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2- Manuscripts must be accompanied by a covering letter signed by all authors that the paper has not been published and will not be submitted to another journal if accepted in the Iraqi Medical Journal.

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6- The main text of the original article should be divided into section, each section should be started on a new page after the title page:

- **Introduction:** is should state clearly the purpose and rationale of the study.
- **Methods:** should include selection of subjects, identification of the methods, apparatus and chemicals used and include statistical analysis.
- **Results:** They presented in a logical sequence preferably with tables and illustrations emphasizing in the text only the important observation.
- **Discussion:** it emphasizes new findings of the study, implications and reference to other relevant studies.
- **Acknowledgement:** it is only to persons who have made substantive contribution to the study.
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sheet. Tables should be numbered consecutively in the text in and each typed on a separate sheet. Vertical lines normally will not be printed.

8- Measurements are preferably expressed in SI (standard international) units.

9- Authors are advised to follow the Webster's collegiate dictionary in spelling.

10- Articles and abstracts which written in Arabic should follow the unified medical dictionary (council of Arab ministers of health/WHO/Arab medical union/ALESCO, 3rd edition)

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Correlation Between the Thyroid Imaging Reporting and Data System and Bethesda System of Cytology in Thyroid Nodule Evaluation

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Abstract

Background: Accurate diagnosis of thyroid nodules is important for avoiding unnecessary surgeries and allowing timely treatment. Ultrasound and fine needle aspiration cytology (FNAC) are the most commonly used diagnostic procedures.

Objective: To correlate ultrasonography with the FNAC report findings using the American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS) and the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) in differentiating malignant from benign thyroid nodules.

Patients and Methods: A prospective study conducted from January 2021 to January 2024 assessed 103 cases of thyroid nodules who underwent ultrasound examination and fine needle aspiration. Ultrasonography findings were analyzed and correlated with FNA cytology reports based on ACR-TIRADS and BSRTC.

Results: Patients were predominantly female, n = 87 (84.4%). Most of the patients were in the 31–40 year group (n = 55, 53.39%). Most of the patient nodules had TIRADS 3 (n = 59, 57.28%), followed by TIRADS 2 (n = 20, 18.44%). When comparing the ACR TI-RADS scoring system with the TBSRTC, the percentage of malignancy for TR1, 2, 3, 4, and 5 was 0, 0, 1.6, 80, and 89%, respectively. In our study, the overall sensitivity and specificity of the TIRADS score were 94.11% and 96.51%, respectively. PPV: 84.21%; NPV: 98.80%; and accuracy: 96.11%. In addition, there was a significant association between TIRADS and the Bethesda system of classification ($P < 0.001$).

Conclusion: ACR-TIRADS scoring is highly sensitive and accurate for diagnosing thyroid malignant nodules. It is a sensitive tool and could be used alone to determine the nature of thyroid nodules.

Keywords: Thyroid malignancies, Ultrasonography, Yemen

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Introduction

Thyroid nodule is a common medical problem with about 5 % of population had a nodule on clinical examination and about 50 to 67 % of those underwent ultrasound [1]. Elderly patients are more prone to thyroid malignancies, and males are at more risk, although nodules are more common in females [2]. Approximately 5–15% of patients with thyroid nodules has thyroid cancer [3]. The prevalence of thyroid cancer among patients with thyroid nodules in the Arab world varies and reported to be 10.5% in Jordan [4], 5% in Saudi Arabia in one study [5] and 10.4% in another [6] and 14.9% in Diyala, Iraq [7]. In Yemen, the prevalence of thyroid cancer was 17.7% of patients with goiter in one study [8] and in another study; its prevalence was higher than other Middle Eastern countries with a higher rate of follicular thyroid cancer than that in other published data in one study [9]. Ultrasound is an important imaging tool for discovering and assessing a thyroid lesion. More importantly, ultrasound can be combined with FNAC to enhance the diagnostic accuracy in the differentiation of benign from malignant nodules [10]. Neck ultrasound remains the most widely used technique for discovering nodules, and sonographic features like margins, calcifications, echogenicity, and vascularity are used to determine the potential risk of malignant nodules. However, US an operator-dependent method, so its use is limited by the technical skill of the operator [11]. TIRADS classification is an ultrasound-based scoring system that allows for a precise selection of a nodule to be aspirated, avoiding unnecessary surgery [12]. This system eases the cross-talk between radiologists and endocrinologists worldwide.

FNAC is a crucial technique in determining the need and extent of surgery. FNAC should be reported in a uniform system among pathologists to pave the road for physicians to make a clear decision [13]. FNAC provides a reliable, cost-effective and robust diagnostic outcome; so, it is the gold standard for diagnosing thyroid nodules [14]. FNA has high sensitivity and specificity in differentiation malignant from benign thyroid lesions. However, it is nondiagnostic in 2–16% of cases and indeterminate in a further 5–20% [15]. Reporting of FNA cytology has improved in the past 10 years with the introduction of classification schemes in order to standardize terminology, to facilitate communication among cytopathologists, endocrinologists and surgeons, and to provide the malignancy risk for specific diagnostic categories [15].

The Bethesda System for Reporting Thyroid Cytopathology (BSRTC) contains six categories for reporting FNAC. It was developed in 2010 and revised in 2017, and is now widely used as a diagnostic tool in thyroid pathology [16]. TBSRTC has been widely adopted in the United States and in many places worldwide and has been endorsed by the American Thyroid Association [17]. It has improved communication and provided a uniform template for sharing data among investigators [16].

The aim of the work is to To the best of our knowledge, there is no study comparing TIRADS with BSRTC in our country, so we decided to conduct a study among Yemeni

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patients referred for US-guided FNA of thyroid masses.

Patients and Methods

This study was an analytical, prospective study conducted in the Bahabara medical radiology center in Mukalla city, Yemen, between January 2021 and January 2024. 103 subjects with thyroid mass were included in the study; these subjects were referred from outpatient's clinics to the center for thyroid ultrasound and FNAC.

Thyroid ultrasound

Conventional thyroid ultrasound and color Doppler were done while the patients were in a supine position, and a probe with a frequency of 12 MHz was used. An experienced radiologist who had more than a decade of experience in the thyroid field performed ultrasonography.

Image analysis

Each nodule was assessed for characteristic features like microcalcification, margins, echogenicity, composition, and shape. Cervical lymph nodes were examined as well. According to ACR TI-RADS, thyroid nodules are categorized as benign, minimally suspicious, moderately suspicious, or highly suspicious for malignancy. Figure 1 shows the characteristic features used to calculate the TIRADS score, which are interpreted as follows: the higher the number of points, the more suspicious for malignancy. TIRADS scores 1 to 3 were considered benign, while other scores were considered positive for malignancy [18].

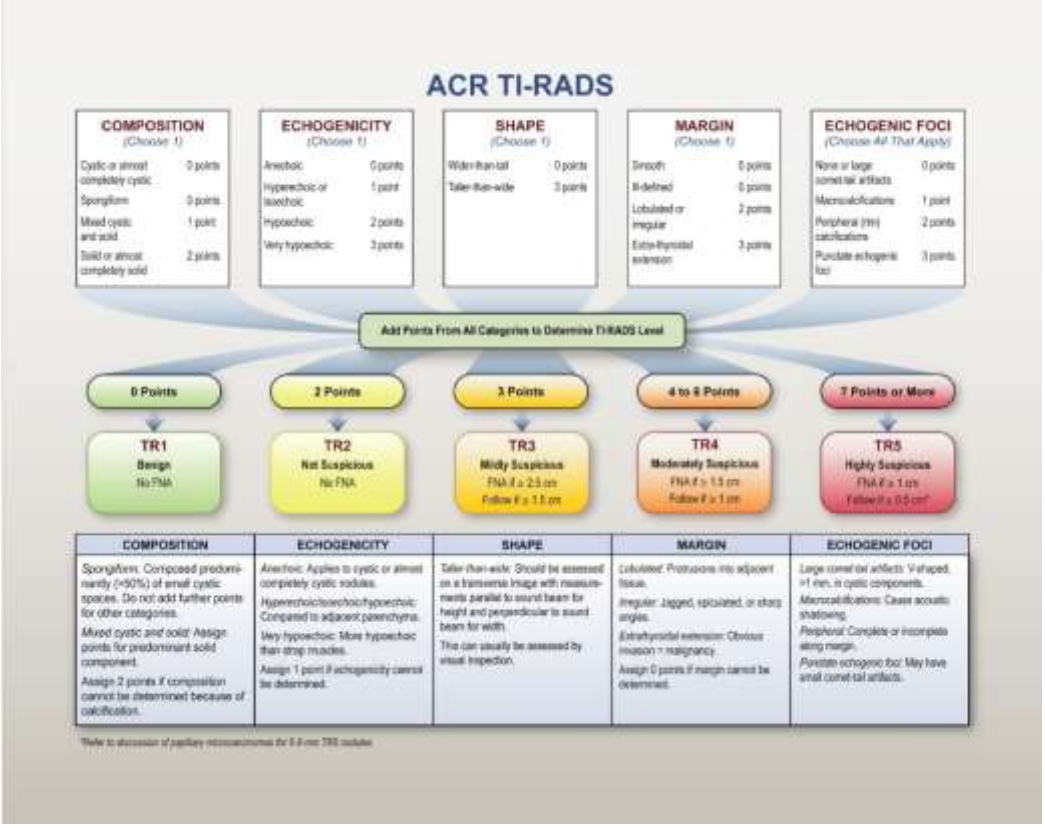

Figure (1): TIRADS categories of thyroid nodules and size of nodule threshold to perform FNA [18].

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Ultrasound-guided FNAC of nodules

FNA was performed following a standard technique by a needle of 23-gauge and freehand technique under US guidance. The same highly expert pathologist did the histopathological evaluation, and the cytological findings of every patient were classified according to the 2017 BSRTC [19], every single patient after giving him the cytopathology report was ordered to go to the doctor who asked for FNAC; in turn, he took a copy of the report and send it back to the corresponding author, who correlated between the patient's report and the ACR TI-RADS system Table (1).

Table (1): The Bethesda System for Reporting Thyroid Cytopathology 2017

Category	Meaning
I	Non-diagnostic or unsatisfactory
II	Benign
III	Atypia/follicular lesion of undetermined significance
IV	Follicular neoplasm or suspicious for follicular neoplasm
V	Suspicious for malignancy
VI	Malignant
Adapted from ref 8	

Statistical Analysis

The statistical package for social sciences (SPSS version 25) was used to summarize the data numerically (mean, standard deviation, and median) and graphically (frequency tables and graphics). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of ACR TI-RADS were calculated for US findings based on FNAC results. $P \leq 0.05$ was considered significant for all statistical analyses.

Results

In this study, most of the patients were female, 84.4% (n = 87). Most of the patients were in the age group of 31–40 years (53.39%; n = 55), ranging from 17 – 54 years Figure (2) and Table (2).

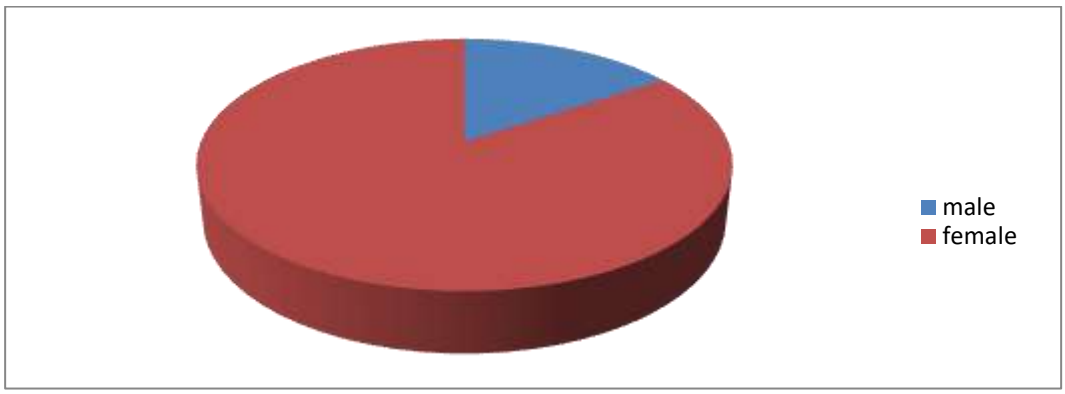

Figure (2): Gender distribution of the participants.

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Table (2): Showing the age groups of the participants.

Age	Number of patients	%
≤ 30 y	15	14.56%
31-40	55	53.39%
41-50	36	34.95%
> 51	7	6.79%

The size of the nodules in our study ranged from 7 mm to 48 mm. solid or almost solid constituted about 57.7% (n = 56), the majority of them were wider than tall (93.20%; n = 96), and had smooth margins of 89.3% (n = 92). About echogenicity, 78.64% (n = 81) were hyperechoic or isoechoic, and 79.11% (n = 82) had no echogenic foci Table (3).

Table (3): Ultrasound features of thyroid nodules based on ACR TI-RADS.

ACR-TIRADS based on	Number (103)	%
Composition		
Cystic/almost completely cystic	5	4.85
Spongiform	0	00
Mixed cystic and solid	42	40.7
Solid/ almost solid	56	57.7
Shape		
Wider than tall	96	93.20
Taller than wide	7	6.79
Echogenicity		
Anechoic	5	4.85
Hyperechoic or isoechoic	81	78.64
Hypoechoic	14	13.59
Very hypoechoic	3	2.91
Margins		
Smooth	92	89.3
Ill defined	6	89.32
Lobulated/ irregular	5	4.85
Extra thyroid extension	0	0
Echogenic foci		
None/ large comet tail artifact	82	79.61
Macro calcification	9	8.73
Peripheral calcifications	3	2.91
Punctate echogenic foci	9	8.73

The category TR3 was the most common among our patients (57.28%; n = 59), followed by TR2 (19.42%; n = 20), and TR1 was the least frequent one Table (4).

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Table (4): ACR TI-RADS for sex of patients.

TI-RADS	n	%	MALE	FEMALE
T1	5	4.85%	0	5
T2	20	19.42%	3	17
T3	59	57.28%	7	52
T4	10	9.71%	5	5
T5	9	8.74%	1	8
Total	103	100%	16	87

Regarding the correlation between ACR TI-RADS and the Bethesda system of thyroid classification scores, we found a moderate correlation ($r = 0.577$). This means that the 5 TIRADS 1 and 20 TIRADS 2 nodules in particular were benign nodules. Regarding the nodules in TIRADS 3, only one was labeled suspicious for follicular neoplasm (Bethesda classification 4), while the remaining 58 nodules were in Bethesda II and 1. The percentage of malignant nodules in our study was 16.5% (n = 17), and the frequency of malignant nodules was higher in nodules with TIRADS scores 4 and 5. The higher the TIRADS classification score, the higher the percentage of malignancy among nodules; TIRADS 4 and 5 carried the highest percentages (80 and 89%, respectively). The comparison between the ACR TI-RADS classification and the TBSRTC demonstrated that the percentage of malignancy for TR1, 2, 3, 4, and 5 was 0, 0, 1.6, 80, and 89%, respectively Table (5).

Table (5): Thyroid Imaging Reporting and Data System (TI-RADS) and Bethesda Correlation.

ACR-TIRADS categorization	BETHESDA system of thyroid classification							
	I	II	III	IV	V	VI	Total n (%)	% of malignancy
TIRADS 1	1	4	0	0	0	0	5(4.8%)	0
TIRADS 2	1	19	0	0	0	0	20(19.41%)	0
TIRADS 3	0	58	0	1	0	0	59(57.28%)	1.6%
TIRADS 4	0	2	0	1	6	1	10(9.70%)	80%
TIRADS 5	0	1	0	0	0	8	9(8.73%)	89%
Total n (%)	2(1.9%)	84(81.6%)	0	2(1.9%)	6(5.8%)	9(5.8%)	103(100%)	

The sensitivity and specificity of ACR TI-RADS calculated based on FNAC results were 94.11% and 96.51%, respectively, while the positive and negative predictive values were 84.21% and 98.8%, respectively. Furthermore, the positive likelihood ratio was 19.62%, the negative likelihood ratio was 0.0585%, and the accuracy was 96.11% Table (6).

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Table (6): TIRADS classification versus FNAC results cross-tabulation.

TIRADS classification	FNA RESULTS		
	Positive	Negative	
positive			
count	16,(a)true positive	3,false positive(b)	19
% of total	15.53%	2.91%	18.44%
negative			
Count	1 ,false negative(c)	83true negative(d)	84
% of total	0.97%	80.58%	81.55%
total			
Count	17	86	103
%of total	16.5%	83.50%	100%

In our study, the association between TIRADS and the Bethesda system of classification was statistically significant ($P < 0.001$).

Discussion

Thyroid ultrasound is an important, non-invasive technique to determine the nature of thyroid nodules, as there is no sensitive sonographic feature to delineate benign from malignant lesions; ACR-TIRADS was proposed for this task [20]. Our study revealed that female patients were predominant (84.4%) with an average age of late thirties (38y). This is in line with previous studies [21,22, 23], in which the prevalence of thyroid nodules in females was 86%. This could be attributed to sex hormonal influences in females [24]. Our study has shown malignancy risk of 0%, 0%, 1.6%, 80%, and 89%, respectively, for TIRADS categories 1, 2, 3, 4, and 5, which is in line with previous studies [20, 25]. In this study, the sensitivity of TIRADS to discover malignant nodules was 80% and 89% for TIRADS 4 and 5, respectively; this is supported by other validation studies carried out by Horvath et al, Zhang et al, and Xu [26, 27,28]. In our study, TIRADS 3 was the most predominant category; this was in contrast to an Indian study that found TIRADS 2 to be the most prevalent [29]. In spite of this difference between the studies in categorizing thyroid nodules, benign thyroid nodules are still the most prevalent. We demonstrated that nodules in the ACR TI-RADS 3 category had the highest negative predictive value (NPV). This was in line with an earlier study that discovered ACR TI-RADS scores of four or greater had the highest NPV [30]. This might explain the lower malignancy rate in TR3, as individual features like the hyperechoic or isoechoic nature of the nodule are not included as possible features to predict malignancy in the TIRADS system. In our study, the sensitivity of a fine needle aspiration biopsy was 94.11%, which was comparable with the previous studies, but the specificity was 96.51%, which was higher than most of the published series [31-37]. On the other hand, the accuracy of TIRADS in our study was 96.11%, which was higher than what was determined by Nighat (76.1%.) [38], Çolakoğlu, and Deniz (73.6%) [39]. The reason for the high accuracy in our study is possibly because of the high PPV and NPV. Our study revealed that all patients

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with Bethesda 1 had benign nodules; this was compatible with several previous studies [40-44]. In our study, 1.9% of patients were classified as Bethesda I, of which all their histopathology reports were benign; this was similar to Cibas [19]. Our study demonstrated a strong positive correlation between the Bethesda scoring system and the ACR TI-RADS; our finding was supported by several studies [40-44].

