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Autopathography should be an honest attempt by every doctor to record his/her personal opinion about his/her illness conscientiously. If this is done by each of us when we fall ill, which happens every now and then to almost all of us, there will be a more authentic textbook of medicine in due course for students. Most, if not all, textbooks now contain second or third hand knowledge, which is anything but authentic to be trusted. Like, for example, I had a stroke some time ago. My own experience was anything but what the textbooks told us. Curiously, around that time some half a dozen of my friends also had strokes.

None of our experiences were alike! Each one of us had a unique history as well as disease course. Was this unexpected? Far from it, very far. That was very much what was expected. Physiotherapy brought muscle power back to normal, but I do not feel fully fine to walk. However, I walk as before and as much as I want. I am only trying to say that the walk is not the same walk as before the stroke.

That will happen only when the brain circuitry gets back to normal, God only knows when? I must now tell the reader what I had preceding the stroke. A week before the stroke, I had sudden blurred vision in a small area which my good student, one of Mangalore’s best eye surgeons, Prashanth Shetty, thought was due to a small oedema in a small area of the retina due to vascular reasons. That, of course, disappeared on its own, never to recur till now. Last week, I had an eye test review. Digital computerised tomography of my retina revealed that the old healing has left no scar on my retina, which has come back to normal.

One other bother I now have is a possibly drug induced sleeping irregularity which does not bother me so much. I cannot pinpoint to say which the offending drug is, as they had put me on a plethora of them over the months, but the problem seems to be easing as the drugs are reduced to the bare minimum. This was one of my bad experiences in life but, I thank God, I am out of it now, hopefully.
Age as the only predictive factor for successful sperm retrieval in patients with Sertoli cell-only syndrome: A single center experience

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ABSTRACT

Objective: To investigate the factors predicting the success of microdissection testicular sperm extraction (mTESE) in patients with Sertoli cell-only syndrome (SCO)

Design: Retrospective study

Setting: Tepecik Training and Research Hospital, Turkey

Subjects: We retrospectively reviewed the medical data of 462 patients diagnosed with non-obstructive azoospermia (NOA) undergoing the mTESE operation at our institution between May 2008 and June 2017. This study enrolled 106 patients diagnosed with NOA with SCO histopathology in testicular tissues. They were grouped into two groups as successful sperm retrieval through mTESE and unsuccessful ones. The two groups were compared regarding the patients' age, duration of infertility, testicular volume, body mass index, total serum testosterone, follicle stimulating hormone, luteinizing hormone, estradiol and prolactin levels.

Intervention: mTESE

Main outcome measure: Sperm retrieval rate

Results: The ages of the patients in the successful and unsuccessful groups were 31.86 ± 4.87 and 35.12 ± 5.19 years, respectively. On comparison of the groups, a statistically significant difference was found between the groups regarding the patients' age (p < 0.001). No other variables demonstrated a statistically significant difference.

Conclusion: In this study, age was identified as the only factor predicting the success of mTESE in patients with SCO. It has been demonstrated that an increase in age negatively affects the success of mTESE in patients with SCO, and the chance of success is higher in patients with SCO undergoing mTESE surgery before 32 years of age.

INTRODUCTION

Non-obstructive azoospermia (NOA) is defined as the minimal presence of mature sperm in the testis, or lack of spermatozoa in the ejaculate due to failure in production of sperm. The frequency of NOA is 1% among all men and 10% among infertile men[1]. In these patients, the first line of treatment is using the sperm retrieved by microdissection testicular sperm extraction (mTESE) in intracytoplasmic sperm injections (ICSI). The most common testicular histopathology patterns seen in patients with NOA are hypospermatogenesis (HS), maturation arrest (MA), and Sertoli cell-only syndrome (SCO)[2]. Sertoli cells directly interact with germ cells to support and regulate spermatogenesis. SCO was first defined by Del Castillo in 1947 as seminiferous tubules of the testes containing only Sertoli cells and complete absence of germ cells[3]. Although its etiology is not precisely known, congenital and acquired factors have been blamed. The congenital cause is related to a blockage in the migration of germ cells from the yolk sac wall to the genital ridge, or failure to preserve viability. The acquired causes responsible include undescended testis, radiation, cytotoxic agents, or viral infections. In 22.5% of patients with SCO, small focal regions of spermatogenesis can be seen in the testis[4]. Hence, sperm can be retrieved by mTESE in these patients. The sperm retrieval rate by mTESE in patients with...
SCO appears to be lower than that of patients with MA and HS. Unsuccessful mTESE operations in patients with SCO lead to significant emotional and financial effects. Knowledge of the factors that could predict the success of this operation before the mTESE procedure is important for avoiding unnecessary surgeries. The purpose of this study was to investigate the variables that predict the success of mTESE in patients with SCO.

**MATERIALS AND METHODS**

**Patients and study design**

We retrospectively reviewed the medical data of 462 patients with the diagnosis of NOA who had undergone the mTESE operations consecutively at our institution between the dates of May 2008 and June 2017. The diagnosis of NOA was confirmed by clinical findings, medical history, physical examination, serum hormone levels, genetic analysis, and as suggested by the World Health Organization guideline, using two semen analyses. The serum total testosterone (T), follicular stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), and the prolactin (PRL) levels of the patients and the results of genetic analyses (karyotype analysis and Y chromosome microdeletion analysis) were evaluated. In our clinic, the Y chromosome microdeletion analysis is performed for all patients before the TESE operation, and TESE is not recommended to patients with AZFa and AZFb deletions. The testicular volume of the patients was measured by ultrasonography. To rule out additional anomalies, examination of the external organs was performed in all patients. For the hormone profile, blood was drawn from the antecubital veins of the patients after at least 8 hours of fasting. The micro-particle enzyme immuno-assay method (Roche/Hitachi, Cobas e601, Indianapolis, IN, USA) was used to determine the hormone levels. For the chromosome analysis, the peripheral venous blood samples of the patients were subjected to 72 hours of phytohemagglutinin-induced cell culture. To identify the testicular histopathology, the tissues sent to pathology during the mTESE operation were examined using the Johnsen’s score (JS). This study was conducted in accordance with the Declaration of Helsinki and approval was obtained from the institutional ethics committee.

This study included 106 NOA patients whose histopathological analysis of the testicular tissues obtained during the mTESE operation demonstrated SCO (mean JS: 2). Patients with histopathological results other than SCO, those with a history of testicular trauma, malignant disease, obstructive azoospermia, and a history of more than one mTESE operation were excluded from the study. In the study group, there were no hormonal imbalances such as hypogonadotropic hypogonadism and hyperprolactinemia. Despite some studies having demonstrated that hormone therapy (aromatase inhibitors, clomiphene citrate, human chorionic gonadotropin) could have beneficial effects, no patients received hormone therapy in our clinic before mTESE, since there were no recommendations in the guidelines. To investigate the factors predicting the success of mTESE in patients with SCO, the patients were grouped as successful and unsuccessful sperm retrieval in mTESE. These two groups were compared with regard to patients’ age, duration of infertility, testicular volume, body-mass index, serum FSH, LH, E2, PRL, and T levels.

**TESE technique**

On the day that the TESE operation was planned, additional sperm samples were obtained, and it was confirmed that there were no sperm present. Informed consent was obtained from all the patients before TESE. All the patients underwent spinal anesthesia for mTESE. A midline scrotal incision was made, and the scrotal content was pushed out from the side with the larger testis. The tunica vaginalis was opened, and the tunica albuginea that surrounds the testicle was visualized. After this stage, the operation was handled under an operating microscope. As described by Schlegel, a avascular area was selected from the antimesenteric area to the tunica albuginea, and a 3 cm incision was made with a thin scalp[18]. Small samples were obtained from opaque, large, white tubules in the testicular parenchyme. Each sample was placed in a petri dish filled with human tubal fluid. All samples were immediately evaluated by an embryologist using a 200-x magnification microscope in order to investigate the presence of spermatozoa. The operation was terminated when suitable spermatozoa were found for ICSI. If spermatozoa were not detected in the first sample, additional samples were obtained from the same testicle. In cases where spermatozoa were not found in the samples sent from the larger testis, the samples were also obtained from the contralateral testis. The biopsy specimen was sent to the pathology laboratory intraoperatively in order to determine the testicular histopathology.

**Histopathological analysis**

In order to define the testicular histopathology, all testicular biopsy samples were fixed in Bouin’s solution and embedded in paraffin blocks following the tissue processing steps. 4 μm-thick sections were obtained, stained using hematoxylin and eosin dye, and evaluated under a microscope with 400 x magnification by the same pathologist, who was experienced in this field for more than 10 years. Germinal epithelia of at least 100 seminiferous tubules were evaluated for each biopsy sample. In the presence of germinal epithelium,
the spermatogenetic situation was assessed using JS. According to JS, the tissue maturation and spermatogenetic situation of the germinal epithelia of each sample were scored between 1 and 10. In this scoring system, tubular necrosis was scored 1, Sertoli cell only was scored as 2, spermatogonia only was scored as 3, arrest at primary spermatocyte was scored as 4 or 5, arrest at early spermatid stage was scored as 6 or 7, arrest at late spermatid stage was scored as 8 or 9, and full spermatogenesis was scored as 10\(^6\). The mean JS was calculated for each sample. Testicular biopsy specimens were classified according to the histopathological criteria as follows: normal spermatogenesis (mean JS: 10), HS (mean JS: 8-9), late maturation arrest (mean JS: 6-7), early maturation arrest (mean JS: 3-4-5), SCO (mean JS: 2) and hyalinization of tubules (mean JS: 1).

### Statistical analysis

The conformity of the variables to normal distribution was assessed by the Shapiro Wilk test. The categorical variables were described using frequency and percentage, and the numerical variables were described using mean and range values. The Student’s t-test and the chi-square test were used for inter-group analysis of continuous variables. We performed univariable and multivariable binary logistic regression analyses to identify factors associated with and predictive of positive sperm retrieval during mTESE. The logistic regression analysis was performed by creating a model that included age, T, FSH, and testicular volume. The ability of the variables to predict the presence of sperm in the TESE procedure was investigated by the receiver operating curve (ROC) analysis, and the threshold values were calculated using the Youden Index Method. The data analysis was carried out using the Statistical Package for the Social Science (SPSS Inc, Chicago, Illinois, USA) version 22.0, and a p-value < 0.05 was considered significant.

### RESULTS

Among the 462 patients undergoing mTESE, the testicular pathology of SCO was identified in the intraoperative biopsy samples of 106 (22.9%) patients. These 106 patients constituted the study cohort. In the study population, the mean age was 33.79 ± 5.2 years, the mean duration of infertility was 6.11 ± 4.3 years, the mean testicular volume was 13.02 ± 1.2 mL, the mean BMI was 22.8 ± 1.3 kg/m\(^2\), the mean total T level was 17.9 ± 9.8 pg/mL, the mean FSH level was 28.7 ± 13.8 mIU/mL, the mean LH level was 11.2 ± 6.8 mIU/mL, and the mean PRL level was 12.2 ± 4.1 ng/mL. Sperm retrieval by mTESE was successful in 43 (40.5%) and unsuccessful in 63 (59.5%) of the 106 patients with SCO enrolled in the study. The ages of patients in the successful and unsuccessful sperm retrieval groups were 31.86 ± 4.87 and 35.12 ± 5.19 years, respectively. When the successful and unsuccessful sperm retrieval groups were compared, a statistically significant difference was determined between the groups with respect to the patient’s age (p < 0.001). No statistically significant difference was determined between the two groups with respect to the other variables. The comparison of the clinical and hormonal features of the patients in these two groups has been summarized in Table 1.

None of the patients included in our study had a history of cryptorchidism or clinical varicocele. Eight of the patients with SCO had non-mosaic Klinefelter syndrome. Sperm was retrieved by mTESE in two (25%) of these patients. One patient with SCO had an AZFc deletion. Sperm retrieval by mTESE was unsuccessful in this patient. No complications were observed in any of the mTESE procedures during the operation or throughout the following three weeks. The logistic regression analysis was performed through a model that included age, T, FSH, and testicular volume (Table 2). The best cut-off value at which the patient age could predict finding sperm by mTESE was identified as 32

### Table 1: The comparison of the clinical and laboratory data of patients with successful and unsuccessful sperm retrieval by mTESE

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (n = 106)</th>
<th>Group 1* (n = 43)</th>
<th>Group 2* (n = 63)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>33.79 ± 5.2</td>
<td>31.86 ± 4.87</td>
<td>35.12 ± 5.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of infertility (years)</td>
<td>6.11 ± 4.3</td>
<td>6.72 ± 4.6</td>
<td>5.71 ± 4.5</td>
<td>0.240</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>22.8 ± 1.3</td>
<td>22.1 ± 1.1</td>
<td>23.4 ± 1.2</td>
<td>0.839</td>
</tr>
<tr>
<td>Testis volume (mL)</td>
<td>13.02 ± 1.2</td>
<td>12.76 ± 1.1</td>
<td>13.21 ± 1.4</td>
<td>0.452</td>
</tr>
<tr>
<td>T (ng/dL)</td>
<td>364.73 ± 175.64</td>
<td>356.08 ± 145.85</td>
<td>370.64 ± 181.85</td>
<td>0.387</td>
</tr>
<tr>
<td>E2 (pg/mL)</td>
<td>17.9 ± 9.8</td>
<td>17.3 ± 9.3</td>
<td>18.4 ± 10.1</td>
<td>0.870</td>
</tr>
<tr>
<td>FSH (mIU/mL)</td>
<td>28.7 ± 13.8</td>
<td>29.03 ± 12.4</td>
<td>28.57 ± 15.5</td>
<td>0.928</td>
</tr>
<tr>
<td>LH (mIU/mL)</td>
<td>11.2 ± 6.8</td>
<td>11.6 ± 7.6</td>
<td>10.7 ± 4.7</td>
<td>0.774</td>
</tr>
<tr>
<td>PRL (ng/mL)</td>
<td>12.2 ± 4.1</td>
<td>11.2 ± 4.9</td>
<td>12.9 ± 3.8</td>
<td>0.606</td>
</tr>
</tbody>
</table>

*Group 1: Spermatozoa were retrieved; Group 2: no Spermatozoa were retrieved

BMI: body-mass index; T: testosterone; E2: estradiol; FSH: follicle-stimulating hormone; LH: luteinizing hormone; PRL: prolactin
years (sensitivity: 61.8%, specificity: 78.1%, p <0.001). The area under the ROC was identified as 0.692 for the patient age (Figure 1).

DISCUSSION

In this study, the factors that could predict the success of mTESE in patients with SCO was investigated, and it was observed that only the age of the patients was able to predict the presence of sperm in mTESE. In this study, our 9-year mTESE experience with SCO patients in our single center has been summarized. There are only few studies in the literature that research the factors that predict the success of mTESE in patients with SCO. It has been stated in various reports that the frequency of SCO testicular pathology is between 10.8 and 44% in patients with SCO[7]. In our study, the SCO histopathology was observed in 22.9% of the patients diagnosed with NOA undergoing the mTESE operation. In the literature, the sperm retrieval rate by mTESE in patients with SCO has been reported to be between 16.3% and 41%[8]. In our study, this rate was found to be 40.5%.

In the limited number of studies published previously, no effect of age was observed on the success of mTESE in patients with SCO. To the best of our knowledge, our study is the first in the literature to demonstrate a statistically significant relationship between age and successful sperm retrieval by mTESE in patients with SCO. In our opinion, this result may be explained by the increase in testicular histology deterioration with age. It has not been possible to establish the exact cause of impaired testicular histology in patients with SCO. It is being considered that genetic, immunological, or environmental factors may be effective. It has been demonstrated that the cytokeratin filaments found in Sertoli cells in the fetal and prepubertal period decrease in number under pathological conditions. Besides, the telomerase activity required for germinal cell proliferation was not observed in patients with SCO either[9]. The increased disruption of Sertoli cells that support the development of germinal cells may result in azoospermia. The likelihood of retrieving sperm by mTESE may be reduced by the disruption of Sertoli cells that increase in number with an increase in the patients’ age.

Okada et al reported the sperm retrieval rates as 6.3% and 33.9% for conventional and mTESE, respectively, in patients with SCO[10]. In another study in which they evaluated 134 patients with SCO undergoing mTESE surgeries with conventional and combined procedures, Gul et al reported the sperm retrieval rate as 27.6% and did not identify any variable that could preoperatively predict the result of mTESE[7]. When compared to the afore-mentioned study, the higher sperm retrieval rate in our study may be due to the exclusive use of the microdissection procedures in our study.

The data in the literature about the role of FSH levels in predicting the success of mTESE are contradictory. While there are studies demonstrating that high FSH levels increase the likelihood of sperm retrieval by mTESE, there are also studies that do not establish any relationship between the FSH level and the success of mTESE. In their study in which they researched factors predicting the success of mTESE in 148 patients with SCO, Modaressi et al identified the sperm retrieval rate as 28.9% in patients with FSH >15.25 mIU/mL and as 11.8% in patients with FSH <15.25 mIU/mL[11]. In another study, it was shown that the FSH level alone did not affect the success of mTESE, but that it could have been effective on the success of mTESE together with the testicular

Table 2: The regression analysis model and independent predictive factors that reflect the possibility of sperm retrieval

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.612</td>
<td>0.461 - 0.742</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TFSH</td>
<td>0.384</td>
<td>0.285 - 0.570</td>
<td>0.474</td>
</tr>
<tr>
<td>Testis volume</td>
<td>0.517</td>
<td>0.329 - 0.645</td>
<td>0.745</td>
</tr>
</tbody>
</table>

CI: confidence interval; T: testosterone; FSH: follicle-stimulating hormone

Fig 1: Receiver operating characteristic (ROC) curve analysis of patients' age. (sensitivity: 61.8%, specificity: 78.1%, p <0.001, area under the curve: 0.692)
volume[12]. Contrary to these studies, no relationship was observed in our study between the FSH levels and sperm retrieval by mTESE.

Many published studies have shown that there is no association between testicular volume and the success of mTESE. Nonetheless, there are also studies that have established the presence of a relationship between testicular volume and sperm retrieval[11,13]. Turunc et al observed a significant relationship between testicular volume and the success of mTESE, and reported that the success of mTESE was significantly low in patients with a testicular volume of under 5 mL[1]. Contrary to this study, we did not identify a statistically significant relationship between the testicular volume and the success of mTESE.

Knowledge of the diagnostic testicular biopsy results before the TESE operation is highly valuable in predicting the success of sperm retrieval by TESE. Diagnostic testicular biopsy has complications similar to those of TESE. Furthermore, in NOA patients, obtaining sperm in the diagnostic testicular biopsy does not guarantee that sperm will be retrieved in the following TESE operation. Diagnostic testicular biopsy is not recommended in clinical practice because the biopsy has an additional cost, patients need to undergo two surgical procedures, and it is an invasive procedure that increases the likelihood of complications[14]. At this point, knowledge of testicular pathology before TESE is only possible if the patients undergo testicular surgery beforehand. Knowledge of testicular histopathology after unsuccessful TESE will provide urologists with valuable information about predicting the success of sperm retrieval in patients who will undergo repeat TESE.

It was observed that the mean duration of infertility in patients included in our study was long. The reason behind long durations may have been the fact that the patient population presenting to our infertility clinic comes from rural areas and has a low socioeconomic status; therefore, patients may have failed to seek the appropriate treatment at the relevant health institutions in time.

Our study has some limitations. The first limitation is the fact that it is retrospective. The other is that the inhibin B levels were not assessed in our study. Not all sperms that are obtained in TESE can be used in ICSI. Non-inclusion of post-ICSI fertility analyses in our study may be regarded as a limitation; however, the ICSI outcomes are primarily affected by many factors, including female fertility, and the primary goal of our study was to define the factors affecting the success of TESE; thus, the ICSI outcomes were not included in our study.

**CONCLUSIONS**

In this study, age was identified as the only factor predicting the success of mTESE in patients with SCO. It has been shown that increasing patient age negatively affects the success of mTESE in SCO patients, and that the chance of success is higher in SCO patients undergoing an mTESE operation before 32 years of age. No relationship was observed between the success of mTESE and the other variables.

**REFERENCES**


Do we really need to insert peritoneal drain after transperitoneal laparoscopic renal cyst decortication?

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Kuwait Medical Journal 2019; 51 (3): 240 - 243

ABSTRACT

Objective: The aim of this study to evaluate the necessity of peritoneal drains in the treatment of transperitoneal laparoscopic renal cyst (RC) decortication.

Design: Retrospective study

Setting: Department of Urology, Sakarya University, Sakarya Training and Research Hospital, Sakarya, Turkey

Subjects: Forty-eight patients who had undergone laparoscopic RC decortication for symptomatic Bosniak class I cortical RCs

Interventions: Patients were divided into two groups according to presence of peritoneal drain. Patient’s age, operation time, cyst size and cyst laterality were recorded.

Main outcome measure: Groups were compared for operation time, postoperative complication rates, estimated blood loss, hospital stay, and radiological and clinical success rate at 3-month follow-up visit.

Results: Patients had a mean age of 55.76 ± 12.16 years, a mean cyst size 65.83 ± 30.15 mm and mean operation time was 41.43 ± 5.69 minutes. Although, there were no significant differences between the two groups in terms of age, sex, laterality, cyst size, complication rate, estimated blood loss and operation time; discharge time was statistically higher in patients with peritoneal drain than patients without peritoneal drain (1.45 ± 0.80 vs 1.04 ± 0.96, respectively) (p = 0.014). All patients in both groups were asymptomatic at 3-month follow-up visit and the radiological success rates of two groups were similar (95.4% vs 96.1%, p = 0.712, respectively).

Conclusion: Peritoneal drain is unnecessary for the postoperative management of patients undergoing laparoscopic decortication of Bosniak type I RCs. Moreover, peritoneal drain may cause delayed bowel movement because of peritoneal irritation, which can result in delayed discharge time.

INTRODUCTION

Renal cysts (RCs) are common with a prevalence of 20 - 50% in the general population, and their frequency tends to increase during adulthood[1,2]. With the widespread use of imaging techniques, RC are being diagnosed with increasing frequency[3]. Although simple RCs are frequently asymptomatic, they occasionally become large enough to cause hematuria, pelvicalyceal obstruction, hypertension and pain[4]. Simple asymptomatic RCs do not require treatment. However, in the presence of the above-mentioned symptoms, RCs should be treated[5]. The treatment options include aspiration with or without instillation of sclerosing agents, percutaneous resection and open or laparoscopic decortication[6]. Laparoscopic management of RCs has become the standard modality of minimally invasive treatment with high success rate[7]. However, there is limited data on the use of peritoneal drain in the treatment of laparoscopic RC decortication. The aim of the present study was to evaluate the necessity of peritoneal drains in the treatment of transperitoneal laparoscopic RC decortication.

KEY WORDS: drainage, kidney, peritoneoscopy

SUBJECTS AND METHODS

This study was approved by the local ethics committee. We retrospectively reviewed the medical records of 48 patients (28 males and 20 females) with cortical RCs who underwent laparoscopic transperitoneal RC decortication between December 2012 and June 2016. All cysts were symptomatic and Bosniak class 1. Patients were divided into two groups

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according to the presence of peritoneal drain. Patient’s age, operation time, cyst size, and cyst laterality were recorded. Groups were compared for operation time, postoperative complication rates, hospital stay, and radiological and clinical success rate at 3-month follow-up visit. Clinical success was defined as the recovery of the complaint and radiological success was defined as the disappearance of the cyst on radiological imaging.

### Laparoscopic transperitoneal RC decortication technique

Under general anesthesia, following insertion of the urethral catheter, patients were placed in a semilateral decubitus position at a 45° angle. To locate the site for entering the peritoneal cavity, we drew a horizontal line between the anterior superior iliac supine and umbilicus and divided it into thirds. We entered the abdominal cavity using a Veress needle at the point in which the two external thirds met. To achieve pneumoperitoneum, CO₂ was delivered under insufflation pressure of 15 mmHg into abdominal cavity. The first 10 mm trocar was advanced through the access tract created with a Veress needle. Then, another 10 mm trocar was inserted into umbilicus to serve as the camera port. A 5 mm trocar was inserted at a site 2 cm below the intersecting point between the midclavicular line and subcostal arch under direct vision. Following the placement of the trocars, the intraperitoneal pressure was dropped to 15 mmHg. Intraperitoneal adhesions were dissected away from abdominal wall and Toldt white line was exposed. The colon was deviated to the medial side. Gerota fascia was uncovered, and the borders of the cyst were exposed. The cyst was opened, excised, and extracted from the connection with the normal renal parenchyma using a laparoscopic harmonic scalpel. After suction and hemostatic control, intraabdominal gas was evacuated, and trocar entry sites were closed. All operations were performed or supervised by a single surgeon and peritoneal drain was optionally used.

### Statistical analysis

All analyses were performed by SPSS 20.0.0 (IBM Corp., Chicago, IL). Numerical variables were presented as mean ± standard deviation, and categorical variables were presented as frequencies/percentages. Since the continuous variables were not distributed normally, Mann-Whitney U test was used to compare the numerical variables across drain groups. Monte Carlo exact Chi-square test was used to determine the relation between drain groups and other categorical variables. P-value of less than 0.05 was considered statistically significant for all analyses.

### RESULTS

In total, 48 patients were enrolled in this study, comprising 28 (58.3%) men and 20 (41.7%) women. Patients had a mean age of 55.76 ± 12.16 years. Mean cyst size was 65.83 ± 30.15 mm, mean operation time was 41.43 ± 5.69 minutes and mean estimated blood loss (EBL) was 55 ± 17.2 ml. The characteristics and results of the 22 patients with drain insertion (group 1) and those of the 26 patients without drain insertion (group 2) are listed in Table 1. Although, there were no significant differences between the two groups in terms of age, sex, laterality, cyst size, complication rate, operation time and EBL, the duration of hospital stay was statistically longer in group 1 than group 2 (1.45 ± 0.80 vs 1.04 ± 0.96 days, respectively; p = 0.014). Clavien type 1 complications such as delayed bowel movement and fever were observed in 5 patients (4 patients in group 1 and 1 patient in group 2, p = 0.109). These patients were treated with intravenous hydration and/or antipyretics. In group 1, all drains were removed on first postoperative day, except in 5 patients. The reason the drain was kept in place in those five patients was

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1* (n = 22)</th>
<th>Group 2* (n = 26)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>51.09 ± 16.89</td>
<td>57.58 ± 11.59</td>
<td>0.233</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>14/8 (63.6/36.4)</td>
<td>14/12 (53.8/46.2)</td>
<td>0.493</td>
</tr>
<tr>
<td>Cyst size (mm)</td>
<td>59.96 ± 26.79</td>
<td>71.96 ± 31.68</td>
<td>0.168</td>
</tr>
<tr>
<td>Laterality</td>
<td></td>
<td></td>
<td>0.398</td>
</tr>
<tr>
<td>Right</td>
<td>10 (45.5%)</td>
<td>15 (57.7%)</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>12 (54.5%)</td>
<td>11 (42.3%)</td>
<td></td>
</tr>
<tr>
<td>Clavien Grade 1 complication</td>
<td>4 (18.2%)</td>
<td>1 (3.8%)</td>
<td>0.109</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>40.05 ± 4.62</td>
<td>42.93 ± 6.31</td>
<td>0.120</td>
</tr>
<tr>
<td>Discharge time</td>
<td>1.45 ± 0.8</td>
<td>1.04 ± 0.96</td>
<td>0.014</td>
</tr>
<tr>
<td>Postoperative day 1</td>
<td>16 (72.7%)</td>
<td>25 (96.2%)</td>
<td>0.023</td>
</tr>
<tr>
<td>Postoperative day 2</td>
<td>2 (9.1%)</td>
<td>1 (3.8%)</td>
<td>0.015</td>
</tr>
<tr>
<td>Postoperative day 3</td>
<td>4 (18.2%)</td>
<td>25 (96.1)</td>
<td>0.712</td>
</tr>
<tr>
<td>Radiological success (%)</td>
<td>51.09 ± 16.89</td>
<td>15 (57.7%)</td>
<td>0.493</td>
</tr>
</tbody>
</table>

*Group 1: patients with drain insertion; Group 2: patients without drain insertion
the leakage and the sample from drain chemistry was compatible with the serum. All patients in both groups were asymptomatic at 3-month follow-up visit and radiological success rates of two groups were similar (95.4% vs 96.1%, $p = 0.712$, respectively).

**DISCUSSION**

Benign cystic diseases of the kidney are common and incidentally diagnosed by radiological examination. In recent years, with the increasing use of diagnostic tools such as ultrasonography and computed tomography, the prevalence of RCs has increased. However, most of these RCs do not require treatment\[8\]. The use of the Bosniak renal cyst classification is a useful tool for the successful management of RCs. In this study, we used the Bosniak classification as a screening method, which was applied to all cases, and only Bosniak type 1 cysts were included.

Simple RCs are usually asymptomatic, and surgical intervention is unnecessary unless patients subsequently develop symptoms or complications. In the present study, the indication of surgical intervention was pain unresponsive to analgesics.

Laparoscopic RC decortication has been shown to be a safe and effective therapy. Furthermore, it has been reported to be a long-term treatment option\[9-11\]. Laparoscopic management of RCs is associated with minimal complications, reduced operative time, reduced hospital stay and rapid convalescence\[12\].

Studies have shown that the success rate of laparoscopic RC decortication varies between 60 to 100%, regardless of the approach used. Additionally, the radiologic success rate has ranged between 88.2% and 93.9% for peripherally located cysts\[13\]. In this present study, at the 3rd month control, symptomatic success rate was 100% for all patients regardless of drain use. There were no significant differences between groups in terms of radiological success rates.

The main advantage of minimal invasive surgery is less complication, shorter hospitalization and rapid recovery. In the present study, discharge time was statistically shorter in the undrained group. The main reason for longer hospital stay in the drained group was leakage. The biochemical study of the liquid from drain gave the same results as serum. In fact, it is well known that cystic liquid is dissimilar to serum\[14\]. However, the sample we collected from the drain consisted of cystic fluid mixed with peritoneal fluid, which may explain why the drain liquid was similar to serum in terms of biochemical composition. The main reason for using a peritoneal drain after RC decortication is to monitor the drain fluid for blood and urine leakage. Urine leakage can occur if the cysts communicate with collection system. Some authors recommended that retrograde pyelography should be used to assess cyst communication with collecting system, especially in those with parapelvic and parenchymal cysts. In a previously published series, there were no significant complications without using retrograde pyelography\[15\]. In the present study, we did not use retrograde pyelography either. Hemorrhage is the other reason for the insertion of the peritoneal drain. However, Clavien grade 2 complications were not observed in our study. Five patients presented Clavien type 1 complication. Additionally, there was no statistically significant difference between groups in terms of complication.

To the best of our knowledge, this is the first study that evaluated whether postoperative drain insertion is really necessary after transperitoneal laparoscopic cyst decortication and demonstrated that drain placement is unnecessary and can cause prolongation of hospital stay.

The limitations of our present study include its retrospective nature and the relatively small number of patients studied. These factors may reduce the reliability of our postoperative results.

**CONCLUSION**

As technology advances, minimally invasive surgery will continue to evolve to find perfection. The present study findings show that there is no need to use peritoneal drain for the postoperative management of patients undergoing laparoscopic decortication of Bosniak type 1 renal cysts. Moreover, peritoneal drain may cause delayed bowel movement because of peritoneal irritation, which can result in delayed discharge time.

**ACKNOWLEDGMENT**

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

**REFERENCES**


Assessment of cervical lymphadenopathy in children: When is malignancy suspected?

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ABSTRACT

Objective: The aim of the study was to evaluate children with cervical lymphadenopathy and to determine risk factors for malignancy.

Design: Retrospective study

Setting: Department of Pediatric Oncology, Adnan Menderes University School of Medicine, Aydin, Turkey

Subjects: We studied 151 patients with cervical mass presenting at our center.

Interventions: The data was collected from the hospital records, and when data was found lacking, it was completed by getting in contact with the parents of the patients by phone.

Main outcome measures: Detailed medical history, duration of lymph node enlargement, features of lymph nodes, size, mobility, extension, laboratory tests, radiologic investigation, mediastinal mass presence, and histopathologic examination were evaluated.

Results: One hundred and thirty (94.9%) children were classified as having a benign cause for lymph node enlargement, while seven (5.1%) were classified as malignant. Excisional lymph node biopsy was made in 14 (10%) cases and half of them had been diagnosed with malignancy. Hodgkin lymphomas were most common in the malignant group. The risk of malignant disease was higher in patients who had supraclavicular lymphadenopathy; firm, rubbery or fixed lymph nodes, or any nodes greater than 3 cm in diameter; and mediastinal enlargement in chest X-ray (p <0.05). The duration of lymphadenopathy was longer for the malignant group, but not statistically significant.

Conclusion: All physicians seeing pediatric patients should be alert since there are suspicious findings suggestive of malignancy. If malignancy is suspected, preliminary radiological test is chest X-ray and excisional lymph node biopsy should be planned.

INTRODUCTION

Lymphadenopathy (LAP) is a common complaint and physical finding in children. A diagnosis of lymphoma or another malignancy must always be considered when evaluating the child with an enlarged peripheral lymph node. However, other causes of lymphadenopathy are much more common and the majority of these children will have a benign, self-limited process[1,2]. The critical challenge for the physician is to identify benign or malignant nature of cervical lymphadenopathy in children. Management algorithms in cases of lymphadenopathy have been established, but there is still a lack of formal guidelines for cervical LAP in the pediatric population[3,4]. In our previous study, we found that most of the patients (87.5%) with cervical mass who first contacted a governmental hospital had longer time to diagnosis[5]. The aim of this study was to define the demographic, clinical, and laboratory findings in children with cervical LAP, and to determine which nodes indicate malignancy or another serious disease requiring specific treatment.

SUBJECTS AND METHODS

The study was approved by the Local Ethic Committee of Adnan Menderes University School of Medicine.

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Study group

The study group included the patients of the outpatient clinic of Pediatric Oncology Department of Adnan Menderes University School of Medicine. They were all referred because of cervical mass. Children who had a tissue diagnosis of cancer (with cervical LAP) made at the hospital prior to referral were excluded. Patients with mediastinal mass/pleural effusion and peripheral adenopathy suggesting Non-Hodgkin lymphoma (NHL) or Hodgkin lymphoma (HL) referred to our service directly were excluded. All leukemias and patients with stage IV NHL diagnosed with bone marrow examinations were also excluded.

Data under interest

The data was collected from the hospital records and when data was lacking, it was completed by getting in contact with the parents of the patients by phone. The following data was evaluated: age, sex, medical history including dental problems, history of an upper respiratory tract infection, fever, cough, chronic usage of medicine, travel history, exposure to animal or biting insect, administration of BCG vaccination, duration of lymph node enlargement [acute (≤ 4 weeks) and chronic (> 4 weeks)], features of lymph nodes [location, characteristics, size (<1 cm, 1-3 cm, and >3 cm), mobility], extension [localized (a single or multiple but adjacent lymph node involved) and generalized (more than two and non-adjacent lymph node involved)], mediastinal mass presence, laboratory tests, radiologic investigation, and histopathologic examination.

Statistical analysis

Statistical analysis was carried out with the SPSS 17.0 statistical program. Pearson Chi-square Test with Continuity Correction and Fisher’s Exact Test were used for categorical comparisons. Type 1 (α) Error was considered as 0.05.

RESULTS

A total of 151 cervical mass was evaluated. Fourteen (9.1%) patients had cervical mass mimicking LAP such as tyroglossal cyst (n = 3), lipoma (n = 3), lymphangioma (n = 3), pilomatrixoma (n = 2), hemangioma (n = 2), epidermoid cyst (n = 1). They were excluded from the study. Out of 137 patients, 46 (34%) were female and 91 (66%) were male. Their ages ranged from 3 months to 18 years (median: 6 years).

