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Review Article

Advances of 3D bioprinting over 2D cell culture models in cancer research

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ABSTRACT

The tumor microenvironment, composed of non-neoplastic cells and the extracellular matrix, plays a pivotal role in cancer progression. Traditional two-dimensional (2D) cell cultures fail to capture its complexity, resulting in disparities in drug responses compared to three-dimensional (3D) models. Recent research highlights the precision of 3D bioprinted cancer models, revolutionizing cancer research. 3D bioprinting offers diverse applications, including personalized tumor models for individualized drug testing. These models replicate physiological conditions, providing accurate drug screening for efficacy and toxicity. It also facilitates the study of metastasis mechanisms and therapeutic target identification. Moreover, 3D bioprinting aids in optimizing cancer treatments, such as gene and immunotherapies, and allows precise drug delivery to cancer cells. It supports medical education with realistic training tools and offers an ethical alternative to animal testing, potentially reducing its necessity in cancer research. In essence, 3D bioprinting is advancing cancer research by providing highly accurate models that closely mimic the tumor microenvironment, enhancing personalized medicine, drug screening, therapeutic development and education. The present review delves into the multifaceted applications of 3D bioprinting in cancer research while exploring future directions and innovations in 3D bioprinting for cancer models.

KEY WORDS: 2D cell culture, 3D bioprinting, animal models, cancer, drug testing

INTRODUCTION

Cancer stands as a leading cause of human mortality, with oncology emerging as the pharmaceutical industry's most expansive therapeutic domain, marked by numerous projects, clinical trials and substantial research investments[1]. The intricate and resource-intensive journey to develop new anticancer agents is characterized by complexity, time constraints and high costs, leading to a notable attrition rate. The standard developmental trajectory for anticancer drugs encompasses a preclinical phase followed by three clinical phases. Presently, regulatory preclinical studies, integral to translational cancer research, heavily rely on two-dimensional (2D) cell cultures and animal models, despite their inherent limitations in capturing the full complexity of cancer biology[2]. The tumor stroma consists of abundant extra cellular matrix along with other supporting cells like cancer-associated fibroblasts, endothelial cells, pericytes and immune cells. While these cells and matrix forms the major part, a less prevalent population of myeloid-derived suppressor cells, platelets and mesenchymal stromal cells also forms a part of the non-neoplastic part of the tumor microenvironment[3]. The orchestrated interactions that occur between the tumor microenvironment and the surrounding stroma

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result in the poor clinical outcome and the aggressive nature of the tumor. Recent research developed evidence that the activated stroma plays a pivotal role in angiogenesis, metastasis, drug resistance, stem cell maintenance and immunosurveillance evasion[4]. The loss of this pivotal cellular interaction within the 2D cell culture model not only affects the morphological characteristics but also imparts differences in crucial biological events such as proliferation, gene/protein expression and apoptosis when compared to that of 3D cell culture model[5]. Considering the pitfalls associated with 2D cell culture and animal models, the present review has attempted to explore the wide applications of 3D bioprinting and its advantages over traditional cancer models.

Applications of 3D bioprinting

1. In tumor cell complexity:

The conventional 2D cancer models inadequately capture the intricate and dynamic interplay between the tumor microenvironment and the surrounding stroma, falling short of replicating their complex interactions accurately[6]. 3D bioprinting allows researchers to create highly complex and realistic tumor models. Unlike traditional 2D cell cultures, which are flat and lack the three-dimensional architecture found in the human body, 3D bioprinted models can mimic the complex structures of tumors, and the advantages of 3D model over 2D model is given in Figure 1. Langer *et al* created an *in vitro* cancer model, incorporating cancer cells along with a variety of stromal cell layers by using Organovo's Novogen MMX system. It was found that cancer cells within this model reacted to the signals from these stromal cells, forming extracellular matrix and organize themselves as the tissue matures. As this model replicated the heterogeneity of the tumor microenvironment, the interaction of different cell populations within the tumor microenvironment was clearly elucidated[7].

Addressing the dynamic nature of the extracellular matrix (ECM) is a significant challenge in *in vitro* modeling. Customizing material properties to align with the physiological process is essential. For instance, in digital light processing based printed cardiac microtissues using methacrylated gelatin (GelMA) scaffolds, meticulous adjustment of crosslinking

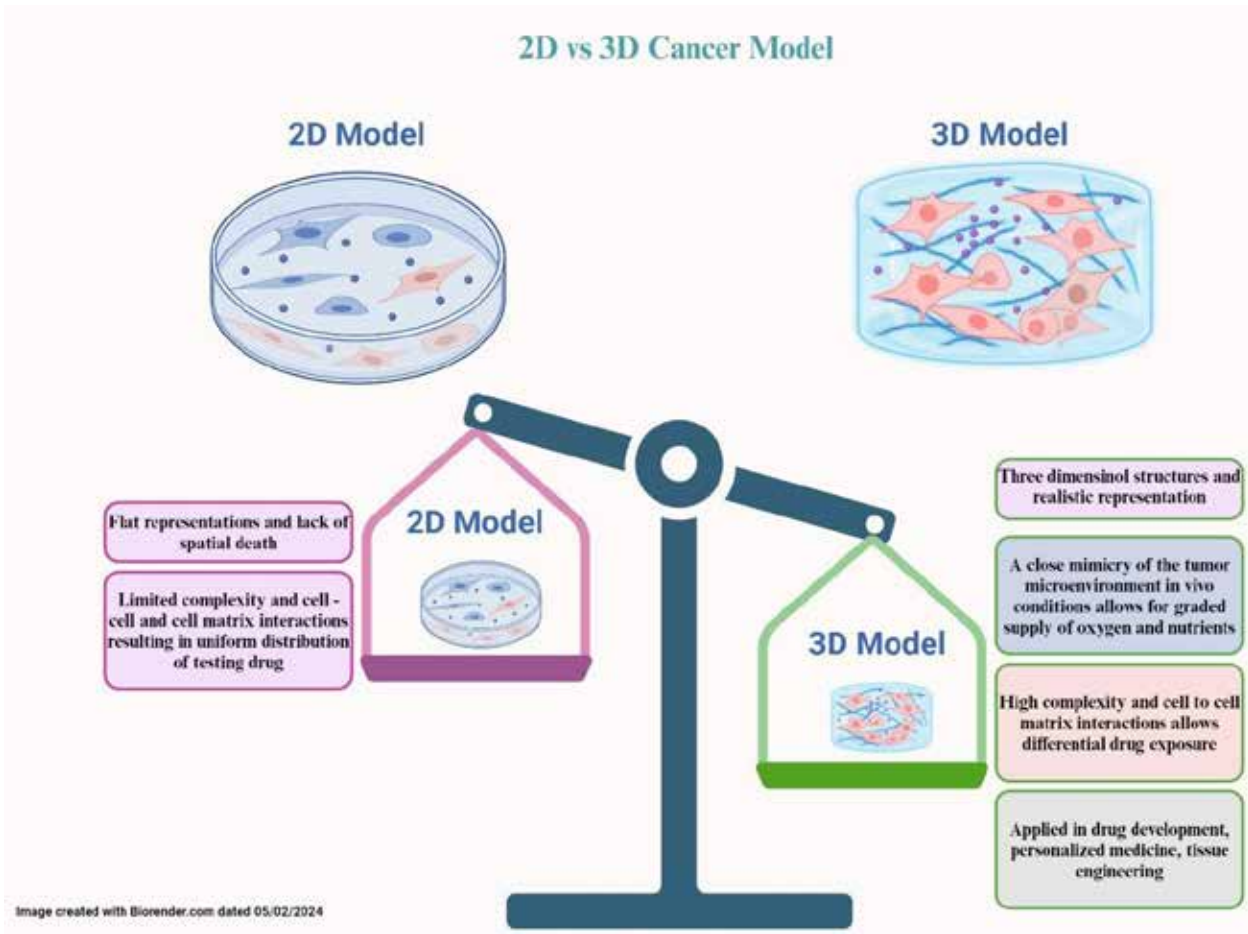

Figure 1: Advantages of 3D over 2D model

density synchronized scaffold degradation with ECM deposition by human cardiac fibroblasts. GelMA and other components in varying concentrations were added to form prepolymer solutions, tailored for specific mechanical and biological properties, aligning with each layer's function in 3D-printed constructs. This synchronization supported the maturation and contraction of the artificial tissue over a week[8]. For enhanced mimicry, an artificial tissue can be combined with a dynamic culture system. In a study conducted by Fang *et al*, a microfluidic chip incorporating pressure channels was devised for culturing colon tumor organoids, replicating the peristaltic motion characteristic of their natural environment. This approach notably boosted organoid proliferation and size compared to static cultures, as media flowed through the pressure channels and provided mechanical stimulation. Peristaltic-stimulated organoids also exhibited reduced absorption and response to ellipticine-laden micelle dosing, suggesting that accurately mirroring ECM dynamics can profoundly impact the in vitro model's reactions to drugs and toxins[9].

3D bioprinting involves the precise deposition of bioinks, which can include tissue spheroids, cell pellets, microcarriers, decellularized ECM components and cell-laden hydrogels layer by layer. This process follows a computer-designed structure to create living 3D constructs[10]. To precisely regulate biochemical cues within scaffolds, researchers have engineered synthetic materials with customized biomolecules. In a collaborative study led by Taubenberger *et al*, they decorated PEG with various bioactive elements, including metalloproteinase-cleavable sites, ECM-mimicking cell adhesion peptides and growth factors. This versatile platform enabled the creation of an *in vitro* bio-microenvironment with multiple controlled biochemical signals and matrix mechanical properties[11]. Examining 3D tumoroids in biomimetic collagen I hydrogel, recent research delved into the unclear origin of early cancer invasion, revealing those fluctuations in invading protrusions and their interactions with the microenvironment correlate with tumor invasion. Notably, protrusion dynamics were identified as a novel biophysical signature for tumors' metastatic potential[12]. 3D cultures, in particular, offer greater precision in managing interactions among cells and between cells and their surrounding matrix. This includes the ability to fine-tune mechanical attributes like stiffness and fluid flow, modify the ECM composition, introduce specific biochemical factors, and adjust tissue density. In sum, 3D cultures empower researchers to customize the microenvironment to closely mimic the characteristics of the target tissue or organ[13,14].

2. In drug screening:

3D bioprinted tumor models provide a more physiologically relevant environment for drug testing compared to traditional cell cultures. This can lead to more accurate predictions of how drugs will perform in the human body. In native tumor tissues, the interaction between tumor cells and endothelial cells (ECs) directly influences nutrient and metabolite transport. When ECs are co-cultured with cancer cells and stromal cells in a 3D system, they establish robust vascular networks and exhibit enhanced cellular functions compared to 2D cultures[15]. In an effort to replicate the intricate liver tumor microenvironment, Fan *et al* conducted a co-culture of human umbilical vein endothelial cells (HUVECs) and C3A (clonal derivative of HepG2 cells) cells to build an endothelialized liver cancer model. They successfully produced this construct by combining GelMA and gelatin microbead printing. This combination offers structural stability as GelMA integrates well with gelatin, while providing ample cell attachment sites for HUVECs to adhere quickly during the sacrificial phase and promoting cell organization and network formation within the 3D structure**.** The developed models exhibited a notable increase in the effectiveness of Sorafenib when contrasted with either mono-cultured liver cancer constructs or 3D C3A spheroids. This improvement is likely attributed to the intact endothelial barrier structure hindering Sorafenib diffusion[16].

Researchers can assess not only the efficacy of potential cancer drugs but also their toxicity within these models. This information is crucial for drug development and clinical trial design. The complexity of native tissues, notably their high vascularity, is crucial for assessing toxicity. Massa *et al* employed extrusion-based 3D printing to create a vascularized liver model with perfusable channels, featuring an endothelial barrier. This model was used to study the toxicity of acetaminophen, which harms liver sinusoid endothelial cells. It enabled testing the drug's effects on both the endothelial layer and the protected HepG2/C3A cells, offering a more realistic *in vivo* exposure simulation[17]. Recent studies have demonstrated that cancer cells grown in 3D cell cultures are less sensitive to anti-cancer drugs when compared to that of their 2D counterparts. This difference in pharmacological responses may lead to higher rate of failure in drug discovery research as many of the drug screening analysis were conducted in 2D cell culture models. The complexity and microenvironmental factors of 3D cell cultures more closely resemble the *in vivo* conditions found in tumors, making them valuable for studying drug resistance mechanisms and for testing the effectiveness of anti-cancer drugs[18,19]. The most frequently utilized 3D cancer models for drug

testing include multicellular tumor spheroid model, multilayered cell cultures, organotypic slices of cancer tissue and cell seeded scaffolds[20].

The construction of *in vitro* tumor models necessitates a crucial requirement, a high level of cellular activity. Keeping this in mind, Duan *et al* created a 3D bioprinted GelMA and polyethylene glycol diacrylate scaffolds, with a 10/2.5% ratio, featured 10x10x1.2 mm dimensions, 0.8 mm spacing and 6 layers in their study. After printing, blue light shaped the scaffolds, followed by 24 hour UV sterilization. Deionized water rinses and storage prepared the scaffolds for cell experiments. The cell counting kit-8 assays were employed to assess cell proliferation in both 2D and 3D scaffold cultures. In the initial stages, cells tend to adhere and proliferate more readily on flat surfaces. However, with prolonged culture, 2D scaffolds exhibit faster cell contact inhibition as cells continue to multiply. In contrast, the three-dimensional structure of 3D scaffolds offers a greater surface area for cell growth, facilitating enhanced proliferation. In comparison to 2D scaffolds, 3D scaffolds prove to be more effective in promoting the aggregation and growth of tumor cells. Within the 3D culture system, A375 cells exhibited increased drug resistance, thus documenting that, the utilization of 3D-bioprinted cell mass models presents a novel avenue for constructing *in vitro* tumor models and conducting anticancer drug screening, showing significant promise for future advancements[21].

3. In Personalized Medicine:

With 3D bioprinting, it's possible to create patient-specific-cancer models using a patient's own cancer cells. This enables the development of models that closely resemble the individual patient's cancer, allowing for personalized drug testing and treatment optimization. Exploration of multiple chemotherapeutic drugs through patient-specific bioprinted cancer models has the potential to pinpoint the most effective combination of drug candidates tailored to individual patients. This approach takes into account not only the molecular subtype of the tumor, but also factors like age, gender and ethnicity, enhancing the understanding of drug effectiveness and mechanisms. Furthermore, it facilitates the identification of optimal drug dosages, paving the way for more precise and patient-centric cancer treatments. Various cancer cell types, encompassing primary cancer cells, circulating tumor cells (CTCs), and stromal cells like fibroblasts, endothelial cells and stem cells can be employed for the fabrication

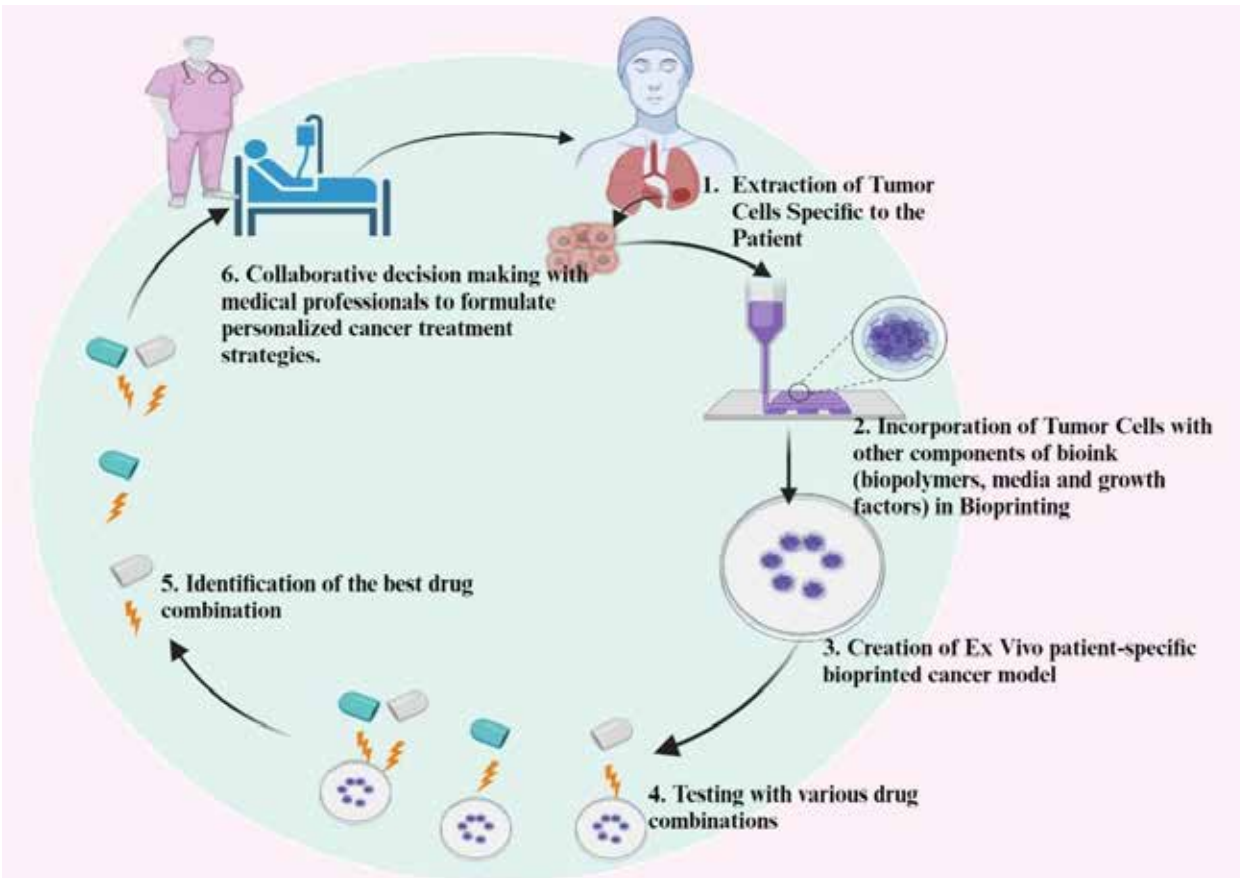

Figure 2: Process of personalized drug testing and treatment optimization using 3D bioprinting

of personalized tumor constructs (Figure 2). Wake *et al* created urologic cancer models by converting the image segments of kidney and prostate cancer into surface mesh and exporting them in 3D PDF, standard tessellation language (.stl) and Alias/Wavefront (.obj) formats for direct visualization, multi-colored 3D printing and augmented reality programming and visualization respectively for patient education before and after their treatment procedures. They used Likert-scale survey to assess patient understanding of disease and procedure. Compared to the other two methods, patients demonstrated significantly improved comprehension and comfort when utilizing 3D printed models across various aspects, including understanding their disease, grasping cancer size, identifying cancer location, comprehending their treatment plan and level of comfort with the treatment plan. By testing potential treatments on patient-specific models, researchers can identify the most effective therapies while minimizing adverse effects, leading to more personalized and targeted cancer treatments[22].

4. Automated high-throughput assays:

There is ample evidence to suggest that 2D cell cultures often fall short in accurately replicating the intricacies of complex diseases and tissue responses. Particularly in drug discovery and development, automated high-throughput assays for metabolism and toxicity are essential. Currently, 2D cell cultures in multi-well plates are used for high-throughput screening (HTS), but quantification techniques like absorbance and fluorescence measurements require extensive standardization. Therefore, the transition to 3D models is frequently considered pivotal. HTS has made notable strides, benefiting from advancements in molecular biology and genomics, leading to well-defined disease models and scalable bioreactors[23]. Among various bioprinting methods, droplet-based bioprinting (DBB) is well-suited for HTS. It can deposit bioinks in a highly synchronized manner, maintaining high cell viability. Laser-based bioprinting can achieve throughput rates of up to 20 Hz but may experience droplet instabilities at high frequencies. DBB shows significant potential for generating tumor tissue models for HTS, even in standard 384- and 1536-well plate sizes[24,25].

5. Metastasis Research:

Metastasis is a critical aspect of cancer progression. 3D bioprinted models can be used to study how cancer cells invade nearby tissues, enter the bloodstream and establish secondary tumors at distant sites. By understanding the mechanisms of metastasis within these models, researchers can identify potential targets for therapies aimed at preventing or treating metastatic cancer. 3D cultures in particular offer greater precision in managing interactions among cells and between cells and their surrounding matrix. This includes the ability to fine-tune mechanical attributes like stiffness and fluid flow, modify the ECM composition, introduce specific biochemical factors and adjust tissue density. Overall, 3D cultures empower researchers to customize the microenvironment to closely mimic the characteristics of the target tissue or organ[13,14]. A study conducted by Meng *et al* introduced a 3D bioprinted tumor model platform with functional vasculature and stromal elements, accompanied by programmable laser triggered endothelial growth factor (EGF) release capsules. This innovative model system allows dynamic exploration of metastatic processes and drug screening. Notable advantages over traditional 2D cultures include matrix remodeling with fibroblasts, realistic vascular networks for drug testing and the collection of circulating tumor cells (CTCs) involved in metastasis. Unique features comprise a developed vasculature, spatially defined tumor sites, material flexibility and temporal control through programmable capsules[26].

6. Therapeutic Development:

Bioprinted models serve as valuable tools for optimizing cancer treatments, including immunotherapies and gene therapies. Scientists can fine-tune treatment protocols and delivery methods within these models. Immunotherapy has revolutionized cancer treatment with approaches like cancer vaccines, cytokine therapies, immune checkpoint inhibitors and adoptive cell transfer. The latter involves extracting immune cells, such as macrophages, T cells or natural killer (NK) cells from peripheral blood and reintroducing them into the patient to enhance existing immune responses, marking significant progress in cancer care[27-29]. NK cell-based immunotherapy is gaining interest due to its safety profile, minimal side effects like cytokine release syndrome, neurotoxicity and low risk of graft-versus-host disease. Despite these benefits, challenges exist, which includes achieving a high expansion rate of immune cells with viability, effective targeting, proper homing to the tumor site and maintaining activity in the tumor microenvironment, impacting long-term anti-tumor efficacy[30-32]. Various efforts have focused on enhancing the functions of immune cells using 3D culture systems and driving immune cells to the tumor site[33].

3D bioprinting is adept at creating 3D culture systems and clinical applications, including structures for insertion into tumor resection sites. Macropores formed through bioprinting facilitate the transport of oxygen, nutrients and essential cytokines. The automatic processing of 3D bioprinting offers a faster alternative to traditional methods, making it

a promising off-the-shelf product platform. Pore-forming hydrogels created through 3D bioprinting with NK cells enhance cell viability, proliferation and activities, particularly in immunotherapy[32]. While macropores formed through bioprinting facilitate the efficient transport of oxygen, nutrients and essential cytokines, intentionally formed micropores can enhance NK cell aggregation, promoting improved cell viability, lysis activity and cytokine release in a 3D bioprinted system[34]. The extracellular matrix-like structure of hydrogels aids in enduring the harsh conditions of the tumor microenvironment, amplifying NK cell activities and preventing recurrence and metastasis post-tumor resection[35,36].

Future perspective

In Precise Delivery:

Anticancer drugs encounter challenges in reaching their target due to potential toxicity in noncancerous organs. Traditional delivery methods, like oral or intravenous administration, face solubility issues. 3D-printed scaffolds utilizing polymers like PCL and PLGA offer a solution, serving as patches with defined drug release over four weeks, improving patient acceptance[37]. These models enable precise delivery of nanoparticles and nanomedicine to cancer cells and facilitate the evaluation of the therapeutic potential of these tiny particles. Maher *et al* employed 3D printing for titanium implants with micro and nanosurface topography, promoting osseo-integration and localized delivery of doxorubicin and Apo2L/TRAIL for targeted chemotherapy in bone cancers, accompanied by the added benefit of fracture support[38]. Chen and colleagues created a 3D-printed microfluidic chip with a multichannel helical structure, for the administration of combinational chemotherapeutics by swift mixing, which demonstrated a synergistic cytotoxic effect on A459 cells[39]. Utilizing 3D-printed templates for radioactive source placement proves more effective than conventional planning techniques. These templates improve the precision of dose distribution and notably reduce implementation time, underscoring their superior performance[40]. Addressing the complexities of fatal diseases like cancer necessitates the development of a meticulously designed, personalized therapeutic system. The imminent fusion of 3D printing and nanotechnology holds promise for creating such intelligent and tailored solutions in the near future.

Education and Training:

Medical students and healthcare professionals can use 3D bioprinted cancer models for hands-on training and practice. This can include simulating surgical procedures, radiation therapy and other treatment modalities. Individual based (IB) models are extensively employed in mathematical oncology and various biomedical systems research due to the realistic simulations they provide, extending their applicability across diverse scientific domains. They focus on solid tumor growth, tumour-immune interactions, invasion and metastasis[41-44]. Macnamara *et al* using their computational IB Model illustrated the interaction between a growing solid tumor and pre-existing vasculature, examining the impact of oxygen diffusion from the blood vessel network on cancer cell growth[41]. Chiu *et al* demonstrated the utility of 3D printing in interstitial brachytherapy training programs by creating low-cost, reusable phantoms. These phantoms, with a material cost of approximately USD 23.98 and a preparation time of 1.5-2 hours each, offer a cost-effective means to acquire procedural skills in brachytherapy[45]. While 3D postprocessed images surpass traditional 2D sets, they often lack adequate information for surgical simulation. Medical 3D printing offers advanced solutions for preoperative planning challenges[46]. In preoperative planning, the versatility of viewing 3D models from any angle proves beneficial. These models aid in determining optimal endograft placement, minimizing surgical risks. Surgeons leverage the detailed anatomical insights offered by 3D models to address critical issues, such as accurately locating pseudoaneurysm lumens[47].

Ethical Alternatives:

Genetically engineered mouse model (GEMM), a pivotal asset in cancer research, outshines cancer cell inoculation models by developing authentic tumors within a natural, immune-proficient microenvironment. These tumors closely emulate histopathological and molecular characteristics of their human counterparts, exhibiting genetic diversity and the ability to progress spontaneously to metastatic disease[48]. Patient-derived xenograft (PDX) models, comprising immunodeficient mice engrafted with patients' cancer cells or tissues, are developed under the assumption that they faithfully replicate the original tumors. These models ensure biological stability, accurately mirroring histopathology, gene expression, genetic mutations, inflammation and therapeutic responses. Consequently, PDX models play a crucial role in assessing human tumor biology, identifying therapeutic targets and conducting preclinical screening for diverse cancers[49]. The creation and validation of PDX and GEMMs are costly, time-intensive and resource-demanding. Additionally, they have a relatively low throughput and face growing ethical scrutiny due to the increasing emphasis on replacement solutions aligned with the principles of the 3Rs in animal experimentation[50]. Bio printed models indeed hold significant promise as an ethical alternative to animal testing in various

fields, including cancer research. The traditional use of animals in experimentation has raised ethical concerns regarding animal welfare, and there is a growing interest in developing alternative methods that can provide reliable data without causing harm to animals.

CONCLUSION

In summary, 3D bioprinting is a versatile technology that enables the creation of highly realistic and personalized cancer models. These models provide valuable insights into cancer biology, drug development and treatment strategies, ultimately advancing our ability to understand and combat this complex disease. While these models often focus on isolated interactions between individual components of the tumor microenvironment and tumor cells, they do not fully replicate the intricate complexity of the tumor stroma *in vitro*. Nonetheless, ongoing developments in new models hold promise for enhancing drug discovery, serving as robust platforms for drug evaluation and facilitating the creation of personalized cancer treatment strategies, in an ethical and scientifically robust manner.

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Original Article

Predictive role of optic nerve sheath diameter for postoperative cognitive dysfunction following long-standing Trendelenburg position in laparoscopic hysterectomy

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ABSTRACT

Objectives: Optic nerve sheath diameter (ONSD) is an indicator of intracranial pressure. This study aimed to examine the role of intraoperative ONSD measurements for predicting postoperative cognitive dysfunction in patients undergoing laparoscopic hysterectomy in Trendelenburg position with pneumoperitoneum.
Design: Prospective observational study
Setting: Marmara University medical faculty, Istanbul, Turkey
Subjects: Forty patients who underwent laparoscopic hysterectomy under long-standing Trendelenburg position (>2.5 hours) were included in this study.
Interventions: In addition to routine intraoperative monitoring, ONSD was measured intraoperatively at five time points. Its predictive role for postoperative cognitive dysfunction was assessed.
Main outcome measures: The role of intraoperative ONSD measurements for predicting postoperative cognitive dysfunction in patients undergoing laparoscopic hysterectomy in long-lasting (>2.5 hours) Trendelenburg position.
Results: ONSD gradually increased in association with pneumoperitoneum and Trendelenburg position. No significant correlation was found between ONSD measurements and postoperative changes on cognitive function at the early postoperative period, day 3 and day 7. Patients who exhibited cognitive decline at day 7 (>2 point reduction in Mini-Mental State Examination score compared to baseline) did not differ in terms of ONSD measurements and other tested variables.
Conclusions: Our findings suggest that intraoperative ONSD measurements do not seem to serve as a predictor for postoperative cognitive dysfunction in patients who underwent laparoscopic gynecological operations in long-standing Trendelenburg position and pneumoperitoneum.

KEY WORDS: laparoscopic hysterectomy, Mini-Mental State Examination (MMSE), optic nerve sheath diameter (ONSD), postoperative cognitive dysfunction (POCD), Trendelenburg position

INTRODUCTION

Hysterectomy is a common major gynecological procedure, which can be performed using abdominal, vaginal or laparoscopic approach. Laparoscopy offers several advantages over more invasive approaches such as better cosmetic results, shorter hospitalization, less bleeding and less postoperative pain. For gynecological laparoscopic procedures, a Trendelenburg position is assumed in addition to pneumoperitoneum, to obtain better surgical field view of the pelvis.

Combined use of a steep Trendelenburg position and pneumoperitoneum has several adverse physiological consequences[1]. Trendelenburg position itself causes increase in venous return,

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which in turn increases central blood volume, arterial pressure and cardiac output, although such physiological changes are reversible in healthy individuals[1]. Addition of pneumoperitoneum has potential to further augment such effects as well as affecting pulmonary function[1]. Another possible alteration is the increased intraabdominal pressure and changes in cerebral hemodynamics resulting in increased intracranial pressure and intraocular pressure[2,3]. To date, several studies have examined intracranial physiological alterations such as changes in intracranial pressure, optic nerve sheath diameter (ONSD) and cerebral oxygenation in association with laparoscopic surgery[4-9]. In addition, data on potential neurological and cognitive complications after laparoscopic surgery have been examined with inconsistent findings[2,10-15]. Nevertheless, current evidence suggests that steep Trendelenburg position assumed in laparoscopic surgery has the potential to cause cognitive decline[2,10,14,15].