Limitations of the study

The small sample size and using cytopathology results despite their false negative results as a standard reference for comparison are the main limitations of our study.

Conclusions

TI-RADS classification is an important tool in the evaluation of thyroid nodules; it can be used to decide whether FNA is necessary or not. The TIRADS score has high diagnostic accuracy in comparison to the BSRTC. However, further large studies, including those at other centers, are necessary to prove the results of this study.

Recommendations

We do recommend using ACR-TIRADS as an indicator of whether to do FNA or not for thyroid nodules in our community.

Source of funding: The current study was funded by our charges with no any other funding sources elsewhere.

Ethical clearance: The study was approved by the Research Ethics Committee, College of Medicine and Health Sciences, Hadhramout University. Written consent was obtained from all patients before inclusion. This study was conducted according to the approval of College of Medicine/ University of Diyala and in accordance with the ethical guidelines of the Declaration of ethical committee of the College (Document no. 2024JOB850).

Conflict of interest: Nil

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مدى تطابق نتائج نظام تيراد التابع للكلية الامريكية للأشعة مع نتائج نظام باثيسدا في تقييم عقيدات الغدة الدرقية

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الملخص

خلفية الدراسة: التشخيص الدقيق لعقيدات الغدة الدرقية أمر بالغ الأهمية لتجنب العمليات الجراحية غير الضرورية وتمكين العلاج في الوقت المناسب. استخدام الموجات فوق الصوتية والشفط بالإبرة الدقيقة من الغدة الدرقية (FNAC) من اهم التقنيات التشخيصية.

اهداف الدراسة: لربط علاقة تقارير الموجات فوق الصوتية باستخدام نظام تيراد التابع للكلية الأمريكية للأشعة (ACR TI-RADS) مع نتائج تقارير (FNAC) باستخدام نظام بيثيسدا لتصنيف أمراض الغدة الدرقية (TBSRTC) لتمييزالعقيدات الخبيثة من الحميدة.

المرضى والطرائق: دراسة استطلاعية أجريت في الفترة من يناير ٢٠٢١ إلى يناير ٢٠٢٤ قيمت ١٠٣ من المرضى يعانون من عقيدات الغدة الدرقية وخضعوا للفحص بالموجات فوق الصوتية والشفط بالإبرة الدقيقة. تم تحليل نتائج التصوير بالموجات فوق الصوتية وربطها بتقارير (FNAC)بناءً على ACR-TIRADS وBSRTC.

النتائج: كان المرضى في الغالب من الإناث، العدد = ٨٧ (٨٤,٤٪). كانت معظم عقيدات المرضى تحتوي على TIRADS 3 (ن ٥٩,٥٧,٢٨٪). عند مقارنة تصنيف ACR TI-RADS مع TBSRTC، كانت نسبة الأورام الخبيثة في TR1 و٢ و٣ و٤ و٥ هي ٠ و٠ و١,٦ و٨٠ و٨٩٪ على الترتيب. بلغت الحساسية العامة والنوعية لتقارير صور الغدة الدرقية ونظام البيانات (TIRADS) في دراستنا ٩٤,١١٪ و٩٦,٥١٪-% على الترتيب. وقد لوحظ وجود ارتباط كبير بين نظامي التصنيف TIRADSو بيثيسدا (P <0.001).

الاستنتاجات: يعتبر تصنيفACR-TIRADS حساسًا للغاية ودقيقًا للكشف عن الأورام الخبيثة في عقيدات الغدة الدرقية.

الكلمات المفتاحية: اورام الغدة الدرقية الخبيثة، الموجات فوق الصوتية، اليمن

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Influence of Some Plant Extracts on Antifungal Properties, Hardness, and Peel Bond Strength of Heat-Cured Denture Soft Liner

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Abstract

Background: Soft liners in dentures play a crucial role in enhancing patient comfort and preventing tissue irritation especially for patients with resorbed ridges. However, microbial colonization presents a challenge to their long-term effectiveness, particularly Candida albicans, leading to conditions like denture-induced stomatitis.

Objective: To evaluate the antimicrobial efficacy and mechanical properties of heat cured soft liners incorporating plant extracts from Olea europaea and Ficus carcia, individually and synergistically.

Patients and Methods: Extracts were obtained through Soxhlet extraction, and their antimicrobial activity against Candida albicans was determined using the broth microdilution method. Soft liner specimens were prepared with varying concentrations of the extracts and subjected to disk diffusion tests, shore A hardness measurements, and peel bond strength tests. Statistical analysis involved the use of one-way ANOVA and Dunnett tests.

Results: Results demonstrated significant antimicrobial activity, with the synergistic mixture exhibiting the highest inhibition zone against Candida albicans. Moreover, the addition of such extracts led to increased shore A hardness, with the highest levels recorded for synergistic groups. The extracts also displayed a significant decrease in peel bond strength, indicating potential challenges in adhesive properties. These findings suggest that while individual extracts show promise in antimicrobial efficacy and mechanical reinforcement of soft liners, their combination may lead to compromised adhesive properties.

Conclusion: The study contributes valuable insights into the development of antimicrobial soft liners reinforced with Olea europaea and Ficus carcia

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extracts, advancing dental materials towards improved patient outcomes and enhanced oral health.

Keywords: Soft liner, Olea europaea, Ficus carcia, Disk diffusion, Compressive strength.

Introduction

Natural rubbers have been used in dentistry since 1869, with Twichell creating the earliest denture soft liners. Since then, advancements in dental materials have led to various soft liner types, each with specific advantages and disadvantages [1]. Denture base poor adaptation to the underlining tissues frequently due to bone resorption can lead to problems to patients, such problems can be controlled by the use of relined dentures [2]. In general, soft liners are useful over the hard denture bearing areas to help patients suffering from irritation during wearing of complete and partial dentures to act as a cushion that can absorb the load created by the masticatory forces, reduces the traumatic effects of occlusal forces, and spread these forces in equal manner and makes the patient more comfortable [3].

The colonization of microbes in the soft lining material is one of the serious problems that affects the long-term efficacy of the material, the most common clinical condition associated with this problem is denture-induced stomatitis which mainly caused by C. albicans which is the most common fungi responsible for oral infections [4]. Olea europaea and Ficus carcia are noted for their therapeutic properties, with chemical analysis revealing the presence of various bioactive compounds such as saponins, tannins, silica, resin, trimethylamine, alkaloids, and phenols [5]. Each of these constituents exhibits distinct pharmacological effects attributable to their chemical nature [6].

Olea europaea, frequently recognized as the olive tree and it is native to, Asia and Africa, and Mediterranean Europe displays different amounts of oleuropein OL, hydroxytyrosol HT, verbascoside, apigenin-7-glucoside, and luteolin-7-glucoside in the leaf extracts. OL and HT have been recognized for their antioxidant and antimicrobial characteristics [7]. Both belong to the Oleaceae family, Ficus carcia is one of the oldest cultivated fruits globally. Phytochemical analyses of F. Carcia leaves have unveiled a plethora of bioactive compounds, including phenols, flavonoids, tannins, alkaloids, and saponins [8]. These compounds contribute to the reported antioxidant, anti-inflammatory, antiviral, and antimicrobial activities of Ficus carcia [9].

Phytotherapy which revolves around the beneficial uses of medicinal herbs and synergistic relations of such plant extracts an give several advantages. These include mitigating undesirable effects, enhancing the efficacy and bioavailability of active agents, and potentially enabling therapeutic effects with lower dosages compared to individual synthetic materials [10]. Additionally, research has demonstrated that incorporating extracts from Olea europaea and Ficus carcia into glass ionomer cement can augment antimicrobial effects [8].

Patients and Methods

Preparation of Two-Plant Extract Mixture

Extracts from Ficus carcia and Olea europaea plants were obtained separately. Each plant

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was washed, dried, and ground into powder. These powders were then added to the thimble of a Soxhlet extractor (Carl Roth GmbH +Co. KG, Karlsruhe, Germany). Ethyl alcohol (70%) was used as solvent for extraction over several hours. The resulting extracts from each plant were filtered (JIAO JIE, China) and proportioned to create a mixture. This mixture underwent ethanol removal using a rotary evaporator, resulting in a crude mix stored in a closed flask at 4°C until further use [11].

Isolation and Identification of Candida albicans

Candida albicans specimens were taken from the oral cavity of four male patient aged between 60 to 65 years old, complete denture wearers, who attended the Collage of Dentistry/ University of Baghdad with signs and symptoms of denture stomatitis, the procedure was accomplished by using sterile cotton swab and gentle rubbing of the intra-oral lesion. Plates were then incubated for 48 h at 37 °C in the incubator. Following which, the cultured plates were preserved in a refrigerator at 4°C for further investigations and tests [12].

The method used to identify Candida was through the morphology of their colonies. In sabouraud dextrose agar medium, the Candidal colonies appear as convex, smooth, creamy and pasty [13]

Minimal Inhibitory Concentration (MIC)

The broth microdilution method was utilized to estimate the Minimum Inhibitory Concentration (MIC) against Candida albicans, a fungal pathogen. Sabouraud dextrose broth was employed as the selective medium for Candida growth. Inoculum preparation involved culturing Candida albicans to a specific cell density, standardized visually using the McFarland standard value of 2. A microdilution plate was prepared with 12 rows of wells. Aqueous extract of Olea europaea and Sabouraud dextrose broth were added to wells 2 through 11, followed by Candida albicans inoculum, resulting in two-fold serial dilutions ranging from 0.032 mg/mL to 16.384 mg/mL. Well 12 served as the negative control, while well 1 acted as the positive control. After 24 hours of incubation in an incubator (Memmert, Germany) at 30°C, MIC was determined by the absence of visible fungal growth, observed as a loss of turbidity compared to the positive control wells. This methodology was similarly applied for determining the MIC of Ficus carcia and synergistic mixtures against Candida albicans [14]. 1 MIC Olea europaea and 1 MIC Ficus carcia were selected. Two synergistic mixtures (1 MIC + 1 MIC, 2 MIC + 2 MIC Olea europaea and Ficus carcia respectively) extracts were chosen based on their minimum inhibitory concentration (MIC) values.

Preparation of Test Specimens

One hundred fifty soft liner (Vertex, Italy) specimens were divided into three groups based on the tests to be conducted (Disk diffusion test, shore A hardness, and peel bond strength). Each group was further subdivided into five groups depending on the type of additive material. Plastic disc models were prepared using AutoCAD software and laser cutting machine (JL-1612, Jinan Link Manufacture and Trading Co., Ltd., China). For disk diffusion test 50 plastic discs measuring 10 mm in diameter and 3.0 mm in thickness [15], and for Shore A hardness 50 disc-shaped plastic discs measuring 35 mm in

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diameter and 6 mm thickness [16]. The plastic patterns were invested in addition silicone and after setting of silicone they were coated with separating medium (Shanghai new century dental material Co., Ltd, China), filled with dental stone in the lower flask half. After setting, it was coated again, and the upper flask half was added. Left to set, after an hour, the flask was opened, and the patterns were removed to create mold spaces.

Heat cured acrylic soft liner is available as powder and liquid; according to the manufacturer instructions mixing ratio of volume/parts by weight is 1mL liquid to 1.2 g of powder.

The specimens were divided into five groups (n=10 specimens per group): Control group (Group 1) without any additive, MIC Olea europaea (Group 2) prepared by adding 4.096 mg/mL of Olea europaea aqueous extracts per ml of monomer, 1 MIC Ficus carcia (Group 3) prepared by adding 2.048 mg/ml of Ficus carcia aqueous extracts per ml of monomer, Synergistic group (Group 4) prepared by adding 4.096 mg/ml of Olea europaea aqueous extracts and 2.048 mg/ml of Ficus carcia aqueous extracts per ml of monomer, and Synergistic group (Group 5) prepared by adding 8.192 mg/ml of Olea europaea aqueous extracts and 4.096 mg/ml of Ficus carcia aqueous extracts per ml of monomer. An electronic balance (Worner lab with 0.001 accuracy) was used.

The monomer and extracts (Olea europaea, Ficus carcia, and synergistic mixtures) were added to a glass container and sonicated to disperse particles. This mixture was then combined with soft liner powder to prevent particle accumulation and maintain the proper ratio. Once the soft liner reached the dough stage, it was loaded into silicone molds and pressed to ensure even distribution. The molds were then placed under hydraulic pressure to remove excess material and achieve uniformity. Afterward, excess material was removed, and the molds were left to dry, followed by securing the flask with a hydraulic press and immersion in a water bath for curing. The curing process involved heating the flasks in a digital water bath at 70°C for 90 minutes, then at 100°C for 30 minutes. After curing, the flasks were cooled gradually, and the specimens were removed, finished using sharp blades and silicon polishing bur. The specimens were conditioned in distilled water at 37 C for 48 hrs. according to ADA specification No.12 (1999).

For peel bond test, 50 Specimens (Acrylic part and soft-liner part) were prepared according to ASTM D903-93 specifications. Flasks made from stainless steel plates with holes were fabricated. The flask consists of four plates, two of them 5 mm in thickness were used as a cover, while the others 2 mm in thickness contain holes inside them, one for soft liner and the second for acrylic with the dimension mentioned above for each material. Two stainless steel plates one contains holes measuring 100 x 10 x 2 mm for acrylic resin, and the other contains holes measuring 150 x 10 x 2 mm for soft liner were fabricated. Heat-cured acrylic resin specimens were fabricated according to the manufacturer. Before packing the soft liner, a part of the acrylic specimen surface of all specimens was wrapped with tinfoil (Figure 1) to guarantee that just 70 mm length of the soft liner is bonded, and the remaining length

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is unbonded [5]. Soft liner specimens were prepared by packing soft liner material into the hollow space designed for soft liner. The specimens were then cured and finished as previously mentioned.

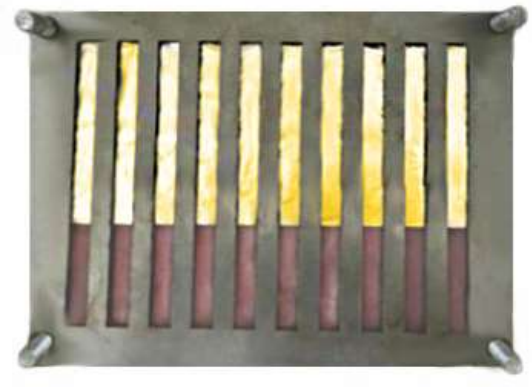

Figure (1): Acrylic specimens covered by tin foil inside the metal flask.

Disc Diffusion test

Sabouraud dextrose agar (Oxoid, England) was prepared according to manufacturer instructions and poured into sterile petri dishes. The disc diffusion method, following WHO recommendations, was utilized to assess the antifungal effects of Olea europaea, Ficus carcia, and their synergistic mixtures incorporated into soft lining material specimens. preparation of fungal suspension was performed after checking the purity of tested yeast; the isolates with 18-24 hrs were transferred to 5ml physiological solution then mixed well to prepare a homogenous yeast suspension with a turbidity equivalent to no. 2 McFarland respectively by using a Densichek instrument (17). Subsequently, a sterile cotton swab was used to inoculate a small portion of the fungal suspension and evenly spread it on the surface of Sabouraud dextrose agar medium by streaking. The inoculated plates were then allowed to dry for 10 minutes. Following this, the specimen discs were carefully inserted onto the agar using sterile forceps and pressed gently to ensure proper contact with the agar surface. Finally, the plates were inverted and incubated for 18-24 hours at 30 ºC. Inhibition zones were then measured using a scale in millimeters [18].

Shore A Hardness Test

Soft denture lining specimens measured using a shore A durometer device (Ezitown, China). Readings were taken from five different points on each sample. The mean of these five readings was calculated as the hardness value for the specimen.

Peel Bond Strength Test Specimens

The peel bond strength test, per ASTM D903-93, used an Instron testing device (LAYREE, China) at a 180º angle and 152 mm/min speed (Figure 2). The non-relined part of acrylic resin was secured on the upper clamp, while the free soft liner was secured in the lower clamp (grip 25mm). Specimen alignment was ensured using an alignment plate.

Peel bond strength (N/mm) was determined by the following equation [19]:

Peel strength = average load / width of the sample ……. 1

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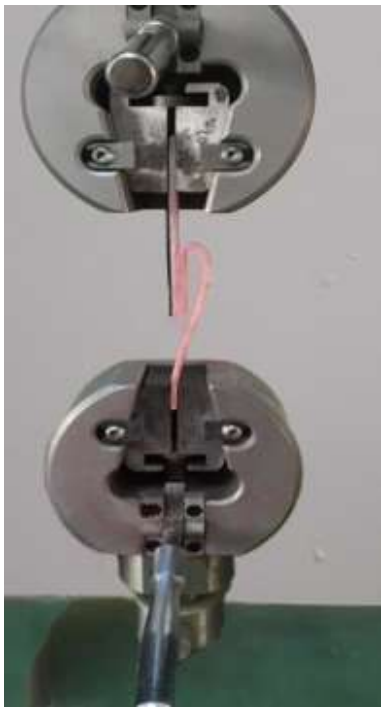

Figure (2): Peel bond strength test.

Statistical Analysis

Statistical Analysis involved the use of SPSS version 26. One way ANOVA and Dunnett post hoc test at significance level of P=0.05 were conducted to determine the difference between groups. P<0.05 was considered significant while P<0.01 was considered highly significant [20].

Results

Candida albicans appearance on sabouraud dextrose agar medium is presented in (Figure 3). MIC determination using a disposable sterile plastic contains 96 well, well 12 served as the negative control, while well 1 acted as the positive control as presented in Figure (4).

Figure (3): Candida albicans on sabouraud dextrose agar medium to be incubated for 48h at 37 °C.

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Figure (4): Minimum inhibitory concentration (MIC) determination using a plastic container that contains 96 wells.

Disk diffusion test

The higher mean value for inhibition zone was recorded for group 5 followed by group 4 while the lowest value was for group 2 Figure (5). Group 1 was not included because no inhibition zone was recorded Table (1).