One hundred and thirty (94.9%) children were classified as having a benign cause for lymph node enlargement (benign LAP group), while seven (5.1%) were classified as malignant. The clinical features of the patients in the benign and malignant groups are shown in Table 1. After the clinical and laboratory investigations, nodes that could not assigned to a specific etiology were considered as LAP of unknown origin and were referred to as benign cases. Half of the patients in the unknown origin group had local infection. These LAPs were considered reactive lymph nodes. Nineteen patients had primary non-specific lymphadenitis. Diagnosis of lymphadenitis was made on the basis of clinical findings. Excisional biopsies were performed to 7 patients (5.4%) with benign LAP group (5 reactive LAP, 1 Castleman disease, 1 Kimura disease). The causes for the LAP are listed in Table 2.

Table 1: The clinical features of the patients in the benign and malignant groups

<table>
<thead>
<tr>
<th>Characteristics of patients</th>
<th>Benign group n (%)</th>
<th>Malignant group n (%)</th>
<th>Total n (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>6.49 ± 4.30</td>
<td>8.71 ± 2.36</td>
<td>6.6 ± 4.25</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>45 (35)</td>
<td>1 (14)</td>
<td>46 (34)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Male</td>
<td>85 (65)</td>
<td>6 (66)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of LAP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>88 (68)</td>
<td>2 (29)</td>
<td>90 (66)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Chronic</td>
<td>42 (32)</td>
<td>5 (71)</td>
<td>47 (34)</td>
<td></td>
</tr>
<tr>
<td>Extension of LAP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localized</td>
<td>111 (85)</td>
<td>5 (71)</td>
<td>116 (85)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Generalized</td>
<td>19 (15)</td>
<td>2 (29)</td>
<td>21 (15)</td>
<td></td>
</tr>
<tr>
<td>Size of LAP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 cm</td>
<td>3 (2)</td>
<td>0 (0)</td>
<td>3 (2)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>1-3 cm</td>
<td>102 (79)</td>
<td>0 (0)</td>
<td>102 (75)</td>
<td></td>
</tr>
<tr>
<td>&gt;3 cm</td>
<td>25 (19)</td>
<td>7 (100)</td>
<td>32 (23)</td>
<td></td>
</tr>
<tr>
<td>Characteristics of LAP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Firm</td>
<td>55 (42)</td>
<td>4 (57)</td>
<td>59 (43)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Tenderness, fluctuant</td>
<td>74 (57)</td>
<td>0 (0)</td>
<td>74 (54)</td>
<td></td>
</tr>
<tr>
<td>Rubbery</td>
<td>1 (1)</td>
<td>3 (43)</td>
<td>4 (3)</td>
<td></td>
</tr>
<tr>
<td>Mobility of LAP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixed</td>
<td>4 (3)</td>
<td>5 (71)</td>
<td>9 (7)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Mobile</td>
<td>126 (97)</td>
<td>2 (29)</td>
<td>128 (93)</td>
<td></td>
</tr>
<tr>
<td>Accompanying mediastinal mass</td>
<td>0 (0)</td>
<td>4 (57)</td>
<td>4 (9)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Table 2: Causes of the benign and malignant lymphadenopathies

<table>
<thead>
<tr>
<th>Causes</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>130</td>
<td>94.9*</td>
</tr>
<tr>
<td>Unknown origin</td>
<td>92</td>
<td>70.8</td>
</tr>
<tr>
<td>Reactive lymph nodes</td>
<td>46</td>
<td>14.6</td>
</tr>
<tr>
<td>Nonspecific lymphadenitis</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Systemic infections</td>
<td>17</td>
<td>13.1</td>
</tr>
<tr>
<td>Infectious mononucleosis</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Cyto megalovirus</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Rubella</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Castleman Disease</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Kimura Disease</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Malignant</td>
<td>7</td>
<td>5.1*</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>6</td>
<td>6/7</td>
</tr>
<tr>
<td>Nasopharyngeal carcinoma</td>
<td>1</td>
<td>1/7</td>
</tr>
<tr>
<td>All</td>
<td>137</td>
<td>100.0</td>
</tr>
</tbody>
</table>

*Benign/All; † Related with local infection; ‡ Benign/All; § Percentage not given because total is less than 10
There were no statistically significant differences between the benign and malignant LAP groups according to laboratory findings. In the benign LAP group, fifty-two patients (40%) had previously applied ultrasonographic (US) evaluation (one or more) that all of them revealed non-specific findings are non-diagnostic. Most of the conventional US reports contained insufficient information about the distinction between benign and malignant LAP.

Excisional lymph node biopsy was made in 14 (10%) cases. Results of histopathologic examination are shown Table 2. Half of the patients who underwent biopsy had been diagnosed with malignancy. HL was most common in the malignant group. Two cases were classified as benign LAP, whereas they were serious lymphoproliferative diseases (Kimura disease and Castleman disease).

There were statistically significant differences between the benign and malignant groups according to features of lymph nodes including location, size and mobility (Table 1). The region of LAP was significantly important for the differential diagnosis and supraclavicular lesions were associated with malignant diseases. The presence of mediastinal or hilar LAP detected by chest X-ray and thorax CT were significantly higher in the malignant group (p < 0.05). Of the five children with abnormal chest roentgenogram, four had HL (Fig 1). None had superior mediastinal syndrome. All of the malignant LAPs were more than 3 cm in diameter (p < 0.05). Tenderness was seen mostly in benign LAP group, whereas rubbery and fixed lymph nodes were seen in malignant LAP group (p <0.05). The duration of LAP was longer for the malignant group, but not statistically significant (p >0.05).

DISCUSSION

A nodal mass, unlike an abdominal, pelvic, or mediastinal mass, is not always an indication for a detailed workup or for a prompt surgical procedure to establish diagnosis[1]. One review noted approximately 50% of children older than 5 years seen for well (44%) or sick (64%) visits had LAP[6]. However, the likelihood of malignancy within the node will determine the urgency for biopsy or other invasive procedures that are undertaken. In our study, 14 out of 137 children (10%) underwent excisional lymph node biopsy. Half of the patients which underwent biopsy had been diagnosed with malignancy. The overall percentage of malignant diseases was 5.1% in our study. In the study of Citak et al[7], the incidence of malignancy in lymph node biopsies was 3.2%. However, Yaris et al[8] reported that pathologic examinations were required in 38.7% of cases, and malignant neoplasms (lymphomas and solid tumors) were determined in 60% of the sampled nodes and 23.7% of all cases. Kumral et al[9] found malignant disorder as the cause of LAP in 30% of patients. Excisional lymph node biopsy was done 57 cases (28.5%). This study was performed in the hematology-oncology department and patients with leukemia (total malignancy: 27%) were included. Two other studies performed in the same hematology-oncology center from our country reported that frequency of malignant disease including the patients with leukemias and solid tumors was 27% and 24.3%, respectively[10,11]. Usually, selected patients are admitted to the hematology-oncology clinic; therefore, frequency of malignant disorders is relatively high. Most of these studies reported that HLs were most common in the malignant group LAP.

The characteristics of lymph node including size, location, fixation to the skin and deep tissue are important factors to distinguish between malignant and benign disorders. Our findings confirm these reports[8-11]. Besides, in the presence of mediastinal enlargement and/or supraclavicular LAP independent of these characteristics, the patients tend to have malignant disease[8,9]. Many studies have shown that the duration of LAP was significantly longer for
malignant disorders\cite{9,11,12}. In our study, malignant LAP group was mostly chronic, but not statistically significant. This result was attributed to the small number of patients in the malignant LAP group. The diagnostic workup for LAP should include important clues from the clinical presentation as a guide. In general, if a lymph node is unresponsive to antibiotics and continues to increase in size over a 2-week period, it should be biopsied. Within 2 or 3 weeks, most non-malignant lymph nodes should have regressed toward normal size\cite{6,13}. We observed that all of the malignant LAPs were more than 3 cm in diameter and the duration of LAP was longer for the malignant group. If lymph node enlargement developed secondary to malignant disorders, they are ordinarily firm, rubbery, and fixed, as in our study. If malignancy is suspected, the essential and preliminary radiological test is chest X-ray. Similar to the results, at least two-thirds of patients diagnosed as HL present with some degree of mediastinal involvement (Fig 1). A chest X-ray is helpful to determine the mediastinal enlargement and should be obtained prior to referral of a patient for biopsy because presence of mediastinal mass compressing to trachea can be a contraindication to general anesthesia\cite{1,2,13}. If the clinician is unsure if a mass lymph node is present or not, ultrasonographic evaluation should be performed. In the study of Yaris et al\cite{8}, 22% of patients who appear to have LAP will instead have some other type of head and neck mass. We found that 14 patients (9.1%) had cervical mass mimicking LAP. In addition, careful ultrasonographic evaluation of LAP can be helpful in discrimination between non-suppurative bacterial lymphadenitis and suppurative lymphadenitis or Kawasaki’s disease. It can be used to guide biopsies of potentially neoplastic masses or drainage of infectious fluid collections\cite{2,4,15}. However, in our study, the decision for the biopsy was not made according to the US findings. In our opinion, conventional US is applied more than necessary by primary care physicians. The value of fine-needle aspiration biopsy (FNAB) is highly controversial in pediatric LAPs. FNAB is sensitive for carcinoma and therefore very useful in adults. The most important limitations of FNAB are inadequate sampling, false-negative diagnoses and incomplete classification of lymphomas\cite{1,3,13,14}. False negative results can lead to patients being out of follow-up and delaying diagnosis. Therefore, we always prefer excisional biopsy.

CONCLUSION
In conclusion, most cases of LAP are self-limited and require no treatment, but occasionally it might herald the presence of a serious disorder or malignancy. Lymph nodes that are rubbery and fixed, more than 3 cm in size, and supraclavicular located have increased significance for malignancy, and merits further investigations including early excisional biopsy. With chronic LAP in children, malignancy becomes the more likely diagnosis. All physicians seeing pediatric patients should be alert since there are suspicious findings suggestive of malignancy.

ACKNOWLEDGMENT

Declaration of Interest: The authors report no conflicts of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES
Can the Hounsfield unit value predict the success of percutaneous nephrolithotomy?

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Department of Urology, Tepecik Training and Research Hospital, Izmir, Turkey

ABSTRACT

Objective: To evaluate the impact of the Hounsfield unit (HU) value of kidney stones on the success and outcomes of percutaneous nephrolithotomy (PCNL)

Design: A retrospective study

Setting: Sakarya Training and Research Hospital, Sakarya, Turkey and Tepecik Training and Research Hospital, Izmir, Turkey

Subjects: We retrospectively reviewed the medical data of 186 kidney stone patients who underwent PCNL between January 2011 and May 2016. We included data on 152 patients in the present study.

Intervention: PCNL

Main outcome measures: Patient demographics and stone characteristics were evaluated, including non-contrast computed tomographic parameters acquired before PCNL. Patients were divided into two groups in terms of their HU values (group 1: HU ≤1000 and group 2: HU >1000). The groups were compared in terms of HU value, age, gender, operative time, stone size, hospital stay time, decrease in haemoglobin level, and the success of surgery.

Results: The medical data of 152 patients were evaluated. Seventy-seven were in group 1 and 75 in group 2. There was no significant difference in mean age, gender, or stone size (all \( p > 0.05 \)) between the low and high-HU groups. The PCNL success rates and outcomes did not differ significantly between the two groups (\( p > 0.05 \)).

Conclusions: The HU value did not affect the success rate of PCNL and was not independently associated with complications. Additionally, we found no statistically significant difference in terms of any variable between the groups.

INTRODUCTION

Currently, percutaneous nephrolithotomy (PCNL) is the most common surgical treatment for large kidney stones (≥2 cm in diameter)\(^1\). PCNL affords a success rate of approximately 80% and is the first choice of treatment for large kidney stones\(^2\). Many studies have explored the effects of stone size, stone location, staghorn stones, and previous surgery on the success rate of PCNL\(^3\)\(^-\)\(^5\). Most patients with kidney stones undergo non-contrast computed tomography (NCCT) prior to PCNL. A recent study explored the utility of the stone Hounsfield unit (HU) value measured via NCCT as an independent predictor of the outcomes of PCNL\(^6\).

The objective of the present study was to determine the effect of the HU value of kidney stones on the outcomes of PCNL. We also evaluated the utility of measuring kidney stone HU values with NCCT in terms of predicting PCNL success.

MATERIALS AND METHODS

We retrospectively reviewed the medical data of 186 kidney stone patients who underwent PCNL between January 2011 and May 2016. Of these 186 patients, we included 152 in the present study. Patient demographics, stone characteristics and perioperative details were recorded, including preoperative and postoperative NCCT parameters. Patients with a previous history of surgery (15 cases) were excluded and patients under the age of 18 years were also excluded because of the high probability of metabolic disease (19 cases). The patients were divided into two groups according to the HU values: group 1 patients had low-HU stones (HU ≤1000) and group 2 had high-

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HU stones (HU >1000). We compared the groups in terms of HU value, age, gender, operative time, stone size, hospital stay time, decrease in haemoglobin (Hgb) level, and surgical success.

All PCNL surgery was performed by a single experienced endourologist (>100 cases). All patients were treated under general anaesthesia in the prone position. We considered the operation successful if NCCT performed in the first month postoperatively revealed no stone >4 mm in diameter. The decrease in Hgb level was calculated based on measurements taken 48 hours before and 24 hours after PCNL (Hgb decrease = preoperative − postoperative Hgb level ± SD; g/dL). All NCCT scans were inspected and mean HUs measured. Three transverse sections were defined for each stone (upper, middle, and lower). A region of interest was created at each level and the mean stone HU value was the average of the three ROIs. Stone surface area was calculated using the following formula: maximum length × maximum width × π × 0.25. Complications were classified using the modified Clavien classification system (MCS). The MCS stratifies perioperative complications into five grades: grade 1 consists of all events that, if left untreated, would resolve spontaneously or require only simple bedside intervention; grade 2 complications require specific medication(s), including antibiotics and blood transfusions; grade 3 complications necessitate surgical, endoscopic, or radiological intervention; grade 4 complications include injuries to neighbouring organs and organ failure; and grade 5 complication is death.

We used Student’s t-test, the Mann–Whitney U-Test, and Pearson’s chi-squared test for comparisons, as appropriate. A p-value <0.05 was accepted as statistically significant. Binary logistic regression analysis was used to seek factors predictive of surgical success.

RESULTS

We evaluated the medical data of 152 patients (91 males and 61 females). Seventy-seven of the patients were in group 1 (low HU) and 75 in group 2 (high HU). We found no significant difference in the mean age, gender, or stone size (all p >0.05) between the low and high-HU groups (Table 1). The PCNL success rate did not differ significantly between the low and high-HU groups (p = 0.779). We found no difference in the operative time, hospital stay time, Hgb decrease, or frequency of complications (as scored using the MCS) between the groups (Table 2). No statistically significant difference in any variable was evident between the two groups. Logistic regression did not identify any factor affecting the PCNL success rate (Table 3). Postoperative, one patient developed pneumothorax, five patients required double-J stents, eight had blood transfusions, and nine needed antibiotics (Table 4).

DISCUSSION

NCCT is used to obtain preoperative stone data (size, shape, number, location, and HU value) and to predict the success of percutaneous nephrolithotomy. We used Student’s t-test, the Mann–Whitney U-Test, and Pearson’s chi-squared test for comparisons, as appropriate. A p-value <0.05 was accepted as statistically significant. Binary logistic regression analysis was used to seek factors predictive of surgical success.
evaluate the success of PCNL\textsuperscript{[7,8]}. The NCCT HU values, which reflect stone densities, are used to select treatment options\textsuperscript{[9]}. Many studies have found that the success of extracorporeal shockwave lithotripsy (ESWL) can be predicted by NCCT-computed HU values\textsuperscript{[10-11]}. Ito \textit{et al} showed that this HU value also predicted the success of flexible ureteroscopy\textsuperscript{[9]}. Erturhan \textit{et al} studied the influence of HU value on the outcomes of medically expulsive therapy (MET), but ultimately found that they could not be used to predict treatment success\textsuperscript{[12]}. The literature indicates that the NCCT HU values predicted the success of ESWL and flexible ureteroscopy, but not that of MET\textsuperscript{[10-12]}. We found that the HU value did not predict the success of PCNL.

Gok \textit{et al} reported that neither the success nor complication rates of PCNL differed significantly between low and high-HU groups\textsuperscript{[13]}. On the other hand, Gücük \textit{et al} found that PCNL was more effective to disperse stones of higher HU values\textsuperscript{[6]}. No correlation was observed between the operative time and the duration of fluoroscopy. By contrast, Gok \textit{et al} found that the operative time, the duration of fluoroscopy, and the mean decrease in the hematocrit were significantly greater in a high-HU than in a low-HU group\textsuperscript{[13]}. A larger study found that very low and high HU values correlated with reduced PCNL treatment success and a longer operative time\textsuperscript{[14]}. Although we found no relationship between the HU value and PCNL outcomes, we suggest that calculation of HU values in kidney stone patients may predict ESWL success and thus aid in the selection of useful treatment methods.

The British Association of Urological Surgeons reported outcomes after PCNL, with an overall complication rate of 21.3%\textsuperscript{[15]}. The Clinical Research Office of the Endourology Society found that, of 5724 patients undergoing PCNL in 96 centres worldwide, the overall complication rate was 20.5%\textsuperscript{[16]}. Tefekli \textit{et al} were the first to use the MCS to evaluate PCNL complications\textsuperscript{[17]}. The overall complication rate (811 cases) was 29.2%, of which grades 1, 2, 3, 4, and 5 complications developed in 4, 16.3, 9.4, 1.4, and 0.1% of patients, respectively. Our overall complication rate was 21.1% (4.6, 9.9, 4.6, 2, and 0% of patients with grades 1, 2, 3, 4, and 5, respectively).

### CONCLUSION

The Hounsfield unit value did not predict the success of percutaneous nephrolithotomy and did not independently affect the complication rate. Additionally, we found no significant difference in any variable between the low and high-HU groups. Our results require confirmation in further prospective randomised studies with more patients.

### REFERENCES


#### Table 4: Complications encountered using the MCS

<table>
<thead>
<tr>
<th>MCS complications</th>
<th>Low-HU (n = 77)</th>
<th>High-HU (n = 75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 Fever</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Grade 2 Blood transfusion</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Urinary tract infection requiring additional antibiotics</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Grade 3a Double-J stent placement for urine leakage &gt;24 hours (local anaesthesia)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Grade 3b Double-J stent placement for urine leakage &gt;24 hours (urethral stone, general anaesthesia)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Grade 4 Pulmonary embolism (requiring intensive-care unit stay)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Urosepsis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>GRADE 5 Death</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>


Original Article

Comparison of epistaxis in the elderly and adults at a teaching hospital in Taiwan

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ABSTRACT

Objective: This study analyzes the clinical features and treatment modalities of patients with epistaxis treated in the otolaryngology emergency room at a teaching hospital in Taiwan over a period of 10 years.

Design: Case series

Setting: Kaohsiung Armed Forces General Hospital, Taiwan

Subjects: A retrospective review was performed on patients older than 18 years of age who presented in the otolaryngology emergency room with a diagnosis of epistaxis from January 2007 to December 2016.

Intervention: None

Main outcome measures: Age, gender, clinical presentations, and treatment modalities

Results: Of the 521 patients with epistaxis, 134 (25.7%) were older than 65 years of age (elderly group), and 387 (74.3%) were between 18 and 65 years old (adult group). Compared with the adult group, the elderly group had significantly higher rates of underlying systemic diseases of hypertension (66.4% versus 22.5%, p <0.001) and diabetes mellitus (14.2% versus 1.6%, p <0.001). The ratio of patients who received nasal packing was significantly higher in the elderly group (94/134, 70.2%) than in the adult group (184/387, 47.5%) with p <0.001. Six patients (4.5%) were hospitalized in the elderly group, and there were 23 patients (5.9%) in the adult group, but the difference was not significant.

Conclusions: Compared to the adult group, the elderly patients with epistaxis had more cases with underlying systemic diseases, and nasal packing. However, the outcome of the elderly group was the same as that of the adult group.

INTRODUCTION

Epistaxis, also known as nosebleed, is defined as bleeding from the nostril, nasal cavity, or nasopharynx. It is a common complaint, and approximately 60% of people will be affected at some point in life⁰. Some cases of massive epistaxis are life-threatening and require urgent care, but most cases are mild, self-limiting, and can be managed with simple treatments or procedures. The causes of epistaxis include local factors such as trauma, anatomic abnormality, inflammatory diseases, and tumors, as well as systemic factors such as hypertension, coagulopathies, and vascular abnormalities⁴. About 80% of patients with epistaxis have anterior nosebleeds.

As the overall population ages gradually, epistaxis in the elderly becomes more prevalent and can become a challenge for physicians. Furthermore, some comorbid conditions may affect the severity of epistaxis, and cognitive impairment may make it difficult for geriatric patients to provide an accurate history. However, the relationship between old age and epistaxis has rarely been discussed before.

The present study aimed to analyze the differences in clinical features and treatment modalities between the elderly and adults in a series of 521 patients treated in the otolaryngology emergency room of a teaching hospital in Taiwan.

MATERIALS AND METHODS

The medical records of patients older than 18 who visited our otolaryngology emergency room between January 2007 and December 2016 were reviewed

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retrospectively. All patients received a comprehensive diagnostic procedure including recording of medical history and physical examinations. The patients were excluded from the study if they were referred from other departments, they were return patients, they had epistaxis secondary to traumatic or previous nasal surgery, and did not complete treatment in the otolaryngology emergency room. A total of 521 patients were included in this study. Patients older than 65 years of age were defined as the elderly group.

The factors included for analysis were age, gender, clinical presentations, and treatment modality. Continuous variables are presented as the means ± standard deviation and were analyzed with the student’s t test. Categorical variables are presented as percentages and were analyzed using the chi-square test. A p-value <0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS version 17.0 for Windows (SPSS, Inc., Chicago, Illinois). The study was approved by the Institutional Review Boards at Kaohsiung Armed Forces General Hospital in Kaohsiung.

RESULTS

Of the 521 patients with a diagnosis of epistaxis, 134 (25.7%) were older than 65 years of age (elderly group), and 387 (74.3%) were between 18 and 65 years of age (adult group). The mean ages of the elderly group and adult group were 78.3 ± 9.1 years (ranging from 65 to 97) and 39.8 ± 14.7 years (ranging from 18 to 64), respectively (Table 1). Among the patients, 194 (37.2%) had underlying systemic diseases including hypertension, diabetes mellitus, or coagulopathy. The most frequent underlying systemic disease was hypertension (33.8%). Compared with the adult group, the elderly group had significantly higher rates of hypertension (66.4% vs 22.5%, p <0.001) and diabetes mellitus (14.2% vs 1.6%, p <0.05). Anterior epistaxis accounted for 95.5% of the cases in the elderly group and 96.1% in the adult group.

Anterior nasal septum was the most frequent lesion site in both the elderly group (60.4%) and the adult group (66.9%) (Table 2). Six patients (1.2%) had nasal bleeding due to a neoplasm and agreed to undergo a biopsy procedure. Among the elderly patients with neoplasms, one had hemangioma of the middle turbinate, and two had a nasopharyngeal carcinoma. Among the adult patients with neoplasms, one had hemangioma of the vestibule, one had squamous cell carcinoma of the middle turbinate, and one had nasopharyngeal carcinoma.

There were 233 patients (44.7%) who could be managed by conservative local soaking with vasoconstrictive agents, while 278 patients (53.4%) needed nasal packing, and 10 patients (1.9%) needed further surgical intervention. Only one patient in the adult group required blood transfusion. The ratio of patients who received nasal packing was significantly higher in the elderly group (94/134, 70.2%) than in the adult group (184/387, 47.5%) with p <0.001 (Table 3). Patients with systemic diseases in both the elderly group and the adult group had significantly higher rates of requiring nasal packing (Table 4). The admission rate was 4.5% (6 of 134) for the elderly group and 5.9% (23 of 387) for the adult group with no significant difference between groups (Table 5). No mortality was observed in either group.

DISCUSSION

Epistaxis is one of the most commonly treated conditions by otolaryngologists and may appear at all ages. Epistaxis in the elderly is more prevalent as the overall population ages gradually.
Table 4: Comparison of treatment modalities of epistaxis patients with and without systemic diseases

<table>
<thead>
<tr>
<th>Variables</th>
<th>Systemic diseases</th>
<th>No systemic diseases</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly</td>
<td>98 (95.5%)</td>
<td>36 (36.1%)</td>
<td></td>
</tr>
<tr>
<td>Local soaking</td>
<td>15 (15.3%)</td>
<td>20 (53.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nasal packing</td>
<td>80 (81.6%)</td>
<td>14 (38.9%)</td>
<td></td>
</tr>
<tr>
<td>Surgical intervention</td>
<td>3 (3.1%)</td>
<td>2 (5.5%)</td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td>96 (96.1%)</td>
<td>291 (94.1%)</td>
<td></td>
</tr>
<tr>
<td>Local soaking</td>
<td>24 (25.0%)</td>
<td>174 (59.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nasal packing</td>
<td>70 (72.9%)</td>
<td>114 (39.2%)</td>
<td></td>
</tr>
<tr>
<td>Surgical intervention</td>
<td>2 (2.1%)</td>
<td>3 (1.0%)</td>
<td></td>
</tr>
</tbody>
</table>

* Chi-square test; * statistically significant with p <0.05

In our study, about one-fourth (134/521, 25.7%) of the patients with epistaxis were elderly. The incidence of epistaxis is higher among males than females in both the elderly and adult groups.

The clinical presentation of epistaxis can range from mild, intermittent, blood-stained discharge to severe, persistent major hemorrhage. If not treated adequately and early, epistaxis can lead to morbidity and mortality. For patients presenting with active nasal bleeding, the principal management protocol is to ensure protection of the airway and adequacy of the circulatory system before attempting to identify the bleeding site and control the epistaxis.

The rate of anterior epistaxis was 95.5% in the elderly group and 96.1% in the adult group. These results are similar to the occurrence rate of 90 to 95% reported in a previous study. Kieselbach’s plexus, also known as Little’s area, is located in the anterior nasal septum and was the most common bleeding site. In our study, anterior nasal septum was the most frequent lesion site in both the elderly group and the adult group.

The treatment strategies for epistaxis include local soaking with vasoconstrictive agents, chemical cautery, electric cautery, nasal packing, and surgical intervention. Cautery or anterior nasal packing is usually sufficient to control anterior epistaxis, but in the patients with posterior epistaxis, posterior nasal packing should first be suggested. In our study, around 70% of the elderly patients with epistaxis required at least nasal packing, in contrast to more than half of the adults with epistaxis, who only required local soaking with vasoconstrictive agents. Our study differs from a previous report in Turkey, where 48.71% of geriatric patients required cautery, and 14.52% of geriatric patients required further nasal packing.

Patients with systemic diseases in both the elderly and adult groups had significantly higher rates of requiring nasal packing procedures, which suggests an association between systemic diseases and bleeding severity in epistaxis. Mangussi-Gomes et al.[7] reported that the association between high blood pressure and the occurrence of epistaxis is still controversial, although high blood pressure makes it difficult to control epistaxis. Before treating patients with epistaxis, blood pressure measurement and correction are initially suggested.

In the current study, only 3.7% of the elderly group and 1.3% of the adult group underwent further surgical intervention. Surgical intervention is reserved for nasal bleeding that is refractory to medical and conservative treatment. Sphenopalatine artery ligation through an endoscopic approach and ethmoid artery ligation through a Lynch incision can be used for uncontrolled epistaxis. Endovascular embolization of the internal maxillary artery and its terminal branches is an alternative treatment if the patient is not suitable for surgical ligation[8].

In our hospital, an otolaryngologist is on duty for direct patient care in the emergency room 24 hours a day. The epistaxis problem can be evaluated and managed immediately by the otolaryngologist on duty. Our treatment strategy was the same for both the elderly and adult groups and was based on the patients’ history and clinical presentations. Despite observing a much higher rate of underlying systemic diseases and requirements for nasal packing in the elderly, no significant difference in treatment outcomes was observed between the elderly and adult groups in our study.

CONCLUSIONS

Otolaryngologists are facing an inevitably increasing number of elderly patients with epistaxis. In the present study, around one-fourth of the patients with epistaxis were elderly. Although the elderly group needed more nasal packing compared with the adult group, most of the patients in both groups did not need surgical intervention under general anesthesia.

ACKNOWLEDGMENT

Disclosure of conflict of interest: None
REFERENCES

Behavioral anger coping strategies are associated with task switching deficits in patients with Bipolar I Affective Disorder and Major Depressive Disorder

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ABSTRACT

Objectives: The present study was designed to assess: (i) behavioral anger response and task switching in patients with bipolar I affective disorder (BP-D), major depressive disorder (MD-D) and healthy control (HC) individuals; (ii) differences between patients with BP-D, MD-D and HC on behavioral anger coping strategies; and (iii) association between behavioral anger coping strategies and task switching.

Design: Experimental research design

Setting: Bahawal Victoria Hospital, Civil Hospital and Nishter Hospital, Pakistan

Subjects: Fifty patients with BP-D, fifty patients with MD-D, and fifty healthy individuals (from April 2016 until February 2017)

Intervention: In a single testing session, participants completed emotion-word task switching experiment.

Main outcome measure: Following the testing session, they were administered behavioral anger response questionnaire.

Results: Patients with BP-D showed higher task switching deficits as compared to MD-D patients and HC (BP-D: 2301.60 vs. MD-D: 1085.22 vs. HC: 681.68 ms, p <0.001). Patients with BP-D used extreme strategies (direct anger out, rumination and avoidance) more frequently and adaptive strategies (diffusion, assertion and social support seeking) less frequently than patients with MD-D. In contrast, HC used adaptive strategies more frequently and extreme strategies less often. Adaptive coping strategies were inversely correlated with task switching deficits, whereas extreme coping strategies were positively correlated with task switching deficits.

Conclusions: Behavioral anger coping strategies are a significant marker of task switching deficits in patients with BP-D and MD-D.

INTRODUCTION

Bipolar I affective disorder (BP-D) and major depressive disorder (MD-D) are characterized by emotional dysfunctions such as disturbances in reactivity, inhibition, control and regulation of emotion[1,2]. These deficits are associated with increased prefrontal cortex activity and subcortical responses in patients with BP-D as compared with MD-D and healthy control individuals (HC)[3]. Previous research demonstrated social cognition deficits and impaired response flexibility in patients with BP-D[4]. A question arises here whether behavioral anger affects task switching abilities in patients with BP-D and MD-D. Task switching employs inhibitory control, which is essential for successful adaptive social functioning. It refers to the ability to sustain attention and exert inhibition to minimize interference between tasks[5]. Lack of inhibition, behavioral control and sustained attention are common in affective disorders[6-8]. Misinterpretation of social cues and affective instability have been linked to the tendency of attributing others behavior as hostile in patients with BP-D[9,10]. Whether anger coping strategies are linked with cognition is still not understood. The present study aimed to examine behavioral anger response (BAR) and its relationship with switching between facial emotion identification and word tasks. It was hypothesized that: (i) patients with BP-D would show higher switch costs (SC) and

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BAR compared with MD-D patients and HC; (ii) patients with BP-D and MD-D would use different BAR coping strategies than HC; and (iii) BAR response coping strategies would correlate with SC.

SUBJECTS AND METHODS
The study had an experimental design and was approved by the board of studies of The Islamia University of Bahawalpur. Fifty patients diagnosed with BP-D and fifty diagnosed with MD-D according to DSM-5[11] criteria were recruited from Bahawal Victoria Hospital, Civil Hospital, Bahawalpur and Nishter Hospital, Multan, Pakistan from April 2016 until February 2017. Fifty demographically matched healthy individuals from the local community participated in the study. Participants were not included in the sample if they reported history or present symptoms of head injury, substance use, or any comorbid disorder as assessed through Mini International Neuropsychiatric Interview[12]. BP-D patients who had no episode of MD or mania in the last six months and no residual manic symptoms as assessed through Altman Self Rating Mania Scale[13] were included in the study. Depression was assessed through Beck Depression Inventory[14]. All patients were on medication (Table 1). Participants and their parents gave written informed consent. Following this, they were given instructions to complete the task switching experiment shown on a laptop screen. They were told that it was a reaction time experiment, so they had to perform as quickly as possible by pressing fixed manual keys. Upon completion of the experiment, they filled in behavioral anger response questionnaire. At the end of the testing session, the participants were thanked for their time.

Instruments
Emotion-Word Identification Task Switching Experiment
Task switching experiment was designed in E-prime software version 2.0[15] with 32 facial images and words imprinted in the center of the face. In emotion identification, the task was to identify facial expression (angry vs. neutral) whereas in word identification, the task was to categorize word (single vs. double vowel).

Table 1: Demographic characteristics of the sample

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>BD-D group (n = 50)</th>
<th>MD-D group (n = 50)</th>
<th>HC group (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range M ± SD</td>
<td>Range M ± SD</td>
<td>Range M ± SD</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>10 - 17 14.64 ± 1.65</td>
<td>10 - 17 15.18 ± 1.69</td>
<td>10 - 17 14.90 ± 1.64</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Medium</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Low</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Education (years)</td>
<td>5 - 12 9.18 ± 1.40</td>
<td>5 - 12 8.92 ± 1.53</td>
<td>5 - 12 9.28 ± 1.40</td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>1 - 5 2.68 ± 1.31</td>
<td>1 - 5 2.56 ± 1.55</td>
<td>-</td>
</tr>
<tr>
<td>BDI scores</td>
<td>16.68 ± 3.64</td>
<td>35.94 ± 5.79</td>
<td>5.00 ± 2.30</td>
</tr>
<tr>
<td>Mild depression</td>
<td>50</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Moderate depression</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Severe depression</td>
<td>- 50</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Normal</td>
<td>-</td>
<td>-</td>
<td>50</td>
</tr>
<tr>
<td>Selective serotonin reuptake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>inhibitors</td>
<td>05</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>atypical antipsychotics</td>
<td>05</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mood stabilizers</td>
<td>10</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lithium</td>
<td>05</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sodium valporate</td>
<td>10</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>05</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>05</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Combination treatment</td>
<td>05</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Antidepressant SSRI</td>
<td>- 15</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Selective noradrenaline reuptake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>inhibitors</td>
<td>-</td>
<td>15</td>
<td>-</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors</td>
<td>- 10</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>- 10</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*statistically significant at p <0.01; M ± SD: mean ± standard deviation; BP-D: bipolar I affective disorder; MD-D: major depressive disorder; HC: healthy controls; BDI: Beck depression inventory
Tasks were cued by different colored screen. Responses were made through manual keys and reaction times were recorded in milliseconds. Tasks alternated every second trial throughout the experiment in an alternating sequence (EWEWED...). Tasks were counterbalanced across participants, as half of the participants started the experiment with emotion task and the other half did word identification first. The experiment followed the task switching alternating run paradigm[16]. The experiment had a total of 129 trials. The first trial of the experiment had no switch, therefore it was not included in the analysis. The remaining 128 trials were comprised of switch (64) and repeat (64).

Behavioral Anger Response Questionnaire (BARQ)

BARQ is a 37-statement measure to assess anger coping strategies on Likert scale (not true of me = 1 to often true of me = 3). Mean of mean score on each subscale is calculated. Avoidance, direct anger-out and rumination are extreme, whereas assertion, diffusion and social support seeking are adaptive strategies. The questionnaire has satisfactory internal consistency and construct validity[17].

Statistical Analysis

Demographic characteristics were analyzed through descriptive statistics and univariate analysis of variance (ANOVA). Mean reaction times (RTs) on switch (n = 64) and repeat (n = 64) trials were computed from task switching data, and SC were calculated with the formula as mean RTs on switch trials minus mean RTs on repeat trials. Higher switch costs represent task switching impairment. Repeated measures ANOVA with factors as Trial 2 (switch vs. repeat) x Group 3 (patients with BP-D vs. MD-D vs. HC). Multivariate ANOVA was used to examine group differences on BAR coping strategies. Bivariate correlations were computed to assess association between SC and BAR coping strategies.

