (median 4 vs. 6 minutes respectively, p <0.009). The complication rates did not differ between the groups according to the modified Clavien classification system.

Conclusions: We found no difference between 16 F and 20 F percutaneous access dilatation of the kidney in terms of stone-free rates and complications. However, mini-PCNL procedure using 16 F sheath appears to decrease fluoroscopy time and exposure to radiation as compared to 20 F procedure.

KEYWORDS: mini percutaneous nephrolithotomy, pediatric age, stone surgery, urolithiasis

INTRODUCTION

Stone disease has more propensity of recurrence in the pediatric population than in adults because of predisposition factors like anatomical and metabolic abnormalities, genetic factors, malnutrition and infections[1]. Therefore, it is becoming increasingly important to use minimal invasive techniques for treatment of pediatric stone disease. Recently, open surgery procedures have become almost completely obsolete. Minimally invasive procedures like shock wave lithotripsy (SWL), percutaneous nephrolithotomy (PCNL), and retrograde intrarenal surgery have been used[2]. At first, adult type PCNL instruments and sheaths 24-30 French (F) percutaneous access sheaths were used for pediatric patients with renal stones. These are both overlarge for children’s relatively small kidneys and associated with complications such as bleeding and damage to the renal parenchyma[3]. In the last decade, standard PCNL instruments have been miniaturized to decrease morbidity. Helal et al first defined a technique for pediatric stone disease using 10 F pediatric cystoscope through 16 F size access tract[4]. Minimally invasive PCNL (mini-PCNL or Mini-Perc) procedure in pediatric population was first described by Jackman et al by using 11 F access tract[5]. Since then, mini-PCNL procedures have developed. Besides, ultra-mini PCNL and micro-PCNL have become more popular[6-8].

The mini-PCNL procedure is the general name given to PCNL procedures that are performed via
smaller percutaneous access dilatation lower than 20 F [9]. Percutaneous dilatation size and preferred nephroscope size may vary according to the age of the child, size of stone, dilatation degree of the kidney and the preference of the surgeon. It is obvious that a smaller nephroscope applies less force to the renal parenchyma, infundibulum and calyx neck. It has been reported that dilatation size is one of the main parameters that affect complications [10].

There are many studies that compare the outcomes between standard PCNL with mini-PCNL [11,12]. However, it is still unclear what size of the access sheath is more appropriate for the stone burden. There is a paucity of literature comparing the outcomes of the size of sheath in mini-PCNL in pediatric groups which match with age and sex. In this clinical study, we compared the efficiency and complication rates of mini-PCNL procedure in pediatric population using 16 F and 20 F access sheaths.

**SUBJECTS AND METHODS**

The records of 122 cases under 13 years of age who underwent mini-PCNL for renal stone disease between February 2011 and February 2017 in a single center were evaluated retrospectively. This study was approved by the Institutional Ethics Committee. Informed consents were provided by parents of all the cases before the operation. Preoperative patients’ records were reviewed including complete blood cell counts, blood urea levels, serum creatinine levels, coagulation tests, urine analyzes, and urine culture results. The patients who had positive urine culture results were treated with appropriate antibiotics. Radiological evaluation was performed with plain Kidney-Urinary-Bladder (KUB) radiography and ultrasound imaging. Computerized tomography was performed if required. Patients whose kidney stones were larger than 20 mm were treated with mini-PCNL. Stones which were 10 - 20 mm localized in the lower calyx or unbroken by SWL were treated with mini-PCNL. Stone burden was calculated by multiplying the two longest distances of stone as millimeters. A single dose of Ceftriaxone that calculated for weight was used for preoperative prophylaxis in all patients. Stone fragments smaller than 3 mm were considered as clinically insignificant residual fragments, which is named if stones are localized in more than two calyx. The patients were classified into two groups which matched with age and sex according to the percutaneous dilatation size of 16 F (group 1) and 20 F (group 2).

**Technique**

All mini-PCNL procedures were performed under general anesthesia and prone position. An open-end ureteric catheter (5F) was inserted into the renal pelvis with fluoroscopy guidance in the lithotomic position. The temperature of the irrigation fluid (0.9% NaCl) was kept between 24 - 26 °C to avoid hypothermia.

**SUBJECTS AND METHODS**

The records of 122 cases under 13 years of age who underwent mini-PCNL for renal stone disease between February 2011 and February 2017 in a single center were evaluated retrospectively. This study was approved by the Institutional Ethics Committee. Informed consents were provided by parents of all the cases before the operation. Preoperative patients’ records were reviewed including complete blood cell counts, blood urea levels, serum creatinine levels, coagulation tests, urine analyzes, and urine culture results. The patients who had positive urine culture results were treated with appropriate antibiotics. Radiological evaluation was performed with plain Kidney-Urinary-Bladder (KUB) radiography and ultrasound imaging. Computerized tomography was performed if required. Patients whose kidney stones were larger than 20 mm were treated with mini-PCNL. Stones which were 10 - 20 mm localized in the lower calyx or unbroken by SWL were treated with mini-PCNL. Stone burden was calculated by multiplying the two longest distances of stone as millimeters. A single dose of Ceftriaxone that calculated for weight was used for preoperative prophylaxis in all patients. Stone fragments smaller than 3 mm were considered as clinically insignificant residual fragments, which is named if stones are localized in more than two calyx. The patients were classified into two groups which matched with age and sex according to the percutaneous dilatation size of 16 F (group 1) and 20 F (group 2).

**Technique**

All mini-PCNL procedures were performed under
Statistical analysis

Using the SPSS statistical package (version 15.0; SPSS, Inc., Chicago, IL, USA), data was analyzed. Data was given as median (percentiles 25% - 75%) and frequencies as percentages. Normality was evaluated using the Shapiro-Wilk test. Abnormally distributed data was compared with the Mann-Whitney U test. To evaluate categorical data, the Pearson Chi-square test was used. P-value <0.05 was considered statistically significant.

RESULTS

A total 122 children who underwent mini-PCNL were evaluated in this study. Groups of PCNL have been equalized according to age and sex for homogeneous distribution between groups. It was noted that the children in each group had the same age, were same in number and the same sex. Mean age of each group was 5.1 ± 3.3 years (38 male, 23 female) and median age of each group was 4 years (25th and 75th quartiles 2 and 8 respectively; range: 1 to 13 years). The median stone burden was 200 mm² in group 1 and 225 mm² in group 2. The most frequent localizations of stones were pelvis and multiple calyces in both groups, respectively. The percentages of pelvis and multiple caliceal stones were 45.9 - 27.9% in group 1 and 62.3 - 13.1% in group 2, respectively. The percentages of staghorn stones were 9.8% in group 1 and 13.1% in group 2. Comparisons of groups’ data according to the sheath size of percutaneous access are summarized in Table 1. There were no statistically significant differences between groups’ data in terms of stone laterality, stone localization, stone burden, operation time, hemoglobin drop, nephrostomy duration and length of hospital stay. Fluoroscopy time was significantly lower in group 1 than group 2 (p <0.009) (median 4 vs. 6 minutes, respectively). The median operative time was 80 minutes in group 1 and 70 minutes in group 2. No statistically significant difference was present when initial stone-free rates were compared (86.9% in group 1, 78.7% in group 2). These rates increased to 95.1% and 90.2% with auxiliary treatment methods (SWL or mini-PCNL), respectively. There was also no statistically significant difference between the groups in terms of final stone-free success rate. The complication rates did not differ between the groups according to the modified Clavien classification system (Table 2). Three patients (4.9%) in group 1 and four patients (6.5%) in group 2 had fever that decreased with symptomatic treatment in the postoperative period (grade I). While two patients (3.2%) received blood transfusion in group 2, no patients received in group 1 (grade II). Four patients (6.5%) in group 1 and two patients (3.2%) in group 2 were treated with antibiotics due to urinary tract infection in the postoperative period (grade II). While a total of three patients (4.9%) experienced grade IIIb Clavien complications in group 1, four patients

<table>
<thead>
<tr>
<th>Table 1: Demographic data of patients</th>
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<tbody>
<tr>
<td><strong>Patient characteristics</strong></td>
</tr>
<tr>
<td>Number of cases</td>
</tr>
<tr>
<td>Gender (male:female)</td>
</tr>
<tr>
<td>Side of operation (right:left:bilateral)</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Stone localization (n, %)</td>
</tr>
<tr>
<td>Upper pole calyx</td>
</tr>
<tr>
<td>Lower pole calyx</td>
</tr>
<tr>
<td>Pelvis</td>
</tr>
<tr>
<td>Multiple calyx</td>
</tr>
<tr>
<td>Staghorn</td>
</tr>
<tr>
<td>Number of access (n, %) (1:2)</td>
</tr>
<tr>
<td>Stone burden (mm²)</td>
</tr>
<tr>
<td>Operation time (min)</td>
</tr>
<tr>
<td>Fluoroscopy time (min)</td>
</tr>
<tr>
<td>Hemoglobin drop (g/dl)</td>
</tr>
<tr>
<td>Nephrostomy time (days)</td>
</tr>
<tr>
<td>Length of hospital stay (days)</td>
</tr>
<tr>
<td>Initial stone-free rate (%)</td>
</tr>
<tr>
<td>Auxiliary procedure (n, %)</td>
</tr>
<tr>
<td>SWL</td>
</tr>
<tr>
<td>Mini-PCNL</td>
</tr>
<tr>
<td>Final stone-free rate (%)</td>
</tr>
</tbody>
</table>

*P: Pearson Chi-Square; b: Mann-Whitney U test; *: Significant at 0.05 level

Data were given as median (25% and 75% percentiles)

SWL: shock wave lithotripsy; Mini-PCNL: minimally invasive percutaneous nephrolithotomy
(6.5%) experienced the same in group 2. Due to urine leak from the nephrostomy tract, double J stent was inserted into the renal pelvis in three patients (4.9%) in both groups. One patient (1.6%) had blood retention requiring cystoscopy in group 2. None of the patients had any major complications.

**DISCUSSION**

Minimally invasive treatment of kidney stones has evolved dramatically in the last four decades. SWL is the treatment procedure for most pediatric renal stones. According to the European Association of Urology guidelines, PCNL is recommended as the primary treatment option for large renal stones (>20 mm), and also for stones that are 10 - 20 mm in size in the lower renal pole[19]. Standard PCNL access sheaths are large (24 – 32 F), especially for the treatment of large renal stones, and associated with high risk of bleeding, renal scarring and more pain. For this reason, smaller access sheaths and procedures have been developed, primarily in pediatric patients[5]. The main goal of surgical treatment of urinary stone disease with smaller instruments is to achieve high stone clearance with minimal complications. The use of smaller instruments is also increasing in adult patients due to the lower risk of complications[17]. Lately, the access sheaths have been reduced in size from standard 30 F access down to 20 F or less, such as mini-PCNL, ultramini-PCNL (11 - 13 F) and now, micro-PCNL (4.8 F). The use of the mini-PCNL technique is becoming increasingly popular in the treatment of kidney stones in pediatric populations because of the small kidneys and their low tolerance to blood loss.

Mini-PCNL has some advantages including decreased blood loss, increased maneuverability, less postoperative pain and decreased hospital stay[18]. However, mini-PCNL has some disadvantages such as prolonged operation time and difficulty in removing residual stone fragments because of necessity to disintegrate stones into small enough fragments to fit through a reduced size sheath. Celik et al reported the number of blood transfusion units in groups that used 26 F (n = 82), 20 F (n = 89), and 12 F (n = 50) tract sizes as 2, 1, and 0, respectively. They reported that the drop in hemoglobin was significantly lower in the 12 F group[11]. Kukreja et al reported that the 22 F tract size was associated with less blood loss than standard dilatation (28 F)[10]. Another study which compared the different tract sizes (26 F, 20 F, 14 F) in PCNL reported that more blood transfusions were performed when 26 F and 20 F tract sizes were used than with 14 F tract size[10]. Overall, the blood transfusion ratio was only 1.6% in our study. We routinely did not control hemoglobin value of every patient in the postoperative period unless more bleeding occurred during the operation. In our study, solely two patients in group 2 received a blood transfusion. No patient received blood transfusion in group 1. There were no significant differences regarding hemoglobin drop between the groups.