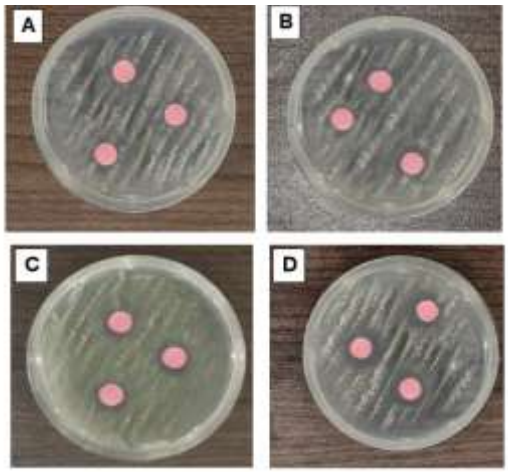

Figure (5): Effect of Ficus carcia and Olea europaea extracts on Candida albicans measured by the diameter of the inhibition zone ± Standard Error (mm) using disk diffusion test; A, Group 2. B, Group 3. C, Group 4. D, Group 5.

Table (1): Effect of Ficus Carcia and Olea europaea extracts on Candida albicans measured by the diameter of the inhibition zone ± Standard Error (mm).

Disk diffusion test (mm)					ANOVA	
Group	Min	Max	Mean	±SD	F	P value
Group 2	4.52	4.79	4.6390	.02838	1940.239	.000
Group 3	6.61	7.60	7.1050	.10532		
Group 4	10.85	11.60	11.2650	.08747		
Group 5	12.61	13.60	13.1050	.10532		
Levene statistics=5.135, p value=0.005 HS						

Dunnett's post hoc was used to determine the differences between the groups. There were highly significant differences (P<0.01) between all the groups Table (2).

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Table (2): Dunnett's post hoc test for disk diffusion test.

(I)	(J)	Std. Error	Sig.
Group 2	Group 3	.10907	.000
	Group 4	.09196	.000
	Group 5	.10907	.000
Group 3	Group 4	.13691	.000
	Group 5	.14894	.000
Group 4	Group 5	.13691	.000

Shore A hardness

The higher mean value for hardness was recorded for group 5 followed by group 4, group3, and group 2, while the lowest value was for group 1 Table (3).

Table (3): Effect of Ficus Carcia and Olea europaea extracts on shore A hardness.

Shore A hardness					ANOVA	
Group	Min	Max	Mean	±SD	F	P value
Group 1	41.61	42.28	41.9440	.22352	644.961	.000
Group 2	42.68	43.61	43.1210	.32354		
Group 3	43.78	44.77	44.2750	.33304		
Group 4	44.71	45.70	45.2050	.33304		
Group 5	47.72	47.75	47.7336	.00892		
Levene statistics=7.374, p value=0.000 HS						

Dunnett's post hoc revealed highly significant differences between all the groups (P<0.01) Table (4).

Table (4): Dunnett's post hoc test for shore A hardness.

(I)	(J)	Std. Error	Sig.
Group 1	Group 2	.12435	.000
	Group 3	.12684	.000
	Group 4	.12684	.000
	Group 5	.07074	.000
Group 2	Group 3	.14683	.000
	Group 4	.14683	.000
	Group 5	.10235	.000
Group 3	Group 4	.14894	.000
	Group 5	.10535	.000
Group 4	Group 5	.10535	.000

Peel bond strength The lowest peel strength value was for group 5 and the highest was for group 1 Table (5).

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Table (5): Effect of Ficus Carcia and Olea europaea extracts on peel bond strength between soft liner and acrylic measured in (N/mm).

Peel bond strength (N/mm)					ANOVA	
Group	Min	Max	Mean	±SD	F	P value
Group 1	3.55	3.75	3.6340	.06653	373.678	.000
Group 2	3.02	3.20	3.1100	.06055		
Group 3	2.65	2.83	2.7400	.06055		
Group 4	2.15	2.76	2.5130	.19945		
Group 5	1.87	2.02	1.9360	.05254		
Levene statistics=7.860, p value=0.000 HS						

There was a highly significant difference between all groups (P<0.01) except between group 4 and group 3 which was significant (P<0.05) Table (6).

Table (6): Dunnett's post hoc test for peel bond strength.

(I)	(J)	Std. Error	Sig.
Group 1	Group 2	.02845	.000
	Group 3	.02845	.000
	Group 4	.06649	.000
	Group 5	.02681	.000
Group 2	Group 3	.02708	.000
	Group 4	.06591	.000
	Group 5	.02535	.000
Group 3	Group 4	.06591	.048
	Group 5	.02535	.000
Group 4	Group 5	.06522	.000

Discussion

Olea europaea contains several phenolic compounds, notably oleuropein, hydroxytyrosol, and tyrosol. These compounds have been extensively studied for their antimicrobial properties, including antifungal activity against Candida albicans such as disruption of cell membranes. Phenolic compounds can disrupt the integrity of fungal cell membranes by interacting with membrane lipids and proteins. This disruption leads to leakage of intracellular components and ultimately cell death [20]. In addition, these phenolic compounds such as oleuropein can inhibit key fungal enzymes involved in metabolic processes, impairing fungal growth and proliferation. Oleuropein belongs to secoiridoids [22]. The precise enzyme that oleuropein can inhibit its activity in fungi is known as β-glucosidase. This enzyme involved in the hydrolysis of β-glucosidic bonds, that are present in various substrates. In fungi, β-glucosidases has critical activities in the metabolism of carbohydrates which includes the breakdown of complex carbohydrates structures into simple sugar that can be used by the fungus to produce energy. By inhibiting β-glucosidase, oleuropein can interfere with the ability of fungus to utilize carbohydrates,

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thus preventing the growth and proliferation [23].

Ficus carcia, similar to olive extract, encompasses compounds such as chlorogenic acid, quercetin, and rutin, these have strong antimicrobial and antioxidant characteristics [24]. Chlorogenic acid can prevent fungal proliferation by interfering with the function and organization of the phospholipid bilayer of the fungal cell membrane. The hydrophobicity of chlorogenic acid enables it to intercalate inside the lipid bilayer, this in turn can lead to changes in the permeability of fungal cell membrane. Also, it prevents vital fungal enzymes involved in metabolic functions, for example glycolysis and the tricarboxylic acid cycle, by adhering to the active sites [25]. In addition, it can generate reactive oxygen species inside the fungal cell, such as superoxide radicals and hydrogen peroxide that can damage cellular elements such as proteins, lipids, and DNA [26].

Another flavonoid abundant in various plant sources is quercetin, which exhibits comprehensive antifungal mechanisms. It inhibits fungal enzyme activity by interrupting key metabolic pathways necessary for growth and survival. Such interference can disrupt processes like glycolysis or nucleic acid synthesis, preventing fungal proliferation. Quercetin also impacts mitochondrial function, preventing energy production and metabolic homeostasis. Such disruption of mitochondrial activity promotes cell dysfunction and ultimate fungal death [27]. Furthermore, quercetin induces oxidative stress by generating reactive oxygen species within the fungal cell [28]. Also, rutin has been reported to modulate virulence factors of Candida albicans, such as adhesion, filamentation, and biofilm formation, thereby attenuating its pathogenicity [26].

The synergistic effects observed with the combination of Olea europaea and Ficus carcia extracts, especially after increasing the MIC of the two extracts, can be attributed to the through complementary mechanisms, with phenolic compounds in olive extract disrupting fungal cell membranes while quercetin and chlorogenic acid in Ficus carcia target different metabolic pathways within the fungal cell, leading to a broader spectrum of antifungal action [26, 29]. Also, the combination of both extracts increases the permeability of the fungal cell wall, facilitating better penetration of antifungal compounds into the fungal cell interior, thus enhancing their efficacy against Candida albicans [30]. Moreover, synergistic interactions between compounds in the two extracts may enhance their bioavailability or cellular uptake, leading to more efficient inhibition of fungal growth [31].

The greater increase in hardness following the addition of Ficus carcia extract compared to Olea europaea extract stems from the distinct chemical composition of these extracts. Ficus carcia extract contains higher concentrations of bioactive compounds, such as chlorogenic acid and quercetin, which exhibit stronger interactions with the polymer matrix of the soft liner. These compounds facilitate enhanced crosslinking or reinforcement effects within the polymer structure, leading to a more substantial increase in hardness [32].

The observed increased hardness levels after the synergistic mixture addition can be related to the fact that bioactive compounds

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in the extracts interact with the polymer matrix, potentially forming additional crosslinks and reinforcing the structure, leading to increased rigidity [33]. Some components act as fillers, reducing polymer chain mobility and increasing density. Furthermore, variations during drying and curing processes could affect the mechanical properties more [34].

The decrease observed in peel bonding after the addition of Olea europaea can be caused by the disruption of the polymer structure which weakens the bonding between soft liner and acrylic part by altering the surface characteristics of the soft-lining material such as surface energy and roughness which affects the ability to adhere to the acrylic [35].

The decrease in peel bonding after the addition of Ficus carcia extract is likely related to the bioactive compounds in the extract, such as chlorogenic acid and quercetin which can disrupt the polymer matrix of the soft-liner. This leads to structural irregularities and weak bonding sites. Also. It can interfere with crosslinking reactions and weaken intermolecular forces between polymer chains that reduces cohesive strength. Furthermore, alterations in the surface properties of the soft-liner material induced by the extract may hinder proper adhesion to the acrylic part [36].

The difference between the effects of the two synergistic mixtures likely stems from the higher concentrations of bioactive compounds. At 2 MIC concentrations, there are more of these compounds present, intensifying their effects on the soft liner. This leads to increased disruption of the polymer structure, cohesion, and adhesive properties, resulting in a more significant decrease in peel bond strength compared to the 1 MIC concentrations [37].

Conclusions

The synergistic mixture exhibited promising antimicrobial efficacy but posed challenges in adhesive properties. These findings highlight the importance of carefully balancing antimicrobial efficacy with mechanical integrity in the formulation of soft liners.

Recommendations

The study highlights the benefits of some plant extracts on soft liners used in conjunction with acrylic dentures. Farther research is recommended after using different plants or in conjunction with different materials.

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Ethical clearance: This study was conducted according to the approval of College of Medicine/ University of Diyala and in accordance with the ethical guidelines of the Declaration of ethical committee of the College (Document no. 2024ASA844).

Conflict of interest: Nil

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تأثير بعض المستخلصات العشبية على الخصائص المضادة للفطريات والصلابة وقوة رابطة القشرة للبطانة الناعمة لأطقم الأسنان المعالجة بالحرارة

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الملخص

خلفية الدراسة: تلعب البطانات الناعمة في أطقم الأسنان دورا حاسما في تعزيز راحة المريض ومنع تهيج الأنسجة وخاصة للمرضى الذين يعانون من نتوءات تمت إعادة الامتصاص. ومع ذلك، فإن الاستعمار الميكروبي يمثل تحديًا لفعاليتها على المدى الطويل، وخاصة المبيضات البيضاء، مما يؤدي إلى حالات مثل التهاب الفم الناجم عن أطقم الأسنان.

اهداف الدراسة: لتقييم الفعالية المضادة للميكروبات والخصائص الميكانيكية للبطانات الناعمة المعالجة بالحرارة والتي تتضمن مستخلصات من أوليا أوروبا و التين الكاريكي ، بشكل فردي وتآزري.

المرضى والطرائق: تم الحصول على المستخلصات من خلال استخلاص سوكسلت وتم تحديد نشاطها المضاد للميكروبات ضد المبيضات البيضاء باستخدام طريقة التخفيف الدقيق للمرق. تم تحضير عينات البطانة الناعمة بتركيزات مختلفة من المستخلصات وإخضاعها لاختبارات انتشار القرص وقياسات صلابة الشاطئ A واختبارات قوة رابطة القشرة. وشمل التحليل الإحصائي استخدام اختبارات ANOVA وDunnett أحادية الاتجاه.

النتائج: أظهرت النتائج نشاطًا كبيرًا مضادًا للميكروبات، حيث أظهر الخليط التآزري أعلى منطقة تثبيط ضد المبيضات البيضاء. علاوة على ذلك، أدت إضافة هذه المستخلصات إلى زيادة صلابة الشاطئ A، مع تسجيل أعلى المستويات للمجموعات التآزرية. أظهرت المستخلصات أيضًا انخفاضًا كبيرًا في قوة رابطة القشرة، مما يشير إلى التحديات المحتملة في خصائص الالتصاق. تشير هذه النتائج إلى أنه على الرغم من أن المستخلصات الفردية تظهر نتائج واعدة في الفعالية المضادة للميكروبات والتعزيز الميكانيكي للبطانات الناعمة، إلا أن مزيجها قد يؤدي إلى ضعف خصائص الالتصاق.

الاستنتاجات: تساهم الدراسة برؤى قيمة في تطوير البطانات الناعمة المضادة للميكروبات المعززة بمستخلصات أوليا أوروبا و التين الكاريكي ، مما يؤدي إلى تطوير مواد طب الأسنان نحو تحسين نتائج المرضى وتعزيز صحة الفم.

الكلمات المفتاحية: بطانة ناعمة؛ أوليا أوروبا, التين الكاريكي ,انتشار القرص قوة الضغط

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Serum Ferritin Level as a Predictor for Intra Uterine Growth Restriction

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Abstract

Background: Maternal serum ferritin is being explored as a potential predictor for Intrauterine Growth Restriction (IUGR). Early detection of IUGR is crucial for improving perinatal outcomes and reducing associated mortality and morbidity.

Objective: To evaluate the role of elevated maternal serum ferritin in predicting the risk of developing IUGR.

Patients and Methods: A prospective case-control study was conducted at Al-Batool Teaching Hospital, Diyala, involving 51 pregnant women divided into two groups based on pregnancy status. Demographic data, obstetric history, and risk factors for IUGR were collected through a questionnaire, and blood samples were taken to measure hemoglobin and serum ferritin levels.

Results: The study found that the mean serum ferritin level was significantly higher in the patient group (209.89±50.95 ng/ml) compared to the control group (66.91±37.49 ng/ml), with a p-value of <0.001. The mean birth weight was significantly lower in the patient group (1873.81±425.62 g) compared to the control group (3078.67±415.56 g), also with a p-value of <0.001. There were no significant differences in age and hemoglobin levels between the two groups.

Conclusion: Elevated maternal serum ferritin levels may suggest an increased risk of IUGR, emphasizing the need for further research to validate its role as a predictive marker.

Keywords: Intrauterine Growth Restriction (IUGR), Serum Ferritin, Pregnancy, Predictive Marker, Perinatal Outcomes.

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Introduction

Intrauterine growth restriction (IUGR) is a significant cause of prenatal morbidity and mortality [1,2,3]. As there is no definitive treatment, predicting IUGR is a key priority in prenatal healthcare [1,2,3]. Serum ferritin, an iron storage protein, has emerged as a crucial biomarker in this context [4], [5]. Ferritin levels are regulated by cellular iron status, with higher intracellular iron concentrations resulting in increased ferritin expression [4]. However, ferritin is also an acute-phase protein, and its serum concentrations can be influenced by inflammation and other factors [4]. Recent

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studies have examined the potential of maternal serum ferritin levels during pregnancy, particularly in the 30–32-week gestational period, to predict the development of IUGR [1]-[3]. The objective of this review is to synthesize the current evidence on the significance of serum ferritin as an indicator of IUGR risk. Iron is known to be an important micronutrient for proper cellular function in all organ systems including the brain as it is needed for neural &glial energy metabolism, neurotransmitter synthesis and myelination [6,7]. Iron deficiency is the most common cause of anemia in pregnancy and , according to World Health Organization (WHO), is defined as the hemoglobin concentration of less than 11 g/dL while low ferritin is defined as serum ferritin (SF) level of less than 10µg/L. Pregnant ladies are grouped into three predelivery concentrations and two SF levels according to WHO grouping: non anemic when Hb≥ 11g/dL, mild to moderate anemic Hb ≥ 7-10.9g/dL and severely anemic (Hb<7 g/dL; and into normal (SF ≥10µg/L and low(SF<10µg/L [8,9]. Many studies revealed that maternal iron deprivation with subsequent low iron stores and iron deficiency anemia in infants may affect cognitive, emotional, motor and neurophysiological development in these infants [10,11]. Pregnant woman requires more iron to meet the expansion in maternal blood volume and fetal red cell mass. Although maternal iron absorption is increased during pregnancy, but still about 50% of pregnant ladies have anemia, mostly iron deficiency anemia with subsequent effect on iron transfer to the fetus [12,13]. Physiological anemia of pregnancy (which is due to maternal blood volume expansion) can be differentiated from iron deficiency anemia in that physiological anemia of pregnancy is normochromic normocytic [14]. Serum ferritin concentration reflects body iron stores and correlates with bone marrow iron, although elevated serum ferritin level is considered as an acute phase reactant that increases in many inflammatory conditions [15,16]. Fetal growth restriction (FGR) affects about 10% of infants with increased perinatal mortality and morbidity [17,18]. Worldwide, a major cause of FGR is maternal malnutrition. Prenatal identification of FGR is crucial as early detection and management is associated with better outcomes and decreasing perinatal mortality and morbidity [19,20].

Patients and Methods

Study design

A prospective case-control study was done in Al-Batool Teaching Hospital, Diyala, during the period from July 2017 –February 2018. Fifty-one pregnant women were included in our study and after taking informed consent from all participants, they were divided into two groups. Group A (30 ladies with normal pregnancy) and Group B (21 pregnant ladies with clinical and ultrasonic features of IUGR). Both groups filled in a questionnaire that included demographic data of the patients, past obstetric history, any risk factors of IUGR (as previous IUGR, hypertension, poverty, maternal malnutrition, cyanotic heart disease etc.). Blood was drawn from antecubital fossa and complete blood count & serum ferritin level was measured.

Statistical Analysis

This is a prospective study, demographic data were presented mean ± SD, comparison

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between two groups were done by using unpaired t-test.

Results

In our study, the two groups of mothers were comparable in terms of age, birth weight, hemoglobin and serum ferritin levels Table (1). Regarding the age and hemoglobin level, there were no significant differences between the two groups. The mean age of the first group (control) was 29.73 ± 7.18 and the second group (patient) was 30.52 ± 6.85. While the mean hemoglobin level in the control was11.31 ± 0.93 and the patient was 11.5 ± 0.88. Whereas birth weight values differed among the two groups (p0.001), the mean birth weight in the control group was 3078.67 ± 415.56 and in the patient, group was 1873.81 ± 425.62. Serum ferritin values differed significantly among the two groups (p0.001), it was within the normal range in the first group (control) with the mean of 66.91 ± 37.49 whereas maternal serum ferritin was higher in the second group (patient) with the mean of 209.89 ± 50.95.