RESULTS

Task switching data showed significant main effect of Trial F (1, 147) = 65.10, p <0.001, ηp2=0.30 and Group F (1, 147) = 5.38, p <0.01, ηp2 = 0.06. The interaction between Trial x Group was significant F (2, 147) = 8.39, p <0.001, ηp2 = 0.10. This interaction was further analyzed through univariate ANOVA with SC (dependent) and Group (fixed) factor. Results showed significant difference between groups on SC (Table 2). BARQ subscales were analyzed through multivariate ANOVA with assertion, direct anger-out, social support seeking, rumination, avoidance, and diffusion (dependent) and Group (fixed) factors. The result

<table>
<thead>
<tr>
<th>Table 3: Scores on subscales of Behavioral Anger Response Questionnaire</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coping strategies</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Direct anger-out</td>
</tr>
<tr>
<td>BP-D</td>
</tr>
<tr>
<td>MD-D</td>
</tr>
<tr>
<td>HC</td>
</tr>
<tr>
<td>Ruminaton</td>
</tr>
<tr>
<td>BP-D</td>
</tr>
<tr>
<td>MD-D</td>
</tr>
<tr>
<td>HC</td>
</tr>
<tr>
<td>Avoidance</td>
</tr>
<tr>
<td>BP-D</td>
</tr>
<tr>
<td>MD-D</td>
</tr>
<tr>
<td>HC</td>
</tr>
<tr>
<td>Diffusion</td>
</tr>
<tr>
<td>BP-D</td>
</tr>
<tr>
<td>MD-D</td>
</tr>
<tr>
<td>HC</td>
</tr>
<tr>
<td>Assertion</td>
</tr>
<tr>
<td>BP-D</td>
</tr>
<tr>
<td>MD-D</td>
</tr>
<tr>
<td>HC</td>
</tr>
<tr>
<td>Social support seeking</td>
</tr>
<tr>
<td>BP-D</td>
</tr>
<tr>
<td>MD-D</td>
</tr>
<tr>
<td>HC</td>
</tr>
</tbody>
</table>

*statistically significant at p <0.01; M ± SD: mean ± standard deviation; LB-UB: lower bound-upper bound; BP-D: bipolar I affective disorder; MD-D: major depressive disorder; HC: healthy controls
showed significant difference between groups on behavioral anger coping strategies (Table 3). Bivariate correlations showed positive association of SC with direct anger-out ($r = 0.26, p < 0.001$), rumination ($r = 0.27, p < 0.001$), avoidance ($r = 0.28, p < 0.001$), whereas inverse association with diffusion ($r = -0.32, p < 0.001$), assertion ($r = -0.33, p < 0.001$), and social support-seeking ($r = -0.34, p < 0.001$) (Table 4).

**DISCUSSION**

The study revealed a number of important results: (i) patients with BP-D were more impaired on task switching as compared with MD-D patients and HC; (ii) patients with BP-D, MD-D and HC used different BAR coping strategies; and (iii) SC correlated with BAR coping strategies. Higher SC in patients with BP-D and MD-D than HC showed that patients were deficient in inhibitory control, so interference between tasks were not minimized. In contrast, HC were efficient to exert control on interference, thus smaller SC was produced. This result can be seen in the context of brain pathology. Neuropsychological studies showed that cognitive deficits such as abnormalities in emotion processing, decreased inhibition, impulsivity and distractibility were due to cerebral white matter lesions and increased prefrontal cortex and subcortical responses in young BP-D patients as compared to HC.$^{[3,18,19]}$. The structural and functional abnormalities including abnormal myelination of hippocampus, gray matter reduction in prefrontal cortex, hyperactivation of limbic cortex and prefrontal cortical regions, and increased glutamatergic transmission in hippocampus have been implicated in cognitive deficits found in BP-D patients.$^{[20-22]}$ Moreover, the higher glutamate (major excitatory neurotransmitter of central nervous system) concentrations in extracellular space have been shown to impair cognition by inducing cytotoxicity (neuronal death) and excitotoxicity, particularly in hippocampus region, which interferes in neuronal regeneration and dendritic branching.$^{[20-22]}$ Expression of neuronal plasticity marker (growth associated protein 43) and Reelin (glycoprotein responsible for brain lamination) positive cell densities were lower in hippocampal hilar in BP-D patients as compared to HC.$^{[23,24]}$. Recent evidence from rodent studies showed that when adolescent rats were exposed to depression, an inhibited activation in extra cellular signal-regulated kinase (ERK), down regulation of response element binding protein (cAMP) and brain derived neurotropic factor in medial prefrontal cortex were observed. ERK signaling was correlated with deficits in set-shifting and mobility.$^{[25]}$ Meta-analysis of studies showed moderate effect sizes across various cognitive domains (e.g. processing speed, attention, memory, executive functions) in patients with MD-D.$^{[26,27]}$ Brain regions involved in controlling cognition and emotion overlap, for instance frontal cortex, controls emotional arousal apart from cognition. Dysfunction of the frontal lobes has been shown to result in excessive anger and impulsivity.$^{[28]}$ Patients with BP-D reported higher use of extreme coping strategies as compared with patients with MD-D. In contrast, HC reported higher use of adaptive coping strategies as compared with BP-D and MD-D patients. This result is consistent with previous reports of misinterpretation of social cues, hostility and sudden anger attacks in BP-D patients.$^{[29,12]}$ Abnormal connectivity between prefrontal and subcortical circuit is responsible for deficient control of emotion in patients with MD-D.$^{[28]}$. It has been found that when patients with MD-D were faced with a situation that demands interaction between cognition and emotion, there was an over activation in frontal areas and hypoactivation in anterior cingulate cortex.$^{[30]}$. These previous findings are consistent with results of the present study which depicted higher SC in patient groups. Task switching experiment in this study required interaction between emotion processing and cognition, thus deficient cognitive control is reflected in higher SC. Further, abnormal brain activation demonstrated in previous studies are consistent with use of extreme anger coping strategies (direct anger out, rumination, avoidance) in patient groups of the present study. On the contrary, HC used adaptive (diffusion, assertion, social support seeking) rather than extreme anger coping strategies.
It was also found that higher use of extreme anger coping strategies in patient groups are associated with impaired task switching abilities. These findings are linked with neuropsychological studies\(^{26,30}\), which demonstrated abnormal connections and activations in brain areas involved in emotion and cognition.

**Limitations**

The current study included transactional one-time examination of patients known to show variation in mental status on a day-to-day basis. In addition, the scope of the study is limited to only the negative emotions. Further reliability of the emotion-word switching task needs to be determined in these patient groups.

**Implications and future research**

Patients with affective disorders must be examined on task switching and BAR. Increased BAR would serve as an indication of set-shifting deficits in these patients, which can be prevented with anger management treatment interventions.

**CONCLUSION**

Behavioral anger response is a social marker of task switching deficits in patients with affective disorders.

**ACKNOWLEDGMENT**

We would like to acknowledge the staff of the BVH, Civil hospital and Nishter Hospital for their cooperation in data collection.

**Conflict of Interest**: No conflict of interest

**Disclosure of grants or other funding**: No grants or funds to be disclosed.

**REFERENCES**


Original Article

Association of Vitamin D receptor gene TaqI variant with type 2 diabetes mellitus in Pakistani population

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ABSTRACT

Objective: The vitamin D receptor (VDR) gene polymorphisms have inconsistent associations with type 2 diabetes mellitus (T2DM) in different ethnic groups. Present case-control study investigated whether there was an association of TaqI (rs731236 C>T) polymorphism in the exon 9 of VDR gene with T2DM in a Pakistani population.

Design: Case-control study

Setting: DHQ hospital, Faisalabad; Clinico-medical biochemistry lab, Department of Biochemistry, University of Agriculture, Faisalabad, Pakistan; and Molecular labs, Department of Medical and Dentistry, Southmead Hospital, University of Bristol, Bristol, UK from March 2015 to May 2016

Subjects: Adult type 2 diabetic subjects

Intervention: Non-interventional study

Main outcome measure: Association of VDR gene polymorphism (TaqI) with T2DM

Results: Fasting blood glucose, HbA1c, and body mass index were significantly (p <0.01) higher in T2DM (n = 150) patients as compared to control group (n = 100). Differences in TaqI genotypes (Tt) of VDR gene analyzed by DNA amplification with polymerase chain reaction and endonuclease digestion following restriction fragment length polymorphism method were significant (p <0.01) between T2DM and normal groups. However, TaqI single nucleotide polymorphism was related non-significantly (p >0.05) to the diabetic complications.

Conclusion: VDR gene TaqI polymorphism may contribute to the onset and progression of T2DM in Pakistani population, but association between VDR genetic polymorphisms and diabetic complications is still not clear and warrants additional studies to validate the current outcome.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a complex disease with genetic, environmental and other factors involved in pathogenesis. Variations in the gene sequences or single nucleotide polymorphisms (SNP) explain the individual differences in traits like disease susceptibility and response to treatment. At least 64 genetic variants are strongly associated with T2DM. However, the pathophysiologic roles of these variants are mostly unknown and require further functional characterization to redefine the individual risk of T2DM. Although gene variants possess an unpretentious influence accounting for only 10% of the T2DM heritability, advances in futuristic gene sequencing may explore unique variants with prominent impact, resulting in the better understanding of pathology and therapeutic approaches.

One environmental factor related to T2DM is vitamin D, a prominent immune-modulator, as it participates in glucose metabolism and insulin release. Hypovitaminosis D predisposes individuals to develop T2DM as it affects immune system, insulin synthesis and secretion. Vitamin D receptor (VDR) belongs to a super-family of nuclear receptor of the ligand-activated transcription factors including thyroid hormone receptors, estrogen receptor, peroxisome proliferators-activated receptors and retinoic acid receptors. VDR acts as transcription factor when bound with vitamin D. These receptors are predominantly found in beta cells of pancreas necessary for insulin production from pancreas. VDR is extensively expressed in immune system; stimulates T and B cells, dendritic cells and macrophages; are directed to recognition of central immune-modulatory function of vitamin D; and

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detection of VDR in pancreas leading to recognition of vitamin D role in the insulin synthesis and secretion[6,9].

VDR gene present on chromosome 12q12-q14[7] mediates vitamin D action as it binds to vitamin D response elements. Genetic polymorphism of four allelic variants of vitamin D receptor gene (ApaI, FokI, BsmI and TaqI) affect insulin secretion, synthesis, transportation and action of vitamin D[8,9]. A number of VDR gene variants have been observed in early 1990s; ApaI, BsmI, EcoRV, TaqI, Tru9I, FokI and CDX2. Though, BsmI, ApaI, FokI and TaqI are four restriction fragment length polymorphisms (RFLP) at VDR gene that have been targeted to explain variation in risk of diabetes mellitus[10]. However, studies on association between VDR genetic polymorphisms and risk of T2DM in different ethnic groups are not conclusive. Progress in identification of novel VDR gene variants predisposing to diabetes mellitus in Pakistan has been limited. Comprehensive understanding of VDR genetic polymorphisms would help uncover their impact in T2DM. The present case-control study was conducted to investigate whether there was an association of TaqI (rs731236 C>T) polymorphism in exon 9 of VDR gene with T2DM in a Pakistani population.

SUBJECTS AND METHODS

The case-control study comprised of 150 T2DM patients along with 100 normal individuals during the period March 2015 to May 2016 recruited through a convenient sampling technique. Patients were subdivided into different subgroups according to their diabetic complications; retinopathy patients, nephropathy patients, cardiac patients and hypertensive patients in order to establish the associations between diabetic complications and TaqI genotypes. Ethical approval of research protocols was procured from Graduate Studies and Research Board, University of Agriculture, Faisalabad, Pakistan and research work was conducted at Clinico-Medical Biochemistry Lab, Department of Biochemistry, University of Agriculture, Faisalabad, Pakistan and Molecular Labs, Department of Medical and Dentistry, Southmead Hospital, University of Bristol, Bristol, UK. Participants gave written informed consent for genotyping of their blood samples. After collection of demographic data (age, gender, body mass index (BMI)), blood samples were used to assess fasting glucose (FG) and HbA1c by kits (Merck, Germany) as per manufacturer’s guidelines using Dade Behring clinical chemistry system for dimension auto-analyzer, Siemens, USA and Diastat auto-analyzer, Randox, UK.

Salting out method for genomic DNA extraction was implied using proteinase K. The quantity and quality of DNA was assessed by spectrophotometric quantification using Nanodrop (Nanophotometer™, Implen, Germany). Purity of the DNA was assessed by measuring optical density as OD260/OD280[11].

Polymerase chain reaction (PCR) primer sequences used were[12]: (F: CCTGTGCCTTCTTCTCTATCC; R: AGCCTGAGTGACAGCATGA). Primers were diluted to 1 μg/μL stock and these stocks were further diluted to working concentration of 10 pmol/μL. The reactions were set in 0.2 mL PCR tubes. The PCR reaction mixture (10 μL) contained 5X Colorless GoTaq® Flexi Buffer (Part# M890A): Proprietary formulation supplied at pH 8.5. The buffer contains 20 mmol. Tris HCl; pH 7.5; 100 mmol NaCl; 0.1 mmol EDTA; 1 mmol dithiothreitol; 1.0 μL of 50% (v/v) glycerol. Other materials used were 1.0 mmol.dNTPs, 0.3 mL of 50 mmol MgCl₂ 5 pmol/ μL forward and reverse primers for their respective DNA fragment (0.4 μL each). Go Taq kit (Promega Madison, Wisconsin USA) was used for about 1.0 mL of genomic DNA (100 ng/ μL). PCR conditions were optimized for annealing temperature (60 °C) and Mg²⁺ concentration.

The exon 9 of VDR gene was amplified using RFLP method for TaqI restriction polymorphism evaluation. The genomic DNA was amplified using specific primers and according to a specific program (PCR thermocycler T100TM, BioRad). The initial denaturation step lasted for 3 minutes at 95 °C, followed by 35 cycles of amplification, denaturation at 95 °C for 30 seconds, an annealing for 30 seconds with annealing temperature optimized for each primer set and an extension step for 30 seconds at 72 °C. Final extension was done for 4 minutes at 72 °C.

After amplification of the VDR fragments with PCR, all the amplified fragments were digested with specific enzymes under specific time and temperature conditions, allowing to assess the genotype of each individual. For the TaqI (rs731236 C>T), the digestion conditions were 37 °C incubation temperature (60 minutes) for 201, 251, 293, 494 bp digestion fragments (New England BioLabs®, R01095). The 4.0 μL of PCR product was used to proceed with the respective fragment digestion, added mixture of 1.0 μL of the respective enzyme and 5.0 μL NE-buffer give appropriate fragments.

Agarose gel (3%) for genomic DNA and 2% for PCR amplified product and digested fragments was prepared by boiling agarose with 1X TBE (Tris-Borate-EDTA) buffer and stained with Medori Green Safe Buffer (1 μL/mL) (Bulldog Bio, USA). The migration in the agarose gel was performed at 110 V for 120 minutes. Molecular weight marker (HyperLadder II, Bioline or VC 100 bp Plus DNA Ladder, Vivantis) compared molecular weight of the DNA fragments. For agarose gel visualization, UV light using UVITEC system (Uvitec Cambridge) was used. Data analysis
was performed using Statistical Package for Social Science (SPSS, version 17; Chicago, USA). The results were considered statistically significant when p-value <0.05 using the Statistical Package for Social Sciences (SPSS version 16.0).

RESULTS
The study comprised of 150 T2DM (age: 45.8 ± 2.99 years) and 100 non-diabetic subjects (age: 45.3 ± 5.1 years; p = 0.422). In diabetic group (DG) and control group (CG), 53% and 56% were male. Significant differences (p <0.01) in BMI (35.3 ± 10.7 kg/m² vs. 22.9 ± 5 kg/m²), FG (144 ± 6.38 mg/dL vs. 83 ± 5.21 mg/dL) and HbA1c (7.13 ± 0.58% vs. 4.46 ± 0.49%) were observed between DG and CG subjects. The TaqI restriction site is located in exon 9 of VDR gene. After amplification of exon 9 by PCR (Fig 1), heterozygosity of exon 9 was confirmed by enzymatic digestion (Fig 2). TaqI restriction among T2DM complications groups were recorded in Figs 3-5. Differences in TaqI genotypes of VDR gene were significant (p < 0.01) between T2DM and normal groups (Table 1). Results confirmed...
the presence of elevated expression of the VDR genotypes including TaqI (Tt) in patients with type 2 diabetes as compared to normal subjects group. In addition, TaqI SNP was related non-significantly (p >0.05) to the diabetic complications (Table 2) in the present study.

**Table 1:** Distribution of genotype, allele frequencies and carriage rate of TaqI among patients and controls groups

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Control Group n (%)</th>
<th>Patient Group n (%)</th>
<th>Total Group n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tt</td>
<td>16 (16)</td>
<td>22 (14.7)</td>
<td>38 (15.2)</td>
</tr>
<tr>
<td>Tt</td>
<td>27 (27)</td>
<td>81 (54)</td>
<td>108 (43.2)</td>
</tr>
<tr>
<td>TT</td>
<td>57 (57)</td>
<td>47 (31.3)</td>
<td>104 (41.6)</td>
</tr>
<tr>
<td>Total</td>
<td>100 (100)</td>
<td>150 (100)</td>
<td>250 (100)</td>
</tr>
</tbody>
</table>

Data expressed as X^2= 19.70; p <0.05; S: significant

**Table 2:** Distribution of genotype, allele frequencies and carriage rate of TaqI among T2DM sub-groups and control group

<table>
<thead>
<tr>
<th>Groups</th>
<th>Genotypes</th>
<th>Total n (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tt (n (%))</td>
<td>Tt (n (%))</td>
<td>TT (n (%))</td>
</tr>
<tr>
<td>Control</td>
<td>16 (16)</td>
<td>27 (27)</td>
<td>57 (57)</td>
</tr>
<tr>
<td>CP</td>
<td>16 (20)</td>
<td>37 (46.3)</td>
<td>27 (33.8)</td>
</tr>
<tr>
<td>NP</td>
<td>2 (10)</td>
<td>7 (35)</td>
<td>11 (55)</td>
</tr>
<tr>
<td>RP</td>
<td>1 (5)</td>
<td>15 (75)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>HP</td>
<td>3 (10)</td>
<td>22 (73.3)</td>
<td>5 (16.7)</td>
</tr>
<tr>
<td>Total</td>
<td>38 (15.2)</td>
<td>108 (43.2)</td>
<td>104 (41.6)</td>
</tr>
</tbody>
</table>

Data expressed as X^2= 35.544; p >0.05

DISCUSSION

T2DM, a multifactorial metabolic disorder is increasing at an alarming rate. Different etiological factors such as genetic and environmental elements express extensive discrepancies among different populations. The recognition of genes provoking T2DM could lead to more insight into the pathogenesis, preventive and management strategies[12,21].

The present data endorsed the association of VDR polymorphism of TaqI genotype with the risk of T2DM in the Pakistani population. Although no noteworthy relation was observed between TaqI polymorphism and diabetic complications in the current study, it is suggested that TaqI polymorphism may contribute to the susceptibility to T2DM complications, as molecular explanation of association between VDR polymorphisms and T2DM is only partially understood[13]. Many previous studies could not explain the relationship of VDR gene polymorphisms with post-diabetic complications, however onset of T2DM was influenced by VDR gene polymorphism[14-17].

Several epidemiologic studies have examined the association of the VDR gene rs731236 C>T (TaqI) SNP and T2DM, and the results are inconsistent across different populations. Nejad et al[18] demonstrated that TaqI VDR polymorphism genotypes might be different in diabetic and control subjects. Ogunkolade et al[19] illustrated a positive relationship between the TaqI (genotype TT) polymorphisms and decreased insulin secretory potential.

Previous results[15,20,21] confirmed that VDR gene genotype TaqI polymorphism is linked with onset of type 2 diabetes mellitus. Furthermore, Al-Daghri et al[22] explained that TaqI SNP is significantly more common in T2DM patients with elevated levels of cholesterol and lower levels of HDL cholesterol. Similarly, substantial association of TaqI with T2DM was reported among Turkish and Chinese populations[12,23,24].

Contrary to these findings, many researchers failed to demonstrate an analogous relationship between TaqI polymorphism and T2DM in Bangladesh, America, Poland, India, Jordan and Morocco[14, 25-30] TaqI had no remarkable association with T2DM in Bangladeshi population[20]. Insulin sensitivity was significantly decreased in T2DM cases of Bangladeshi origin. The reasons for these discrepancies might be elucidated by the differences in genetic background among ethnic groups. To date, no data exists on VDR gene polymorphism in Pakistani diabetic population.

**CONCLUSION**

VDR gene TaqI polymorphism may contribute to the onset and progression of T2DM in Pakistani population, but association between VDR genetic polymorphisms and diabetic complications is still not clear and warrants additional studies to validate the genetic susceptibility of VDR gene to T2DM onset and progression.
ACKNOWLEDGMENT
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REFERENCES


Original Article

The factors affecting sleep quality in type 2 diabetes patients

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ABSTRACT

Objective: Research was planned with the aim of determining the sleep quality of individuals with type 2 diabetes and the factors affecting this.

Design: Descriptive and cross-sectional study

Setting: Endocrinology Department of the Internal Medicine Section of Ege University Medical Faculty Hospital, Manisa Celal Bayar University Hafsa Sultan Hospital, and Balıkesir University Medical Faculty Hospital

Subjects: The research was conducted between May 2014 and February 2015 on 366 individuals with type 2 diabetes.

Intervention: Non-interventional

Main outcome measure: The sleep quality of individuals with type 2 diabetes and the factors affecting this

Results: The total Pittsburgh Sleep Quality Index (PSQI) scores of individuals who had had diabetes for 1 - 4 years and 5 - 9 years were found to be significantly higher than the scores of those who had had diabetes for less than one year or more than ten years (f = 10.85, p = 0.000). The total PSQI scores of individuals using oral anti diabetic (OAD) and insulin diabetes treatment were significantly higher than the scores of patients receiving only diet treatment or OAD + insulin (f = 3.03, p = 0.029). A significant relationship was found between the HbA1c of the individuals in the study with type 2 diabetes and their total PSQI scores (p <0.01).

Conclusion: It can be said that such socio-demographic characteristics as age, gender, income, duration of diabetes and diabetes treatment, and metabolic values such as the glycated haemoglobin (Hemoglobin A1c- HbA1c), fasting blood glucose and body mass index negatively affect sleep quality.

INTRODUCTION

One of the most important factors in remaining healthy is sleep[1]. As well as being a reversible state of unconsciousness, it is not only a state of motionlessness enabling the body to rest, but also an active state of renewal, enabling the whole body to prepare itself anew for life[1]. Sleep is a basic human need which has a positive effect on not only productivity, but also on cognitive functions such as memory and concentration, and which brings about a state of physical and psychological wellbeing[2]. Along with the beneficial effects of sleep, sleep disorders and irregularities have a negative effect on individuals, causing such problems as lack of concentration, memory loss, anxiety, depression, psychosis, an increase in sensitivity to pain, irritability, loss of appetite, and evacuation difficulties[3-5].

Chronic loss of sleep and the problems it brings are seen very commonly in society. Long-term sleep loss and deterioration in the quality of sleep have an effect on the rates of both death and illness. Many experimental studies have shown that they cause a reduction in insulin sensitivity and glucose tolerance[6-9]. It has been determined that impaired sleep quality in those who sleep for less than six hours a night is a risk factor for type 2 diabetes[9,10]. Studies have determined that poor sleep quality is an important risk factor not only for type 2 diabetes mellitus (DM), but also for the development of obesity, and that type 2 diabetes and obesity are commonly seen together with male gender
and sleep apnea\textsuperscript{[11-13]}. Some studies have suggested a strong link between an increase in HbA1c and sleep loss\textsuperscript{[12-14]}. It has been reported that in those with type 2 diabetes, such problems as frequent urination and restless leg syndrome commonly cause sleep disturbances\textsuperscript{[15-16]}. In those individuals, sleep disturbances which continue for a long time are reported to cause daytime sleepiness, a reduction in mental acuity, and a disruption in general health and functions, and poor sleep quality resulting from these sleep problems has a negative effect on the quality of life relating to health\textsuperscript{[15]}. For this reason, a basic aim of nursing practice must be early diagnosis of sleep problems and improvement of sleep quality, and as a result of this, an increase in quality of life. Nurses play a key role in the diagnosis and treatment of both acute and chronic sleep disturbances, the assessment of sleep needs of patients, and ensuring their comfort\textsuperscript{[15]}. Problems with sleeping patterns and sleep disturbances have increased in the past ten years, and at the same time, type 2 DM and obesity have reached epidemic proportions in the world in general\textsuperscript{[17]}. Recent studies have reported that approximately 37\% of the world’s population is obese or severely overweight, and the number of individuals with a diagnosis of diabetes has been calculated as 382 million\textsuperscript{[18]}. In understanding metabolic diseases like diabetes, determining the role of risk factors is important for preventing the development and progress of the disease. It has been reported that sleep disturbance is an important factor in the development of both type 2 diabetes and other metabolic diseases\textsuperscript{[14]}. The most recent epidemiological study reported that 50 - 70 million people experience such chronic sleep disturbances as insufficient sleep, insomnia and sleep apnea in America\textsuperscript{[9]}. It is thought that sleep disturbances affect metabolic health and bodily functions including the endocrine system and the immune system\textsuperscript{[11]}. It is thought that by determining how and in what areas diabetes affects an individual’s sleep problems, patients’ sleep and life quality will be improved with treatment, as care can be planned with the help of the data obtained. The study was planned with the purpose of examining sleep quality and the factors affecting sleep in type 2 diabetes patients.

\textbf{Purpose}

The purpose of this study was to examine the sleep quality of type 2 DM patients in three provinces in the west of Turkey.

\textbf{SUBJECTS AND METHODS}

\textbf{Design}

The research was planned as a descriptive and cross-sectional study with the aim of establishing sleep quality and the factors affecting sleep in type 2 diabetic patients and determining how and in what areas this affects the sleep problems of diabetics.

\textbf{Sample}

The research was conducted between May 2014 and February 2015 with 366 individuals with type 2 diabetes who fitted the inclusion criteria of the study and gave voluntary oral and written consent, and who were undergoing treatment at the Endocrinology Department of the Internal Medicine Section of Ege University Medical Faculty Hospital, the Endocrinology Science Department of the Internal Medicine Section of Celal Bayar University Hafsa Sultan Hospital, and the Internal Medicine clinics and outpatient clinics of Balikesir University Medical Faculty Hospital.

\textbf{Ethical considerations}

Permission regarding the choice of topic of the research and its planning and preparation and to carry out the study was obtained from “The Ethics Committee of Ege University Nursing Faculty” with number of 49-3257 and date 01.06.2013 in accordance with the Declaration of Helsinki in 1995 (as revised in Brazil 2013). The necessary permission to perform the research and to collect data was obtained from the Chief Physician’s Offices of Ege University Medical Faculty Hospital, Celal Bayar University Hafsa Sultan Hospital, and Balikesir University Medical Faculty Hospital. Prior to the study, written and verbal permission was obtained from all patients.

\textbf{Data collection}

A personal information form with 33 questions on socio-demographic characteristics and sleep problems was applied to the type 2 diabetes patients, along with the Pittsburgh Sleep Quality Index (PSQI).

\textbf{I – Personal Information Form}

This section consisted of 33 questions for patients to determine socio-demographic variables (age, gender, place of residence, education status, profession, marital status and monthly income), information about the patient’s diabetes, treatment, previous history, length of stay in hospital and sleep problems experienced (Attachment I).

\textbf{II – Pittsburgh Sleep Quality Index}

The PSQI was developed in 1989 by Buysse \textit{et al} to determine sleep quality in psychiatry and clinical research. The items in the PSQI were formed with the help of clinical observations of patients with sleep disturbances, other scales found in the literature on sleep quality, and an 18-month clinical monitoring period of the PSQI. A global score of more than 5 on the PSQI indicates poor sleep quality. Testing
of the validity and reliability of the scale for Turkey was carried out in 1996 by Ağargün et al, and the Cronbach’s alpha reliability coefficient of the scale was found to be 0.804.

The PSQI evaluates sleep quality within the previous month. It comprises 24 questions, 19 of which are self-reporting questions, while five questions are answered by partners or room-mates. The last five questions are only used for clinical information and are not included in the scoring. The last of the self-reporting questions (question 19) concerns whether or not the patient has a room-mate or partner, and is not included in the scoring. The self-reporting questions cover various factors concerning sleep quality. These are to do with sleep duration, sleep latency and an estimation of the frequency and severity of specifically sleep-related problems. The 18 items which are scored are grouped into seven component points. Some of these components are determined by a single item, while others are obtained by grouping a number of items. Each item is evaluated on a scale of 0 to 3. The total score of the seven components gives the total PSQI score, which has a value of 0 - 21. A high total score indicates poor sleep quality[19,20].

The seven components of the PSQI are the standardized application of the points which are most emphasized during clinical interviews with patients with complaints of sleeplessness or excessive sleep. These components are: 1) subjective sleep quality; 2) sleep latency; 3) sleep duration; 4) accustomed sleep efficacy; 5) sleep disturbance; 6) use of sleep medication; and 7) daytime sleep function disturbance.

Component scores are determined from the totals of the following items:

- Component 1 (question 6)
- Component 3 (question 4)
- Component 6 (question 7)
- Component 2 (questions 2 and 5a)
- Component 4 (questions 1, 3 and 4)
- Component 5 (questions 5b-j)
- Component 7 (questions 8 and 9).

Question 4 is used in both components 3 and 4. The whole index takes from five to ten minutes to complete, and scoring takes about five minutes. The PSQI gives a quantitative measure of sleep quality, making use of the definitions ‘good sleep’ and ‘poor sleep’. It can be used easily and widely for both clinical and in research purposes in psychiatry and general medicine[19,20].

Data analysis

Data analysis was performed on the program SPSS 15.0 with the use of numbers, percentages and means, t-test, ANOVA, Kruskal-Wallis and correlation tests.

## RESULTS

Table 1 shows the distribution of the individuals with diabetes according to their identifying characteristics. It was found that 59.6% of the individuals with diabetes were female, 54% were aged 58 years or more, 80% were married, 53.6% were educated to primary school level, 67.21% were working, and 70.5% had an income equal to their expenses (Table 1).

<table>
<thead>
<tr>
<th>Socio-demographic characteristics</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>218</td>
<td>59.6</td>
</tr>
<tr>
<td>Male</td>
<td>148</td>
<td>40.4</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>57 years or less</td>
<td>168</td>
<td>46</td>
</tr>
<tr>
<td>58 years or more</td>
<td>198</td>
<td>54</td>
</tr>
<tr>
<td>Mean age</td>
<td>57.3 ± 13.61</td>
<td>min = 19, max = 84</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>269</td>
<td>80</td>
</tr>
<tr>
<td>Single/widowed/divorced</td>
<td>97</td>
<td>40</td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Literate</td>
<td>44</td>
<td>12</td>
</tr>
<tr>
<td>Primary school</td>
<td>196</td>
<td>53.6</td>
</tr>
<tr>
<td>Middle school</td>
<td>46</td>
<td>12.6</td>
</tr>
<tr>
<td>High school</td>
<td>43</td>
<td>11.7</td>
</tr>
<tr>
<td>Higher education</td>
<td>37</td>
<td>10.1</td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working</td>
<td>120</td>
<td>67.21</td>
</tr>
<tr>
<td>Not working</td>
<td>246</td>
<td>32.79</td>
</tr>
<tr>
<td>Income status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Income less than expenditure</td>
<td>93</td>
<td>25.4</td>
</tr>
<tr>
<td>Income equal to expenditure</td>
<td>258</td>
<td>70.5</td>
</tr>
<tr>
<td>Income less than expenditure</td>
<td>15</td>
<td>4.1</td>
</tr>
<tr>
<td>Total</td>
<td>366</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 2 shows characteristics relating to the individuals’ diabetes. According to their statements, 38.3% had had diabetes for more than 10 years, 49.5% realized they had diabetes when they went for treatment for another illness, 32.2% were suspicious and went to a doctor, 64.5% had first degree relatives with diabetes, the diabetes treatment type of 34.7% was oral anti diabetic (OAD), while that of 48.1% was insulin. According to the patients’ own statements, the perception of conformity to diabetes treatment of 47.5% was average, the perception of conformity to diabetes treatment of 33.1% was good, and according to 19.4% it was poor. Finally, 45.4% of the individuals reported that they had diabetes check-ups once in three months, 65.3% that they did not smoke, 65.3% that they did not consume alcohol, and 74.9% that they did not exercise.

Table 3 shows the distributions of the individuals with diabetes according to their sleep characteristics. According to their statements, 40.4% of the individuals
with diabetes had total sleep problems and 39% had partial sleep problems. Of those who stated that they had a sleep problem, 23.7% reported that they woke up frequently, 20.9% that they had difficulty getting to sleep, 14.9% that they dozed during the daytime, 13.3% that they did not sleep at all, and 13.3% reported that they had difficulty waking up. They stated that when they were in hospital, they could not sleep because of the physical conditions (noise, lighting, heating, ventilation, etc.) (33.9%), because of pain or illness-related complaints (18.2%), because too many people were staying in the same room (16.1%), or because there was too much coming and going in the room (12.7%). Finally, of the 47.9% of the individuals who used some method to get to sleep, 55.7% reported that they watched TV, 13% that they got up and walked around, 10.7% that they read a book, and 10% that they took a hot shower.

When the distribution of mean metabolic monitoring values of the individuals with diabetes were examined, it was found that their mean fasting blood glucose level was \(187.47 \pm 132.82 \text{ mg/dl} \) (min = 50, max = 689), their mean HbA1c was \(8.49 \pm 2.97\%\) (min = 5, max = 15), their total cholesterol was \(204.11 \pm 55.89 \text{ mg/dl} \) (min = 66, max = 508), and their mean BMI was \(29.48 \pm 6.96 \text{ kg/m}^2 \) (min = 15.43, max = 49) (Table 4).

The correlation between various identifying characteristics of the individuals with diabetes and their total mean scores on the PSQI were examined, and it was found that the total PSQI scores of patients in the 57 years and below age group were significantly higher than those of the 58 years and above age group (t = 5.60, p = 0.000). Age affected sleep quality negatively in type 2 diabetes patients, and they suffered sleep problems (Table 5).

<table>
<thead>
<tr>
<th>Table 2: Characteristics relating to the individuals’ diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>Duration of diabetes</td>
</tr>
<tr>
<td>Less than one year</td>
</tr>
<tr>
<td>1 - 4 years</td>
</tr>
<tr>
<td>5 - 9 years</td>
</tr>
<tr>
<td>10 years or more</td>
</tr>
<tr>
<td>The emergence of diabetes</td>
</tr>
<tr>
<td>By glucose level measurement</td>
</tr>
<tr>
<td>When I went for treatment for another illness</td>
</tr>
<tr>
<td>I was suspicious and went to the doctor</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>You have first degree relatives with diabetes</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Diabetes treatment</td>
</tr>
<tr>
<td>Only diet treatment</td>
</tr>
<tr>
<td>Oral antidiabetic</td>
</tr>
<tr>
<td>Insulin</td>
</tr>
<tr>
<td>Oral antidiabetic + insulin</td>
</tr>
<tr>
<td>Perception of conformity to current diabetes treatment</td>
</tr>
<tr>
<td>Good</td>
</tr>
<tr>
<td>Average</td>
</tr>
<tr>
<td>Poor</td>
</tr>
<tr>
<td>Perception of conformity to current diet</td>
</tr>
<tr>
<td>Good</td>
</tr>
<tr>
<td>Average</td>
</tr>
<tr>
<td>Poor</td>
</tr>
<tr>
<td>Frequency of diabetes check-up</td>
</tr>
<tr>
<td>Once a month</td>
</tr>
<tr>
<td>Once every three months</td>
</tr>
<tr>
<td>Once every six months</td>
</tr>
<tr>
<td>Once a year</td>
</tr>
<tr>
<td>Smoking status</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>I’ve stopped smoking</td>
</tr>
<tr>
<td>Alcohol consumption status</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>I’ve stopped drinking</td>
</tr>
<tr>
<td>Exercise status (n = 358)</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3: Characteristics of individuals with diabetes relating to sleep and sleep problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>Do you have a sleeping problem?</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>Somewhat</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>What is your sleeping problem? (n=249)</td>
</tr>
<tr>
<td>I can’t sleep at all</td>
</tr>
<tr>
<td>I have difficulty getting to sleep</td>
</tr>
<tr>
<td>I keep on waking up</td>
</tr>
<tr>
<td>I have difficulty waking up</td>
</tr>
<tr>
<td>I wake up with a breathing problem</td>
</tr>
<tr>
<td>Dozing in the daytime</td>
</tr>
<tr>
<td>Irregularity in sleeping time</td>
</tr>
<tr>
<td>Waking up very early</td>
</tr>
<tr>
<td>Disorders relating to sleeping (sleepwalking, nightmares, snoring, etc.)</td>
</tr>
<tr>
<td>Reason for inability to sleep in hospital</td>
</tr>
<tr>
<td>Too many people in the same room</td>
</tr>
<tr>
<td>Being alone in the room</td>
</tr>
</tbody>
</table>
| Physical conditions (noise, lighting, heating, ventilation, etc.) (33.9%), because of pain or illness-related complaints (18.2%), because too many people were staying in the same room (16.1%), or because there was too much coming and going in the room (12.7%). Finally, of the 47.9% of the individuals who used some method to get to sleep, 55.7% reported that they watched TV, 13% that they got up and walked around, 10.7% that they read a book, and 10% that they took a hot shower.