Celik et al reported their stone burden as 126 mm² in the 12 F group, 168 mm² in the 20 F group and 208 mm² in the 26 F group. Their stone-free rate was 78% in the 12 F group, 75.8% in 20 F group, and 71.4% in the 26 F group. The reason why higher success rate in the 12 F group was considered is the relatively lower stone burden. In our study, there was similar stone burden between the groups, and stone free rate was higher in group 1, but this difference was not statistically significant. A recently published review reported initial stone free rates of mini-PCNL series ranging from 80.6% to 91.9%. Stone burden is also ranging from 170 mm² to 1456 mm²[19]. In our study, overall stone burden was 200 mm² and overall stone free rate was 86.8% and showed correlation with these studies. There was no statistically significant difference between groups in terms of stone burden and stone-free rates.

Theoretically, a lower calibration access size may increase the operation time and may not be preferred for larger stones. Giusti et al reported from their study to evaluate the result of mini PCNL and standard PCNL that operation time was longer in mini PCNL than standard PCNL (155.5 vs. 106.6 min, respectively)[20].

<table>
<thead>
<tr>
<th>Modified Clavien Grading System</th>
<th>Group 1 (16 F) (n = 61)</th>
<th>Group 2 (20 F) (n = 61)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (n, %)</td>
<td>3 (4.9)</td>
<td>4 (6.5)</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>3 (4.9)</td>
<td>4 (6.5)</td>
<td></td>
</tr>
<tr>
<td>Grade 2 (n, %)</td>
<td>4 (6.5)</td>
<td>4 (6.5)</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4 (6.5)</td>
<td>2 (3.2)</td>
<td></td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>0</td>
<td>2 (3.2)</td>
<td></td>
</tr>
<tr>
<td>Grade 3b (n, %)</td>
<td>3 (4.9)</td>
<td>4 (6.5)</td>
<td></td>
</tr>
<tr>
<td>Requiring DJ stent insertion</td>
<td>3 (4.9)</td>
<td>3 (4.9)</td>
<td></td>
</tr>
<tr>
<td>for urine leakage &gt; 24h</td>
<td>0</td>
<td>1(1.6)</td>
<td></td>
</tr>
</tbody>
</table>

*Pearson Chi-Square*
Zeng et al reported operation time as 77.5 minutes using 14 - 16 F percutaneous access and Resorlu et al reported operation time as 76.3 minutes using 12 - 20 F percutaneous access. In our study, the overall operation time was median 80 minutes. Although group 1’s operation time was longer than group 2 (80 vs. 70 minutes, respectively) the difference was not significant (p = 0.265). This prolongation of operation time is acceptable when considering that none of the patients required any blood transfusion.

Fluoroscopy time was significantly longer in group 2 than group 1 (6 vs. 4 minutes respectively, p = 0.009). Saad et al reported a fluoroscopy time of 3.1 ± 1.1 minutes from their study which used 22 F access dilatation. Sakr et al reported the fluoroscopy time as 4.3 ± 1.3 minutes in their study which used 16.5 F dilatation tract in 81 renal units[21]. In our opinion, larger sheaths require longer fluoroscopy usage to access collecting renal system. The longer duration of fluoroscopy in group 2 may be considered a disadvantage when exposure to radiation is concerned in the pediatric age group.

The composition of the stones which were analyzed was recorded in 44 cases. Stones were composed of calcium oxalate in 54.5% of cases, cystine in 13% of cases, and carbonate apatite in 9% of cases. The remaining stones (22% of cases) consisted of mix type (uric acid ± magnesium ammonium phosphate ± calcium oxalate ± calcium phosphate ± calcium carbonate ± carbonate apatite).

Mini-PCNL is a safer procedure for postoperative blood loss when compared with adult dilatation size (26 - 30 F). So, it may be unnecessary to check hemoglobin levels for every patient, unless there is any extraordinary preoperative situation.

Previous studies reported that ratios of grade I and II (fever and urinary tract infection) complications, which were the most common ones, were ranging from 8.5% to 23%[20]. Grade III and IV complications, which are considered as major complications, are rare (0 - 13.6%) [22,23]. Total complications vary from 11 to 37.9% in a review[19]. In our study, overall minor complications (Clavien 1 and 2) were 11.4% in group 1 and 13.1 in group 2. Grade IIIb complications were 4.9% and 6.5% respectively and there was no Grade IV complication. Our complication rates were similar to previous studies and there were no statistically significant differences between the groups. Therefore, both 16 F and 20 F access sheaths may be safely used in a pediatric patient group.

CONCLUSION

We found no difference between 16 F and 20 F percutaneous access dilatation of the kidney in terms of efficiency and complications. However, mini-PCNL procedure using 16 F sheath appears to decrease fluoroscopy time and exposure to radiation, as compared to 20 F procedure.

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REFERENCES

Case Report

A rare case of multiple myeloma and cast nephropathy involving renal allograft

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ABSTRACT

Post-transplantation lymphoproliferative disorder (PTLD) is an uncommon but well-recognized complication of solid organ and bone marrow transplantation. The overall incidence of PTLD is 1.5% in all solid organ transplant recipients. Multiple myeloma (MM) associated cast nephropathy is rarely seen after solid organ transplantation, estimated at <4% of all PTLD. Our 45-year-old male patient presented with chest pain and a rise in serum creatinine after 2.3 years of renal transplant. He has MM without involving peripheral blood and other lymph nodes / organs. He was treated with therapeutic plasma exchange and Bortezomib. Some recent observations show that abnormalities in immune dysregulation with high level of immunosuppressive therapy may precede the development of MM, leading to poor outcome of renal allograft as well as patient survival.

INTRODUCTION

Malignancy is an important long-term complication of a successful renal transplantation. The major reasons for this increased risk are thought to be perturbation in immunosurveillance mechanisms secondary to the chronic use of immunosuppressive agents and infection with oncogenic virus[1]. Some of the malignancies seen with increased frequency include skin cancers, genitourinary tumors, lymphomas, Kaposi’s sarcoma and gastrointestinal malignancies. The prevalence of neoplasm is reportedly 14% in first 10 years and increased to 40% by 20 years post-transplant. Amongst the hematological malignancies occurring post-transplant, lymphomas are the most common, followed by leukemias and multiple myeloma (MM). The overall incidence of post-transplant lymphoproliferative disorders (PTLD) is about 1.5% in all solid organ transplant recipients. Amongst all solid organ transplant recipients, renal allograft recipients have the lowest frequency of PTLD (<1%). MM is rarely seen after solid organ transplantation, estimated at <4% of all PTLD. Renal allograft recipients are at 4.4 times higher risk of developing MM and rarely associated with cast nephropathy as compared to general population[2,3]. It is difficult to establish whether the immune dysregulation which characterizes MM is a phenomenon that precedes or follows malignant disease[4].

CASE REPORT

A 45-year-old male with end stage renal disease secondary to hypertension was subjected to renal transplantation 2.3 years ago with wife’s kidney (HLA 1/6 match). He had undergone hemodialysis twice before transplantation. Induction was done with rabbit anti-thymocyte globulin, 0.75 mg. He was maintained on triple immunosuppression of Tacrolimus, 0.08 mg/kgBW/ day, Mycofenolate sodium, 720 mg twice
a day, and Prednisone, 20 mg/day decreased to 10 mg/day after 1 month. He was discharged after 3 weeks with serum (s.) creatinine (SCr) of 1.25 mg/dL. Posttransplant period was uneventful. After 3 months, SCr increased to 1.6 mg/dL with rise in Tacrolimus levels of 17 ng/ml (reference range: 4 to 8 ng/ml). Tacrolimus dose was reduced to 0.06 ng/ml. SCr then reduced to 1.13 mg/dL. After 2 uneventful years posttransplant, he presented with chest pain, breathlessness and rise in SCr to 7.71 mg/dL. X-ray chest showed pleural effusion and collapsed left lung with right second rib margin erosion. Renal allograft biopsy performed revealed de novo cast nephropathy with acute T+B-cell mediated rejection, C4d positive in 40% peritubular capillaries (Figure 1). He was anti-rejected with methylprednisone, 500 mg/day x 3 days and immunosuppression regime was switched to Cyclosporin 3 mg/kgBW/day, Prednisone 10 mg/day and Mycofenolate sodium 720 mg twice a day. Further radiological evaluation was performed which included X-ray skull, spine and pelvis along with CT-chest. CT-chest was suggestive of multiple lytic lesions involving ribs on both sides (Figure 2). X-ray skull showed multiple punched out lytic lesions. Spine and pelvic bones appeared normal. Lab investigations revealed serum protein of 6 gm/dL with albumin/globulin ratio of 3.6/2.4 and normal S. electrophoresis with absence of M-Band. Free kappa chain was elevated to 31.8 mg/L (reference range: 3.3 to 19.4 mg/L) and free lambda chain to 5892.2 mg/L (reference range: 5.71 to 26.3 mg/L) with ratio of 0.01 (reference range: 0.26-1.65). His S.Calcium was 10.2 mg/dL (reference range: 8.5 to 10 mg/dL), S. uric acid was 6.5 mg/dL and urine albumin was +2 with absence of Bence Jones proteins. Bone marrow aspiration was unremarkable; however trephine biopsy was suggestive of multiple myeloma (focal interstitial pattern) (Figure 3a-b). He was seronegative for Epstein-Barr virus (EBV) and cytomegalovirus infections. At this stage, immunosuppression was stopped. He was treated anti-rejected with methylprednisone, 500 mg/day x 3 days and immunosuppression regime was switched to Cyclosporin 3 mg/kgBW/day, Prednisone 10 mg/day and Mycofenolate sodium 720 mg twice a day. Further radiological evaluation was performed which included X-ray skull, spine and pelvis along with CT-chest. CT-chest was suggestive of multiple lytic lesions involving ribs on both sides (Figure 2). X-ray skull showed multiple punched out lytic lesions. Spine and pelvic bones appeared normal. Lab investigations revealed serum protein of 6 gm/dL with albumin/globulin ratio of 3.6/2.4 and normal S. electrophoresis with absence of M-Band. Free kappa chain was elevated to 31.8 mg/L (reference range: 3.3 to 19.4 mg/L) and free lambda chain to 5892.2 mg/L (reference range: 5.71 to 26.3 mg/L) with ratio of 0.01 (reference range: 0.26-1.65). His S.Calcium was 10.2 mg/dL (reference range: 8.5 to 10 mg/dL), S. uric acid was 6.5 mg/dL and urine albumin was +2 with absence of Bence Jones proteins. Bone marrow aspiration was unremarkable; however trephine biopsy was suggestive of multiple myeloma (focal interstitial pattern) (Figure 3a-b). He was seronegative for Epstein-Barr virus (EBV) and cytomegalovirus infections. At this stage, immunosuppression was stopped. He was treated
with 6 cycles of therapeutic plasma exchange with 4 doses of Bortezomib, 1.3 mg/m² on every third day. SCr was stabilized around 5.4 mg/dL and he was declared as a case of chronic graft dysfunction with multiple myeloma associated cast nephropathy and is maintained conservatively. He died 4 months after diagnosis.