Table (1): Comparison of numeric data between control and patient groups by unpaired t- test.

Parameters	Control N=30 Mean±SD	Patients N=21 Mean±SD	P-Value
Age(yr)	29.73±7.18	30.52±6.85	0.693*
Bodyweight(g)	3078.67±415.56	1873.81±425.62	<0.001*
Hemoglobin (g/dl)	11.31±0.93	11.5±0.88	0.452*
S. Ferritin (ng/ml)	66.91±37.49	209.89±50.95	<0.001*

The Table (1) shows a comparison of numeric data between the control group (N=30) and the patient group (N=21). The parameters evaluated include age, body weight, hemoglobin, and serum ferritin levels. The mean age was similar between the control group (29.73±7.18 years) and the patient group (30.52±6.85 years), with a non-significant p-value of 0.693, indicating no statistically significant difference in age between the two groups. However, the mean body weight was significantly lower in the patient group (1873.81±425.62 g) compared to the control group (3078.67±415.56 g), with a p-value of <0.001, suggesting that the patient group had a significantly lower body weight. The mean hemoglobin levels were not significantly different between the control group (11.31±0.93 g/dl and the patient group (11.5±0.88 g/dl), with a p-value of 0.452, indicating no statistically significant difference in hemoglobin levels. Importantly, the mean serum ferritin level was significantly higher in the patient group (209.89±50.95 ng/ml) compared to the control group (66.91±37.49 ng/ml), with a p-value of <0.001. This suggests that higher serum ferritin levels are associated with the patient group, which may be a predictor for intrauterine growth restriction, the key findings from this table are the significantly lower body weight and significantly higher serum ferritin levels in the patient group compared to the control group, while age and hemoglobin levels were not significantly different between the two groups.

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Table (2): Comparison of categorical data between control and patient groups by unpaired t-test.

Parameters		Control N=30 No. (%)	Patients N=21 No. (%)	P-value
Gestational age	Term	29 (96.7)	0 (0)	<0.001*
	Preterm	1 (3.3)	21 (100)	
Gravida	1	3 (10.0)	1 (4.8)	0.958**
	2-4	18 (60.0)	12 (57.1)	
	≥5	9 (30.0)	8 (38.1)	
Parity	0-1	6 (20.0)	7 (33.3)	0.693**
	2-4	19 (63.3)	10 (47.6)	
	≥5	5 (16.7)	4 (19.0)	
Abortion	0	15 (50.0)	8 (38.1)	0.725**
	1	12 (40.0)	12 (57.1)	
	≥2	3 (10.0)	1 (4.8)	
Risk factors	Negative	22 (73.3)	2 (9.5)	<0.001**
	DM	6 (20.0)	1 (4.8)	
	HT	2 (6.7)	6 (28.6)	
	IUGR	0 (0)	7 (33.3)	
	Miscellaneous	0 (0)	7 (33.3)	

The Table (2) presents a comparison of categorical data between the control group (N=30) and the patient group (N=21) for various parameters, including gestational age, gravida, parity, abortion, and risk factors. For gestational age, 96.7% of the control group had term pregnancies, while 100% of the patient group had preterm pregnancies, with a highly significant p-value of <0.001.

This indicates that the patient group had a significantly higher rate of preterm births compared to the control group. The distribution of gravida (number of pregnancies) and parity (number of births) was similar between the control and patient groups, with no statistically significant differences (p-values of 0.958 and 0.693, respectively). The number of abortions was also comparable between the two groups, with no significant differences (p-value of 0.725).

Regarding risk factors, the majority (73.3%) of the control group had no identified risk factors, while in the patient group, a significant proportion had various risk factors, including hypertension (28.6%), intrauterine growth restriction (IUGR) (33.3%), and miscellaneous conditions (33.3%). The difference in the distribution of risk factors between the groups was statistically significant (p-value <0.001), the key findings from this table are the significantly higher rate of preterm births and the presence of various risk factors, such as hypertension and IUGR, in the patient group compared to the control group, while the distribution of gravida, parity, and abortions was similar between the two groups.

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Table (3): Correlation between numeric parameters within the control group.

		Age	B. W	Hb	Serum ferritin
Age	R	1.000	-0.099	0.016	-0.174
	P		0.602	0.932	0.359
B. W	R		1.000	0.249	0.374
	P			0.185	0.042
Hb	R	R		1.000	0.542
	P	P			0.002

This Table (3) presents the correlation analysis between various numeric parameters within a group of patients. The study appears to be investigating the relationship between serum ferritin levels and intra-uterine growth restriction (IUGR). The Table (3) shows the correlation coefficient (r) and the corresponding p-value (p) for each pair of variables, which include age, birth weight (B.W.), hemoglobin (Hb), and serum ferritin. The results indicate that there is a moderate positive correlation between age and birth weight (r = 0.350), but this correlation is not statistically significant (p = 0.120). Similarly, there is a weak negative correlation between age and hemoglobin levels (r = -0.137), but this correlation is also not statistically significant (p = 0.555). The correlation between age and serum ferritin levels is very weak and positive (r = 0.034), and it is not statistically significant (p = 0.885).

When examining the relationship between birth weight and other variables, the table shows a moderate negative correlation between birth weight and hemoglobin levels (r = -0.357), but this correlation is not statistically significant (p = 0.112). The correlation between birth weight and serum ferritin levels is weak and negative (r = -0.132), and it is not statistically significant (p = 0.569), the table indicates a moderate positive correlation between hemoglobin and serum ferritin levels (r = 0.400), and this correlation is approaching statistical significance (p = 0.073).

Overall, the results presented in this table do not show a statistically significant correlation between serum ferritin levels and intra-uterine growth restriction. The study may need to investigate other factors or expand the sample size to better understand the potential relationship between these variables.

Table (4): Correlation between numeric parameters within patients' group.

		Age	B. W	Hb	Serum ferritin
Age	R	1.000	0.350	-0.137	0.034
	P		0.120	0.555	0.885
B.W	R		1.000	-0.357	-0.132
	P			0.112	0.569
Hb	R			1.000	0.400
	P				0.073

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This Table (4) presents the correlation analysis between various numeric parameters within a group of patients. The study appears to be investigating the relationship between serum ferritin levels and intra-uterine growth restriction (IUGR). The first row of the table shows the correlation coefficients (r) and p-values (p) for the relationships between age and the other variables. There is a moderate positive correlation between age and birth weight (r = 0.350), but this correlation is not statistically significant (p = 0.120). The correlation between age and hemoglobin levels is weak and negative (r = -0.137), and it is also not statistically significant (p = 0.555). Finally, the correlation between age and serum ferritin levels is very weak and positive (r = 0.034), and it is not statistically significant (p = 0.885).

Moving to the second row, the table shows the correlations involving birth weight. There is a moderate negative correlation between birth weight and hemoglobin levels (r = -0.357), but this correlation is not statistically significant (p = 0.112). The correlation between birth weight and serum ferritin levels is weak and negative (r = -0.132), and it is also not statistically significant (p = 0.569). The third row of the table presents the correlation involving hemoglobin. There is a moderate positive correlation between hemoglobin and serum ferritin levels (r = 0.400), and this correlation is approaching statistical significance (p = 0.073), the results presented in this table do not show a statistically significant correlation between serum ferritin levels and intra-uterine growth restriction. The study may need to investigate other factors or expand the sample size to better understand the potential relationship between these variables.

Discussion

The study aimed to evaluate the potential of serum ferritin levels as a predictor for intrauterine growth restriction (IUGR). The findings revealed significant differences between the control and patient groups in terms of serum ferritin levels, birth weight, and the presence of risk factors.

The patient group exhibited significantly higher serum ferritin levels (209.89 ± 50.95 ng/ml) compared to the control group (66.91 ± 37.49 ng/ml), with a p-value of <0.001 [3]. This suggests that elevated serum ferritin levels could be associated with IUGR, making it a potential biomarker for early detection. The higher serum ferritin levels in the patient group could be indicative of an inflammatory response or oxidative stress, which are known to contribute to adverse pregnancy outcomes [2]. Additionally, the mean birth weight was significantly lower in the patient group (1873.81 ± 425.62 g) compared to the control group (3078.67 ± 415.56 g), with a p-value of <0.001 [3]. This aligns with previous studies that have shown a correlation between high serum ferritin levels and low birth weight, further supporting the hypothesis that serum ferritin could be a useful predictor for IUGR.

The study also found that the patient group had a significantly higher rate of preterm births (100%) compared to the control group (3.3%), with a p-value of <0.001 [4]. This is consistent with the literature indicating that preterm birth is a common complication in pregnancies affected by IUGR [1].

Interestingly, there were no significant differences in age and hemoglobin levels

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between the two groups, suggesting that these factors do not play a significant role in the development of IUGR in this study population [3]. This highlights the importance of focusing on serum ferritin levels and other potential biomarkers for early detection and management of IUGR, the study provides compelling evidence that elevated serum ferritin levels are significantly associated with IUGR. These findings could pave the way for further research to validate serum ferritin as a reliable biomarker for early detection of IUGR, potentially improving maternal and fetal outcomes.

The morbidity associated with FGR may not affect the antenatal period only but may extend to childhood and even adulthood periods and thus early detection and management is important [21,22]. In this study we found that serum ferritin is higher in patient with IUGR compared to normal pregnancy, this agrees with Neeta Bindal [22], NemanjaVisnjevas [23] and Vsoubasi [24] who found that serum ferritin is higher in a group of patient who develop IUGR this can be explained by the fact that fetal growth is regulated by the balance between fetal nutrient demand and maternal placenta nutrient supply. Iron deficiency has its known effect in pregnancy as it increases fetal corticotropins and fetal cortisol causing inhibition of fetal growth [36].

Various studies showed that lower level of trans ferritin receptor expression in placenta is associated with preeclampsia and IUGR. This leads to decrease extraction of iron by placenta from maternal serum leading to increase maternal serum ferritin. In addition, placental iso ferritin levels also decrease in IUGR [24]. Our study showed that IUGR occurs in approximately 33.3% of the patients with a previous history of IUGR, which agrees with the study of V Soubasi [24].

Conclusions

The study found that elevated maternal serum ferritin levels may be associated with an increased risk of Intrauterine Growth Restriction (IUGR). However, there was no statistically significant correlation between serum ferritin levels and IUGR, indicating the need for further validation before it can be used as a standalone predictive marker.

Recommendations

Conduct further longitudinal studies to better understand the relationship between serum ferritin levels and the development of Intrauterine Growth Restriction (IUGR).

Explore a multifactorial approach when studying the potential link between elevated serum ferritin and IUGR to account for various influencing factors.

Validate the role of elevated maternal serum ferritin as a predictive marker for IUGR through additional research.

Consider monitoring maternal serum ferritin levels during pregnancy, particularly in the 30-32-week gestational period, to potentially predict the risk of IUGR development. Emphasize the importance of early detection of IUGR through the evaluation of maternal serum ferritin levels to improve perinatal outcomes and reduce associated mortality and morbidity.

Acknowledgement:

The study was conducted at Al-Batool Teaching Hospital, Diyala, from July 2017 to February 2018, involving 51 pregnant women who provided informed consent. The

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authors acknowledge the participants for their involvement in the research.

Source of funding: Patients with IUGR had significantly higher serum ferritin levels compared to those with normal pregnancies, suggesting a potential link between elevated serum ferritin and IUGR. The study also highlighted the importance of considering a multifactorial approach and conducting longitudinal studies to better understand the relationship between serum ferritin levels and IUGR development.

Ethical clearance: This study was conducted according to the approval of College of Medicine/ University of Diyala and in accordance with the ethical guidelines of the Declaration of ethical committee of the College (Document no. 2024IFM854).

Conflict of interest: Nil

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مستوى الفيريتين في الدم كمؤشر لتقييد النمو داخل الرحم

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الملخص

خلفية الدراسة: يتم استكشاف فيريتين مصل الأم كمؤشر محتمل لتقييد النمو داخل الرحم (IUGR). يعد الكشف المبكر عن IUGR أمرا بالغ الأهمية لتحسين نتائج الفترة المحيطة بالولادة والحد من الوفيات والمراضة المرتبطة بها.

اهداف الدراسة: لتقييم دور ارتفاع فيريتين مصل الأم في التنبؤ بخطر الإصابة ب IUGR.

المرضى والطرائق: أجريت دراسة مستقبلية للحالات والشواهد في مستشفى البتول التعليمي في ديالى، شملت ٥١ امرأة حامل مقسمة إلى مجموعتين بناء على حالة الحمل. تم جمع البيانات الديموغرافية وتاريخ التوليد وعوامل الخطر ل IUGR من خلال استبيان ، وتم أخذ عينات الدم لقياس مستويات الهيموجلوبين والفيريتين في الدم.

النتائج: وجدت الدراسة أن متوسط مستوى الفيريتين في الدم كان أعلى بكثير في مجموعة المرضى (٢٠٩,٨٩±٥٠,٩٥ نانوغرام / مل) مقارنة بالمجموعة الضابطة (٦٦,٩١±٣٧,٤٩ نانوغرام / مل) ، مع قيمة p تبلغ <٠,٠٠١. كان متوسط الوزن عند الولادة أقل بكثير في مجموعة المرضى (١٨٧٣,٨١±٤٢٥,٦٢ جم) مقارنة بالمجموعة الضابطة (٣٠٧٨,٦٧±٤١٥,٥٦ جم)، أيضا بقيمة p تبلغ <٠,٠٠١. لم تكن هناك فروق ذات دلالة إحصائية في العمر ومستويات الهيموغلوبين بين المجموعتين.

الاستنتاجات: قد يشير ارتفاع مستويات الفيريتين في مصل الأم إلى زيادة خطر الإصابة ب IUGR ، مما يؤكد الحاجة إلى مزيد من البحث للتحقق من دوره كعلامة تنبؤية.

الكلمات المفتاحية: تقييد النمو داخل الرحم (IUGR) ، مصل الفيريتين ، الحمل ، العلامة التنبؤية ، نتائج الفترة المحيطة بالولادة.

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Clinical Manifestations of Runny nose among Patients Attending Baqubah Teaching Hospital

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Abstract

Background: The runny nose refers to a discharge (fluid) coming from the nasal passages.Runny nose is associated with inflammation and swelling (congestion) of the inner lining of the nasal passages and sinuses. May associated with atopic condition the patient complain from nasal obstruction, runny nose, episode of sneezing, and nasal pruritis.

Objective: To examine the demographic distribution, clinical features, and age disparities among male and female patients with Runny nose (Rhinorrhea).

Patients and Methods: A study was done on 100 AR patients at Baqubah Teaching Hospital. Information on demographics, clinical symptoms, and age variations between males and females were gathered and examined through the use of descriptive statistics and independent sample t-tests.

Results: The Findings revealed that most of the subjects were women (56%) and homemakers (38%), with an average age of 29.73 years. Frequent symptoms comprised of sneezing (93%), runny nose (83%), itchy nose (74%), and stuffy nose (92%). There was no notable variation in age between males and females (p = 0.139).

Conclusion: Clinical symptoms of runny nose are often recognized consist of rhinorrhea, sneezing, obstruction of the nasal passages with lacrimation and pruritus of the nasal mucosa, conjunctiva and oropharynx with history of allergic rhinitis. Conditions commonly associated with allergic rhinitis include asthma, sinusitis, allergic conjunctivitis and atopic dermatitis. Long standing disease can lead to mucosa remodeling, atrophic skin changes, nasal infection and overall increased morbidity.

Keywords: Runny nose, nasal obstractions , nasal pruritis, stuffy nose

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Introduction

The runny nose refers to a discharge (fluid) coming from the nasal passages. ... runny nose is associated with inflammation and swelling (congestion) of the inner lining of the nasal passages and sinuses. A runny nose is excess nasal drainage. It may be a thin clear fluid, thick mucus or something in between. The drainage may run out of your nose, down the back of your throat or both. The terms "rhinorrhea" and "rhinitis" are often used to refer to a runny nose. Rhinorrhea actually refers to a thin, mostly

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clear nasal discharge. Rhinitis refers to the inflammation of nasal tissues. Rhinitis often results in a runny nose. Symptoms like those of allergic rhinitis (AR) are seen in atopic individuals.

Nasal congestion, runny nose, sneezing, drainage down the back of the throat, and itching in the nose. It affects approximately one in six individuals and is linked to considerable morbidity, reduced productivity, and healthcare expenditures. Traditionally perceived as a nasal airway disorder, the unified airway theory has redefined AR as part of a systemic allergic response, sharing underlying systemic pathology with conditions like asthma and atopic dermatitis [1].

AR can be categorized as seasonal (intermittent) or perennial (chronic), with around 20% of cases being seasonal, 40% perennial, and 40% exhibiting features of both [2]. Besides nasal symptoms, individuals with AR may also experience associated allergic conjunctivitis, non-productive cough, Eustachian tube dysfunction, and chronic sinusitis. Upon diagnosis, AR is manageable through various approaches, with intra-nasal glucocorticoids serving as first-line therapy [1].The prevalence of allergic rhinitis (AR) has seen a significant rise since the 1990s [3,4,5]. Globally, it affects approximately 25% and 40% of children and adults, respectively. Notably, about 80% of AR symptoms manifest before the age of 20, peaking between the ages of 20 and 40 before gradually declining [6, 7]. In children, the incidence rate of AR within the first 5 years of life stands at 17.2%, with the highest diagnosis frequency occurring between 24 and 29 months (2.5%) [8]. Meta-analyses have revealed sex-specific differences in AR prevalence, with males being more affected during childhood and females showing a higher prevalence in adolescence [9, 10].

The increasing prevalence of AR over the years can be attributed to various risk factors, including global urbanization. Studies comparing AR prevalence between urban and rural areas have consistently demonstrated higher rates in urban settings [11,12]. Urbanization brings about elevated levels of pollutants, such as traffic- related pollutants and particulate matter 2.5 (PM2.5), which can exacerbate pollen- sensitized AR [13-15]. Reports indicate a higher prevalence of AR in urban locales compared to rural regions [12]. Moreover, climate changes have led to prolonged pollen seasons, as observed in Europe over the last three decades, contributing to more frequent seasonal allergies [16].