When the distribution of mean metabolic monitoring values of the individuals with diabetes were examined, it was found that their mean fasting blood glucose level was \(187.47 \pm 132.82 \text{ mg/dl} \) (min = 50, max = 689), their mean HbA1c was \(8.49 \pm 2.97\%\) (min = 5, max = 15), their total cholesterol was \(204.11 \pm 55.89 \text{ mg/dl} \) (min = 66, max = 508), and their mean BMI was \(29.48 \pm 6.96 \text{ kg/m}^2 \) (min = 15.43, max = 49) (Table 4).

The correlation between various identifying characteristics of the individuals with diabetes and their total mean scores on the PSQI were examined, and it was found that the total PSQI scores of patients in the 57 years and below age group were significantly higher than those of the 58 years and above age group (t = 5.60, p = 0.000). Age affected sleep quality negatively in type 2 diabetes patients, and they suffered sleep problems (Table 5).
It was found that the total PSQI scores of females were significantly higher than those of men \( (t = 2.70, p = 0.007) \). Gender had a negative effect on sleep quality in type 2 diabetic patients, and they suffered sleep problems (Table 5).

The total PSQI scores of patients who were single, widowed or divorced were significantly higher than those of married individuals \( (t = -5.03, p = 0.000) \). Being single and maybe living alone had a negative effect on the sleep quality of individuals with type 2 diabetes and caused them to have sleep problems (Table 5).

The total PSQI scores of individuals who were educated to middle or high school levels were significantly higher than those of individuals who were literate or educated to high school or university level \( (f = 2.39, p = 0.050) \). Sleep quality was negatively affected in type 2 diabetes patients who were educated to middle or high school levels (Table 5).

The total PSQI scores of individuals who were working were significantly higher than those of individuals who were not working (housewives, retired, unemployed, etc.) \( (t = 4.22, p = 0.000) \). Sleep was negatively affected in type 2 diabetic patients who were working (Table 5).

The total PSQI scores of individuals whose income was found to be less than their expenditure were significantly higher than those of individuals whose income was equal to or in excess of their expenditure \( (f = 31.02, p = 0.000) \). The sleep quality of individuals with type 2 diabetes whose income was less than their expenditure was affected negatively (Table 5).

The total PSQI scores of individuals who had diabetes for 1 - 4 years and 5 - 9 years were found to be significantly higher than the scores of those who had had diabetes for less than one year or more than ten years \( (f = 10.85, p = 0.000) \). The sleep quality of type 2 diabetes patients who had had diabetes for 1 - 4 years or 5 - 9 years was negatively affected (Table 5).

The total PSQI scores of individuals who consumed alcohol were significantly higher than those of individuals who did not \( (t = 3.44, p = 0.001) \). Alcohol consumption by individuals with type 2 diabetes negatively affected sleep quality (Table 5).

The total PSQI scores of individuals who perceived their conformity to diet as average or poor were significantly higher than those of individuals who perceived it as good \( (f = 13.87, p = 0.000) \). The sleep quality of individuals who perceived their conformity to diet as average or poor was negatively affected (Table 5).

The total PSQI scores of individuals who did not exercise were significantly higher than those of individuals who did \( (t = -2.70, p = 0.007) \). The sleep quality of individuals with type 2 diabetes who did not exercise was negatively affected (Table 5).

The total PSQI scores of individuals who had sleep problems or partial sleep problems was found to be significantly higher than those of individuals without sleep problems \( (f = 40.76, p = 0.000) \). The sleep quality of individuals with type 2 diabetes who had sleep problems or partial sleep problems was negatively affected (Table 5).

The sleep problems of those who said that they could not sleep at all, that they had difficulty getting to sleep, that they kept waking up, that they had difficulty waking up, that they woke up with breathing difficulties, or that they dozed during the day were significantly greater than those who reported irregularity in their time of going to sleep, waking up very early, or sleep disturbances (sleepwalking, nightmares, snoring, etc.) \( (x^2 = 45.13, p = 0.000) \). In terms of sleep problems, the total sleep quality of type 2 diabetes patients who reported that they could not sleep at all, that they had difficulty getting to sleep, that they kept waking up, that they had difficulty waking up, that they woke up with breathing difficulties, or that they dozed during the day was negatively affected (Table 5).

The total PSQI scores of those who perceived their conformity to diabetes treatment as average and poor were significantly higher than those of patients who perceived them as good \( (f = 15.39, p = 0.000) \). The sleep quality of individuals with type 2 diabetes who perceived their conformity to diabetes treatment as good was negatively affected (Table 5).

The total PSQI scores of smokers was significantly higher than that of non-smokers \( (t = 5.74, p = 0.000) \). The sleep quality of individuals with type 2 diabetes who smoked was negatively affected (Table 5).

### Table 4: Distribution of individuals with diabetes according to mean metabolic monitoring values

<table>
<thead>
<tr>
<th>Metabolic values</th>
<th>Avg ± SD</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting blood glucose (mg/dl)</td>
<td>187.47 ± 132.82</td>
<td>50</td>
<td>689</td>
</tr>
<tr>
<td>Hemoglobin-A1c (%)</td>
<td>8.49 ± 2.97</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>204.11 ± 55.89</td>
<td>66</td>
<td>508</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29.48 ± 6.96</td>
<td>15.43</td>
<td>49</td>
</tr>
</tbody>
</table>

The total PSQI scores of those who perceived their conformity to diabetes treatment as average and poor were significantly higher than those of patients who perceived them as good \( (f = 15.39, p = 0.000) \). The sleep quality of individuals with type 2 diabetes who perceived their conformity to diabetes treatment as good was negatively affected (Table 5).
The factors affecting sleep quality in type 2 diabetes patients

Table 5: Correlation between certain identifying characteristics of individuals with diabetes and their total mean scores on the Pittsburg Sleep Quality Index

<table>
<thead>
<tr>
<th>Pittsburg Sleep Quality Index (PSQI) total mean score</th>
<th>n</th>
<th>Avg ± SD</th>
<th>t / f / x²</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;57 years</td>
<td>168</td>
<td>12.31 ± 5.31</td>
<td>5.60</td>
<td>0.000*</td>
</tr>
<tr>
<td>58 years and over</td>
<td>198</td>
<td>9.34 ± 4.79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>218</td>
<td>11.31 ± 5.25</td>
<td>2.70</td>
<td>0.007*</td>
</tr>
<tr>
<td>Male</td>
<td>148</td>
<td>9.81 ± 5.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>269</td>
<td>9.9 ± 5.04</td>
<td>-5.03</td>
<td>0.000*</td>
</tr>
<tr>
<td>Single/widowed/divorced</td>
<td>97</td>
<td>12.93 ± 5.17</td>
<td>2.39</td>
<td>0.050**</td>
</tr>
<tr>
<td>Education status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Literate</td>
<td>44</td>
<td>10.55 ± 4.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>196</td>
<td>10.07 ± 5.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle school</td>
<td>46</td>
<td>12.34 ± 5.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>43</td>
<td>11.83 ± 5.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher education</td>
<td>37</td>
<td>10.89 ± 5.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working</td>
<td>120</td>
<td>12.33 ± 5.59</td>
<td>4.22</td>
<td>0.000*</td>
</tr>
<tr>
<td>Not working</td>
<td>246</td>
<td>9.91 ± 4.88</td>
<td>31.02</td>
<td>0.000***</td>
</tr>
<tr>
<td>Income status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Income less than expenditure</td>
<td>93</td>
<td>13.19 ± 5.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Income equal to expenditure</td>
<td>258</td>
<td>9.91 ± 4.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Income greater than expenditure</td>
<td>15</td>
<td>9.06 ± 4.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than one year</td>
<td>58</td>
<td>9.93 ± 5.33</td>
<td>10.85</td>
<td>0.000**</td>
</tr>
<tr>
<td>1-4 years</td>
<td>102</td>
<td>13.02 ± 5.74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-9 years</td>
<td>66</td>
<td>10.62 ± 5.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 years or more</td>
<td>140</td>
<td>9.33 ± 4.34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current type of diabetes treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only diet treatment</td>
<td>27</td>
<td>8.81 ± 3.97</td>
<td>3.03</td>
<td>0.029**</td>
</tr>
<tr>
<td>Oral antidiabetic</td>
<td>127</td>
<td>11.66 ± 5.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>176</td>
<td>10.48 ± 5.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral antidiabetic + Insulin</td>
<td>36</td>
<td>9.86 ± 6.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perception of conformity to current diabetes treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>121</td>
<td>8.94 ± 5.14</td>
<td>15.39</td>
<td>0.000**</td>
</tr>
<tr>
<td>Average</td>
<td>174</td>
<td>10.97 ± 5.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>71</td>
<td>13.07 ± 4.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>82</td>
<td>13.52 ± 4.54</td>
<td>5.74</td>
<td>0.000*</td>
</tr>
<tr>
<td>No / Stopped</td>
<td>284</td>
<td>9.89 ± 5.16</td>
<td>3.44</td>
<td>0.001*</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>33</td>
<td>13.66 ± 4.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No / Stopped</td>
<td>333</td>
<td>10.41 ± 5.19</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pittsburg Sleep Quality Index (PSQI) total mean score</th>
<th>n</th>
<th>Avg ± SD</th>
<th>t / f / x²</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perception of conformity to current diet</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>108</td>
<td>8.62 ± 4.86</td>
<td>13.87</td>
<td>0.000**</td>
</tr>
<tr>
<td>Average</td>
<td>155</td>
<td>11.21 ± 5.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>103</td>
<td>12.12 ± 4.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise (n=338)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>89</td>
<td>9.35 ± 5.4</td>
<td>-2.70</td>
<td>0.007*</td>
</tr>
<tr>
<td>No</td>
<td>269</td>
<td>11.07 ± 5.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of sleeping problems</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>127</td>
<td>13.11 ± 4.49</td>
<td>40.76</td>
<td>0.000**</td>
</tr>
<tr>
<td>Somewhat</td>
<td>123</td>
<td>12.03 ± 4.76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>66</td>
<td>7.28 ± 4.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleeping problems (n=249)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I can't sleep at all</td>
<td>33</td>
<td>11.09 ± 3.12</td>
<td>45.13</td>
<td>0.000**</td>
</tr>
<tr>
<td>I have difficulty getting to sleep</td>
<td>52</td>
<td>12.78 ± 4.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I keep waking up</td>
<td>59</td>
<td>12.62 ± 4.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I have difficulty waking up</td>
<td>33</td>
<td>13.6 ± 4.59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I wake up with breathing difficulty</td>
<td>10</td>
<td>12.6 ± 3.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I doze during the day</td>
<td>37</td>
<td>14.45 ± 4.79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irregularity in sleeping time</td>
<td>10</td>
<td>6.20 ± 3.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I wake up very early</td>
<td>6</td>
<td>10 ± 6.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep-related disorders (sleep-walking, nightmares, snoring, etc.)</td>
<td>9</td>
<td>5.14 ± 2.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reason for inability to sleep in hospital</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Too many people in one room</td>
<td>38</td>
<td>13.84 ± 4.18</td>
<td>5.29</td>
<td>0.000***</td>
</tr>
<tr>
<td>Being alone in the room</td>
<td>10</td>
<td>8.60 ± 3.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical conditions (noise, lighting, heating, ventilation, etc.)</td>
<td>80</td>
<td>12.62 ± 4.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Too much coming and going in the room</td>
<td>30</td>
<td>14.53 ± 3.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Being in strange surroundings</td>
<td>28</td>
<td>13 ± 5.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain or illness-related complaints</td>
<td>43</td>
<td>10.13 ± 4.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
<td>10.57 ± 4.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>You have a habitual way of getting to sleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>149</td>
<td>10.43 ± 4.15</td>
<td>-3.48</td>
<td>0.001*</td>
</tr>
<tr>
<td>No</td>
<td>162</td>
<td>12.35 ± 5.43</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Independent t-test; **ANOVA; ***Kruskall Wallis

too much coming and going in the room, or because they were in a strange environment were found to be significantly higher than those who said that they did not sleep because of being alone in the room, or because of pain or other disease-related complaints (x² = 5.29, p = 0.000). The sleep quality of type 2 diabetes patients who stated that they could not sleep while in hospital because there were too many people in the same room, because of physical conditions (noise, lighting, heating, ventilation, etc.), because there was too much coming and going in the room or because they were in a strange environment was negatively affected (Table 5).

The total PSQI scores of individuals who did not have habitual ways of getting to sleep were significantly higher than those who did (t = -3.48, p = 0.001). The sleep quality of type 2 diabetes patients who did not have a habitual way of getting to sleep was negatively affected (Table 5).
Correlation at a significant level was found between the HbA1c, fasting blood glucose and body mass index of the type 2 diabetes patients and their total PSQI scores (p <0.01). As their glycated haemoglobin (Hemoglobin A1c- HbA1c), fasting blood glucose and body mass index increased, their PSQI sleep quality scores also increased, so that it can be said that the metabolic values of the type 2 diabetes patients had a negative effect on their sleep quality (Table 6).

<table>
<thead>
<tr>
<th>PSQI total mean scores</th>
<th>HbA1c</th>
<th>FBG</th>
<th>Total cholesterol</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>0.41*</td>
<td>0.26*</td>
<td>0.07</td>
<td>0.17*</td>
</tr>
<tr>
<td>p</td>
<td>0.000</td>
<td>0.000</td>
<td>0.270</td>
<td>0.000</td>
</tr>
<tr>
<td>n</td>
<td>227</td>
<td>289</td>
<td>227</td>
<td>317</td>
</tr>
</tbody>
</table>

* Correlation is significant at P <0.01 level

**DISCUSSION**

The mean age of the individuals with diabetes in our study was 57.3 ± 13.61 years (Table 1). Gupta and Wang reported a mean age of type 2 DM patients as 59.9 ± 12.2 years, Lou et al as 47.2 ± 15.6 years, and Zhu et al as 59.48 ± 11.19 years [6,11]. In studies conducted in the USA, Norway, Ireland, Korea, Taiwan and China, mean ages varied from 58 to 65 years [21-28]. These are similar to the mean age found in our study.

Of the patients included in the research sample, 59.6% were female. In other studies, the proportion of females in the study groups was 61% for Arıbaş et al, 59.5% for Gupta and Wang, and 66% for Zhu et al [10,27,28]. As in the other studies, the majority in our study group were female.

It was determined that 38.3% of the individuals in the study had had diabetes for ten or more years, 34.7% were receiving OAD treatment and 48.1% insulin (Table 2). Zhu et al found the mean duration of diabetes of subjects to be 9.77 years [28]. In the study by Arıbaş et al, the mean duration of diabetes was found to be six years [27]. Zhu et al found that 60% of the individuals with diabetes in the study used insulin [28]. In the study by Arıbaş et al, 30% of the individuals with diabetes used insulin [27]. In our study, both the duration of diabetes and the rates of insulin use were different from those in the other studies. It is thought that these different results may be because the study was conducted in three different provinces in the west of Turkey with different populations.

A significant relationship was found between socio-demographic characteristics such as age, gender, marital status, educational level, employment status, exercise, smoking and alcohol consumption and the PSQI scale (Table 5). In the study by Gupta and Wang, a statistically significant correlation was found between socio-demographic characteristics such as age, gender, income level, marital status, employment status, smoking and exercise and the PSQI scale [11]. Examining the correlation between type 2 DM and the PSQI, it was determined in many studies that socio-demographic characteristics such as age, gender, marital status, education, income status, smoking and alcohol consumption affected PSQI scores [21-26,28].

A significant relationship was found between the HbA1c of the individuals in the study with type 2 diabetes and their total PSQI scores (p <0.01) (Table 4). It has been stated in studies on the topic of high blood glucose and HbA1c shortening sleep duration that HbA1c and blood glucose levels are correlated with sleep duration. In the same studies, a significant correlation has been reported between HbA1c levels and sleep quality [9,25-33].

Similar to our study, it has been found that disturbed sleep quality affects nutrient uptake, the amounts of nutrient taken up, energy balance, inflammation, disturbed glucose tolerance and insulin sensitivity [12,33-34]. It is thought that disturbance of sleep quality in diabetic patients reduces their ability to maintain self-care, and this in turn causes a rise in blood glucose levels.

In this study, the sleep quality of individuals with type 2 diabetes who said that they could not sleep at all, that they had difficulty getting to sleep, that they kept waking up, that they had difficulty waking up, that they woke up with breathing difficulties, or that they dozed during the day was negatively affected. The sleep quality of individuals with type 2 diabetes who stated that they could not sleep because there were too many people in the room, because of the physical conditions (noise, lighting, heating, ventilation, etc.), because there was too much coming and going in the room, or because they were in a strange environment was affected negatively. The sleep quality of individuals with type 2 diabetes who did not have a habitual way of getting to sleep (watching TV, reading a book, etc.) was negatively affected. It has been reported in studies of sleep in individuals with type 2 diabetes that sleep duration, sleep apnea and disrupted sleep both lowered sleep quality and had a negative effect on blood glucose levels and HbA1c levels. In addition, it was found that these kinds of sleep problems needed treatment, and that lack of treatment resulted in severe depression, which could put the patient’s life in danger [5,35-37].

**CONCLUSION**

As a conclusion of this study, it was found that socio-demographic characteristics of individuals...
with type 2 diabetes such as age, gender, income, duration of diabetes and diabetes treatment as well as metabolic values such as HbA1c, fasting blood glucose and body mass index have a negative effect on sleep quality. Regarding sleep problems, the sleep quality of individuals with type 2 diabetes who said that they did not sleep at all, that they had trouble getting to sleep, that they kept waking up, that they had difficulty waking up, that they woke up with breathing difficulties or that they dozed during the day was negatively affected.

ACKNOWLEDGMENTS

We wish to thank the participating type 2 diabetes mellitus patients for their participation.

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Author contributions

NGT: Study design, data collection, data analysis, preparation of manuscript and revisions.
SKS: Study design, data collection, data analysis, research supervision and manuscript editing.
TMA: Study design, data collection, data analysis, research supervision and manuscript editing.
AA: Study design, manuscript preparation and critical revisions for important intellectual content.

Conflicts of Interest: The authors declared no conflict of interest.

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The relationship between geriatric type 2 diabetes mellitus, fear of falling and gait: A controlled study

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ABSTRACT

Objectives: To investigate the fear of falling (FoF) and spatiotemporal and phase parameters of gait in geriatric type 2 diabetes mellitus (DM) patients
Design: Controlled trial
Setting: Department of Internal Medicine and Physical Therapy, Dumlupinar University, Kutahya
Subjects: Thirty-one patients who were diagnosed with type 2 DM and 29 healthy individuals were included in the study.
Intervention: FoF was assessed on the Falls Efficacy Scale International (FES-I). The timed up and go test (TUG) was used to assess the mobility of the participants. Spatiotemporal and phase parameters of gait were measured with the Zebris™ FDM-2 instrument and recorded instantaneously.
Main outcome measures: FoF, mobility, spatiotemporal and phase parameters of gait

Results: There was a statistically significant difference between the TUG scores (p <0.05) of the two groups but not between the FES-I scores (p >0.05). There was a statistically significant difference between the two groups’ step length and gait velocity (p <0.05), but there was no difference in step width, cadence and step time (p >0.05). In the diabetes group, FoF showed a significantly negative correlation with step length, cadence, gait velocity, left swing phase, and right swing phase. Step duration was in positive correlation with left stance phase, right stance phase, and double support phase (p <0.05). In the control group, there was no statistically significant correlation between FoF and gait parameters (p >0.05).

Conclusion: FoF can affect spatiotemporal and phase parameters of gait in diabetic patients, but not in healthy geriatric individuals.

INTRODUCTION

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both[1]. Among the estimated 8.3% of people with diabetes, 90% have type 2 diabetes mellitus (DM), and the number of affected people is expected to increase by 55% by 2035[2]. DM is very common and is especially seen in the elderly population[3]. Associated diseases, such as age-related insulin secretion, increased insulin resistance, obesity, a low level of physical activity and medications may be cited as reasons for the high prevalence of diabetes in the elderly population[4].

While 1 in 3 geriatric individuals experience falling every year, 1 in every 10 falls results in injury[5]. Patients with diabetes are more likely to fall than their peers[6,7]. Falling causes short and long-term problems. In the long term, there is a decrease in muscle strength and physical activity, and an increase in fatigue and fear of falling (FoF); while the short term results are problems such as injury, fracture and traumatic brain injuries. Tinetti et al have defined FoF as a decline in perceived self-sufficiency to avoid falling in doing necessary and non-dangerous daily tasks[8,9]. FoF is the major cause of falling and falling injuries[8,10]. Fear of falling could be more common in diabetes given the high rate of gait
Gait assessment
Spatiotemporal and phase parameters of gait were recorded using Zebris\textsuperscript{TM} FDM-2. The Zebris FDM-2 is a device used in gait and balance assessment that has a frequency range of 120 Hz, a length of 2122 cm, a width of 605 mm and a height of 21 mm, and 15,360 sensors. The data obtained from the device were recorded in a report via Zebris software installed on the computer. Participants were asked to walk at the device for 5 meters on the gait platform (3 meters) and at least 8 steps on the gait analysis platform (2 meters) at a comfortable velocity. Spatiotemporal gait characteristics were simultaneously recorded on the Zebris device; gait velocity (m/s), stride length (m), cadence (steps/min) and stride time (s) were recorded for each stride. The percentage of stance phase, the percentage of swing phase, and the double support phase were recorded from the phase parameters.

Data analysis
The Statistical Package for the Social Sciences, Version 13 for Windows (SPSS, Inc., Chicago, IL, USA) was used to conduct the statistical tests. The Kolmogorov-Smirnov test was used to analyze the normal distribution of the parameters. The independent t-test was used for testing the significance of the difference between the measurement averages of the two groups. In both the diabetic and control groups, the relationship between FoF and gait parameters was analyzed with Pearson’s correlation test. A significance level of p <0.05 was determined for the statistical analysis parameters.

The effect size of differences in spatiotemporal and phase parameters of gait in the diabetes group and the control group was assessed. If Cohen’s d value is less than 0.2, the effect size is weak; if it is 0.5, it is medium; and if it is larger than 0.8, it is defined as strong.

RESULTS
Clinical evaluation and gait analysis of 60 participants were performed; a total of 31 diabetic patients and 29 healthy individuals were included in the study. Clinical variables and demographic information are given in Table 1. No significant differences were found regarding age, height, weight, body mass index (BMI), presence of chronic disease, visual impairment and fall history between patients and controls (p>0.05). There was no statistical difference in FoF between patients and controls (p>0.05). There was a statistically significant difference between the two groups in the TUG test (p <0.05).

There was a statistically significant difference regarding step length and gait velocity between the
two groups (p <0.05), but there was no difference in step width, cadence and step time (p >0.05, Table 2). In the diabetic group, it was determined that the step length and gait velocity were lower than in the control group.

A significant difference was found between the two groups in all phase parameters of gait (p <0.05, Table 3). In the diabetes group, right, left stance phase and double support phase percentages were higher than in the control group.

### Table 1: Demographic information

<table>
<thead>
<tr>
<th>Variable</th>
<th>Diabetes</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.9 ± 6.1</td>
<td>60.93 ± 5.25</td>
<td>0.186</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.48 ± 9.01</td>
<td>78.6 ± 18.57</td>
<td>0.491</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>84.6 ± 16.30</td>
<td>164.17 ± 9.84</td>
<td>0.232</td>
</tr>
<tr>
<td>BMI</td>
<td>31.82 ± 5.6</td>
<td>29.0 ± 5.98</td>
<td>0.065</td>
</tr>
<tr>
<td>TUG (sn)</td>
<td>11.87 ± 3.98</td>
<td>9.31 ± 2.17</td>
<td>0.03*</td>
</tr>
<tr>
<td>Fear of Falling</td>
<td>22.16 ± 9.57</td>
<td>20.62 ± 6.17</td>
<td>0.465</td>
</tr>
<tr>
<td>Chronic Disease (%)</td>
<td></td>
<td></td>
<td>0.209</td>
</tr>
<tr>
<td>Yes</td>
<td>67.7</td>
<td>51.7</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>32.3</td>
<td>48.3</td>
<td></td>
</tr>
<tr>
<td>Fall History (%)</td>
<td></td>
<td></td>
<td>0.265</td>
</tr>
<tr>
<td>Yes</td>
<td>12.9</td>
<td>24.1</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>87.1</td>
<td>75.9</td>
<td></td>
</tr>
<tr>
<td>Visual Problem (%)</td>
<td></td>
<td></td>
<td>0.080</td>
</tr>
<tr>
<td>Yes</td>
<td>58.1</td>
<td>79.3</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>41.9</td>
<td>20.7</td>
<td></td>
</tr>
</tbody>
</table>

Data are shown as mean ± standard deviation or percentage. * p <0.05, TUG: timed up and go test

### Table 2: Spatiotemporal parameters of gait

<table>
<thead>
<tr>
<th>Spatiotemporal parameters of gait</th>
<th>Diabetes (n = 31) (mean ± SD)</th>
<th>Control (n = 29) (mean ± SD)</th>
<th>p-value</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step length (cm)</td>
<td>92.2903 ± 15.20349</td>
<td>112.3484 ± 12.75392</td>
<td>0.000*</td>
<td>1.357</td>
</tr>
<tr>
<td>Step width (cm)</td>
<td>15.6452 ± 2.88153</td>
<td>14.5172 ± 2.87378</td>
<td>0.135</td>
<td>0.393</td>
</tr>
<tr>
<td>Step time (s)</td>
<td>1.2023 ± 0.09674</td>
<td>1.1776 ± 0.13948</td>
<td>0.427</td>
<td>0.268</td>
</tr>
<tr>
<td>Cadence</td>
<td>100.3548 ± 8.10575</td>
<td>103.4828 ± 12.70720</td>
<td>0.265</td>
<td>0.293</td>
</tr>
<tr>
<td>Speed (km/h)</td>
<td>2.8226 ± 0.55840</td>
<td>3.5034 ± 0.61265</td>
<td>0.000*</td>
<td>1.170</td>
</tr>
</tbody>
</table>

* p <0.05

### DISCUSSION

The current study compared gait, FoF and mobility in geriatric patients with type 2 DM and in age and gender-matched controls.

FoF has been shown to be affected by being of the female gender, aging, visual impairment, cognitive function, frailty, previous experience with falling, chronic diseases, BMI, depression and educational

### Table 3: Phase parameters of gait

<table>
<thead>
<tr>
<th>Phase parameters of gait</th>
<th>Diabetes (n = 31) (mean ± SD)</th>
<th>Control (n = 29) (mean ± SD)</th>
<th>p-value</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left stance phase (%)</td>
<td>67.1000 ± 15.20349</td>
<td>65.1241 ± 12.75392</td>
<td>0.012*</td>
<td>0.675</td>
</tr>
<tr>
<td>Right stance phase (%)</td>
<td>3.12741</td>
<td>2.73282</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left swing phase (%)</td>
<td>67.3677 ± 14.5172</td>
<td>65.2276 ± 12.70720</td>
<td>0.02*</td>
<td>0.826</td>
</tr>
<tr>
<td>Right swing phase (%)</td>
<td>2.81997</td>
<td>2.35279</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double support time (%)</td>
<td>32.9000 ± 34.8759</td>
<td>34.8774 ± 34.7724</td>
<td>0.012*</td>
<td>0.672</td>
</tr>
</tbody>
</table>

* p <0.05

### Table 4: The effect of fear of falling of gait parameters

<table>
<thead>
<tr>
<th>Parameters of gait</th>
<th>Control</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step length (cm)</td>
<td>-0.065</td>
<td>-0.660</td>
</tr>
<tr>
<td>r</td>
<td>&gt;0.05</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Step width (cm)</td>
<td>-0.180</td>
<td>-0.160</td>
</tr>
<tr>
<td>r</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Step time (s)</td>
<td>0.045</td>
<td>0.390</td>
</tr>
<tr>
<td>r</td>
<td>&gt;0.05</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Cadence</td>
<td>-0.053</td>
<td>-0.401</td>
</tr>
<tr>
<td>r</td>
<td>&gt;0.05</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Speed (km/h)</td>
<td>-0.070</td>
<td>-0.651</td>
</tr>
<tr>
<td>r</td>
<td>&gt;0.05</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Left stance phase %</td>
<td>0.041</td>
<td>0.572</td>
</tr>
<tr>
<td>r</td>
<td>&gt;0.05</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Right stance phase %</td>
<td>0.226</td>
<td>0.447</td>
</tr>
<tr>
<td>r</td>
<td>&gt;0.05</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Left swing phase %</td>
<td>-0.041</td>
<td>-0.572</td>
</tr>
<tr>
<td>r</td>
<td>&gt;0.05</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Right swing phase %</td>
<td>-0.226</td>
<td>-0.447</td>
</tr>
<tr>
<td>r</td>
<td>&gt;0.05</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Double support phase %</td>
<td>0.143</td>
<td>0.628</td>
</tr>
<tr>
<td>r</td>
<td>&gt;0.05</td>
<td>&lt;0.05*</td>
</tr>
</tbody>
</table>

* p <0.05

The relationship between FoF and gait parameters in the diabetes group and control group are shown in Table 4. In the diabetes group, FoF showed a significant negative correlation in terms of step length, cadence, gait velocity, left swing phase, and right swing phase. Step duration was in positive correlation with left stance phase, right stance phase, and double support phase (p <0.05). In the control group, there was no statistically significant correlation between FoF and gait parameters (p >0.05).
level\textsuperscript{13,14}. Balance and mobility impairments, obesity, depression and diabetes-related complications have been pointed out as potential factors for increased prevalence of FoF in diabetic individuals\textsuperscript{7}. Previous studies have demonstrated that diabetes is associated with increased prevalence of FoF\textsuperscript{9,11}. Our study however showed that there was no difference in FoF between the diabetic and healthy elderly. This could be related to the fact that there was no difference between the two groups with regard to aging, previous experience with falling, chronic diseases, BMI, and visual impairment. The major limitation of the study was that cognitive function, frailty and depression in patients with type 2 DM was not evaluated, which could also have been an underlying reason that no difference was found between the fear of falling of type 2 DM and healthy elderly individuals.

Changes in microcirculation associated with poor glycemic control cause damage to vestibular, somatic and autonomic systems. For this reason, making changes in walking are compensatory strategies for diabetic individuals to improve stability and to maintain balance\textsuperscript{15,16}.

Studies have shown that gait velocity and step length of type-2 DM patients are lower\textsuperscript{15,17}. In our study, gait velocity and step length in patients with type-2 DM were significantly lower. Our results showed that the difference in the mean scores of the non-diabetic and diabetic older adults was 0.68 m/s, which exceeds the value of 0.10 m/s that is considered to signify a substantial clinical change, as suggested in a study about clinically significant changes in older adults\textsuperscript{18}. One study emphasized that type-2 DM patients with FoF have lower gait velocity and step length\textsuperscript{19}, while another study did not find gait velocity and step length to be affected by diabetes\textsuperscript{20}. However, in our study, increased FoF affected gait velocity and step length negatively in the diabetic group; it did not affect the control group.

Brach \textit{et al} reported that step width is wider in diabetics. The changes of the motor circuit of the basal ganglia may be related to the wider step\textsuperscript{21}. The basal ganglia are a highly metabolic area that requires good circulation and energy to function properly. Diabetes mellitus, which is known to affect circulation and blood glucose levels, could have a detrimental effect on basal ganglia\textsuperscript{14}. In our study, however, there was no difference between the control group and the diabetic group in terms of step width. FoF did not affect step width in either diabetic or healthy individuals. Increased step width related to aging may indicate that dynamic balance control has impaired the gait\textsuperscript{21}. People with visual impairment and impairments in sensing vibrations in the lower extremities have a lower capacity to adjust step width\textsuperscript{18}. To compensate for the impaired balance, elderly individuals either increase their step size or increase the duration of the double support phase to control the center of gravity in the base of support\textsuperscript{22}. Since these adaptations are important for maintaining dynamic equilibrium, reduced step width may increase the risk of falling\textsuperscript{20}. There was no difference between the two groups in terms of visual problems and falling history, which may have caused the difference between the two groups. The fact that the duration of the double support phase of our diabetic group was higher than in the control group suggests that this group may have been maintaining balance control by increasing the duration of the double support phase.

We found in our study that the percentages of stance and double support phases in diabetic patients were higher than in healthy individuals. Other studies have also shown in a similar manner that percentages of stance phase and duration of double support phase are longer in diabetic patients\textsuperscript{23}. Increasing the duration of the double support phase is an adaptation for maintaining balance\textsuperscript{12}. Moreira \textit{et al} suggested that in diabetic people with FoF, the double support phase percentage is higher than in diabetic people without FoF\textsuperscript{22}. Our study revealed no difference in FoF between diabetic and healthy individuals. There was however a negative correlation between FoF and the duration of the double support phase in diabetic individuals.

The TUG test is a commonly used method of assessing the functional status of geriatric individuals\textsuperscript{15}. Bruce \textit{et al} showed that the functional status measured by the TUG test of type 2 diabetic patients was worse than in normoglycemic subjects\textsuperscript{24}. However, diabetics reported no more falling history than normoglycemic subjects. This may be related to the mobility limitation of individuals with type 2 DM due to fear of activity-related falls, and to preventing the recurrence of falls\textsuperscript{7}. Guerrero \textit{et al} assessed that the TUG scores of geriatric type 2 DM patients were higher\textsuperscript{20}. Tander \textit{et al} showed that increased FoF decreased mobility\textsuperscript{17}. In our study, it was found that the TUG scores of geriatric type 2 DM patients were higher than geriatric healthy individuals. Based on this, we cannot say that FoF by itself impacted mobility in diabetic individuals.

**CONCLUSION**

In conclusion, our study showed that gait velocity and step length of geriatric type 2 DM patients were lower, duration of the stance phase and double support phase were longer and their functionality was lower than in healthy individuals. FoF had a negative impact on gait parameters in type 2 DM patients. It is therefore important to understand the
changes that occur in gait so that complications that may occur in diabetic patients may be prevented, early diagnosis and intervention may be achieved in the event of a problem, and a decision about appropriate approaches for treatment can be made. For future studies, the recommendation would be that studies are undertaken to explore the short and long-term effects of gait training in geriatric type 2 DM patients.

REFERENCES

Original Article

Investigation of genetic variations of IL17 for vitiligo disease

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ABSTRACT

Objective: Vitiligo is a disorder of pigmentation characterized by the presence of depigmented skin macules due to a chronic and progressive loss of melanocytes from the cutaneous epidermis. Among many different etiologic hypotheses that have been suggested so far for vitiligo, the most compelling one involves a combination of environmental and genetic factors that cause autoimmune melanocyte destruction. The purpose of this study is then to determine whether there is any relationship between vitiligo and IL17 gene Glu126Gly, His161Arg and G197A polymorphisms.