Measurement of ONSD is a simple, reliable and non-invasive method to evaluate intracranial pressure[5,16,17]. Its elevation following laparoscopic hysterectomy has been associated with postoperative nausea/vomiting and headache[18]; however, its potential relation to postoperative cognitive dysfunction is still obscure.

This study aimed to examine the role of intraoperative ONSD measurements for predicting postoperative cognitive dysfunction in patients undergoing laparoscopic hysterectomy in long-lasting (>2.5 hours) Trendelenburg position.

SUBJECTS AND METHODS

Patients

A total of 40 patients aged between 30 and 75 with ASA 2-3 status who underwent laparoscopic hysterectomy were included in this prospective observational study. Exclusion criteria were as follows: history of ocular disease or ocular surgery, neurological disease and transient ischemic attack. Patients who required open surgical intervention during laparoscopy procedure were also excluded. The study protocol was approved by local ethics committee (Marmara University Medical Faculty Ethics Committee for Clinical Research; no, 09.2021.1035; date, September 3, 2021) and patients provided informed consent prior to study entry. The study was conducted in accordance with the Declaration of Helsinki. Clinical trial registry: clinicaltrials.gov; no, NCT05286697.

Anesthesia management

General anesthesia was induced by propofol 2 mg/kg, remifentanil 0.5 μg/kg and rocuronium 0.6 mg/kg. Anesthesia was maintained with sevoflurane at MAC 1 (minimum alveolar concentration) and remifentanil infusion 0.25. Rocuronium was repeated according to train of four (TOF) ≥2 values. Following intubation, ventilatory support was provided to keep tidal volume and end-tidal CO_2 at 6-8 ml/kg and 30-35 mmHg, respectively. In addition to standard anesthesia monitoring with electrocardiography, pulse oximetry, TOF monitor and non-invasive arterial blood pressure measurements, patients were monitored with near-infrared spectroscopy (NIRS) for cerebral oxygen saturation measurements throughout the surgical procedure. Two NIRS sensors were placed on the left and right sides of the forehead 2 cm above the eyebrows, before anesthesia induction. Measurements started before induction with an initial fraction of inspiration oxygen (FiO_2) value of 60%. In case there is more than 20% decrease or a decrease below 50% in cerebral oxygenation, patient was re-positioned or FiO_2 was increased.

None of the patients received ventilation with positive end-expiratory pressure. Intraabdominal pressure was kept below 15 mmHg. At the termination of anesthesia, all patients received intravenous 1 g paracetamol and 100 mg tramadol for postoperative analgesia.

Intraoperative measurements

For potential predictors of postoperative cognitive dysfunction, four intraoperative time points were defined in relation to Trendelenburg position: T0, five minutes after anesthesia induction at supine position; T1, five minutes after the initiation of pneumoperitoneum; T2, five minutes after the assumption of Trendelenburg position (40-45 degrees); T3, two hours after the assumption of Trendelenburg position; and T4, five minutes after the return to supine position at the end of surgery. ONSD was measured at all these five time points (T0 to T4). ONSD measurements were done by the same experienced anesthesiologist using a linear 5-10 MHz ultrasound probe over the closed eyelid following the application of sterile water-soluble gel forming a thin layer. ONSD measurements were done on both sides in millimeters and the average value was used for the analyses. Peak inspiratory airway pressure (pPEAK) and end-tidal carbon dioxide ($EtCO_2$) were measured at T0 to T3 (at 4 time points). Partial pressure of carbon dioxide was measured before and after the operation. Cerebral oxygen saturation measurements were made throughout the operation and were recorded every 30 minutes. Durations of surgery and anesthesia were also recorded as well as body mass indexes of the patients.

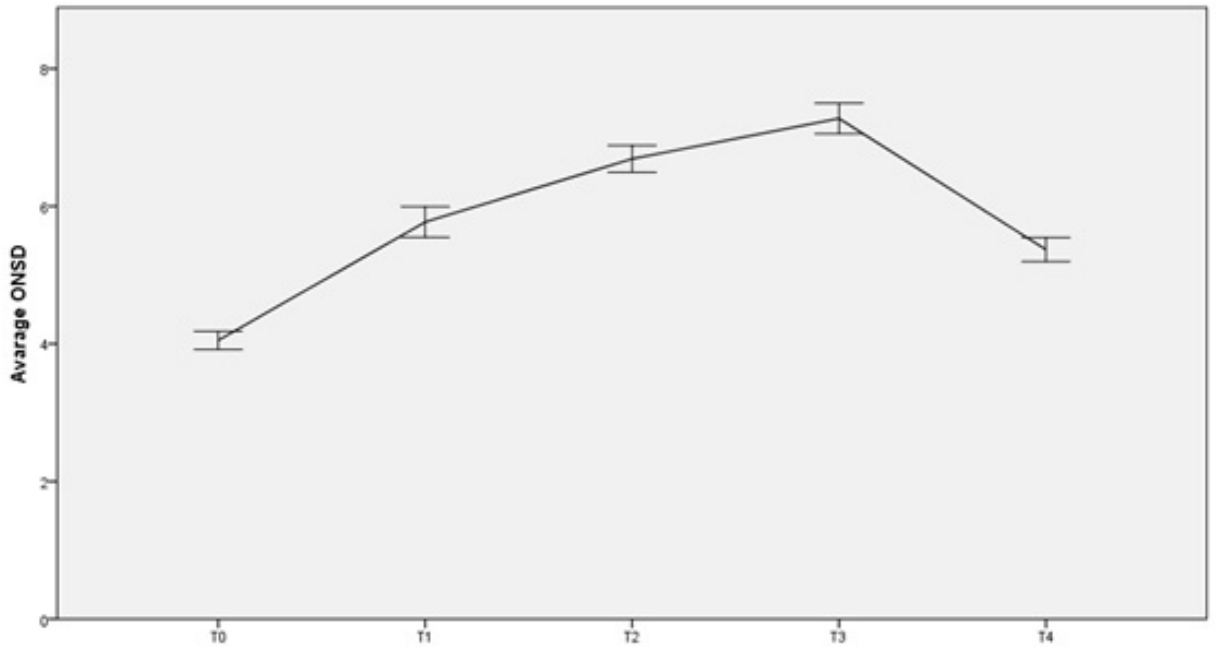

Fig 1: Changes in optic nerve sheath diameter (ONSD) in millimeters throughout the operation at predefined time points. Error bars indicate 95% confidence intervals.

Mini Mental State Examination

The Mini-Mental State Examination (MMSE) was used to evaluate the cognitive function preoperatively, at the early postoperative period, at day 3 and at day 7. Measurements at day 7 served to identify postoperative cognitive function, which was defined as >2 points decline from baseline[19].

Statistical analysis

SPSS (Statistical Package for Social Sciences) version 21 software was used for the analysis of data. Both hypothesis tests and graphical methods were used to test the normality of continuous variables. Intraoperative changes in ONSD measurements were examined using one-way ANOVA for repeated measurements and time points were compared with student t test for paired samples with Bonferroni correction. Correlations between continuous variables were tested using Pearson or Spearman correlation test, where appropriate. For the comparison of two groups for continuous variables, student t test for independent samples or Mann-Whitney U test was used, depending on the distribution of data. Two-sided *P*-values <0.05 were considered indication of statistical significance.

RESULTS

A total of 40 patients with a mean BMI of 28.8±5.3 kg/m^2 were included. The mean duration of anesthesia and surgery was 291.8±41.7 and 265.9±39.7 minutes, respectively.

Cognitive change and ONSD

Figure 1 shows the changes in average ONSD measurements (average of right and left eye) at predefined intraoperative time points. The change was significant (*P*<0.001) and pairwise comparisons revealed a continuous gradual increase at each time point up to T3 when compared to baseline and previous measurements, then a significant decline was evident at T4 (*P*<0.001 for all comparisons). Table 1 shows the correlation of ONSD measurements with cognitive function score change compared to baseline (at early postoperative period, at day 3 and day 7). No significant correlations were found between these parameters (*P*>0.005 for all). At the early postoperative period and at day 3, all patients exhibited a significant cognitive impairment (>2 point decrease) compared to baseline. At day 7, 15 patients showed cognitive

Table 1: Correlation of average optic nerve sheath diameter measurements in millimeters with cognitive function score change compared to baseline

Time point	MMSE score change Early postop vs. baseline	MMSE score change Day 3 vs. baseline	MMSE score change Day 7 vs. baseline
T0	-0.064, 0.694	-0.022, 0.892	0.076, 0.641
T1	-0.175, 0.281	-0.032, 0.846	0.083, 0.611
T2	-0.147, 0.342	-0.028, 0.864	0.023, 0.888
T3	-0.081, 0.264	-0.136, 0.403	-0.066, 0.685
T4	-0.301, 0.059	-0.258, 0.108	-0.095, 0.558

Data presented as r (correlation coefficient), *P*-value

impairment. Table 2 shows the difference between patients with and without cognitive impairment at day 7 in terms of their preoperative average ONSD measurements at different time points. The two groups did not differ regarding ONSD values.

Table 2: Comparison of the patients with and without impairments at day 7 in terms of their preoperative average optic nerve sheath diameter measurements in millimeters at different time points.

Time point	No cognitive impairment (n=25)	Cognitive impairment (n=15)	*P*
T0	4.1±0.5	4.0±0.4	0.512
T1	5.8±0.7	5.7±0.7	0.518
T2	6.7±0.6	6.7±0.7	0.862
T3	7.3±0.8	7.3±0.6	0.780
T4	5.4±0.5	5.4±0.6	0.892

Data presented as mean ± standard deviation

Cognitive change and other intraoperative parameters

Among the other parameters tested at T0 to T3, following significant but weak correlations were found: early postoperative change in cognitive function was correlated with $EtCO_2$ at T2 (r=0.332, *P*=0.036), cognitive function change at day 3 was correlated with $EtCO_2$ at T0 (r=0.331, *P*=0.037), and cognitive function change at day 7 was correlated with pPEAK at T3 (r=-0.428, *P*=0.047). However, the two groups (patients with and without cognitive impairment at day 7) did not differ in terms of any parameters tested: $EtCO_2$, pPEAK and NIRS measurements as well as BMI and anesthesia or surgery durations (*P*>0.05 for all).

DISCUSSION

This study examined potential relation of ONSD measured during surgery and postoperative cognitive function in patients undergoing laparoscopic hysterectomy in Trendelenburg position with pneumoperitoneum; however, no predictive role for ONSD could be identified. To the best of our knowledge, no study has examined such relation in this group of patients so far. In addition, no clinically important relation with cognitive impairment was found in relation to other parameters measured.

In line with several previous studies, ONSD values increased in association with position and pneumoperitoneum in the present study. In a study by Bang *et al* with 67 patients undergoing robot-assisted laparoscopic prostatectomy with Trendelenburg position and pneumoperitoneum, ONSD measured throughout the surgical procedure increased compared to baseline, similar to the present study, although the increase was not gradual[20]. Another study also demonstrated an increase in ONSD -as a measure of increased intracranial pressure- in robot-assisted laparoscopic radical prostatectomy in association with steep Trendelenburg position and pneumoperitoneum[8]. On the other hand, Kim *et al* found no difference in ONSD of patients in association with position during laparoscopic surgery[9]. In that study, female patients undergoing laparoscopic surgery either under Trendelenburg position (gynecological surgery) or reverse-Trendelenburg position (cholecystectomy) were included. Following pneumoperitoneum and assuming of the position, ONSD increased in both groups and then returned to baseline, but no difference was found between the two positions[9].

The effect of steep Trendelenburg position and pneumoperitoneum on postoperative cognitive function has been examined in two comparative studies and no evidence in line with detrimental cognitive effects was found. A recent study compared the postoperative cognitive outcomes of patients who underwent robot-assisted radical prostatectomy in steep Trendelenburg position versus those who underwent open retropubic radical prostatectomy in supine position. The study did not find any difference between the two groups in terms of neurocognitive dysfunction at the early postoperative period or at 3 months[21]. Similarly, another study compared similar groups of patients (robot-assisted radical cystectomy in Trendelenburg position versus open abdominal surgery in horizontal position)[13]. The two groups did not significantly differ in terms of the incidence of postoperative cognitive dysfunction at one week, although the incidence was numerically higher in the laparoscopy group (45.8% vs. 26.1%). In the laparoscopy group, cerebral oxygen saturation increased when Trendelenburg and pneumoperitoneum was prolonged but without causing excessive cerebral perfusion.

Potential short-term effects of Trendelenburg position on cognition were also examined in healthy volunteers[15]. Volunteers assumed Trendelenburg position for 3 hours and then, supine position for 30 minutes and cognitive function was assessed every 30 minutes. Gradually more volunteers exhibited cognitive decline by the increasing duration of Trendelenburg position, and one third showed cognitive decline on moving to supine position. This study gives an idea about potential effect of Trendelenburg position in laparoscopic procedures on cognitive function, but its findings can only explain consequences in ultrashort term.

Although predictive value of intraoperatively measured ONSD, which reflects intracranial

pressure, for postoperative cognitive dysfunction has not been examined in patients undergoing laparoscopic procedures with Trendelenburg position and pneumoperitoneum before, its association with postoperative nausea/vomiting and headache has been examined in a recent study[18]. Similar to the present study, 61 patients undergoing laparoscopic hysterectomy were included and ONSD was measured intraoperatively. In line with our findings, ONSD increased compared to baseline values, decreased following the assumption of supine position and release of pneumoperitoneum, but remained higher than baseline. In addition, ONSD increase was significantly correlated with postoperative nausea/vomiting and headache, and a cut-off value of 5.85 mm predicted postoperative nausea/vomiting.

A study provided indirect information on potential relation between ONSD and postoperative cognitive function[2]. In elderly patients undergoing robot-assisted radical prostatectomy in Trendelenburg position, ONSD as well as the cross-sectional area of the internal jugular vein and the internal jugular vein valve competency were assessed during the operation[2]. Cognitive outcomes were assessed and compared between patients with and without internal jugular vein valve incompetency and the former had lower cognitive function scores early after surgery[2]. In addition, patients with internal jugular vein valve incompetency had higher ONSD during the operation[2].

Although laparoscopic interventions with Trendelenburg position and pneumoperitoneum seem to result in increased intracranial pressure as evidenced by increased ONSD in the present study as well as previous studies, such physiological alterations seem to be transient in nature and they readily return to baseline values. Such transient physiological alterations may be easily compensated by otherwise healthy low-risk individuals; thus, clinically evident postoperative cognitive dysfunction can be avoided. Due to these evidence, intraoperative measurements of ONSD do not seem to be a reliable predictor of postoperative cognitive impairment in patients undergoing laparoscopic hysterectomy. However, these alterations have the potential to translate into clinically important cognitive alterations in vulnerable populations, particularly for those who are prone to or already having cognitive impairment.

A control group probably undergoing open surgery would shed light on the potential cognitive consequences of Trendelenburg position and pneumoperitoneum in combination as well as their individual contributions. This may be considered a limitation of the present study.

CONCLUSION

In conclusion, findings of this study showed a gradual increase in intraoperative ONSD measurements in patients undergoing laparoscopic hysterectomy; however, do not support any predictive role of these measurements for postoperative cognitive dysfunction. Future large studies with subgroups of vulnerable patients would shed light not only on the potential cognitive consequences of steep Trendelenburg position and/or pneumoperitoneum but also on predictive role of ONSD.

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Original Article

Assessment of complete blood count and systemic inflammatory indices in small for gestational age preterm newborns

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ABSTRACT

Objectives: Scarce data exist about the complete blood count of preterm newborns with small for gestational age (SGA). It is not known how SGA affects systemic inflammatory indices in preterm infants. The aim of our study was to compare the levels of six systemic inflammatory indices in preterm infants with SGA and appropriate for gestational age (AGA).
Design: A retrospective cohort study
Setting: A tertiary neonatal intensive care unit
Subjects: Data of preterm infants <32 weeks of gestational age were evaluated.
Interventions: No intervention was performed.
Main outcome measures: Six systemic inflammatory indices, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), systemic immune ratio inflammation index (SII), pan immune inflammation value (PIV), and systemic inflammation response index (SIRI) values, were calculated from the results obtained from the complete blood count. Demographical features and clinical outcomes, complete blood count and systemic inflammatory indices were compared between the AGA and SGA groups.
Results: 895 infants were included in the study: 103 preterm infants with SGA and 792 preterm infants with AGA. There was no difference between the groups regarding leukocyte, monocyte, lymphocyte count, MLR and SIRI values (P>0.05). Neutrophil, platelet count, NLR, PLR, PIV and SII values were significantly lower in SGA infants than in AGA infants (P=0.001, P<0.001, P<0.001, P<0.001, P=0.016 and P<0.001, respectively).
Conclusions: We found that NLR, PLR, PIV and SII values were lower in SGA preterm infants than those in AGA preterm infants. Additional studies are required to evaluate the clinical significance of these values.

KEY WORDS: infant, premature, small for gestational age, systemic inflammatory indices

INTRODUCTION

Small for gestational age (SGA) is defined as less than 10 percentile of birth weight according to gestational age (GA)[1]. Infants with SGA have a higher risk of mortality and morbidity compared to infants with appropriate for gestational age (AGA). The coexistence of prematurity and SGA means much higher risks for both mortality and preterm morbidities[2,3]. For instance, there is an increase in morbidities such as bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP) and intraventricular/periventricular hemorrhage (IVH) in preterm SGA infants compared to AGA preterm infants. Although immune cells are thought to have a role in the pathophysiology of some increased morbidities in SGA preterm infants, the cause is still unknown[3-4]. Some of the whole blood cells in SGA infants may differ from those in AGA infants. The frequency of polycythemia and thrombocytopenia, especially in SGA infants, is the most well-known outcome. Apart from this, there is limited information about leukocyte lineage cells in SGA infants[5-7]. However, the change in leukocyte lineage cells in preterm SGA infants is not

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known exactly. Additionally, the effect of being an SGA preterm infant on systemic inflammatory indices has not been evaluated.

In studies conducted outside neonatal medicine, it has been reported that systemic inflammatory indices can be an effective parameter for evaluating the diagnosis and prognosis of infectious diseases, oncology patients, cardiovascular and respiratory system-related diseases and neurological diseases[8-14]. In newborn infants, it has been declared that some systemic inflammatory indices may be useful parameters for diagnosing diseases such as sepsis, hypoxic- ischemic encephalopathy, patent ductus arteriosus (PDA), ROP and NEC[15-19]. It is seen that there is limited information about the change of leukocyte cells in SGA infants and that systemic inflammatory indices have not been evaluated before in preterm infants with SGA. Accordingly, the aim of our study was to figure out whether both leukocyte cells and systemic inflammatory indices changed in preterm infants <32 weeks of GA and SGA.

SUBJECTS AND METHODS

Study protocol

Medical records of all infants admitted to our neonatal intensive care unit (NICU) between March 2021 and April 2022 were evaluated retrospectively. This retrospective study was conducted in the NICU of Health Science University Ankara Bilkent City Hospital, Ankara, Turkey. The NICU at our hospital is a referral Level III facility with 150 incubators, approximately 16000 births and treating 3500 newborns per year. Premature infants <32 weeks of gestational age were included in the study. Infants ≥32 weeks of gestational age, known or suspected major chromosomal anomalies, and infants with hematological disorders were excluded from the study. Ethical approval was obtained from the local ethics committee of the hospital before starting the study.

Demographical features and clinical outcomes in premature infants

GA, birth weight (BW), antenatal steroid, male gender, delivery mode, maternal preeclampsia, maternal diabetes mellitus, maternal thyroid disease, maternal chorioamnionitis, administration of maternal magnesium sulfate, SGA, AGA, intrauterine growth retardation (IUGR), umbilical artery Doppler abnormalities, 1st and 5th minutes Apgar scores, duration of mechanical ventilation (MV) support, early onset sepsis (EOS), late-onset sepsis (LOS), respiratory distress syndrome (RDS), IVH, PDA, NEC, BPD, ROP, duration of hospitalization, mortality, umbilical cord pH, and complete blood count were recorded.

Definition of preterm morbidities

Considering the blood culture positivity, sepsis within the first 3 days after birth was defined as EOS, and detection of sepsis after the 3rd day of life was defined as LOS[20]. Preterm infants with respiratory failure requiring surfactant were recognized as RDS[21]. In addition to clinical findings, PDA detected by Doppler echocardiography was recorded as hemodynamically significant PDA[22]. Infants with moderate or advanced (stage ≥2) NEC were enrolled[23]. According to BPD classification, it was defined as moderate if the infant postmenstrual age of 36th week needed <30% oxygen, and severe BPD if the infant needed positive pressure respiratory support or ≥30% oxygen[24]. Infants who were diagnosed with severe ROP retinopathy in retinal scanning examination and received laser treatment were registered as ROP[25]. Infants with grade ≥3 IVH were recorded by cranial ultrasonography[26].

Analysis of complete blood count

Peripheral venous blood samples were taken into ethylenediaminetetraacetic acid tubes for a complete blood count within the first hour after delivery. Cell-Dyn 3700 automatic hemocytometer (Abbott, Abbott Park, IL, USA) device was used for complete blood count analysis. C-reactive protein (CRP) and interleukin-6 (IL-6) were studied from the centrifuged blood samples. Leukocyte count (10^3 μ/L), neutrophil (N) count (10^3 μ/L), monocyte (M) count (10^3 μ/L), lymphocyte (L) count (10^3 μ/L) and platelet (P) count (10^3 μ/L) were obtained from medical records and recorded in the statistical analysis program.

Calculation of systemic inflammatory indices

Six systemic inflammatory indices including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte (MLR), systemic immune ratio-inflammation index (SII), pan immune inflammation value (PIV) and systemic inflammation response index (SIRI) were evaluated. The formulations of the systemic inflammatory indices are as follows: N/L for NLR, P/L for PLR, M/L for MLR, P x N/L for SII, N x M/L for SIRI and P x N x M/L for PIV[15].

Eligible patients were divided into two groups as SGA and AGA. The two groups were compared in terms of demographical features and clinical outcomes, mortality, results of complete blood count and systemic inflammatory indices.

Data analysis

Statistical Package for Social Sciences (SPSS), version 20.0 (SPSS Inc, Chicago, IL, USA) package program was used to analyze the patients' data. Histogram and Kolmogorov-Smirnov Test were used

Table 1: Demographic characteristics and clinical outcomes between small for gestational age preterm neonates and appropriate for gestational age preterm neonates

Characteristics	Appropriate for gestational age (n=792)	Small for gestational age (n=103)	*P*-value
Gestational age, weeks [a]	28.1±1.2	28.4±0.9	0.068
Birth weight, g [a]	1102±209	718±123	<0.001
Antenatal steroid, n (%)	545 (68.8)	76 (73.7)	0.393
Male gender, n (%)	441 (55.6)	50 (48.5)	0.085
Cesarean section, n (%)	655 (82.7)	94 (91.2)	0.027*
Maternal preeclampsia, n (%)	139 (17.5)	42 (40.7)	<0.001*
Maternal diabetes mellitus, n (%)	103 (13.0)	16 (15.5)	0.287
Maternal thyroid disease, n (%)	39 (4.9)	103 (5.8)	0.219
Maternal chorioamnionitis, n (%)	86 (10.8)	17 (16.5)	0.068
Administration of maternal magnesium sulfate, n (%)	367 (45.1)	48 (46.6)	0.355
Apgar 1st min, [b]	5 (2)	5 (2)	0.089
Apgar 5th min, [b]	8 (2)	7 (2)	0.443
Duration of MV, days [b]	1 (4)	3 (6)	0.760
EOS, n (%)	26 (3.2)	2 (1.9)	0.214
LOS, n (%)	168 (21.2)	25 (24.2)	0.095
RDS, n (%)	493 (62.2)	71 (68.9)	0.066
IVH, n (%)	61 (7.7)	17 (16.5)	0.001*
PDA, n (%)	313 (39.5)	43 (41.7)	0.668
NEC, n (%)	19 (2.4)	7 (6.7)	0.020*
BPD, n (%)	145 (18.3)	27 (26.2)	0.043*
ROP, n (%)	71 (8.9)	19 (18.4)	<0.001*
Duration of NICU, days, [b]	52 (35)	63 (66)	0.072
Mortality, n (%)	86 (10.8)	23 (22.3)	<0.001*

[a] mean ± standard deviation; [b] median (interquartile range).
*P<0.05 was considered statically significant.
BPD: bronchopulmonary dysplasia; EOS: early onset sepsis; IVH: intraventricular hemorrhage; LOS: late onset sepsis; MV: mechanical ventilation; NEC: necrotising enterocolitis; NICU: newborn intensive care unit; PDA: patent ductus arteriosus; RDS: respiratory distress syndrome; ROP: retinopathy of prematurity.

to analyze the distribution of the data. Fisher's Exact test or Pearson Chi-Square test was used for the analysis of categorical data, t-test or Mann-Whitney U test was used for continuous data analysis. If the data were normally distributed, they were presented as mean ± standard deviation, and data that did not show normal distribution were presented as the median and interquartile range. The results of categorical variables were presented as frequency. 95% confidence interval (CI) and the odds ratios (ORs) were performed in logistic regression analysis. A *P*-value of <0.05 obtained by statistical analysis was considered significant.

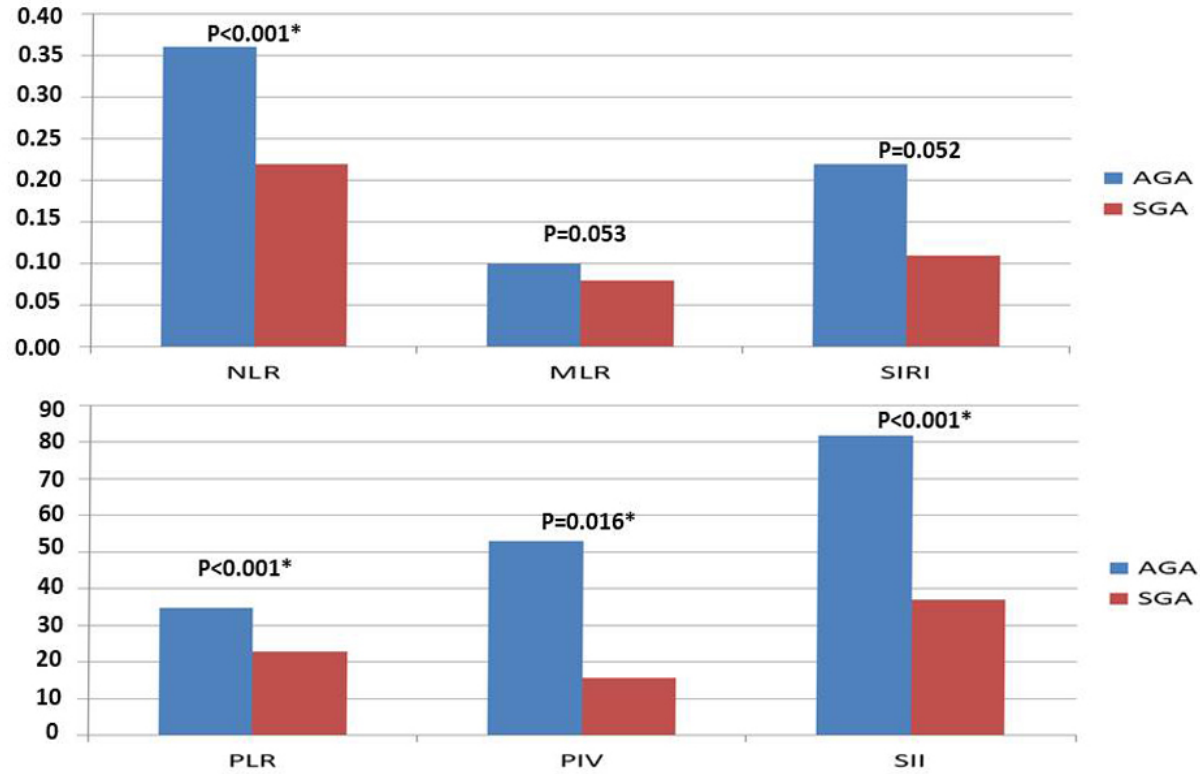
RESULTS

During the study period, 901 premature infants <32 weeks of GA who met the inclusion criteria were followed up in the NICU. A total of 6 infants, including 5 infants with congenital anomalies and 1 infant with Down syndrome, were excluded. A total of 895 infants were analyzed, involving 103 premature infants in the SGA and 792 premature infants in the AGA group. IUGR was detected in 37 (36%) of 103 patients with SGA and umbilical artery Doppler abnormalities were defined in 41 (39%) patients with SGA.

GA, antenatal steroid administration, maternal diabetes mellitus, maternal thyroid disease, maternal chorioamnionitis, administration of maternal magnesium sulfate, male gender, Apgar scores at 1st and 5th minutes, duration of MV, EOS, LOS, RDS, PDA and duration of NICU results were similar between groups (P>0.05). BW in the SGA group was significantly lower than in the AGA group (P<0.001). Cesarean section, maternal preeclampsia, IVH, NEC, BPD, ROP and mortality rates were significantly higher in the SGA group than in the AGA group (P=0.027, P<0.001, P=0.001, P=0.020, P=0.043, P<0.001 and P<0.001, respectively; Table 1).

Leukocyte, monocyte, lymphocyte count, MLR, SIRI umbilical cord pH, CRP and IL-6 were similar between groups (P>0.05). Neutrophil, platelet count, NLR, PLR, PIV and SII values were found to be statistically significantly lower in SGA infants (P=0.001, P<0.001, P<0.001, P<0.001, P=0.016 and P<0.001, respectively; Table 2 and Figure 1).

The potential confounder risk factors such as GA, BW, maternal chorioamnionitis, mode of delivery and maternal preeclampsia were entered to the multivariable regression model. Multiple analysis showed that lower levels of NLR, PLR, PIV and SII



*P <0.05 was considered statically significant.
AGA, appropriate for gestational age; MLR, monocyte to lymphocyte ratio; NLR, neutrophil to lymphocyte ratio; PIV, pan immune inflammation value; PLR, platelet to lymphocyte ratio; SGA, small for gestational age; SII, systemic immune inflammation index; SIRI, systemic inflammation response index.