Rhinitis encompasses a spectrum of inflammatory conditions affecting the nasal mucosa, with etiological classifications providing insights into their diverse origins ,IgE-mediated rhinitis, characterized by allergic reactions, involves inflammation driven by IgE antibodies and eosinophilic infiltration, manifesting as either intermittent or persistent symptoms. Autonomic rhinitis encompasses various causes, including vasomotor disturbances, drug-induced reactions, hormonal fluctuations, and non-allergic rhinitis with eosinophilia syndrome (NARES). Infectious rhinitis, commonly viral in nature, arises from viral, bacterial, or fungal infections.

Finally, idiopathic rhinitis denotes cases where the underlying cause remains elusive

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despite investigation. Understanding these classifications aids in targeted diagnosis and management strategies tailored to the specific etiological factors contributing to rhinitis onset and progression [17].

Patients and Methods

A cross-sectional study of One hundred patients complaining of runny nose were conducted randomly at the outpatient clinic for otolaryngology at Baquba teaching hospital. from the period of 1st July 2023 to 1st march 2024. A comprehensive history was taken as well as a clinical examination was performed., the patient underwent systematic anterior rhinoscopy, posterior rhinoscopy, nasal endoscopy, and computed tomography (CT) of the nose and paranasal sinuses for diagnoses nasal smear analysis.

Statistical Analysis

Data analysis was performed using SPSS version 25.0. Descriptive statistics were used to summarize sociodemographic characteristics, and clinical manifestations. Independent sample t tests were applied for quantitative variables comparison. A significance level of $p < 0.05$ and a 95% confidence interval were used.

Results

Demographic Distribution of Study Participants

The study included 100 participants diagnosed with runny nose , comprising 56% females and 44% males. Regarding occupations, the majority were housewives (38%) and students (33%) Farmer(11%) Worker(10%) Animal Breeder (2%) baker (2%) . The mean age of the participants was 29.73 years with a standard deviation of 11.522. Among the participants, 13% reported history of eczema and asthma, 52% reported a history of conjunctivitis, and 17% reported a history of drug sensitivity.

Table (1): Demographic Distribution of Study Participants.

Demographic	Frequency	Percent%
Sex		
Female	56	56
Male	44	44
Occupation		
Worker	2	2
Animal Breeder	2	2
Baker	2	2
Farmer	11	11
Housewife	38	38
Student	33	33
Teacher	2	2
Worker	10	10
History of Asthma		
No	87	87
Yes	13	13
History of Eczema		
No	87	87

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Yes	13	13
History of Conjunctivitis		
No	48	48
Yes	52	52
History of Drug Sensitivity		
No	83	83
Yes	17	17
Total	**100**	**100**
Age Mean ± Sd. (Years)		**29.73 ± 11.522**

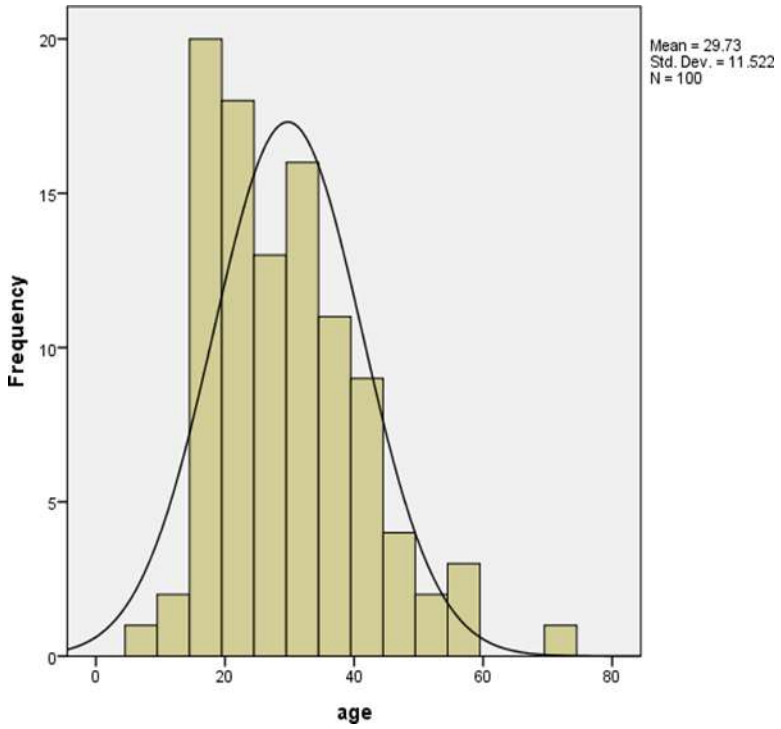

Figure (1): Age Distribution of Study Participants.

Runny nose with allergic rhinitis Manifestations

Runny nose with allergic rhinitis manifestations were evaluated among the participants. Sneezing was reported by 93% of the participants, rhinorrhea by 83%, nasal itching by 74%, and nasal obstruction by 92%.

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Table (2): Runny nose with allergic rhinitis Manifestations.

Symptom	Frequency	Percent%
Sneezing		
No	7	7
Yes	93	93
Total	100	100
Rhinorrhea		
No	17	17
Yes	83	83
Total	100	100
Nasal Itching		
No	26	26
Yes	74	74
Total	100	100
Nasal Obstruction		
No	8	8
Yes	92	92
Total	100	100

Age Difference between Genders among Patients with Allergic Rhinitis

Among patients with allergic sinusitis, the mean age for females was 28.21 years (SD = 10.337) and for males was 31.66 years (SD = 12.735). An independent sample t-test showed a non-significant difference in age between genders (p = 0.139).

Table (3): Age Difference between Genders among Patients with Allergic Rhinitis.

Mean	Age Mean ± Sd. (Years)	Independent sample t test *p* value
Female	28.21 ± 10.337	0.139
Male	31.66 ± 12.735	

Discussion

The demographic breakdown of participants enrolled in this study on Runny nose and allergy it is hypersensitive reaction of nasal mucosa. The study included 100 participants diagnosed with Runny nose, the study reveals mostly occur in female in 56%, housewives (38%) and students (33%). And less occure in male 44% with mean age of the participants was 29.73 years this agree with Widuri A e ,tal show the runny nose and allergic rhinitis occur in female also This finding aligns with existing research, which consistently shows a higher occurrence of allergic rhinitis in women compared to men [18].

Multiple factors, including hormonal influences and differences in immune responses between genders, contribute to the gender disparity. Researchers may discover new treatment targets and intervention strategies for allergic rhinitis in female patients by studying how hormones, genetics, and the immune system interact.

The average age of participants, set at 29.73 years, is a crucial sign that allergic rhinitis affects people of all ages, appearing in different age ranges and highlighting its

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widespread presence over a lifetime. This observation is consistent with results from previous studies, which also align with this conclusion documented a peak prevalence of allergic rhinitis among both young adults and older individuals [19].

In the research show the main clinical feature of runny nose is. Sneezing was reported by 93% of the participants, rhinorrhea by 83%, nasal itching by 74%, and nasal obstruction by 92%. These agree with many authorize describe the distraction of mast cells lead to release of allergen material like histamine, interleukin ,cytokines and T - helper cells active the inflammatory proses [20].

Revealing occurrences of asthma, eczema, conjunctivitis, and drug sensitivity in participants' medical histories highlights the complex connection between allergic rhinitis and other allergies. There for in Auer study show the 13% of patient reported history of eczema and asthma, 52% reported a history of conjunctivitis, and 17% reported a history of drug sensitivity.

The allergic material effect all the body specially the eye and the skin these explain by mane authorize [21]. The presence of these allergic conditions in one person implies common causes and requires a comprehensive approach to patient treatment. Similar results from a research project in Tehran, Iran, continue to emphasize the significance of combined strategies for managing allergic diseases [20]. Similar results from a research show there is very common relationship between allergic rhinitis and drug allergy like aspirin, and penicillin, also all patient with history of asthma had allergic rhinitis the diagnosis and treatment of atopic patient occur by implementing strategies that recognize how different allergic conditions are linked, healthcare providers can improve treatment results, reduce symptoms, and improve the overall quality of life of patients.

Conclusions

According to the findings of this research , the most prevalent symptom of the runny nose is nasal itch ing and nasal obstructions . the patient with asthma ,eczema ,drug allergy more reliable to allergy of nose ,the exposure to allergen like air pollen ,drug ,dust mite it is the most common causes skin prick test and nasal smear very important for diagnoses

Recommendations

The initial treatment of runny nose is avoid of allergen material like dust mites,drugs,pollens from tree.

The allergic rhinitis mostly higher in patient with asthma, eczema therefore should be investigating the patient carefully and take the family history to reach the diagnosis and treatment.

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Conflict of interest: Nil

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المظاهر السريرية لالتهاب الأنف التحسسي والمرضى الأكثر إصابة به

قيس جعفر خلف[١]، على لفته سلمان[٢], محمد عبد المجيد الخطاطبة [٣],سرى نبهان حسين[٤]

الملخص

خلفية الدراسة: التهاب الأنف التحسسي هو حالة مرضية سائدة تتميز بأعراض الأنف مثل انسداد الأنف، وسيلان الأنف، والعطس، والحكة.

اهداف الدراسة: للمظاهر السريرية والفروق العمرية بين الجنسين بين المرضى الذين يعانون من سيلان الانف التحسسي وكذألك من هم الذين أكثر عرضة للإصابة.

المرضى والطرائق: أجريت دراسة مقطعية على ١٠٠ مريض تم تشخيص إصابتهم حساسية الانف في مستشفى بعقوبة التعليمي. تم جمع وتحليل البيانات المتعلقة بالخصائص الديموغرافية والمظاهر السريرية والفروق العمرية بين الجنسين باستخدام الإحصائيات الوصفية واختبارات للعينة المستقلة.

النتائج: غالبية المشاركين كانوا من الإناث (٥٦٪) وربات البيوت (٣٨٪)، بمتوسط عمر ٢٩,٧٣ سنة. وشملت الأعراض الشائعة العطس (٩٣٪)، وسيلان الأنف (٨٣٪)، والحكة الأنفية (٧٤٪)، وانسداد الأنف (٩٢٪). لم يكن هناك فرق كبير في العمر بين الجنسين (ع = ٠,١٣٩).

الاستنتاجات: غالبًا ما يتم التعرف على الأعراض السريرية لسيلان الأنف والتي تتكون من سيلان الأنف والعطس وانسداد الممرات الأنفية مع تمزق وحكة في الغشاء المخاطي للأنف والملتحمة والبلعوم مع اعراض التهاب الأنف التحسسي. تشمل الحالات المرتبطة عادةً بالتهاب الأنف التحسسي الربو والتهاب الجيوب الأنفية والتهاب الملتحمة التحسسي والتهاب الجلد. يمكن أن يؤدي المرض طويل الأمد إلى تشكيل الغشاء المخاطي، وتغيرات الجلد الضامرة، وعدوى الأنف، وزيادة معدلات الإصابة بالمرض بشكل عام.

الكلمات المفتاحية: التهاب الأنف التحسسي، التوزيع الديموغرافي، المظاهر السريرية، الفروق بين الجنسين، الإدارة الشخصية

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Response Rate, Side Effect and Reduction in Tumor Size of Vinorelbine, Gemcitabine and Taxanes as First Line Setting of Advanced Squamous Cell Carcinoma of the Lung

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Abstract

Background: Squamous-cell carcinoma (SCC) of the lung is a kind of non-small-cell lung carcinoma. Cytotoxic chemotherapy has been found to deliver benefits to patients in advanced disease settings.

Objective: To compare response rate and side effects between first-line chemotherapies vinorelbine, gemcitabine, and taxanes in patients with metastatic SCC of the lung.

Patients and Methods: This is a retrospective study including 45 patients with metastatic lung SCC. All patients had received platinum-based doublet chemotherapy for 4-6 cycles. Patients were allocated into three groups based on the additional treatment protocol, with fifteen patients per group. A reduction in tumor size was assessed from tumor measurements for patients who had at least two evaluable assessments with computed tomography. The side effects of each drug were evaluated.

Results: The reduction in tumor size in the gemcitabine, taxan, and vinorelbine arms was -5.59±35.62 cm3, 1.3±39.98 cm3 and -10.55±14.62 cm3, respectively, with no significant differences. The response rates in the taxan, gemcitabine, and vinorelbine arms were 73.33%, 80%, and 86.67%, respectively, with no significant differences. The side effects, including nausea, alopecia, diarrhea, arthralgia, and peripheral neuropathy, were, in particular, more common in patients in the taxan arm than in other arms, with significant differences.

Conclusion: The three therapeutic arms, vinorelbine, gemcitabine, and taxanes, had similar efficiency based on response rate, with a mild preponderance of vinorelbine.

Keywords: Squamous-cell carcinoma,vinorelbine, gemcitabine,taxanes

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Introduction

Lung cancer stands as the leading cause of cancer-related fatalities worldwide. Among non-small cell lung cancer (NSCLC) cases, squamous cell carcinoma (SCC) comprises nearly 30% [1], with Iraq experiencing approximately 1250 new cases annually and over 400,000 cases globally. SCC remains strongly associated with cigarette smoking

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[2]. The primary pulmonary symptoms typically include cough, dyspnea, and hemoptysis [3].

The most recent (eighth) edition of the lung cancer stage classification (TNM) is used for non-small and small cell lung cancer, as well as carcinoid tumors. Surgical resection is the standard of care for stage I and II non-small cell lung cancers [4]. In the case of stage III disease, treatment decisions usually depend on the status of mediastinal lymph nodes to determine the inclusion or exclusion of surgery with adjuvant chemotherapy and/or radiotherapy [5].

Metastatic lung SCC is treated with cytotoxic chemotherapy, primarily utilizing a platinum-based doublet. These regimens employ either cisplatin or carboplatin as the platinum backbone, while drugs such as paclitaxel, nabpaclitaxel, docetaxel, vinorelbine, or gemcitabine serve as the cytotoxic partners [6]. Taxanes and vinorelbine drugs belong to the group of mitotic spindle chemotherapies [7].

Nivolumab improved overall survival compared to second-line docetaxel therapy, regardless of programmed death-ligand 1 (PD-L1) immunohistochemistry expression [8]. The Food and Drug Administration (FDA) has specifically approved nivolumab for the treatment of advanced SCC patients who have progressed after platinum-based chemotherapy [9].

The gemcitabine drug belongs to the group of chemotherapy-named antimetabolites, and the length of time that the cells are exposed to the drug is directly proportional to its killing potential [7]. Assessment of the response to treatment can be done through RECIST criteria [10, 11].

This study aims to assess the response rate, side effects, and reduction in tumor size of first-line chemotherapy vinorelbine doublet, gemcitabine doublet, and taxanes doublet for patients with metastatic SCC of the lung in Iraqi patients.

Patients and Methods

The Study Population

This is a retrospective study including 45 patients with metastatic pulmonary SCC confirmed by histopathological biopsy. Those patients were attending the Oncology Teaching Hospital in Baghdad during the period from the first of January 2020 to the thirty-first of June 2020. Patients with SCC confirmed by histopathology of trans-bronchial or trans-thoracic biopsies of the lung and metastases samples, which identified CT examination, were eligible for the study. The study included ECOG Performance Status (PS) ≤1, adequate hematopoietic, liver, and renal functions, and stage IV tumor SCC. Conversely, those with Performance Status (PS) 2 or more, inability or refusal to perform informed consent, patients treated with other chemotherapy or immunotherapy protocols, patients diagnosed with other primary malignancies in another site, and patients with metastatic lung cancer from other primary cancers were excluded from the study. The approval of the concerned health authority was obtained before data collection.

The Study Groups

A history and physical examination were done for all the patients, including TNM staging. Every patient was given platinum-based doublet chemotherapy, according to national comprehensive cancer network guidelines [12], with 4-6 cycles of

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carboplatin AUC 5 i.v. over 60 minutes (manufactured by the Hospira) combined with one of the following drugs (groups):

Group A: 15 patients treated with vinorelbine (manufactured by Ebewe Pharma) at 25 mg/m^2 on days 1 and 8 i.v. over 5–10 minutes.

Group B: 15 patients treated with gemcitabine (manufactured by Ebewe Pharma) 1000 mg/m^2 days 1 and 8 i.v. over 30 minutes.

Group C: 15 patients treated with taxanes: paclitaxel (manufactured by Hospira) 175 mg/m2 i.v. over 3 hours or docetaxel (manufactured by Pfizer) 75 mg/m^2 IV over 60 minutes.

Treatment was postponed for about 1 week for patients with neutropenia, thrombocytopenia, or anemia and hemoglobin less than 9 mg/dl. Treatment was stopped if the patient experienced complications, progression, or a decrease in his performance status.

Evaluation of Response

Patient responses were assessed in accordance with the RECIST guidelines, utilizing clinical evaluations and conventional CT scans conducted every three treatment cycles. A complete response was defined as the complete vanishing of all target lesions. Progressive disease was identified by a minimum 20% rise in the sum of the longest diameters of the target lesions or the presence of one or more new lesions. Additionally, the side effects associated with each treatment protocol were evaluated.

Statistical Analysis

The SPSS software (ver. 24) was used for all statistical analysis. Continuous data underwent a normality test, and if they had a normal distribution, they were expressed as mean and standard deviation (SD). These data sets were then analyzed using the Student t-test or analysis of variance (ANOVA) as required. Non-normally distributed data were presented as median and range and were analyzed with the Mann-Whitney U test or Kruskal-Wallis as required. Categorical variables were presented as numbers and percentages and were analyzed using the Chi-square (χ^2) test. The Spearman's correlation test was utilized to explore potential correlations between tumor reduction and other continuous variables. A p-value ≤ 0.05 was considered significant.

Results

Demographic characteristics of patients

The study included a total of 45 patients with pulmonary SSC treated with three types of anticancer drugs. The mean ages of Taxan, gemcitabine, and navelbine arms were 58.93±10.4 years, 62.07±13.63 years, and 66.0±9.91 years, respectively, with no significant differences (p-value = 0.413). The vast majority of the patients (84.44%) were males, who were distributed evenly between the three groups. The total male-female ratio was 1: 0.18. The male-to-female ratio in taxan, gemcitabine, and navelbine was 1:0.25, 1:0.15, and 1:0.15, respectively. The three arms were comparable regarding body mass index (BMI) with no significant differences. Smokers accounted for 80%, 86.67%, and 60% of patients in taxan, gemcitabine, and navelbine, respectively, with no significant differences. Most patients had a zero ECOG score Table (1).