DISCUSSION

The term PTLD was introduced in 1984 by Starzl[5]. PTLDs are a serious life-threatening complication of solid organ transplantation (SOT) and bone marrow transplantation leading to high mortality (30 to 60%). PTLD was reported to occur at a median of 6 months after SOT (80% within 1 year), although recent data suggest the interval is longer. Patients with early PTLD more often express EBV, whereas late onset disease (i.e. >12 months after SOT) is typically EBV-negative. PTLD represents a heterogeneous group of lymphoproliferative disorders which range from reactive, polyclonal plasmacytic hyperplasia to those that are morphologically and genotypically indistinguishable from typical non-Hodgkin’s lymphomas. PTLDs can be classified into three distinct categories; plasmacytic hyperplasia, polymorphic B-cell hyperplasia or lymphoma and multiple myeloma. PTLD in SOT is rare[6-8]. One Indian report by Joshi K et al mentions 27 cases of PTLD out of 2400 renal transplant recipients encountered 41.6 ± 38.6 months after transplantation[1]. Histology showed diffuse large B-cell lymphoma in over 70%, plasmacytoma in 4%, Burkitt’s lymphoma in 4% and T-cell lymphoma in 11%. Sheil et al., who reviewed more than 4000 renal transplant recipients over a period of 19 years, documented one case of myeloma amongst these[9]. X-sun et al reported higher number of MM in renal transplants other than heart and liver[10]. A rare cause of renal allograft dysfunction due to myeloma cast nephropathy in a patient with no prior history of MM before transplantation was reported by Goel et al[11]. Most of the patients present with lytic bone lesions, and serum and urinary paraproteinaemias. Our patient presented with chest pain with pleural effusion 2.3 years after renal transplantation; and light chain ratio of 0.01 (0.26 - 1.65) with lytic lesions in skull and ribs favored MM with light chain deposition disease which was confirmed on trephine biopsy. Interestingly, he has MM without involving peripheral blood and other lymph nodes/organisms. Out of 3730 renal transplants performed in last 25 years in our center, this is the first case of MM with cast nephropathy. Our patient died 4 months after diagnosis of this associated lesion, which suggests poor outcome of survival and renal allograft function.

CONCLUSION

MM and cast nephropathy are a rare complication noted in solid organ transplant recipients, which usually occurs 2 years after transplantation and may not be related to any viral infections. Long term prognosis is guarded.

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REFERENCES

Case Report

Burned out testicular germ cell tumor diagnosed with retroperitoneal seminoma: A case report

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ABSTRACT

A 34 year-old male was admitted with complaints of abdominal pain to our hospital. A 4 cm mass was detected on computed tomography scan in the right of the aorta. Physical examination of the patient was normal. In scrotal ultrasonography, there was a hypoechoic solitary lesion having the size of 18x21 mm in the right testis. Retroperitoneal mass was removed by laparotomy. One month after laparotomy, right radical orchiectomy was performed. Retroperitoneal seminoma and testicular intratubular germ cell neoplasia were the pathologies reported.

KEYWORDS: burned-out tumor, germ cell tumor, seminoma, testicular tumor

INTRODUCTION

The majority of testicular tumors are germ cell tumors (GCT, 98%) and are frequently seen in men between the ages of 15 and 35 years[1]. In the diagnosis, about 20% of patients may have metastatic disease[2]. It can be confusing to distinguish the primary tumor and nature of metastasis. Rarely seen “burned-out” testicular tumor is defined as GCT, characterized by histologic regression and disappearance of the primary testicular tumor lesion without any treatment[3]. Retroperitoneal seminoma is the rarest among extragonadal tumors, and tumor markers may not be elevated in them[4]. We report a case of burned out testicular tumor presenting as retroperitoneal seminoma.

CASE REPORT

A 34 year-old male presented with complaint of abdominal pain to our hospital. The physical examination of the patient was normal. Abdominal computed tomography showed retroperitoneal mass (4 cm) in the right of the aorta (Figure 1). Then, the patient underwent scrotal ultrasonography (USG). At scrotal USG, the left testis was normal while there was a hypoechoic solitary lesion having the size of 18x21 mm in the right testis. Biochemical values were within normal range. Alpha-fetoprotein (aFP) was detected as 2.4 IU/l (0 – 9 IU/l), beta-human chorionic gonadotropin (B-hCG) was 0.8 U/L (<1.2) and lactate dehydrogenase (LDH) was 188 IU/l (100 – 190 IU/l).

Treatment and diagnostic options were discussed with the patient, but the patient did not accept radical orchiectomy. Retroperitoneal mass was removed by laparotomy. Pathology report was seminoma (Figure 2). One month after laparotomy, right radical orchiectomy was performed. The pathologic evaluation of orchiectomy was reported as intratubular germ cell neoplasia (Figure 3). Twelve months after operation, there was no recurrence in the patient.

DISCUSSION

In the literature, burned out phenomenon in GCT is very rare[4-6]. In a 16-year retrospective study from Spain, a total of 17 spontaneously regressed testicular tumors have been identified in four centers which treats a population of 1.2 million people[5]. In a study from France during a period of 13 years, five cases of burned out testicular tumor have been reported[6]. There are two theories to elucidate burned out phenomenon. The first is spontaneous regression of a primary GCT.
after metastasis of the GCT. The other hypothesis is the de-novo development of a primary GCT in extra gonadal tissues[7]. Some studies suggest that primary retroperitoneal GCTs and primary testicular tumors with retroperitoneal metastases are two completely different diseases[8]. However, the definition of normal testicular pathology should be controversial in patients defined as primary retroperitoneal GCTs. Primary retroperitoneal GCT is probably seen as an undiagnosed primary metastatic disease of testicular tumor origin[9].

In our patient with retroperitoneal seminoma, he presented with complaints of abdominal pain without elevation of tumor markers (B-hCG, LDH, aFP). When there are no physical examination findings and absence of tumor markers, radiological imaging procedures are important. USG is the first preferred method as it is a non-invasive, easily accessible and relatively inexpensive technique. Echogenic abnormalities and calcifications can be observed in suspected areas on USG of burned-out tumors[6]. In our patient’s scrotal USG, there was a hypoechoenic solitary lesion of 18x21 mm in the right testis.

CONCLUSION
Burned-out phenomena are rare tumors, and specially with seminoma, the diagnosis can sometimes be difficult. In case of retroperitoneal seminoma with burned-out phenomenon, tumor markers may be normal. Testicular surgery should be practiced as soon as possible to confirm diagnosis and treatment.

REFERENCES
Case Report

Recurrent giant myofibroblastoma of a female breast leading to a diagnostic dilemma: A lesson learnt!

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ABSTRACT

Myofibroblastoma (MFB) is a rare benign mesenchymal tumor of the breast commonly reported in males. It is a spindle cell neoplasm exhibiting myofibroblastic differentiation with characteristic immunohistochemical staining. We report the case of a 68-year-old postmenopausal lady who had undergone left breast lump excision 4 months back that was reported as malignant, now presenting with a rapidly growing hard mass in the same breast with no palpable axillary lymph nodes. Metastatic work-up was negative and she was planned for a lumpectomy, frozen section and if malignant, proceed to a modified radical mastectomy. Frozen section revealed a benign tumor. The final histopathology was reported to be MFB of the breast. The purpose of this report is to highlight that MFB can also occur in postmenopausal women, can recur and the diagnostic dilemma of this condition, which could have led to a mastectomy, but was avoided.

KEYWORDS: breast, carcinoma, myofibroblastoma, recurrence, surgery

INTRODUCTION

Myofibroblastoma (MFB) of the breast is a rare benign neoplasm of mesenchymal origin that belongs to the family of the ‘benign spindle cell tumors of the mammary stroma’ and commonly occurs in men, but few cases have been reported in women[1]. Currently, it is believed that MFB occurs mainly in older men and postmenopausal women. The median age of presentation is 55 years. The incidence in women is on the rise in the last 2 decades and probably could be due to increased mammographic screening[2]. It is essential to diagnose and distinguish MFB from other spindle cell tumors and malignancy for deciding the exact line of management. Local excision is curative, with no evidence of recurrence or distant metastasis after a follow-up period of 15 years[3]. This seems to be the first case of a recurrent MFB in an elderly lady.

CASE REPORT

A 68-year-old lady from rural India with no comorbidities, who had undergone left breast lump excision 4 months back reported with a recurrent, rapidly growing lump at the previously operated site with no other associated symptoms. She was told that the previously excised lump was cancerous and required further treatment. Due to financial constraints, she was lost to follow-up, only to present with a large left breast lump to us. General examination was unremarkable. Examination of left breast revealed a single, 20x15cm, hard, lobular, mobile, nontender lump with slit-like nipple retraction but no discharge. The previous surgical scar had healed well with primary intention (Fig 1). The skin was pinchable all over the lump. Left axillary lymph nodes were not palpable. The right breast, axilla, bilateral supraclavicular fossa, per-abdominal and musculoskeletal examination did not reveal any abnormality. At this point, as the previous histopathology report was not available, a clinical diagnosis of a recurrent phyllodes tumor was made. The metastatic work-up was normal. As patient refused a mammogram and a fine needle aspiration cytology (FNAC)/trucut biopsy, she was planned for a lumpectomy, frozen section (FS) and if malignant, proceed to modified radical mastectomy.

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Intraoperatively, the lump was well capsulated and could be excised without any difficulty as there was no local infiltration either to the skin, pectoral fascia or the pectoralis major. FS indicated that it was a benign tumor but final diagnosis could be given only with a paraffin section. Hence, the incision was closed over a suction tube drain. Final histopathology revealed diffuse sheets and interlacing bundles of spindle shaped cells and stellate myofibroblasts replacing adipose tissue with plump elongated nuclei and eosinophilic cytoplasmic processes showing positivity with CD 34 immunohistochemistry (IHC) with free margins, that was consistent with a recurrent MFB of the breast (Fig 2). In this case, only CD 34 was tested, other markers such as desmin, S-100 and SMA were not done. With difficulty, we could procure the previous slides and a slide review confirmed it to be a MFB and not infiltrating duct carcinoma. She made a good postoperative recovery and on close follow-up after two years, has no local recurrence.

DISCUSSION

MFBs are considered to be fibroblastic cells with smooth muscle differentiation and normally play a key role in wound healing. Cytokines released cause fibroblasts to aggregate at the site of tissue injury. These cells then develop actin fibers and develop the ability to contract, transforming into myofibroblasts. This contractile ability makes wound healing faster[4].

First described in 1981 as a benign spindle cell breast tumor, it was later named as MFB in 1987[5,6]. The incidence of non-palpable MFB has increased with the use of routine screening mammography[7]. However, these tumors most often present as palpable breast masses, especially in men and generally present as unilateral, mobile, painless, slow growing breast masses, which are firm in consistency[2,6]. They are most commonly reported in the age group of 40 - 87 years[4]. Due to the rarity of these tumors and

<table>
<thead>
<tr>
<th>Reference</th>
<th>Reported cases</th>
<th>Number of females</th>
<th>Cytodiagnosis</th>
<th>Age of females (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bardales et al[5]</td>
<td>1</td>
<td>1</td>
<td>Spindle cell tumor, well differentiated</td>
<td>45</td>
</tr>
<tr>
<td>Deligeorgi-Politi et al[6]</td>
<td>2</td>
<td>1</td>
<td>Spindle cell tumor, benign</td>
<td>31</td>
</tr>
<tr>
<td>Simsir et al[7]</td>
<td>1</td>
<td>1</td>
<td>Phyllodes tumor</td>
<td>70</td>
</tr>
<tr>
<td>Odashiro et al[8]</td>
<td>2</td>
<td>2</td>
<td>Suggestive of MFB</td>
<td>77</td>
</tr>
<tr>
<td>Álvarez-Rodriguez et al[9]</td>
<td>6</td>
<td>1</td>
<td>Suspicious of malignancy</td>
<td>42</td>
</tr>
<tr>
<td>Salemis et al[10]</td>
<td>1</td>
<td>1</td>
<td>MFB</td>
<td>45</td>
</tr>
<tr>
<td>Present study</td>
<td>1</td>
<td>1</td>
<td>MFB</td>
<td>68</td>
</tr>
</tbody>
</table>

MFB: myofibroblastoma
scarce mention in literature, the influence of various demographic factors such as genre, race, presence of comorbid conditions or drug therapy on appearance of these tumors is not known. However, it is believed that certain cytokines, particularly TGF β and TNF play a key role in the genesis of these tumors. Mammary type MFB classically presents as a slow growing painless lump, with a slightly increased incidence in males (male to female ratio of 1:0.7). The mean size reported is 5.5 cm (range 2-13 cm) and there are no reported cases of metastasis after surgical excision.