Figure 1: Systemic inflammatory indices based on small for gestational age preterm neonates and appropriate for gestational age in preterm neonates.

were independently associated with SGA (OR: 3.020, CI: 1.812-4.013, *P*: 0.011, OR: 1.447, CI: 1.150-1.834, *P*: 0.036, OR: 1.207, CI: 1.108-1.319, *P*: 0.014, and OR: 4.017, CI: 3.718-9.627, *P*: 0.002, respectively).

Moreover, the results of maternal chorioamnionitis, mode of delivery and maternal preeclampsia variables were evaluated. The levels of NLR, PLR, PIV and SII were not associated with maternal chorioamnionitis

Table 2: Systemic inflammatory indices in small for gestational age preterm neonates and appropriate for gestational age preterm neonates

Parameters	Appropriate for gestational age (n=792)	Small for gestational age (n=103)	*P*-value
Leukocyte count (10^3 μ/L) [a]	11.10 (8.61)	13.00 (11.83)	0.649
Platelet count (10^3 μ/L) [a]	228.00 (105.00)	181.00 (79.00)	<0.001*
Neutrophil count (10^3 μ/L) [a]	2.42 (3.16)	1.71 (2.17)	0.001*
Monocyte count (10^3 μ/L) [a]	0.66 (0.63)	0.69 (0.71)	0.078
Lymphocyte count (10^3 μ/L) [a]	7.17 (5.99)	9.10 (10.27)	0.571
NLR [a]	0.36 (0.61)	0.22 (0.35)	<0.001*
MLR [a]	0.10 (0.11)	0.08 (0.12)	0.053
PLR [a]	34.92 (24.62)	22.91 (14.10)	<0.001*
PIV [a]	53.01 (84.50)	15.75 (20.83)	0.016*
SII [a]	81.65 (83.21)	37.06 (56.38)	<0.001*
SIRI [a]	0.22 (0.41)	0.11 (0.18)	0.052
Umbilical cord pH [b]	7.22±0.09	7.24±0.09	0.057
CRP (mg/L) [b]	2.51±1.15	2.07±1.68	0.315
IL-6 (pg/ml) [b]	84.06±26.89	89.84±23.74	0.612

[a] median (interquartile range); [b] mean ± standard deviation
**P* <0.05 was considered statically significant.
CRP: C-reactive protein; IL-6: interleukin 6; MLR: monocyte to lymphocyte ratio; NLR: neutrophil to lymphocyte ratio; PIV: pan immune inflammation value; PLR: platelet to lymphocyte ratio; SII: systemic immune inflammation index; SIRI: systemic inflammation response index.

Table 3: Multivariate regression model for potential confounding risk factors effecting NLR, PLR, PIV, and SII

Multivariable regression model	NLR	PLR	PIV	SII
Gestational age and birth weight				
Odds ratio	0.320	1.448	1.207	4.017
Confidence interval	1.812-4.013	1.150-1.1834	1.108-1.319	3.718-9.627
P	0.011*	0.036*	0.014*	0.002*
Maternal chorioamnionitis				
Odds ratio	1.456	0.981	0.391	0.909
Confidence interval	0.949-2.331	0.632-1.523	0.108-1.418	0.583-1.415
P	0.085	0.932	0.153	0.672
Mode of delivery				
Odds ratio	0.755	0.956	1.294	0.942
Confidence interval	0.542-1.052	0.608-1.503	0.766-2.184	0.565-1.570
P	0.097	0.845	0.335	0.817
Maternal preeclampsia				
Odds ratio	1.102	0.488	0.910	1.147
Confidence interval	0.437-2.782	0.170-1.401	0.530-1.366	0.891-1.471
P	0.084	0.182	0.846	0.279

*$P<0.05$ was considered statically significant.
NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to- lymphocyte ratio; PIV: pan immune inflammation value; SII: systemic immune ratio inflammation index.

(OR: 1.456, CI: 0.949-2.331, *P*: 0.085, OR: 0.981, CI: 0.632-1.523, *P*: 0.932, OR: 0.391, CI: 0.108-1.418, *P*: 0.153 and OR: 0.909, CI: 0.583-1.415, *P*: 0.672, respectively).

The levels of NLR, PLR, PIV and SII were not associated with mode of delivery (OR: 0.755, CI: 0.542-1.052, *P*: 0.097, OR: 0.956, CI: 0.608-1.503, *P*: 0.845, OR: 1.294, CI: 0.766-2.184, *P*: 0.335 and OR: 0.942, CI: 0.565-1.570, *P*: 0.817, respectively).

The levels of NLR, PLR, PIV and SII were not associated with maternal preeclampsia (OR: 1.102, CI: 0.437-2.782, *P*: 0.084, OR: 0.488, CI: 0.170-1.401, *P*: 0.182, OR: 0.910, CI: 0.530-1.366, *P*: 0.846 and OR: 1.147, CI: 0.891-1.471, *P*: 0.279, respectively; Table 3).

DISCUSSION

It is known that SGA negatively affects the number of megakaryocyte serial cells and positively affects the number of erythrocyte serial cells[6,7]. However, it is not known exactly how preterm infants with SGA affect the leukocyte series and systemic inflammatory indices. To our knowledge, this is the first study to evaluate the effect of SGA on whole blood cell count and systemic inflammatory indices, especially in preterm infants born <32 weeks of gestation. We found that neutrophil, platelet count, NLR, PLR, PIV and SII values were significantly lower in SGA preterm infants compared to AGA infants. The frequency of morbidities such as IVH, NEC, BPD, ROP and mortality rate were higher in SGA infants.

Term SGA infants are at higher risk than term AGA infants in terms of many morbidities and mortality. Preterm infants have increased morbidities and mortality rates compared to term infants. Being SGA and preterm means a much higher risk for morbidities and mortality. In this case, increased intrauterine hypoxia as the major reason for adverse outcomes[2-4]. For example, the cause of impaired platelet production in growth retarded fetuses is probably related to chronic fetal hypoxia. Chronic hypoxia can induce increased erythropoietin production and erythroblastosis, resulting in suppression of platelet production in the bone marrow and subsequently thrombocytopenia[27]. IUGR occurs not only due to inadequate transport of nutrients through the placenta, but also due to hypoxic placental conditions, increased oxidative stress, cytokine production and associated inflammation. Uteroplacental insufficiency triggers uncontrolled immunological inflammation. Increasing inflammation occurs both in the placental area and systemically. Therefore, tracing early signs of systemic inflammation may be important in determining SGA-related morbidities and mortality[28]. As noted in our study, the increased frequency of IVH, NEC, BPD, ROP and mortality in SGA preterm infants may result from inflammation[3-6].

Although it has been reported that there may be a decrease in the number of neutrophils in SGA infants, the mechanism of neutropenia is not fully understood. In addition to the decreased neutrophil count in SGA infants, the reason for the change in other leukocyte parameters has not been fully elucidated, but hypoxia and inflammation are thought to play a role. As a result of the deteriorated balance of anti-inflammatory and pro-inflammatory cytokines, other leukocyte parameters, especially the neutrophil count, may be affected[29,30]. It is thought that increased production in the erythrocyte lineage due to chronic intrauterine hypoxia causes a decrease in myelocytic and megakaryocytic lineage cells in the bone marrow[6]. As in our results, lower neutrophil and platelet counts

in SGA preterm infants compared to AGA infants can be explained by this mechanism. This change in laboratory values in SGA infants may bring an increase in other preterm morbidities to the clinical settings[4-7].

NLR, which is one of the systemic inflammatory indices, was found to be higher in infants with IVH and NEC compared to those without these morbidities[18,31]. In preterm infants with ROP, NLR, MLR, PLR and SII values were not different between the groups at birth, while NLR and SII values were found to be high in the group with ROP at the postnatal 1st month, but the PLR value was low, and the MLR value did not change significantly between the groups[32]. Subsequently, these studies concluded that preterm morbidities based on inflammation are associated with systemic inflammatory indices[18,31,32]. Systemic inflammatory indices in SGA infants have not been previously evaluated. There seems to be limited data on this subject. Levy *et al* reported that high maternal NLR values in pregnant mothers in the first trimester are used for the prediction of SGA. Moreover, they pointed out that maternal PLR values are not an indicator of SGA delivery[28]. In the present study, we showed that low NLR, PLR, PIV and SII values measured in preterms after birth are associated with SGA. Furthermore, the increased frequency of IVH, NEC, BPD, ROP and mortality in preterm infants with SGA may possibly be related to these systemic inflammatory indices. Since the aim of our study was to evaluate the effect of SGA on systemic inflammatory indices, the relationship between morbidities and systemic inflammatory indices was not evaluated.

Considering the association of SGA and inflammation, according to the hypothesis of our study, systemic inflammatory indices may be different in infants with SGA compared to infants with AGA. As a result of this hypothesis, NLR, PLR, PIV and SII values were lower in preterm infants with SGA than in AGA preterm infants. Ceran *et al* found that NLR, PIV and SII values were higher in term infants with HIE than healthy controls, and PLR was similar between the groups[15]. On the contrary, we thought that the lower NLR, PLR, PIV and SII values in SGA infants compared to AGA infants might be due to the different duration of hypoxia. Nevertheless, SGA infants are exposed to chronic fetal hypoxia, whereas infants with HIE are exposed to intrapartum acute hypoxia. Thus, in chronic hypoxia, there may be a decrease in the number of neutrophils and platelets due to the decrease in pre-hematopoietic cells in the bone marrow over time. However, in acute hypoxia, there is a sudden release of bone marrow depot and precursor cells into the peripheral blood[6,27,28]. Therefore, changes in complete blood count parameters resulting from acute and chronic hypoxia and systemic inflammatory indices may differ. Interpretation of the results of blood count and systemic inflammatory indices by considering the pathophysiological processes of the disease seems to be a more accurate approach.

The mechanism of some changes in CBC results in SGA infants and their effects on the patient's clinic are still not fully understood. Moreover, the effect of systemic inflammatory indices on the development of SGA is unknown. In our study, only these four systemic inflammatory indices were lower in patients with SGA than those in infants with AGA, which can be explained by the formulations used. Since NLR, PLR, PIV and SII values, which were predominantly calculated by using neutrophil and platelet counts, may be a reflection of low neutrophil and platelet counts in infants with SGA. In our results, these four indices were low in infants with SGA, but the impact of the patient on clinical outcomes should be determined. Therefore, our results may shed light on future studies evaluating the relationship between morbidity and mortality and systemic inflammatory indices in infants with SGA.

The most important limitation of our study was that it was retrospective and conducted from a single center. It is known that complete blood count values, which are adversely affected in infants with SGA, improve within the first few days or weeks and reach normal ranges[6,7]. Since the complete blood count values obtained immediately after birth were evaluated in our study, the complete blood count values and the levels of systemic inflammatory indices in the later postnatal days could not be evaluated. Symmetrical or asymmetrical differentiation could not be made for infants with SGA. The effect of systemic inflammatory indices on SGA morbidity and mortality could not be evaluated. Additionally, maternal complete blood count results, systemic inflammatory indices values, placental histopathological examination, delayed cord clamping and drugs could not be evaluated. SGA group also had IUGR patients with abnormal Doppler.

CONCLUSION

Our study is the first to evaluate the level of systemic inflammatory indices in SGA preterm infants. Low NLR, PLR, PIV and SII values were associated with SGA, while MLR and SIRI values were not associated with SGA. The clinical significance and cut-off values of systemic inflammatory indices in preterm infants with SGA need to be evaluated in future studies.

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Original Article

Is rapid on-site evaluation of thyroid fine-needle aspiration material by a cytotechnologist necessary?

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ABSTRACT

Objectives: This study aimed to measure the diagnostic value of rapid on-site evaluation (ROSE) of samples obtained using ultrasound-guided fine-needle aspiration (FNA) of thyroid lesions by cytotechnologists.
Design: Retrospective observational study
Setting: Department of Pathology, King Saud University Medical City, Riyadh, Saudi Arabia
Subjects: Patients who underwent ultrasound-guided thyroid FNA between January 2015 and July 2020 were enrolled and reviewed.
Interventions: None
Main outcome measure: Diagnostic material deemed satisfactory according to the 2017 Bethesda System for Reporting Thyroid Cytopathology criteria
Results: Out of the 1400 cases investigated, ROSE was performed on 1011 cases. The non-diagnostic samples in cases with ROSE comprised 6.82% of all samples in cases with ROSE while the non-diagnostic samples in cases without ROSE comprised 12.34% of all samples in cases without ROSE. Thus, the number of thyroid FNA cases with non-diagnostic samples identified using ROSE was significantly lower than that without using ROSE (P <0.002). In addition, less samples were identified as atypia of undetermined significance in cases with ROSE (15.63%) as compared to those without ROSE (17.74%).
Conclusions: ROSE is an effective method for decreasing the number of cases with non-diagnostic samples resulting in unsatisfactory diagnosis as well as the number of cases with borderline results, thus increasing the diagnostic value of thyroid FNA.

KEY WORDS: biopsy, cytology, diagnosis, thyroid gland

INTRODUCTION

The thyroid gland is the endocrine gland that is most commonly affected by cancer, accounting for 2% of all cancers worldwide[1]. The incidence of thyroid cancer varies according to age, sex, geographic population and ethnicity[2]. Thyroid cancer is the second and eighth most common cancer among the Saudi female and male populations, respectively[3].

Thyroid fine-needle aspiration (FNA) is a preoperative evaluation procedure that facilitates the segregation of patients for proper medical or surgical treatment[4-6]. Currently, thyroid FNA is used for evaluating thyroid lesions and has proven to be reasonably affordable and reliable[7]. However, some limitations remain, including the retrieval of unsatisfactory samples for diagnostic categorization, which leads to disappointing outcomes[8,9]. Thus, FNA cytology is a screening tool rather than a diagnostic tool, and presently, definite diagnosis can only be made via tissue biopsy[10].

Previous studies have shown that 3-34% of FNA procedures result in the collection of non-diagnostic samples[11,12], which are known to harbor a 5-10% risk for malignancy[13]. Consequently, repeated FNA with ultrasound guidance is recommended. However, it increases the cost, waiting time and patient anxiety[14].

To improve the adequacy of the samples obtained through FNA, cytotechnologists can be present during the ultrasound-guided thyroid FNA procedures, to evaluate the sampled cytological material by staining it and observing the smears under the microscope on the spot, which is known as rapid on-site evaluation

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Table 1: Statistical analysis of thyroid fine-needle aspiration cases classified according to Bethesda categories.

Year	Category												Total
	I		II		III		IV		V		VI		
	Number	%	Number	%	Number	%	Number	%	Number	%	Number		
2015	13	5.60	147	63.36	33	14.22	7	3.02	9	3.88	23	9.91	232
2016	19	5.41	241	68.66	51	14.53	12	3.42	14	3.99	14	3.99	351
2017	30	8.17	230	62.67	63	17.17	5	1.36	7	1.91	32	8.72	367
2018	27	13.11	122	59.22	38	18.45	5	2.43	5	2.43	9	4.37	206
2019	25	12.50	112	56.00	36	18.00	6	3.00	10	5.00	11	5.50	200
2020	3	6.82	31	70.45	6	13.64	1	2.27	1	2.27	2	4.55	44
Total	117	8.36	883	63.07	227	16.21	36	2.57	46	3.29	91	6.50	1400

(ROSE)[15]. Studies have shown that on-the-spot evaluation can decrease unsatisfactory thyroid FNA results by improving sample adequacy[16-20]. However, although this method prolongs the procedural time and increases the cost of the procedure, it has failed to decrease the non-diagnostic rates of FNA significantly in some studies[14,21]. Therefore, the application of on-the-spot evaluation by cytotechnologists for FNA is still debatable[22,23]. In this study, we aimed to evaluate the impact of ROSE of samples obtained using ultrasound-guided thyroid FNA by a cytotechnologist.

SUBJECTS AND METHODS

In this retrospective study, the medical profiles of all patients who underwent ultrasound-guided thyroid FNA at King Saud University Medical City in Riyadh, Saudi Arabia between January 2015 and July 2020 were perused. The ultrasound-guided thyroid FNA procedures were predominantly performed by radiologists. Three passes were usually made when FNA was performed without ROSE whereas two or three passes were made when FNA was performed with ROSE. During ROSE, Diff-Quik staining was performed, and the stained slides were screened by a cytotechnologist to ensure the adequacy of the samples. Ethical approval was obtained from the Institutional Review Board (E-20-5416). All data from the medical reports were handled anonymously and used for experimental purposes alone. Informed consent was not sought from the patients because of the retrospective nature of this study.

FNA results were categorized according to the 2017 Bethesda System for Reporting Thyroid Cytopathology[24] into six categories: category I, non-diagnostic; category II, benign; category III, atypia of undetermined significance; category IV, follicular/Hurthle-cell neoplasm; category V, suspicious for malignancy; and category VI, malignant. An endocrine pathologist reviewed the collected data to determine the adequacy of the sampled material.

Data were recorded and analyzed using the statistical software IBM SPSS version 23 (IBM Corp, Armonk, NY, USA). Categorical data were calculated using descriptive statistics, while continuous data were calculated using inferential statistics to obtain the mean and standard deviation. We considered the results of this study to be significant when the *P*-values were less than or equal to 0.05.

RESULTS

In total, 1400 thyroid FNA cases were reviewed from the archive of pathology and medical records at King Saud University Medical City. Of these cases, 117 (8.36%), 883 (63.07%), 227 (16.21%), 36 (2.57%), 46 (3.29%) and 91 (6.50%) yielded results classified as categories I, II, III, IV, V and VI, respectively (Table 1). ROSE was performed in 1011 cases, of which 69 (6.82%) cases yielded category I results. It was not performed in 389 cases, of which 48 (12.34%) cases yielded category I results. The average number of cases with category I results was 117 (8.36%). The percentage of thyroid FNA cases with category I results relative to the total number of cases revealed a significant decrease in the number of cases with category I results from ROSE compared with the number without ROSE (P <0.002; Table 2).

The percentage of cases with category III results identified without ROSE (17.74%) was higher than the percentage of those identified with ROSE (15.63%). In addition, the percentage of cases with category V results identified without ROSE (3.60%) was higher than the percentage of those identified with ROSE (3.17%). However, the percentages of cases where category II and VI results were identified with ROSE were higher than those identified without ROSE (64.99% and 6.82% vs. 58.10% and 5.66%, respectively). No changes were observed in the percentage of cases with category IV results identified with and without ROSE (Table 2 and Fig 1).

DISCUSSION

Thyroid FNA is considered one of the most comprehensive diagnostic methods for the preoperative diagnosis of thyroid nodules, triage

Table 2: Statistical analysis of thyroid fine-needle aspiration cases classified according to Bethesda categories with and without rapid on-site evaluation (ROSE).

Involvement of ROSE	Category												Total	*P* value
	1		2		3		4		5		6			
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%		
With ROSE	69	6.82	657	64.99	158	15.63	26	2.57	32	3.17	69	6.82	1011	0.002*
Without ROSE	48	12.34	226	58.10	69	17.74	10	2.57	14	3.60	22	5.66	389	
Total	117	8.36	883	63.07	227	16.21	36	2.57	46	3.29	91	6.50	1400	

of patients, and determination of the need, urgency and type of surgery for these patients. However, the inadequacy of the specimens obtained using FNA and atypia of undetermined significance remain challenges for clinicians, radiologists and pathologists. For accurate diagnosis of thyroid FNA, the sample should be adequate. According to the Bethesda System for Reporting Thyroid Cytopathology, which is used to standardize the terminology used by pathologists and surgeons for the proper management of patients requiring thyroid FNA, an adequate sample is defined as six or more groups of follicular cells, with each group containing ten or more follicular cells with some exceptions[24]. Factors that lead to an insufficient number of follicular cells and thus influence the adequacy of a sample include artificial effects (e.g., obscuration by blood) and poorly fixed or prepared slides. Other possible factors include the radiological characteristics of the nodule (e.g., size and whether the nodule is solid or cystic), number of FNA passes, and radiologist's skills and experience[16].

To decrease the inadequacy of samples, many laboratories send cytotechnologists or pathologists to the radiology department for ROSE of sample adequacy and sometimes for preliminary reports. However, the shortage of cytotechnologists, the cost of sending them, and the COVID-19 pandemic make it necessary to minimize the number of people involved and maintain distance to prevent viral transmission. Nevertheless, in comparison with other methods used to increase the adequacy of samples (e.g., flow cytometry, molecular analysis, cell block, etc.), ROSE increases the adequacy of the sampled material not only by decreasing the chances of obtaining non-diagnostic material, which has an estimated risk of malignancy of 5-10%[24], but also by reducing procedural complications by decreasing the number of needle passes[25].

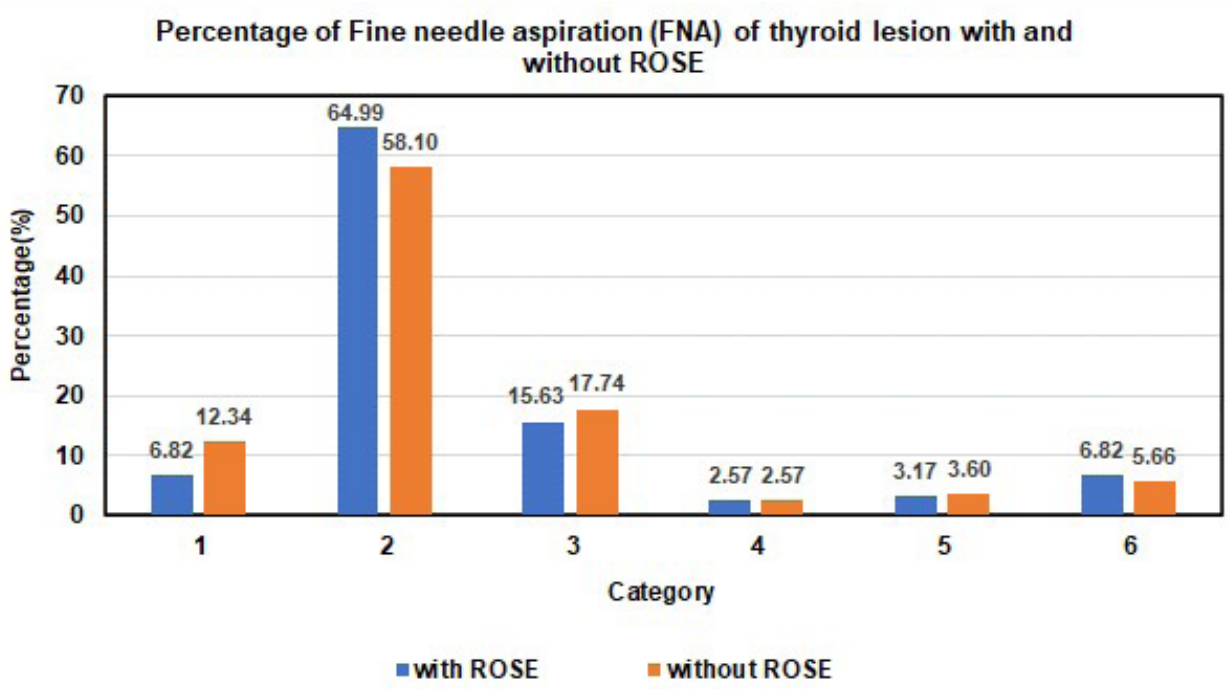

Fig 1: Percentage of various categories of samples obtained from fine-needle aspiration of thyroid lesions with and without rapid on-site evaluation.

In our study, sample inadequacy was significantly affected by ROSE; the percentage of inadequate samples was estimated to be 6.8% with ROSE compared to 12.3% without ROSE. Muri *et al* reported a significant decrease in the non-diagnostic rate from 40.3% to 3.6% after including ROSE in the FNA procedure[23].

In addition to obtaining non-diagnostic or unsatisfactory material, another diagnostic limitation of thyroid FNA is the retrieval of category III samples, which is controversial and can be difficult to manage because such samples do not meet the criteria for suspicious lesions (category IV or more). Muri *et al* reported that the percentage of category III cases decreased from 3.7% to 2.1% after including ROSE[23]. These findings are consistent with those of our study wherein the percentage of cases with category III results identified without ROSE (17.74%) was higher than the percentage of those identified with ROSE (15.63%). According to the 2015 American Thyroid Association Management Guidelines, category III thyroid nodules must be managed by repeated FNA or molecular testing[13], which increases the rate of repeated FNA and the cost of additional testing. However, the identification of Bethesda category III cases is relatively subjective and may vary among pathologists.

CONCLUSION

ROSE is an effective method for decreasing the number of cases with non-diagnostic/unsatisfactory results as well as the number of cases with borderline results, i.e., category III results, thus increasing the diagnostic value of thyroid FNA. In conclusion, the presence of cytotechnologist during FNA procedures for thyroid lesions can lead to improved quality and accuracy of the diagnostic process, ultimately resulting in better patient outcomes. More studies of a similar nature may further corroborate these findings and encourage the use of ROSE, especially in remote and basic clinical setups in developing countries where patient follow-up and successful motivation of the patient to return for repeated medical procedures is challenging.

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Original Article

Correlation of PD-L1 expression and autophagy-related markers p62, LC3, Beclin1 in patients with ovarian cancer

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ABSTRACT

Objective: Ovarian cancer (OC) is one of the most common malignant tumors in women, with the highest mortality rate of all gynecological tumors. OC cells are able to upregulate PD-1/PD-L1 checkpoint and autophagy which could be in close and significant interaction. The aim of the study was to analyze the expression of PD-L1 immunosuppressive and autophagy markers p62, LC3 and Beclin1 in OC and evaluate their prognostic potential.
Design: Retrospective cross-sectional study
Setting: Tertiary university hospital
Subjects: The study has included 122 subjects with OC.
Intervention: The expression of PD-L1, p62, LC3 and Beclin1 was analyzed by immunohistochemistry combined with tissue microarray.
Main outcome measures: Four categories were defined: negative (0) without positive cells or with a single positive cell (<1%); low (1+) expression with less than 10% positive cells; moderate (2+) expression with 10-50% positive cells; and strong (3+) expression with more than 50% positive cells. Expression levels of analyzed markers were correlated with histopathology parameters.
Results: High grade serous carcinoma showed significant level of PD-L1, p62 and LC3 expressions, compared to all other histology types. Advanced International Federation of Gynaecology and Obstetrics stages were associated with increased levels of PD-L1, p62 and LC3 expressions. Beclin1 expression did not show significant correlation with analyzed parameters.
Conclusion: The combined presence of PD-L1, p62 and LC3 expressions indicates simultaneous activation of immunosuppressive and autophagy mechanism in ovarian cancer cells. It could suggest synergistic therapy with PD-L1 and autophagy inhibitors in OC treatment.

KEY WORDS: immune checkpoint, ovary, target molecules

INTRODUCTION

Ovarian cancer (OC) is one of the most common malignant tumors in women, with the highest mortality rate of all gynecological tumors[1]. Despite improved therapy procedures, prognosis of this disease is still unsatisfactory. Patients with OC were the most common diagnosed in advanced stages, when therapy methods become limited and less effective[2].

Cancers frequently use immunosuppressive mechanisms for survival and further progression. PD-1/PD-L1 regulatory mechanism is important in maintaining immune homeostasis. PD-L1 is a significant transmembrane molecule with immunosuppressive function, frequently overexpressed on cancer cells. Interaction of PD-L1 on tumor cells with PD-1 receptor on T lymphocytes is upregulated in OC. PD-L1

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expressed cancer cells avoid cytotoxic T lymphocytes and disrupt cancer immunity[3,4]. Cancers with activated PD-L1 molecule could have benefits from immune antitumor therapy. Immunotherapy is based on the evaluation of target molecules which could be modulated by different therapy agents[5,6].

Autophagy is a complex mehanism, significant for the tumor progresion. Autophagy can contribute to the survival or the destruction of cancer cells because of its dual function in tumorigenesis. In early tumor development, autophagy has tumor suppressor function, while later it becomes tumor promoting mehanism[7,8]. OC is able to activate autophagy mechanism and make the tumor more aggressive[9,10].

The PD-1/PD-L1 signaling pathway is significant for regulation of intracellular functions of tumor cells. Autophagy is one of these functions that is controlled by PD-L1 receptors. On the other hand, autophagy has an immunomodulatory function and could determine using PD-L1 inhibitors. Therapy resistance could be attributed to inhibition of tumor suppressors or upregulation of autophagy[4,11,12].

PD-L1 positive staining in cancer cells is usually membrane, with variable expression in the cytoplasm and nucleus. Only membrane positivity correlates with therapy response using PD-L1 inhibitors. Cytoplasmic and nuclear positivity are usually the product of the accumulation of PD-L1 splice variants that are not effectively localized to membranes[5,13,14]. Evaluation of the autophagic mechanism in cancer cells could be defined using the most common analized autophagy markers: p62, LC3 and Beclin1[15]. The most reliable indicator of the autophagy process is "dot like" cytoplasmic staining in cancers cells[16,17].

The main aim of the study was to analyze the expression of PD-L1 immunosuppressive and autophagy markers p62, LC3 and Beclin1 in OC and evaluate their prognostic potential.

MATERIALS AND METHODS

Patient cohort

This study includes 122 patients with OC who underwent surgery due to primary tumors in a three-year period at Clinic for Gynecology and Obstetrics, University Clinical Center of Serbia. There were 91 high grade serous cancer (HGSC), 12 low grade serous cancer (LGSC), 10 mucinous and 9 endometrioid histology types. Ovarian tissue was sampled as part of standard diagnostic procedure. Tumor staging was done according to the current International Federation of Gynaecology and Obstetrics (FIGO) classification. Other considered parameters were patient's age, menopausal status, histological type of tumor and tumor differentiation. Secondary ovarian tumors, ovarian tumors from non-epithelial origin and patients younger than 18 years were excluded from the study. Approval for the study was obtained from the Ethics Committee of the University Clinical Center of Serbia and all study participants gave their informed consent.

Histopathological evaluation

The resected specimens were fixed in 10% buffered formalin and embedded in paraffin. For each case, the most representative block was selected. Evaluation of histopathological parameters was performed on 4μm thick, full hematoxylin and eosin stained sections, using a Leica DM1000LED microscope, according to current WHO classification (2020).

Tissue microarray construction

The tissue microarray was constructed from formalin-fixed and paraffin-embedded tumor samples using tissue cylinders from each paraffin block with a 3 mm puncture needle. The recipient paraffin block was constructed as a set of 28 cylinders[18]. Covering trophoblast and syncytiotrophoblast of placental tissue was serve as a positive control for immunostaining[19]. In the first row of each block, placental tissue was placed for block orientation.