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Table (1): Demographic characteristics of the patients.

Variables	Taxan (n=15)	Gemcitabine (n=15)	Navelbine (n=15)	p-value
Age, years				
Mean±SD	58.93±10.4	62.07±13.63	66.0±9.91	0.413
Range	42-74	21-75	43-80	
Gender				
Male	12(80%)	13(86.67%)	13(86.77%)	0.844
Female	3(20%)	2(13.33%)	2(13.33%)	
BMI, kg/m^2				
Mean±SD	23.48±3.65	25.0±3.6	24.41±6.21	0.332
Range	19.2-33.6	18.4-31.7	20.12-28.7	
Smoking				
Never	3(20%)	2(13.33%)	6(40%)	0.209
Ex/current	12(80%)	13(86.67)	9(60%)	
ECOG				
Zero	5(33.33%)	8(53.33%)	5(33.33%)	0.435
One	10(66.67%)	7(46.47%)	10(66.67%)	

Therapeutic and clinical characteristics of patients

Hypertension was more frequent among patients in the taxan arm (40%) than in either the gemcitabine arm (13.33%) or the navelbine arm (0%), with a significant difference (p value 0.014). Patients in the taxan arm had remarkably smaller initial and final tumor sizes (25.85±23.44 cm3 and 27.16±34.28 cm3, respectively) than those in the gemcitabine arm (42.26±33.18 cm3 and 47.86±43.8 cm3, respectively) or the navelbine arm (45.15±36.67 cm3 and 34.6±30.94 cm3, respectively). However, the differences were not significant. Patients in all arms mostly received 6 cycles of treatment or, less commonly, 4 cycles Table (2).

Table (2): Therapeutic and clinical characteristics of the patients.

Variables	Taxan (n=15)	Gemcitabine (n=15)	Navelbine (n=15)	p-value
Comorbidities				
No comorbidity	7(46.67%)	12(80%)	10(66.67%)	0.158
Hypertension	6(40%)	2(13.33%)	0(0%)	**0.014**
Diabetes mellitus	1(6.67%)	1(6.67%)	2(13.33%)	0.760
Ischemic heart disease	2(13.33%)	1(6.67%)	5(33.33%)	0.139
Others	2(13.33%)	0(0%)	0(0%)	0.123
Initial tumor size, cm^3				
Mean±SD	25.85±23.44	42.26±33.18	45.15±36.67	0.142
Range	2.0-99.75	14.94-127.6	3.48-120.96	
Final tumor size, cm^3				
Mean±SD	27.16±34.28	47.86±43.8	34.6±30.94	0.386
Range	0-144.9	0-142.74	0.5-101.92	
Treatment cycles				
4	2(13.33%)	4(26.67%)	2(13.33%)	0.544
6	13(86.67%)	11(73.33%)	13(86.67%)	

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Reduction in tumor size

The reduction in tumor size (based on CT scan examination) in the Navelbine arm was -5.59±35.62 cm^3 (range -85.74-52.6 cm^3), compared with -1.3±39.98 cm^3 (range -111.27-90.51 cm^3) in the gemcitabine arm and 10.55±14.62 cm^3 (range -9.75-34.0 cm^3 in the Taxan arm. Despite this variation, the Kruskal-Wallis test revealed no significant differences in the reduction of tumor size between the three arms Figure (1).

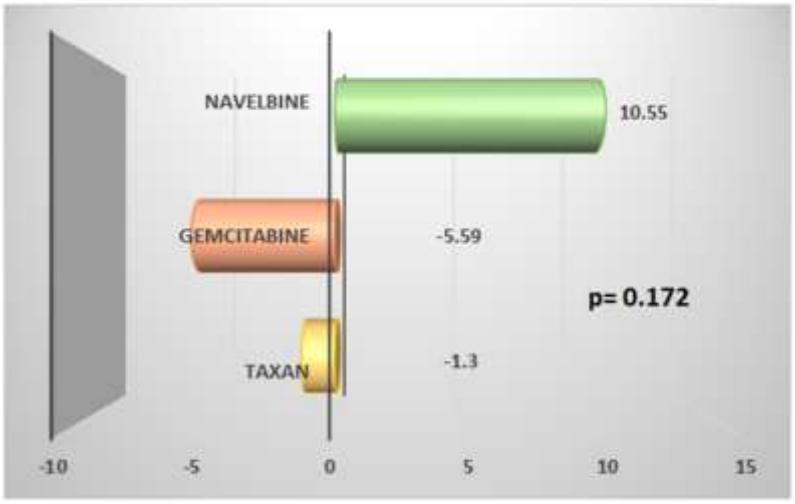

Figure (1): Reduction in tumor sizes in three treatment protocols.

Response to treatment

The response to treatment was almost compatible between the three arms, with some preponderance to the navelbine arm, in which there were only 2 (13.33%) non-responders compared to 4 (26.67%) among the taxan arm and 3 (20%) among the gemcitabine arm, with no significant differences Figure (2). Interestingly, there were only two patients with complete remission: one in the taxan arm and the other in the gemcitabine arm Figure (2).

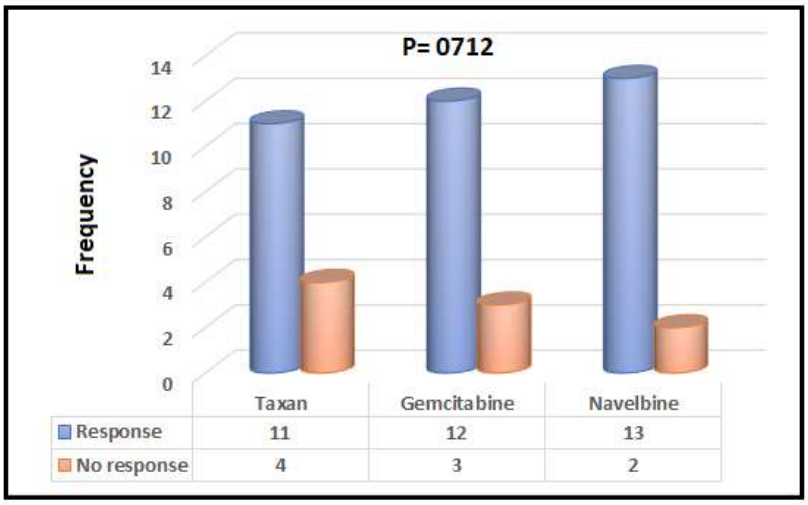

Figure (2): Response rate in the three treatment protocols.

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Correlation of tumor reduction with other variables: Spearman's correlation test was used to explore the possible correlation between tumor reduction and other continuous variables. In general, none of the included variables had a significant correlation with tumor reduction Table (3).

Table (3): Spearman's correlation between tumor reduction and other continuous variables.

Variable	Taxan		Gemcitabine		Navelbine	
	r	p-value	r	p-value	r	p-value
Age	-0.03	0.915	0.154	0.584	0.068	0.327
BMI	0.106	0.706	154	0.584	0.057	0.840
No. of cycles	0.074	0.734	0.267	0.337	0.277	0.317
ECOG score	0.006	0.982	-0.436	0.3104	0.345	0.208

Association of tumor reduction with gender, smoking, and co-morbidity: Similarly, there was no significant effect of gender, smoking habit, or the presence of co-morbidity on the reduction rate Table (4).

Table (4): Association of tumor reduction with gender, smoking, and comorbidities.

Variables	Taxon	Gemcitabine	Navelbine
Gender			
Males	-0.171±44.92	-8.34±37.67	9.52±13.93
Females	-5.84±7.34	12.22±0.37	17.29±23.63
p-value	0.448	0.171	0.800
Smoking			
Yes	-5.77 ±37.89	634±395	8.87±14.14
No	-4.44±23.2	1090±155.6	13.08±16.31
p- value	0.438	0.865	0.554
Comorbidity			
Yes	-2.91±60.1	10.07±12.89	10.26±22.27
No	0.1±9.83	-9.51±38.74	10.71±10.59
p-value	0.613	0.312	0.768

* Non-parametric Mann Whitney test was used for comparison

Side effects of the treatment

A total of 14 side effects were reported for the three treatment arms., eight of which differed significantly between different arms. Nausea, alopecia, diarrhea, arthralgia, and peripheral neuropathy were, in particular, more common in patients in the taxan arm than in the gemcitabine or vinorelbine arms, with significant differences (P<0.05). On the other hand, vomiting was significantly associated with the gemcitabine arm, while fatigue and constipation were more common with gemcitabine and vinorelbine than taxan, with significant differences (P<0.05) Table (5).

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Table (5): Side effects of the three treatment arms, Baghdad, 2020.

Effects	Taxan (n=15)	Gemcitabine (n=15)	Navelbine (n=15)	p-value
Leukopenia	5(33.33%)	6(40%)	6(40%)	0.083
Neutropenia	10(66.57%)	6(40%)	6(40%)	0.182
Nausea	9(60%)	5(33.33%)	7(46.67%)	0.016
Vomiting	6(40%)	13(86.67)	6(40%)	0.022
Alopecia	14(93.33%)	1(6.67)	1(6.67)	<0.001
Diarrhea	8(53.33%)	0(0%)	0(0%)	<0.001
Arthralgia	8(53.33%)	0(0%)	0(0%)	<0.001
Peripheral neuropathy	12(80%)	0(0%)	6(40%)	<0.001
Anemia	12(80%)	14(93.33%)	8(53.33%)	0.271
Hematuria	0(0%)	2(13.33%)	0(0%)	0.198
Thrombocytopenia	0(0%)	1(6.67)	0(0%)	0.455
Pain	0(0%)	1(6.67)	1(6.67)	0.079
Fatigue	0(0%)	3(20%)	4(26.67%)	<0.001
Constipation	0(0%)	4(26.67%)	3(20%)	0.002

Discussion

According to the outcomes of the existing study, there were no significant differences in the reduction of tumor size between taxan, gemcitabine, and navelbine, nor in the response to treatment. In line with these results, there are many studies worldwide [13-15]. In one study, gemcitabine/cisplatin was compared with some standard protocols [13]. The study demonstrated almost similar response rates among the three experimental arms: cisplatin/docetaxel, carboplatin/paclitaxel, and gemcitabine/cisplatin, compared with cisplatin/paclitaxel. However, the gemcitabine/cisplatin arm was associated with a longer time-to-disease progression compared with cisplatin/paclitaxel. Furthermore, there was also an improved 2-year survival with this arm.

In another trial, the gemcitabine/paclitaxel combination protocol was found to have an equivalent result to paclitaxel/carboplatin in terms of the patient's response [14]. A further study demonstrated equivalent efficacy between gemcitabine/vinorelbine and carboplatin/paclitaxel in previously untreated patients with advanced NSCLC [15].

In contrast, one study compared gemcitabine "1000 mg/m^2 days 1 and 8" plus carboplatin (300 mg/m^2) against cisplatin (first-generation). The study established that gemcitabine/carboplatin was associated with improved 1-year survival but had a comparable toxicity profile [16].

In a study assessing the effectiveness of navelbine on a total of 202 patients diagnosed with advanced NSCLC, there were no statistically significant differences between NC and PC regarding response rate (28% vs.

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25%), survival (8 months in both groups), or 1-year survival rate (38% vs. 36%) [17].

In a separate study conducted in Japan, 602 patients with advanced SCC were allocated to: NC (navelbine 25 mg/m^2 plus cisplatin 80 mg/m^2), PC (paclitaxel 200 mg/m^2 and carboplatin), IC (irinotecan 60 mg/m^2 plus cisplatin 80 mg/m^2), or GC (gemcitabine 1000 mg/m^2 plus cisplatin 80 mg/m^2). The study found no considerable differences in response rates among patients in the four treatment groups [18].

However, in a phase three trial involving 612 patients with advanced NSCLC, three different chemotherapeutic regimens were compared: Navelbine only (N), NC (navelbine 30 mg/m^2 plus cisplatin 120 mg/m^2), or vindesine and cisplatin. The NC regimen demonstrated statistical superiority over both N alone and the vindesine combination regarding response rate (30% vs. 14% vs. 19%) and survival (40 weeks vs. 31 weeks vs. 32 weeks) [19].

These variations in the results can be attributed to several factors, the most important of which are the patient's demographics, genetic factors, the presence of comorbidities, and treatment schedules.

In a comparative study investigating navelbine and taxanes, a total of 1218 patients diagnosed with advanced NSCLC were allocated to: NC (navelbine 25 mg/m^2 and cisplatin 100 mg/m^2), DC docetaxel 75 mg/m2 plus cisplatin 75 mg/m^2, or DCb docetaxel 75 mg/m^2 plus carboplatin. The results revealed no significant differences in these variables between the VC and DCb groups. However, patients who received DC exhibited better outcomes in terms of survival (11.3 months for DC vs. 10.1 months for VC) and the 2-year survival rate (21% vs. 14%) [20].

In another trial, 153 patients with NSCLC were allocated to have cisplatin plus oral navelbine (NC) or cisplatin plus pemetrexed (PC); after 4 cycles, patients achieving at least disease stabilization received single-agent maintenance with oral NC or with PC. Treatment consequences, in terms of disease control and survival, were equivalent between the two arms [21].

Furthermore, the current findings support a meta-analysis that indicated comparable survival outcomes between carboplatin-based doublets and more recent non-platinum doublets [22]. However, they do not confirm the results of Tan et al.'s study [23], which suggested that NG was superior to NC.

In another trial, there was a tendency towards elongated PFS with PC compared to PG (4.2 months versus 3.5 months, p = 0.044), while GC showed a PFS of 5.1 months [24]. Notably, nearly one-third of the patients in this trial were treated with second-line chemotherapy, predominantly platinum-based (86%), after receiving non-platinum-based first-line chemotherapy.

In the current study, nausea, alopecia, diarrhea, arthralgia, and peripheral neuropathy were more common in the taxan arm than in the gemcitabine or navelbine arms, with significant differences. Vomiting was significantly associated with the gemcitabine arm, while fatigue and constipation were more common in gemcitabine and navelbine than taxan, with significant differences.

Numerous studies conducted worldwide have yielded somewhat similar findings. One particular study indicated that PC was related

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to higher rates of alopecia and PN compared to NC [25] or GC, as well as higher rates of NAV compared to GP [24].

Toxicities normally linked with paclitaxel-platinum regimens include neutropenia, leukopenia, anemia, and neurotoxicity. In comparison to PG, PC demonstrated generally comparable toxicity profiles [44]. Paclitaxel-carboplatin exhibited lower incidences of neutropenia (50–57% versus 65–76%) and nausea and vomiting (<1–7% versus 12–18%) compared to NC [25], but higher rates of neurotoxicity (13% versus 3%) [17].

In another study, the mixture of vinorelbine (30 mg/m^2 weekly) and cisplatin (100 mg/m^2 every 4 weeks) was associated with hematologic complications such as neutropenia, anemia, and febrile neutropenia [26].

Furthermore, other side effects were reported in various studies. Initially, when gemcitabine was given on days 1, 8, and 15 with a protocol given every 28 days, very high rates of thrombocytopenia fluctuating from 40% to 60% were noted [27]. The relatively low occurrence of thrombocytopenia in the present study may be attributed to the small sample size.

Conclusions

The three therapeutic protocols—vinorelbine, gemcitabine, and taxanes—had similar efficacy, based on response rate, in the treatment of SCC with a mild preponderance of vinorelbine.

Recommendations

Taxane is associated with more frequent side effects, including nausea, alopecia, diarrhea, arthralgia, and peripheral neuropathy.

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Ethical clearance: This study was conducted according to the approval of College of Medicine/ University of Diyala and in accordance with the ethical guidelines of the Declaration of ethical committee of the College (Document no.2023SAA768).

Conflict of interest: Nil

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معدل الاستجابة والتأثيرات الجانبية وتراجع حجم الورم باستخدام الفينوريلبين والجيمسيتابين والتاكسان كخط أول لعلاج سرطان الخلايا الحرشفية المتقدم في الرئة

شهباء احمد القادسي [١] , أزهر صبيح الزبيدي [٢]

الملخص

خلفية الدراسة: سرطان الخلايا الحرشفية في الرئة هو نوع من سرطان الرئة ذو الخلايا غير الصغيرة. استخدم العلاج الكيميائي السام للخلايا لتحقيق فائدة للمرضى في حالات المرض المتقدمة.

اهداف الدراسة: لمقارنة معدل الاستجابة والآثار الجانبية بين ثلاث علاجات كيمائية اساسية: فينوريلبين، وجيمسيتابين والتاكسان في المرضى الذين يعانون من سرطان الخلايا الحرشفية النقيلي في الرئة.

المرضى والطرائق: شملت هذه الدراسة الاسترجاعية ٤٥ مريضًا مصابين بسرطان الخلايا الحرشفية النقيلي في الرئة. تلقى جميع المرضى علاج كيميائي مزدوج يعتمد على البلاتين لمدة ٤-٦ دورات. قسم المرضى إلى ثلاث مجموعات على أساس بروتوكول العلاج الإضافي لكل مجموعة خمسة عشر مريضا. تم تقييم التراجع في حجم الورم من قياسات الورم للمرضى الذين لديهم على الأقل تقييمين باستخدام التصوير المقطعي المحوسب. كما تم تقييم الآثار الجانبية لكل دواء.

النتائج: بلغ معدل الانخفاض في حجم الورم في أذرع جيمسيتابين وتاكسان وفينوريلبين-٥,٥٩±٣٥,٦٢ سم٢، ١,٣±٣٩,٩٨ سم٢ و-١٠,٥٥±١٤,٦٢ سم٢ على التوالي مع عدم وجود فروق معنوية. وبلغ معدل الاستجابة في أذرع التاكسان والجيمسيتابين والفينوريلبين ٧٣,٣٣٪ و٨٠٪ و٨٦,٦٧٪ على التوالي مع عدم وجود فروق معنوية. كانت الآثار الجانبية بما في ذلك الغثيان، والثعلبة، والإسهال، وآلام المفاصل، والاعتلال العصبي المحيطي، على وجه الخصوص، أكثر شيوعًا في المرضى في ذراع التاكسان مقارنة بالأذرع الأخرى مع وجود اختلافات معنوية.