MFB exhibit a wide range of histological patterns ranging from epitheloid, myxoid, lipomatous, fibrous and decidual variants that are characterized by absence of mammary ducts or lobules, and composed of bipolar spindle shaped cells arranged in fascicles interrupted by collagen bands. IHC is a must and are positive for vimentin and variably positive for desmin and SMA. However, S100, CD117 and they are positive for vimentin and variably positive for desmin and SMA. However, S100, CD117 and CD10 are consistently negative and these IHC features represent the myofibroblastic nature of the neoplastic cells, which was seen in our patient.

Investigations to rule out malignancy are required to plan further management. MFBs have no characteristic features on imaging. On sonomammogram, MFBs resemble fibroadenomas, appearing as well-circumscribed solid masses. Mammography shows well-circumscribed round to oval masses with no calcifications. Imaging modalities can seldom differentiate MFBs from other benign breast conditions such as hamartomas, lipomas or fibroadenomas.

Sometimes, nonspecific clinical and radiological appearance can lead to a diagnostic dilemma and the diagnosis is often made on core needle biopsy. In the past, MFB was thought to occur primarily in men, however, recent reports suggest that this rather benign condition occurs in both men and women. Table 1 shows reported cases of MFB occurring in women.

The differential diagnosis for MFB includes conditions such as spindle cell lipoma, angiomatoid fibroblastoma, soft tissue perineurioma, and nodular fasciitis. Spindle cell lipoma, another benign tumor comprised of CD 34 positive spindle cells with adipose tissue, closely resembles MFB, but does not stain with desmin, a pathognomonic feature of MFB.

A standard triple assessment, comprising of clinical examination, USG of breast and tissue diagnosis by either FNAC or core needle biopsy will lead to an accurate diagnosis. MFBs are treated with wide local excision. Due to the well encapsulated nature of this neoplasm, excision is easy with a good cleavage plane, as was in our patient. There have been no reports of metastasis, and local recurrence is unlikely if all margins are free of tumor. It has been recommended to follow-up these patients for a minimum of 24 months.

CONCLUSION

The importance in knowing about this benign, easy to treat condition is to avoid a wrong diagnosis from far more aggressive, malignant conditions, which will lead to overtreatment of a very benign condition. Recurrence probably occurred in our patient due to incomplete excision.

REFERENCES


Changing trends in epidemiology and antifungal susceptibility patterns of six bloodstream Candida species isolates over a 12-year period in Kuwait

Khan Z1, Ahmad S1, Al-Sweih N1,2, Mokaddas E1,3, Al-Banwan K1,4, Al-Fouzan W1,5, Al-Obaid I6, Al-Obaid K7, Asadzadeh M1, Jeragh A8, Joseph L1, Varghese S1, Vayalil S9, Al-Musallam O9

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3Department of Microbiology, Ibn-Sina Hospital, Shuwaikh, Kuwait.
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7Department of Microbiology, Mubarak Al-Kabeer Hospital, Jabriya, Kuwait.
8Department of Microbiology, Al-Adan Hospital, Hadyia, Kuwait.
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ABSTRACT
Changing trends in incidence and antifungal susceptibility patterns of six Candida species causing candidemia in Kuwait between 2006-2017 are reported. A total of 2075 isolates obtained from 1448 patients were analyzed. Identity of Candida species isolates was determined by phenotypic methods and confirmed by PCR amplification/PCR-sequencing of rDNA and/or MALDI-TOF MS. Antifungal susceptibility was determined by Etest. C. albicans accounted for 539 (37.22%) cases followed by C. parapsilosis (n = 502, 34.67%), C. tropicalis (n = 210, 14.5%), C. glabrata (n = 148, 10.22%), C. krusei (n = 27, 1.81%) and C. dubliniensis (n = 22, 1.5%). The comparative percent distribution of Candida species causing candidemia between 2006-2011 and 2012-2017 was as follows: C. albicans 41.8% and 33.1%, C. parapsilosis complex 32.01% and 37.04%, C. tropicalis 13.59% and 15.31%, and C. glabrata 8.77% and 11.51%, C. krusei 2.0% and 1.7%, and C. dubliniensis 1.75 and 1.3%, respectively. Three of 371 C. albicans isolates during 2006-2011 and five of 363 during 2012-2017 were resistant to fluconazole. Among C. parapsilosis isolates, one of 310 during 2006-2011 and 21 of 446 during 2012-2017 were resistant to this drug. Furthermore, at an epidemiologic cutoff value (ECV) of \( \leq 0.5 \) μg/ml, 70.1% C. albicans isolates were wild-type for fluconazole during 2006-2011 and 93.4% during 2012-2017. Clonal spread of fluconazole-resistant C. parapsilosis in one major hospital was documented. An 8.8% shift in favor of non-albicans Candida species with concomitant increase in MICs between the two periods preludes emergence of fluconazole-resistant candidemia cases in Kuwait.
Economic burden of multiple sclerosis on Kuwait health care system

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2Department of Neurology, Ibn Sina Hospital, Sabah Medical Area, Kuwait.
3Department of Neurology and Psychiatry, Minia University, Minia, Egypt.
4Department of Medicine, Faculty of Medicine, Kuwait University, Jabriya, Kuwait.
5Division of Neurology, Department of Medicine, Amiri Hospital, Sharq, Kuwait.


ABSTRACT

BACKGROUND
Multiple Sclerosis (MS) is a chronic neurological disease with heavy economic and social burdens resulting in significant disability.

OBJECTIVE
This study aims to (1) measure the cost of health resources utilization by MS patients and (2) to examine the difference in utilization and its attributed costs amongst patients who may have a different course of MS and expanded disability status scale (EDSS) scores.

METHODS
A cross-sectional study using Kuwait National MS registry was conducted to estimate the costs of utilization of resources from 2011 to 2015.

RESULTS
Between the period 2011-2015, 1344 MS patients were included in the registry. The average annual cost per MS patient has increased from $10,271 in 2011 to $17,296 in 2015. Utilization of disease-modifying therapies (DMTs) was the main driver of costs reaching 89.9% in 2015. Throughout the five-year period, the occurrence of relapses decreased from 21.8% to 12.2% (p <0.0001). During this same period, ambulatory relapse treatment increased by 5.8% while hospitalizations decreased by 2.6%. Patients with a moderate EDSS score (3.5-6) had the highest average cost (p<0.0001) compared to mild and severe EDSS scores.

CONCLUSIONS
Multiple sclerosis has been a significant economic burden on the Kuwait healthcare system. DMTs are the main driver of cost.
Forthcoming Conferences and Meetings

Compiled and edited by
Vineehta Elizabeth Mammen

Kuwait Medical Journal 2019; 51 (2): 216 - 221

Sports Medicine, Pediatric Allergy & Immunology, Telemedicine, and Electronic Medical Records
Jun 01 - 08, 2019
United States / Fort Lauderdale, Florida
Contact: Continuing Education, Inc.
Phone: 1-800-422-0711
Email: contactus@continuingeducation.net

14th World Congress of Biological Psychiatry
Jun 02 - 06, 2019
Canada / Vancouver, British Columbia
Contact: World Federation of Societies of Biological Psychiatry (WFSBP)
Phone: 49-40-670882 90
Email: info@wfsbp.org

International Conference on HIV-AIDS, STD's & STI's by SciTech Conferences
Jun 03 - 04, 2019
United Kingdom / London, England
Organized by: SciTech Conferences
Phone: 215-664-5492
Email: hiv@scitechconferences.org

Introduction to Good Clinical Practice (GCP) - Wessex (Jun 03, 2019)
Jun 03, 2019
United Kingdom / Wessex, England
Contact: National Institute for Health Research (NIHR)
Phone: 023 8059 5628
Email: sharon.davies-dear@uhs.nhs.uk

Primary Care Issues in Internal Medicine and Hospital Medicine
Jun 03 - 07, 2019
United States / San Diego, California
Contact: American Medical Seminars (AMS)
Phone: 941-388-1766
Email: mail@ams4cme.com

Inflammation, Pain Management & Functional Nutrition Therapy Course
Jun 04, 2019
United States / Albuquerque, New Mexico
Contact: CE International
Phone: 214.624.9870
Email: info@ceinternational.com

5th World Parkinson Congress (WPC)
Jun 04 - 07, 2019
Japan / Kyoto, Kansai
Contact: World Parkinson Coalition (WPC)
Phone: +1 514 287 9898 ext. 335
Email: secretariat@worldpdcoalition.org

European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Annual Meeting 2019
Jun 05 - 08, 2019
United Kingdom / Glasgow, Scotland
Contact: European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)
Phone: +41 (0)22 527.7630
Email: info@espghan.org

16th International Conference on Innate Immunity
Jun 07 - 12, 2019
Greece / Rhodes, South Aegean
Contact: Aegean Conferences
Phone: +1.610.527.7630
Email: info@aegeanconferences.org

Psychopharmacology in Plain English: Essential Information for Mental Health Professionals - Raleigh
Jun 07, 2019
United States / Raleigh, North Carolina
Contact: PESI HealthCare
Phone: (800) 844-8260
Email: info@pesi.com

Paris 5th International Conference on “Medical, Medicine and Health Sciences” (MMHS- 2019 Paris)
France / Jun 08 - 09, 2019
Contact: Academic Fora
Phone: (+6) 03 6735 6566
Email: par269@academicfora.com

2019 International Conference on Opioids
Jun 09 - 11, 2019
United States / Boston, Massachusetts
Contact: Boston University School of Medicine
Continuing Medical Education (BUSM CME)
Phone: 617.358.5005
Email: cme@bu.edu
2019 Essential Procedures in Emergency Medicine Course (Jun 11, 2019)
Jun 11, 2019
United States / Baltimore, Maryland
Contact: University of Maryland School of Medicine
Phone: 410-706-7478
Email: admissions@som.umaryland.edu

World Society for Reconstructive Microsurgery (WSRM) World Congress 2019
Jun 12 - 15, 2019
Italy / Bologna, Emilia-Romagna
Contact: World Society for Reconstructive Microsurgery (WSRM)
Phone: 1-312-263-7150
Email: kristagreco@isms.org

Complex Coronary Cases (CCC) Symposium 2019
Jun 13 - 14, 2019
United States / New York City, New York
Contact: Gaffney Events
Phone: 425.442.1314
Email: jennifer@gaffneyevents.com

EACPT 2019 - 14th Congress of the European Association for Clinical Pharmacology and Therapeutics
Jun 29 - Jul 02, 2019
Sweden / Stockholm, Stockholm
Contact: European Association for Clinical Pharmacology and Therapeutics (EACPT)
Phone: +45 3946 0508
Email: mari.ekstrom@mci-group.com

3rd World Congress & Expo on Nanotechnology & Materials Science
Jul 01 - 02, 2019
United Arab Emirates / Dubai, Dubai
Contact: Biocore Group
Phone: +1-425-6052667
Email: nanotech.biocore@gmail.com

Hypermobility/Ehlers Danlos Syndrome in Adults & Children: Clinical assessment and management 2019 by NCORE
Jul 02, 2019
United Kingdom / Derby, England
Contact: National Centre of Rehabilitation Education (NCORE)
Phone: (01332) 254679
Email: dhft.ncore@nhs.net

2nd World Congress on Drug Safety and Pharmacovigilance
Jul 03 - 04, 2019
United Arab Emirates / Dubai, Dubai
Contact: Biocore Group
Phone: +1-425-6052667
Email: drugsafety.biocore@gmail.com

8th Congress of European Microbiologists - FEMS2019
Jul 07 - 11, 2019
United Kingdom / Glasgow, Scotland
Contact: Federation of European Microbiological Societies (FEMS) | Society for Applied Microbiology (SFAM)
Phone: +45 70 20 03 05
Email: info@cap-partner.eu

American Academy of Aesthetic Medicine Masters Course in Aesthetic Gynaecology, Dubai
Jul 07 - 08, 2019
United Arab Emirates / Dubai, Dubai
Contact: International Business Consult (IBC) Medical Services | American Academy of Aesthetic Medicine (AAAM)
Phone: +971 4 337 0400
Email: info@ibcme.com