Design: Controlled prospective study
Setting: Department of Molecular Biology and Genetics, Bulent Ecevit University
Subjects: Genetic polymorphisms of IL17 gene were detected by using polymerase chain reaction based restriction fragment length polymorphism in 86 vitiligo patients and 90 healthy controls.

Intervention: For genetic analysis, 5 ml of venous blood was drawn into tubes containing EDTA from each patient.

Main outcome measures: IL17 gene Glu126Gly, His161Arg and G197A polymorphisms in vitiligo patients

Results: As a result of our study, we have found a significant relation between His161Arg polymorphism of IL17F gene and vitiligo patients (p = 0.045).

Conclusions: Our findings suggest that the IL17F His161Arg gene polymorphism has a protective role in susceptibility to vitiligo. This may be regarded as hypothesis-generating and should further be investigated in independent studies.

KEY WORDS: cytokines, IL17, polymorphism, vitiligo

INTRODUCTION

Vitiligo is defined as an acquired disorder of skin pigmentation. Generally, this complex disorder resulting from functional loss of melanocytes in epidermis is characterized by milky white macules of various sizes and shapes that tend to enlarge peripherally in the course of time. Vitiligo is the most frequent cause of depigmentation worldwide[1]. In fact, vitiligo reportedly affects 0.5 to 2% of the world’s population. India shows the highest incidence in the world (up to 8.8%). In Turkey, the incidence is about 0.59%/2. Vitiligo affects both genders equally, although it is a common observation that women complain earlier and more frequently about vitiligo, possibly because in some places, vitiligo is considered as a stigma or a cosmetic problem[3]. Vitiligo can develop at any age, but almost 50% of patients present before 20 years of age[4], and many of these present before 12 years of age[5].

Familial aggregation of cases is not uncommon; about 20% of probands have at least one affected first-degree relative, with a non-Mendelian pattern of inheritance suggestive of a polygenic, multifactorial disorder. However, although a number of genes and chromosomal regions have been implicated in vitiligo susceptibility, none have yet been confirmed[6]. Indeed, various genetic linkage studies and genome-wide association studies have indicated almost 50 genetic loci as important factors that contribute to vitiligo risk[7]. The devastating majority of these genes
are immune genes, supporting a critical role for the immune system in vitiligo pathogenesis. Some are known as key factors in innate immunity (TICAM1, CASP7, IFIH1, NLRP1 and others), while others play a role in mediating adaptive immunity (FOXP3, CD80, GZMB, CTLA4, HLA, PTPN22 and others) [8-9]. In addition to immune genes, a small subset of risk alleles is only expressed in melanocytes (MC1R, OCA2, and TYR), confirming a role for melanocytes in initiating disease[9].

Many studies have been attempted to illustrate the pathogenesis of vitiligo, but it still remains unclear. Several theories have been proposed so far to disclose vitiligo pathogenesis[10,11]. The autoimmune theory has recently gained more attention since they are sustained by some important clinical and experimental evidence. For instance, studies have shown increased levels of proinflammatory cytokines and receptors like interleukin 6, interleukin 8, tumor necrosis factor α and interferon-gamma, which suggests that vitiligo is mediated by a T helper cell-1 (Th1) and IL-2R in vitiligo patients[12,13]. For the treatment of vitiligo, methods for altering or decreasing immunological reactions have been developed[14].

Vitiligo is characterized by progressive autoimmune destruction of mature epidermal melanocytes, and it is estimated that humoral and cellular immunity systems are working together for the destruction of the melanocytes[15]. Recently, a novel subset of interleukin (IL)-17-producing CD4+ Th17 cells has been reported, which is distinct from Th1 and Th2 cells[16]. A wealth of data have supported the importance of the Th17 cytokines in the development and progression of this autoimmune, allergic and infectious disease[17-19].

The IL17 is a proinflammatory cytokine that includes six members: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F. Among the members of IL-17 family, IL-17F is the most recently discovered one to share the highest homology with IL-17A[20]. Furthermore, IL-17F and IL-17A bind the same receptor complexes[21] and the IL17A-152 G/A (rs2275913) and the IL17F7488T/C (rs763780) have been associated with several immunopathologies related to inflammation[22,23]. The IL17F gene single nucleotide polymorphism 7488T/C in the third exon causes a His-to-Arg amino acid change. Kawaguchi et al revealed that the IL17F His161Arg variant failed to induce proinflammatory cytokines and chemokines, and antagonized the activity of wildtype IL17F[24].

The aim of our study has been to find some puzzle component of cytokine and vitiligo. We investigated the genetic variation of IL17A and IL17F gene in vitiligo patients. To the best of our knowledge, this is the first study to have been carried out to evaluate the contribution of IL17AG197A (rs2275913), IL17F 7488A/G (His161Arg; rs763780) and IL17F 7383 A/G (Glu126Gly; rs2397084) polymorphisms to vitiligo pathogenesis.

**SUBJECTS AND METHODS**

**Study population**

The objects of our study were patients who were diagnosed with vitiligo by Dermatology Department of Bulent Ecevit University Medical School between 2013 and 2015. The clinical characteristics of vitiligo patients and healthy controls are shown in Table 1. There were 86 cases, and the average age was 36.68 ± 16.91 years (47 male, 39 female). The control group, which consisted of 90 people, was selected from the same area, and all participants were essentially healthy with no evidence of diseases related to vitiligo. Their mean age was 37.4 ± 15.74 years (41 male, 49 female). This study was approved by the ethical committee of Bulent Ecevit University Hospital with informed consent of patients.

The patients were further divided into subgroups

<table>
<thead>
<tr>
<th>Table 1: Clinical characteristics of vitiligo patients and healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical characteristics</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Gender#</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Family history#</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Vitiligo types#</td>
</tr>
<tr>
<td>Generalize</td>
</tr>
<tr>
<td>Segmental</td>
</tr>
<tr>
<td>Localize</td>
</tr>
<tr>
<td>Acrofacial</td>
</tr>
<tr>
<td>Vulgaris</td>
</tr>
<tr>
<td>Focal</td>
</tr>
<tr>
<td>Stability#</td>
</tr>
<tr>
<td>Stable</td>
</tr>
<tr>
<td>Active (Unstable)</td>
</tr>
<tr>
<td>Age onset#</td>
</tr>
<tr>
<td>Early onset</td>
</tr>
<tr>
<td>Late onset</td>
</tr>
</tbody>
</table>

*: values given as mean ± standard deviation
#: values given as n(%)
20 years or after. Female (n = 39) and male (n = 47) patients were analyzed separately with their respective controls (female: 49; male: 41).

Genotype analysis
DNA was extracted from peripheral blood leukocytes with Macherey-Napel Nucleospin blood® DNA extraction kit (Cat no. 740.951.250); polymerase chain reaction (PCR) was performed in a 25-μL volume with 100 ng DNA, 100 μm dNTPs, 20 pmol of each primer, 1.5 mM MgCl₂, 1 x PCR buffer with (NH₄)₂SO₄, and 2 U Taq DNA polymerase. Amplification was performed on a conventional Thermal Cycler (Primus 25; MWG Biotech, Milton Keynes, United Kingdom). These genetic polymorphisms were determined by fragment separation at 120 V for 40 – 50 minutes on a 3.5% agarose gel containing 0.5 mg/mL ethidium bromide. PCR-RFLP conditions for the Glu126Gly, His161Arg and G197A polymorphisms of the IL17 gene are shown in Table 2.

Statistical analysis
The data were summarized as numbers, percentages or means ± standard deviation, and were analyzed using the SPSS 18 for Windows software package (SPSS, Chicago, Illinois, USA). The Hardy–Weinberg equilibrium was verified by using the chi-square test and estimating the expected genotype frequencies on the basis of the development of the square of the binomial for these polymorphisms. Simple descriptive statistics were used to describe the variables among the participants. The differences in the measurements gathered from different groups were compared with the Student t test and a one-way analysis of variance. The IL17 gene polymorphisms genotypes and frequencies were analyzed with Pearson’s χ² test.

Table 2: The primer sequences, annealing Tm, restriction enzymes and digest Tm for detecting each single nucleotide polymorphism

<table>
<thead>
<tr>
<th>SNP</th>
<th>Reference SNP ID</th>
<th>Forward primer</th>
<th>Reverse primer</th>
<th>Annealing Tm</th>
<th>Restriction enzyme</th>
<th>Digest Tm</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-17F</td>
<td></td>
<td>5'-AGCTGGGAATGCAAAACAAAC-3</td>
<td>3'-TGCCCAAGTGCCAGAAATAC-3</td>
<td>52 °C</td>
<td>AvaI</td>
<td>37 °C</td>
</tr>
<tr>
<td>Glu126Gly</td>
<td>rs2397084</td>
<td></td>
<td></td>
<td>50 °C</td>
<td>NlaIII</td>
<td></td>
</tr>
<tr>
<td>His161Arg</td>
<td>rs763780</td>
<td></td>
<td></td>
<td>55 °C</td>
<td>EcoNI</td>
<td></td>
</tr>
<tr>
<td>IL-17A</td>
<td></td>
<td>5'-GCTATTCTTCTGCGCCTGAAT-3</td>
<td>3'-AGCTGGGAATGCAAAACAAAC-3</td>
<td>52 °C</td>
<td>AvaI</td>
<td>37 °C</td>
</tr>
<tr>
<td>G197A</td>
<td>rs2275913</td>
<td></td>
<td></td>
<td>55 °C</td>
<td>EcoNI</td>
<td></td>
</tr>
</tbody>
</table>

SNP: single nucleotide polymorphism; Tm: temperature

Table 3: IL17 genotype frequencies of the patients and the controls

<table>
<thead>
<tr>
<th>SNP</th>
<th>Genotype</th>
<th>Controls* (n = 90)</th>
<th>Vitiligo patients* (n = 86)</th>
<th>OR (95 % CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL17F Glu126Gly</td>
<td>AA</td>
<td>76 (84.4)</td>
<td>73 (84.9)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>12 (13.3)</td>
<td>12 (14)</td>
<td>1.041 (0.440-2.466)</td>
<td>0.927</td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>2 (2.2)</td>
<td>1 (1.2)</td>
<td>0.521 (0.046-5.865)</td>
<td>0.397</td>
</tr>
<tr>
<td>IL17F His161Arg</td>
<td>TT</td>
<td>64 (71.1)</td>
<td>73 (84.9)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TC</td>
<td>21 (23.3)</td>
<td>9 (10.5)</td>
<td>0.376 (0.161-0.879)</td>
<td>0.024</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td>5 (5.6)</td>
<td>4 (4.6)</td>
<td>0.701 (0.181-2.724)</td>
<td>0.608</td>
</tr>
<tr>
<td>IL17A G197A</td>
<td>GG</td>
<td>39 (43.3)</td>
<td>35 (40.7)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GA</td>
<td>38 (42.2)</td>
<td>41 (47.7)</td>
<td>1.202 (0.637-2.268)</td>
<td>0.570</td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td>13 (14.4)</td>
<td>10 (11.6)</td>
<td>0.857 (0.334-2.199)</td>
<td>0.748</td>
</tr>
</tbody>
</table>

*: values given as n(%) SNP: single nucleotide polymorphism; OR: odds ratio; 95% CI: 95% confidence interval from conditional logistic regression

Table 4: IL17 allele frequencies of the patients and the controls

<table>
<thead>
<tr>
<th>SNP</th>
<th>Allele</th>
<th>Controls* (n = 90)</th>
<th>Vitiligo patients* (n = 86)</th>
<th>p-value</th>
<th>OR (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL17F Glu126Gly</td>
<td>A</td>
<td>164 (91.1)</td>
<td>158 (91.9)</td>
<td>0.85</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>16 (8.9)</td>
<td>14 (8.1)</td>
<td></td>
<td>0.908 (0.429-1.922)</td>
</tr>
<tr>
<td>IL17F His161Arg</td>
<td>T</td>
<td>149 (82.8)</td>
<td>155 (90.1)</td>
<td>0.045</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>31 (17.2)</td>
<td>17 (9.9)</td>
<td></td>
<td>0.527 (0.280-0.993)</td>
</tr>
<tr>
<td>IL17A G197A</td>
<td>G</td>
<td>116 (64.4)</td>
<td>112 (64.7)</td>
<td>1.0</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>64 (35.6)</td>
<td>61 (35.3)</td>
<td></td>
<td>0.987 (0.638-1.527)</td>
</tr>
</tbody>
</table>

*: values given as n(%) SNP: single nucleotide polymorphism; OR: odds ratio; 95% CI: 95% confidence interval from conditional logistic regression
A total of 86 patients with vitiligo (47 males and 39 females) and 90 controls subjects (41 males and 49 females) participated in this study. The mean ages of patients and controls (± SD) were 36.68 ± 16.91 and 37.4 ± 15.74 years, respectively. There have been no significant differences in mean ages and genders between these two groups (p = 0.919, p = 0.291, respectively).

To evaluate the effect of the genetic variant of IL17 on vitiligo pathogenesis, the allele and genotype distributions of the IL17 polymorphisms are presented in Tables 3 and 4. The distribution of the genotypes in the controls was in Hardy-Weinberg equilibrium. The frequencies of TT, TC, and CC genotypes for the IL17 His161Arg polymorphism were 84.9%, 10.5%, and 4.6% in the patients and 71.1%, 23.3%, and 5.6% in the controls, respectively. The frequency of the TC genotype was higher in the control group compared with the patient group. As for IL17 His161Arg polymorphism, TC genotype may act as a protective allele in the development of vitiligo (odds ratio = 0.376, 95% confidence interval = 0.161 - 0.879). We have not found any association between genotypes of Glu126Gly and G197A polymorphisms of the IL17 gene and vitiligo (p = 0.857 and p = 0.729, respectively).

In these two groups, the allele frequencies of the gene polymorphisms of IL17 were analyzed. The result of these analyses showed that T alleles of His161Arg gene polymorphism also has a protective effect on vitiligo pathogenesis (p = 0.045).

The patients were also compared with the control group according to the stability of vitiligo (Table 5). However, we have not found any relation between genotypes and alleles of Glu126Gly, His161Arg and G197A polymorphisms of the IL17 gene in terms of vitiligo stability.

Genotype and allele distribution of IL17 gene polymorphisms (Glu126Gly, His161Arg and G197A) was analyzed with respect to gender differences in vitiligo patients and control. However, we did not find any significant difference in the genotype and allele distribution based on gender differences (Table 6). There is also no significant association between controls and vitiligo patients according to age of onset of vitiligo (Table 7).

**DISCUSSION**

Although immunological factors have been considered to play a crucial role in the pathogenesis of vitiligo, the precise mechanisms have remained unknown. In this work, we have aimed to analyze the potential roles of IL17 gene polymorphisms in patients with vitiligo.

Vitiligo lesions are frequently infiltrated by T cells reactive against melanocytes, which supports an etiologic involvement of cell mediated autoimmunity[20]. The ultimate destruction of melanocytes may partly be
due to an imbalance in the local cytokine environment. Indeed, it was reported that proinflammatory cytokine levels were increased in vitiligo-affected skin when compared with nonlesional skin \[26,27\]. Multiple triggers, including infectious agents, might precipitate such cytokine imbalances. In fact, recent evidence suggests that viral infections might trigger melanocyte secretion of proinflammatory cytokines, which ultimately results in disease development \[28\]. Also, there is direct tissue evidence implicating active Th17 cells and IL-

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Controls* (n = 49)</th>
<th>Vitiligo* (n = 39)</th>
<th>p-value</th>
<th>Controls* (n = 41)</th>
<th>Vitiligo* (n = 47)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL17F Glu126Gly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>43 (87.8)</td>
<td>33 (84.6)</td>
<td>0.436</td>
<td>33 (80.5)</td>
<td>40 (85.1)</td>
<td>0.844</td>
</tr>
<tr>
<td>AG</td>
<td>5 (10.2)</td>
<td>6 (15.4)</td>
<td></td>
<td>7 (17.1)</td>
<td>6 (12.8)</td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>1 (2.0)</td>
<td>0 (0)</td>
<td></td>
<td>1 (2.4)</td>
<td>1 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Allele frequency A</td>
<td>91 (92.9)</td>
<td>72 (92.3)</td>
<td>1.000</td>
<td>73 (89.0)</td>
<td>86 (91.5)</td>
<td>0.617</td>
</tr>
<tr>
<td>G</td>
<td>7 (7.1)</td>
<td>6 (7.7)</td>
<td></td>
<td>9 (11.0)</td>
<td>8 (8.5)</td>
<td></td>
</tr>
<tr>
<td>IL17F His161Arg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT</td>
<td>37 (75.5)</td>
<td>33 (84.6)</td>
<td>0.418</td>
<td>27 (65.9)</td>
<td>40 (85.1)</td>
<td>0.098</td>
</tr>
<tr>
<td>TC</td>
<td>10 (20.4)</td>
<td>4 (10.3)</td>
<td></td>
<td>11 (26.8)</td>
<td>5 (10.6)</td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>2 (4.1)</td>
<td>2 (5.1)</td>
<td></td>
<td>3 (7.3)</td>
<td>2 (4.3)</td>
<td></td>
</tr>
<tr>
<td>Allele frequency T</td>
<td>84 (85.7)</td>
<td>70 (89.7)</td>
<td>0.496</td>
<td>65 (79.3)</td>
<td>85 (90.4)</td>
<td>0.054</td>
</tr>
<tr>
<td>C</td>
<td>14 (14.3)</td>
<td>8 (10.3)</td>
<td></td>
<td>17 (20.7)</td>
<td>9 (9.6)</td>
<td></td>
</tr>
<tr>
<td>IL17A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>21 (42.9)</td>
<td>13 (33.3)</td>
<td>0.446</td>
<td>18 (43.9)</td>
<td>22 (46.8)</td>
<td>0.950</td>
</tr>
<tr>
<td>GA</td>
<td>21 (42.9)</td>
<td>22 (56.4)</td>
<td></td>
<td>17 (41.5)</td>
<td>19 (40.4)</td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>7 (14.3)</td>
<td>4 (10.3)</td>
<td></td>
<td>6 (14.6)</td>
<td>6 (12.8)</td>
<td></td>
</tr>
<tr>
<td>Allele frequency G</td>
<td>63 (64.3)</td>
<td>48 (61.5)</td>
<td>0.754</td>
<td>53 (64.6)</td>
<td>63 (67)</td>
<td>0.752</td>
</tr>
<tr>
<td>A</td>
<td>35 (35.7)</td>
<td>30 (38.5)</td>
<td></td>
<td>29 (35.4)</td>
<td>31 (33)</td>
<td></td>
</tr>
</tbody>
</table>

*: values given as n(%)
17 in vitiligo skin lesions\cite{39}. Th17, a newly recognized subset of CD4+ T helper cells, have been demonstrated to play critical roles in the pathogenesis of several autoimmune diseases, which is considered the main source of IL-17\cite{30}. Cytokines exert their effects on epithelial cells in various tissues and can be protective against infections, but might also become pathological in several inflammatory diseases. IL-17 is largely pro-inflammatory and destructive\cite{31}. Serum levels of IL-17 were reported to increase in psoriatic arthritis as well as in rheumatoid arthritis and systemic lupus erythematosis, and to correlate with disease activity\cite{32-34}. Recent studies have shown an increase in the serum levels of IL-17 in vitiligo patients\cite{35,36}. Also, Bassiouney et al found enhanced levels of T cells synthesizing IL-17 in the peripheral blood of vitiligo patients. In addition, an increase in tissue levels of IL-17 was observed in vitiligo lesions when compared with the normal skin of healthy controls. Furthermore, a significant positive correlation was found between IL-17 level in skin and duration and extent of vitiligo. Another noteworthy positive correlation was found between the levels of IL-17 in serum and in lesional skin in patients with vitiligo. All these suggest an important role for IL-17 in the pathogenesis of vitiligo\cite{36}. Yet, the role of IL17 gene polymorphism on the pathogenesis of vitiligo still remains unclear.

Several studies have investigated the possible role of IL17 gene polymorphisms in inflammatory and autoimmune diseases. Once, IL17 rs3804513 polymorphism was reported to be associated with early rheumatoid arthritis\cite{37}. Also, a former study found that the IL17 GG genotype was associated with susceptibility to alopecia areata\cite{38}. In another study, it was suggested that the CC genotype of IL17 polymorphism (rs10484879) may contribute to the pathogenesis of peri-implantitis and periodontitis\cite{39}. To our knowledge, this is the first study conducted to investigate the relationship between IL17F Glu126Gly, His161Arg and IL17A G197A polymorphism and susceptibility of Turkish vitiligo patients. Our results have shown that for IL17F His161Arg polymorphism, the TC genotype and C allele frequency in control was higher than that of vitiligo patients. IL17F His161Arg polymorphism TC genotype and C alleles may act as a protective allele in the development of vitiligo. His161Arg polymorphism has been proved to have a strong functional role by antagonizing the normal function of wild-type IL17F in the asthma model\cite{31}. Taking these and IL-17’s pro-inflammatory and destructive role into account, we could suggest His161Arg polymorphism TC genotype and C allele have protective effect on vitiligo pathogenesis. However, we could not find any significant differences in the frequencies of genotypes and alleles IL17F Glu126Gly, IL17A G197A polymorphism between vitiligo patients and controls.

In our study, we investigated the relationship between vitiligo and IL17F (His161Arg, Glu126Gly) and IL17A (G197A) polymorphisms. Our findings suggest that the IL17F His161Arg gene polymorphism has a protective role in susceptibility to vitiligo.

**CONCLUSION**

Vitiligo is an acquired pigmented disorder of unknown etiology, although several hypotheses have been proposed in the literature, the leading theory is still the auto-immune etiology linked to specific genetic mutations, and IL17 could be involved in vitiligo pathogenesis through His161Arg polymorphism. IL17F His161Arg substitution suggests a protective role against vitiligo by inducing a lower amount of downstream cytokines and chemokines. This is the first report on vitiligo susceptibility and IL17 polymorphisms in the Turkish population. We speculated that genetic polymorphisms within the IL17 gene might contribute to the pathogenesis of vitiligo. Further studies in other populations are required to validate our findings.

**ACKNOWLEDGMENT**

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Original Article

Investigation of the relationship between urinary tract infection and free particles seen within the bladder

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²Department of Internal Medicine, Faculty of Medicine, Adıyaman University, Turkey

ABSTRACT

Objective: To investigate the frequency of urinary tract infections in free particles seen within the bladder detected by ultrasonography

Design: Retrospective study

Setting: Department of Internal Medicine and Radiology, Adıyaman University, Turkey

Subjects: Eighty-four patients with free bladder particles enrolled in this present study.

Intervention: None

Main outcome measures: Patients’ age, gender, ultrasound reports and urine culture results were documented retrospectively from the records of Adıyaman University Medical Faculty Hospital.

Results: Fifty-eight of the patients were female and 26 were male. The mean age of the patients was 32.5 ± 11.4 years. Positive urine culture was detected in 15 patients. The most common etiologic microorganism detected in the urine culture was Escherichia coli.

Conclusion: Free particles in the bladder are seen very frequently in daily practice and often identified as cystitis. In this present study, positive urine culture was detected in only 17.9% of the patients with free particles. Therefore, we can say that clinicians should not empirically prescribe antibiotic for particles in the bladder without evaluation of the urine culture results and symptoms.

KEYWORDS: cystitis, ultrasonography, urinary bladder

INTRODUCTION

Urinary tract infections (UTI) are the most common bacterial infections in women, with one-half of all women experiencing UTI at least once in their lifetime[1]. UTIs are a common condition in the general population and they are therefore a frequent cause of visits to the emergency department[2]. Clinical forms of UTI varies from asymptomatic bacteriuria to sepsis[3]. Acute cystitis more commonly affects women. The diagnosis is made clinically[4]. In bladder, the inflammatory process usually extends beneath the mucosa into the submucosal and muscular layers of the bladder, and may be associated with white cell infiltration. Varying degrees of fibrosis, which compromises detrusor function, may decrease bladder capacity and/or accumulation of residual urine[4]. Clinical history is the most important tool for diagnosis of acute uncomplicated cystitis, and it should be supported by a focused physical examination and urinalysis. Classic lower urinary tract symptoms include dysuria, frequent voiding of small volumes, and urinary urgency[5]. It is important to rule out a serious complicated UTI with imaging investigations[6].

Free particles seen within the bladder are reported frequently in patients undergoing abdominal and urinary tract ultrasound. Although free particle echoes noted within the lumen of the renal pelvis are diagnostic for pyonephrosis[7], there are various causes of the particles seen within the bladder[8-10]. However, most clinicians consider the particles seen within the bladder as an UTI.

More often, unnecessary antibiotics are prescribed by clinicians to these patients with particles. Herein, we studied the relationship between UTI and free particles seen within the bladder. Besides, we aimed to prevent unnecessary antibiotic prescription.
MATERIALS AND METHODS

Eighty-four patients with particles detected within the bladder (Figure 1) by ultrasonography in Adıyaman University Medical Faculty Department of Radiology enrolled in this present study between January 2015 and January 2016. Patients’ age, gender, ultrasound reports and urine culture results were documented from the hospital record retrospectively. Ages of patients ranged from 16 to 87 years old and both genders were included. Ultrasound images were acquired on a Toshiba Aplio 500 ultrasound system (Japan) with 3.5 - 5 MHz transducers. Patients with renal cysts, stones or crystalloid, hydronephrosis, residual urine and urinary abnormalities were excluded from the study.

All analyses were performed using the SPSS for Windows [version 21.0;SPSS/IBM, Chicago, IL]. Normality was tested using the Kolmogrov-Smirnov test. The descriptive statistics, independent sample t test and Mann Whitney U tests were used for the collected parameters when suitable. The statistical significance level was accepted as a p-value of less than 0.05.

RESULTS

Fifty-eight of the patients (69%) were female and 26 (31%) were male (Figure 2). The mean age of the patients was 32.5 ± 11.4 years (min: 16, max: 87). Positive urine culture was detected in 15 patients (17.9%) (Figure 3). The most common etiologic microorganism detected in the urine culture was E. coli species (60%). The other etiologic microorganisms were: Streptococcus species (26.6%), Staphylococcus species (6.6%) and Candida species (6.6%) respectively (Figure 4). Age and gender were not significantly related to positive urine culture (p >0.05). Table 1 summarizes the factors associated with urine culture proliferation.

DISCUSSION

UTIs are the most common bacterial infections in women, with one-half of all women experiencing at least one UTI in their lifetime. Females are susceptible to lower tract infections more than males because of anatomical alterations. First step for the diagnosis of...
UTI is the microscopic and chemical analysis of urine. Quantitative urine culture is the gold standard method for the diagnosis of UTI. Thus, UTI should be confirmed by urine culture for accurate diagnosis\(^\text[11]\). Diagnostic imaging investigations aren’t necessary in order to confirm the UTI\(^\text[2]\). The history is the most important tool for diagnosing acute uncomplicated cystitis, and it should be supported by a focused physical examination and urinalysis. UTI are more frequently seen in patients with structural abnormalities. It is also important to rule out complicated UTI by diagnostic imaging investigations\(^\text[3]\).

The urinary bladder is a hollow muscular organ that serves as a reservoir for urine. The adult bladder normally has a capacity of 400 – 500mL. Bladder can be scanned by the supra-pubic transabdominal route, whereas the perineal and the intravesical routes are rarely used. Optimal ultrasonic visualization of the bladder and other pelvic structures necessitates a full bladder. On ultrasound, the bladder wall appears as a three layer structure. The detrusor muscle is of medium homogeneous echogenicity. The outer serosa (adventitia) layer and the inner mucosa (urothelial) layer are hyper-echoic compared with the middle detrusor smooth muscle (muscularis propria) layer\(^\text[13]\).

Understanding the layers and regional anatomy of the bladder will help assessment of the mucosal, mural and juxta bladder pathologies.

The normal ultrasonographic appearance of the bladder is shaped anechoic cystic structure. Ultrasonographic findings of cystitis are varied depending on the severity of the inflammation and type of cystitis\(^\text[14-18]\). Ultrasonography can diagnose predisposing factors, such as bladder calculi, tumors, an enlarged prostate, diverticula, or neurogenic bladder.

In clinical practice, empirical antibiotics are written for the bladder particles by most of the clinicians. However, UTI is only one of the reasons that cause particles in the bladder. There are many other causes for the particles which are seen within the bladder.

There are few studies on the relationship between UTI and free particles detected in bladder by ultrasonography. Thus, we aimed to investigate the association between UTI and particles seen within the bladder.

In a study conducted on bladder particles which were detected with trans vaginal sonography, Ronald H et al found that 75% of the patients’ urinalysis were normal\(^\text[3]\). In another study, Wilches C et al found that free particles in urine as a criterion for UTI has a sensitivity of 72% and a specificity of 48%\(^\text[2]\).

In this present study, we investigated the UTI prevalence in 84 patients with particles detected within the bladder by ultrasonography. Patients with urinary stones and crystalloids, cellular debris, mucin, blood, developing gas bubbles secondary to catheter usage, the gas-forming bacterial infection, bladder outlet obstruction induced urinary stasis and residual urine were excluded from this study. UTI was detected in 17.9% (n = 15) of the patients with particles in this present study.

CONCLUSION

We demonstrated that particles may be related to UTI. However, all the particles seen within the bladder weren’t related to UTI. Thus, we can say ultrasonographic findings should be confirmed with laboratory investigations for UTI.

ACKNOWLEDGMENTS

We have received no financial support and study design was retrospective. Adiyaman University Medical Faculty data records were investigated retrospectively.

Declaration of authorship: All authors have directly participated in the planning, execution, analysis or reporting of this research paper. All authors have read and approved the final version of the manuscript.

Conflict of interest: The authors declare no conflict of interest.

REFERENCES

Original Article

Universal precautions needed for preventing blood-borne infections: Knowledge, attitude, and practices of health care workers at King Abdulaziz University Hospital, Jeddah, Saudi Arabia

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3Sixth year medical students at King Abdulaziz University, Jeddah, Saudi Arabia

ABSTRACT

Objectives: To assess knowledge, attitudes & practice (KAP) of physicians and nurses working at King Abdulaziz University Hospital (KAUH) towards the universal precautions (UP) needed for preventing blood-borne pathogens (BBP)
Design: Cross-sectional design
Setting: KAUH, Jeddah, Saudi Arabia
Subjects: A total of 400 health care workers (HCWs) were selected from the inpatient and outpatient departments of KAUH.

Intervention(s): A validated, anonymous, interviewing questionnaire was used during 2016/2017. Knowledge of HCWs was assessed through nine questions. Attitudes were determined through twelve statements answered on a three-point Likert scale. Self-reported practices were evaluated through twelve questions. Knowledge and practice scores were calculated. Descriptive and inferential statistics were done.

Main outcome measure(s): KAP of physicians and nurses towards UP needed for preventing BBP

Results: Most of the participants correctly identified that UP are required for all body fluids and for all patients. Younger participants, those with shorter working experience, physicians (especially resident), and those from non-surgical departments had significantly (p <0.05) better knowledge scores compared to others. HCWs had generally good attitudes towards UP. Nurses, females, older participants, and those with longer working experience had significantly better UP practices than others.

Conclusion: Health care workers have relatively good attitudes and practices towards UP needed for preventing BBP. However, some areas of knowledge need improvement like knowledge about the infectivity of BBP, and the required post exposure prophylaxis. Conduction of more specific pre-service, on job training and educational programs on UP are required for all HCWs.

INTRODUCTION

Occupational exposures to blood-borne pathogens (BBP) have been documented as one of several occupational hazards that can affect health care workers (HCWs)1-4. Furthermore, patient safety represents an ultimate important discipline in the medical field3. There are many BBP which can be transmitted between patients and HCWs. The most important and frequent ones are hepatitis B virus (HBV), hepatitis C virus (HCV) and the human immunodeficiency virus (HIV)6. Other BBP such as hepatitis G, herpes simplex type 1, group A Streptococcus and Human Parvovirus B19 may also be transmitted by needle stick injuries (NSI), but less frequently than the others6.

The risk of transmission of the main BBP after a NSI or cut exposure was estimated to be about 6 – 30% for HBV, 1.8% for HCV, and 0.3% for HIV/AIDS7. The global burden of diseases that resulted from unsafe injection practices was estimated to be 21 million new cases of HBV, 2 million cases of HCV and 260,000 cases...
of HIV/AIDS, annually\(^8\). These BBP can lead to serious complications including cancers\(^1\).

Exposure to infected blood and body fluids can be reduced in health care settings by proper applications of universal precautions (UP). These precautions need to be applied by HCWs for preventing transmission of BBP while providing patients’ care\(^9,10\). Wearing latex gloves when dealing with patient’s blood and different body fluids or mucous membranes is one of these precautions. The other personal protective equipment (PPE) include the using of gowns, masks, protective eye goggles, etc. Precautions are required when handling instruments or surfaces stained with blood or body fluids. Hands and other skin surfaces should be correctly washed after dealing with patients and following each glove change. HCWs should avoid recapping the used needles\(^1-4\). In addition, vaccination of HCWs against HBV has been included as an important precaution\(^11\). All these measures should be followed for all patients, regardless of the patients’ blood-borne infection status\(^9\). A study reported from China in 2010 showed that nurses who were more compliant with the UP are less likely to be exposed to sharp injury contamination\(^12\).

Appropriate information and proper compliance with the standard infection control practices are the most important factors to confirm low rates of accidental injuries and low infection rates of HCWs and patients\(^13\). Improving infection control practices can be attained by identifying gaps of HCWs’ knowledge and practice about such important issue\(^14\). However, inadequate studies were conducted about this topic in Jeddah. So, such a study is needed.

The current cross-sectional study assessed the knowledge, attitudes and practice of physicians and nurses working at King Abdulaziz University Hospital (KAUH) towards the universal precautions needed for preventing blood-borne pathogens.

### SUBJECTS AND METHODS

A cross-sectional study was conducted during 2016/2017. The study enrolled nurses and physicians from the wards and outpatient clinics of KAUH, Jeddah, Kingdom of Saudi Arabia (KSA). All HCWs who agreed to participate, and signed the written consent were included.

A convenience sample method was used and the sample size was calculated according to the formula\(^15\):

\[
  n = \frac{z^2 \times p \times q}{d^2}
\]

Where \(z = 1.96\), \(p\) is the estimated prevalence of good knowledge about BBP. It was set as 0.5 due to lack of similar studies done in Jeddah. So, \(q = 0.5\), and \(d\) was set at 0.05. The minimum calculated sample size was 384, which was rounded to 400 participants.

A validated, interviewing questionnaire was used. The face and content validity of the questionnaire was evaluated by 2 experts. The internal consistency reliability was assessed using Cronbach’s alpha and found to be 80%.

### The questionnaire consisted of four parts:

- Personal and socio-demographic data such as age, sex, job, degree, etc.
- HCWs’ knowledge about BBP and UP was assessed through nine multiple choice questions. These questions inquired about the correct applications of UP. Another question asked about the post exposure prophylaxis (PEP) needed for a non-immunized HCW (by HBV vaccine) who was exposed to infected blood by HBV. Questions were inquired also about the highest (HBeAg infected blood) and lowest (HIV/AIDS) possibility of catching infections by BBP through infected NSI. Information about HBV vaccine regarding the minimum number of doses, and the route of its administration were assessed.
- HCWs’ attitudes towards UP were determined through responses of HCWs to 12 statements answered on three-point Likert scale.
- HCWs’ self-reported practices were assessed through answers on questions about receiving at least 3 doses of HBV immunization, their exposure to NSI, the number of exposure to NSI (if any), and the measures taken by HCWs in response to such an event. Compliance of HCWs with UP was assessed through 12 questions which asked about their practices towards certain case scenarios related to BBP and how they can be prevented.