الاستنتاجات: كانت للعلاجات الكيمياوية الثلاثة: فينوريلبين، وجيمسيتابين، وتاكسانيس، كفاءة مماثلة، بناءً على معدل الاستجابة مع رجحان بسيط للفينوريلبين.

الكلمات المفتاحية: سرطان الخلايا الحرشفية، فينورلبين ، جمسيتابين ، تاكسان

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Vitamin D3 Deficiency's Impact on Atrial Fibrillation in Hyperthyroidism Patients

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Abstract

Background: Atrial fibrillation (AFi) is more common as people get older. Additionally, a further indicator of the occurrence of AFi is subclinical hyperthyroidism, which is linked to a 3-fold increased risk. Lack of vitamin D causes the renin-angiotensin-aldosterone pathway to become active, which has an impact on the cardiovascular system.

Objective: To examine the association between 25-hydroxyvitamin D3 insufficiency and AFi and hyperthyroidism cases with valvular and nonvalvular AFi that required treatment at our medical center.

Patients and Methods: Samples taken from 200 cases of AFi (50-65 years old) divided into: group A cases with nonvalvular AFi and group B cases with valve AFi, and 100 healthy individuals with sinus rhythm who were age-matched chosen as control groups. Standard biochemical measurements, including levels of 25-OHvit.D3,the hormone of the thyroid gland, and parathyroid hormone, were made.

Results: Cases in group A had decreased 25-OHvit.D3 levels compare to those in the control and B groups ($P \leq 0.05$).In comparison to the control group, the patients in groups A and B had larger left atriums and greater systolic pulmonary artery pressures.

Conclusion: Thus, the study shows a connection between nonvalvular AFi cases with hyperthyroidism and 25-OHvit D3 deficiency.

Keywords: 25-hydroxyvitamin D3, Atrial fibrillation, Valvular, Parathyroid hormone, Hyperthyroidism.

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Introduction

Among heart rhythm disorders, atrial fibrillation (AFi) is the most prevalent. In the population as a whole, the prevalence of (AFi) is predicted to range from 0.4% to 15% and to rise with age. The risk of mortality, heart failure, and stroke is all raised by atrial fibrillation, which is a significant public health concern [1]. Up to about 15% of hyperthyroid patients experience AFi, compared to 4% prevalence in the population as a whole [2]. Atrial fibrosis, atrial dilatation, and diminished atrial muscle mass are frequently seen in AFi. The renin-angiotensin-aldosterone system is assumed to be primarily responsible for these physiopathologic alterations [3]. Additionally, it is well recognized that calcium is crucial for AFi and electrophysiologic reorganization. By reducing the atrial refractory duration and the action potential time, intracellular calcium excess inside the atrial myocytes contributes

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to the onset and maintenance of Afi [4]. The sarcoplasmic reticulum (SR) releases More calcium readily spontaneously when angiotensin is present, and it also encourages the proliferation of fibroblasts, both of which are crucial for the growth and maintenance of AFi. Age, gender, valvular heart disease, congestive heart failure, and ischemic heart disease are hazard issues for AFi in hyperthyroid patients that are similar to those in the population as a whole [5]. Vitamin D impacts heart function both directly and indirectly. Additionally, vitamin D controls blood pressure and guards against heart hypertrophy by suppressing renin activity [6]. Given this knowledge, we surmised that AFi might be associated with 25-hydroxyvitamin D3 insufficiency. The current study aiming to examine the association between 25-hydroxyvitamin D3 insufficiency, AFi , hyperthyroidism cases with both valvular, and nonvalvular AFi of the routine patients at our medical center.

Patients and Methods

Two hundrad hyperthyroid patients between the ages of 50 and 65 who were diagnosed with persistent (AFi) visited the cardiology outpatient clinic and the National Diabetes Center/AL-Mustansiriyah University in Baghdad between December 2022 and July 2023. The Center Ethical Committee approved the trial since physicians make diagnoses for every patient. The cases were divided into two groups: group A cases with nonvalvular (AFi) and group B cases with valvular (AFi), and 100 healthy individuals with sinus rhythm who were age-matched were chosen as control groups (SiR). The patients were required to sign formal informed consent forms in accordance with the research protocol that was certified by the ethical council of the University of the Middle Technical, Institute of AL-Suwaira Technical, Medical Laboratory Department, Iraq. Patients with other diseases were omitted from this study. The cases' blood pressure was gauged. Patients classified as hypertensive were those with a systolic blood pressure ≥140 mm Hg and/or a diastolic blood pressure ≥90 mm Hg, as well as those on antihypertensive medications.

Parathyroid hormone (PTH),T3,T4,25-OHVitD3,phosphorus, and calcium analysis in serum was carried out on Roche Modular E 170 Analytic System equipment utilizing the electrochemiluminescence technique. For the winter season, the reference values are 25-OHVit. D3 was set at 30 to 60 ng/mL, and for the summer season, at 30 to 130 ng/mL[1,7].

The protocol for transthoracic echocardiographic assessment was achieved by a 3.5 MHz transducer on a Vivid 7 Pro TTE. The test is conducted by a sonographer, a professional skilled in the use of ultrasound technology, who then provides the results to the physician. The European Association of Echocardiography and the American Society of Echocardiography instructions were followed for all echocardiographic examinations[8]. The patient remained in the position of lateral decubitus throughout the whole recording of the echocardiographic images.international units should be used in this section and throughout the manuscript.

Statistical Analysis

The SPSS version 22 were used to conduct the statistical analyses. Categorical data were shown as percentage values, whereas

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numerical variables were displayed as the mean ± SD. A P value≤ 0.05 was chosen as the cutoff for significance in all statistical studies.

Results

Parameters such as body mass index [BMI], gender distribution, and age did not vary statistically between the three groups, but the biochemical factors revealed that group A cases had higher PTH, T3, T4, TSH,Ca, and Pi levels than other groups, while having lower 25-OH vit D3 levels than group B and the control group, as seen in Table (1).

The mean LA diameter of the two case groups with AFi was substantially larger than that of the members of the SiR group when the initial conventional echocardiographic parameters of those in the group were assessed (P ≤ 0.05). As indicated in Table (2), the average systolic PA of groups A and B diagnosed with AFi was significantly greater than that of the persons in the SiR group (P ≤ 0.05). There was no significant difference in mean (edi), (esy) LV diameter, posterior wall and interventricular septum thickness between the all groups.

All biochemical markers were evaluated for potential linkage; the only significant correlation found was between PTH and 25-OH vitamin D3. Table (3) shows a substantial negative association between Upth and 25-OH vitamin D3 and a non-significant negative correlation between PTH and each of T3 and T4.

Table (1): Comparing of the biochemical characteristics of (AFi) cases and (SiR) groups.

Item	Patients (AFi)		Control	P value
	Group A No. 100	GroupB No. 100	(SiR) No. 100	
BMI kg/m^2	23.1±1.22	21.95±1.75	24.35 ±2.48	0.09
Age Year	62.51 ±5.8	61.5 ± 5.05	61.35 ±5.44	0.07
Hb g/dl	15.2 ± 1.4	13.7 ±1.15	14.2 ±1.89	0.057
Cre mg/dL	0.91 ±0.24	0.71 ± 0.1	0.84 ± 0.21	0.06
25-OH vit.D3, ng/Ml	5.22 ±2.30	10.1 ±4.28	12.10 ±4.63	0.01*i
TSH, mcIU/mL	1.52 ±0.98	1.27 ±0.95	1.61 ±0.54	0.081
T3(nmol/L)	3.12±0.23	2.0±0.369	1.296±0.36	0.03*
T4(nmol/L)	199.1±25.1	181.2±31.1	103.9±23.6	0.00*
PTH, pg/ml	88.6±25.1	80.3±33.9	75.27±29.3	0.03*i
Ca (mg/dL)	9.02±0.52	8.99±0.68	8.7±0.12	0.09
Pi mg/dL	3.6±0.21	3.2±0.51	3.0±0.11	0.08

AFi, atrial fibrillation, SiR, sinus rhythm, Hb, hemoglobin ,Cre, creatinine, TSH, thyroid-stimulating hormone, 25-OH vit.D3,25hydroxyvitaminD,T3,triiodothyronine,T4,thyroxin,Ca,calcium,Pi,phosphorous. (*) significant p value ≤ 0.05, (i) non-significant for group B against control.

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Table (2): Comparison of traditional echocardiographic characteristics of two (AFi) and SiR groups.

Item	Patients (AFi)		Control	P value
	Group A No. =100	Group B No. =100	(SiR) No. =100	
LA	45.1 ±4.1	47.9±3.1	36.6 ±3.4	0.002*
RA	32.6 ±3.6	39.0±3.8	30.9±3.6	0.08
PA	35.0±2.96	40.1±2.9	29.5±2.9	0.004*
LV-ej	63.6 ±3.77	60.4±4.1	63.9 ±4.2	0.002*
LV -sy	29.1 ±3.56	27.9±1.1	28.7±2.6	0.07
LV-edi	45.1± 3.23	46.8±2.2	44.9 ±3.9	0.054

LA: Left atrium(diameter, mm), RA: Right atrium(diameter, mm),PA, pulmonary artery (systolic pressure, mm Hg), LV, left ventricular(%), ej: ejection fraction , esy : end-systolic diameter(mm) ,edi : end-diastolic diameter(mm). (*) significant p value ≤ 0.05.

Table (3): Reduction in tumor sizes in three treatment protocols The relationship between PTH and 25-OH vitamin D3, T3, and T4 levels in hyperthyroid patients.

Correlation	Pearson Correlation	Significant (2-tailed)
PTH and 25-OH vitamin D3	-0.22	0.02*
PTH and T3	-0.14	0.32
PTH and T4	-0.12	0.43

Table (4) displays the outcomes of the forward progressive logistic regression test. The independent primary indicators of AFi in group A were found to be the LA diameter and 25-OH vitamin D3 level.

Table (4): Analysis of independent risk factors for AFi using logistic regression (Group A).

Character	HR(CI :95%)	P-value
PTH	1.75 (0.45–1.98)	0.51
LAdiameter	3.11(1.712-2.751)	0.02*
LV-ej	1.16 (0.37–1.43)	0.45
25-oH vit.D3	0.91(0.652-0.865)	0.01*

As demonstrated in Table (5), systolic PA, LA, and RA diameters were the independent primary indicators of (AFi group B) and predisposes to the development of (AFi). Heart failure, myocardial infarction, myocardial fibrosis, and hypertensive cardiac disorders are all linked to the renin-angiotensin-aldosterone pathway [10].

Table (5): Analysis of independent risk factors for AFi (Group B) using logistic regression.

Character	HR(CI :95%)	P-value
PA systolic pressure	1.75 (1.412-2.311)	0.03*
LA diameter	2.58 (1.911-2.790)	0.00*
RA diameter	1.86 (1.458-2.312)	0.004*

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Discussion

Primary hyperaldosteronism causes an increase in the incidence of Afi [11]. Angiotensin II, which is created locally in primary hyperaldosteronism, is linked to fibrosis in the reactive tissues and myocyte death [12,13].

Angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors, which are RAAS inhibitors, have been shown to protect against AFi by this mechanism. These medications had an 18% reduction in new-onset AF. Among patients with heart failure, the rate can reach 43% [14,15]. RAAS blockage reduces the likelihood of AFi recurrence and failure rates following cardioversion [16]. Reentry cycles are made easier by AFi's reduced effectiveness refractory period and lower atrial impulse velocity [17,18,19,20]. Action potential duration, shorter action potential plateau time, refractory period, and wavelength—the distance traversed by the electrical impulse throughout the refractory period—are all effects of the decline in calcium channels of the L type in the short term as well as the long term. These alterations are typical of Afi [21]. Another study revealed that vitamin D serves purposes aside from those related to bone metabolism [22]. According to the previous studies 25-OH vit. D3 deficiency may impact the onset of inflammatory bowel disease, autoimmune disorders, rheumatoid arthritis, some cancers, psoriasis, multiple sclerosis, diabetes, stroke, cardiac failure and infectious diseases like pneumonia and tuberculosis [23,24]. Supplementation with vitamin D is also effective in these people [23] by blocking RAAS and PTH, vitamin D maintains blood pressure homeostasis [24]. The research demonstrated that vitamin D and its equivalents could lower levels of angiotensin II and renin [16]. Calcium is crucial for both AFi initiation and electrophysiological modification [25]. By reducing the atrial refractory action and potential duration, intracellular calcium excess inside the atrial myocytes contributes to the growth and ongoing functioning of the AFi[4].We suggested that 25-OH vit.D3 insufficiency might be connected to AFi, given the significance of RAAS in the pathological process of AFi and the harmful regulating role that vitamin D plays for renin[16].

In current reasearch, three groups were contrasted using 25-OHvit. D3 patients with nonvalvular AFi disease had considerably lower 25-OHvit,D3 levels than patients without (AFi),and those with valvular (AFi) disease had higher 25-OHvit. D3 levels ($P \leq 0.05$). It is well established that vitamin D decreases levels of pro-inflammatory cytokines and raises levels of IL-10[6]. This result has led to the hypothesis that 25-OH vit. D3 insufficiency may contribute to the emergence and maintenance of AFi. Under conditions of normal atrial action potential, normal ventricular function and structure and transforming growth factor B1increases atrial fibrosis. Additionally, it increases conduction heterogeneity and AFi vulnerability [26]. According to certain theories, vitamin D insufficiency makes people more susceptible to AFi via increased TGFB1expression, conduction heterogeneity, and atrial fibrosis. In the start of AFi and electrophysiological remodeling, calcium is crucial [27]. PTH raises intracellular calcium levels by decreasing cardiomyocyte cellular calcium

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absorption and sarcoplasmic reticulum calcium reuptake [28]. In contrast to the assertion made by Rienstra et al. that vit. D3 status was unrelated to incident (AFi), our investigation found a link between 25-OH vit. D3 insufficiency and nonvalvular (AFi) [29]. In line with the findings of the literature, it was discovered in our investigation that both the LA and RA diameters were related to AF. PTH levels of individuals who had AFi were much greater than PTH concentrations of individuals without AFi when three groups were examined. This finding implies that AFi contributes to intracellular calcium overload by causing hyperparathyroidism due to vit.D deficiency. However, given the limited sample size and short follow-up period, the link between 25-OHVit.D3 and AFi needs to be verified in bigger, well-designed investigations.

Conclusions

Our investigation thus demonstrated a link between nonvalvular (AFi) and 25-OHVit.D3 insufficiency in hyperthyroid patients. However, it was discovered that both the control group and individuals with valvular AFi mitral valve disease had comparable vitamin D levels. This circumstance shows that valvular heart disease in these individuals causes AFi. Additionally, 25-OHVit.D3 insufficiency may contribute to nonvalvular AFi in patients with hyperthyorid.

Recommendations

To better understand the link between nonvalvular (AFi) and 25-OHVit.D3 insufficiency in hyperthyroid patients, the quantity of samples must be increased, and the disease must be researched in more than one location.

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Ethical clearance: The examination configuration is approved by the ethical committee of National Diabetes Center and cardiology outpatient clinic approved and the research protocol that was certified by the ethical council of the University of the Middle Technical, Institute of AL-Suwaira Technical, Medical Laboratory Department, Iraq. This study was conducted according to the approval of College of Medicine/ University of Diyala and in accordance with the ethical guidelines of the Declaration of ethical committee of the College (Document no.2023IHD801).

Conflict of interest: Nil

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تأثير نقص فيتامين د٣ على الرجفان الأذيني لدى مرضى فرط نشاط الغدة الدرقية

اقبال حنش ضفير [١]

الملخص

خلفية الدراسة: الرجفان الأذيني (AFi) أكثر شيوعًا مع تقدم الأشخاص في السن. بالإضافة إلى ذلك، هناك مؤشر آخر لحدوث الـ AFI وهو فرط نشاط الغدة الدرقية تحت الإكلينيكي، والذي يرتبط بزيادة خطر الإصابة بثلاثة أضعاف. يؤدي نقص فيتامين د إلى تنشيط مسار الرينين-أنجيوتنسين-الألدوستيرون، مما يؤثر على نظام القلب والأوعية الدموية.

اهداف الدراسة: لتقييم العلاقة بين قصور ٢٥-هيدروكسي فيتامين د٣ وحالات الـ AFI وفرط نشاط الغدة الدرقية مع الـ AFI الصمامي وغير الصمامي الذي يتطلب العلاج في المركز الطبي.

المرضى والطرائق: عينات مأخوذة من ٢٠٠ حالة رجفان اذيني AFi اعمارهم (من (٥٠-٦٥ سنة مقسمة إلى: حالات المجموعة أ مع AFi غير الصمامي وحالات المجموعة بAFi مع صمام ، و١٠٠ فرد سليم مع إيقاع الجيوب الأنفية الذين كانوا متطابقين مع العمر تم اختيارهم كمجموعات مراقبة. تم إجراء قياسات كيميائية حيوية قياسية، بما في ذلك مستويات ٢٥-هيدروكسي فيتامين د٣ , هرمون الغدة الدرقية، وهرمون الغدة الجار الدرقية.

النتائج: انخفضت الحالات في المجموعة (أ) من مستويات ٢٥-هيدروكسي فيتامين د٣ مقارنة بتلك الموجودة في المجموعتين الضابطة والمجموعة ب ($P \geq 0.05$) وبالمقارنة مع المجموعة الضابطة، كان لدى المرضى في المجموعتين أ وب الأذين الأيسر أكبر وضغط انقباضي وضغوط الشريان الرئوي أكبر.

الاستنتاجات: وهكذا، أظهرت الدراسة وجود علاقة بين حالات AFI غير الصمامية مع فرط نشاط الغدة الدرقية ونقص مستويات ٢٥-هيدروكسي فيتامين د٣.

الكلمات المفتاحية: -هيدروكسي فيتامين د٣، الرجفان الأذيني، الصمامات، هرمون الغدة الدرقية، فرط نشاط الغدة الدرقية.