Immunohistochemical analysis

Immunohistochemical staining for PD-L1, p62, LC3 and Beclin1 markers was performed on the Autostainer Link 48, Agilent, Denmark. For PD-L1 and LC3B antibody epitope unmasking was done in EnVision FLEX epitope unmasking solution pH 6.1 (K8005, Agilent), and for p62 and Beclin1 in EnVision FLEX solution for epitope unmasking pH 9.0 (K8004, Agilent). Visualization system EnVision FLEX (Agilent) was used for immunohistochemical analysis. The following primary antibodies were used: monoclonal anti-human PD-L1 antibody (clone 22C3, M3653, Agilent) in dilution of 1:50; polyclonal rabbit anti-human p62 antibody (ab155686, Abcam) in dilution 1:500; monoclonal recombinant rabbit anti-human Beclin-1 antibody (EPR20473, Abcam) in dilution 1:50; and polyclonal rabbit anti-human LC3B antibody (ab4839zhen, Abcam) in dilution 1:200. A positive reaction for the PD-L1 antibody was membrane staining, while cytoplasmic staining was considered positive for autophagy markers. Positive tumor cells were analyzed on the x400 power field. Their percentage was determined from the total number of positive tumor cells. The following score was used to describe the expression of all analyzed markers: negative (0) without positive cells or with a

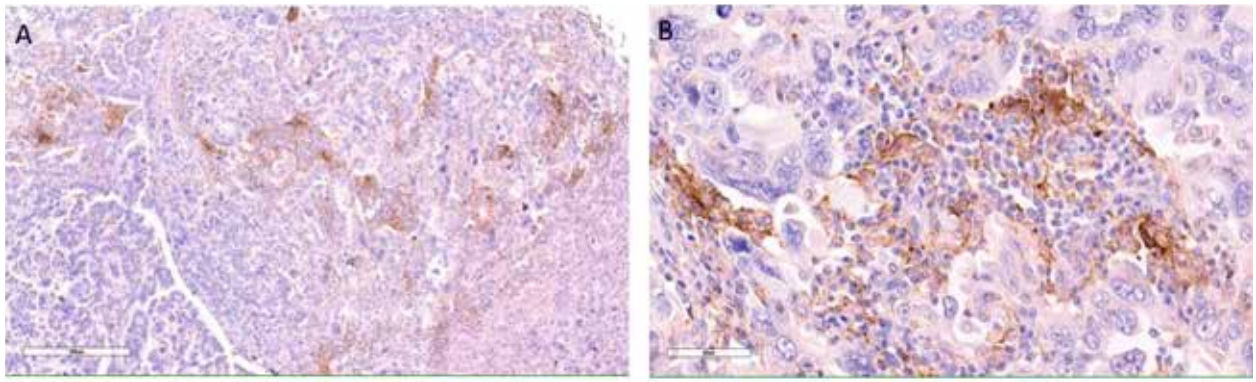

Figure 1: Expression of PD-L1 and autophagy markers in high grade serous ovarian carcinomas. A. Low PD-L1 expression; B. High PD-L1 expression.

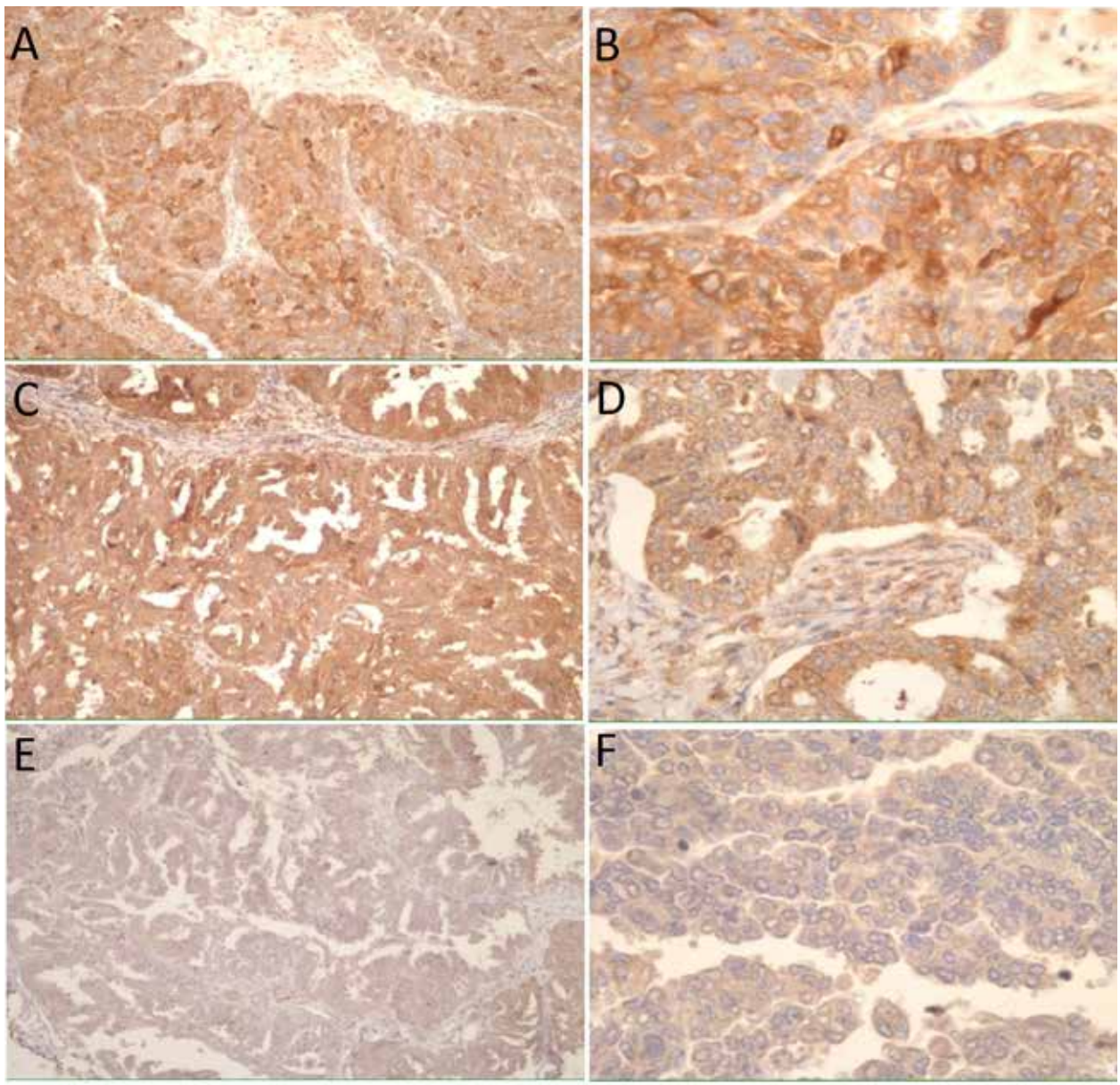

Figure 2: Expression of PD-L1 and autophagy markers in high grade serous ovarian carcinomas. A. Low p62 expression; B. High p62 expression; C. Low LC3 expression; D. High LC3 expression; E. Low Beclin1 expression; F. High Beclin1 expression.

Table 1: Comparison of PD-L1 expression with expression of autophagic markers p62, LC3 and Beclin1 considering the histological type of ovarian cancer.

Histology type	Marker	Expression level	Expression level of PD-L1 n (%)		*P*
			1+	≥2+	
Serous	p62	1+	2 (100.0)	0 (0.0)	/
		≥2+	5 (62.5)	3 (37.5)	
	LC3	1+	3 (100.0)	0 (0.0)	/
		≥2+	4 (57.1)	3 (42.9)	
	Beclin1	1+	3 (100.0)	0 (0.0)	0.270
		≥2+	4 (57.1)	3 (42.9)	
Mucinous	p62	1+	0 (0.0)	0 (0.0)	1.000
		≥2+	21 (20.4)	82 (79.6)	
	LC3	1+	0 (0.0)	0 (0.0)	0.475
		≥2+	21 (20.4)	82 (79.6)	
	Beclin1	1+	1 (8.3)	11 (91.7)	0.475
		≥2+	20 (22.0)	71 (78.0)	
Endometrioid	p62	1+	1 (100.0)	0 (0.0)	1.000
		≥2+	5 (62.5)	3 (37.5)	
	LC3	1+	0 (0.0)	0 (0.0)	/
		≥2+	6 (66.7)	3 (33.3)	
	Beclin1	1+	0 (0.0)	0 (0.0)	/
		≥2+	6 (66.7)	3 (33.3)	

single positive cell (<1%); low (1+) expression with less than 10% positive cells; moderate (2+) expression with 10-50% positive cells and strong (3+) expression with more than 50% positive cells. Associated moderate and strong positivity were considered as high expressions.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences 20.0 (SPSS Inc., Chicago, Illinois, USA). Data were expressed as mean±standard deviation (SD) for continuous variables and percentages for categorical variables. The analysis of demographic, clinical and histopathology parameters was performed using one-way ANOVA tests with Tuckey posthoc testing, $\chi 2$ test or its counterpart Fisher's test of exact probability. Analysis of PD-L1, p62, LC3 and Beclin1 expression in relation to histology cancer types and other histopathology parameters was done using the $\chi 2$ test, *i.e.* Fisher's test of exact probability. The same tests were used for comparison of all analyzed markers considering analyzed parameters. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

Demographic and histopathological characteristics

The mean age of 122 study subjects was 61.75±10.08 (age range: 15-84 years). Women in menopause were the most common (86.9%). Serous OCs were the most frequent (84.4%) comparing mucinous (8.2%) or endometrioid (7.4%) histology type. The vast majority of ovarian cancers were in advanced FIGO stages (68.0%).

Immunohistochemical analysis of PD-L1 expression in ovarian carcinoma

Serous ovarian cancers showed the highest level of PD-L1 expression, in 79.6% from all ovarian cancers. It was statistically significant ($P<0.001$) considering PD-L1 expression in mucinous (30.0%) and endometrioid (33.3%) types. High PD-L1 expression was more frequent ($P=0.007$) in HGSC (83.5%), then in LGSC (50%) histology type. PD-L1 expression was significantly predominant in advanced FIGO stages (95.2%) and the highest tumor grades (84.2%). High PD-L1 expression is shown in the Figure 1 (A, B).

Immunohistochemical analysis of p62, LC3 and Beclin1 in ovarian carcinoma

Expression of autophagy markers were the most common in patients with HGSC, compared to all other histological types ($P<0.001$). p62 (75.8%) and LC3 (81.3%) expressions were significantly frequent in HGSC, in contrast to Beclin1 expression (33.0%). Advanced FIGO stages and higher tumor grades showed statistically significant association with a higher expression of p62 and LC3 markers. Immunohistochemical analysis in ovarian HGSC with high expression levels of analyzed markers are shown in Figure 2 (A-F).

Correlation of PD-L1, p62, LC3 and Beclin1 expression considering histopathological parameters in ovarian carcinoma

Considering patients age and menopausal status, there were no statistically significant differences in expression levels of PD-L1 and autophagy markers.

Table 2: Comparison of PD-L1 expression with expression of autophagic markers p62, LC3 and Beclin1 considering serous ovarian histhology subtypes.

Marker	Expression level	Expression level of PD-L1 in serous carcinoma, n (%)					
		HGSC			LGSC		
		1+	≥2+	*P*	1+	≥2+	*P*
p62	1+	0 (0,0)	0 (0,0)	/	0 (0,0)	0 (0,0)	/
	≥2+	15 (16,5)	76 (83,5)		6 (50,0)	6 (50,0)	
LC3	1+	0 (0,0)	0 (0,0)	/	0 (0,0)	0 (0,0)	/
	≥2+	15 (16,5)	76 (83,5)		6 (50,0)	6 (50,0)	
Beclin1	1+	1 (8,3)	11 (91,7)	0,414	0 (0,0)	0 (0,0)	/
	≥2+	14 (17,7)	65 (82,3)		6 (50,0)	6 (50,0)	

HGSC: High grade serous carcinoma; LGSC: Low grade serous carcinoma

Marker expressions in different cancer types are presented in Table 1. Differences between HGSC and LGSC types are emphasized in Table 2. The high expression categories of p62 and LC3 markers show significantly higher values compared to the high expression of PD-L1 markers. Comparisons of PD-L1 and Beclin1 marker expressions did not show statistical significance, although values of high PD-L1 expression were more frequent compared to high Beclin1 expression.

DISCUSSION

In this study, we analyzed combined immunoexpression of PD-L1, p62, LC3 and Beclin1 markers in relation to the most common histological types of ovarian cancers. Comparison of the expressions of immunosuppressive and autophagy markers is not adequately presented in the previous literature. So far, such a comparison has only been analyzed in cell cultures[20]. Comparative immunohistochemical analysis of these markers on histology samples of OCs has not been performed. Clark *et al* were among the first to investigate the association between the mechanism of autophagy and the PD-1/PD-L1 signaling pathway, suggesting that PD-L1 expression on tumor cells may influence the therapeutic effects of autophagy inhibitors in certain cancer types[21,22]. The following studies show that inhibition of interaction PD-L1 with its PD-1 receptor, stimulates catabolic processes in tumor cells, which provide nutrients to the tumor cell and enable its survival[20,23,24]. Since PD-1/PD-L1 inhibition stimulates autophagy processes, tumor cells should become more sensitive to the effects of autophagy inhibitors. The combined use of autophagy inhibitors in patients with pronounced expression of PD-L1 markers on tumor cells should bring to better therapy responses in the treatment of OC[20,23].

The significance of the synergistic effects of autophagy mechanism and immune response was supported by studies which described that activation of autophagy in tumor cells ensures their survival as well as avoidance of the immune response by preserving the ability of tumor cells to degrade antitumor enzymes and factors secreted from immune cells, primarily CD8+ T lymphocytes and NK cells[8, 25, 26]. One of the main contributions of autophagy to immunity is cellular autonomic control of inflammation, which affects the differentiation of immune cells, significant for making the population of effector T lymphocytes[27]. Immunological cells such as macrophages, T regulatory (Treg) lymphocytes and dendritic cells use autophagy processes in their maturation. During maturation, metabolic intracellular mechanisms are regulated by autophagy. The type and function of maturing immune cells in relation to inflammatory processes indirectly indicates a significant influence of autophagy in the regulation of inflammation, which is common in tumors[28]. Inflammation in the tumor microenvironment stimulates autophagy processes and promotes tumor growth and survival[8,29].

Our results represent the HGSC as the histology type with the most common high PD-L1, p62 and LC3 expressions. On the contrary, Beclin1 marker showed remarkably lower expression levels. HGSC in the FIGO III stage showed a predominant frequency of high marker expressions, with a high prevalence of p62 and LC3 expressions and a little bit lower PD-L1 expression. We did not find such comparison in the previous literature. These high expressions could point to possibility of potential target therapy in OC with HGSC histology type. Considering simultaneous regulation of these mechanisms, the synergistic therapy effect of the autophagy and PD-1/PD-L1 inhibitors could improve therapy outcomes. Since autophagy is not only one immunologically controlled intracellular mechanisms of cell death, many other associated cellular processes could be the subject of further research in order to find more effective therapeutic solutions[23].

The aim of comparative immunohistochemical analysis of immunosuppression and autophagy marker expressions is to evaluate significant prognostic parameters that could determine more effective therapy procedures. The significant expression associations of the analyzed markers indicates the combined activated immunosuppressive tumor mechanisms and activated intratumoral autophagy processes. Significantly high expression of the analyzed markers suggests an indication of the simultaneous use of PD-L1 and autophagy inhibitors in the treatment of ovarian cancers. Poor expression of these markers could determine a low therapy response and a higher risk of disease relapse. Expression levels analysis of immunosuppression and autophagy markers could determine "cut-offs", significant in selecting patients for targeted therapy. The use of these markers in clinical practice could bring better therapy outcomes in the treatment of especially aggressive ovarian cancers[30].

CONCLUSION

HGSC type of OC showed the significant PD-L1, p62 and LC3 expression in higher FIGO stages of tumor disease. Beclin1 expression did not show significant association with histology type, FIGO and grade. Co-activation of immunosuppressive and autophagic mechanisms in OC cells may be an indication for synergistic therapy with PD-L1 and autophagy inhibitors in OC treatment.

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

Consent to publish: The authors affirm that human research participants provided informed consent for publication of the images in Figures 1 and 2.

Author contributions: All authors contributed to the study conception and design. Credit author statement: Ljubisa Jovanovic: conceptualization, methodology, investigation, resources, data curation, writing- original draft preparation, visualization. Andja Cirkovic: methodology, investigation, data curation, writing- original draft preparation. Milena Jovic: methodology, investigation, resources. Slavisa Djuricic: methodology, investigation, resources, writing- reviewing and editing. Svetlana Milenkovic: methodology, investigation, resources. Radmila Jankovic: methodology, investigation, resources, writing- reviewing and editing, supervision. All authors read and approved the final manuscript.

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Case Report

An uncommon form of adult osteopetrosis: A case report

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ABSTRACT

Osteopetrosis is a rare hereditary bone disease that causes osteoclasts dysfunction resulting in insignificant radiological density increase. There is a defect in calcified cartilage and primitive bone resorption. In this case, we presented the clinical and radiological signs of an uncommon form of adult osteopetrosis.

KEY WORDS: complication, osteopetrosis, physiotherapy

INTRODUCTION

Osteopetrosis is a rare hereditary bone disease characterized by very different clinical symptoms, age onset, prognosis (from mild to severe) and well-recognized radiological features density[1]. Four types of osteopetrosis have been described based on different clinical, radiological, histopathological and genetic features in the literature. Osteopetrosis congenita (marble bone disease) is an autosomal recessive and severe form of osteoporosis type. Hepatosplenomegaly, blindness, deafness, cranial nerve dysfunction, hydrocephalus and bone marrow failure are all associated with a clinical presentation[2,3]. Density enhancement in the cranium and long bones (osteosclerosis) is easily diagnosed radiographically with the typical appearance of the vertebrae (rugger-jersey cheese appearance).

Osteopetrosis tarda is defined as the adult or benign type of osteopetrosis with autosomal dominant transition and was first described by the German Albert Schonberg in the early twentieth century[2,3]. Generally, it does not require any treatment and most of them are found incidentally because they are asymptomatic. Although the etiology is not completely known, it is responsible for the inadequacy of osteoclasts required for the resorption of osteochondral tissue. As a result of that, mature bone formation is inhibited and sclerotic thickening is observed. The patients can be cropped up due to pathologic factors, cranial nerve palsies or dental problems. Radiological findings are similar to autosomal recessive forms; however, they are more severe. Diffuse osteosclerotic changes in bones are basically in the forms of osteosclerotic changes, cortex thickening, irregular lamina and collapsing of vertebral end plates, and radiolucent bands in the diaphysis of tips and bone in bone[4,5]. Osteopetrosis tarda may be of 2 types: type 1 sclerosis in the cranial bones is frequent and the spinal cord is rarely affected. In type 2, sclerosis based on the cranium is prominent, thickening and increasing sclerosis in the pelvis, iliac wings and vertebral terminations are predominant. Apart from this, there have also been osteoporosis variants described as recessive intermediate and tubular acidosis types[5-7].

CASE REPORT

A 30-year-old male patient was admitted to our polyclinic with a complaint of left hip and left knee pain. The patient was operated on due to a fracture related to trauma from his right hip and prosthetic treatment was applied seven years ago. After the operation, the right hip prosthesis was removed due to the development of chronic osteomyelitis in the right hip of the patient. The patient was operated on nine times from both sides of the hips. The patient had an increment in pain for the last three months. The

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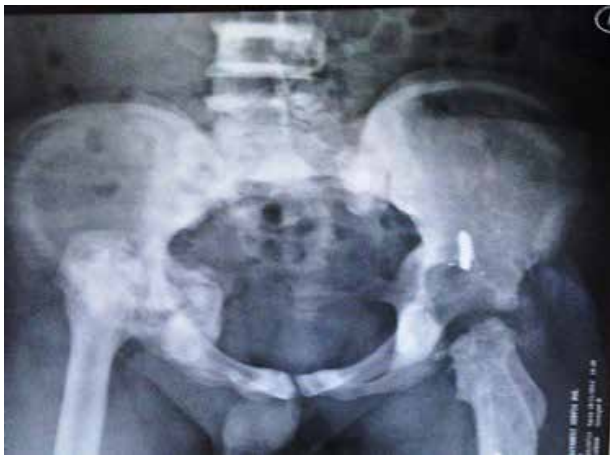

Figure 1: Osteosclerosis in the pelvis and ilium, left hip joint stenosis, excessive degenerative changes and protruding acetabuli were observed.

pain was a mechanical characteristic that increased with walking and decreased with non-steroidal anti-inflammatory drugs and rest. The pain severity of the patient was assessed as 8 with a visual analog scale (VAS). There were multiple fractures of the elbow and hips in the patients history. There was no osteopetrosis in her family history and the patient's system questioning also had no specific feature.

On physical examination, there were no growth retardation, hepatosplenomegaly and patient's apathy. Visual and auditory tests were also normal. The patient was independent and unsupported in the musculoskeletal examination. The upper extremity neurologic examination was normal. Cervical range of motion (ROM), bilateral shoulder ROM, elbow ROM and hand-wrist ROM was open and painless. Lumber flexion, extension, lateral flexion and rotations were minimal-restricted, painless at the last degree of ROM. There was c-type scoliosis in the thoracic cavity with the left facing open. The right hip was in the external rotation. Right hip movements were open and painful in all directions. The actual leg length (distance from spina iliac superior-ankle inner product) was 72 cm on the right and 80 cm on the left. Left hip movements were limited and painful in the middle of the range in all directions. Muscle strength in all muscles around the right hip was 3/5. The knee joint gap was open on the right, painless; it was open, painful on the left. Quadriceps diameter left: 41/ right: 37.5cm, gastrocnemius diameter left: 33/ right: 32 cm have been measured. Acute inflammation and effusion were not observed in the knees. Lower extremity neurologic examination was normal.

During the radiological examination, osteosclerosis in the pelvis and ilium bone within the bone appearance (bones in sclerotic bands) were observed. The left hip joint stenosis, excessive degenerative changes and protruding acetabuli were observed. A metal residue was observed in the right hip joint for the operation of removing the prosthesis (Fig 1). His lumbar spine radiography revealed lumbar vertebrae sclerosis and bone within a bone appearance (Fig 2). Cortical thickening, symmetric diffuse dense sclerosis and metaphyseal linearization were detected in both the tibia and fibula (Fig 3).

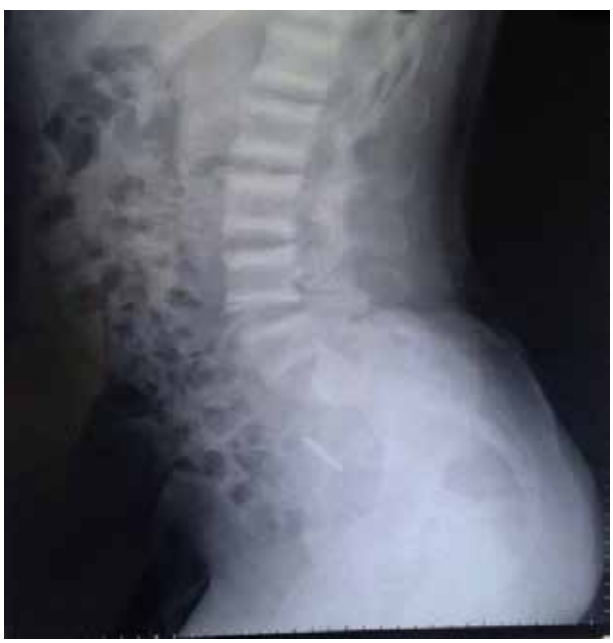

Figure 2: Lumbar vertebrae sclerosis and bone within bone appearance.

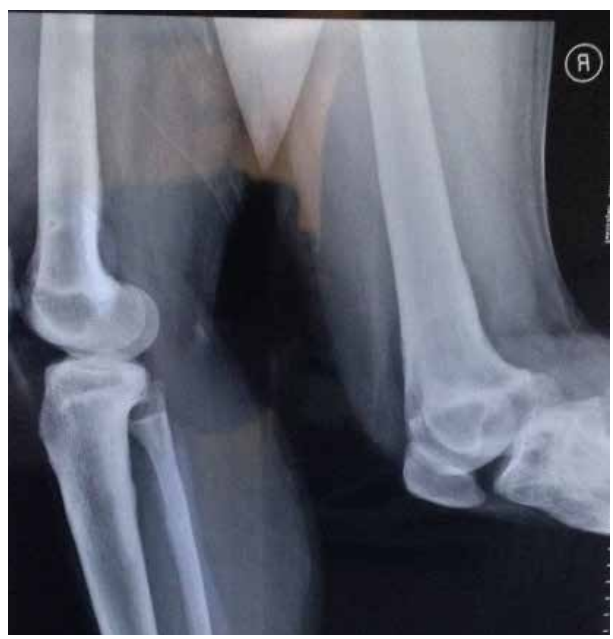

Figure 3: Cortical thickening, symmetric diffuse dense sclerosis and metaphyseal linearization were detected in both the tibia and fibula.

The patient was diagnosed with osteopetrosis tarda based on clinical and radiological findings. He was then referred to the physiotherapy wing and physiotherapy rehabilitation was started. Interference current to the left hip of the patient, hot pack to the left hip and left knee, and ultrasound treatments were applied. For knee ROM and stretching exercises, strengthening of the hip circumference muscles and posture exercises were performed for both hips. The patient's pain was significantly reduced, and the VAS score was evaluated as 3. A significant improvement was observed in the ROM measurements of the left knee and left hip. The patient was discharged with prophylaxis and a home exercise program prescription. The patient's consent was obtained for this case study.

DISCUSSION

Benign or adult osteopetrosis is a rare autosomal dominant or recessive bone disease that causes an apparent radiographic density increase in bones. Widespread sclerosis in all skeletal, pathological bone fractures, delayed physical growth, anemia and neurological deficits are clinical characteristics[2]. In addition, there are some reports on osteomyelitis in the literature. It has been reported that benign osteopetrosis is clinically manifested as chronic osteomyelitis that can be serious and difficult to treat[8,9].

The etiology is not precisely known. Most patients are asymptomatic and are diagnosed with characteristic findings coincidentally radiographs. Benign osteopetrosis which is an autosomal dominant transitional disease and diagnosed in adulthood can be seen mainly in two types. The most striking finding in type 1 is the increase in thickness in cranium-specific sclerosis and calvarium. Vertebral endings show diffuse spinal osteosclerosis accompanied by thickening. In type 2, sclerosis is apparent on the cranium base. Pelvic sclerosis bands (bone appearance in bone) can be detected. The vertebra end plates have a sandwich vertebra view in the form of increased density and thickening[10,11]. The risk of fracture in type 1 does not increase; however, fracture may occur in type 2 even after minor traumas, especially in long bones. Fracture history is seen in 70% of these patients[12,13]. Our patient also had a recurrent fracture with mild trauma. Treatment of adult osteopetrosis depends on the specific symptoms present and complications of the disease may require intervention. Patients have a higher risk of postoperative infection and healing is protracted. Treatment of osteopetrosis becomes more difficult and it may be continued for a longer period if surgery is complicated by osteomyelitis[14]. After hip fractures, our patient had many surgeries and arthroplasty. In addition, a hip prosthesis was removed due to the development of osteomyelitis.

Since diffuse sclerosis appearance in the skeleton is not a specific finding; heavy metal, fluoride intoxications, myelosclerosis, idiopathic hypocalcaemia, Paget's disease, bone tumors, hyperparathyroidism, hypothyroidism, endocrine disorders such as acromegaly should also be considered in the differential diagnosis. Our patient did not have any findings related to these. Based on benign clinical condition, typical radiological findings, multiple fractures and osteomyelitis, the patient was diagnosed with benign osteopetrosis. A physiotherapy rehabilitation program was applied to the patient for joint complaints.

CONCLUSION

In conclusion, we presented the clinical and radiological findings of an adult patient with osteopetrosis which has rarely been reported in the literature. The patient with diffuse osteosclerosis in the skeleton should be kept in mind for adult osteopetrosis disease. Furthermore, physiotherapy rehabilitation is quite effective in the symptomatic treatment of osteopetrosis and exercise programs should also be applied to these patients.

ACKNOWLEDGMENT

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Case Report

Desmoid fibromatosis of spermatic cord: case report and review of literature

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ABSTRACT

Desmoid fibromatosis (DF) is a rare, locally aggressive, deep-localized connective tissue neoplasia that develops in musculoaponeurotic tissues with a high recurrence rate. DF is non-metastatic, locally aggressive, fibroblastic/ myofibroblastic neoplasm. The tumor often arises in the extremities, abdominal wall and mesentery. Spermatic cord-located DF is extremely rare and has been reported in only a few case reports. Here, we present the clinical, radiological, histological and genetic characteristics of a 28-year-old male patient who was admitted to the hospital with the complaint of swelling in the left testis and was diagnosed with paratesticular DF after surgery.

KEY WORDS: desmoid, fibromatosis, paratesticular, spermatic cord

INTRODUCTION

Desmoid fibromatosis (DF) is a soft tissue tumor consisting of monoclonal fibroblastic/ myofibroblastic cells with a locally aggressive course, infiltrative growth and non-metastasis, constituting approximately 3% of soft tissue tumors[1].

Although its pathogenesis has not been clarified, multifactorial causes such as genetic, hormonal and trauma are thought to play a role in the etiology[2]. The tumor is most often located in the extremities (32%), the abdominal cavity (23%) or the abdominal wall (21%), and the thorax (15%)[3]. Here, a case with the diagnosis of DF located in the spermatic cord, which is very rarely reported in the literature, is presented with its clinical, radiological, histopathological and genetic data.

CASE REPORT

A 28-year-old male patient presented to the urology outpatient clinic with the complaint of swelling in the left testis that had been present for approximately 1.5 years. Physical examination of the case revealed two interconnected hard nodular masses associated with the left epididymis. Doppler ultrasonography showed herniated omental fat tissue and intestinal loops, extending from the inguinal canal into the scrotum, pushing the left testis inferiorly. In pelvic magnetic resonance imaging (MRI), three hypointense lesions, the largest of which is 5 cm in diameter, were observed in the omental hernia sac (Fig. 1).