### Ethical approval

The study was approved by the Unit of Biomedical Ethics of KAUH (Reference Number: 91-16). Administrative approvals were taken from the Vice dean of University Hospital Director and from the Nursing Administrators. Confidentiality was maintained throughout the study.

### Statistical methods

Data was analyzed using Statistical Package of Social Sciences (SPSS) Version 21. For each knowledge question, a score of “1” was given for the correct answer and “zero” for the incorrect or don’t know answers. A total knowledge score was calculated and ranged from zero to nine. It was then classified into three categories:

- Poor score ≤4 (≤50% of the correct answers), fair score: 5 - 6 (>50% - 66.6% of the correct answers) and satisfactory score ≥7 (>66.6% of the correct answers).

For the 12 self-reported practices; a score of “1”
was given for the correct practice and “zero” for the incorrect. A total practice score was calculated (ranging from 0 to 12).

Descriptive statistics was done. Inferential statistics including Chi-square test, Student’s t-test and one-way analysis of variance (ANOVA) tests were performed. Post-Hoc test for ANOVA was done by the least significant difference (LSD). All p-values <0.05 were considered statistically significant.

**RESULTS**

A total of 400 HCWs participated in the current study, consisting of 227 physicians (56.7%) and 173 nurses (43.3%). Their age ranged from 21 - 60 years, with a mean of 31.8 ± 9.2 years.

Table 1 reveals that physicians had significantly better knowledge than nurses regarding most of the questions about BBP. For example, 83.3% of physicians knew the correct number of doses of HBV vaccine compared to 69.4% of nurses (p <0.001). A similar trend was also seen regarding other questions about BBP. On the other hand, nurses had better knowledge than physicians regarding the route of administration of HBV vaccine and about UP. The table also shows that 78.2% of all HCWs knew that UP should be applied while dealing with all body fluids, and a similar percentage (78.5%) identified that UP should be taken for all patients. However, only 46% of the participants knew the PEP is required to prevent HBV among non-immunized HCWs exposed to blood infected with the virus. A similar percentage (43.8%) also identified the correct duration of survival of HBV outside the body. The table reveals that only 11% of the HCWs knew that the highest risk of acquiring infection with BBP is by accidental exposure to blood from individual with HBeAg positive status. On the other hand, 41.5% of health-care personnel identified that the lowest risk of infection by BBP occurred by exposure to HIV-infected blood.

Table 2 reveals that younger participants (<30 years), and those who had working experience less than two years obtained significantly better knowledge.
(higher levels of satisfactory knowledge scores) about BBP and UP compared to others. Similarly, physicians had significantly better level of knowledge compared to nurses (p <0.01), and residents obtained the best knowledge scores compared to other HCWs (p <0.05).

Regarding attitudes, Table 3 illustrates that most of the participants agreed that HCWs need to wash their hands after removing and disposing PPE (97%), and to change used gloves after dealing with patients or touching the equipment (93%). About three-fourths (76.5%) of our HCWs agreed that they should refrain from direct patient’s care if they have exudative lesions or weeping dermatitis.

Concerning practice, 96% of our participants received three doses of HBV vaccine. On the other hand, 21.2% of HCWs reported their exposure to at least one accidental NSI during their work (ranged from 1 - 8 times). Regarding their responses to such NSI, 10.4% of the exposed participants reported that they didn’t do anything in response to such occasion, and 20.8% reported that they only washed the injured area with water. The rest of the HCWs (68.8%) said that they reported the responsible authorities about the event, and did multiple action including seeking treatment from the Hospital Infection Control Unit.

Regarding participants’ self-reported practices and compliance with UP for prevention of BBP, 87.8% of HCWs reported that they always wash their hands after taking-off PPE, and 79.3% always changed gloves after dealing with patients or touching instruments.

Table 2: Levels of knowledge of health-care workers about blood-borne pathogens and universal precautions, according to the study variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Poor knowledge n</th>
<th>%</th>
<th>Fair knowledge n</th>
<th>%</th>
<th>Satisfactory knowledge n</th>
<th>%</th>
<th>χ² (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>68</td>
<td>48.9</td>
<td>54</td>
<td>38.8</td>
<td>17</td>
<td>12.2</td>
<td>0.74 (0.690)</td>
</tr>
<tr>
<td>Female</td>
<td>119</td>
<td>45.6</td>
<td>113</td>
<td>43.3</td>
<td>29</td>
<td>11.1</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>95</td>
<td>42</td>
<td>96</td>
<td>42.5</td>
<td>35</td>
<td>15.5</td>
<td>9.72 (0.008)</td>
</tr>
<tr>
<td>≥ 30</td>
<td>92</td>
<td>52.9</td>
<td>71</td>
<td>40.8</td>
<td>11</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>Job</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician</td>
<td>97</td>
<td>42.7</td>
<td>94</td>
<td>41.4</td>
<td>36</td>
<td>15.9</td>
<td></td>
</tr>
<tr>
<td>Nurse</td>
<td>90</td>
<td>52.0</td>
<td>73</td>
<td>42.2</td>
<td>10</td>
<td>5.8</td>
<td></td>
</tr>
<tr>
<td>Job title</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Post graduate</td>
<td>17</td>
<td>45.9</td>
<td>16</td>
<td>43.2</td>
<td>4</td>
<td>10.8</td>
<td></td>
</tr>
<tr>
<td>Resident</td>
<td>33</td>
<td>35.9</td>
<td>43</td>
<td>46.7</td>
<td>16</td>
<td>17.4</td>
<td></td>
</tr>
<tr>
<td>Nurse</td>
<td>84</td>
<td>52.2</td>
<td>68</td>
<td>42.2</td>
<td>9</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>Interns</td>
<td>53</td>
<td>48.2</td>
<td>40</td>
<td>36.4</td>
<td>17</td>
<td>15.5</td>
<td></td>
</tr>
<tr>
<td>Department</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-surgical</td>
<td>98</td>
<td>44.7</td>
<td>86</td>
<td>39.3</td>
<td>35</td>
<td>16</td>
<td>9.58 (0.008)</td>
</tr>
<tr>
<td>Surgical</td>
<td>89</td>
<td>49.2</td>
<td>81</td>
<td>44.8</td>
<td>11</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td>Work experience (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2 years</td>
<td>65</td>
<td>43.9</td>
<td>56</td>
<td>37.8</td>
<td>27</td>
<td>18.2</td>
<td>13.09 (0.011)</td>
</tr>
<tr>
<td>2-10 years</td>
<td>62</td>
<td>44</td>
<td>67</td>
<td>47.5</td>
<td>12</td>
<td>8.5</td>
<td></td>
</tr>
<tr>
<td>&gt; 10 years</td>
<td>60</td>
<td>54.1</td>
<td>44</td>
<td>39.6</td>
<td>7</td>
<td>6.3</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Attitudes of health-care workers towards universal precautions needed for preventing blood-borne infections, King Abdulaziz University Hospital

<table>
<thead>
<tr>
<th>Statement</th>
<th>Agree n (%)</th>
<th>No Opinion n (%)</th>
<th>Disagree n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCWs need to wash hands after removing and disposing PPE.</td>
<td>338 (97)</td>
<td>11 (2.8)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>HCWs need to change gloves after patient interaction, touching portable computer keyboards or other mobile equipment</td>
<td>372 (93)</td>
<td>20 (5)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Gloves are the last thing that HCWs wear when using PPE.</td>
<td>271 (67.8)</td>
<td>26 (6.5)</td>
<td>103 (25.7)</td>
</tr>
<tr>
<td>HCWs need to wash hands immediately after removing gloves.</td>
<td>367 (91.8)</td>
<td>23 (5.8)</td>
<td>10 (2.4)</td>
</tr>
<tr>
<td>HCWs need to remove gowns before leaving the patient’s care area.</td>
<td>364 (91)</td>
<td>22 (5.5)</td>
<td>14 (3.5)</td>
</tr>
<tr>
<td>HCWs need to take off the gloves and wash hands before removal of face shield, goggles and mask.</td>
<td>246 (61.5)</td>
<td>47 (11.8)</td>
<td>107 (26.8)</td>
</tr>
<tr>
<td>HCWs need to use sterile, disposable needle for each injection.</td>
<td>386 (96.5)</td>
<td>11 (2.8)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>HCWs need to change gloves between patients.</td>
<td>381 (95.3)</td>
<td>16 (4)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>HCWs should not recap the used needles.</td>
<td>346 (86.5)</td>
<td>16 (4)</td>
<td>38 (9.5)</td>
</tr>
<tr>
<td>HCWs need to cover their wound(s) or lesions with waterproof dressing before caring for patient.</td>
<td>341(85.3)</td>
<td>53 (13.3)</td>
<td>6 (1.5)</td>
</tr>
<tr>
<td>HCWs need to wear eye shield/goggles when may be exposed to splashing of bloody discharge/fluid.</td>
<td>384 (96)</td>
<td>12 (3)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>HCWs need to refrain from patient’s care or handling equipment if they have exudative lesions or weeping dermatitis.</td>
<td>306 (76.5)</td>
<td>57 (14.3)</td>
<td>37 (9.3)</td>
</tr>
</tbody>
</table>
Furthermore, 76.8% of HCWs reported that gloves are the last things of PPE they wear, and 82.5% of them reported washing their hands immediately after removing used gloves. In addition, 94% and 85.3% of HCWs reported changing gloves between patients, and removing gowns before leaving the patient’s care area, respectively. However, only 58% of them notified that they remove gloves and wash their hands before taking off the rest of PPE. Furthermore, 70.8% of HCWs notified wearing eye goggles when they were exposed to bloody discharge.

Concerning injection safety, all HCWs reported usage of disposable needles and syringes, and 76% of them reported that they don’t recap needles after usage. Concerning patients’ safety, 80.8% and 71.5% of the HCWs reported that they cover their wound(s) with waterproof dressing before providing patient’s care and withhold all patients’ care if they have exudative lesions, respectively.

Table 4 illustrates that females exhibited significantly better compliance with UP compared to males (t = 6.31, p <0.001). Furthermore, nurses had better compliance with the standard precautions compared to physicians (F= 47.98, p <0.001). Post-Hoc LSD test reveals that nurses’ practice differs significantly from all other HCWs. The table also reveals that participants with the shortest duration of working experience had the lowest compliance with UP compared to others (F = 33.73, p <0.001). The table also reveals absence of statistical association (t = 1.69, p = 0.092) between the compliance with the UP among HCWs from surgical and non-surgical departments. HCWs who obtained poor knowledge score reported slightly lower compliance with UP compared to those who had fair and satisfactory scores (p >0.05).

**DISCUSSION**

Infection with BBP represents an important public health challenge that face many nations’ health care systems[3]. In the current study, physicians generally had better knowledge than nurses regarding most of the questions about BBP. This difference may be attributed to higher physicians’ information gained from their medical education. However, nurses had better knowledge than physicians regarding UP and the route of administration of HBV vaccine, and this difference may be due to their on-job training programs related to work and UP.

In the present study, most of our HCWs (78.2%) correctly recognized that UP should be applied for all body fluids, which coincides with the findings from West Indies, Jamaica[4]. A similar percentage of our participants knew that UP should be applied for all patients, which agrees with findings from France[6] and Afghanistan[17].

More than three-fourths of our HCWs knew the correct number of doses of HBV vaccination, which concurs with a study done among HCWs from Cameroon[18].

Our results found that 35.3% of our nurses had sound knowledge about PEP after exposure of non-immunized HCW to HBV infected blood. This result is better than the percentage (12.1%) reported by nurses from Ghana in 2017[19]. This discrepancy may be attributed to the differences between both countries or due to training programs done in KAUH.

Presence of HBeAg reflects viral replications, and it is associated with the highest HBV infectivity rates after percutaneous exposure[20]. On the other hand, the risk of HIV transmission after a percutaneous exposure to the virus is considered the lowest compared to other BBP[21]. In the current study, only 11% and 41.5% of our HCWs correctly recognized these facts regarding HBeAg and HIV, respectively. The cause of such low knowledge regarding these two questions may be due to being specific questions that require a great amount of information about the infectivity rates resulting from different BBP. However, our rate regarding HIV infectivity is better than that reported

**Table 4**: Health care workers’ practice scores regarding their compliance with the universal precautions according to study variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Practice score Mean ± SD</th>
<th>Test of significance</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8.42 ± 3.01</td>
<td>t = -6.31</td>
<td>0.000</td>
</tr>
<tr>
<td>Female</td>
<td>10.12 ± 2.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>8.69 ± 2.7</td>
<td>t = -7.64</td>
<td>0.000</td>
</tr>
<tr>
<td>≥ 30</td>
<td>10.62 ± 2.23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Job</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician</td>
<td>8.43 ± 2.82</td>
<td>t = -10.63</td>
<td>0.000</td>
</tr>
<tr>
<td>Nurse</td>
<td>10.97 ± 1.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Job title</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post graduate</td>
<td>8.51 ± 3.25</td>
<td>F = 47.98</td>
<td>0.000</td>
</tr>
<tr>
<td>Resident</td>
<td>8.65 ± 2.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nurse</td>
<td>11.2 ± 1.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>intern</td>
<td>8.16 ± 2.96</td>
<td></td>
<td></td>
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Post-Hoc LSD test: * significantly differs from a,b,d

| Department                  |                          |                      |         |
|----------------------------|--------------------------|                      |         |
| Non-surgical               | 9.74 ± 2.51              | t = 1.69             | 0.092   |
| Surgical                   | 9.28 ± 2.85              |                      |         |
| Work experience (in years) |                          | F = 33.73            | 0.000   |
| < 2 years                  | 8.34 ± 2.86              |                      |         |
| 2-10                       | 9.71 ± 2.40              |                      |         |
| > 10                       | 10.88 ± 1.98             |                      |         |

Post-Hoc LSD test shows that * differs from b and c and d differs from a and c

| Knowledge score            |                          |                      |         |
|----------------------------|--------------------------|                      |         |
| Poor                       | 9.43 ± 2.87              | t = -0.64            | 0.5     |
| Fair and satisfactory      | 9.61 ± 2.50              |                      |         |

LSD: least significant difference
by dental students and staff (32.1%) from India\cite{21}. This inconsistency in results may be attributed to the differences between both target populations.

The present work revealed that younger HCWs obtained better knowledge score about BBP and UP compared to others, which is in line with the results from Afghanistan\cite{17}. This finding may be because younger HCWs are usually newly graduated and they usually have more recent and updated medical information compared to others. This explanation can also elucidate our finding that residents obtained the highest level of knowledge compared to others, which may also be due to their repeated examinations.

Our study found that gender didn’t affect HCWs’ knowledge. These two findings coincide with results of Vaz et al from Jamaica\cite{22}.

HCWs from non-surgical departments in our study had better knowledge regarding BBP compared to others. On the other hand, Askarian et al\cite{24} reported the absence of a significant association between knowledge scores among surgeons or physicians.

HBV vaccine is 95% effective in preventing HBV infection and its chronic consequences, and is the first anti-cancer vaccine\cite{1}. Regarding practice, a very high percentage (96%) of our participants were fully immunized against HBV. This rate is greater than that reported by physicians (87.2%) from PHCCs of Jazan, KSA\cite{11}. The cause of this discrepancy may be due to differences between both settings. Our rate is also much better than that reported by nurses from Ghana (44.4%)\cite{19}. This discrepancy may be due to differences between the economic status of both countries.

In the current study, most HCWs reported complying with sound hand hygiene practices, which coincides with the results from Afghanistan\cite{17}. In contrast, Ogoina et al\cite{24} reported much lower rates of such good hand hygienic practices between HCWs from two Nigerian hospitals. This discrepancy may be attributed to the training programs in KAUH.

Our study found that 21.2% of HCWs reported exposure to NSI, and 68.8% of the exposed personnel reported the Infection Control Unit. On the other hand, about half of the dental students and staff from the Indian study reported exposure to NSIs, and more than half of them did not report their injuries to Infection Control Unit\cite{21}. Similarly, another study from Ethiopia revealed that 34.8% of HCWs suffered from such injury and 58.7% of them didn’t report their exposure\cite{6}. These discrepancies may be attributed to the differences between the type of the target populations, or to the educational programs received by our staff.

All our healthcare personnel reported using disposable syringes and needles, which coincides with the results from Jazan\cite{11}. However, a lower rate was notified from the study of Oyewusi et al\cite{25}. Furthermore, 94% of our participants reported changing gloves between patients, which is better than the rate reported from Afghanistan (68.2%)\cite{17}. These discrepancies may be attributed to the availability of more resources in KAUH due to differences in the economic status, or due to more training available in the hospital.

A high percentage (76%) of our participants reported discarding needles without recapping. On the other hand, lower rates were reported from West Indies (31.7%)\cite{4} and Afghanistan (42.2%)\cite{17}. These inconsistencies may also be due to training courses done for our staff about “safe injection practices”.

In the current study, wearing eye goggles was notified by 70.8% of HCWs, which is better than the rate reported from Afghanistan (59.3%)\cite{17}. On the other hand, a study from Georgia showed that 24% of their participants used eye shields\cite{20}. These discrepancies may be explained by the deficiency of PPE in their settings.

Regarding patient safety, 80.8% of our HCWs reported covering their wounds with waterproof dressing before caring for patients, which agrees with the study from Afghanistan (82.6%)\cite{17}.

Nurses and females in the present study displayed significantly better compliance with UP compared to the physicians and males. This may be due to more training available for nurses at KAUH as they are more exposed to NSIs. Furthermore, most of the nurses are females (generally and in our study) and this can explain better practice among females. Similar associations were reported from an older study done in Birmingham teaching hospitals, UK\cite{27}. However, another Nigerian study reported absence of such associations\cite{28}.

In the present study, increasing the age of HCWs and having longer working experience are associated with better compliance with UP, which agree with the results from Pakistan\cite{3}. This may be due to the gained cumulative practice’s experience or the increasing number of training received overtime. However, a study from Malaysia found an absence of association between practice and the years of experience\cite{10}.

We found an absence of statistical association between practices of HCWs from medical or surgical departments, which may be attributed to the adequate training available for all hospital departments. In contrast, a study from Shiraz, Iran, reported significant association between compliance of HCWs from the two departments\cite{23}.

HCWs in the present study exhibited good attitudes towards using UP needed for prevention of BBP, which agree with the studies from Jazan\cite{11} and Nigeria\cite{24}.
CONCLUSION

HCWs in the current study have relatively good attitudes and practices concerning standard UP needed for prevention of BBP. The occupational exposure to NSI was relatively low (21.2%) among our HCWs. About two-thirds of them reported the event and searched for suitable PEP. However, some areas of HCWs’ knowledge need improvement, like their knowledge about the infectivity of BBP and the required PEP after exposure to BBP. It is recommended that all elements of UP should be strictly utilized by HCWs for their own safety as well as for patients’ safety. Intensifying the surveillance system about BBP and UP is recommended. Conduction of more comprehensive educational programs, wide-range pre-service and on job training programs are required. Intensifying educational programs such as sharp injury prevention programs is required to improve knowledge and practices of all HCWs regarding UP.

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Bilateral femoral neck fractures after minor trauma: Two cases of Gross Motor Functional Classification System (GMFCS) level II cerebral palsy patients

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ABSTRACT

Bilateral simultaneous femur fractures in children are unusual cases. Renal osteodystrophy, osteomalacia, osteoporosis, osteopetrosis, anti-epileptic drug usage history, low calcium and vitamin D levels are the most possible causes of reduced bone strength. Systemic diseases and iatrogenic causes may lead to unexpected fractures by lowering fracture threshold. Children with cerebral palsy are prone to bone metabolism abnormalities due to reduced mobility and ineffective balance. Even in Gross Motor Functional Classification System (GMFCS II) cerebral palsy patients, who are normally able to walk in most settings and climb stairs, diagnosis of the fracture in these patients following minor trauma may be challenging. In this study, we present two cases categorized as GMFCS II mobility level with bilateral femoral neck fractures secondary to epileptic seizures.

KEYWORDS: cerebral palsy, children, immobilization, fractures, low bone density

INTRODUCTION

Cerebral palsy (CP) is a non-progressive neuromuscular disease with involvement of cognitive, sensitive, metabolic disturbances and it mostly has variable effects on patient’s ambulatory status depending on the severity of the disease. Incidence is approximately 3/1000 live births and majority of them who manage to survive to adulthood suffer from the advanced state of diseases[1]. Skeletal abnormalities, posture and movement impairment, and bone metabolism defects are frequently observed in CP patients due to abnormal weight bearing, inadequate nourishment and anti-epileptic drug usage[2]. Metabolic and external causes effecting bone metabolism disrupt durability of bone and cause tendency to fractures. Weakened bone micro-structure may be triggered by muscle contractions of seizures and cause fractures. Bilateral femoral neck fractures in children are unusual cases. Underlying bone-related metabolic diseases like renal osteodystrophy, osteomalacia, osteoporosis, osteopetrosis, history of anti-epileptic drug usage, low calcium and vitamin D levels are the possible reasons for attenuated bone microstructure. Systemic diseases and iatrogenic causes affecting bone metabolism lowers fracture threshold and may lead to unexpected fractures[3]. Children with CP are prone to bone metabolism abnormalities due to reduced mobility and ineffective balance. Motor function disability of the individual described with Gross Motor Functional Classification System (GMFCS) divides CP patients into 5 subgroups depending on their ability of movement. GMFCS II corresponds to patients who may have trouble walking long distances and balancing on uneven terrain, inclines, in crowded areas or confined spaces and may walk with physical assistance[4]. The aim of this study is the presentation of two GMFCS II patients who had bilateral femoral neck fractures secondary to epileptic seizures along with literature review.

CASE REPORT

Case 1: An eighteen-year-old male with CP was admitted to the emergency medicine department complaining about inability to walk following grand-
mal epileptic seizure. On physical examination, both of the lower extremities were rotated externally and severe tenderness was present over both of the hip joints. Passive range of motion (ROM) evaluation of hip joint was increasing the pain significantly. Patient history reveals that he was able walk shortly without support (GMFCS II) before having the seizure, and no history of trauma was present. Patient has been taking anti-epileptic drugs for 16 years and cognitive abilities were preserved. Radiological examination revealed bilateral displaced femoral neck fracture type I according to the Delbet Classification (Fig 1). Patient was operated 4 hours after admission to the emergency department. Closed reduction of the right femur neck was achieved under fluoroscopy guidance and sliding hip screw (SHS) was preferred for fixation. Unfortunately, instrument trays of the SHS were contaminated while transferring to opposite side of patient. Following the reduction of the left femur, cannulated screws were preferred as an alternative fixation material. Passive in-bed exercises of hip joint started immediately after surgery. Weight bearing on fracture site was avoided for the next 10 weeks. Healing signs and bone formation was observed three months after surgery. Bone mineral density measurement with dual-energy X-ray absorptiometry (DEXA) revealed marked osteoporosis (Z score: -3) of lumbar vertebrate. 25-OH vitamin D3 level was 12 and below the limits (reference: 20 - 120 μg/L).

Case 2: A sixteen-year-old male was admitted to the orthopaedic outpatient clinic with persisting pain for two days after being discharged from the emergency department due to epileptic seizure. No abdominal pathology was found in previous evaluation in emergency department. Physical examination reveals severe pain in both hip joints. Marked ROM restriction of the hip joints were present due to pain and patient was not able to walk anymore. Radiographic evaluation of the hip joint detected bilateral femoral neck fractures type II according to Delbet Classification (Fig 2). Patient underwent surgery 6 hours after his admission. First, anatomic reduction of the right femoral neck obtained under fluoroscopy guidance and fixation was achieved using 3 cannulated screws. Identical procedure was repeated for left femur too. Passive exercises were started immediately, and active exercises and full weight bearing were started 3 months following surgery. Patient was followed up with routine anteroposteior and lateral radiographs monthly after full weight bearing. Healing signs and bone formation was observed at left hip three months after surgery. Bone mineral density measurement with DEXA revealed severe osteoporosis (Z score: -4.2) of lumbar vertebrate. Serum 25-OH vitamin D3 level was 12 and also low (reference: 20 - 120 μg/L).

**DISCUSSION**

CP is the term used to describe a group of non-progressive diseases of movement and posture resulting from damage to the brain\(^1\). Many subgroups of CP patients have been described, since progression of the disease manifests itself...
in different ways for each individual. GMFCS is a clinical standardized system to describe gross motor function of the patient focusing on self-initiated movement abilities\(^4\). Non-ambulatory status, anticonvulsant use, joint contractures, prolonged immobilization, poor nutrition and lack of mechanical loading reduce the fracture threshold of the bone. Fractures without clear history and trauma or known external cause are called ‘spontaneous fracture’ in literature. CP patients are prone to fractures secondary to low energy traumas which may occur during routine daily activities, especially in moderate to severe CP patients (GMFCS IV- V). One large epidemiologic study reports a fracture prevalence ranging from 6% to 12% in children with CP\(^3\). According to literature, 9.7% of GMFCS III- V CP patients have at least one fracture during their lifetime\(^6\). Many studies have reported that CP patients have lower bone mineral density (BMD) and Z score than peers with the same age. Factors effecting bone mineralization causes lowered Z scores and increases fragility\(^7\). BMD screening for these patients is a strong predictor of possible fragility. In a study involving 59 children (GMFCS II-IV) screened for possible fractures, 17% of the patients had fractures after minor trauma and it emphasizes a five to seven fold increased risk of fracture observed in patients with low BMD score and hypercalcirea\(^8\). Wren and colleagues pointed out that bone density was significantly lower in CP patients with GMFCS III – IV in comparison with those with GMFCS I- II\(^9\). Both of our patients had low BMD scores. Although ideal values of serum vitamin D levels are controversial, it is known that healthy microstructure and optimal strength of the bone demands adequate vitamin D levels. Vitamin D insufficiency not only increases the risk of fracture, but also enhances the severity of fracture against similar force applied\(^10\). Both of our patients had low serum 25-OH vitamin D3 levels. Femoral neck fractures of young adults only account for 2 - 3% of fractures and are mostly due to high energy trauma\(^11\). Our patients are different from the literature because they are bilateral femoral neck fractures and due to low energy trauma. They are classified as GMFCS II patients, who are expected to have sufficient BMD, whereas both patients had bilateral spontaneous femoral neck fractures.

**CONCLUSION**

Bilateral femoral neck fracture in cerebral palsy is a rare injury. Due to bone quality reduction, fixation of fracture is difficult and mobilization of patient should be delayed. Bone metabolic status and bone mineral density should be assessed, and appropriate treatment instituted to prevent further fractures.

**REFERENCES**

Left paraduodenal hernia: A rare cause of small intestinal strangulation in young adult

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ABSTRACT

Left paraduodenal hernia (LPDH) is a very rare cause of strangulated small intestinal obstruction. High index of suspicion and abdominal computed tomography is paramount in preoperative diagnosis. A 28-year-old female patient presented with a history of diffuse colicky abdominal pain for 2 days associated with vomiting, progressive distention of the abdomen and constipation. Physical examination revealed distended, diffusely tender, tense abdomen with hyperactive bowel sounds. Abdominal computed tomography revealed complete small intestinal obstruction. Exploratory laparotomy showed strangulated small intestine in LPDH. Resection of strangulated small intestine with end to end anastomosis and closure of the hernial sac was performed. LPDH should be considered among the underlying causes of small intestinal obstruction without previous abdominal surgery or pathology.

KEY WORDS: intestinal obstruction, intestinal strangulation, paraduodenal hernia

INTRODUCTION

Left paraduodenal hernia (LPDH) is the most common type of internal hernias and is responsible of about 0.1 - 0.4% of intestinal obstruction[1]. Although the majority of cases are found incidentally, patients may present with clinical features of small intestinal obstruction[2]. A rare case of LPDH causing complete strangulated small intestinal obstruction, in which the treatment was resection of the affected small intestinal segment with primary end to end anastomosis and closure of the hernial sac, is herein presented. The objective in presenting this case is to increase awareness among surgeons of this rare etiology of small intestinal obstruction. The case has been discussed in the context of other similar reported cases in the literature.

CASE REPORT

A 28-year-old female patient was brought to the emergency department (ED) with a history of diffuse colicky abdominal pain since 2 days, associated with vomiting, progressive distention of the abdomen and constipation. She gave a history of similar episodes one year ago. She had no history of abdominal operations. On physical examination, she looked unwell, dehydrated, and in pain, with pulse rate of 98 beats/minute, and blood pressure of 110/65 mm Hg. She had a distended, diffusely tender, tense abdomen with hyperactive bowel sounds. Anorectal examination showed empty rectum with no evidence of anorectal pathology. Resuscitation had been initiated immediately in ED with infusion of intravenous crystalloid fluids. A nasogastric tube insertion was performed, with drainage of large amount of bilious fluids. Foley’s catheter was inserted with drainage of concentrated urine. Blood sample was extracted and sent for complete blood count, creatinine, urea, electrolytes and coagulation profile. She then underwent plain abdominal radiograph which showed distended small intestine with multiple air fluid levels with no gas in the colon. Abdominal computed tomography (CT) scan showed dilated small intestine with complete obstruction. Exploratory laparotomy was performed with...
A professional diagnosis of complete small intestinal obstruction due to unknown etiology. Laparoscopic converted to open abdominal exploration was done, which revealed hugely distended, dusky, small bowel proximal to the encased distal jejunum and proximal ileum in hernial sac to the left of the duodenum. The bowel at the neck of hernia was narrowed and gangrenous. The neck was widened and the encased small intestine was reduced to the peritoneal cavity with resection of the gangrenous part at the neck of the hernia and primary intestinal anastomosis was performed. The hernia sac was closed with uneventful postoperative recovery. The abdominal CT scan was reviewed with a senior radiologist and the typical imaging of LPDH was identified (Fig 1).

**DISCUSSION**
Paraduodenal hernia is a herniation of small intestine into a peritoneal sac at the fourth part of the duodenum as a result of midgut malrotation during embryonic development. It is classified into two types, left and right paraduodenal hernias. LPDH (hernia of Lanzert) is more common than the right paraduodenal hernia (Walayer’s hernia)\[3\]. LPDH develops at the

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**Fig 1:** Abdominal computed tomography, (a, b) showing cluster of small bowel loops in the left upper quadrant with engorged and crowded vessels running to the centre of the clustered loops and dilated proximal small bowel. Intraoperative photography, (c) showing the hernial sac to the left of the duodenum, and (d) herniated small bowel with ischemic segment.
fossa of Lanzert, which is a congenital defect present in about 2% of population, located at the left branch of the middle colic artery and inferior mesenteric vein[4]. The majority of patients with paraduodenal hernias present between the 4th and 6th decade of life, with a male to female ratio of 3:1[5]. The clinical diagnosis of LPDH is difficult due to the rarity of the condition and the absence of specific clinical features. The non-specific symptoms are usually attributed to gastroesophageal reflux, gastritis or biliary disease[6]. Delay in diagnosis and surgical intervention increases complications such as necrosis and perforation[7]. Although this patient gave a history of frequent attacks of colicky central abdominal pain for 2 years, she presented in this attack with classical features of small intestinal obstruction. However, the diagnosis was only reached during surgery and by review of CT scan, which showed typical appearance of LPDH. CT scan with oral and intravenous contrast is the most helpful tool for diagnosis. It reveals: 1) encapsulated cluster of small intestinal loops in the hernia sac with abnormal location; 2) distended, obstructed segmental intestinal loops; 3) displacement of left or transverse colon; 4) stomach is pushed forward; and 5) mesenteric vessels look engorged and stretched[8]. Surgical intervention is the treatment of choice for LPDH due to the high lifetime probability (50%) of incarceration and strangulation[7]. Laparoscopic intervention has been reported in the last few years as a safe and feasible option in selected patients with LPDH[8]. Hernia content reduction and repair of the defect, as for all hernias, are the basic management principles[7]. During surgery, vascular injuries must be avoided, which may compromise blood supply of the small and large intestines[10]. In this case, laparoscopy was initially attempted, but it was unsuccessful due to bowel distention and was converted to open surgery. During surgery, the neck of the hernia was widened without iatrogenic injury. Reduction of encased small intestine and resection of ischemic segment of the bowel at the neck of hernia with primary anastomosis was performed.

CONCLUSION
LPDH should be considered among the underlying causes of small intestinal obstruction without previous abdominal surgery or pathology.

REFERENCES
Case Report

Spontaneous appendico-cutaneous fistula - A dilemma neopathy: A case report and literature review

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ABSTRACT

Spontaneous appendico-cutaneous fistula is a serious neopathy that is extremely rarely seen in appendicitis, and only a small number of cases are reported. We report a case of a 57-year-old male who received conservative treatment for acute appendicitis and was discharged from hospital successfully two years ago. However, over the past two years, the atypical abdominal pain has happened again and again. In the last 8 months, the patient has undergone recurrent abscess of the right lumbar region. Multiple surgical drainage and antibiotics treatment was ineffective. The patient had an unexplained recurrent fistula in the right lumbar region for the last 2 months. Magnetic resonance imaging revealed abscess formation in the right waist, which raised doubts about the appendix as a possible cause of the disease. On exploratory laparotomy, we found that the fistula tract communicated with the appendix. Appendectomy with sinus resection and ileotransverse colonic were performed and treated successfully.

KEYWORDS: appendico-cutaneous fistula, neopathy, spontaneous

INTRODUCTION

The formation of fistulas between the appendix and adjacent organs is a rare condition; spontaneous appendico-cutaneous fistula (SACF) are even more rare, and so far, few cases have been reported in the literature. As we all know, SACF is a rare complication for appendicitis[1]. The manifestations of SACF are varied and preoperative diagnosis is sometimes difficult[2]. If the treatment is improper, it will even have a life-threatening consequence. Furthermore, many pathological states in the appendix can lead to SACF, such as appendix abscess, acute perforating appendicitis or inappropriate treatment and so on[3]. Appendectomy combined with fistula excision is the first choice of treatment for SACF. Sometimes, right hemicolecotomy or ileotransverse colonic bypass may be an alternative treatment for this disease. This paper presents such a rare case of SACF following acute appendicitis after conservative treatment.

CASE REPORT

A 57-year-old male patient complained to us about a sinus formation and exudation repeatedly at the right lumbar region 8 months ago. Inquiring about medical history, he had a history of conservative treatment for acute appendicitis and was discharged successfully two years ago. However, over the past two years, atypical abdominal pain has occurred again and again. The patient’s appetite is poor, and he suffered from abdominal distention, sicchasia and mild fever during the attack. The patient seldom sought advice from doctors and used antibiotics and analgesic drugs to relieve symptoms by himself. As conditions began to deteriorate in the last 6 months, he went to the hospital and was diagnosed with an abscess of the right psoas muscle and underwent open surgical drainage treatment. Nevertheless, he was just temporarily relieved and suffered palindromia one month later. Since then, he repeatedly had ulcerated sinus
formation and fluid discharge. He underwent repeated surgical drainage and treatment with antibiotics and antituberculous therapy, but the treatment had no apparent effect. The imaging examinations of the preceding hospitalization included ultrasonography, endoscopy, barium meal examination of the digestive tract and abdominal CT scan. However, all of the examinations failed to show appendiceal perforation into the retroperitoneum. The physical examination showed a cutaneous opening discharging purulent liquid in the right lumbar region. Fistula of cutaneous opening was measured as 4 mm in diameter at the tip of the scar with surrounding indurations in the right lumbar region (Fig 1). The culture of fistula secretions prompted *Escherichia coli* and *Bacteroides*. The T2 weighted image of magnetic resonance images (MRI) revealed a nonuniform signal enhancement region of fluid collection in retroperitonium of right lower quadrant, which was then found to be the fistulous tract of the right lumbar region communicating with the cutaneous opening (Fig 2). At laparotomy, a retrocecal appendix with a perforation tip was found closely attached to the retroperitoneal cavity which was connected with the cutaneous opening in right lumbar region near one end of the operation scar by a fistula passing through the posterolateral abdominal wall (Fig 3). The appendix and fistula tract were connected in the right lumbar region. Fistula resection together with ileo-transeverse colonic were performed (Fig 4). Postoperative recovery was satisfactory. No recurrence was noted one year after operation. Histopathological examination showed features of phlegmonous appendicitis, inflammatory cells around the appendix and fistula lining. They were not characterized by tuberculosis or Crohn’s disease.