Introduction to Emergency Medicine Ultrasound (POCUS) - 5 Day Course (Jul 08 - 12, 2019)
Jul 08 - 12, 2019
Australia / Gold coast, Queensland
Contact: Australian Institute of Ultrasound (AIU)
Phone: +61 7 552 66655
Email: info@aiu.edu.au

The 1st Congress on Women's Health Innovations and Inventions: Addressing Unmet Needs
Jul 09 - 11, 2019
Israel / Tel Aviv, Tel Aviv
Contact: ComtecMed
Phone: +972 3 566 6166
Email: womenshealth-marketing@comtecmed.com

British Society of Gerontology (BSG) Conference 2019
Jul 10 - 12, 2019
United Kingdom / Liverpool, England
Contact: British Society of Gerontology (BSG)
Phone: 07898 184893
Email: bsgconference2019@britishgerontology.org

World Congress on Food Science and Technology by Inovine Conferences
Jul 15 - 17, 2019
Italy / Rome, Lazio
Contact: Inovine Conferences
Phone: 1-408-648-2233
Email: foodtechnology@inovineconferences.com

26th International Meeting on Advanced Spine Techniques (IMAST) Conference
Jul 17 - 20, 2019
Netherlands / Amsterdam, Noord Holland
Contact: Scoliosis Research Society (SRS)
Phone: (414) 289-9107
Email: info@srs.org
Masters Training in **Reproductive Medicine and IVF** for Obstetricians and Gynaecologists - Part 1
Bangkok
Jul 23 - 24, 2019
Thailand / Bangkok, Bangkok
Contact: International Business Consult (IBC) Medical Services
Phone: +971 4 337 0400
Email: info@ibcme.com

American Academy of **Aesthetic Medicine** (AAAM) Level 1 Certificate Course in Aesthetic Medicine 2019
Jul 27 - 29, 2019
Netherlands / Amsterdam, North Holland
Contact: CBB Medical Training Pte Ltd | American Academy of Aesthetic Medicine (AAAM)
Phone: 65 31575910
Email: jessicamok@aaamed.org

**29th Annual Open Scientific Meeting by Musculoskeletal Infection Society (MSIS)**
Aug 02 - 03, 2019
United States / New York City, New York
Contact: Musculoskeletal Infection Society (MSIS)
Phone: (512) 301-7328
Email: info@msis-na.org

Stanford **Facial Nerve** Symposium
Aug 03, 2019
United States / Stanford, California
Contact: Stanford Center for Continuing Medical Education
Phone: (650) 724-9549
Email: ycervant@stanford.edu

9th International **Traditional and Complementary Medicine** Conference (INTRACOM)
Aug 03 - 05, 2019
Malaysia / Petaling jaya, Selangor
Contact: Ministry of Health Malaysia
Email: intracom2019@moh.gov.my

Intensive Review of **Nephrology** 2019
Aug 05 - 09, 2019
United States / Boston, Massachusetts
Contact: Harvard Medical School (HMS) | The Penzias Group
Phone: 781-999-1998
Email: betsy.ragan@penzias.com

**Blood-Brain Barrier Delivery** Summit (B3DD)
Aug 13 - 15, 2019
United States / Boston, Massachusetts
Contact: Hanson Wade
Contact No.: +44 (0)203 141 8700
Email: info@hansonwade.com

National Conference on **Addiction Disorders** (NCAD) East
Aug 15 - 18, 2019
United States / Baltimore, Maryland
Contact: Healthcare Made Practical (HMP) Communications LLC
Phone: 603-836-0329
Email: ceventurina@hmpglobal.com

**Alzheimer’s Disease** International (ADI) Asia Pacific Regional Conference
Aug 16 - 18, 2019
Malaysia / Kuala Lumpur, Kuala Lumpur
Contact: Alzheimer’s Disease International (ADI)
Phone: +44 20 79810880
Email: info@alz.co.uk

Pioneer Century Science (PCS) 3rd International Conference of **Neuroscience** (ICN-2019)
Aug 17 - 18, 2019
Portugal / Lisbon, Lisboa
Contact: Global Century Science Group
Phone: (+86) 010-52065931
Email: info@pcsconference.com

**Current Topics in Primary Care, Palliative Care, and Addiction Medicine**
Aug 17 - 24, 2019
United States / Honolulu, Hawaii
Contact: Continuing Education, Inc.
Phone: 1-800-422-0711
Email: contactus@continuingeducation.net

Internal Medicine for Primary Care: **Cardio/ENT/ID/OB**
Aug 18 - 22, 2019
United States / Wailea, Hawaii
Contact: Medical Education Resources (MER)
Phone: 303-798-9682
Email: info@mer.org

**Advanced Cranial Radiosurgery** - Introductory Course (Aug, 2019)
Aug 19 - 23, 2019
United States / Cleveland, Ohio
Contact: Cleveland Clinic Center for Continuing Education
Phone: 216.444.9990
Email: mycme@ccf.org
Total Joint Replacement Class by University Health Care System - Augusta, Georgia, USA (Aug 20, 2019)
Aug 20, 2019
United States / Augusta, Georgia
Contact: University Health Care System
Phone: 706-722-9011
Email: BEcchols@uh.org

3rd Annual Idiopathic Pulmonary Fibrosis (IPF) Summit 2019
Aug 27 - 29, 2019
United States / San Diego, California
Contact: Hanson Wade
Phone: +44 (0)203 141 8700
Email: georgina.fitzgerald@hansonwade.com

Middle East Meetings on Psychology, Psychotherapy and Mental Health
Aug 28 - 29, 2019
United Arab Emirates / Dubai, Dubai
Contact: Lexis Conferences Ltd
Phone: +3280070948
Email: meetings@lexisconferences.com

13th International Congress of the Asian Society Against Dementia & 6th Singapore International Neurocognitive Symposium
Aug 28, 2019
Singapore / Singapore, Singapore
Contact: National Neuroscience Institute (NNI)
Phone: (65) 6357 7095
Email: appointments@nni.com.sg

Asthma, Allergies, and Anaphylaxis Conference
Aug 29 - 30, 2019
Australia / Brisbane, Queensland
Contact: Ausmed Education Pty Ltd
Phone: (03) 9326 8101
Email: ausmed@ausmed.com.au

Principles of Shoulder Arthroplasty
Aug 30, 2019
Venezuela / Cartagena, Bolivar
Contact: AO Foundation
Phone: +41 81 414 21 171
Email: bas.wijburg@aorecon.org

Physical Activity and Exercise in the Management of Cardiovascular Disease Part II: Advanced Applications
Aug 31 - Sep 01, 2019
United Kingdom / Dunfermline, Scotland
Contact: British Association for Cardiovascular Prevention and Rehabilitation (BACPR)
Phone: 01252 854510
Email: vstockley@bacpr.com

Emergency Ultrasound for Rural and Remote Medicine - 3 Day POCUS Course - Australia
Sep 02 - 04, 2019
Australia / Ivanhoe, Victoria
Contact: Zedu Ultrasound Training Solutions (UTS)
Phone: 0422 000 750
Email: oriana@ultrasoundtraining.com.au

Pancreatic Cancer: Advances in Science and Clinical Care 2019
Sep 06 - 09, 2019
United States / Boston, Massachusetts
Contact: American Association for Cancer Research (AACR)
Phone: 215-440-9300
Email: aacr@aacr.org

Hot Topics in Pediatric Emergencies 2019
Sep 09 - 20, 2019
Italy / Rome, Lazio
Contact: Symposia Medicus
Phone: (800) 327-3161,
Email: info@symposiamedicus.org

Pain Management Programme (PMP) SIG Conference 2019
Sep 11 - 12, 2019
United Kingdom / Bristol, England
Contact: The British Pain Society (BPS)
Phone: 020 7269 7840
Email: info@britishpainsociety.org

Understanding Urodynamics 2019
Sep 11 - 12, 2019
United Kingdom / London, England
Contact: Royal College of Obstetricians and Gynaecologists (RCOG)
Phone: +44 20 7772 6423
Email: jthorn@rcog.org.uk

2019 Annual conference on Pharmaceutical & Drug Discovery by Nurtific
Sep 11 - 12, 2019
United Arab Emirates / Dubai, Dubai
Contact: Nurtific
Phone: 044 562 035
Email: info@nurtific.com

5th Abu Dhabi International Conference in Dermatology and Aesthetics (AIDA)
Sep 12 - 14, 2019
United Arab Emirates / Abu Dhabi, United Arab Emirates
Contact: MENA Conference
Phone: 971565033749
Email: jerico@menaconference.com
Advances in Critical Care Conference
Sep 13 - 14, 2019
United States / Houston, Texas
Contact: Michael E. DeBakey Department of Surgery at Baylor College of Medicine
Phone: 713-798-5755
Email: sholmes24@comcast.net

11th European Congress on Tropical Medicine and International Health (ECTMIH 2019)
Sep 16 - 20, 2019
United Kingdom / Liverpool, England
Contact: Royal Society of Tropical Medicine and Hygiene (RSTMH)
Phone: +44 (0)20 7405 2628
Email: amelia.finchem@rstmh.org

Comprehensive Bronchoscopy with Endobronchial Ultrasound September 2019
Sep 19 - 21, 2019
United States / Glenview, Illinois
Contact: American College of Chest Physicians (ACCP)
Phone: +1 (224) 521-9800
Email: kdaniels@chestnet.org

Ultrason for Rheumatology Practice
Sep 24 - 25, 2019
United Kingdom / Belfast City, North Ireland
Contact: British Society for Rheumatology (BSR)
Phone: 44 20 7842 0900
Email: nwalsh@rheumatology.org.uk

NRP - Neonate Resuscitation Program 7th Edition (Sep 25, 2019)
Sep 25, 2019
United States / Orange, California
Contact: Sure Fire CPR
Phone: (888) 277-3143
Email: info@surefirecpr.com

Challenges in Clinical Cardiology: A Case-Based Update 2019
Sep 27 - 29, 2019
United States / Chicago, Illinois
Contact: Mayo Clinic
Phone: +1 507-284-2511
Email: cvcme@mayo.edu

Advanced Medicine Congress (AMC) 2019
Sep 27 - 28, 2019
United Arab Emirates / Abu Dhabi, Abu Dhabi
Contact: Imperial College London Diabetes Centre (ICLDC)
Phone: +971 2 404 0800
Email: diabetessuae@iclcenter.ae

Physical Activity and Exercise in the Management of Cardiovascular Disease Part II: Advanced Applications (Sep, 2019)
Sep 28 - 29, 2019
United Kingdom / Manchester, England
Contact: British Association for Cardiovascular Prevention and Rehabilitation (BACPR)
Phone: 020 7380 1919
Email: vstockley@bacpr.com

International Society of Vascularized Composite Allotransplantation (ISVCA) 2019
Sep 30 - Oct 01, 2019
India / Noida, Uttar Pradesh
Contact: EventGurus
Phone: +91 9895322827
Email: ceo@eventgurus.net

2nd International Forum of Cardiology and Heart Diseases (IFCHD)
Oct 01 - 03, 2019
Germany / Berlin, Berlin
Contact: Innovinc International
Phone: 1-408-352-1010
Email: cardiology@innovinc.org

Phoenix World Burn Congress 2019
Oct 02 - 05, 2019
United States / Anaheim, California
Contact: The Phoenix Society for Burn Survivors, Inc.
Phone: (800) 888-2876,
Email: info@phoenix-society.org

Anaesthesia for Emergency Surgery 2019
Oct 02, 2019
United Kingdom / London, England
Contact: The Association of Anaesthetists of Great Britain and Ireland (AAGBI)
Phone: +44 (0)20 7631 1650
Email: info@aagbi.org