Left radical orchiectomy was performed with the preliminary diagnosis of extratesticular scrotal mass, leiomyoma/ leiomyosarcoma/ liposarcoma.

In the macroscopic examination of the left orchiectomy material sent to pathology, two firm nodular lesions with a total size of 8x5.5x5 cm were observed, related to the spermatic cord. The cross-sectional faces of the lesions were solid, cream-white in color and had a moire appearance. Testicular tissue was normal.

Hematoxylin-eosin sections prepared from the lesion demonstrated a tumor of mesenchymal origin, consisting of spindle cells, with eosinophilic cytoplasm, growing in the form of long fascicles. Tumor cells had thin chromatin nuclei without significant atypia (Fig. 2).

In some sections of the tumor, there were keloid-like, coarse, hyalinized areas of collagenization between the

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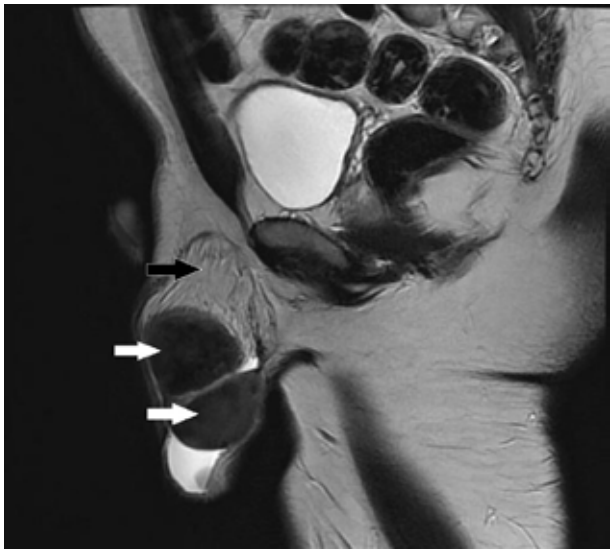

Fig. 1: MRI shows hypointense lesions growing in nodular appearance adjacent to the hernia sac in the inguinal canal. Desmoid fibromatosis in spermatic cord has been indicated by white arrows, inguinal hernia is indicated by black arrow.

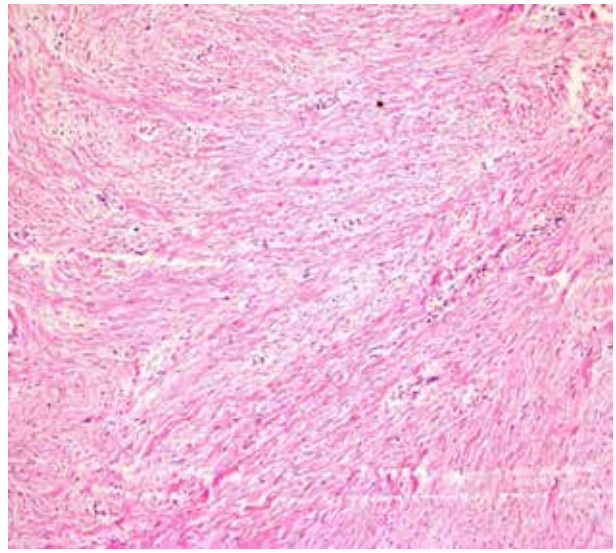

Fig. 2: Spindle tumor cells growing in the form of long fascicles (HEX100)

spindle tumor cells (Fig. 3). Immunohistochemically, tumor cells showed negative reaction with CD34, S100 and desmin, and diffuse positive reaction with SMA and beta catenin (Fig. 4). Genetic examination of the case, which was thought to be DF with morphological findings, was requested. After DNA isolation from sections taken from the lesion, NGS analysis using Nextseq500 (Illumina) (ONCO/RevealTM Solid Tumor Panel: Pillar Biosciences) led us to define that tumor tissue harbored c.121A>G (p.T41A) missense pathogenic variant on the CTNNB1 (Catenin, Beta-1) (RefSeq accession number NM_001904.4) gene exon 3. With these findings, the case was reported as "DF with spermatic cord localization".

DISCUSSION

The term "fibromatosis" was first defined by Macfarlane in 1832. The term "desmos" was used by Mueller in 1838 to indicate similarity to tendons[4]. In the latest World Health Organization classification, fibromatosis is divided into superficial (palmar, plantar, penile) and deep (desmoid type). In addition, the deep subtype is divided into three: extra-abdominal, intra-abdominal (deep pelvic) and abdominal wall[5].

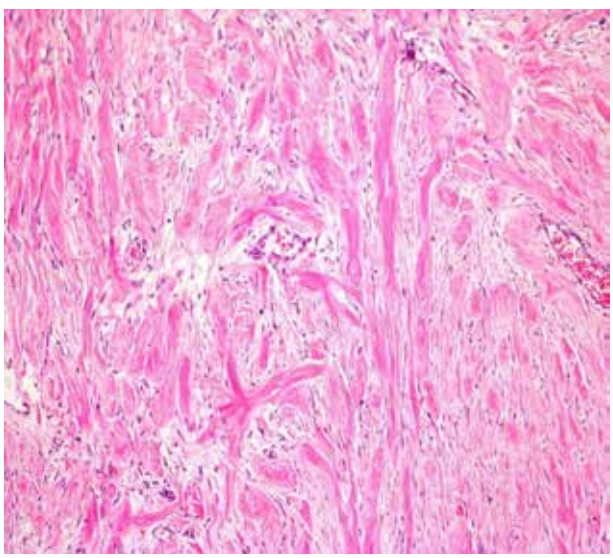

Fig. 3: Coarse, hyalinized collagenization between spindle tumor cells (HEX200)

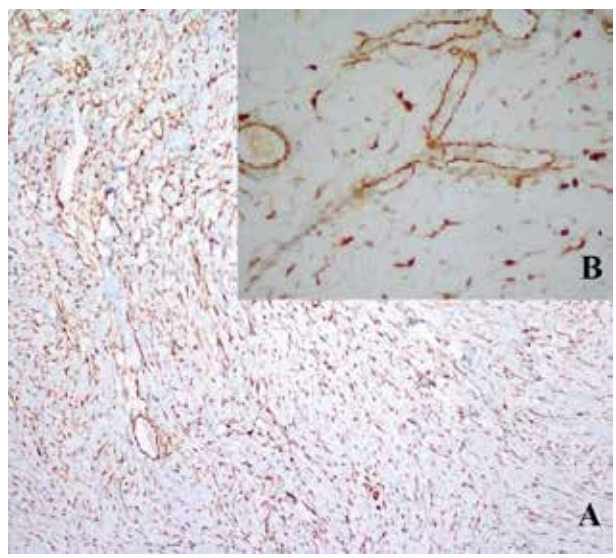

Fig. 4: Diffuse nuclear positivity with beta catenin immunohistochemical marker in tumor cells; A: DABX100, B: DABX400

Depending on the location of the tumor, clinical symptoms may occur as pain, fever, function impairment or loss of function of the organ involved[4].

Desmoid fibromatosis is observed very rarely and its frequency is reported to be 4/1,000,000 per year[6]. It is observed more frequently in women than in men. Although it has been reported to be seen in a wide age range, it is observed more frequently in the third decade[7,8].

The exact etiopathogenic mechanism of DF still remains unknown but it seems to have multifactorial origin with genetic factors, hormonal, trauma, pregnancy and surgical resections (typically after C/S) being involved[9,10].

Most of the cases are sporadic, and somatic point mutations are observed in the CTNNB1 gene, which encodes beta-catenin, in approximately 85%. In a study in which 138 patients were evaluated, the mutation distribution in patients carrying mutations was determined as follows; 59% T41A, 33% S45F, 8% S45P[11]. The T41A mutation, which is the most frequently observed mutation in the literature, was also observed in our case.

Desmoid tumors observed in patients with Gardner and FAP syndrome have been associated with APC germline mutations. Intra-abdominal desmoid tumors are frequently observed in these patients[12].

Desmoid fibromatosis is most frequently observed in the extremities (32%), followed by the abdominal wall, retroperitoneum or intra-abdominal and chest wall, respectively[3]. In the literature, DF with spermatic cord localized has been reported as case reports and is very rare[13-17].

The first case described was a 62-year-old male patient who presented with a six-month of enlarged right scrotal mass, identified by Gluck *et al* in 1987. It has been reported that the patient had a 7x11 cm mass in right scrotum. The follow-up information of the case was not given[13].

The second case reported by Lai *et al* in 1995 belongs to a 31-year-old male. It has been reported that the mass in the patient who applied with the complaint of a painless left inguinal mass was 7 cm in diameter and the growth rate increased in the last year. In the follow-up of the case, it was reported that local recurrence developed with an 8 cm diameter mass compressing the distal ureter in the third year after surgery[14].

The third case was reported in 2000 by Sumi *et al* of a 65-year-old male patient with a painless, inguinoscrotal mass of increasing size, and it was found that the mass was adjacent to the testicular superior. In exploratory surgery, it has been reported that the mass extends into the retroperitoneum and invades the bladder, sigmoid colon, left ureter and left external iliac vessels. The follow-up information of this case also was not given[15].

Reporting the fourth case in 2007, Shi *et al* showed a 40-year-old male patient who presented with a painless, slowly growing scrotal mass. It has been reported that the mass is 3 cm in diameter and extends to the dartos fascia, and there is still no recurrence in the 7th year of untreated follow-up after tumor resection[16].

The fifth case was identified in 2020 by Hogan *et al*. A 64-year-old patient presented with a painless scrotal mass. On physical examination, a paratesticular mass of 3.5 cm in diameter and adherent to the lower pole of the left testis was detected. It has been reported that there is still no recurrence in the 3rd year of follow-up after surgical treatment[17].

Genetic analysis was not mentioned in any of these cases reported in the literature. To the best of our knowledge, our case is the first case of DF in the spermatic cord, whose genetic analysis was performed.

Treatment of DF is planned according to tumor location and symptoms. Complete surgical resection remains the therapeutic mainstay and the medical treatment after surgery is still controversial. Although there is no generally accepted medical treatment in the literature, medical treatment options comprise dacarbazine-doxorubicin, anti-estrogen therapy, NSAIDs, imatinib mesylate, sunitinib, sorafenib[18].

Our case is the sixth case reported in the English literature, and its specific mutation was also shown by genetic analysis. He had no relapse until now with 3 years and 3 months of follow-up.

CONCLUSION

In conclusion, DF is a locally aggressive non-malignant tumor of soft tissue. It often presents in the extremities, abdominal wall and mesentery. Genetic analysis of the cases may be considered in the diagnostic process. Although DF in the spermatic cord is rarely observed, it should be considered in the differential diagnosis of testicular masses.

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Conflict of Interest: None

Author contributions: Nesrin Akcan, Erdem Kisa, Ulku Kucuk: acquisition of data, analyzed the clinical data and designed the clinical experiments; Nesrin Akcan, Ulku Kucuk: wrote the manuscript; Ulku Kucuk: conceptualization, interpretation of data, supervised the study and review the manuscript. All authors read and approved the final manuscript.

Data availability statement: Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Case Report

Encysted papillary carcinoma of breast: A rare and intriguing tumor

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ABSTRACT

Encysted papillary carcinoma of the breast (EPC) is one of the papillary breast tumor (PTB) variants that may pose a diagnostic difficulty, particularly on core needle biopsy. It shows overlapping cytological features with other PTB leading to diagnostic pitfalls; more so with invasive papillary carcinoma, which is an aggressive malignancy with a less favorable prognosis. Histopathological examination helped us to diagnose and characterize this rare and intriguing entity. We also emphasize the need for early and accurate diagnosis of EPC because of its indolent nature, conservative management and favorable outcome.

KEY WORDS: breast neoplasm, diagnosis, encysted, papillary carcinoma

INTRODUCTION

The papillary tumors of the breast (PTB) are an unusual group of tumors comprising less than 3% of breast tumors. Although rare, these tumors comprise a varied group of lesions ranging from benign to malignant and remain a controversial entity regarding histopathological features, classification and clinical management[1,2]. The spectrum of PTB includes intraductal papilloma (IDP), IDP with ductal carcinoma in situ (DCIS); papillary DCIS, encapsulated papillary carcinoma (EPC), solid papillary carcinoma (SPC), invasive papillary carcinoma (IPC) and metastatic papillary carcinomas to the breast. EPC is one of the PTB variants that may pose a diagnostic difficulty, particularly in core needle biopsy[3]. Given the overlapping cytological features with other PTB and more so with IPC which is an invasive malignancy with a less favorable prognosis. Histopathological examination plays an important role in the diagnosis and proper characterization of not only EPC but other PTBs as well. Early and accurate diagnosis of EPC is important because of its indolent nature, conservative management and favorable outcome.

CASE REPORT

A 65-year-old woman presented to the surgery department with a 3-month history of a gradually enlarging right breast lump. Physical examination revealed a 2x2 cm mobile, firm mass in the upper outer quadrant. The overlying skin was unremarkable. There was no history of any nipple discharge. Axillary lymph nodes were not palpable. Ultrasound examination revealed a heterogenous well-circumscribed cystic mass with a solid nodule (Fig 1). A core needle biopsy was performed, which revealed discohesive clusters of monomorphic columnar cells arranged in papillary structures showing cytologic atypia. Myoepithelial cells were conspicuously absent (Fig 2 (a-d)). Given the varied and overlapping histological features observed in a spectrum of PTB, a guarded tentative diagnosis of a papillary breast lesion with atypia was signed out and histopathological correlation was advised. Taking into consideration the clinical, imaging and cytological features, lumpectomy was carried out. Histopathological examination showed a papillary tumor in a cystic space surrounded by a well-defined fibrous capsule. The papillary structures

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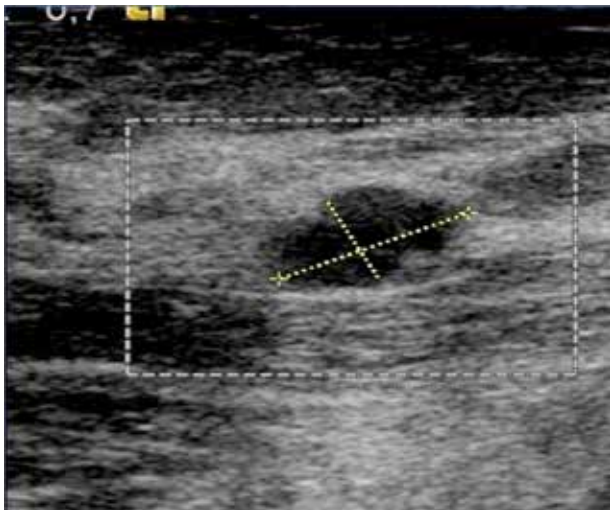

Figure 1: Ultrasound examination showed a heterogeneous well-circumscribed cystic lesion with a solid nodule.

were lined by neoplastic epithelial cells showing mild to moderate nuclear atypical features (Fig 3(a-b)). Immunohistochemical examination with p63, a myoepithelial cell marker, did not reveal any positivity in the tumor but can be found in the adjacent normal breast tissue (Fig 3(c-d)). Follow-up of the patient after 6 months did not reveal any evidence of recurrence.

DISCUSSION

PTB is one of the rare categories of breast tumors comprised of lesions with varied but overlapping histological features, making it difficult to diagnose them solely on core needle biopsy, which is one of the preferred investigations for diagnosis of breast lesions. Accurate diagnosis of these lesions is necessary as some of these lesions are indolent and have favorable prognoses. EPC is an uncommon and intriguing tumor accounting for 0.5-1% of all breast malignancies[4,5]. It usually affects elderly females in the 6th to 7th decade of life and can present as either a palpable lump and/or bloody nipple discharge[6]. Ultrasound examination is the most effective radiological investigation in the diagnosis of EPC. Usually, the tumor size ranges from 0.3-9 cm and appears heterogeneous with solid and cystic areas. Mammography, though less effective, will show a round to oval, well-circumscribed lobulated mass.

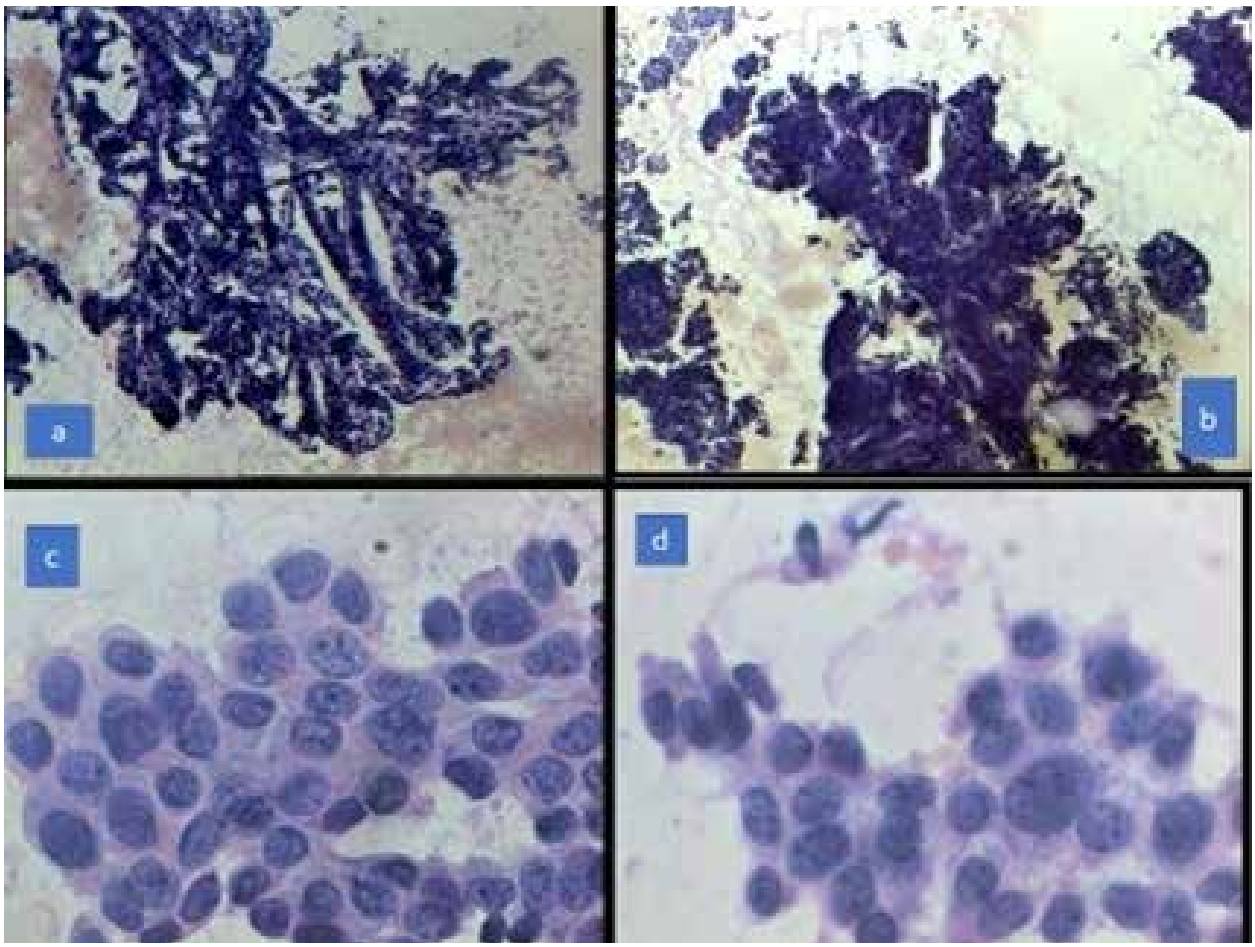

Figure 2 (a-b): 40X shows papillary structures, and **(c-d)**: 100x revealed cytologic atypia.

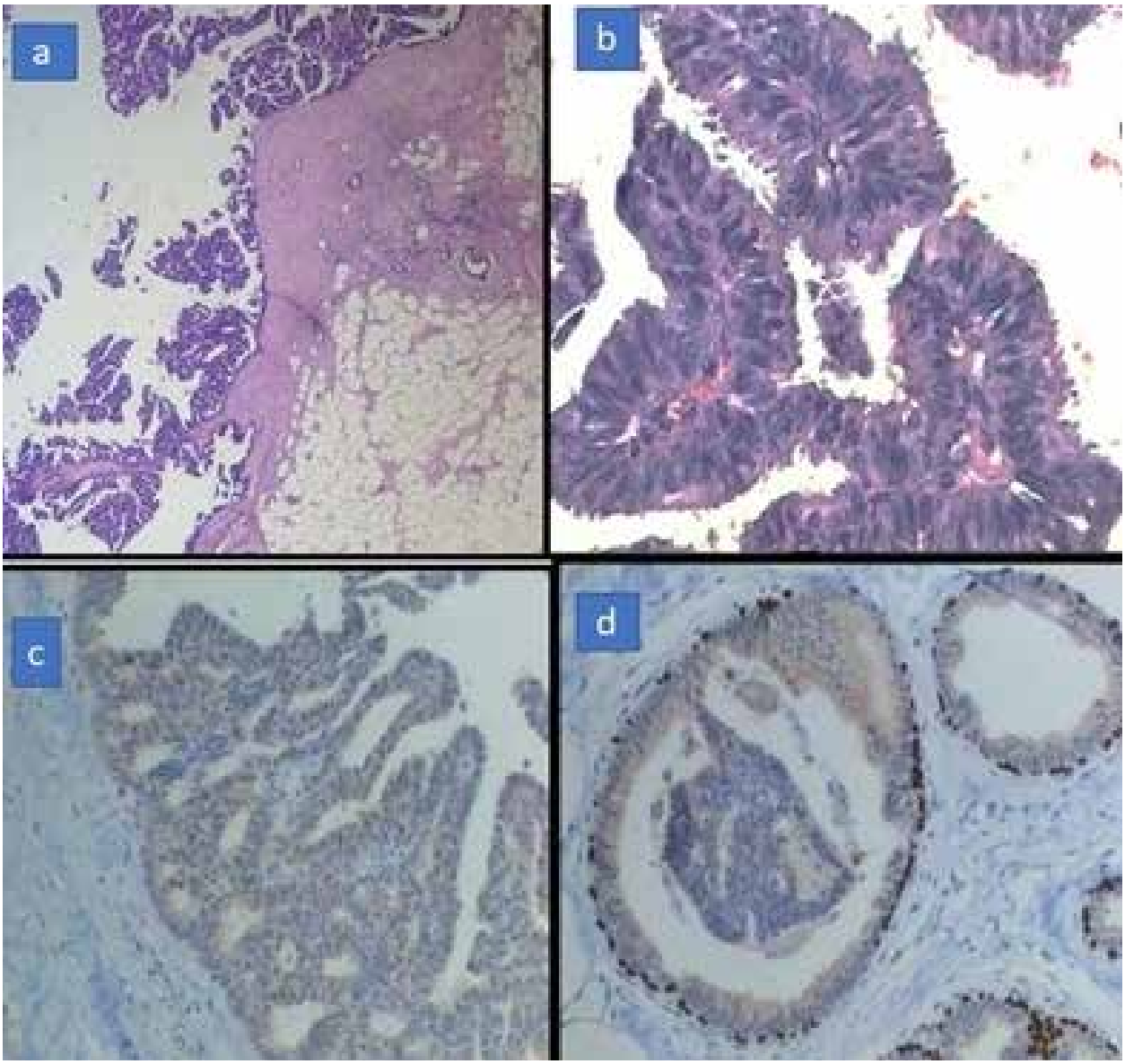

Figure 3: (a) (H&E stain, 40x)- papillary tumor surrounded by a fibrous capsule; **(3b)** H&E stain, 100x-papillary structures lined by cells showing mild to moderate nuclear grade; **(3c)** p63 immunostain, 40x- absent myoepithelial cells around the tumor; **(3d)** p63 immunostain, 40x- myoepithelial cells present in adjacent breast.

Core needle biopsy in our case showed discohesive clusters of tumor cells arranged in papillary structures. The tumor cells were monomorphous with mild to moderate nuclear atypia. Myoepithelial cells were conspicuously absent. The differential diagnoses of IDP with DCIS, papillary DCIS, EPC, SPC and IPC were considered. However, because of overlapping cytological features and different modalities of treatment, a guarded diagnosis of a papillary breast lesion with atypical features was made, and histopathological correlation was advised. Excision of the lump revealed a papillary tumor in a cystic space lined by neoplastic cells showing mild to moderate nuclear atypical features and surrounded by a well-defined capsule. p63, an immunohistochemical marker of myoepithelial cells, was absent. IDP with DCIS and papillary DCIS are characterized by the presence of myoepithelial cells, whereas EPC is characteristically devoid of any myoepithelial cells[7-9]. There was no evidence of any solid growth pattern or any invasive component, which effectively ruled out the possibility of SPC and IPC. Taking into consideration the clinical, imaging and histopathological features, the final diagnosis of EPC was signed out.

EPC is characterized by a tumor in a cystic space composed of a fibrovascular core lined by neoplastic epithelial cells of low to moderate nuclear grade and surrounded by a distinct fibrous capsule[7,10].

The presence of the myoepithelial cell layer plays an important role in distinguishing in-situ from invasive malignancies. EPC are characteristically devoid of this layer in both periphery as well as around the papillae, thereby significantly decreasing the utility of the myoepithelial markers as an adjunct in differentiating EPC from IPC. Although EPC is classified as a non-invasive malignancy, the lack of immunophenotypic markers for myoepithelial cells creates a dilemma regarding the true nature of the tumor and may lead to a misdiagnosis of invasive malignancy. EPC usually has a favorable prognosis and can be adequately treated with local therapy[8,10]. Rarely, EPC may involve axillary lymph nodes and progress to an invasive malignancy[10]. Therefore, the need for sentinel lymph node biopsy as well as the use of adjuvant radiotherapy and/or chemotherapy can be avoided. Hence, proper diagnosis and characterization of EPC are essential[3]. The mainstay of treatment is complete surgical resection[6,9,11,12]. EPC associated with DCIS and an invasive component may recur and the use of adjuvant radiotherapy and /or chemotherapy may be considered in these patients. EPC has a 10-year survival of 96%. During long-term follow-up, the cause of death of these patients was primarily ischemic heart disease and hepatobiliary cancer[13]. One of the largest studies comprising 917 patients with EPC reported cumulative survival rates of 96.8%[14].

CONCLUSION

We present this case to highlight the pitfalls in the cytodiagnosis of encysted papillary carcinoma of the breast which is one of the rare variants of PBT. We also emphasize the importance of histopathology for the diagnosis and differentiation of EPC, which is an indolent entity requiring a conservative approach in its management and having a long-term favorable prognosis, from the more aggressive IPC of the breast.

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Case Report

Iatrogenic suprascapular nerve injury after excision of lymph node in posterior triangle of the neck: A case report and review of the literature

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ABSTRACT

We present a patient who developed an isolated suprascapular nerve (SSN) injury after the excision of the lymph node in the posterior triangle of the neck. The common etiologies of an SSN injury include recurrent overhead activities, scapulothoracic dyskinesia, traumatic or iatrogenic (open or arthroscopic shoulder operations) injuries, systemic inflammatory diseases, and entrapment conditions due to suprascapular and spino-glenoid notch space-occupying lesions. To our knowledge, SSN injury as a result of lymph node excision surgery in the posterior triangle of the neck has not yet been described.

KEY WORDS: iatrogenic injury, posterior triangle of the neck, suprascapular nerve

INTRODUCTION

Accurate anatomical knowledge of nerve structures in the neck is important to avoid serious negative consequences. The suprascapular nerve (SSN) is a mixed-type peripheral nerve originating from the C5-C6 nerve roots, deviating from the upper truncus of the brachial plexus, and then passes from the posterior triangle of the neck. The SSN has its main originating contributions from the upper part of the brachial plexus, more specifically from the C5 and C6 vertebral rami, with variable contributions from the fourth cervical ramus[1]. After exiting the brachial plexus, the SSN travels along the posterior cervical triangle towards the suprascapular notch[2].

The SSN provides motor innervation of the supraspinatus and infraspinatus muscles, and sensory innervation of the acromioclavicular and glenohumeral joints. SSN damage results in atrophy of the supraspinatus and infraspinatus muscles, weakness in shoulder abduction and external rotation, and backache.

The neck is separated into anterior and posterior triangles by the sternocleidomastoid muscle. Our patient had undergone posterior triangle of the neck surgery. The anatomical structures included in this section include the spinal accessory nerve, cervical plexus branches, roots and trunks of the brachial plexus, phrenic nerve, subclavian, transverse cervical, suprascapular arteries, external jugular vein, lymph nodes, omohyoid, anterior-mid-posterior scalene, levator scapula and splenius muscles.

CASE REPORT

A 23-year-old woman was admitted to our hospital with increased shoulder girdle pain going on for 1 month and decreased active range of motion (ROM) of the shoulder. In the inspection, atrophy was detected in the supraspinatus and infraspinatus muscles (Fig 1a, Fig 1b), and positive results were obtained in Jobe, Drop arm, and infraspinatus stress tests, which are special examination tests of the shoulder. There was no limitation in the passive ROM. Superficial sensory examination was normal.

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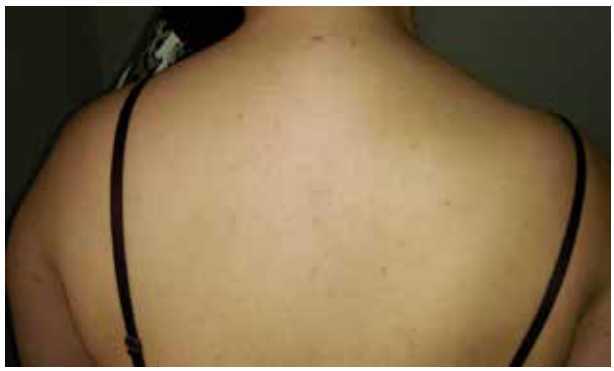

Fig. 1a: Supraspinatus and infraspinatus muscle atrophies

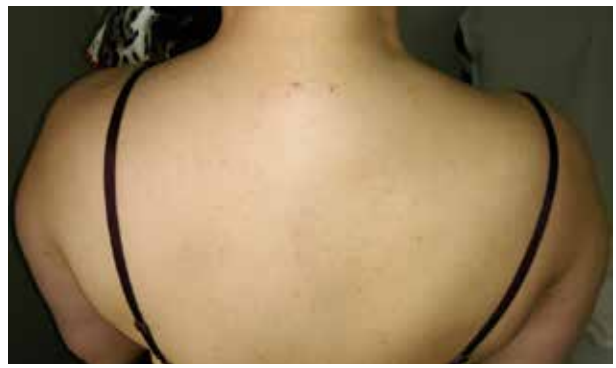

Fig. 1b: Supraspinatus and infraspinatus muscle atrophies

An incision scar was visible in the right posterior triangle of her neck (Fig 2). It was learned that she had an operation in the specified area three months ago. Chronic nonspecific lymphadenitis with a macroscopic size of 1.5x1x0.8 cm was excised from the posterior triangle of the neck. It was determined that the complaints started after the operation and gradually increased.