Fig 1: Physical examination revealed a cutaneous fistula in the right lumbar region, measuring about 4 mm in diameter (yellow arrow).

Fig 2: MRI showing a nonuniform signal enhancement region of fluid collection in retroperitonium of right lower quadrant (A), which was then seen communicating with the cutaneous opening (B) with a fistulous tract (C) over the right psoas muscle.

Fig 3: Laparotomy showed that the appendix presented with acute appendicitis (white arrow). The perforation of the appendix was located at the caudal end and communicated with the fistulous tract (yellow arrow).
DISCUSSION

Many pathological conditions of the appendix can lead to SACF; for example, drainage of an appendix abscess, appendicectomy or a complication of acute perforating appendicitis[4]. A recent review of the English literature found several appendico-cutaneous fistula which were secondary to various etiologies except conservative treatment for acute appendicitis, and many of these were just single case reports. Six case reports described cutaneous fistula developed after appendectomy or drainage of an appendix abscess as a complication of complex appendicitis[2,5-8]. One case report described cutaneous fistula developed as a neopathy of occult appendicitis[4]. Two case reports described appendico-cutaneous fistula developed after abdominal drainage of intra-abdominal abscess without obvious appendicitis or a right lumbar abscess[3,9]. In our patient, it was even more astonishing that SACF occurred after conservative treatment for acute appendicitis. SACF may behave as an illness of simple fistula or it could be a worse case, such as necrotizing fasciitis in the right waist. Even with the help of advanced diagnostic (radiological) techniques, diagnosis can be challenging at times[9]. A severe complication of acute appendicitis with perforation is retroperitoneal abscess formation. This secondary abscess has a mortality rate of up to 16.7% and early diagnosis is required[5]. Psoas spasm sign may help to indicate the relationship between retroperitoneal lesions and intraabdominal. However, intraabdominal pathology cannot be ruled out in some cases without abdominal symptoms. The location of the tip of the appendix varies leading to changes in the position of SACF.

In addition, taking into account the retrocaecal location of the appendix as the most common, the retroperitoneal perforation of appendix leading to psoas abscess cannot be emphasized too much[6]. In cases with a typical presentation, the opening location of appendico-cutaneous fistula can be at the right hip, right iliac fossa, groin or umbilicus. We usually can’t understand the origin of the fistula by the cutaneous opening[9]. However, MRI can provide improved visualization of these fistula, surgical planning of the disease, and evaluation of the extension. This also contributed to the diagnosis in our case.

This case of intractable right psoas abscess is an unusual manifestation of recurrent appendicitis. The diagnosis of retroperitoneal perforation of the appendix was delayed, which lead to SACF. This was an uncommon case of psoas abscess after conservative treatment of acute appendicitis, which avoided naturally closed and lead to duration of fistula.

Surgical treatment continues to be the best initial treatment modality for SACF. Surgery is performed only when external fistula and purulent or fecal fistula are considered. Exploratory laparotomy allows the removal of the appendix and the fistula all together. It is the golden standard for the diagnosis and treatment of this rare complication of appendicitis[11]. We performed an open appendectomy with fistula resection and ileo-transverse colonic, which is a major form of surgical treatment.

Fig 4: A) The appendix was fairly complete, with only tail perforations. B) The appendiceal stump was securely embedded (yellow arrow) after appendectomy, and ileo-transverse colonic (white arrow) were carried out.
CONCLUSION

The SACF is a rare neopathy of acute appendicitis after conservative treatment. It provides a diagnostic challenge, most of all when abnormal life-threatening retroperitoneal perforation and psoas abscess are present. SACF should always be regarded as antidiastole of any dermatocellulitis in the right lumbar region or the lower quadrant of the right abdomen with little or no sign of the abdomen. MRI is a great help for preoperative accurate diagnosis. Open appendectomy with fistula resection and ileo-tanverse colonic could be a necessary cure for this disease.

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Phase II/III Randomized Controlled Trial of Concomitant Hyperfractionated Radiotherapy plus Cetuximab (Anti-EGFR Antibody) or Chemotherapy in Locally Advanced Head and Neck Cancer

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INTRODUCTION
Globally, there is marked variation in overall incidence and presentation of head and neck cancers, these cancers account for 11.5 per 100,000 population in G.C.C states. Concomitant chemotherapy and external beam radiotherapy (EBRT) is indicated in such cancers with aim of organ preservation, control and possible cure. Hyper fractionated radiotherapy with concomitant chemotherapy or cetuximab is a lesser explored option. In this study we wish to assess the tolerability and efficacy of cetuximab with altered fractionation and compare this with the chemotherapy (cisplatin).

MATERIALS AND METHODS
This is a randomized controlled study from a single institute in Kuwait. Locally advanced head and neck cancer cases excluding cancer nasopharynx are enrolled for the study. Stage III or stage IV-A cases were enrolled with histopathology squamous cell carcinoma. Patients were randomized into 2 arms. Arm A: to receive platinum-based CT i.e. cisplatin in a dose of 100 mg/m² 3-weekly or 40 mg/m² weekly during radiation; Arm B: received cetuximab with a loading dose 400 mg/m², one week before radiation followed by weekly dose of 250 mg/m² during radiation. Radiotherapy was delivered using intensity modulated radiotherapy (IMRT) or 3D-conformal radiotherapy (CRT). The primary objective was to evaluate whether the use of cetuximab with concurrent hyperfractionated radiation regimen will have loco regional control rates (LC) and Disease-free survival (DFS) that are comparable to concurrent cisplatin in patients with LAHNC. The secondary endpoints were to compare the impact of using concurrent cetuximab vs chemotherapy regimen on Overall Survival of patients (OS) and acute and late adverse events.

RESULTS
From November 2012 to November 2017, 40 patients were randomized. The median age of was 51 years (range 27-72 years). Thirty-five patients are male and remaining was female. 14 patients have their primaries in larynx, 11 in oropharynx, 8 in oral cavity, and 5 has tumor in hypopharynx. Two patients had disease in nasal sinus or overlapping subsides. 50% has T4 lesions while 35% has T3 lesions, Nodal status was (N0-1) in 20 patients and (N2-3) in 20 patients. Overall staging showed a majority to have stage IV disease (63%). HPV was negative in 2 cases in Arm 1 and positive in 2 cases in Arm 2. 22 patients were randomly allocated in Arm A (platinum-based) while 18 were in Arm B (cetuximab). CR was achieved in 59% in arm A vs 50% in Arm B, while PR was 27.3% and 27.8% respectively. Disease progressed in 2 patients in Arm B only. Out of these 40 patients, 14 patients failed (6 and 8 in arm A and B respectively). Locoregional failure was documented in 6 (27.3%) vs 7 (38.9%) of arm A and B respectively, which was statistically not significant possibly related with lower number of cases. 2 years DFS was 56.5% vs 77.3% in cisplatin vs cetuximab arm (denoting nonsignificant increase of relapse rate in cisplatin arm). However, 2 years OS was 80.7% vs 57.3% in cisplatin and cetuximab arm respectively (p value=0.04).
CONCLUSION
Though cetuximab has lesser side effects but it is not indicated in treatment of LAHNC. Concurrent cisplatin is a trusted option for concomitant setting regardless of the HPV status and tumor location. However, in the context of cisplatin ineligible patients, cetuximab should be used only with hyperfractionation. This preliminary study could represent a good core of large international multicenter RCT.

Risk of relapses during pregnancy among multiple sclerosis patients

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BACKGROUND
Relapse rate in women with Multiple Sclerosis (MS) is reduced during pregnancy especially in the third trimester according to the previous studies.

OBJECTIVES
To measure the annual relapse rate (ARR) in women with MS during pregnancy.

METHODS
A retrospective study was conducted using prospectively collected data from two MS registries in Kuwait and Lebanon. Demographics, clinical characteristics including relapses, disease modifying therapies (DMTs) and their washout periods were extracted. The annual relapse rates pre and post pregnancies were compared and the relationship between relapses and prior use of different DMTs was assessed.

RESULTS
Data of 164 pregnancies (132 MS patients) was reviewed. Mean age and disease duration at the time of pregnancy confirmation were 32.4 ± 5.3 and 7.8 ± 4.7 years respectively. Most patients (91.7%; n = 121) were on DMTs in the year prior to pregnancy. The pre-pregnancy ARR was 0.10 (95% CI: 0.04 - 0.13), which increased to 0.20 (95% CI: 0.13- 0.29) during pregnancy. Most relapses occurred either during the 1st (ARR = 0.24; 95% CI: 0.12 - 0.44) or 3rd (ARR = 0.32; 95%CI: 0.17 - 0.53) trimesters. Fingolimod (31.8%) and natalizumab (22.7%) were the most commonly prescribed DMTs in patients who sustained relapses during pregnancy. The mean washout period was significantly longer among subjects with relapses (9.3 ± 6.6 vs. 2.5 ± 3.9; p < 0.001) than those of without relapses.

CONCLUSIONS: Relapse rate during pregnancy was higher than previous studies conducted in patients on platform therapies or untreated. Longer washout period prior to conception was associated with increased relapses especially in fingolimod and natalizumab treated patients.
Hepatitis B virus, hepatitis C virus and human immunodeficiency virus infections among people who inject drugs in Kuwait: A cross-sectional study

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Injection drug use (IDU) is one of the most significant risk factors for viral hepatitis (B and C) and human immunodeficiency virus (HIV) infections. This study assessed seroprevalence rates of hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) in people who inject drugs (PWID) in Kuwait. We conducted a cross-sectional study from April to September 2017. A total of 521 consecutive subjects, admitted at Al-Sabah Hospital. The serological and virological markers of HBV, HCV, and HIV were tested using automated platforms. The mean age of the participants was 32.26 yrs, and the sex ratio (Male/Female) was 15.28. The prevalence rates of HBsAg, anti-HCV, and anti-HIV antibodies were 0.38% (95% CI: 0.07-1.53%), 12.28% (95% CI: 9.65-15.48), and 0.77% (95% CI: 0.25-2.23%), respectively. HCV-RNA was evident in 51.72% (95% CI: 38.34-64.87%) among anti-HCV positive participants. Multivariate analysis showed that the high prevalence of HCV infection amongst PWID is associated with age. Whereas, multivariate analysis revealed no significant associations with age and gender regarding HIV and HBV infections. The results suggest that high rates of HBV, HCV, and HIV infections among injecting drug users than the general population. These findings emphasize the importance of introducing interventions and harm reduction initiatives that have a high impact on reducing needle sharing.

Ureteropelvic Junction Obstruction and Parathyroid Adenoma: Coincidence or Link?

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2Pediatric Nephrology, Armand Trousseau Hospital, APHP, Paris, France.
3Division of Pediatric Nephrology, Department of Pediatrics, American University of Beirut, Beirut, Lebanon.


Congenital ureteropelvic junction obstruction (UPJO) is the most common cause of upper urinary tract obstruction in children. It is generally diagnosed in the routine work-up during antenatal period and is characterized by spontaneous recovery. It can be associated with urolithiasis; hence further investigation should be carried out. We report the case of a 15-year-old boy, who is known to have right UPJO, presented with right renal colic and discovered to have bilateral kidney stones. Further studies showed primary hyperparathyroidism and genetic analysis revealed a CDC73 mutation (initially HRPT2). We believe that association of UPJO and PHPT is a rare coincidence that can be linked. Careful work-up of children with UPJO and urolithiasis is recommended to exclude an underlying metabolic disease. Surgical correction can be evitable as treatment of the primary cause can lead to complete dissolution of kidney stones and improvement of the medical condition.
Current perspectives of sickle cell disease in Nigeria: changing the narratives

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⁴Department of Molecular Biology and Biotechnology, Nigerian Institute of Medical Research, Lagos, Nigeria.
⁵Department of Paediatrics, Faculty of Medicine, Kuwait University, Kuwait City, Kuwait.


INTRODUCTION
Sickle cell disease (SCD) is an inherited blood disorder characterized by clinical heterogeneity that may be influenced by environmental factors, ethnicity, race, social and economic factors as well as genetic and epigenetic factors.

AREAS COVERED
The present review was carried out to provide a comprehensive assessment of the current burden of SCD and treatments available for persons with SCD in Nigeria with the aim of identifying surveillance and treatment gaps, informing to guide the planning and implementation of better crisis prevention measures for SCD patients and set an agenda for new areas of SCD research in the country. This review assessed medical, biomedical and genetic studies on SCD patients in Nigeria and other endemic countries of the world.

EXPERT OPINION
Integration of hydroxyurea therapy into the management of SCD and surveillance via new-born screening (NBS) for early detection and management will improve the survival of persons with SCD in Nigeria. However, it will be important to carry out pilot studies, initiate strategic advocacy initiatives to educate the people about NBS benefits, develop collaborations between potential stakeholders and design sustainable financing scheme.
Forthcoming Conferences and Meetings

Compiled and edited by
Vineetha Elizabeth Mammen

Kuwait Medical Journal 2019; 51 (3): 316 - 322

Echo in Congenital Heart Disease: Special Emphasis on Adult Congenital Heart Disease: Including Uses of Multimodality Imaging 2019
Oct 02 - 05, 2019
United States / Bonita Springs, Florida
Contact: Mayo Clinic Cardiovascular Medicine CME (CV CME)
Email: cvcme@mayo.edu

Ultrasoundography for Intensivists and Emergency Medicine Clinicians 2019
Oct 04 - 06, 2019
United States / Cambridge, Massachusetts
Contact: Harvard Medical School (HMS) Department of Continuing Education | Beth Israel Deaconess Medical Center
Phone: (617) 384-8600
Email: ceprograms@hms.harvard.edu

Heart Failure Summit 2019
Oct 05, 2019
United States / Sacramento, California
Contact: UC Davis Conference and Event Services (CES)
Phone: (530) 747-3851; (530) 754-0672
Email: cdatanagan@ucdavis.edu

Topics in Emergency Medicine Course
Oct 07 - 11, 2019
United States / Utah, Utah
Contact: Northwest Seminars (NWS)
Phone: 1 (800) 222-6927
Email: info@northwestseminars.com

Emergency and Urgent Care Course
Oct 09 - 12, 2019
United States / San Antonio, Texas
Contact: American Academy of Family Physicians (AAFP)
Phone: 800-274-2237; 913-906-6000
Email: aafp@aafp.org

61st Annual World Congress-International College of Angiology (ICA)
Oct 10 - 12, 2019
United States / Columbus, Ohio
Contact: International College of Angiology (ICA)
Phone: 1-802-988-4065
Email: denisemrossignol@cs.com

International Federation for Diabetes and Cardiometabolic Disorders (IFDCD) Winter Summit
Oct 10 - 12, 2019
South Korea / Jeongwipo, Jeju
Contact: International Federation for Diabetes and Cardiometabolic Disorders (IFDCD) | Conferences and Incentives Management (CIM Global) India Pvt. Ltd.
Phone: +31 20 3121212
Email: prasant@cimglobal.net

Essential Topics in Cardiology and Pulmonology: 2019 Update
Oct 12 - 26, 2019
Japan / Yokohama, Tokyo
Contact: Continuing Education, Inc.
Phone: 800-422-0711
Email: contactus@continuingeducation.net

Topics in Emergency Medicine
Oct 14 - 18, 2019
United States / Lahaina, Hawaii
Contact: Northwest Anesthesia Seminars (NWAS)
Phone: (800) 222-6927; (509) 547-7065
Email: info@northwestseminars.com

Cardiology in Primary Care 2019
Oct 17 - 19, 2019
United States / Atlanta, Georgia
Contact: Emory University School of Medicine Office of Continuing Medical Education (OCME)
Phone: 404-727-3612, 404-727-6123
Email: milini.mingo@emory.edu

Hospitalist and Emergency Procedures course
Oct 19, 2019
United States / New Orleans, Louisiana
Contact: Hospital Procedures Consultants (HPC)
Phone: 8053390225
Email: jesherick@hospitalprocedures.org

Intensive Course in Transcranial Magnetic Stimulation (TMS)
Oct 28 - Nov 01, 2019
United States / Boston, Massachusetts
Contact: Berenson-Allen Center for Noninvasive Brain Stimulation (BA CNBS)
Phone: 617.667.0307, 617-667-0203
Email: tms@bidmc.harvard.edu
Hypospadias International Society (HIS) 3rd World Congress
Oct 29 - Nov 01, 2019
United States / Philadelphia, Pennsylvania
Contact: Children’s Hospital of Philadelphia (CHOP)
Phone: 215-590-5263; 1-800-879-2467
Email: CMEOFFICE@email.chop.edu

Dermatologic & Aesthetic Surgery International League (DASIL) 8th Annual Congress
Oct 30 - Nov 02, 2019
India / Goa, Goa
Contact: Dermatologic Aesthetic Surgery International League (DASIL)
Phone: (847) 577-6543
Email: info@thedasil.org

45th National Hematology Congress
Oct 30 - Nov 02, 2019
Turkey / Antalya, Antalya
Contact: Turkish Hematology Association / Turk Hematoloji Derneği (THD)
Phone: +90 312 490 98 97 (pbx)
Email: thd@thd.org.tr

18th Emirates Society of Ophthalmology Conference
Oct 31 - Nov 02, 2019
United Arab Emirates / Abu Dhabi
Contact: DiaEdu Management Consultancy
Phone: +971 4 453 2975
Email: sara@diaedu.com

Middle East Fertility Society (MEFS) 2019 Conference
Oct 31 - Nov 02, 2019
Egypt / Nasr, Cairo
Contact: Middle East Fertility Society (MEFS)
Phone: +961-1-610400
Email: info@mefs.org

Master Class in Anti-Aging Hormone and Regenerative Therapies - Dubai
Oct 31 - Nov 02, 2019
United Arab Emirates / Dubai
Contact: American Academy of Anti-Aging Medicine (A4M)
Phone: 561-997-0112; 888-997-0112
Email: info@a4m.com

Frontiers in Addiction Treatment 2019
Nov 01, 2019
United States / Rochester, Minnesota
Contact: Mayo Clinic
Phone: 1-800-323-2688
Email: cme@mayo.edu

XXVIII National conference of Indian Association of Oral & Maxillofacial Pathologists (IAOMP) 2019
Nov 01 - 03, 2019
India / Thiruvananthapuram, Kerala
Contact: EventGurus
Phone: 91 9895322827; 9495677888
Email: ceo@eventgurus.net

First Annual Middle East & North Africa Immuno-Oncology Forum (MOIF)
Nov 01 - 02, 2019
Lebanon / Beirut, Beirut
Contact: Infomed - International for Events
Phone: +961 1 510881 / 2 / 3
Email: infomed@infomedweb.com

Cardiac Imaging in Cardiomyopathies and Heart Failure
Nov 02, 2019
Australia / Westmead, New South Wales
Contact: Australasian Society for Ultrasound in Medicine (ASUM)
Phone: +61 2 9438 2078
Email: asum@asum.com.au

Healthcare Information and Management Systems Society (HIMSS) Saudi Arabia 2019
Nov 02 - 05, 2019
Saudi Arabia / Riyadh, Riyadh
Contact: Healthcare Information and Management Systems Society (HIMSS)
Phone: (312) 664 - 664-4467
Email: himss@himss.org

Nanotech Middle East 2019 Conference and Exhibition
Nov 03 - 05, 2019
United Arab Emirates / Dubai, Dubai
Contact: Science, Engineering, Technology Conferences Organisers (SETCOR)
Phone: +33148728898, + 33 (0) 6 4557 4009
Email: r.mimouni@setcor.org

Interstitial lung diseases
Nov 04 - 06, 2019
Germany / Heidelberg, Baden-Wurttemberg
Contact: European Respiratory Society (ERS)
Phone: +41 21 213 01 01
Email: webmaster@ersnet.org

Breast MR with Guided Biopsy
Nov 04 - 05, 2019
United States / Reston, Virginia
Contact: American College of Radiology (ACR)
Phone: 1-800-227-5463; 703-648-8900
Email: info@acr.org
Primary Care and Cancer Matters
Nov 06, 2019
United Kingdom / Doncaster, England
Contact: Royal College of General Practitioners (RCGP)
Phone: 020 3188 7400
Email: info@rcgp.org.uk

IHF 2019 - 43rd World Hospital Congress
Nov 06 - 09, 2019
Oman / Muscat, Muscat
Contact: MCI Middle East | International Hospital Federation (IHF)
Phone: +971 4 311 6300
Email: ihf2019@mci-group.com

Southern Thoracic Surgical Association (STSA) 66th Annual Meeting
Nov 06 - 09, 2019
United States / Marco Island, Florida
Contact: Southern Thoracic Surgical Association (STSA)
Phone: 312.202.5892
Email: stsa@stsa.org

Emirates Pediatric Neonatal Intensive Care Conference (EPNIC)
Nov 06 - 08, 2019
United Arab Emirates / Dubai, Dubai
Contact: MCI Middle East
Phone: +971 4 311 6300; +971 4 311 6300
Email: neha.choudhary@mci-group.com
epnic2019@mci-group.com

British Geriatrics Society (BGS) Autumn Meeting 2019
Nov 06 - 08, 2019
United Kingdom / Leicester, England
Contact: British Geriatrics Society (BGS)
Phone: 0203 747 6940
Email: registrations@bgs.org.uk

International Symposia by International Society for Stem Cell Research (ISSCR) International Symposia 2019
Nov 06 - 08, 2019
Canada / Toronto, Ontario
Contact: International Society for Stem Cell Research (ISSCR)
Phone: +1 224-592-5700
Email: isscr@isscr.org

31st ICC - 4th GCCMID 2019
Nov 06 - 09, 2019
United Arab Emirates / Dubai, Dubai
Contact: Meeting Minds Experts
Phone: 9714 4270492
Email: soumya@meetingmindsdubai.com

MAP 2019 - Molecular Analysis for Personalised Therapy
Nov 07 - 09, 2019
United Kingdom / London, England
Contact: European Society for Medical Oncology (ESMO) | UNICANCER Group | Cancer Research UK
Phone: +41 (0)91 973 19 16
Email: map@esmo.org

8th Emirates Oncology Conference (EOC)
Nov 07 - 09, 2019
United Arab Emirates / Abu Dhabi
Contact: Tawam Hospital
Phone: +971529834137
Email: angelica@asgeventservices.com

4th Derma Gulf International Dermatology & Aesthetic medicine conference
Nov 07 - 08, 2019
United Arab Emirates / Dubai, Dubai
Contact: CME Conferences Organizing
Phone: 971 4361 5929; +971 52 646 5538
Email: Info@dubaicme.com

3rd Annual Dubai International Asthma, Allergy & COPD Forum
Nov 08 - 09, 2019
United Arab Emirates / Dubai, Dubai
Contact: Maarefah Management
Phone: +97143619616; +971 4 361 9616
Email: basma.t@maarefah-management.org

Pediatric Dermatology for the Practitioner 2019
Nov 09, 2019
United States / Chicago, Illinois
Contact: Ann & Robert H. Lurie Children’s Hospital of Chicago
Phone: 312.227.6062
Email: mejones@luriechildrens.org

Mastery of Chiropractic Principles and Practice - London
Nov 09 - 10, 2019
United Kingdom / West Drayton, England
Contact: International Chiropractic Pediatric Association (ICPA)
Phone: (610) 565-2360
Email: info@icpa4kids.com

The Essentials of Chiropractic: Adjusting the Infant and Education in the Perinatal Period
Nov 09 - 10, 2019
Canada / Ottawa, Ontario
Contact: International Chiropractic Pediatric Association (ICPA)
Phone: (610) 565-2360
Email: info@icpa4kids.com
16th DIA Japan Annual Meeting 2019
Nov 10 - 12, 2019
Japan / Tokyo, Kanto
Contact: Drug Information Association (DIA)
Phone: +1.215.442.6100
Email: India@DIAglobal.org

FT Global Pharmaceutical and Biotechnology Conference
Nov 11 - 12, 2019
United Kingdom / London, England
Contact: Financial Times (FT) Live
Phone: 02078733634
Email: alexsandra.silva@ft.com

Cell & Gene Therapy Asia 2019
Nov 11 - 12, 2019
Japan / Kobe, Hyogo
Contact: Select Biosciences
Phone: +1 510 857 4865
Email: enquiries@selectbio.com

Next Generation Organoids for Biomedical Research and Drug Discovery
Nov 12, 2019
United States / New York City, New York
Contact: The New York Academy of Sciences (NYAS)
Phone: 212.298.8600
Email: nyas@nyas.org

AOCMF Seminar - Recent Advances in Management of Trauma, Reconstruction and Orthognathic Surgery
Nov 12 - 13, 2019
India / Bangalore, Karnataka
Contact: AOCMF
Phone: +91 8587899960; +919811388960
Email: mittal.bhavnesh@ao-courses.com

International Conference on Biotechnology & Microbiology
Nov 12 - 14, 2019
United Arab Emirates / Dubai, Dubai
Contact: Impact Conferences
Phone: 3028277933; +1-3028277933
Email: biotech@impactcolloquiums.com

International Summit on Neurology and Brain Disorders
Nov 12 - 14, 2019
United Arab Emirates / Dubai, Dubai
Contact: Impact Conferences
Phone: 3028277933; +1-3028277933
Email: neurology@impactcolloquiums.com

Neonatal Pharmacology 2019 by Medical University of South Carolina (MUSC)
Nov 13 - 15, 2019
United States / Charleston, South Carolina
Contact: Medical University of South Carolina (MUSC)
Phone: 843-876-1925
Email: cmeoffice@musc.edu

Major Trauma Course
Nov 13, 2019
United Kingdom / London, England
Contact: The Royal College of Emergency Medicine (RCEM)
Phone: +44 (0) 20 7404 1999
Email: events@rcem.ac.uk

39th Annual Conference of National Academy of Neuropsychology (NAN)
Nov 13 - 16, 2019
United States / San Diego, California
Contact: National Academy of Neuropsychology (NAN)
Phone: (303) 691-3694
Email: office@nanonline.org

Diagnostic Problems in Head & Neck, Soft Tissue, GI and Pancreaticobiliary: A Practical Approach for the Practicing Pathologist
Oct 14 - 17, 2019
United States / Wailea, Hawaii
Contact: Scientific Symposiums International
Phone: 925-376-0217
Email: carolhaag7@gmail.com

How to Manage: Advance care planning in paediatric palliative care
Oct 14, 2019
United Kingdom / London, England
Contact: Royal College of Paediatrics and Child Health (RCPCH)
Phone: +44 (0)20 7092 6000
Email: enquiries@rcpch.ac.uk

Annual Radiology Meeting in UAE - ARM 2019
Oct 15 - 17, 2019
United Arab Emirates / Dubai, Dubai
Contact: INDEX Conferences & Exhibitions / Radiology Society of the Emirates (RSE)
Phone: +971-4-255-6655; 00971 4 520 8888
Email: info@rse.org.ae

International Conference on Neurology and Cardiology by Citations International
Oct 15 - 17, 2019
United Arab Emirates / Dubai, Dubai
Contact: Citations International
Phone: +1 646-893-6299
Email: contact@citationsinternational.com
<table>
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<th>Conference</th>
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| **Day Case Hip & Knee Arthroplasty**                                       | Oct 15, 2019          | United Kingdom / Newcastle upon Tyne, England | Northumbria Healthcare NHS Foundation Trust  
Phone: 0207 9730308  
Email: bads@bads.co.uk |
| **Diagnosing and Treating Irritable Bowel Syndrome**                       | Oct 16, 2019          | United States / Scottsdale, Arizona | University of Louisville (UL) School of Medicine  
Phone: (253) 432-4023  
Email: cme@scquirer.com |
| **International Biochemistry Conference by Outlook Conferences (OLC)**     | Oct 17 - 18, 2019     | United Arab Emirates / Dubai, Dubai | Outlook Conferences (OLC)  
Phone: +91779901270  
Email: olcbcc-2019@outlookconferences.com |
| **The premier international diabetic foot conference 2019**                | Oct 17 - 19, 2019     | United States / Los Angeles, California | DFCon - Diabetic Global Foot Conference  
Phone: +1 323 442 2555  
Email: dfcon@cap-partner.eu |
Phone: +971 4 520 8888  
Email: tanaya.priya@index.ae |
| **Gastroenterology Update: A Case-Based Approach to Common GI Problems 2019** | Oct 18 - 19, 2019     | United States / Plymouth, Michigan | University of Michigan Department of Internal Medicine  
Phone: +1 734-936-4000, (734) 936-4340  
Email: intmedmarketing@umich.edu |
| **Microbiology SIG Seminar 2019**                                          | Oct 18 - 19, 2019     | New Zealand / Auckland, Auckland | The New Zealand Institute of Medical Laboratory Science (NZIMLS) Inc  
Phone: +64 3 313 4761  
Email: fran@nzimls.org.nz |
| **Stroke Imaging and Intervention**                                        | Oct 19 - 20, 2019     | United States / Las Vegas, Nevada | Educational Symposia (ESI)  
Phone: 813-806-1000  
Email: info@edusymp.com |
| **Haematology SIG Seminar**                                                | Oct 19, 2019          | New Zealand / Napier, Hawke’s Bay | The New Zealand Institute of Medical Laboratory Science (NZIMLS) Inc  
Phone: +64 3 313 4761  
Email: fran@nzimls.org.nz |
| **Systems Genetics of Metabolic Disease: A Team Science Approach**         | Oct 20 - 26, 2019     | United States / Bar Harbor, Maine | The Jackson Laboratory  
Phone: 207-288-6659  
Email: erin.mcdevitt@jax.org |
Phone: 971 4 520 8888  
Email: tanaya.priya@index.ae  
info@wacem2019.com |
| **Global Conference on Surgery and Anesthesia (GCSA) 2019**                | Oct 21 - 23, 2019     | United Arab Emirates / Dubai, Dubai | Magnus Group (MG)  
Phone: 17029882320  
Email: surgerymeeting@magnus-group.org |
| **AOCMF Seminar - Advances in Modern Orthognathic Surgery**                | Oct 24, 2019          | Thailand / Bangkok, Bangkok        | AOCMF  
Phone: +6623228501  
Email: buc@loxinfo.co.th |
Phone: +971 4 520 8888  
Email: tanaya.priya@index.ae |
22nd Annual National Conference of Otalaryngology & Head & Neck Surgeons
Oct 25 - 26, 2019
Oman / Muscat, Muscat
Contact: MCI Middle East | Oman ORL Society
Phone: +971 4 311 6300
Email: omanorl@mci-group.com

XXIV World Congress of Neurology - WCN 2019
Oct 27 - 31, 2019
United Arab Emirates / Dubai, Dubai
Contact: Kenes Group
Phone: +41 22 9080488, +44 (0)20 3542 1657 / 1658
Email: jmargo@kenes.com

Essential Strategies for Chronic Pain Management
Oct 28, 2019
Canada / Calgary, Alberta
Contact: University of Calgary - Continuing Medical Education and Professional Development
Phone: 403.943.9910; 403.210.6272
Email: sylvia.vespa@albertahealthservices.ca

8th Annual Cell Culture & Bioprocessing Congress 2019
Oct 29 - 30, 2019
United Kingdom / London, England
Contact: Oxford Global Marketing Ltd.
Phone: 4401865248455
Email: marketing@oxfordglobal.co.uk

Society for Minimally Invasive Spine Surgery (SMISS) Annual Forum 2019
Oct 31 - Nov 02, 2019
United States / Las Vegas, Nevada
Contact: Society for Minimally Invasive Spine Surgery (SMISS)
Phone: 331-218-0780
Email: info@smiss.org

Critically thinking through the critically ill in the ICU and Acute Care Settings
Nov 01 - 02, 2019
United States / Indianapolis, Indiana
Contact: Education Resources, Inc. (ERI)
Phone: 508-359-6533; 800-487-6530
Email: info@educationresourcesinc.com

37th Annual Fall Conference on Obstetrics
Nov 06 - 09, 2019
United States / Big Island, Hawaii
Contact: Symposia Medicus
Phone: (800) 327-3161; (925) 969-1789
Email: info@symposiamedicus.org

3rd Annual Dubai International Asthma, Allergy & COPD Forum
Nov 08 - 09, 2019
United Arab Emirates / Dubai, Dubai
Contact: Maarefah Management
Phone: +97143619616; +971 4 361 9616
Email: basma.t@maarefah-management.org

48th American Association of Gynecologic Laparoscopists (AAGL) Global Congress on Minimally Invasive Gynecologic Surgery (MIGS)
Nov 09 - 13, 2019
Canada / Vancouver, British Columbia
Contact: American Association of Gynecologic Laparoscopists (AAGL)
Phone: 714-503-6200
Email: generalmail@aagl.org

WSMOS Fall 2019 Oncology Conference
Nov 15, 2019
United States / Seattle, Washington
Contact: Washington State Medical Oncology Society (WSMOS)
Phone: 360.258.0443
Email: wsmos@comcast.net

Essentials in Palliative and End of Life Care
Nov 18, 2019
United Kingdom / Manchester, England
Contact: The Christie NHS Foundation Trust
Phone: 0161 446 3000
Email: info@christie.nhs.uk

Into Clinical Practice: Meeting the Challenges of Gram-negative Infection Management
Nov 19, 2019
United Kingdom / London, England
Contact: British Society for Antimicrobial Chemotherapy (BSAC)
Phone: +44 (0) 121 236 1988, +44 (0) 121 262 1830
Email: Ecarruthers@bsac.org.uk

Care of the Critically Ill Surgical Patient (CCrISP) Course
Nov 21 - 22, 2019
United Kingdom / Portsmouth, England
Contact: The Royal College of Surgeons (RCS) of England
Phone: 020 7869 6002; +44 (0)20 7405 3474
Email: mandy.smale@porthosp.nhs.uk

Changing Landscapes: Innovation and Challenges in the Treatment of Trauma and Dissociation
Nov 22 - 24, 2019
New Zealand / Christchurch, Canterbury
Contact: International Society for the Study of Trauma and Dissociation (ISSTD)
Phone: 202-803-6332
Email: info@isst-d.org
Cancer control in low- and middle-income countries: New solutions to evolving challenges
Nov 25, 2019
United Kingdom / London, England
Contact: The Royal Society of Medicine (RSM)
Phone: 020 7290 2900
Email: info@rsm.ac.uk

Palliative Care and Radiotherapy - A Course on Prognosis, Symptom Control, Re-Irradiation and Oligometastases
Nov 26 - 28, 2019
Belgium / Brussels, Brussels
Contact: European Society for Radiotherapy and Oncology (ESTRO)
Phone: +32 2 775 93 40
Email: info@estro.org

International Symposium on Molecular Allergology (ISMA) 2019
Nov 28 - 30, 2019
Netherlands / Amsterdam, North Holland
Contact: European Academy of Allergy and Clinical Immunology (EAACI)
Phone: +41 44 205 55 33
Email: info@eaaci.org

British & Irish Society for Minimally Invasive Cardiac Surgery (BISMACS) 2019
Dec 02 - 03, 2019
United Kingdom / Manchester, England
Contact: Millbrook Medical Conferences Ltd
Phone: +44 (0) 1455 552559
Email: harriet@millbrookconferences.co.uk

United States / New York City, New York
Contact: Weill Cornneld Medicine (WCM)
Phone: (212) 746-5454
Email: wcms-admissions@med.cornell.edu

World Allergy Congress (WAC) 2019
Dec 12 - 14, 2019
France / Lyon, Auvergne-Rhone-Alpes
Contact: World Allergy Organization (WAO)
Phone: +33 4 67 10 92 23
Email: wac2019@ant-congres.com

11th Annual Conference on Emergencies & Challenges in Pediatrics
Dec 13 - 14, 2019
United States / New York city, New York
Contact: Symposia Medicus
Phone: (800) 327-3161; (925) 969-1789
Email: info@symposiamedicus.org

3rd Allied Health Rehabilitation Course for Parkinson’s Disease
Dec 13, 2019
United Arab Emirates / Dubai, Dubai
Contact: International Parkinson and Movement Disorder Society (MDS)
Phone: +1 (414) 276-2145
Email: info@movementdisorders.org

63rd All India Congress of Obstetrics and Gynaecology (AICOG)
Jan 29 - Feb 02, 2020
India / Lucknow, Uttar Pradesh
Contact: Concept Conferences Pvt. Ltd.
aicog2020@gmail.com

13th Annual Congress of European Association for Haemophilia and Allied Disorders (EAHAD)
Feb 05 - 07, 2020
Netherlands / The Hague, South Holland
Contact: European Association for Haemophilia and Allied Disorders (EAHAD)
Phone: +32 (0) 479 25 47 72
Email: info@eahad.org

Internal Medicine for Primary Care: Addiction/Endo/Palliative 2020
Feb 07 - 09, 2020
United States / Vail, Colorado
Contact: Medical Education Resources (MER)
Phone: 303-798-9682
1-800-421-3756
Email: info@mer.org
1. HUMAN PAPILLOMAVIRUS (HPV) AND CERVICAL CANCER

KEY FACTS

- Human papillomavirus (HPV) is a group of viruses that are extremely common worldwide.
- There are more than 100 types of HPV, of which at least 14 are cancer-causing (also known as high risk type).
- HPV is mainly transmitted through sexual contact and most people are infected with HPV shortly after the onset of sexual activity.
- Cervical cancer is caused by sexually acquired infection with certain types of HPV.
- Two HPV types (16 and 18) cause 70% of cervical cancers and pre-cancerous cervical lesions.
- There is also evidence linking HPV with cancers of the anus, vulva, vagina, penis and oropharynx.
- Cervical cancer is the second most common cancer in women living in less developed regions with an estimated 570,000 new cases (1) in 2018 (84% of the new cases worldwide).
- In 2018, approximately 311,000 women died from cervical cancer; more than 85% of these deaths occurring in low- and middle-income countries.
- Comprehensive cervical cancer control includes primary prevention (vaccination against HPV), secondary prevention (screening and treatment of pre-cancerous lesions), tertiary prevention (diagnosis and treatment of invasive cervical cancer) and palliative care.
- Vaccines that protect against HPV 16 and 18 are recommended by WHO and have been approved for use in many countries.
- Screening and treatment of pre-cancer lesions in women of 30 years and more is a cost-effective way to prevent cervical cancer.
- Clinical trials and post-marketing surveillance have shown that HPV vaccines are very safe and very effective in preventing infections with HPV infections.
- Cervical cancer can be cured if diagnosed at an early stage.