33rd Annual Fall Conference on High Risk Obstetrics
Oct 03 - 05, 2019
United States / Washington, Dist Of Col
Contact: Symposia Medicus
Phone: (800) 327-3161
Email: info@symposiamedicus.org
<table>
<thead>
<tr>
<th>Event</th>
<th>Location</th>
<th>Contact Details</th>
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</table>
| Advanced Therapies for Pediatric Obesity 2019                       | United States / Minneapolis, Minnesota | Contact: University of Minnesota - Continuing Professional Development  
Phone: 612-626-7600 
Email: cme@umn.edu |
| Ultrasonography for Intensivists and Emergency Medicine Clinicians 2019 | United States / Boston, Massachusetts | Contact: Harvard Medical School (HMS)  
Phone: 617-432-1000 
Email: hms-cme@hms.harvard.edu |
| Heart Rhythm Congress (HRC) 2019                                    | United Kingdom / Birmingham, England | Contact: British Heart Rhythm Society (BHRS) | Arrhythmia Alliance (A-A) UK  
Phone: +44 1789 867523  
Email: info@heartrhythmcongress.org.uk |
| World Cardiology & Heart Conference by SciTech Conferences          | United Arab Emirates / Dubai, Dubai | Contact: SciTech Conferences  
Phone: +1 215-664-5492  
Email: info@scitechconferences.com |
| Current Perspectives in Haematological Malignancies (Oct 09, 2019)   | United Kingdom / Edinburgh, Scotland | Contact: Hartley Taylor Medical Communications Ltd  
Phone: ++44 (0)1565 621967  
Email: kim@hartleytaylor.co.uk |
| 14th Annual Cardiometabolic Health Congress (CMHC)                  | United States / Chicago, Illinois | Contact: Cardiometabolic Health Congress (CMHC)  
Phone: 877.571.4700  
Email: info@cardiometabolichealth.org |
| 2019 - 20th International Conference on Research in Life-Sciences & Healthcare (ICRLSH) | United Arab Emirates / Dubai, Dubai | Contact: Eurasia Research  
Phone: +91 7290808650  
Email: convener@eurasiaresearch.info |
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| 4th World Congress and Expo on Immunology                           | United Arab Emirates / Dubai, Dubai | Contact: Scientific Federation  
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| Annual Radiology Meeting in UAE - ARM 2019                         | United Arab Emirates / Dubai, Dubai | Contact: INDEX Conferences & Exhibitions | Radiology Society of the Emirates (RSE)  
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| International Conference on Neurology and Cardiology by Citations International | United Arab Emirates / Dubai, Dubai | Contact: Citations International  
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| International Biochemistry Conference by Outlook Conferences (OLC)  | United Arab Emirates / Dubai, Dubai | Contact: Outlook Conferences (OLC)  
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| Breast cancer, Cardiology & Family Medicine Update                  | India / New Delhi, Delhi | Contact: The College of Family Physicians of Canada (CFPC)  
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WHO-Facts Sheet

1. Asthma
2. Congenital anomalies
3. Human rights and health
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5. Radon and health

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1. ASTHMA

KEY FACTS

• Asthma is one of the major noncommunicable diseases. It is a chronic disease of the air passages of the lungs which inflames and narrows them.
• Some 235 million people currently suffer from asthma. It is a common disease among children.
• Most asthma-related deaths occur in low- and lower-middle income countries.
• According to the latest WHO estimates, released in December 2016, there were 383 000 deaths due to asthma in 2015.
• The strongest risk factors for developing asthma are inhaled substances and particles that may provoke allergic reactions or irritate the airways.
• Medication can control asthma. Avoiding asthma triggers can also reduce the severity of asthma.
• Appropriate management of asthma can enable people to enjoy a good quality of life.

Asthma is a major noncommunicable disease characterized by recurrent attacks of breathlessness and wheezing, which vary in severity and frequency from person to person. Symptoms may occur several times in a day or week in affected individuals, and for some people become worse during physical activity or at night. During an asthma attack, the lining of the bronchial tubes swell, causing the airways to narrow and reducing the flow of air into and out of the lungs. Recurrent asthma symptoms frequently cause sleeplessness, daytime fatigue, reduced activity levels and school and work absenteeism. Asthma has a relatively low fatality rate compared to other chronic diseases.

Facts about asthma

• WHO estimates that 235 million people currently suffer from asthma. Asthma is the most common noncommunicable disease among children. Most deaths occur in older adults.
• Asthma is a public health problem not just for high-income countries; it occurs in all countries regardless of the level of development. Most asthma-related deaths occur in low- and lower-middle income countries.
• Asthma is under-diagnosed and under-treated. It creates substantial burden to individuals and families and often restricts individuals’ activities for a lifetime.

The causes

The fundamental causes of asthma are not completely understood. The strongest risk factors for developing asthma are a combination of genetic predisposition with environmental exposure to inhaled substances and particles that may provoke allergic reactions or irritate the airways, such as:
• indoor allergens (for example, house dust mites in bedding, carpets and stuffed furniture, pollution and pet dander)
• outdoor allergens (such as pollens and moulds)
• tobacco smoke
• chemical irritants in the workplace
• air pollution.

Other triggers can include cold air, extreme emotional arousal such as anger or fear, and physical exercise. Even certain medications can trigger asthma: aspirin and other non-steroid anti-inflammatory drugs, and beta-blockers (which are used to treat high blood pressure, heart conditions and migraine).

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Urbanization has been associated with an increase in asthma. But the exact nature of this relationship is unclear.

**Reducing the asthma burden**

Although asthma cannot be cured, appropriate management can control the disease and enable people to enjoy a good quality of life. Short-term medications are used to relieve symptoms. Medications such as inhaled corticosteroids are needed to control the progression of severe asthma and reduce asthma exacerbation and deaths.

People with persistent symptoms must take long-term medication daily to control the underlying inflammation and prevent symptoms and exacerbations. Inadequate access to medicines and health services is one of the important reasons for the poor control of asthma in many settings.

Medication is not the only way to control asthma. It is also important to avoid asthma triggers - stimuli that irritate and inflame the airways. With medical support, each asthma patient must learn what triggers he or she should avoid.

Although asthma does not kill on the scale of chronic obstructive pulmonary disease (COPD) or other chronic diseases, failure to use appropriate medications or to adhere to treatment can lead to death.

**WHO strategy for prevention and control of asthma**

WHO recognizes that asthma is of major public health importance. The Organization plays a role in coordinating international efforts against the disease. The aim of its strategy is to support Member States in their efforts to reduce the disability and premature death related to asthma.

**WHO’s programme objectives are:**

- surveillance to map the magnitude of asthma, analyse its determinants and monitor trends, with emphasis on poor and disadvantaged populations;
- primary prevention to reduce the level of exposure to common risk factors, particularly tobacco smoke, frequent lower respiratory infections during childhood, and air pollution (indoor, outdoor, and occupational exposure); and
- improving access to cost-effective interventions including medicines, upgrading standards and accessibility of care at different levels of the health care system.

**Global Alliance against Chronic Respiratory Diseases**

The Global Alliance against Chronic Respiratory Diseases (GARD) contributes to WHO’s work to prevent and control chronic respiratory diseases. It is a voluntary alliance of national and international organizations and agencies from many countries. It focuses on the needs of low- and middle-income countries and vulnerable populations, and fosters initiatives that are tailored to local needs.

**2. CONGENITAL ANOMALIES**

**KEY FACTS**

- An estimated 303,000 newborns die within 4 weeks of birth every year, worldwide, due to congenital anomalies.
- Congenital anomalies can contribute to long-term disability, which may have significant impacts on individuals, families, health-care systems, and societies.
- The most common, severe congenital anomalies are heart defects, neural tube defects and Down syndrome.
- Although congenital anomalies may be the result of one or more genetic, infectious, nutritional or environmental factors, it is often difficult to identify the exact causes.
- Some congenital anomalies can be prevented. Vaccination, adequate intake of folic acid or iodine through fortification of staple foods or supplementation, and adequate antenatal care are just 3 examples of prevention methods.
- Congenital anomalies are important causes of infant and childhood deaths, chronic illness and disability. Through the resolution on birth defects of the Sixty-third World Health Assembly (2010), Member States agreed to promote primary prevention and improve the health of children with congenital anomalies by:
  - developing and strengthening registration and surveillance systems
  - developing expertise and building capacity
  - strengthening research and studies on etiology, diagnosis and prevention
  - promoting international cooperation.

**Definition**

Congenital anomalies are also known as birth defects, congenital disorders or congenital malformations. Congenital anomalies can be defined as structural or functional anomalies (for example, metabolic disorders) that occur during intrauterine life and can be identified prenatally, at birth, or sometimes may only be detected later in infancy, such as hearing defects.

In simple terms, congenital refers to the existence at or before birth.
Causes and risk factors

Although approximately 50% of all congenital anomalies cannot be linked to a specific cause, there are some known genetic, environmental and other causes or risk factors.

Genetic factors

Genes play an important role in many congenital anomalies. This might be through inherited genes that code for an anomaly, or resulting from sudden changes in genes known as mutations.

Consanguinity (when parents are related by blood) also increases the prevalence of rare genetic congenital anomalies and nearly doubles the risk for neonatal and childhood death, intellectual disability and other anomalies. Some ethnic communities (such as Ashkenazi Jews or Finns) have a comparatively high prevalence of rare genetic mutations such as Cystic Fibrosis and Haemophilia C.

Socioeconomic and demographic factors

Low-income may be an indirect determinant of congenital anomalies, with a higher frequency among resource-constrained families and countries. It is estimated that about 94% of severe congenital anomalies occur in low- and middle-income countries. An indirect determinant, this higher risk relates to a possible lack of access to sufficient, nutritious foods by pregnant women, an increased exposure to agents or factors such as infection and alcohol, or poorer access to healthcare and screening. Factors often associated with low-income may induce or increase the incidence of abnormal prenatal development.

Maternal age is also a risk factor for abnormal intrauterine fetal development. Advanced maternal age increases the risk of chromosomal abnormalities, including Down syndrome.

Environmental factors

Maternal exposure to certain pesticides and other chemicals, as well as certain medications, alcohol, tobacco and radiation during pregnancy, may increase the risk of having a fetus or neonate affected by congenital anomalies. Working or living near, or in, waste sites, smelters or mines may also be a risk factor, particularly if the mother is exposed to other environmental risk factors or nutritional deficiencies.

Infections

Maternal infections such as syphilis and rubella are a significant cause of congenital anomalies in low- and middle-income countries.

More recently, the effect of in utero exposure to Zika virus on the developing fetus has been reported.
• screening for infections, especially rubella, varicella, and syphilis, and consideration of treatment.

Detection
Health care before and around the time of conception (preconception and peri-conception) includes basic reproductive health practices, as well as medical genetic screening and counselling. Screening can be conducted during the 3 periods listed:
• Preconception screening can be useful to identify those at risk for specific disorders or at risk of passing a disorder onto their children. Screening includes obtaining family histories and carrier screening, and is particularly valuable in countries where consanguineous marriage is common.
• Peri-conception screening: maternal characteristics may increase risk, and screening results should be used to offer appropriate care, according to risk. This may include screening for young or advanced maternal age, as well as screening for use of alcohol, tobacco or other risks. Ultrasound can be used to screen for Down syndrome and major structural abnormalities during the first trimester, and for severe fetal anomalies during the second trimester. Maternal blood can be screened for placental markers to aid in prediction of risk of chromosomal abnormalities or neural tube defects, or for free fetal DNA to screen for many chromosomal abnormalities. Diagnostic tests such as chorionic villus sampling and amniocentesis can be used to diagnose chromosomal abnormalities and infections in women at high risk.
• Neonatal screening includes clinical examination and screening for disorders of the blood, metabolism and hormone production. Screening for deafness and heart defects, as well as early detection of congenital anomalies, can facilitate life-saving treatments and prevent progression towards some physical, intellectual, visual, or auditory disabilities. In some countries, babies are routinely screened for abnormalities of the thyroid or adrenal glands before discharge from the maternity unit.

Treatment and care
Many structural congenital anomalies can be corrected with paediatric surgery and early treatment can be administered to children with functional problems such as thalassaemia (inherited recessive blood disorders), sickle cell disorders, and congenital hypothyroidism (reduced function of the thyroid).