Fig. 2: Incision scar

Conventional radiography was normal. Magnetic resonance imaging (MRI) was performed. There was supraspinatus and infraspinatus atrophy in the T1-weighted oblique sagittal section (Fig 3) and no rotator cuff tear was observed in the T2-weighted oblique coronal section (Fig 4).

An SSN conduct study showed that axonal damage occurred in the right SSN (Table 1). Electromyography (EMG) was performed, which demonstrated a normal insertional activity and interference pattern in the biceps, deltoid muscles and supraspinatus. There were no positive sharp waves and fasciculation in the supraspinatus and infraspinatus muscles. EMG study did not show any signs of acute denervation; on the other hand, spontaneous long-term, high amplitude, polyphasic neurogenic changes were observed in the right supraspinatus (Table 2). Additionally, normal EMG examination of multiple C5–C6 scapular and upper extremity muscles, as well as the cervical paraspinal, ruled out the hypothesis of cervical radiculopathy or

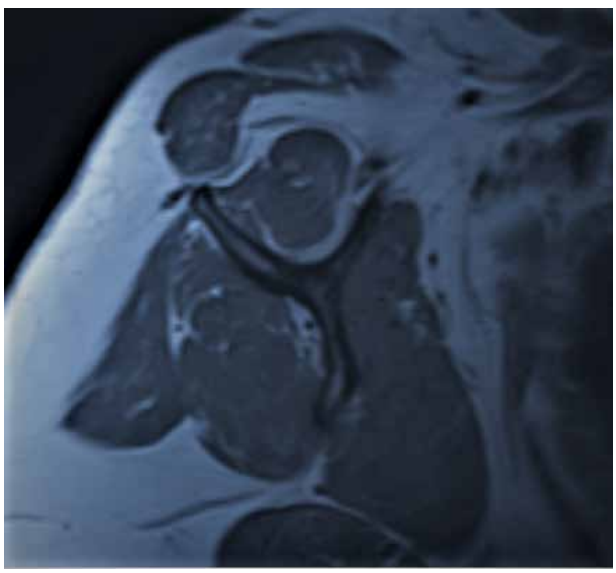

Fig. 3: T1 Oblique sagittal section on MRI

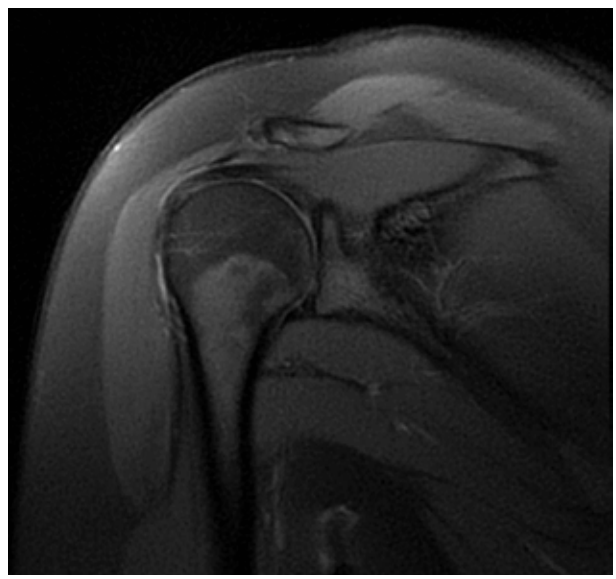

Fig. 4: T2 Coronal section on MRI

Table 1: Suprascapular nerve conduct study

Site	Latency (ms)	Amplitude (mV)	Area (mVms)
Right infraspinatus	4.9	8.22	21.13
Left infraspinatus	3.25	10.80	31.89
Right supraspinatus	4.55	8.15	19.58
Left supraspinatus	3.2	16.98	34.40

upper trunk or lateral cord injury. Normal median and ulnar nerve conduction studies and normal EMG examination of multiple muscles in the upper extremities argued against a diffuse neuropathic process involving the upper extremities.

History, physical examination, imaging and laboratory results showed that SSN injury was iatrogenic, and it was seen that it developed as a result of lymph node excision surgery.

Neurophysiological findings obtained three months later have revealed that acute denervation findings were not observed on the SSN on the right, yet partial axonal damage was identified with partial reinnervation findings. Remission in complaints started in the 6th month after the operation.

DISCUSSION

A complete understanding of the relevant anatomy, including the shoulder joint and brachial plexus anatomy, is essential in comprehending the pathophysiology involved in suprascapular neuropathy. In this case, SSN injury, which is an unexpected complication after lymph node excision from the posterior triangle of the neck, was described.

Iatrogenic SSN injury is one of the causes of nerve pathology; SSN injuries are commonly associated with brachial plexus injuries due to trauma or traction injuries, neuritis and compressive lesions. Reported iatrogenic SSN injury causes are very rare, and they include open and arthroscopic shoulder joint procedures in the literature[3-5]. The other presented articles are anatomic cadaver studies that have been conducted to prevent SSN damage during surgeries[6-9]. Excisional lymph node biopsy is a method that should be applied very frequently in the definitive diagnosis of conditions such as infection and tumoral pathologies. Insufficient knowledge of anatomical structures can cause undesirable side effects. In this case, we tried to present a situation that developed as an unexpected complication.

The diagnosis of a nerve injury can be made with complete history and physical examination. These findings can be confirmed with EMG and nerve conduction studies[10-11]. The diagnosis was confirmed in this case with EMG and nerve conduction studies performed after the examination.

Treatment is initially nonoperative and early rehabilitation involving active and passive ROM exercises with the hopes of delaying muscle atrophy and preventing secondary shoulder joint pathology. Although conservative methods can be used in the treatment, open or arthroscopic surgery may also be necessary[11].

Conservative treatment methods were used in this case.

The incidence might increase with greater awareness of the condition. We believe that there may be many cases that developed and were missed without being aware of it. In addition to the examination, a careful history should be taken by paying attention to MRI and electrodiagnostic studies. SSN injury, which can be relatively difficult to define, should be carefully examined after neck operations. In terms of neurovascular pathologies that may be overlooked, both a good knowledge of anatomy before the operation and a careful physical examination after the operation are important.

CONCLUSION

Since it may be necessary to go beyond the standards in tumor surgery, the risk of damage to vessels and nerves is higher. The risk increases even more when approaching the masses in areas with dense vascular and nerve structures. This situation can be prevented

Table 2: Right suprascapular nerve EMG study

Muscle/Site	Insertional activity	Interference pattern	Pos. Wave	Fasciculation	Fibrillation	Time	Amplitude	Polyphase
Biceps Bra.	N	N	0	0	0	N	N	N
Deltoid	N	N	0	0	0	N	N	N
Triceps	N	N	0	0	0	N	N	N
Ext. Dig C.	N	N	0	0	0	N	N	N
Supraspinatus	N	N	0	0	0	N-↑↑	N-↑↑	↑↑

↑↑: high-level increase

with a good knowledge of specified area anatomy and careful surgical dissection. In this case, SSN pathology that developed after surgery on the posterior triangle of the neck, which is a dense region in terms of vessels and nerves, was reported.

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Brief Communication

Indications for bronchoscopic lung volume reduction: a review

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ABSTRACT

Bronchoscopic lung volume reduction using a one-way valve is now well known to play a role in the treatment of severe chronic obstructive pulmonary disease (COPD), and therefore understanding the indications is important. In selected patients, the treatment of severe COPD may include surgery or bronchoscopic lung volume reduction. Indications for bronchoscopic lung volume reductions are heterogenous emphysema, air trapping, an intact interlobar fissure, severe COPD population who have stopped smoking and participation in a pulmonary rehabilitation program.

KEY WORDS: bronchoscopic lung volume reduction, emphysema, indications, Kuwait, treatment, valve

INTRODUCTION

Lung volume reduction is achieved by insertion of a one-way valve in the airway supplying a target lung lobe. Air is allowed to gradually leave the target lung lobe, which then collapses gradually. The role of bronchoscopic lung volume reduction in the treatment of chronic obstructive pulmonary disease (COPD) has become more established in recent years, and this is due to technological developments and ongoing research within this field[1]. It is now well known that bronchoscopic lung volume reduction plays a role in the treatment of COPD; however, in the majority of cases, severe COPD should be treated medically. In severe COPD more specifically, bronchoscopic lung volume reduction may continue to play an increasing role in the future[2]. This is why it is important to review indications and establish the relevant clinical applications of this procedure. In this review, we will discuss the indications of bronchoscopic lung volume reduction.

Indications

1. Heterogenous emphysema

Heterogenous emphysema is defined as emphysema that is incongruous, in other words, it is a CT finding seen when emphysema in one lobe is more significant compared to emphysema in the surrounding lobe. For example, when there is significant emphysema in the right upper lobe compared to the right middle and right lower lobes, this is characterized as heterogenous emphysema. This is an important indication because identifying the target lobe for bronchoscopic lung volume reduction should be done with view to achieve long term benefit to the patient, and therefore this targeted therapy will be successful[3]. In this same example, the right upper lobe would be the target lobe. It is also important to understand that there are CT findings and conditions that exclude patients, and these are bronchiectasis, para-septal emphysema, fibrosis, lung nodules and any accidental findings.

2. Air trapping with intact interlobar fissure

Air trapping is defined as enlargement of the diseased part of the lung and compression of the healthy part of the lung due to pulmonary obstruction. We identify this on CT by comparing inspiration and expiration view. Air trapping is revealed as enlargement of the diseased lobe in the expiration phase CT compared to that same disease lobe in the inspiration CT. Air trapping is associated with

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an intact interlobar fissure which can be confirmed using a quantitative CT. The lobe of the lung with air trapping (and therefore with intact interlobar fissures) should be the target lobe for bronchoscopic lung volume reduction[4]. Air trapping causes the patients symptoms of shortness of breath and using a valve to achieve lung volume reduction will reduce dead space. This prevents the diseased part of the lung from compressing the healthy part of the lung. Reversely, the healthy part of the lung will expand and compress the diseased part of the lung.

3. Severe COPD

Bronchoscopic lung volume reduction should be considered in cases of severe COPD only. This is mainly because long term outcomes are unknown and therefore it is not clear if the balance of risk and benefit is in favor of this treatment in the moderate COPD population. It is also important to weigh the risks and benefits of bronchoscopic lung volume reduction versus surgical lobectomy. Each case should be assessed individually, and patients should be appropriately managed[5].

Smoking cessation is a standard requirement. Patients should be aware this procedure is contraindicated in patients who smoke. Smoking cessation support should be provided if available. Pulmonary rehabilitation should be offered because patients will benefit from this service when available.

There are important limitations to the use of this procedure, the most important of which remains adequate training of nursing staff and the availability of specialized health care associated staff, such as trained coordinators that can support patients and treatment pathways. Additionally, there are significant cost considerations and therefore, adequate selection of patients should always be aimed at achieving the most benefit. Patients should be educated with regards to complications and all other measures should be taken to help patients make informed decisions.

CONCLUSION

In selected patients, the treatment of severe COPD may include surgery or bronchoscopic lung volume reduction. Indications for bronchscopic lung volume reductions are heterogenous emphysema, air trapping, an intact interlobar fissure, severe COPD population who have stopped smoking and participation in a pulmonary rehabilitation program.

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Brief Communication

Redefining health communication in the age of AI: a strategic response to public trust in health information generated by AI in Kuwait

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ABSTRACT

The rapid integration of artificial intelligence (AI) into digital health ecosystems has sparked a paradigm shift in how the public accesses, interprets and acts upon medical information. Generative models, such as ChatGPT and symptom-checking tools, now shape public knowledge of disease, diagnosis and treatment, which are often outside the supervision of health authorities, thus raising concerns regarding trust, accuracy and patient safety. This brief communication reframes a previously published study on AI and public trust to present a Kuwaiti-centric analysis. It proposes a strategic framework that aligns with Kuwait's centralized healthcare system, high digital penetration and strong institutional trust. The paper advocates for national standards on AI-mediated health messaging, critical health literacy interventions and clinician education to ensure responsible innovation rooted in ethical governance.

INTRODUCTION

Artificial intelligence is no longer on the edge of healthcare—it is at the forefront of public medical dialogue[1, 2]. AI-generative platforms capable of generating health information are increasingly becoming the first point of search for the public. The implications of this shift are profound: while these technologies can simplify access to information, they may simultaneously deepen inequalities, propagate inaccuracies and undermine professional authority.

Kuwait presents a distinctive ratio of digital connectivity use in healthcare delivery[3,4]. Whilst this provides a robust foundation for national health communication strategies, it also necessitates the urgency of population-specific oversight[4,5] of AI-generated content. Understanding how diverse segments of the Kuwaiti public interpret and act on algorithmically produced information is essential in terms of safeguarding trust, accuracy and clinical safety.

Methods Overview (derived from original work)

A structured online survey was disseminated among adult residents in Kuwait which assessed:

- Awareness and usage of AI-generated health information
- Perceived credibility of AI content
- Trust determinants (e.g. tone, platform, presence of source citation)
- Willingness to act on advice produced by AI without clinical verification

The survey combined Likert-scale questions and open-ended feedback. While originally presented in an international context, this communication revisits findings to derive specific applications within Kuwait's health policy and public engagement landscape.

Key findings

- Widespread exposure, conditional trust: 61% of participants had encountered AI-generated health information in recent months; however, only 38% expressed unqualified trust in such content without clinical validation[1].
- Age-related variations in trust: Younger participants were more open to using AI-generated health information- which relates to convenience and familiarity with digital tools. Older participants expressed greater scepticism about AI, highlighting the importance of tailoring communication strategies by age group.
- Accuracy checks: Participants identified that accuracy checks on these software, performed

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by professional healthcare professionals would be influencing their level of trust in AI-generated health information.
- Trust disparities: Participants revealed their concerns regarding accuracy, potential biases, privacy and ethical implications of health information generated by AI including the concern of "AI hallucinations" in some cases[6, 2].
- Professional amplification enhances credibility: Responses found that endorsement by a healthcare professional (e.g. Ministry of Health (MOH)) channel would significantly boost their trust in AI-generated content.

Discussion: a framework for responsible AI health messaging in Kuwait

The insights above expose a critical tension between the perceived and actual reliability of AI-generated health information. With 99% digitalised usage in Kuwait[3,4], it offers an ideal testing ground in terms of integrating AI tools into public health strategies. However, the absence of localised regulation might create a potential for misinformation and erosion of clinical authority. Correct use of AI technologies enables the public timely access to general medical knowledge and fosters proactive health behaviours. Health professionals may also benefit from reducing routine inquiries and open pathways for more digitally engaged care. Thus, responsible AI use can broaden Kuwait's digital agenda through enhancing health systems efficiency[3,7], reducing misinformation and aligning with global benchmarks in innovation and ethical governance. This can become an opportunity to lead the GCC in developing AI governance structures, protecting patients without stifling innovation. Current dynamics suggest that language tone, cultural alignments and institutional endorsements shape public trust more than digital accuracy alone.

Strategic recommendations

1. Establish a National Digital Health Literacy Agenda

Develop state-led programs—via MOH and KIMS[3] — to promote critical thinking, digital scepticism and safe information-seeking behaviours among the public and when to consult healthcare professionals.

2. Amplification through education

Allow public use of AI tools but require platforms to disclose whether content is AI-generated[2,7]. Impose digital ethics education in undergraduate and postgraduate medical progams, equipping healthcare professionals to engage with patients relying on AI-generated content.

3. Alignment with clinical authority

Train healthcare professionals to acknowledge, engage and redirect patients using AI tools. MOH, in collaboration with academic institutions, could publish a regulatory framework specifying requirements and standards.

CONCLUSION

AI-driven health information is reshaping the outlines of patient engagement in Kuwait. As this exposure increases, scepticism rises along with it. Thus, as institutional trust remains high and public reliance on digital content continues to grow, the opportunity to lead the region in ethical AI governance is clear. By combining patient education, regulatory clarity and clinician vigilance, Kuwait can build a sustainable and trust-based model for future-facing health communication.

ACKNOWLEDGMENT

This manuscript draws upon insights from the author's (Ashkanani, J) previously published research in Medical Writing and has been substantially adapted to present original analysis within the Kuwaiti healthcare policy context. No data duplication or textual replication has occurred.

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Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

Kuwait Medical Journal 2025; 57 (4): 274 - 276

Outcomes and Complications of Total Hip Arthroplasty for Crowe Type-IV Dysplasia of the Hip: An International Multicenter Study

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INTRODUCTION
Crowe type-IV developmental dysplasia of the hip (DDH) represents the most severe form of hip dislocation and poses major technical challenges for total hip arthroplasty (THA). This study aimed to evaluate outcomes and complications of THA in Crowe IV hips across multiple international centers, highlighting outcomes that may be relevant across practices in technique and implant selection.

METHODS
A retrospective review of 37 patients (49 hips) who had Crowe type-IV DDH who underwent THA between 2013 and 2022 at four centers in three countries was conducted. Clinical and radiographic data included Harris Hip Score (HHS), Oxford Hip Score (OHS), leg-length discrepancy (LLD), component positioning, and complications. Subtrochanteric osteotomy, surgical approach, and implant type were documented. The mean follow-up was 7.8 years (range, three to 12).

RESULTS
The LLD improved from 4.10 ± 1.20 cm preoperatively to 0.70 ± 0.42 cm postoperatively ($P < 0.001$). The HHS improved from 36.7 to 80.1 ($P < 0.001$) and OHS from 14.0 to 40.2 ($P < 0.001$). Abductor lurch decreased from 100 to 29.7%. Return to independent mobility was achieved in 81% of patients. Shortening osteotomy was performed in 64.9% of cases. Complications occurred in 21% of patients (16% of hips); the most common was periprosthetic fracture (n = five, 10%), and osteotomy nonunion occurred in two cases (4.1%), one of which was associated with overlengthening and required revision with a shortening osteotomy. There were no dislocations or infections reported. Kaplan-Meier analysis of 37 patients showed 97.3% implant survival at a mean 7.6-year follow-up, with only one early revision. Outcomes between unilateral and bilateral DDH were similar.

CONCLUSION
A THA for Crowe type-IV DDH can provide good outcomes with careful planning, restoration of the hip center, and leg-length adjustment. However, variable functional recovery and a relatively high complication rate, particularly with tapered stems, warrant caution, and surgeons should set realistic expectations, as not all patients achieve optimal results.

Sex Differences in the Association of Obesity with Prediabetes and Dyslipidemia Among Adolescents: A Cross-Sectional Study

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Obes Sci Pract. 2025 Nov 11;11(6):e70096. doi: 10.1002/osp4.70096. eCollection 2025 Dec.

Background
Limited knowledge exists on whether obesity during early life stages demonstrates sex-specific associations with cardiometabolic conditions. Therefore, this study aimed to determine if the association of obesity with prediabetes and dyslipidemia differs according to sex among adolescents.

Methods
Adolescents aged 14-19 years were enrolled in a cross-sectional study. Capillary blood was used to measure glycated hemoglobin and lipids. Prediabetes and dyslipidemia were determined according to international guidelines. Associations and statistical interactions (body mass index-for-age × sex) were evaluated using multivariable logistic regression models.

Results
Data from a total of 1584 adolescents (826 female participants) were analyzed in the current report. Obesity (38.6% vs. 24.4%) and dyslipidemia (54.2% vs. 36.7%) were more prevalent in male than female participants; however, prediabetes prevalence did not differ between male and female participants (34.8% vs. 33.8%). The association between obesity and prediabetes differed according to sex ($P_{interaction} = 0.046$), with obesity showing a stronger association among female participants (adjusted odds ratios [aOR]: 3.24; 95% confidence interval [CI]: 2.25, 4.66) compared with male participants (aOR: 1.64; 95% CI: 1.12, 2.39). However, obesity showed a stronger association with dyslipidemia among male participants (aOR: 2.74; 95% CI: 1.93, 3.90) compared with female participants (aOR: 1.49; 95% CI: 1.04, 2.13; $P_{interaction} = 0.016$).

Conclusion
Obesity demonstrated sex-specific associations with cardiometabolic conditions in adolescents, showing a stronger association with prediabetes in females but with dyslipidemia in males.

Probiotic Lactobacillus casei Inhibits Oral Squamous Cell Carcinoma Growth and Induces Apoptosis In Vitro

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Int Dent J. 2025 Oct 31;76(1):103960. doi: 10.1016/j.identj.2025.103960. Online ahead of print.

OBJECTIVES
Oral squamous cell carcinoma (OSCC) is a significant cause of mortality. Probiotic bacteria like Lactobacillus casei have shown anti-cancer and immune-modulatory properties. This study aimed to investigate the anti-proliferative effects of L. casei on OSCC and its apoptotic mechanisms.

METHODS
Human head and neck squamous cell carcinoma (HNSCC) cells of the oral cavity (HNO97 cell line) were exposed to L. casei at concentrations of 1×10^8 CFU/ml and 5×10^7 CFU/ml, and the viability of HNO97 cells was assessed by MTT assay. Bacterial attachment was studied by live confocal microscopy, and apoptosis was confirmed by Nexin staining. The underlying mechanisms of apoptosis were studied by examining the expression of the TRAIL gene and its encoding protein, TNF-related apoptosis-inducing ligand (TRAIL) by RT-PCR and ELISA, respectively.

RESULTS
L. casei adhered to HNO97 cells and demonstrated an anti-proliferative effect, reducing cell viability of L. casei-treated HNO97 cells by 50%. Compared to untreated cells (90%), only 45% of L. casei-treated cells remained live and intact, with 20.5%-31.5% of cells in the late apoptotic stage. Further, the cell growth inhibition was accompanied by the upregulation of the TRAIL gene, which surprisingly did not corroborate with the expression of TRAIL protein in the HNO97 cells.
Conclusions: L. casei exhibits anti-proliferative and apoptotic effects on OSCC. The TRAIL gene upregulation without translation into TRAIL protein suggests a potential caspase-independent mechanism of apoptosis. Further exploration is needed to understand the inhibitory effects of L. casei and its potential

Kuwait Heart Foundation Registry of Acute Coronary Events: Design and Rationale of Large Contemporary Registry of Acute Coronary Syndromes

Mohammad Zubaid [1], Mousa Akbar [2], Abdullah Alenezi [3], Fahad Alenezi [4], Mohammad Aljarallah [5], Ahmad Alkharaza [6], Samah Alkharji [6], Darar Alkhudair [7], Muhammad Alshammari [8], Abdullah Esmaiel [9], Ibrahim Farrag [9]
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Heart Views. 2025 Apr-Jun;26(2):71-74. doi: 10.4103/heartviews.heartviews_26_25. Epub 2025 Oct 1.

AIM
The aim of this study was to describe the design and rationale of a registry of patients with acute coronary syndromes (ACSs) in Kuwait.

METHODS
Kuwait Heart Foundation Registry of Acute Coronary Events (KHF RACEs) is a prospective, multicenter, observational, cohort-based registry of consecutive patients admitted to hospitals in Kuwait with a working diagnosis of ACSs. The trial is registered at "Clinical Trials.gov" number NCT05857735 and enrollment started on May 15, 2023. It involved 8 hospitals and 124 investigators. Data were collected prospectively and entered into an online system specifically created for this registry. This included demographic data, risk factors, past medical history, medications at admission and discharge, pertinent findings on physical examination at admission, inhospital investigations, and management including cardiac catheterization and subsequent percutaneous coronary interventions. The observed outcomes included inhospital and 30-day mortality and major adverse cardiac events.

CONCLUSION
KHF RACE is the largest contemporary ACS registry in the Middle East. It provides an example of how large multicenter registries can be carried out successfully in this part of the world. Results are expected to shed light on the adherence to guidelines in our daily practice and its influence on patients' outcomes. Several analyses of the data are planned, including the influence of age, gender, diabetes, and insurance status on outcomes. Other planned analyses will be relating to cardiac catheterization and its related outcomes.

Forthcoming Conferences and Meetings

Compiled and edited by
Vineetha Elizabeth Mammen

Kuwait Medical Journal 2025; 57 (4): 277 - 285

International Conference on **Medical Health Science, Pharmacology & Bio Technology**
Dec 01, 2025
United States, New York
Organized by: ISSRD
Email ID: papers.issrd@gmail.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Dec 01, 2025
Australia, Sydney
Organized by: WRFER
Email ID: contact.wrfer@gmail.com

International Conference on Recent Advances in **Medical and Health Sciences**
Dec 02, 2025
United Arab Emirates, Ras al Khaimah
Organized by: Academics world
Email ID: info@academicsworld.org

International Conference on **Health and Medicine**
Dec 02, 2025
United Arab Emirates, Sharjah
Organized by: ISER
Email ID: info@iser.co

International Conference on **Women's Mental Health**
Dec 03, 2025
Canada, Abbotsford
Organized by: Science Guru
Email ID: info.scienceguru@gmail.com

International Conference on **Positive Psychology and Mental Health**
Dec 03, 2025
India, Kodaikanal, Tamil Nadu
Organized by: IISTEM
Email ID: papers.iistem@gmail.com

World Conference on **Bioethics, Medical Ethics and Health Law**
Dec 04, 2025
Armenia, Vanadzor
Organized by: All Conference Series
Email ID: info.allconferenceseries@gmail.com

International Conference on **Medical and Health Sciences**
Dec 05, 2025
United Kingdom, Bristol
Organized by: Science Plus
Email ID: papers.scienceplus@gmail.com

International Conference on **Public Health and Nutrition**
Dec 05, 2025
Italy, Rome
Organized by: aserd.org
Email ID: info.aserd@gmail.com

International Conference on **Pediatrics and Child Health**
Dec 05, 2025
India, Pune, Maharashtra
Organized by: Science Guru
Email ID: info.scienceguru@gmail.com

International Conference on **Medical, Pharmaceutical and Health Sciences**
Dec 06, 2025
Japan, Yokohama
Organized by: GSRD
Email ID: info.gsrd@gmail.com

International Conference on Recent Advancement in **Medical Education, Nursing and Health Sciences**
Dec 07, 2025
Japan, Kobe
Organized by: IRF Conference
Email ID: info.irfconference@gmail.com

International Research Conference on **COVID-19** and its Impact on **Mental Health**
Dec 07, 2025
Czech Republic, Brno
Organized by: Research Conferences
Email ID: info.researchconferences@gmail.com

9th Annual Congress on **Women's Health, Wellness and Reproductive Medicine**
Dec 08, 2025
France, Paris
Organized by: womenshealth.a
Email ID: contact@europeconferences.net

International Conference on **Youth Mental Health**
Dec 09, 2025
United States, Texas
Organized by: Canadian Association for Scientific Research and Publication
Email ID: info@casrp.org

International Conference on **Women's Health and Breast Cancer**
Dec 09, 2025
Bahrain, Muharraq
Organized by: Science and Research
Email ID: summit.scienceandresearch@gmail.com

International Conference on **Epidemiology and Public Health**
Dec 09, 2025
United Kingdom, Reading
Organized by: Japanese Society for Academic Research and Publication
Email ID: info.jsarap@gmail.com

International Conference on **Medical and Health Sciences**
Dec 10, 2025
Egypt, Cairo
Organized by: Academics conference
Email ID: papers.academicsconference@gmail.com

The International Arabian Summit on **Gynecology & Women's Health**
Dec 10, 2025
United Arab Emirates, Dubai
Organized by: Conference minds
Email ID: Contact@ConferenceMinds.com

International Conference on **Urology and Renal Health**
Dec 11, 2025
Hong Kong, Kowloon City
Organized by: Science and research
Email ID: summit.scienceandresearch@gmail.com

9th Asia-Pacific **Bone Health** Conference
Dec 11, 2025
Japan, Tokyo
Organized by: iof-regional
Email ID: secretariat@iof-regional.org

International Conference on **Food, Nutrition, Health & Lifestyle**
Dec 12, 2025
France, Paris
Organized by: Biofora
Email ID: papers.biofora@gmail.com

International Conference on **Medical and Health Sciences**
Dec 12, 2025
United States, Florida
Organized by: Inderscience
Email ID: info.inderscience@gmail.com

International Conference on **Trauma Care and Mental Health**
Dec 13, 2025
Belgium, Ghent
Organized by: Universal Research Cluster
Email ID: info.universalconference@gmail.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Dec 14, 2025
Russia, Moscow
Organized by: WRFER
Email ID: contact.wrfer@gmail.com

International Conference on **Physical Education, Health and Sports**
Dec 14, 2025
Russia, Moscow
Organized by: Global Conference
Email ID: summit.globalconference@gmail.com

International Conference on **Sexual and Reproductive Health**
Dec 15, 2025
United States, Los Angeles, California
Organized by: Canadian Association for Scientific Research and Publication
Email ID: info@casrp.org

International Conference on **Gynecology, Obstetrics and Women's Health**
Dec 16, 2025
Ecuador, Quito
Organized by: Research Era
Email ID: info.researcheraconference@gmail.com

International Conference on **Pediatrics, Perinatology and Child Health**
Dec 16, 2025
Canada, St. Johns, Newfoundland and Labrador
Organized by: Research Era
Email ID: info.researcheraconference@gmail.com

International Conference on Recent Advancement in **Medical Education, Nursing and Health Sciences**
Dec 17, 2025
Australia, Sydney
Organized by: IRF Conference
Email ID: info.irfconference@gmail.com

International Research Conference on **COVID-19** and its Impact on **Mental Health**
Dec 17, 2025
Japan, Nagoya
Organized by: Research Conferences
Email ID: info.researchconferences@gmail.com

International Conference on **Urology and Renal Health**
Dec 18, 2025
Canada, Edmonton, Alberta
Organized by: Science Guru
Email ID: info.scienceguru@gmail.com

International Conference on **Health Policy Statistics**
Dec 19, 2025
United Kingdom, Glasgow
Organized by: United Science Research Society
Email ID: info.usrsociety@gmail.com

International Conference on **Public Health and Nutrition**
Dec 19, 2025
Canada, British Columbia
Organized by: Japanese Society for Academic Research and Publication
Email ID: info.jsarap@gmail.com