What is HPV?

Human papillomavirus (HPV) is the most common viral infection of the reproductive tract. Most sexually active women and men will be infected at some point in their lives and some may be repeatedly infected.

The peak time for acquiring infection for both women and men is shortly after becoming sexually active. HPV is sexually transmitted, but penetrative sex is not required for transmission. Skin-to-skin genital contact is a well-recognized mode of transmission.

There are many types of HPV, and many do not cause problems. HPV infections usually clear up without any intervention within a few months after acquisition, and about 90% clear within 2 years. A small proportion of infections with certain types of HPV can persist and progress to cervical cancer.

Cervical cancer is by far the most common HPV-related disease. Nearly all cases of cervical cancer can be attributable to HPV infection.

The infection with certain HPV types also causes a proportion of cancers of the anus, vulva, vagina, penis and oropharynx, which are preventable using similar primary prevention strategies as those for cervical cancer.

Non-cancer causing types of HPV (especially types 6 and 11) can cause genital warts and respiratory papillomatosis (a disease in which tumours grow in the air passages leading from the nose and mouth...
into the lungs). Although these conditions very rarely result in death, they may cause significant occurrence of disease. Genital warts are very common, highly infectious and affect sexual life.

How HPV infection leads to cervical cancer

Although most HPV infections clear up on their own and most pre-cancerous lesions resolve spontaneously, there is a risk for all women that HPV infection may become chronic and pre-cancerous lesions progress to invasive cervical cancer.

It takes 15 to 20 years for cervical cancer to develop in women with normal immune systems. It can take only 5 to 10 years in women with weakened immune systems, such as those with untreated HIV infection.

Risk factors for HPV persistence and development of cervical cancer

- HPV type – its oncogenicity or cancer-causing strength;
- immune status – people who are immunocompromised, such as those living with HIV, are more likely to have persistent HPV infections and a more rapid progression to pre-cancer and cancer;
- coinfection with other sexually transmitted agents, such as those that cause herpes simplex, chlamydia and gonorrhea;
- parity (number of babies born) and young age at first birth;
- tobacco smoking

Global burden of cervical cancer

Worldwide, cervical cancer is the fourth most frequent cancer in women with an estimated 570,000 new cases in 2018 representing 7.5% of all female cancer deaths. Of the estimated more than 311,000 deaths from cervical cancer every year, more than 85% of these occur in less developed regions.

In developed countries, programmes are in place which enable girls to be vaccinated against HPV and women to get screened regularly. Screening allows pre-cancerous lesions to be identified at stages when they can easily be treated. Early treatment prevents up to 80% of cervical cancers in these countries.

In developing countries, there is limited access to these preventative measures and cervical cancer is often not identified until it has further advanced and symptoms develop. In addition, access to treatment of such late-stage disease (for example, cancer surgery, radiotherapy and chemotherapy) may be very limited, resulting in a higher rate of death from cervical cancer in these countries.

The high mortality rate from cervical cancer globally (Age Standardized Rate: 6.9/100,000 in 2018) could be reduced by effective interventions.
Cervical cancer control: A comprehensive approach

WHO recommends a comprehensive approach to cervical cancer prevention and control. The recommended set of actions includes interventions across the life course. It should be multidisciplinary, including components from community education, social mobilization, vaccination, screening, treatment and palliative care.

Primary prevention begins with HPV vaccination of girls aged 9-14 years, before they become sexually active.

Other recommended preventive interventions for boys and girls as appropriate are:
- education about safe sexual practices, including delayed start of sexual activity;
- promotion and provision of condoms for those already engaged in sexual activity;
- warnings about tobacco use, which often starts during adolescence, and which is an important risk factor for cervical and other cancers; and
- male circumcision.

Women who are sexually active should be screened for abnormal cervical cells and pre-cancerous lesions, starting from 30 years of age.

If treatment of pre-cancer is needed to excise abnormal cells or lesions, cryotherapy (destroying abnormal tissue on the cervix by freezing it) is recommended.

If signs of cervical cancer are present, treatment options for invasive cancer include surgery, radiotherapy and chemotherapy.

HPV vaccination

There are currently 3 vaccines protecting against both HPV 16 and 18, which are known to cause at least 70% of cervical cancers. The third vaccine protects against three additional oncogenic HPVs, which cause a further 20% of cervical cancers. Given that the vaccines which are only protecting against HPV 16 and 18 also have some cross-protection against other less common HPV types which cause cervical cancer, WHO considers the three vaccines equally protective against cervical cancer. Two of the vaccines also protect against HPV types 6 and 11, which cause anogenital warts.

Clinical trials and post-marketing surveillance have shown that HPV vaccines are very safe and very effective in preventing infections with HPV infections. HPV vaccines work best if administered prior to exposure to HPV. Therefore, WHO recommends to vaccinate girls, aged between 9 and 14 years, when most have not started sexual activity.

The vaccines cannot treat HPV infection or HPV-associated disease, such as cancer.

Some countries have started to vaccinate boys as the vaccination prevents genital cancers in males as well as females, and two available vaccines also prevent genital warts in males and females. WHO recommends vaccination for girls aged between 9 and 14 years, as this is the most cost-effective public health measure against cervical cancer.

HPV vaccination does not replace cervical cancer screening. In countries where HPV vaccine is introduced, screening programmes may still need to be developed or strengthened.

Screening and treatment of pre-cancer lesions

Cervical cancer screening involves testing for pre-cancer and cancer among women who have no symptoms and may feel perfectly healthy. When screening detects pre-cancerous lesions, these can easily be treated, and cancer can be avoided. Screening can also detect cancer at an early stage and treatment has a high potential for cure.

Because pre-cancerous lesions take many years to develop, screening is recommended for every woman from aged 30 and regularly afterwards (frequency depends on the screening test used). For women living with HIV who are sexually active, screening should be done earlier, as soon as they know their HIV status.

Screening has to be linked to access to treatment and management of positive screening tests. Screening without proper management is not ethical.

There are 3 different types of screening tests that are currently recommended by WHO:
- HPV testing for high-risk HPV types.
- visual inspection with Acetic Acid (VIA)
- conventional (Pap) test and liquid-based cytology (LBC)

For treatment of pre-cancer lesions, WHO recommends the use of cryotherapy and Loop Electrosurgical Excision Procedure (LEEP). For advanced lesions, women should be referred for further investigations and adequate management.

Management of invasive cervical cancer

When a woman presents symptoms of suspicion for cervical cancer, she must be referred to an appropriate facility for further evaluation, diagnosis and treatment.

Symptoms of early stage cervical cancer may include:
- Irregular blood spotting or light bleeding between periods in women of reproductive age;
- Postmenopausal spotting or bleeding;
- Bleeding after sexual intercourse; and
- Increased vaginal discharge, sometimes foul smelling.

As cervical cancer advances, more severe symptoms may appear including:
Persistent back, leg and/or pelvic pain;
- Weight loss, fatigue, loss of appetite;
- Foul-smell discharge and vaginal discomfort; and
- Swelling of a leg or both lower extremities.

Other severe symptoms may arise at advanced stages depending on which organs cancer has spread.

Diagnosis of cervical cancer must be made by histopathologic examination. Staging is done based on tumor size and spread of the disease within the pelvis and to distant organs. Treatment depends on the stage of the disease and options include surgery, radiotherapy and chemotherapy. Palliative care is also an essential element of cancer management to relieve unnecessary pain and suffering due the disease.

WHO response

WHO has developed guidance on how to prevent and control cervical cancer through vaccination, screening and management of invasive cancer. WHO works with countries and partners to develop and implement comprehensive programmes.

In May 2018 the WHO Director-General made a call to action towards the elimination of cervical cancer and engage partners and countries to increase access to and coverage of these 3 essential interventions to prevent cervical cancer: HPV vaccination, screening and treatment of pre-cancer lesions, and management of cervical cancer.

REFERENCES


What are natural toxins?

Natural toxins are toxic compounds that are naturally produced by living organisms. These toxins are not harmful to the organisms themselves but they may be toxic to other creatures, including humans, when eaten. These chemical compounds have diverse structures and differ in biological function and toxicity.

Some toxins are produced by plants as a natural defense mechanism against predators, insects or microorganisms, or as consequence of infestation with microorganisms, such as mould, in response to climate stress (such as drought or extreme humidity).

Other sources of natural toxins are microscopic algae and plankton in oceans or sometimes in lakes that produce chemical compounds that are toxic to humans but not to fish or shellfish that eat these toxin-producing organisms. When people eat fish or shellfish that contain these toxins, illness can rapidly follow.

Some of the most commonly found natural toxins that can pose a risk to our health are described below.

2. NATURAL TOXINS IN FOOD

KEY FACTS

- Some natural toxins can be formed in food as defense mechanisms of plants, through their infestation with toxin-producing mould, or through ingestion by animals of toxin-producing microorganisms.
- Natural toxins can cause a variety of adverse health effects and pose a serious health threat to both humans and livestock. Some of these toxins are extremely potent.
- Adverse health effects can be acute poisoning ranging from allergic reactions to severe stomachache and diarrhoea, and even death.
- Long-term health consequences include effects on the immune, reproductive or nervous systems, and also cancer.

Aquatic biotoxins

Toxins formed by algae in the ocean and fresh water are called algal toxins. Algal toxins are generated during blooms of particular naturally occurring algal species. Shellfish such as mussels, scallops and oysters are more likely to contain these toxins than fish. Algal toxins can cause diarrhea, vomiting, tingling, paralysis and other effects in humans, other mammals or fish. The algal toxins can be retained in shellfish and fish or contaminate drinking water. They have no taste or smell, and are not eliminated by cooking or freezing.

Another example is ciguatera fish poisoning (CFP) which is caused by consuming fish contaminated with dinoflagellates that produce ciguatoxins. Some fish known to harbour ciguatoxins include barracuda, black grouper, dog snapper, and king mackerel. Symptoms of ciguatera poisoning include nausea, vomiting, and neurologic symptoms, such as tingling sensation on fingers and toes. There is currently no specific treatment for ciguatera poisoning.

Cyanogenic glycosides

Cyanogenic glycosides are phytotoxins (toxic chemicals produced by plants) which occur in at least
2000 plant species, of which a number of species are used as food in some areas of the world. Cassava, sorghum, stone fruits, bamboo roots and almonds are especially important foods containing cyanogenic glycosides. The potential toxicity of a cyanogenic plant depends primarily on the potential that its consumption will produce a concentration of cyanide that is toxic to exposed humans. In humans, the clinical signs of acute cyanide intoxication can include: rapid respiration, drop in blood pressure, dizziness, headache, stomach pains, vomiting, diarrhoea, mental confusion, cyanosis with twitching and convulsions followed by terminal coma. Death due to cyanide poisoning can occur when the cyanide level exceeds the limit an individual is able to detoxify.

**Furocoumarins**

These toxins are present in many plants such as parsnips (closely related to carrots and parsley), celery roots, citrus plants (lemon, lime, grapefruit, bergamot) and some medicinal plants. Furocoumarins are stress toxins and are released in response to stress, such as physical damage to the plant. Some of these toxins can cause gastrointestinal problems in susceptible people. Furocoumarins are phototoxic, they can cause severe skin reactions under sunlight (UVA exposure). While mainly occurring after dermal exposure, such reactions have also been reported after consumption of large quantities of certain vegetables containing high levels of furocoumarins.

**Lectins**

Many types of beans contain toxins called lectins, and kidney beans have the highest concentrations – especially red kidney beans. As few as 4 or 5 raw beans can cause severe stomachache, vomiting and diarrhoea. Lectins are destroyed when the dried beans are soaked for at least 12 hours and then boiled vigorously for at least 10 minutes in water. Tinned kidney beans have already had this process applied and so can be used without further treatment.

**Mycotoxins**

Mycotoxins are naturally occurring toxic compounds produced by certain types of moulds. Moulds that can produce mycotoxins grow on numerous foodstuffs such as cereals, dried fruits, nuts and spices. Mould growth can occur before harvest or after harvest, during storage, on/in the food itself often under warm, damp and humid conditions.

Most mycotoxins are chemically stable and survive food processing. The effects of food-borne mycotoxins can be acute with symptoms of severe illness and even death appearing quickly after consumption of highly contaminated food products. Long term effects on health of chronic mycotoxin exposure include the induction of cancers and immune deficiency.

- Fact sheet on Mycotoxins

**Solanines and chaconine**

All solanacea plants, which include tomatoes, potatoes, and eggplants, contain natural toxins called solanines and chaconine (which are glycoalkaloids). While levels are generally low, higher concentrations are found in potato sprouts and bitter-tasting peel and green parts, as well as in green tomatoes. The plants produce the toxins in response to stresses like bruising, UV light, microorganisms and attacks from insect pests and herbivores. To reduce the production of solanines and chaconine it is important to store potatoes in a dark, cool and dry place, and not to eat green or sprouting parts.

**Poisonous mushrooms**

Wild mushrooms may contain several toxins, such as muscimol and muscarine, which can cause vomiting, diarrhoea, confusion, visual disturbances, salivation, and hallucinations. Onset of symptoms occurs 6–24 hours or more after ingestion of mushrooms. Fatal poisoning is usually associated with delayed onset of symptoms which are very severe, with toxic effect on the liver, kidney and nervous systems. Cooking or peeling does not inactivate the toxins. It is recommended to avoid any wild mushrooms, unless definitively identified as non-poisonous.

**Pyrrolizidine alkaloids**

Pyrrolizidine Alkaloids (PAs) are toxins produced by an estimated 600 plant species. The main plant sources are the families Boraginaceae, Asteraceae and Fabaceae. Many of these are weeds that can grow in fields and contaminate food crops. PAs can cause a variety of adverse health effects; they can be acutely toxic and of main concern is the DNA-damaging potential of certain PAs, potentially leading to cancer.

PAs are stable during processing, and have been detected in herbal teas, honey, herbs and spices and other food products, such as cereals and cereal products. Human exposure is estimated to be low, however. Due to the complexity of the subject and the large number of related compounds, the overall health risk has not been fully evaluated yet. Guidance is under development by the FAO/WHO Codex Committee on Contaminants in Food on management strategies to prevent PA-containing plants from entering the food chain.
How can I minimize the health risk from natural toxins?

When it comes to natural toxins it is important to note that they can be present in a variety of different crops and foodstuff. In a usual balanced, healthy diet, the levels of natural toxins are well below the threshold for acute and chronic toxicity.

To minimize the health risk from natural toxins in food, people are advised to:

- not assume that if something is ‘natural’ it is automatically safe;
- throw away bruised, damaged or discolored food, and in particular mouldy foods;
- throw away any food that does not smell or taste fresh, or has an unusual taste; and
- only eat mushrooms or other wild plants that have definitively been identified as nonpoisonous.

WHO response

WHO, in collaboration with FAO, is responsible for assessing the risks to humans of natural toxins – through contamination in food – and for recommending adequate protections.

Risk assessments of natural toxins in food done by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) are used by governments and by the Codex Alimentarius Commission (the intergovernmental standards-setting body for food) to establish maximum levels in food or provide other risk management advice to control or prevent contamination. Codex standards are the international reference for national food supplies and for trade in food, so that people everywhere can be confident that the food they buy meets the agreed standards for safety and quality, no matter where it was produced.

JECFA sets the tolerable intake level for natural toxins

JECFA or ad hoc FAO/WHO scientific expert groups consist of independent, international experts who conduct scientific reviews of all available studies and other relevant data on specific natural toxins. The outcome of such health risk assessments can either be a maximum tolerable intake (exposure) level, or other guidance to indicate the level of health concern (such as the Margin of Exposure), including advice on risk management measures to prevent and control contamination, and on the analytical methods and monitoring and control activities.

Exposure to natural toxins needs to be kept as low as possible to protect people. Natural toxins not only pose a risk to both human and animal health, but also impact food security and nutrition by reducing people’s access to healthy food. WHO encourages national authorities to monitor and ensure that levels of the most relevant natural toxins in their food supply are as low as possible and comply with both national and international maximum levels, conditions and legislation.

3. PNEUMONIA

KEY FACTS

- Pneumonia accounts for 16% of all deaths of children under 5 years old, killing 920,136 children in 2015.
- Pneumonia can be caused by viruses, bacteria, or fungi.
- Pneumonia can be prevented by immunization, adequate nutrition, and by addressing environmental factors.
- Pneumonia caused by bacteria can be treated with antibiotics, but only one third of children with pneumonia receive the antibiotics they need.

Pneumonia is a form of acute respiratory infection that affects the lungs. The lungs are made up of small sacs called alveoli, which fill with air when a healthy person breathes. When an individual has pneumonia, the alveoli are filled with pus and fluid, which makes breathing painful and limits oxygen intake.

Pneumonia is the single largest infectious cause of death in children worldwide. Pneumonia killed 920,136 children under the age of 5 in 2015, accounting for 16% of all deaths of children under five years old. Pneumonia affects children and families everywhere, but is most prevalent in South Asia and sub-Saharan Africa. Children can be protected from pneumonia, it can be prevented with simple interventions, and treated with low-cost, low-tech medication and care.

Causes

Pneumonia is caused by a number of infectious agents, including viruses, bacteria and fungi. The most common are:

- Streptococcus pneumoniae – the most common cause of bacterial pneumonia in children;
- Haemophilus influenzae type b (Hib) – the second most common cause of bacterial pneumonia;
- respiratory syncytial virus is the most common viral cause of pneumonia;
- in infants infected with HIV, Pneumocystis jiroveci is one of the most common causes of pneumonia, responsible for at least one quarter of all pneumonia deaths in HIV-infected infants.
Transmission

Pneumonia can be spread in a number of ways. The viruses and bacteria that are commonly found in a child’s nose or throat, can infect the lungs if they are inhaled. They may also spread via air-borne droplets from a cough or sneeze. In addition, pneumonia may spread through blood, especially during and shortly after birth. More research needs to be done on the different pathogens causing pneumonia and the ways they are transmitted, as this is of critical importance for treatment and prevention.

Presenting features

The presenting features of viral and bacterial pneumonia are similar. However, the symptoms of viral pneumonia may be more numerous than the symptoms of bacterial pneumonia. In children under 5 years of age, who have cough and/or difficult breathing, with or without fever, pneumonia is diagnosed by the presence of either fast breathing or lower chest wall indrawing where their chest moves in or retracts during inhalation (in a healthy person, the chest expands during inhalation). Wheezing is more common in viral infections.

Very severely ill infants may be unable to feed or drink and may also experience unconsciousness, hypothermia and convulsions.

Risk factors

While most healthy children can fight the infection with their natural defences, children whose immune systems are compromised are at higher risk of developing pneumonia. A child’s immune system may be weakened by malnutrition or undernourishment, especially in infants who are not exclusively breastfed.

Pre-existing illnesses, such as symptomatic HIV infections and measles, also increase a child’s risk of contracting pneumonia.

The following environmental factors also increase a child’s susceptibility to pneumonia:

- indoor air pollution caused by cooking and heating with biomass fuels (such as wood or dung)
- living in crowded homes
- parental smoking.

Treatment

Pneumonia should be treated with antibiotics. The antibiotic of choice is amoxicillin dispersable tablets. Most cases of pneumonia require oral antibiotics, which are often prescribed at a health centre. These cases can also be diagnosed and treated with inexpensive oral antibiotics at the community level by trained community health workers. Hospitalization is recommended only for severe cases of pneumonia.

Prevention

Preventing pneumonia in children is an essential component of a strategy to reduce child mortality. Immunization against Hib, pneumococcus, measles and whooping cough (pertussis) is the most effective way to prevent pneumonia.

Adequate nutrition is key to improving children’s natural defences, starting with exclusive breastfeeding for the first 6 months of life. In addition to being effective in preventing pneumonia, it also helps to reduce the length of the illness if a child does become ill.

Addressing environmental factors such as indoor air pollution (by providing affordable clean indoor stoves, for example) and encouraging good hygiene in crowded homes also reduces the number of children who fall ill with pneumonia.

In children infected with HIV, the antibiotic cotrimoxazole is given daily to decrease the risk of contracting pneumonia.

Economic costs

The cost of antibiotic treatment for all children with pneumonia in 66 of the countdown to 2015 countries for maternal, newborn and child survival is estimated at around US$ 109 million per year. The price includes the antibiotics and diagnostics for pneumonia management.

WHO response

The WHO and UNICEF integrated Global action plan for pneumonia and diarrhoea (GAPPD) aims to accelerate pneumonia control with a combination of interventions to protect, prevent, and treat pneumonia in children with actions to:

- protect children from pneumonia including promoting exclusive breastfeeding and adequate complementary feeding;
- prevent pneumonia with vaccinations, hand washing with soap, reducing household air pollution, HIV prevention and cotrimoxazole prophylaxis for HIV-infected and exposed children;
- treat pneumonia focusing on making sure that every sick child has access to the right kind of care -- either from a community-based health worker, or in a health facility if the disease is severe -- and can get the antibiotics and oxygen they need to get well;

A number of countries including Bangladesh, India, Kenya, Uganda and Zambia have developed district, state and national plans to intensify actions for the control of pneumonia and diarrhoea. Many more have integrated diarrhoea and pneumonia specific action into their national child health and child survival
strategies. For many countries the post Millenium Development Goal agenda has explicitly included ending preventable diarrhoea and pneumonia deaths as a priority action.

4. SEPSIS

KEY FACTS

- Sepsis arises when the body’s response to an infection injures its own tissues and organs, potentially leading to death or significant morbidity.
- The global epidemiological burden of sepsis is difficult to ascertain. It is estimated to affect more than 30 million people worldwide every year, potentially leading to 6 million deaths (1). The burden of sepsis is most likely highest in low- and middle-income countries.
- It is estimated that 3 million newborns and 1.2 million children suffer from sepsis globally every year (2). Three out of every ten deaths due to neonatal sepsis are thought to be caused by resistant pathogens (3).
- One in ten deaths associated with pregnancy and childbirth is due to maternal sepsis with over 95% of deaths due to maternal sepsis occurring in low- and middle-income countries (4). One million newborn deaths are associated with maternal infection, such as maternal sepsis, each year (5).
- Sepsis can be the clinical manifestation of infections acquired both in the community setting or in health care facilities. Health care-associated infections are one of, if not the most frequent type of adverse event to occur during care delivery and affect hundreds of millions of patients worldwide every year (6). Since these infections are often resistant to antibiotics, they can rapidly lead to deteriorating clinical conditions.

Background

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection (7). If not recognized early and managed promptly, it can lead to septic shock, multiple organ failure and death. Any type of infectious pathogen can potentially cause sepsis. Antimicrobial resistance is a major factor determining clinical unresponsiveness to treatment and rapid evolution to sepsis and septic shock. Sepsis patients with resistant pathogens have been found to have a higher risk of hospital mortality.

Who is at risk?

Anyone affected by an infection can progress to sepsis conditions but some vulnerable populations such as elderly people, pregnant women, neonates, hospitalized patients, and people with HIV/AIDS, liver cirrhosis, cancer, kidney disease, autoimmune diseases and no spleen, are at higher risk (8).

Signs and symptoms

Sepsis is a medical emergency. However, because of the characteristics of sepsis as a disease condition with multiple causative organisms and its evolving nature over time, people with sepsis can present various signs and symptoms at different times. Warning signs and symptoms include fever or low temperature and shivering, altered mental status, difficulty breathing/rapid breathing, increased heart rate, weak pulse/low blood pressure, low urine output, cyanotic or mottled skin, cold extremities, and extreme body pain or discomfort (9-11). Suspecting sepsis is a first major step towards early recognition and diagnosis.

Prevention

There are two main steps to preventing sepsis:

- prevention of microbial transmission and infection
- prevention of the evolution of an infection to sepsis conditions.

Prevention of infection in the community involves using effective hygiene practices, such as hand washing, and safe preparation of food, improving sanitation and water quality and availability, providing access to vaccines, particularly for those at high risk, as well as appropriate nutrition, including breastfeeding for newborns.

Prevention of infection in health care facilities mainly relies on having functioning infection prevention and control (IPC) programmes and teams, effective hygiene practices and precautions, including hand hygiene, along with a clean, well-functioning environment and equipment.

Prevention of the evolution to sepsis in both community and health care facilities requires the appropriate antibiotic treatment of infection, including reassessment for optimization, prompt seeking of medical care, and early detection of sepsis signs and symptoms.

Scientific evidence has clearly demonstrated the effectiveness of infection prevention. For instance, improved hand hygiene practice in health care can reduce infection by as much as 50% (12), while, in community settings, it can cut the risk of diarrhoea by at least 40% (13). Water, sanitation and hygiene (WASH) improvements could result in a 10% reduction of the total burden of disease worldwide (14). Vaccinations prevent 2–3 million infection-associated deaths every year (15).
Diagnosis and clinical management

Identifying and not underestimating the signs and symptoms listed above, along with the detection of some biomarkers (such as procalcitonin), are crucial elements for early diagnosis of sepsis and the timely establishment of its appropriate clinical management. After early recognition, diagnostics to help identify a causal pathogen of infection leading to sepsis are also important to guide targeted antimicrobial treatment. Antimicrobial resistance (AMR) can jeopardize clinical management of sepsis because empirical antibiotic treatment is often required. Therefore, understanding of the epidemiology of AMR in the local setting is important. Once the source of infection is determined, the source control such as drainage of an abscess is also critical. Early fluid resuscitation to improve volume status is also important in the initial phase of sepsis management. In addition, vaspressors may be required to improve and maintain tissue perfusion. Repeated exams and diagnostics, including monitoring vital signs, will guide the appropriate management of sepsis over time.

Sepsis and the Sustainable Development Goals

Sepsis is a very relevant cause of maternal mortality, and also of death in neonates and children under five years of age. Consequently, combating sepsis will clearly contribute to achievement of Sustainable Development Goals (SDGs) targets 3.1 and 3.2. For these two SDG targets, maternal, neonatal and under-five mortality rates are the indicators. Sepsis ranks highly among the causes leading to this avoidable mortality. It can also be the clinical condition that ultimately leads to death in patients affected by HIV, tuberculosis, malaria and other infectious diseases that are included in target 3.3, but it is not usually recorded as the cause of death in these patients and thus is not captured as part of the indicators for SDG target 3.3.

Even if less directly, sepsis is also relevant to other health targets in SDG 3. For instance, the prevention and/or appropriate diagnosis and management of sepsis is also linked to adequate vaccine coverage, quality universal health coverage, capacity to comply with the International Health Regulations, preparedness, and water and sanitation services. The challenge, however, remains how to achieve universal prevention, diagnosis and management of sepsis.

WHO response

Supported by a WHO Secretariat report, the Seventieth World Health Assembly adopted a resolution on sepsis in May 2017.

- Resolution WHA70.7: Improving the prevention, diagnosis and clinical management of sepsis
- WHO Secretariat Report A70/13: Improving the prevention, diagnosis and clinical management of sepsis

In collaboration and coordination with WHO regional offices, Member States and other stakeholders, several WHO headquarters programmes listed below are currently working on the public health impact of sepsis, and are providing guidance and country support on sepsis prevention, early and appropriate diagnosis, and timely and appropriate clinical management, in order to address sepsis comprehensively. The Infection Prevention and Control (IPC) global unit in the Service Delivery and Safety Department at WHO headquarters provides coordination of sepsis activities and leads activities on sepsis prevention.

REFERENCES

5. SPINAL CORD INJURY

KEY FACTS

- Every year, around the world, between 250 000 and 500 000 people suffer a spinal cord injury (SCI).
- The majority of spinal cord injuries are due to preventable causes such as road traffic crashes, falls or violence.
- People with a spinal cord injury are two to five times more likely to die prematurely than people without a spinal cord injury, with worse survival rates in low- and middle-income countries.
- Spinal cord injury is associated with lower rates of school enrollment and economic participation, and it carries substantial individual and societal costs.
- The term ‘spinal cord injury’ refers to damage to the spinal cord resulting from trauma (e.g. a car crash) or from disease or degeneration (e.g. cancer).
- There is no reliable estimate of global prevalence, but estimated annual global incidence is 40 to 80 cases per million population. Up to 90% of these cases are due to traumatic causes, though the proportion of non-traumatic spinal cord injury appears to be growing.

Symptoms of spinal cord injury depend on the severity of injury and its location on the spinal cord. Symptoms may include partial or complete loss of sensory function or motor control of arms, legs and/or body. The most severe spinal cord injury affects the systems that regulate bowel or bladder control, breathing, heart rate and blood pressure. Most people with spinal cord injury experience chronic pain.

Demographic trends

Males are most at risk in young adulthood (20-29 years) and older age (70+). Females are most at risk in adolescence (15-19) and older age (60+). Studies report male-to-female ratios of at least 2:1 among adults, sometimes much higher.

Mortality

Mortality risk is highest in the first year after injury and remains high compared to the general population. People with spinal cord injury are 2 to 5 times more likely to die prematurely than people without SCI.

Mortality risk increases with injury level and severity and is strongly influenced by availability of timely, quality medical care. Transfer method to hospital after injury and time to hospital admission are important factors.

Preventable secondary conditions (e.g. infections from untreated pressure ulcers) are no longer among the leading causes of death of people with spinal cord injury in high-income countries, but these conditions remain the main causes of death of people with spinal cord injury in low-income countries.

Health, economic and social consequences

Spinal cord injury is associated with a risk of developing secondary conditions that can be debilitating and even life-threatening—e.g. deep vein thrombosis, urinary tract infections, muscle spasms, osteoporosis, pressure ulcers, chronic pain, and respiratory complications. Acute care, rehabilitation services and ongoing health maintenance are essential for prevention and management of these conditions.

Spinal cord injury may render a person dependent on caregivers. Assistive technology is often required to facilitate mobility, communication, self-care or domestic activities. An estimated 20-30% of people with spinal cord injury show clinically significant signs of depression, which in turn has a negative impact on improvements in functioning and overall health.

Misconceptions, negative attitudes and physical barriers to basic mobility result in the exclusion of many people from full participation in society. Children with spinal cord injury are less likely than their peers to start school, and once enrolled, less likely to advance.

Adults with spinal cord injury face similar barriers to economic participation, with a global unemployment rate of more than 60%.

Existing data do not allow for global cost estimates
of spinal cord injury, but they do offer a general picture.

- The level and severity of the injury have an important influence on costs--injuries higher up on the spinal cord (e.g. tetraplegia vs. paraplegia) incur higher costs.
- Direct costs are highest in the first year after spinal cord injury onset and then decrease significantly over time.
- Indirect costs, in particular lost earnings, often exceed direct costs.
- Much of the cost is borne by people with spinal cord injury.
- Costs of spinal cord injury are higher than those of comparable conditions such as dementia, multiple sclerosis and cerebral palsy.

Prevention
The leading causes of spinal cord injury are road traffic crashes, falls and violence (including attempted suicide). A significant proportion of traumatic spinal cord injury is due to work or sports-related injuries. Effective interventions are available to prevent several of the main causes of spinal cord injury, including improvements in roads, vehicles and people’s behaviour on the roads to avoid road traffic crashes, window guards to prevent falls, and policies to thwart the harmful use of alcohol and access to firearms to reduce violence.

Improving care and overcoming barriers
Many of the consequences associated with spinal cord injury do not result from the condition itself, but from inadequate medical care and rehabilitation services, and from barriers in the physical, social and policy environments.

Implementation of the UN Convention on the Rights of Persons with Disabilities (CRPD) requires action to address these gaps and barriers.

Essential measures for improving the survival, health and participation of people with spinal cord injury include the following.
- Timely, appropriate pre-hospital management: quick recognition of suspected spinal cord injury, rapid evaluation and initiation of injury management, including immobilization of the spine.
- Acute care (including surgical intervention) appropriate to the type and severity of injury, degree of instability, presence of neural compression, and in accordance with the wishes of the patient and their family.
- Access to ongoing health care, health education and products (e.g. catheters) to reduce risk of secondary conditions and improve quality of life.
- Access to skilled rehabilitation and mental health services to maximize functioning, independence, overall wellbeing and community integration. Management of bladder and bowel function is of primary importance.
- Access to appropriate assistive devices that can enable people to perform everyday activities they would not otherwise be able to undertake, reducing functional limitations and dependency. Only 5-15% of people in low- and middle-income countries have access to the assistive devices they need.
- Specialized knowledge and skills among providers of medical care and rehabilitation services.

Essential measures to secure the right to education and economic participation include legislation, policy and programmes that promote the following:
- physically accessible homes, schools, workplaces, hospitals and transportation;
- inclusive education;
- elimination of discrimination in employment and educational settings;
- Vocational rehabilitation to optimize the chance of employment;
- micro-finance and other forms of self-employment benefits to support alternative forms of economic self-sufficiency;
- access to social support payments that do not act as disincentive to return to work; and
- correct understanding of spinal cord injury and positive attitudes towards people living with it.

WHO response
WHO works across the spectrum from primary prevention of traumatic and non-traumatic causes of spinal cord injury, improvements in trauma care, strengthening health and rehabilitation services, and support for inclusion of people with spinal cord injuries. WHO:
- works in a multisectoral manner, in partnership with national stakeholders from a variety of sectors (e.g. health, police, transport, education) to improve prevention of spinal cord injury including of road traffic injuries, falls, violence and neural tube defects;
- guides and supports Member States to increase awareness of disability issues, and promotes the inclusion of disability as a component in national health policies and programmes;
- facilitates data collection and dissemination of disability-related data and information;
- develops normative tools, including guidelines and good practice examples to strengthen primary prevention (road traffic crashes, falls and violence), trauma care, health care, rehabilitation and support
and assistance;
• builds capacity among health policy-makers and service providers;
• promotes scaling up of community-based rehabilitation; and
• promotes strategies to ensure that people with disabilities are knowledgeable about their own health conditions, and that health-care personnel support and protect the rights and dignity of persons with disabilities.