WHO response
The report accompanying the resolution of the Sixty-third World Health Assembly (2010) on congenital anomalies describes the basic components for creating a national programme for the surveillance, prevention and care of congenital anomalies before and after birth. It also recommends priorities for the international community to assist in establishing and strengthening these national programmes.
• World Health Assembly report on birth defects
• World Health Assembly resolution WHA63.17 on birth defects

The “Global Strategy for Women’s, Children’s and Adolescents’ Health, 2016-2030” aims to achieve the highest attainable standard of health for all women, children, and adolescents, to transform the future and to ensure that every newborn, mother and child not only survives, but thrives. Updated in 2015 through a process of collaboration with stakeholders led by WHO, the strategy builds on the success of the 2010 strategy and its “Every Woman Every Child” movement, which helped accelerate the achievement of the health-related Millennium Development Goals and will act as a platform to put women, children and adolescents at the heart of the new UN Sustainable Development Goals.
• Global Strategy for Women’s, Children’s and Adolescents’ Health, 2016-2030

WHO is also working with the United States Centers for Disease Control and Prevention’s (CDC) National Center on Birth Defects and Developmental Disabilities and other partners, to establish a global policy for folic acid fortification at the country level. WHO is also working with partners to provide the required technical expertise for the surveillance of neural tube defects, for monitoring fortification of staple foods with folic acid, and for improving laboratory capacity for assessing risks for folic acid-preventable congenital anomalies.

The International Clearinghouse for Birth Defects Surveillance and Research is a voluntary non-profit international organization in official relations with WHO. This organization brings together congenital anomalies surveillance and research programmes from around the world, in order to investigate and prevent congenital anomalies and to lessen the impact of their consequences.

The WHO Departments of Reproductive Health and Research and Nutrition for Health and Development, in collaboration with the International Clearinghouse for Birth Defects Surveillance and Research and CDC’s National Center on Birth Defects and Developmental Disabilities, convene annual training programmes on the surveillance and prevention of congenital anomalies and preterm births. The WHO Department of HIV and AIDS collaborates with these partners, to strengthen the surveillance of congenital anomalies for women receiving antiretroviral drugs during
pregnancy, as an integral part of the monitoring and evaluation of national HIV programmes.

GAVI, the Vaccine Alliance, of which WHO is a partner, is assisting low- and middle-income countries in improving control and elimination of rubella and congenital rubella syndrome through immunization.

WHO develops normative tools, including guidelines and a global plan of action, to strengthen medical care and rehabilitation services to support the implementation of the United Nations Convention on the Rights of Persons with Disabilities. Similarly, WHO supports countries to integrate medical care and rehabilitation services into overall primary health care, supports the development of community-based rehabilitation programmes, and facilitates the strengthening of specialized rehabilitation centres and their links with community-based rehabilitation.

- United Nations Convention on the Rights of Persons with Disabilities

The WHO Department of Public Health and Environment focuses on a number of activities, and defines interventions, to address the environmental and social determinants of child development. These include children’s unique vulnerabilities to polluted indoor and outdoor air, contaminated water, lack of sanitation, toxicants, heavy metals, waste components and radiation; combined exposures with social, occupational and nutrition factors; and the settings in which children dwell (home, school).

The current Zika virus outbreaks and their association with an increase in microcephaly and other congenital malformations have raised great concern across the world, particularly in the Americas. In 2016, WHO declared a Public Health Emergency of International Concern (PHEIC). In countries where there is spread of Zika virus and increased congenital malformations / neurological syndromes, a full range of response activities have been implemented. These include enhanced surveillance and outbreak response, community engagement, vector control and personal protective measures, care for people and families with potential complications, field investigations, and public health research towards better understanding risk and mitigation measures.

3. HUMAN RIGHTS AND HEALTH

KEY FACTS

- The WHO Constitution (1946) envisages “…the highest attainable standard of health as a fundamental right of every human being.”
- Understanding health as a human right creates a legal obligation on states to ensure access to timely, acceptable, and affordable health care of appropriate quality as well as to providing for the underlying determinants of health, such as safe and potable water, sanitation, food, housing, health-related information and education, and gender equality.
- A States’ obligation to support the right to health – including through the allocation of “maximum available resources” to progressively realise this goal - is reviewed through various international human rights mechanisms, such as the Universal Periodic Review, or the Committee on Economic, Social and Cultural Rights. In many cases, the right to health has been adopted into domestic law or Constitutional law.
- A rights-based approach to health requires that health policy and programmes must prioritize the needs of those furthest behind first towards greater equity, a principle that has been echoed in the recently adopted 2030 Agenda for Sustainable Development and Universal Health Coverage. (1)
- The right to health must be enjoyed without discrimination on the grounds of race, age, ethnicity or any other status. Non-discrimination and equality requires states to take steps to redress any discriminatory law, practice or policy.
- Another feature of rights-based approaches is meaningful participation. Participation means ensuring that national stakeholders – including non-state actors such as non-governmental organizations – are meaningfully involved in all phases of programming: assessment, analysis, planning, implementation, monitoring and evaluation.

“The right to the highest attainable standard of health” implies a clear set of legal obligations on states to ensure appropriate conditions for the enjoyment of health for all people without discrimination.

The right to health is one of a set of internationally agreed human rights standards, and is inseparable or ‘indivisible’ from these other rights. This means achieving the right to health is both central to, and dependent upon, the realisation of other human rights, to food, housing, work, education, information, and participation.

The right to health, as with other rights, includes both freedoms and entitlements:

- Freedoms include the right to control one’s health and body (for example, sexual and reproductive rights) and to be free from interference (for example, free from torture and non-consensual medical treatment and experimentation).
- Entitlements include the right to a system of health protection that gives everyone an equal opportunity to enjoy the highest attainable level of health.
Focus on disadvantaged populations

Disadvantage and marginalization serve to exclude certain populations in societies from enjoying good health. Three of the world’s most fatal communicable diseases – malaria, HIV/AIDS and tuberculosis – disproportionately affect the world’s poorest populations, and in many cases are compounded and exacerbated by other inequalities and inequities including gender, age, sexual orientation or gender identity and migration status. Conversely the burden of non-communicable diseases – often perceived as affecting high-income countries – is increasing disproportionately among lower-income countries and populations, and is largely associated with lifestyle and behaviour factors as well as environmental determinants, such as safe housing, water and sanitation that are inextricably linked to human rights.

A focus on disadvantage also reveals evidence of those who are exposed to greater rates of ill-health and face significant obstacles to accessing quality and affordable healthcare, including indigenous populations. While data collection systems are often ill-equipped to capture data on these groups, reports show that these populations have higher mortality and morbidity rates, due to noncommunicable diseases such as cancer, cardiovascular diseases, and chronic respiratory disease. These populations may also be the subject of laws and policies that further compound their marginalization and make it harder for them to access healthcare prevention, treatment, rehabilitation and care services.

Violations of human rights in health

Violations or lack of attention to human rights can have serious health consequences. Overt or implicit discrimination in the delivery of health services – both within the health workforce and between health workers and service users – acts as a powerful barrier to health services, and contributes to poor quality care.

Mental ill-health often leads to a denial of dignity and autonomy, including forced treatment or institutionalization, and disregard of individual legal capacity to make decisions. Paradoxically, mental health is still given inadequate attention in public health, in spite of the high levels of violence, poverty and social exclusion that contribute to worse mental and physical health outcomes for people with mental health disorders.

Violations of human rights not only contribute to and exacerbate poor health, but for many, including people with disabilities, indigenous populations, women living with HIV, sex workers, people who use drugs, transgender and intersex people, the health care setting presents a risk of heightened exposure to human rights abuses – including coercive or forced treatment and procedures.

Human rights-based approaches

A human rights-based approach to health provides a set of clear principles for setting and evaluating health policy and service delivery, targeting discriminatory practices and unjust power relations that are at the heart of inequitable health outcomes.

In pursuing a rights-based approach, health policy, strategies and programmes should be designed explicitly to improve the enjoyment of all people to the right to health, with a focus on the furthest behind first. The core principles and standards of a rights-based approach are detailed below.

Core principles of human rights

Accountability

States and other duty-bearers are answerable for the observance of human rights. However, there is also a growing movement recognising the importance of other non-state actors such as businesses in the respect and protection of human rights. (2)

Equality and non-discrimination

The principle of non-discrimination seeks ‘...to guarantee that human rights are exercised without discrimination of any kind based on race, colour, sex, language, religion, political, or other opinion, national or social origin, property, birth or other status such as disability, age, marital and family status, sexual orientation and gender identity, health status, place of residence, economic and social situation’.

Any discrimination, for example in access to health care, as well as in means and entitlements for achieving this access, is prohibited on the basis of race, colour, sex, language, religion, political or other opinion, national or social origin, property, birth, physical or mental disability, health status (including HIV/AIDS), sexual orientation, and civil, political, social or other status, which has the intention or effect of impairing the equal enjoyment or exercise of the right to health.

The principle of non-discrimination and equality requires WHO to address discrimination in guidance, policies, and practices, such as relating to the distribution and provision of resources and health services. Non-discrimination and equality are key measures required to address the social determinants affecting the enjoyment of the right to health. Functioning national health information systems and availability of disaggregated data are essential to be able to identify the most vulnerable groups and diverse needs.

Participation

Participation requires ensuring that all concerned stakeholders including non-state actors have ownership and control over development processes
in all phases of the programming cycle: assessment, analysis, planning, implementation, monitoring, and evaluation. Participation goes well beyond consultation or a technical addition to project design; it should include explicit strategies to empower citizens, especially the most marginalized, so that their expectations are recognised by the State.

Participation is important to accountability as it provides “…checks and balances which do not allow unitary leadership to exercise power in an arbitrary manner”.

Universal, indivisible and interdependent

Human rights are universal and inalienable. They apply equally, to all people, everywhere, without distinction. Human Rights standards – to food, health, education, to be free from torture, inhuman or degrading treatment – are also interrelated. The improvement of one right facilitates advancement of the others. Likewise, the deprivation of one right adversely affects the others.

Core elements of a right to health

Progressive realization using maximum available resources

No matter what level of resources they have at their disposal, progressive realisation requires that governments take immediate steps within their means towards the fulfilment of these rights. Regardless of resource capacity, the elimination of discrimination and improvements in the legal and juridical systems must be acted upon with immediate effect.

Non-retrogression

States should not allow the existing protection of economic, social, and cultural rights to deteriorate unless there are strong justifications for a retrogressive measure. For example, introducing school fees in secondary education which had formerly been free of charge would constitute a deliberate retrogressive measure. To justify it, a State would have to demonstrate that it adopted the measure only after carefully considering all the options, assessing the impact and fully using its maximum available resources.

Core components of the right to health

The right to health (Article 12) was defined in General Comment 14 of the Committee on Economic, Social and Cultural Rights – a committee of Independent Experts, responsible for overseeing adherence to the Covenant. (4) The right includes the following core components:

Availability

Refers to the need for a sufficient quantity of functioning public health and health care facilities, goods and services, as well as programmes for all. Availability can be measured through the analysis of disaggregated data to different and multiple stratifiers including by age, sex, location and socio-economic status and qualitative surveys to understand coverage gaps and health workforce coverage

Accessibility

Requires that health facilities, goods, and services must be accessible to everyone. Accessibility has four overlapping dimensions:

- non-discrimination
- physical accessibility
- economical accessibility (affordability)
- information accessibility.

Assessing accessibility may require analysis of barriers – physical financial or otherwise – that exist, and how they may affect the most vulnerable, and call for the establishment or application of clear norms and standards in both law and policy to address these barriers, as well as robust monitoring systems of health-related information and whether this information is reaching all populations.

Acceptability

Relates to respect for medical ethics, culturally appropriate, and sensitivity to gender. Acceptability requires that health facilities, goods, services and programmes are people-centred and cater for the specific needs of diverse population groups and in accordance with international standards of medical ethics for confidentiality and informed consent.