International Conference on **Smart Living and Public Health**
Dec 20, 2025
United States, Philadelphia, Pennsylvania
Organized by: Canadian Association for Scientific Research and Publication
Email ID: info@casrp.org

International Conference on **Clinical Child Psychology and Mental Health**
Dec 20, 2025
Germany, Munich
Organized by: Universal Research Cluster
Email ID: info.universalconference@gmail.com

International Conference on **Family Medicine and Integrative Health**
Dec 21, 2025
Germany, Wurzburg
Organized by: Conference Research Network
Email ID: info@conferenceresearchnetwork.com

International Conference on **Physical Education, Health and Sports**
Dec 22, 2025
Egypt, Cairo
Organized by: All Conference Series
Email ID: info.allconferenceseries@gmail.com

International Conference on Advances in **Medical Science and Health care**
Dec 22, 2025
Spain, Madrid
Organized by: Academics era
Email ID: info@academicsera.com

Global Conference on **Health and Lifestyle**
Dec 22, 2025
Spain, Malaga
Organized by: Global Science Society
Email ID: info@globalsciencesociety.com

International Conference on **Mental Health at the Workplace**
Dec 23, 2025
Italy, Verona
Organized by: Global Science Society
Email ID: info@globalsciencesociety.com

International Conference on **Public Health and Infectious Diseases**
Dec 23, 2025
United States, Seattle, Washington
Organized by: Global Science Society
Email ID: info@globalsciencesociety.com

International Conference on **Medical Health Science, Pharmacology & Bio Technology**
Dec 24, 2025
Italy, Rome
Organized by: ISSRD
Email ID: papers.issrd@gmail.com

International Conference on **Pediatrics, Perinatology and Child Health**
Dec 24, 2025
Australia, Melbourne
Organized by: All Conference Series
Email ID: info.allconferenceseries@gmail.com

World Congress on **Women's Health, Reproduction and Fertility**
Dec 25, 2025
United Kingdom, Newcastle
Organized by: Science Guru
Email ID: info.scienceguru@gmail.com

International Research Conference on **COVID-19** and its Impact on **Mental Health**
Dec 27, 2025
Singapore, Singapore
Organized by: Research Conferences
Email ID: info.researchconferences@gmail.com

International Conference on Recent Advances in **Medical and Health Sciences**
Dec 28, 2025
Kuwait, Kuwait City
Organized by: Academics world
Email ID: info@academicsworld.org

International Conference on **Health Care Reform, Health Economics and Health Policy**
Dec 28, 2025
United States, Texas
Organized by: Conference Research Network
Email ID: info@conferenceresearchnetwork.com

13th International Conference on **Hospital Management and Health Care**
Dec 29, 2025
Netherlands, Amsterdam
Organized by: Hospital management
Email ID: contact@speakermeeting.com

International World Research Congress on **Dentistry and Oral Health**
Dec 30, 2025
South Korea, Seoul
Organized by: Biofora
Email ID: papers.biofora@gmail.com

International Conference on **Physical Education, Health and Sports**
Dec 30, 2025
United Kingdom, Liverpool
Organized by: Global Science Networks
Email ID: info.globalsciencenetworks@gmail.com

International Conference on **Pediatrics, Perinatology and Child Health**
Dec 31, 2025
Czech Republic, Prague
Organized by: Global Science Networks
Email ID: info.globalsciencenetworks@gmail.com

International Conference on **Mental Health and Psychiatry**
Jan 02, 2026
Spain, Seville
Organized by: Universal Research Cluster
Email ID: info.universalconference@gmail.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Jan 03, 2026
United Arab Emirates, Dubai
Organized by: WRFER
Email ID: contact.wrfer@gmail.com

International Conference on **Urology and Renal Health**
Jan 03, 2026
Australia, Brisbane
Organized by: United Science Research Society
Email ID: info.usrsociety@gmail.com

International World Research Congress on **Dentistry and Oral Health**
Jan 03, 2026
United States, Denver, Colorado
Organized by: Biofora
Email ID: papers.biofora@gmail.com

International Conference on **Clinical Child Psychology and Mental Health**
Jan 04, 2026
United Arab Emirates, Dubai
Organized by: Universal Research Cluster
Email ID: info.universalconference@gmail.com

International Conference on **Trauma Care and Mental Health**
Jan 06, 2026
United Kingdom, London
Organized by: Universal Research Cluster
Email ID: info.universalconference@gmail.com

International Conference on **Gynecology, Obstetrics and Women's Health**
Jan 07, 2026
United States, Orlando, Florida
Organized by: Academic Research Network
Email ID: info@academicresearchnetwork.com

International Congress on **Physical Activity and Public Health**
Jan 10, 2026
Italy, Prato
Organized by: All Conference Series
Email ID: info.allconferenceseries@gmail.com

International Conference on **Science, Health and Medicine**
Jan 11, 2026
Azerbaijan, Baku
Organized by: ISER
Email ID: info@iser.co

International Conference on **Pediatrics, Perinatology and Child Health**
Jan 11, 2026
Italy, Prato
Organized by: United Research
Email ID: info.unitedresearch@gmail.com

International Conference on **Women's Health and Breast Cancer**
Jan 12, 2026
Uzbekistan, Kattakurgan
Organized by: Science and research
Email ID: summit.scienceandresearch@gmail.com

International Conference on **Biology Education and Health**
Jan 12, 2026
Slovakia, Presov
Organized by: Conference Research Network
Email ID: info@conferenceresearchnetwork.com

International Conference on **Medical and Health Sciences**
Jan 12, 2026
Saudi Arabia, Dammam
Organized by: ISERD
Email ID: info@iserd.co

International Conference on **Trauma Care and Mental Health**
Jan 13, 2026
Jordan, Amman
Organized by: Universal Research Cluster
Email ID: info.universalconference@gmail.com

International Conference on **Digital Health and Telemedicine**
Jan 13, 2026
Oman, Muscat
Organized by: aserd.org
Email ID: info.aserd@gmail.com

International Conference on **Psychology and Mental Health**
Jan 15, 2026
China, Chengdu
Organized by: ISER
Email ID: info@iser.co

International Conference on **Health Care Reform, Health Economics and Health Policy**
Jan 15, 2026
German, Nuremberg
Organized by: Inexed Conferences
Email ID: contact.inexed@gmail.com

International Conference on **Epidemiology and Public Health**
Jan 16, 2026
Argentina, Buenos Aires
Organized by: Science and research
Email ID: summit.scienceandresearch@gmail.com

International Conference on **Health Policy Statistics**
Jan 17, 2026
Saudi Arabia, Mecca
Organized by: United Science Research Society
Email ID: info.usrsociety@gmail.com

World Conference on **Bioethics, Medical Ethics and Health Law**
Jan 17, 2026
United States, San Diego, California
Organized by: Academic Research Network
Email ID: info@academicresearchnetwork.com

15th Pan Arab **Blood Transfusion Conference**
Jan 18-21, 2026
Kuwait, Grand Hyatt
Organized by: Ministry of Health, Kuwait
Email ID: info@pabt2026.com

International Conference on Recent Advances in **Medical and Health Sciences**
Jan 18, 2026
United Kingdom, London
Organized by: Academics world
Email ID: info@academicsworld.org

International Conference on **Clinical Child Psychology and Mental Health**
Jan 18, 2026
Czech Republic, Bata
Organized by: Universal Research Cluster
Email ID: info.universalconference@gmail.com

5th Kuwait Pediatric **Stem Cell Transplant, Cellular & Gene Therapy** 2026
Jan 19-20, 2026
Kuwait, Four Seasons Hotel
Organized by: Ministry of Health, Kuwait
Website: www.kpsctc.com

International Conference on **Climate Change and Human Health Impacts**
Jan 19, 2026
Turkey, Istanbul
Organized by: International Society for Environment and Climate Change
Email ID: info.isfecc@gmail.com

International Conference on Advances in **Medical Science and Health Care**
Jan 20, 2026
Bahrain, Riffa
Organized by: Flexz conference
Email ID: flexzconference@gmail.com

International Conference on **Medical, Pharmaceutical and Health Sciences**
Jan 21, 2026
Japan, Kawasaki City
Organized by: GSRD
Email ID: info.gsrd@gmail.com

World Congress on **Women's Health, Reproduction and Fertility**
Jan 22, 2026
Australia, Melbourne
Organized by: Academic Research Network
Email ID: info@academicresearchnetwork.com

International Conference on **Epidemiology & Public Health**
Jan 23, 2026
South Africa, Cape Town
Organized by: Meeting fora
Email ID: info@meetingfora.com

International Conference on **Biology Education and Health Education in Sustainability**
Jan 24, 2026
United States, Los Angeles, California
Organized by: Global Conference
Email ID: summit.globalconference@gmail.com

International Conference on **Mental Health and Treatment**
Jan 26, 2026
Kuwait, Salmiya
Organized by: All Conference Series
Email ID: info.allconferenceseries@gmail.com

International World Research Congress on **Dentistry and Oral Health**
Jan 28, 2026
Qatar, Doha
Organized by: Biofora
Email ID: papers.biofora@gmail.com

International Conference on **Epidemiology and Public Health**
Jan 29, 2026
United Arab Emirates, Ajman
Organized by: United Science Research Society
Email ID: info.usrsociety@gmail.com

International Conference on **Positive Psychology and Mental Health**
Jan 29, 2026
India, Bhubaneswar, Odisha
Organized by: IISTEM
Email ID: papers.iistem@gmail.com

World Conference on **Medicine, Yoga and Mental Health**
Jan 30, 2026
Sweden, Malmo Municipality
Organized by: Universal Research Cluster
Email ID: info.universalconference@gmail.com

International Conference on **Trauma Care and Mental Health**
Jan 30, 2026
Japan, Kyoto
Organized by: Universal Research Cluster
Email ID: info.universalconference@gmail.com

International Conference on Recent Advances in **Medical and Health Sciences** (ICRAMHS)
Feb 01, 2026
Ireland, Dublin
Organized by: Academics world
Email ID: info@academicsworld.org

International Conference on **Trauma Care and Mental Health** (ICTCMH)
Feb 03, 2026
Canada, Abbotsford
Organized by: Universal Research Cluster
Email ID: info.universalconference@gmail.com

International Conference on **Epidemiology and Public Health** (ICEPH)
Feb 03, 2026
Hungary, Szeged
Organized by: Japanese Society for Academic Research and Publication
Email ID: info.jsarap@gmail.com

Kuwait Annual **Radiology** Conference 2026
Feb 4-7, 2026
Kuwait, Waldorf Astoria
Organized by: Ministry of Health, Kuwait

World Congress on **Public Health & Global Wellness** (WCPHGW)
Feb 04, 2026
Maldives, Male
Organized by: World Research Society
Email ID: contact@worldresearchsociety.com

International World Research Congress on **Dentistry and Oral Health** (IWRCDOH)
Feb 04, 2026
Germany, Nuremberg
Organized by: Biofora
Email ID: papers.biofora@gmail.com

Kuwait **Dermatology** Council Conference 2026
Feb 5-6, 2026
Kuwait, Four Seasons Hotel
Organized by: Ministry of Health, Kuwait
Website: www.dermacouncilconferencekw.com

International Conference on **Medical & Health Science** (ICMHS)
Feb 06, 2026
Lebanon, Beirut
Organized by: Research fora
Email ID: info@researchfora.com

International Conference on **Animal Health Surveillance** (ICAHS)
Feb 07, 2026
Bahrain, Manama
Organized by: Academic Research Network
Email ID: info@academicresearchnetwork.com

International Conference on **Medical, Pharmaceutical and Health Sciences** (ICMPH)
Feb 08, 2026
United Kingdom, London
Organized by: GSRD
Email ID: info.gsrd@gmail.com

International Conference on **Public Health and Infectious Diseases** (ICPHID)
Feb 08, 2026
Bulgaria, Sofia
Organized by: Global Conference
Email ID: summit.globalconference@gmail.com

World Health Expo
Feb 09, 2026
United Arab Emirates, Dubai
Organized by: showsbee
Email ID: bill.newmaker@gmail.com

International Conference on **Health and Medicine** (ICHM)
Feb 10, 2026
Qatar, Doha
Organized by: ISER
Email ID: info@iser.co

International Conference on **Physical Education, Health, and Sports** (ICPEHS)
Feb 10, 2026
Japan, Tokyo
Organized by: Inexed Conferences
Email ID: contact.inexed@gmail.com

Kuwait Derma - Annual Conference for **Dermatology, Laser and Aesthetic Medicine**
Feb 12-14, 2026
Kuwait, Grand Hyatt Hotel
Organized by: Kuwait Society of Dermatologists
Website: https://kuwaitderma2026.com/

12th Kuwait **Anesthesia, Critical Care & Pain Management** Conference 2026
Feb 13-15, 2026
Kuwait, The Regency Hotel
Organized by: Ministry of Health, Kuwait
Email ID: https://kuwaitanesthesia2026.com/

International Conference on Advances in **Medical Science and Health care** (ICAMSH)
Feb 13, 2026
United Arab Emirates, Riyadh
Organized by: Academics era
Email ID: info@academicsera.com

International Conference on **Epidemiology and Public Health** (ICEPH)
Feb 13, 2026
Australia, Sydney
Organized by: Science and research
Email ID: summit.scienceandresearch@gmail.com

International World Research Congress on **Dentistry and Oral Health** (IWRCDOH)
Feb 15, 2026
United Arab Emirates, Dubai
Organized by: Biofora
Email ID: papers.biofora@gmail.com

International Conference on **Public Health Care System** (ICPHCS)
Feb 16, 2026
New Zealand, Napier
Organized by: All Conference Series
Email ID: info.allconferenceseries@gmail.com

International Conference on **Smart Living and Public Health** (ICSLPH)
Feb 17, 2026
United States, Charlotte, North Carolina
Organized by: Canadian Association for Scientific Research and Publication
Email ID: info@casrp.org

International Conference on **Clinical Child Psychology and Mental Health** (ICCCPMH)
Feb 18, 2026
Taiwan, Taichung
Organized by: Universal Research Cluster
Email ID: info.universalconference@gmail.com

International Conference on **Trauma Care and Mental Health** (ICTCMH)
Feb 20, 2026
Brazil, Macapa
Organized by: Universal Research Cluster
Email ID: info.universalconference@gmail.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences** (ICRAMMHS)
Feb 20, 2026
Turkey, Ankara
Organized by: WRFER
Email ID: contact.wrfer@gmail.com

International Conference on **Paediatrics and Child Health** (ICPCH)
Feb 23, 2026
Spain, Malaga
Organized by: Global Conference
Email ID: summit.globalconference@gmail.com

International Conference on **Emergency Medicine and Public Health** (ICEMPH)
Feb 23, 2026
Saudi Arabia, Al Khobar
Organized by: Global Conference
Email ID: summit.globalconference@gmail.com

International Conference on **Mental Health and Human Resilience** (ICMHHR)
Feb 27, 2026
Australia, Melbourne
Organized by: United Research
Email ID: info.unitedresearch@gmail.com

International Conference on Recent Advances in **Medical and Health Sciences** (ICRAMHS)
Feb 28, 2026
Kuwait, Kuwait City
Organized by: Academics world
Email ID: info@academicsworld.org

International Conference on **Youth Mental Health** (ICYMH)
Mar 01, 2026
United States, Chicago, Illinois
Organized by: Canadian Association for Scientific Research and Publication
Email ID: info@casrp.org

International Conference on **Climate Change and Human Health Impacts** (I3C2HI)
Mar 02, 2026
Germany, Hamburg
Organized by: International Society for Environment and Climate Change
Email ID: info.isfecc@gmail.com

International Conference on **Public Health and Healthcare Research** (ICPHHR)
Mar 04, 2026
Turkey, Ephesus
Organized by: Universal Research Cluster
Email ID: info.universalconference@gmail.com

International Conference on **Epidemiology and Public Health** (ICEPH)
Mar 04, 2026
Greece, Ioannina
Organized by: aserd.org
Email ID: info.aserd@gmail.com

International Conference on Advances in **Medical Science and Health care** (ICAMSH)
Mar 05, 2026
New Zealand, Auckland
Organized by: Academics era
Email ID: info@academicsera.com

International World Research Congress on **Dentistry and Oral Health** (IWRCDOH)
Mar 08, 2026
United States, Chicago, Illinois
Organized by: Biofora
Email ID: papers.biofora@gmail.com

41st Asian **Dental & Oral Health** Conclave
Mar 09, 2026
United Arab Emirates, Dubai
Organized by: Dental congress
Email ID: contact@conferenceseries.com

International Conference on **Youth Mental Health** (ICYMH)
Mar 10, 2026
France, Paris
Organized by: Meeting fora
Email ID: info@meetingfora.com

International Conference on **Alternative Medicine and Integrative Health** (ICAMIH)
Mar 12, 2026
Bulgaria, Sofia
Organized by: Conference Research Network
Email ID: info@conferenceresearchnetwork.com

International Conference on **Mental Health at the Workplace** (ICMHW)
Mar 14, 2026
United Kingdom, Portsmouth
Organized by: Inexed Conferences
Email ID: contact.inexed@gmail.com

World Congress on **Women's Health, Reproduction and Fertility** (WCWRF)
Mar 16, 2026
United States, Hartford, Connecticut
Organized by: Research Era
Email ID: info.researcheraconference@gmail.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences** (ICRAMMHS)
Mar 17, 2026
United Kingdom, Cambridge
Organized by: WRFER
Email ID: contact.wrfer@gmail.com

International Conference on **Sexual and Reproductive Health** (ICSRH)
Mar 20, 2026
Japan, Osaka
Organized by: Canadian Association for Scientific Research and Publication
Email ID: info@casrp.org

International Conference on **Health Care Reform, Health Economics and Health Policy** (ICHCRHEHP)
Mar 20, 2026
Germany, Frankfurt
Organized by: Society for Engineering and Research
Email ID: sfer.conference@gmail.com

International Conference on Recent Advances in **Medical and Health Sciences** (ICRAMHS)
Mar 21, 2026
Czech Republic, Prague
Organized by: Academics world
Email ID: info@academicsworld.org

International Conference on **Pediatrics, Perinatology and Child Health** (ICPPCH)
Mar 22, 2026
Australia, Vienna
Organized by: United Research
Email ID: info.unitedresearch@gmail.com

3rd World Congress on **Addiction Medicine, Behavioral Health and Psychiatry**
Mar 23, 2026
United Kingdom, London
Organized by: Addiction scholars conferences
Email ID: info@scholarsconferences.com

World Conference on **Bioethics, Medical Ethics and Health Law** (WCBMEHL)
Mar 23, 2026
Denmark, Billund
Organized by: Global Science Networks
Email ID: info.globalsciencenetworks@gmail.com

International Conference on **Trauma Care and Mental Health** (ICTCMH)
Mar 26, 2026
Azerbaijan, Baku
Organized by: Universal Research Cluster
Email ID: info.universalconference@gmail.com

World Conference on **Lung Health** (WCLH)
Mar 27, 2026
Qatar, Doha
Organized by: Conference Research Network
Email ID: info@conferenceresearchnetwork.com

International Conference on **Public Health and Infectious Diseases** (ICPHID)
Mar 28, 2026
Spain, Seville
Organized by: Global Conference
Email ID: summit.globalconference@gmail.com

International Research Conference on **COVID-19** and its Impact on **Mental Health** (IRCCIMH)
Mar 28, 2026
United States, Springfield, Illinois
Organized by: Research Conferences
Email ID: info.researchconferences@gmail.com

International Conference on **Sports Science, Health and Nutrition** (ICSSHN)
Mar 30, 2026
United States, Hartford, Connecticut
Organized by: Conference Research Network
Email ID: info@conferenceresearchnetwork.com

International Conference on **Women's Mental Health** (ICWMH)
Mar 31, 2026
United Kingdom, London
Organized by: United Science Research Society
Email ID: info.usrsociety@gmail.com

WHO-Facts Sheet

1. Candidiasis
2. Diabetes
3. Hypertension
4. Malaria
5. Obesity and overweight

Compiled and edited by
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1. Candidiasis

KEY FACTS

- Candidiasis is a common fungal infection mostly caused by yeasts of the Candida species.
- Candidiasis can affect various parts of the body, including the mouth (oral candidiasis or thrush), vagina (vaginal candidiasis), oesophagus, skin and bloodstream (invasive candidiasis).
- Vulvovaginal candidiasis (VVC), or vaginal yeast infection, affects millions of women worldwide.
- Oral candidiasis is more common in babies, people with weakened immune systems, individuals using steroid inhalers, denture wearers, people who inject drugs and those with conditions like uncontrolled diabetes.
- Candidiasis can be treated with antifungal medications. Treatment can be more complex when infections are caused by drug-resistant species.
- Candida auris is a fungal species that can be multi-drug resistant, cause invasive disease and lead to hospital outbreaks.

Overview

Candidiasis, also known as a yeast infection, is a fungal infection primarily caused by Candida yeasts. Many of these yeasts are normally present in the human body as part of the natural microbiome, or in the surrounding environment, often without causing any problems. However, when conditions allow, such as a weakened immune system or changes in the body's natural environment (e.g., due to hormonal changes, antibiotic use or other reasons), Candida can overgrow and cause an infection. Candidiasis can affect various parts of the body, leading to a range of symptoms.

Common types of candidiasis include vulvovaginal candidiasis (vaginal yeast infection), which affects the vagina; oral candidiasis (thrush), which affects the mouth and throat; and invasive candidiasis, which is a serious systemic infection that can affect any organ in the body. Invasive candidiasis is a significant concern in critically ill and immunocompromised patients.

While generally treatable with antifungal medications, some types can be hard to treat. For example, Candida auris is a multi-drug-resistant fungal species that has been responsible for outbreaks in hospitals and long-term care facilities. Prevention and proper management are crucial to reduce the risk and spread of these infections.

Vaginal yeast infections (vulvovaginal candidiasis)

Vulvovaginal candidiasis (VVC), commonly known as a vaginal yeast infection, is an infection of the vagina and vulva caused by an overgrowth of Candida yeast.

Causes

Several factors can contribute to the overgrowth of Candida in the vagina. Changes in the vagina's normal acidity, natural microbiome or hormonal balance can create an environment that encourages yeast overgrowth. Antibiotics can kill healthy bacteria in the vagina, which help maintain balance and keep yeast in check. Fluctuations in hormone levels, such as those during pregnancy, the menstrual cycle or the use of birth control pills, can increase the risk of yeast infections. Uncontrolled diabetes, leading to persistently high blood sugar levels, can also promote yeast growth. Additionally, a weakened immune system due to conditions or medications can make one more susceptible to yeast infections.

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Symptoms

The symptoms of a vaginal yeast infection can be uncomfortable. Intense itching in the vagina and around the vulva is a common complaint. Redness and soreness of the vulva might also be experienced, accompanied by a thick, white, curd-like vaginal discharge. Painful urination and discomfort or pain during sexual intercourse can also occur. Yeast infections primarily affect the vagina and vulva and are not a typical cause of urinary tract infections.

Treatment

Treatment for vaginal yeast infections typically involves antifungal medications. Topical treatments, such as creams, ointments or suppositories containing antifungal medications like clotrimazole, are commonly used. Prescription oral antifungal drugs, such as fluconazole, are also available. However, resistance to some antifungal medications is spreading and treatment does not always work. Home remedies should be used with caution and discussed with a health-care provider before use.

Prevention

While not officially classified as a sexually transmitted infection, sexual activity can contribute to the development of VVC. Treating male partners is generally not recommended unless they exhibit symptoms themselves.

Oral Thrush

Oral thrush is a candidiasis that occurs in the mouth and throat.

Causes

Several factors can lead to the development of oral thrush. People with compromised or immature immune systems, such as infants, older people and individuals living with HIV, are more prone to oral thrush. Antibiotics can disrupt the normal balance of microorganisms in the mouth, allowing Candida to overgrow. Steroid inhalers for asthma can also increase the risk of oral thrush. Additionally, ill-fitting dentures or poor oral hygiene can create an environment conducive to yeast overgrowth.

Symptoms

Oral thrush is characterized by creamy, white lesions on the tongue, inner cheeks and gums, or hard white plaques that cannot be scraped off. Individuals may experience pain or soreness in the mouth, making it difficult to eat or swallow. Cracking and redness at the corners of the mouth, red, shiny patches on the palate or tongue, as well as altered or lost sense of taste, can also occur.

Treatment

Treatment for oral thrush typically involves antifungal medications. Topical treatments, such as antifungal mouthwashes or lozenges, are commonly used. Oral antifungal drugs may also be prescribed. Maintaining good oral hygiene through regular brushing and flossing can help prevent yeast overgrowth.

Thrush in babies

Thrush is a common condition in babies, especially newborns, often appearing as white patches on the tongue or inner cheeks. While generally not harmful, it can cause discomfort during feeding. Treatment typically involves a liquid antifungal medication prescribed by a doctor.

Invasive candidiasis

Hospitalized patients with cancer or who have received antibiotics, had invasive procedures such as intravenous catheters (drips) or had surgery can get invasive Candida infections, such as through the bloodstream. Some Candida species, including Candida auris, are developing resistance to antifungal drugs, making them difficult to eradicate from hospital surfaces and equipment. These infections are serious and require urgent intravenous antifungal therapy. Tests and treatments also need to improve and be more widely available, especially in low- and middle-income countries.

Candida and diet

There is extensive discussion about the connection between diet and candidiasis, including whether high sugar intake can cause yeast infections. Some individuals follow strict diets to limit yeast overgrowth, but scientific evidence supporting their effectiveness is limited. Consult a health-care professional or registered dietitian before making significant dietary changes.

Prevention

Maintaining good hygiene, especially in moist areas, is important in preventing candidiasis on the skin. Good oral hygiene, cleaning dentures properly, controlling diabetes, avoiding smoking and using steroid inhalers properly can help prevent oral candidiasis.

Using antibiotics only when prescribed and necessary can help prevent disruptions in the body's natural microbiome. Managing underlying conditions such as diabetes can reduce the risk of candidiasis. For those with weakened immune systems, regular medical check-ups and prophylactic antifungal medications may be necessary to prevent invasive candidiasis.

For vulvovaginal candidiasis, wearing cotton underwear and loose clothing, avoiding synthetic fabrics, changing out of sweaty gym wear and swimsuits quickly, and not douching can all help to prevent yeast infections. Avoiding scented or harsh personal care products can also help prevent irritation and reduce the risk of yeast infections.

Athletes and individuals who engage in intense physical activity, as well as children, should be mindful of their hygiene. In environments where physical contact is frequent (e.g. gyms and sports facilities), it is important to clean and dry equipment and clothing regularly.

WHO response

WHO recognizes the increasing global public health concern posed by fungal infections and is committed to addressing this threat through various initiatives.

In 2022, WHO published the first-ever fungal priority pathogens list (FPPL) to guide research, development and public health action.

In 2024, WHO published Recommendations for the treatment of Trichomonas vaginalis, Mycoplasma genitalium, Candida albicans, bacterial vaginosis, and human papillomavirus (anogenital warts).

In 2025, WHO published its first-ever reports on fungal tests and treatments. By prioritizing fungal pathogens and promoting evidence-based strategies, WHO aims to strengthen the global response to fungal infections and antifungal resistance, ultimately improving public health outcomes.

2. Diabetes

KEY FACTS

- The number of people living with diabetes rose from 200 million in 1990 to 830 million in 2022. Prevalence has been rising more rapidly in low- and middle-income countries than in high-income countries.
- More than half of people living with diabetes did not take medication for their diabetes in 2022. Diabetes treatment coverage was lowest in low- and middle-income countries.
- Diabetes causes blindness, kidney failure, heart attacks, stroke and lower limb amputation.
- In 2021, diabetes and kidney disease due to diabetes caused over 2 million deaths. In addition, around 11% of cardiovascular deaths were caused by high blood glucose.
- A healthy diet, regular physical activity, maintaining a normal body weight and avoiding tobacco use are ways to prevent or delay the onset of type 2 diabetes.
- Diabetes can be treated and its consequences avoided or delayed with diet, physical activity, medication and regular screening and treatment for complications.

Overview

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood glucose. Hyperglycaemia, also called raised blood glucose or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels.

In 2022, 14% of adults aged 18 years and older were living with diabetes, an increase from 7% in 1990. More than half (59%) of adults aged 30 years and over living with diabetes were not taking medication for their diabetes in 2022. Diabetes treatment coverage was lowest in low- and middle-income countries.

In 2021, diabetes was the direct cause of 1.6 million deaths and 47% of all deaths due to diabetes occurred before the age of 70 years. Another 530 000 kidney disease deaths were caused by diabetes, and high blood glucose causes around 11% of cardiovascular deaths *(1)*.

Since 2000, mortality rates from diabetes have been increasing. By contrast, the probability of dying from any one of the four main noncommunicable diseases (cardiovascular diseases, cancer, chronic respiratory diseases or diabetes) between the ages of 30 and 70 decreased by 20% globally between 2000 and 2019.

Symptoms

Symptoms of diabetes may occur suddenly. In type 2 diabetes, the symptoms can be mild and may take many years to be noticed.

Symptoms of diabetes include:

- feeling very thirsty
- needing to urinate more often than usual
- blurred vision
- feeling tired
- losing weight unintentionally

Over time, diabetes can damage blood vessels in the heart, eyes, kidneys and nerves.

People with diabetes have a higher risk of health problems including heart attack, stroke and kidney failure. Diabetes can cause permanent vision loss by damaging blood vessels in the eyes. Many people with diabetes develop problems with their feet from nerve damage and poor blood flow. This can cause foot ulcers and may lead to amputation.

Type 1 diabetes

Type 1 diabetes (previously known as insulin-dependent, juvenile or childhood-onset) is characterized by deficient insulin production and requires daily administration of insulin. In 2017 there were 9 million people with type 1 diabetes; the majority of them live in high-income countries. Neither its cause nor the means to prevent it are known.

Type 2 diabetes

Type 2 diabetes affects how your body uses sugar (glucose) for energy. It stops the body from using insulin properly, which can lead to high levels of blood sugar if not treated. Over time, type 2 diabetes can cause serious damage to the body, especially nerves and blood vessels.

Type 2 diabetes is often preventable. Factors that contribute to developing type 2 diabetes include being overweight, not getting enough exercise, and genetics. Early diagnosis is important to prevent the worst effects of type 2 diabetes. The best way to detect diabetes early is to get regular check-ups and blood tests with a healthcare provider.

Symptoms of type 2 diabetes can be mild. They may take several years to be noticed. Symptoms may be similar to those of type 1 diabetes but are often less marked. As a result, the disease may be diagnosed several years after onset, after complications have already arisen.

More than 95% of people with diabetes have type 2 diabetes. Type 2 diabetes was formerly called non-insulin dependent, or adult onset. Until recently, this type of diabetes was seen only in adults but it is now also occurring increasingly frequently in children.

Gestational diabetes

Gestational diabetes is hyperglycaemia with blood glucose values above normal but below those diagnostic of diabetes. Gestational diabetes occurs during pregnancy.

Women with gestational diabetes are at an increased risk of complications during pregnancy and at delivery. These women and possibly their children are also at increased risk of type 2 diabetes in the future. Gestational diabetes is diagnosed through prenatal screening, rather than through reported symptoms.

Impaired glucose tolerance and impaired fasting glycaemia

Impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG) are intermediate conditions in the transition between normality and diabetes. People with IGT or IFG are at high risk of progressing to type 2 diabetes, although this is not inevitable.

Prevention

Lifestyle changes are the best way to prevent or delay the onset of type 2 diabetes.

To help prevent type 2 diabetes and its complications, people should:

- reach and keep a health body weight
- stay physically active with at least 150 minutes of moderate exercise each week
- eat a healthy diet and avoid sugar and saturated fat
- not smoke tobacco.

Diagnosis and treatment

Early diagnosis can be accomplished through relatively inexpensive testing of blood glucose. People with type 1 diabetes need insulin injections for survival. One of the most important ways to treat diabetes is to keep a healthy lifestyle.

Some people with type 2 diabetes will need to take medicines to help manage their blood sugar levels. These can include insulin injections or other medicines. Some examples include:

- metformin
- sulfonylureas
- sodium-glucose co-transporters type 2 (SGLT-2) inhibitors.

Along with medicines to lower blood sugar, people with diabetes often need medications to lower their blood pressure and statins to reduce the risk of complications.

Additional medical care may be needed to treat the effects of diabetes:

- foot care to treat ulcers
- screening and treatment for kidney disease
- eye exams to screen for retinopathy (which causes blindness).

WHO response

WHO aims to stimulate and support the adoption of effective measures for the surveillance, prevention and control of diabetes and its complications, particularly in low- and middle-income countries. To this end, WHO:

- provides scientific guidelines for the prevention of major noncommunicable diseases including diabetes;
- develops norms and standards for diabetes diagnosis and care;
- builds awareness on the global epidemic of diabetes, marking World Diabetes Day (14 November); and
- conducts surveillance of diabetes and its risk factors.

In April 2021 WHO launched the Global Diabetes Compact, a global initiative aiming for sustained improvements in diabetes prevention and care, with

a particular focus on supporting low- and middle-income countries.

In May 2021, the World Health Assembly agreed a Resolution on strengthening prevention and control of diabetes. In May 2022 the World Health Assembly endorsed five global diabetes coverage targets to be achieved by 2030.

To learn more about the Global Diabetes Compact, to access diabetes-related technical publications to get involved in upcoming initiatives, visit the Global Diabetes Compact webpage.

REFERENCES

1. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2021. Results. Institute for Health Metrics and Evaluation. 2024 (https://vizhub.healthdata.org/gbd-results/).

3. Hypertension

KEY FACTS

- An estimated 1.4 billion adults aged 30–79 years worldwide had hypertension in 2024; this represents 33% of the popluation in this age range.
- Two-thirds of adults aged 30–79 years who have hypertension live in low- and middle-income countries.
- An estimated 600 million adults with hypertension (44%) are unaware that they have the condition.
- Approximately 630 million adults with hypertension (44%) are diagnosed and treated.
- Approximately 320 million adults with hypertension (23%) have it under control.
- Hypertension is a major cause of premature death worldwide.
- One of the global targets for noncommunicable diseases is to reduce the prevalence of uncontrolled hypertension by 25% between 2010 and 2025.

Overview

Hypertension (high blood pressure) is when the pressure in your blood vessels is too high (140/90 mmHg or higher). It is common but can be serious if not treated. People with high blood pressure may not feel symptoms. The only way to know is to get your blood pressure checked.

Things that increase the risk of having high blood pressure include:

- older age
- genetics
- being overweight or obese
- not being physically active
- high-salt diet
- drinking too much alcohol

Lifestyle changes like eating a healthier diet, quitting tobacco and being more active can help lower blood pressure. Some people may still need to take medicines. Blood pressure is written as two numbers. The first (systolic) number represents the pressure in blood vessels when the heart contracts or beats. The second (diastolic) number represents the pressure in the vessels when the heart rests between beats. Hypertension is diagnosed if, when it is measured on two different days, the systolic blood pressure readings on both days is ≥140 mmHg and/or the diastolic blood pressure readings on both days is ≥90 mmHg.

Risk factors

Modifiable risk factors include unhealthy diets (excessive salt consumption, a diet high in saturated fat and trans fats, low intake of fruits and vegetables), physical inactivity, consumption of tobacco and alcohol, and being overweight or obese. In addition, there are environmental risk factors for hypertension and associated diseases, where air pollution is the most significant.

Non-modifiable risk factors include a family history of hypertension, age over 65 years and co-existing diseases such as diabetes or kidney disease.

Symptoms

Most people with hypertension don't feel any symptoms. Very high blood pressures can cause headaches, blurred vision, chest pain and other symptoms.

Checking your blood pressure is the best way to know if you have high blood pressure. If hypertension isn't treated, it can cause other health conditions like kidney disease, heart disease and stroke.

People with very high blood pressure (usually 180/120 or higher) can experience symptoms including:

- severe headaches
- chest pain
- dizziness
- difficulty breathing
- nausea
- vomiting
- blurred vision or other vision changes
- anxiety
- confusion
- buzzing in the ears
- nosebleeds
- abnormal heart rhythm

If you are experiencing any of these symptoms and a high blood pressure, seek care immediately.

The only way to detect hypertension is to have a health professional measure blood pressure. Having blood pressure measured is quick and painless. Although individuals can measure their own blood pressure using automated devices, an evaluation by a health professional is important for assessment of risk and associated conditions.

Treatment

Lifestyle changes can help lower high blood pressure. These include:

- eating a healthy, low-salt diet
- losing weight
- being physically active
- quitting tobacco.

If you have high blood pressure, your doctor may recommend one or more medicines. Your recommended blood pressure goal may depend on what other health conditions you have.

Blood pressure goal is less than 130/80 if you have:

- cardiovascular disease (heart disease or stroke)
- diabetes (high blood sugar)
- chronic kidney disease
- high risk for cardiovascular disease.

For most people, the goal is to have a blood pressure less than 140/90.

There are several common blood pressure medicines:

- ACE inhibitors including enalapril and lisinopril relax blood vessels and prevent kidney damage.
- Angiotensin-2 receptor blockers (ARBs) including losartan and telmisartan relax blood vessels and prevent kidney damage.
- Calcium channel blockers including amlodipine and felodipine relax blood vessels.
- Diuretics including hydrochlorothiazide and chlorthalidone eliminate extra water from the body, lowering blood pressure.

Prevention

Lifestyle changes can help lower high blood pressure and can help anyone with hypertension. Many who make these changes will still need to take medicine.

These lifestyle changes can help prevent and lower high blood pressure.

Do:

- Eat more vegetables and fruits.
- Sit less.
- Be more physically active, which can include walking, running, swimming, dancing or activities that build strength, like lifting weights.
    - Get at least 150 minutes per week of moderate-intensity aerobic activity or 75 minutes per week of vigorous aerobic activity.
    - Do strength building exercises 2 or more days each week.
- Lose weight if you're overweight or obese.
- Take medicines as prescribed by your health care professional.
- Keep appointments with your health care professional.

Don't:

- eat too much salty food (try to stay under 2 grams per day)
- eat foods high in saturated or trans fats
- smoke or use tobacco
- drink too much alcohol (1 drink daily max for women, 2 for men)
- miss or share medication.

Reducing hypertension prevents heart attack, stroke and kidney damage, as well as other health problems.

Reduce the risks of hypertension by:

- reducing and managing stress
- regularly checking blood pressure
- treating high blood pressure
- managing other medical conditions
- reducing exposure to polluted air.

Complications of uncontrolled hypertension

Among other complications, hypertension can cause serious damage to the heart. Excessive pressure can harden arteries, decreasing the flow of blood and oxygen to the heart. This elevated pressure and reduced blood flow can cause:

- chest pain, also called angina;
- heart attack, which occurs when the blood supply to the heart is blocked and heart muscle cells die from lack of oxygen. The longer the blood flow is blocked, the greater the damage to the heart;
- heart failure, which occurs when the heart cannot pump enough blood and oxygen to other vital body organs; and
- irregular heart beat which can lead to a sudden death.

Hypertension can also burst or block arteries that supply blood and oxygen to the brain, causing a stroke.

In addition, hypertension can cause kidney damage, leading to kidney failure.

Prevalence of hypertension

The prevalence of hypertension varies across regions and country income groups. The WHO Eastern Mediterranean Region has the highest prevalence of hypertension (38%) while the WHO Western Pacific Region has the lowest prevalence of hypertension (29%).

The number of adults with hypertension increased from 650 million in 1990 to 1.4 billion in 2024, with

the increase seen largely in low- and middle-income countries. This increase is due mainly to a rise in the number of older adults in those countries.

WHO response

The World Health Organization (WHO) supports countries to reduce hypertension as a public health problem. In 2021, WHO released a new guideline for on the pharmacological treatment of hypertension in adults. The publication provides evidence-based recommendations for the initiation of treatment of hypertension, and recommended intervals for follow-up. The document also includes target blood pressure to be achieved for control, and information on who, in the health-care system, can initiate treatment.

To support governments in strengthening the prevention and control of cardiovascular disease, WHO and the United States Centers for Disease Control and Prevention (U.S. CDC) launched the Global Hearts Initiative in September 2016, which includes the HEARTS technical package. The six modules of the HEARTS technical package (Healthy-lifestyle counselling, Evidence-based treatment protocols, Access to essential medicines and technology, Risk-based management, Team-based care, and Systems for monitoring) provide a strategic approach to improve cardiovascular health in countries across the world.

In September 2017, WHO began a partnership with Resolve to Save Lives, an initiative of Vital Strategies, to support national governments to implement the Global Hearts Initiative. Other partners contributing to the Global Hearts Initiative are the CDC Foundation, the Global Health Advocacy Incubator, the Johns Hopkins Bloomberg School of Public Health, the Pan American Health Organization (PAHO) and the U.S. CDC. Since implementation of the programme in 2017, in more than 40 low- and middle-income countries, 13.5 million people have been put on protocol-based hypertension treatment through person-centred models of care. These programmes demonstrate the feasibility and effectiveness of standardized hypertension control programmes.

4. Malaria

KEY FACTS

- Globally in 2023, there were an estimated 263 million malaria cases and 597 000 malaria deaths in 83 countries.
- The WHO African Region carries a disproportionately high share of the global malaria burden.
- In 2023, the WHO African Region was home to 94% of malaria cases (246 million) and 95% (569 000) of malaria deaths.
- Children under 5 accounted for about 76% of all malaria deaths in the Region.

Overview

Malaria is a life-threatening disease spread to humans by some types of mosquitoes. It is mostly found in tropical countries. It is preventable and curable. The infection is caused by a parasite and does not spread from person to person.

Symptoms can be mild or life-threatening. Mild symptoms are fever, chills and headache. Severe symptoms include fatigue, confusion, seizures, and difficulty breathing. Infants, children under 5 years, pregnant women and girls, travellers and people with HIV or AIDS are at higher risk of severe infection.

Malaria can be prevented by avoiding mosquito bites and with medicines. Treatments can stop mild cases from getting worse. Malaria mostly spreads to people through the bites of some infected female *Anopheles* ***mosquitoes. Blood transfusion and contaminated needles may also transmit malaria. The first symptoms may be mild,*** similar to many febrile illnesses, and difficulty to recognize as malaria. Left untreated, *P. falciparum* ***malaria can progress to severe illness and death within 24 hours.***

There are 5 *Plasmodium* ***parasite species that cause malaria in humans and 2 of these species*** – *P. falciparum* ***and*** *P. vivax* – ***pose the greatest threat.*** *P. falciparum* ***is the deadliest malaria parasite and the most prevalent on the African continent.*** *P. vivax* ***is the dominant malaria parasite in most countries outside of sub-Saharan Africa. The other malaria species which can infect humans are*** *P. malariae, P. ovale* ***and*** *P. knowlesi*.

Symptoms

The most common early symptoms of malaria are fever, headache and chills. Symptoms usually start within 10–15 days of getting bitten by an infected mosquito. Symptoms may be mild for some people, especially for those who have had a malaria infection before. Because some malaria symptoms are not specific, getting tested early is important.

Some types of malaria can cause severe illness and death. Infants, children under 5 years, pregnant women, travellers and people with HIV or AIDS are at higher risk. Severe symptoms include:

- extreme tiredness and fatigue
- impaired consciousness
- multiple convulsions
- difficulty breathing
- dark or bloody urine

- jaundice (yellowing of the eyes and skin)
- abnormal bleeding.

People with severe symptoms should get emergency care right away. Getting treatment early for mild malaria can stop the infection from becoming severe. Malaria infection during pregnancy can also cause premature delivery or delivery of a baby with low birth weight.

Disease burden

According to the latest World malaria report, there were 263 million cases of malaria in 2023 compared to 252 million cases in 2022. The estimated number of malaria deaths stood at 597 000 in 2023 compared to 600 000 in 2022.

The WHO African Region continues to carry a disproportionately high share of the global malaria burden. In 2023 the Region was home to about 94% of all malaria cases and 95% of deaths. Children under 5 years of age accounted for about 76% of all malaria deaths in the Region.

Over half of these deaths occurred in four countries: Nigeria (30.9%), the Democratic Republic of the Congo (11.3%), Niger (5.9%) and United Republic of Tanzania (4.3%).

Prevention

Malaria can be prevented by avoiding mosquito bites and by taking medicines. Talk to a doctor about taking medicines such as chemoprophylaxis before travelling to areas where malaria is common.

Lower the risk of getting malaria by avoiding mosquito bites:

- Use mosquito nets when sleeping in places where malaria is present.
- Use mosquito repellents (containing DEET, IR3535 or Icaridin) after dusk.
- Use coils and vaporizers.
- Wear protective clothing.
- Use window screens.

Vector control

Vector control is a vital component of malaria control and elimination strategies as it is highly effective in preventing infection and reducing disease transmission. The 2 core interventions are insecticide-treated nets (ITNs) and indoor residual spraying (IRS).

Progress in global malaria control is threatened by emerging resistance to insecticides among *Anopheles* ***mosquitoes. However, new generation nets, which provide better protection against malaria than pyrethroid-only nets, are becoming more widely available and represent an important tool in global efforts to combat malaria.***

Anopheles stephensi ***presents an added challenge for malaria control in Africa. Originally native to parts of south Asia and the Arabian Peninsula, the invasive mosquito species has been expanding its range over the last decade, with detections reported to date in eight African countries.*** *An. stephensi* ***thrives in urban settings, endures high temperatures and is resistant to many of the insecticides used in public health.***

Chemoprophylaxis

Travellers to malaria endemic areas should consult their doctor several weeks before departure. The medical professional will determine which chemoprophylaxis drugs are appropriate for the country of destination. In some cases, chemoprophylaxis drugs must be started 2–3 weeks before departure. All prophylactic drugs should be taken on schedule for the duration of the stay in the malaria risk area and should be continued for 4 weeks after the last possible exposure to infection since parasites may still emerge from the liver during this period.

Preventive chemotherapies

Preventive chemotherapy ***is the use of medicines, either alone or in combination, to prevent malaria infections and their consequences. It requires giving a full treatment course of an antimalarial medicine to*** vulnerable populations at designated time points during the period of greatest malarial risk, regardless of whether the recipients are infected with malaria.

Preventive chemotherapy includes perennial malaria chemoprevention (PMC), seasonal malaria chemoprevention (SMC), intermittent preventive treatment of malaria in pregnancy (IPTp) and school-aged children (IPTsc), post-discharge malaria chemoprevention (PDMC) and mass drug administration (MDA). These safe and cost-effective strategies are intended to complement ongoing malaria control activities, including vector control measures, prompt diagnosis of suspected malaria, and treatment of confirmed cases with antimalarial medicines.

Vaccine

Since October 2021, WHO has recommended broad use of the RTS,S/AS01 malaria vaccine among children living in regions with moderate to high *P. falciparum* ***malaria transmission. The vaccine has been shown to significantly reduce malaria, and deadly severe malaria, among young children. In October 2023, WHO recommended a second safe and effective malaria vaccine, R21/Matrix-M. Vaccines are now being rolled out in routine childhood immunization*** programmes across Africa. Malaria vaccines in Africa are expected to save tens of thousands of young lives every year. The highest impact will be achieved, however, when the vaccines are introduced

alongside a mix of other WHO-recommended malaria interventions such as bed nets and chemoprophylaxis.

Treatment

Early diagnosis and treatment of malaria reduces disease, prevents deaths and contributes to reducing transmission. WHO recommends that all suspected cases of malaria be confirmed using parasite-based diagnostic testing ***(through either microscopy or a rapid diagnostic test).***

Malaria is a serious infection and always requires treatment with medicine. Multiple medicines are used to prevent and treat malaria. Doctors will choose one or more based on:

- the type of malaria
- whether a malaria parasite is resistant to a medicine
- the weight or age of the person infected with malaria
- whether the person is pregnant.

These are the most common medicines for malaria:

- Artemisinin-based combination therapy medicines are the most effective treatment for *P. falciparum* ***malaria.***
- Chloroquine is recommended for treatment of infection with the *P. vivax* ***parasite only in places where it is still sensitive to this medicine.***
- Primaquine should be added to the main treatment to prevent relapses of infection with the *P. vivax* ***and P.*** *ovale* ***parasites.***

Most medicines used are in pill form. Some people may need to go to a health centre or hospital for injectable medicines.

Antimalarial drug resistance

Subsequent to the emergence of partial artemisinin resistance in the Greater Mekong subregion, WHO is very concerned about confirmed partial artemisinin resistance in Eritrea, Rwanda, Uganda and the United Republic of Tanzania. Based on available evidence, such resistance is also suspected in Ethiopia, Namibia, Sudan and Zambia. In 2022, WHO developed a strategy to curb antimalarial drug resistance in Africa. Regular monitoring of antimalarial drug efficacy is needed to inform treatment policies in malaria-endemic countries, and to ensure early detection of, and response to, drug resistance.

For more on WHO's work on antimalarial drug resistance in the Greater Mekong subregion, visit the Mekong Malaria Elimination Programme webpage.

Genetic mutations

Most rapid diagnostic tests (RDTs) for malaria target one or two specific proteins produced by the *P. falciparum* ***malaria*** parasite: HRP2 and HRP3. However, parasites with genetic mutations, that prevent the expression of these proteins, are not detected by these tests. This means that malaria patients may not be diagnosed, allowing these mutated parasites to spread. In 2023, these mutated parasites were reported in 41 malaria endemic countries, including in Burkina Faso, Chad, Togo, and Indonesia for the first time. Although their prevalence is still low in most countries, it exceeds 15% in Brazil, Djibouti, Eritrea, Nicaragua and Peru.

Elimination

Malaria elimination is defined as the interruption of local transmission of a specified malaria parasite species in a defined geographical area as a result of deliberate activities. Continued measures to prevent re-establishment of transmission are required.

In 2023, 35 countries reported fewer than 1000 indigenous cases of the disease, up from just 13 countries in 2000. Countries that have achieved at least 3 consecutive years of zero indigenous cases of malaria are eligible to apply for the WHO certification of malaria elimination. Since 2015, 14 countries have been certified by the WHO Director-General as malaria-free, including Maldives (2015), Sri Lanka (2016), Kyrgyzstan (2016), Paraguay (2018), Uzbekistan (2018), Argentina (2019), Algeria (2019), China (2021), El Salvador (2021), Azerbaijan (2023), Tajikistan (2023), Belize (2023), Cabo Verde (2024) and Egypt (2024).

Surveillance

Malaria surveillance is the continuous and systematic collection, analysis and interpretation of malaria-related data, and the use of that data in the planning, implementation and evaluation of public health practice. Improved surveillance of malaria cases and deaths helps ministries of health determine which areas or population groups are most affected and enables countries to monitor changing disease patterns. Strong malaria surveillance systems also help countries design effective health interventions and evaluate the impact of their malaria control programmes.

WHO response

The WHO Global technical strategy for malaria 2016–2030, updated in 2021, provides a technical framework for all malaria-endemic countries. It is intended to guide and support regional and country programmes as they work towards malaria control and elimination.

The strategy sets ambitious but achievable global targets, including:

- reducing malaria case incidence by at least 90% by 2030
- reducing malaria mortality rates by at least 90% by 2030

- eliminating malaria in at least 35 countries by 2030
- preventing a resurgence of malaria in all countries that are malaria-free.

Guided by this strategy, the Global Malaria Programme coordinates the WHO's global efforts to control and eliminate malaria by:

- playing a leadership role in malaria, effectively supporting member states and rallying partners to reach universal health coverage and achieve goals and targets of the Global Technical Strategy for Malaria;
- shaping the research agenda and promoting the generation of evidence to support global guidance for new tools and strategies to achieve impact;
- developing ethical and evidence based global guidance on malaria with effective dissemination to support adoption and implementation by national malaria programmes and other relevant stakeholders; and
- monitoring and responding to global malaria trends and threats.

5. Obesity and overweight

KEY FACTS

- In 2022, 1 in 8 people in the world were living with obesity.
- Worldwide adult obesity has more than doubled since 1990, and adolescent obesity has quadrupled.
- In 2022, 2.5 billion adults (18 years and older) were overweight. Of these, 890 million were living with obesity.
- In 2022, 43% of adults aged 18 years and over were overweight and 16% were living with obesity.
- In 2024, 35 million children under the age of 5 were overweight.
- Over 390 million children and adolescents aged 5–19 years were overweight in 2022, including 160 million who were living with obesity.

Overview

Overweight is a condition of excessive fat deposits. Obesity is a chronic complex disease defined by excessive fat deposits that can impair health. Obesity can lead to increased risk of type 2 diabetes and heart disease, it can affect bone health and reproduction, it increases the risk of certain cancers. Obesity influences the quality of living, such as sleeping or moving.

The diagnosis of overweight and obesity is made by measuring people's weight and height and by calculating the body mass index (BMI): weight (kg)/ height^2 (m^2). The body mass index is a surrogate marker of fatness and additional measurements, such as the waist circumference, can help the diagnosis of obesity.

The BMI categories for defining obesity vary by age and gender in infants, children and adolescents.

Adults

For adults, WHO defines overweight and obesity as follows:

- overweight is a BMI greater than or equal to 25; and
- obesity is a BMI greater than or equal to 30.

For children, age needs to be considered when defining overweight and obesity.

Children under 5 years of age

For children under 5 years of age:

- overweight is weight-for-height greater than 2 standard deviations above WHO Child Growth Standards median; and
- obesity is weight-for-height greater than 3 standard deviations above the WHO Child Growth Standards median.

Children aged between 5–19 years

Overweight and obesity are defined as follows for children aged between 5–19 years:

- overweight is BMI-for-age greater than 1 standard deviation above the WHO Growth Reference median; and
- obesity is greater than 2 standard deviations above the WHO Growth Reference median.

Facts about overweight and obesity

In 2022, 2.5 billion adults aged 18 years and older were overweight, including over 890 million adults who were living with obesity. This corresponds to 43% of adults aged 18 years and over (43% of men and 44% of women) who were overweight; an increase from 1990, when 25% of adults aged 18 years and over were overweight. Prevalence of overweight varied by region, from 31% in the WHO South-East Asia Region and the African Region to 67% in the Region of the Americas.

About 16% of adults aged 18 years and older worldwide were obese in 2022. The worldwide prevalence of obesity more than doubled between 1990 and 2022.

In 2024, an estimated 35 million children under the age of 5 years were overweight. Once considered a high-income country problem, overweight is on the rise in low- and middle-income countries. In Africa, the number of overweight children under 5 years has increased by nearly 12.1% since 2000. Almost half of the children under 5 years who were overweight or living with obesity in 2024 lived in Asia.

Over 390 million children and adolescents aged 5–19 years were overweight in 2022. The prevalence of overweight (including obesity) among children and adolescents aged 5–19 has risen dramatically from just 8% in 1990 to 20% in 2022. The rise has occurred similarly among both boys and girls: in 2022 19% of girls and 21% of boys were overweight.

While just 2% of children and adolescents aged 5–19 were obese in 1990 (31 million young people), by 2022, 8% of children and adolescents were living with obesity (160 million young people).

Causes of overweight and obesity

Overweight and obesity result from an imbalance of energy intake (diet) and energy expenditure (physical activity). In most cases obesity is a multifactorial disease due to obesogenic environments, psychosocial factors and genetic variants. In a subgroup of patients, single major etiological factors can be identified (medications, diseases, immobilization, iatrogenic procedures, monogenic disease/genetic syndrome).

The obesogenic environment exacerbating the likelihood of obesity in individuals, populations and in different settings is related to structural factors limiting the availability of healthy sustainable food at locally affordable prices, lack of safe and easy physical mobility into the daily life of all people, and absence of adequate legal and regulatory environment.

At the same time, the lack of an effective health system response to identify excess weight gain and fat deposition in their early stages is aggravating the progression to obesity.

Common health consequences

The health risks caused by overweight and obesity are increasingly well documented and understood. In 2021, higher-than-optimal BMI caused an estimated 3.7 million deaths from noncommunicable diseases (NCDs) such as cardiovascular diseases, diabetes, cancers, neurological disorders, chronic respiratory diseases, and digestive disorders *(1)*.

Being overweight in childhood and adolescence affects children's and adolescents' immediate health and is associated with greater risk and earlier onset of various NCDs, such as type 2 diabetes and cardiovascular disease. Childhood and adolescent obesity ***have adverse psychosocial consequences; it affects school performance and quality of life, compounded by stigma, discrimination and bullying. Children with obesity are very likely to be adults with obesity and are also at a higher risk of developing NCDs in adulthood.***

The economic impacts of the obesity epidemic are also important. If nothing is done, the global costs of overweight and obesity are predicted to reach US$ 3 trillion per year by 2030 and more than US$ 18 trillion by 2060 *(2)*.

Finally, the rise in obesity rates in low-and middle-income countries, including among lower socio-economic groups, is fast globalizing a problem that was once associated only with high-income countries.

Facing a double burden of malnutrition

Many low- and middle-income countries face a so-called double burden of malnutrition. While these countries continue to deal with the problems of infectious diseases and undernutrition, they are also experiencing a rapid upsurge in noncommunicable disease risk factors such as obesity and overweight.

It is common to find undernutrition and obesity co-existing within the same country, the same community and the same household. Children in low- and middle-income countries are more vulnerable to inadequate pre-natal, infant, and young child nutrition. At the same time, these children are exposed to high-fat, high-sugar, high-salt, energy-dense, and micronutrient-poor foods, which tend to be lower in cost but also lower in nutrient quality. These dietary patterns, in conjunction with lower levels of physical activity, result in sharp increases in childhood obesity while undernutrition issues remain unsolved.

Prevention and management

Overweight and obesity, as well as their related noncommunicable diseases, are largely preventable and manageable.

At the individual level, people may be able to reduce their risk by adopting preventive interventions at each step of the life cycle, starting from pre-conception and continuing during the early years. These include:

- ensure appropriate weight gain during pregnancy;
- practice exclusive breastfeeding in the first 6 months after birth and continued breastfeeding until 24 months or beyond;
- support behaviours of children around healthy eating, physical activity, sedentary behaviours and sleep, regardless of current weight status;
- limit screen time;
- limit consumption of sugar sweetened beverages and energy-dense foods and promote other healthy eating behaviours;
- enjoy a healthy life (healthy diet, physical activity, sleep duration and quality, avoid tobacco and alcohol, emotional self-regulation);
- limit energy intake from total fats and sugars and increase consumption of fruit and vegetables, as well as legumes, whole grains and nuts; and
- engage in regular physical activity.

Health practitioners need to

- assess the weight and height of people accessing the health facilities;
- provide counselling on healthy diet and lifestyles;
- when a diagnosis of obesity is established, provide integrated obesity prevention and management health services including on healthy diet, physical activity and medical and surgical measures; and
- monitor other NCD risk factors (blood glucose, lipids and blood pressure) and assess the presence of comorbidities and disability, including mental health disorders.

The dietary and physical activity patterns for individual people are largely the result of environmental and societal conditions that greatly constrain personal choice. Obesity is a societal rather than an individual responsibility, with the solutions to be found through the creation of supportive environments and communities that embed healthy diets and regular physical activity as the most accessible, available and affordable behaviours of daily life.

Stopping the rise in obesity demands multisectoral actions such as food manufacturing, marketing and pricing and others that seek to address the wider determinants of health (such as poverty reduction and urban planning).

Such policies and actions include:

- structural, fiscal and regulatory actions aimed at creating healthy food environments that make healthier food options available, accessible and desirable; and
- health sector responses designed and equipped to identify risk, prevent, treat and manage the disease. These actions need to build upon and be integrated into broader efforts to address NCDs and strengthen health systems through a primary health care approach.

The food industry can play a significant role in promoting healthy diets by:

- reducing the fat, sugar and salt content of processed foods;
- ensuring that healthy and nutritious choices are available and affordable to all consumers;
- restricting marketing of foods high in sugars, salt and fats, especially those foods aimed at children and teenagers; and
- ensuring the availability of healthy food choices and supporting regular physical activity practice in the workplace.

WHO response

WHO has recognized the need to tackle the global obesity crisis in an urgent manner for many years.

The World Health Assembly Global Nutrition Targets aiming to ensure no increase in childhood overweight, and the NCD target to halt the rise of diabetes and obesity by 2025, were endorsed by WHO Member States. They recognized that accelerated global action is needed to address pervasive and corrosive problem of the double burden of malnutrition.

At the 75th World Health Assembly in 2022, Member States demanded and adopted new recommendations for the prevention and management of obesity and endorsed the WHO Acceleration plan to stop obesity. Since its endorsement, the Acceleration plan has shaped the political environment to generate impetus needed for sustainable change, created a platform to shape, streamline and prioritize policy, support implementation in countries and drive impact and strengthen accountability at national and global level.

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