Quality

Facilities, goods, and services must be scientifically and medically approved. Quality is a key component of Universal Health Coverage, and includes the experience as well as the perception of health care. Quality health services should be:

- Safe – avoiding injuries to people for whom the care is intended;
- Effective – providing evidence-based healthcare services to those who need them;
- People-centred – providing care that responds to individual preferences, needs and values;
- Timely – reducing waiting times and sometimes harmful delays.
- Equitable – providing care that does not vary in quality on account of gender, ethnicity, geographic location, and socio-economic status;
- Integrated – providing care that makes available the full range of health services throughout the life course;
- Efficient – maximizing the benefit of available resources and avoiding waste
WHO response

WHO has made a commitment to mainstream human rights into healthcare programmes and policies on national and regional levels by looking at underlying determinants of health as part of a comprehensive approach to health and human rights.

In addition, WHO has been actively strengthening its role in providing technical, intellectual, and political leadership on the right to health including:

- strengthening the capacity of WHO and its Member States to integrate a human rights-based approach to health;
- advancing the right to health in international law and international development processes; and
- advocating for health-related human rights, including the right to health.

Addressing the needs and rights of individuals at different stages across the life course requires taking a comprehensive approach within the broader context of promoting human rights, gender equality, and equity.

As such, WHO promotes a concise and unifying framework that builds on existing approaches in gender, equity, and human rights to generate more accurate and robust solutions to health inequities. The integrated nature of the framework is an opportunity to build on foundational strengths and complementarities between these approaches to create a cohesive and efficient approach to promote health and well-being for all.

1. Transforming our World: The 2030 Agenda for Sustainable Development. UN General Assembly. 2015. 21 October. UN Doc. A/RES/70/1.

4. MENTAL HEALTH IN EMERGENCIES

KEY FACTS

- People suffer from a wide range of mental health problems during and long after emergencies.
- People will be more likely to recover if they feel safe, connected, calm and hopeful; have access to social, physical and emotional support; and find ways to help themselves.
- Agencies agree on an intervention pyramid – from basic services and actions at the base to highly specialized at the top – to help countries match response strategies with community needs and appropriate expertise.
- WHO recommends at least 1 supervised health care staff member in every general health facility during humanitarian emergencies to assess and manage mental health problems.
- Emergencies, in spite of their tragic nature and adverse effects on mental health, are also opportunities to build better mental health systems for all people in need.
- Global progress on mental health reform will happen more quickly if, in every crisis, efforts are made to convert short-term interest in mental health into momentum for long-term improvement.
- Mental health is crucial to the overall wellbeing, functioning, and resilience of individuals, societies, and countries recovering from emergencies.

During and after emergencies, people are more likely to suffer from a range of mental health problems. Some people develop new mental disorders after an emergency, while others experience psychological distress. Those with pre-existing mental disorders often need more help than before.

WHO-recommended psychological first aid involves humane, supportive and practical help to people who are suffering after a crisis. This support should be provided to people in ways that respect their dignity, culture and abilities. It covers both social and psychological support.

Psychological and psychiatric help need to be made available immediately for specific, urgent mental health problems as part of the health response.

Communities affected by emergencies need long-term access to mental health care as adversity is a potent risk factor for a wide range of mental health problems.

Impact of emergencies

Some problems are brought on by the emergency, some by the response to the event, and others are pre-existing or more serious.

Significant social problems are:
- emergency-induced: family separation, safety, discrimination, loss of livelihoods and the social fabric of everyday life, low trust and resources;
- humanitarian response-induced: overcrowding, lack of privacy in camps, loss of community or traditional support; and
- pre-existing: belonging to a marginalized group.

Problems of a more psychological nature are:
- pre-existing: depression, alcoholism or severe mental disorders such as schizophrenia;
• emergency-induced: grief, distress, alcohol and substance abuse, depression and anxiety, including post-traumatic stress disorder (PTSD); and
• humanitarian-response induced: anxiety due to a lack of information about food distribution, or how to obtain other basic services.

**Symptoms of distress**

Some common ways that people show their distress in reaction to a crisis are:
• physical symptoms: headaches, fatigue, loss of appetite, aches and pains;
• crying, sadness, grief;
• anxiety, fear;
• being on guard, or jumpy;
• insomnia, nightmares;
• irritability, anger; or
• confused, in a daze;

Not everyone who experiences a crisis will need or want support. Most people will recover well over time, if they are able to restore their basic needs, find ways to return to normalcy, and get some support when they need it. Access to clinical management is important whenever symptoms interfere with daily functioning.

**Effective emergency response**

Evidence and experience show that people who feel safe, connected, calm and hopeful; have access to social, physical and emotional support; and find ways to help themselves after a disaster will be better able to recover long-term from mental health effects.

WHO and partners have developed an intervention pyramid – from basic services and actions at the base to highly specialized at the top – to help countries match response strategies with community needs and appropriate expertise. For example, clinical mental health services at the apex of the pyramid should be provided under the supervision of mental health specialists such as psychiatric nurses, psychologists or psychiatrists.

Psychological first aid can be provided by field workers, including health workers, teachers or trained volunteers, and does not always need mental health professionals.

Trained and supervised general health care staff members can offer first-line care for mental disorders.

Looking forward: emergencies can build better mental health systems

In spite of their tragic nature, many countries have capitalized on emergency situations to build better mental health systems. The surge of international donor aid combined with increased attention to mental health issues creates opportunities to improve mental health care.

For example, access to mental health care in general health care facilities is better in many areas of the Syrian Arab Republic in 2017 than before the war. Mental health care was only available in the large cities before the war. During the war, over 500 primary health care staff were trained and are providing mental health care in primary care settings.

**WHO response**

WHO is the leading agency in technical advice on mental health and emergencies. In 2017 WHO is operational on mental health in the Central African Republic, Guinea, Iraq, Lebanon, Liberia, Sierra Leone, Syrian Arab Republic, Turkey, the West Bank and Gaza Strip, and Yemen.

WHO works globally to ensure that the humanitarian mental health response is coordinated and effective, and that afterwards mental health systems are rebuilt and sustained.

WHO develops and evaluates tools to meet the mental health needs of people in emergencies. These include tools on assessment, psychological first aid, clinical management of mental disorders, and mental health system recovery.

• Assessment
• Psychological first aid
• Clinical management of mental disorders
• Mental health system recovery

WHO’s advice and tools are used by the vast majority of international humanitarian organizations active in mental health.

5. RADON AND HEALTH

**KEY FACTS**

• Radon is a naturally occurring radioactive gas which may be found in indoor environments such as homes, schools, and workplaces.
• Radon is the most important cause of lung cancer after smoking.
• Radon is estimated to cause between 3–14% of all lung cancers in a country, depending on the national average radon level and smoking prevalence.
• The lower the radon concentration in a home, the lower the risk of lung cancer as there is no known threshold below which radon exposure carries no risk.
• Well-tested, durable and cost-efficient methods exist for preventing radon in new houses and reducing radon in existing dwellings.

Radon is a naturally occurring radioactive gas. It has no smell, colour or taste. Radon is produced from the natural radioactive decay of uranium, which is found in all rocks and soil. Radon can also be found in water.
Radon escapes easily from the ground into the air, where it decays and produces further radioactive particles. As we breathe, the particles are deposited on the cells lining the airways, where they can damage DNA and potentially cause lung cancer.

Outdoors, radon quickly dilutes to very low concentrations and is generally not a problem. The average outdoor radon level varies between 5–15 Bq/m³. However, indoors, radon concentrations are higher, with highest levels found in places like mines, caves and water treatment facilities. In buildings such as homes, schools, and offices, radon levels in the range of 10 Bq/m³ to more than 10 000 Bq/m³ have been found.

Health effects of radon

Radon is the most important cause of lung cancer after smoking. It is estimated that radon causes between 3–14% of all lung cancers in a country, depending on the average radon level and the smoking prevalence in a country.

An increased rate of lung cancer was first seen in uranium miners exposed to high concentrations of radon. In addition, studies in Europe, North America and China have confirmed that even low concentrations of radon – such as those found in homes – also confer health risks and contribute significantly to the occurrence of lung cancers worldwide.

The risk of lung cancer increases by 16% per 100 Bq/m³ increase in long time average radon concentration. The dose-response relation is linear – for example, the risk of lung cancer increases proportionally with increasing radon exposure.

Radon is much more likely to cause lung cancer in people who smoke. In fact, smokers are estimated to be 25 times more at risk from radon than non-smokers. To date, no other cancer risks have been established.

Radon in homes

For most people, the greatest exposure to radon occurs in the home. The concentration of radon in a home depends on:

- the amount of uranium in the underlying rocks and soils;
- the routes available for the passage of radon from the soil into the home; and
- the rate of exchange between indoor and outdoor air, which depends on the construction of the house, the ventilation habits of the inhabitants, and the air-tightness of the building.

Radon enters homes through cracks in the floors or at floor-wall junctions, gaps around pipes or cables, small pores in hollow-block walls, or sumps or drains. Radon levels are usually higher in basements, cellars or living spaces in contact with soil.

Radon concentrations vary between adjacent homes, and can vary within a home from day today and from hour to hour. Residential radon levels can be measured in an inexpensive and simple manner. Because of these fluctuations, it is preferable to estimate the annual mean concentration of radon in indoor air by measurements for at least 3 months. However, measurements need to be based on national protocols to ensure consistency as well as reliability for decision-making.

Reducing radon in homes

Well-tested, durable and cost-efficient methods exist for preventing radon in new houses and reducing radon in existing dwellings. Radon prevention should be considered when new houses are built, particularly in radon prone areas. In many countries of Europe and in the United States of America, the inclusion of protective measures in new buildings has become a routine measure. In some countries it has become a mandatory procedure.

Radon levels in existing homes can be reduced by:

- increasing under-floor ventilation;
- installing a radon sump system in the basement or under a solid floor;
- avoiding the passage of radon from the basement into living rooms;
- sealing floors and walls; and
- improving the ventilation of the house.

Passive systems of mitigation have been shown to be capable of reducing indoor radon levels by more than 50%. When radon ventilation fans are added radon levels can even be reduced further.

Radon in drinking water

In many countries, drinking water is obtained from groundwater sources such as springs, wells and boreholes. These sources of water normally have higher concentrations of radon than surface water from reservoirs, rivers or lakes.

To date, epidemiological studies have not found an association between consumption of drinking-water containing radon and an increased risk of stomach cancer. Radon dissolved in drinking-water can be released into indoor air. Normally, a higher radon dose is received from inhaling radon compared with ingestion.

The “WHO guidelines for drinking water quality” (2011) recommend that screening levels for radon in drinking-water be set on the basis of the national reference level for radon in air. In circumstances where high radon concentrations might be expected in drinking-water, it is prudent to measure radon concentrations. Straightforward and effective techniques exist to reduce the concentration of radon in
drinking-water supplies by aeration or using granular activated carbon filters.

- WHO Guidelines for drinking-water quality

**WHO response**

In 2009, WHO published the “WHO handbook on indoor radon: A public health perspective”, which provides policy options for reducing health risks from residential radon exposure through:

- providing information on levels of radon indoors and the associated health risks;
- implementing a national radon programme aimed at reducing both the overall population risk and the individual risk for people living with high radon concentrations;
- establishing a national annual average concentration reference level of 100 Bq/m³, but if this level cannot be reached under the prevailing country-specific conditions, the reference level should not exceed 300 Bq/m³;
- implementing radon prevention in building codes to reduce radon levels in homes under construction, and radon programmes to ensure that the levels are below national reference levels; and
- developing radon measurement protocols to help ensure quality and consistency in radon testing.

These recommendations are consistent with the International Basic Safety Standards (2014) and the IAEA Safety guide on radon (2014), both co-sponsored by WHO.

- WHO Handbook on Indoor Radon: A Public Health Perspective
- Radiation Protection and Safety of Radiation Sources: International Basic Safety Standards

1. Radioactivity is measured in units called Becquerels (Bq). One Becquerel corresponds to the transformation (disintegration) of 1 atomic nucleus per second. Radon concentration in air is measured by the number of transformations per second in a cubic meter of air (Bq/m³).