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The Relations Between High Body Mass Index and Breast Cancer Characteristics

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Abstract

Background: In the context of rising obesity rates globally, understanding the effect of high body mass index (BMI) on breast cancer characteristics is crucial. Previous research has hinted at associations between obesity and some specific features, such as tumor receptor status and axillary lymph node involvement. However, a comprehensive investigation into these relationships is essential for informing targeted interventions and advancing our understanding of breast cancer in the context of obesity.
Objective: To investigate the relationship between high BMI and some key tumor characteristics such as hormone receptor status, HER2 receptor status, tumor grade, tumor size and axillary lymph node status.
Patients and Methods: A retrospective analysis of the medical records of 186 female breast cancer patients treated at Rizgary Teaching Hospital's Oncology Department in Erbil City during the year 2021.
Results: The study revealed a statistically significant association between elevated BMI and certain pivotal breast tumor characteristics, particularly HER2 receptor status. Additionally, obese individuals exhibited a significantly greater probability of having axillary lymph node-positive disease compared to their non-obese counterparts.
Conclusion: This study establishes a noteworthy association between high BMI and some critical breast cancer characteristics, which may underscore the clinical relevance of body mass index in shaping breast cancer profiles.
Keywords: Body mass index (BMI), breast cancer, tumor characteristics.

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Introduction

Nowadays, a high body mass index (BMI), encompassing both overweight and obesity, is a prevalent health issue with a rising occurrence on a global scale. The United Nation's World Health Organization (WHO) considers the global obesity as an epidemic; for instance, in 2016 more than 1.9 billion adults worldwide were overweight, and 650 million adults (13 percent of the world's adult population) were obese [1,2]. Contemporary research conducted worldwide has indicated a correlation between global obesity and heightened susceptibility to various chronic health conditions, including cardiovascular diseases, diabetes mellitus, and cancer. It is noteworthy that these associations may exhibit variations among diverse ethnic and racial groups [3,4].

The complexity of relationships between obesity and cancer is multifactorial that involves a numerous combination of many factors such as genetics, environmental and

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lifestyle influences, some of which are very intricate and not fully understood. Some explanations explicate that obesity induces a state of persistent low-grade inflammation, especially in white adipose tissue, resulting in immune dysfunction characterized by heightened production of pro-inflammatory cytokines, alternative macrophage activation, and impaired T-cell function. Given that the breast by itself consists predominantly of white adipose tissue, the development of breast cancer involves direct interactions with cells and signals from the adipose tissues, which are influenced by the state of obesity [5,6,7,8,9].

Importantly, variations in breast cancer subtypes and tumor characteristics could contribute to prognosis in obese individuals. According to several studies, obesity is linked to an elevated risk of hormone receptor-positive breast cancer, which may be influenced by an increase in circulating estrogen levels [10,11,12,13,14]. The higher adiposity in obese patients can lead to elevation in aromatase production and subsequently increase the circulating estrogen. Additionally, obese patients may experience a decrease in sex hormone-binding globulin (SHBG), a liver-produced glycoprotein that restricts estrogen biological activity.

Consequently, a reduction in SHBG levels in obese women could elevate the risk of hormone receptor-positive breast cancer [15,16,17]. Also, there is a complex and incompletely-understood relationship between obesity and human epidermal growth factor receptor (HER2) status in breast cancer. Based on some studies, obesity consistently correlates with poorer overall survival in early HER2-positive breast cancer [18,19,20].

Additionally, some studies have shown that obesity has linked to a higher disease stage, increased tumor size, elevated lymph node ratio, and the presence of more aggressive tumors at the time of diagnosis [10,21]. Notably, individuals with breast cancer and obesity face a up to 46% higher likelihood of developing distant metastases a decade after diagnosis of the disease [22]. Besides, obesity in breast cancer patients might also be related to increased frequencies of disease recurrence, diminished quality of life, second primary tumors, and heightened risk of disease-related complications such as lymphedema and other comorbidities like diabetes mellitus, hypertension, and cardiovascular diseases [23].

The aim of this study was to investigate the relationship between high body mass index (BMI) and key breast cancer tumor characteristics, including hormone receptor status, HER2 receptor status, tumor grade, primary tumor size and axillary lymph node status. Through this exploration, we sought to identify potential associations that could enhance our understanding of the impact of BMI on breast cancer presentation and progression.

Patients and Methods

Data source and study design

In this retrospective study, data were extracted from the medical records of patients diagnosed and treated for breast cancer at Rizgary Teaching Hospitals Oncology Center in Erbil, Iraq, covering the period from the beginning to the end of 2021. The aim was to comprehensively investigate the relationship between high body mass

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index (BMI) and breast cancer characteristics. The study exclusively included the records of 186 female patients aged 23 to 84 with histologically confirmed breast cancer. Cases with incomplete data in their records were excluded to ensure a focused and relevant dataset for analysis.

To systematically collect relevant data from patient records, a structured data collection form was designed. This form included fields for essential variables such as patient demographics, high BMI indicators, and breast cancer characteristics (e.g., hormone receptor status, HER2 receptor status, tumor grade, and disease stage). The form was meticulously crafted to ensure comprehensive data extraction aligned with the study objectives.

The body mass index (BMI) was calculated based on the recorded weight and height of the patients, using the following equation: BMI = weight (kg) ÷ squared height (meters). It placed patients into four distinct categories: underweight (BMI<18.5), healthy (normal) weight (BMI=18.5–24.9), overweight (BMI=25.0–29.9) and obese (BMI≥30.0) [24].

The variables of interest in breast cancer characteristics, including hormone receptor status, HER2 receptor status, tumor grade, tumor size, and axillary lymph node status, were precisely extracted from the patients' pathology and immunohistochemistry reports. In addition to histopathology reports, medical imaging reports such as CT scans and MRI scans were employed for the tumor staging based on the TNM Staging System of Union for International Cancer Control (UICC), 8th edition [25]. This comprehensive approach, combining histopathological assessment and imaging data, aimed to provide a thorough and accurate representation of the breast cancer cases under scrutiny in this study.

Statistical Analysis

The statistical analysis was conducted utilizing the Statistical Package for the Social Sciences (SPSS) software, version 25. Descriptive statistics were employed to summarize the demographic characteristics of the study population. Cross tabulation and the Chi-Square test in SPSS were utilized to assess significant associations between body mass index and other studied variables. In instances where tables exhibited small frequencies, Fisher's Exact test was employed for a more robust analysis. The significance level was set at a threshold of 0.05 ($p < 0.05$), indicating statistical significance.

Results

This retrospective study included 186 patients' records with confirmed breast cancer diagnosis. Table (1) shows the frequency distribution of body mass index (BMI) amongst the studied cases. Of note, there were no any underweight patients; only minority (around 11%) had a normal (healthy) weight; while the rest of the studied patients were either overweight or obese, at 58.1 percent and 30.6 percent respectively.

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Table (1): Distribution of patients with breast cancer according to BMI. (no=186).

Body Mass Index	Frequency	Percentage (%)
Underweight	0	0.0%
Healthy weight	21	11.3%
Overweight	108	58.1%
Obese	57	30.6%
Total	186	100.0%

The frequency distribution of various breast cancer tumor characteristics, including hormone receptor status, HER2 receptor status, tumor grade, tumor size, and axillary lymph node status were examined. This is in addition to identifying their relations with the patients' body mass index.

Regarding the associations between body mass index and the hormone receptor status in the studied patients' records, as seen in Table (2), generally just under three quarters of the patients were hormone receptor negative. There were no statistically significant differences in hormone receptor status expression among different BMI categories. The Pearson Chi-Squared p-value was 0.734.

Table (2): Association between BMI and hormone receptor status. (no=186).

BMI Category	Hormone Receptor Status			p-value
	Negative	Positive	Total	
Healthy, n (%)	6 (28.6%)	15 (71.4%)	21 (100%)	0.734
Overweight, n (%)	23 (21.3%)	85 (78.7%)	108 (100%)	
Obese, n (%)	14 (24.6%)	43 (75.4%)	57 (100%)	
Total	43 (23.1%)	143 (76.9%)	186 (100%)	

On the other hand, in regard to the distribution of HER2 receptor status among the breast cancer patients, as depicted in Table (3), around 80 percent of the patients had negative HER2 receptor status. This distribution was statistically different between various BMI subgroups. For instance, comparing to the obese patients, the non-obese (healthy and overweight) patients were significantly more likely to have HER2 negative disease at the time of presentation. The Fisher's Exact two-tailed p-value was 0.007.

Table (3): Correlation between BMI and HER2 receptor status. (no=186).

BMI Category	HER2 Receptor Status			p-value
	Negative	Positive	Total	
Healthy, n (%)	17 (81.0%)	4 (19.0%)	21 (100%)	0.007
Overweight, n (%)	93 (86.1%)	15 (13.9%)	108 (100%)	
Obese, n (%)	37 (64.9%)	20 (35.1%)	57 (100%)	
Total	147 (79.0%)	39 (21.0%)	186 (100%)	

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Another important studied variable was tumor grade. Table (4) shows the distributions of the three tumor grades amongst the studied patients' records. Referring to data in Table (4), only seven percent of the patients had grade I (low grade) disease, around half of them had grade II (intermediate grade) disease, and more than a third of them had grade III (high grade) breast cancer. This distribution of the tumor grades was almost similar between the different BMI categories without any significant difference between them. The p-value was very close to one.

Table (4): Relations between tumor grade and BMI. (no=186).

BMI Category	Tumor Grade				p-value
	Grade I	Grade II	Grade III	Total	
Healthy, n (%)	2 (9.5%)	10 (47.6%)	9 (42.9%)	21 (100%)	0.914
Overweight, n (%)	8 (7.4%)	59 (54.6%)	41 (38.0%)	108 (100%)	
Obese, n (%)	3 (5.3%)	32 (56.1%)	22 (38.6%)	57 (100%)	
Total	13 (7.0%)	101 (54.3%)	72 (38.7%)	186 (100%)	

Similarly, there were no statistically meaningful association between the primary tumor size and body mass index of the studied patients. Table (5) illustrates that about three quarters of the patients, regardless of their BMI groups, had small tumor sizes (T1 and T2), and about 10 percent of the patients, whether healthy, overweight or obese, have advanced (T4) disease. Obviously, there was no any statistically significant difference between the BMI categories related to the primary breast tumor size at the time of presentation. The Fisher's Exact p-value was 0.599.

Table (5): Exploring the connection between tumor size and BMI. (no=186).

BMI Category	Tumor Size						p-value
	Tis	T1	T2	T3	T4	Total	
Healthy, n (%)	0 (0.0%)	5 (23.8%)	11 (52.4%)	3 (14.3%)	2 (9.5%)	21 (100%)	0.599
Overweight, n (%)	4 (3.7%)	25 (23.1%)	58 (53.7%)	10 (9.3%)	11 (10.2%)	108 (100%)	
Obese, n (%)	0 (0.0%)	7 (12.3%)	37 (64.9%)	7 (12.3%)	6 (10.5%)	57 (100%)	
Total	4 (2.2%)	37 (19.9%)	106 (57.0%)	20 (10.8%)	19 (10.2%)	186 (100%)	

Another crucial tumor characteristic in breast cancer patients is the status of axillary lymph nodes, indicating whether they are affected by the malignancy. Examining Table (6) indicates that, in general, just under 60% of patients had axillary node-positive disease at the time of breast cancer diagnosis. Notably, obese patients were significantly more susceptible to axillary node-positive disease, surpassing 70%, compared to approximately half of the healthy and overweight patients. The Pearson Chi-Square analysis yielded a p-value of 0.039.

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Table (6): Association between BMI and axillary lymph node status. (no=186).

BMI Category	Axillary Nodal Status			p-value
	Node Negative	Node Positive	Total	
Healthy, n (%)	10 (47.6%)	11 (52.4%)	21 (100%)	0.039
Overweight, n (%)	52 (48.1%)	56 (51.9%)	108 (100%)	
Obese, n (%)	16 (28.1%)	41 (71.9%)	57 (100%)	
Total	78 (41.9%)	108 (58.1%)	186 (100%)	

Discussion

Because many studies link the associations between excess body weight and cancer, many health establishments such as the World Health Organization (WHO), have recently advocated for ongoing monitoring of body mass index to assess obesity trends in populations over time [26].

Regarding the relationship between body mass index and the hormone receptor status expression in breast cancer, the current study showed that there was no statistically significant effect of overweight or obesity on the types of hormone receptor characteristics (positive vs. negative). Based on previous studies, there are contradicting results about that. For instance, akin to the findings of the present study, research conducted in Indonesia demonstrated a lack of a substantial association between obesity and the hormone receptor status of primary breast cancer [27]. On the other hand, some other studies are opposing the results of our study. For example, a study found that obese women, with body mass index of 35 or higher, have a strong likelihood to develop estrogen receptor-positive/progesterone receptor-positive breast cancer, but not estrogen-negative breast cancer [28]. This could be primarily attributed to elevated levels of free estradiol circulating in the blood stream of obese individuals. Discrepancies in population characteristics and other factors influencing hormone receptor expression in primary breast cancer may contribute to variations in this outcome [11,29].

On the contrary, our study revealed a strong relationship between obesity and human epidermal growth factor receptor (HER2) expression status in the studied women with breast cancer. Based on the current study, the chance of being obese were about three times higher in those with HER2-positive disease, compared with those with HER2-negative disease. The connection between obesity and HER2-positive breast cancer remains not fully comprehended. According to certain studies on this matter, obesity consistently correlates with poorer overall survival in early-stage HER2-positive breast cancer patients. However, the evidence regarding the association between obesity and advanced HER2-positive breast cancer is still diverse [18].

Concerning the relationship between excessive body weight and breast cancer staging characteristics, while the present study did not identify a significant link between excess body weight and the grade and size of the primary tumor, it did establish a statistically significant association between obesity and axillary lymph node status. These

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findings, to some extent, align with other studies investigating the impact of excess body weight on breast cancer staging. For instance, research conducted at the Geneva Cancer Registry in Switzerland compared diagnostic features among obese and non-obese breast cancer patients. The results indicated that obese patients more frequently presented with advanced disease stages, experiencing higher rates of surgical delays and extended hospital stays post-surgery The authors suggested that weight-related embarrassment might contribute to reluctance among obese women for physical examinations. They propose that educating obese women about breast self-examination and clinical breast examination may be less effective, highlighting the need to develop strategies to prevent advanced disease upon diagnosis in this expanding patient demographics [26,30].

To end with, more studies in this field are necessary to elucidate the link between elevated body mass index and the occurrence of breast cancer, and to gain deeper insights into how obesity influences breast cancer behavior. Revealing the mechanisms associated with obesity could help identify at-risk populations, and interventions targeting these mechanisms may mitigate breast cancer-related morbidities and fatalities [31,32].

Conclusions

In conclusion, this study underscores a significant association between high body mass index (BMI) and some important breast cancer prognostic characteristics, particularly impacting tumor receptor status and axillary lymph node involvement. Compared to non-obese individuals, obese patients exhibited a significantly higher prevalence of HER2-receptor positive disease, and a higher rate of axillary lymph node positivity, emphasizing the clinical relevance of BMI in breast cancer staging and prognosis.

Moving forward, further investigations should explore the underlying mechanisms of this relationship, providing a more nuanced understanding. This study contributes valuable insights into the complex interplay between obesity and breast cancer, paving the way for targeted interventions and personalized treatment strategies.

Recommendations

Further studies in this field are necessary to better clarify the mechanisms of links between elevated body mass index and the breast cancer tumor characteristics; and to further understand how obesity affects breast cancer behavior and aggressiveness.

Source of funding: The current study was funded by our charges with no any other funding sources elsewhere.

Ethical clearance: The study was approved by the Research Ethics Committee in Hawler Medical University/College of Dentistry in May 2022. There were minimal ethical implications since the study was retrospective; and the participants' identities were protected by assigning each single patient with a specific serial number.

This study was conducted according to the approval of College of Medicine/ University of Diyala and in accordance with the ethical guidelines of the Declaration of ethical committee of the College (Document no.2023SSM797).

Conflict of interest: Nil

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العلاقات بين ارتفاع مؤشر كتلة الجسم وخصائص سرطان الثدي

شوان سلام معروف [١]

الملخص

خلفية الدراسة: في سياق ارتفاع معدلات السمنة على مستوى العالم، فإن فهم تأثير ارتفاع مؤشر كتلة الجسم (BMI) على خصائص سرطان الثدي أمر بالغ الأهمية. وقد أشارت الأبحاث السابقة إلى وجود ارتباطات بين السمنة وخصائص محددة للورم، مثل حالة مستقبلات الورم وتورط العقدة الليمفاوية الإبطية. ومع ذلك، فإن إجراء تحقيق شامل في هذه العلاقات أمر ضروري لإبلاغ التدخلات المستهدفة وتعزيز فهمنا لسرطان الثدي في سياق السمنة.

اهداف الدراسة: لدراسة العلاقة بين مؤشر كتلة الجسم المرتفع وبعض خصائص الورم الرئيسية مثل حالة مستقبل الهرمون، وحالة مستقبل (HER2)، ودرجة الورم، وحجم الورم، وحالة العقدة الليمفاوية الإبطية.

المرضى والطرائق: تحليل بأثر رجعي للسجلات الطبية لـ ١٨٦ مريضة بسرطان الثدي تم علاجهن في قسم الأورام في مستشفى رزكاري التعليمي في مدينة أربيل خلال عام ٢٠٢١.

النتائج: كشفت الدراسة عن وجود علاقة ذات دلالة إحصائية بين ارتفاع مؤشر كتلة الجسم وبعض خصائص أورام الثدي المحورية، وخاصة حالة مستقبل (HER2). بالإضافة إلى ذلك، أظهر المرضى الذين يعانون من السمنة المفرطة احتمالية أكبر بكثير للإصابة بمرض العقدة الليمفاوية الإبطية الإيجابية مقارنة بنظرائهم غير المصابين بالسمنة.

الاستنتاجات: هذه الدراسة تثبت وجود علاقة جديرة بالملاحظة بين ارتفاع مؤشر كتلة الجسم وبعض خصائص سرطان الثدي الحرجة، والتي قد تؤكد الأهمية السريرية لمؤشر كتلة الجسم في تشكيل ملامح سرطان الثدي.

الكلمات المفتاحية: مؤشر كتلة الجسم (BMI)، سرطان الثدي، خصائص الورم

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The effect of gender and site on the condylar head measurements in Diyala

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Abstract

Background: The condylar process of mandible is an ellipsoid hard tissue (bony structure) with a thin neckline that joins to the mandibular ramus. The condylar processes are a critical anatomic component of the mandible that development of mandibular bone is attributed in the sagittal and vertical directions by condylar process.

Objective: To radiographical assessment of condylar head measurements according to gender and site by uses cone beam computed tomography.

Patients and Methods: The study samples consisted of sixty-five individuals (19 male and 46 female) with age range from (20-50) years old. Width of condylar head, length of condylar head and condylar head height were measured in the study by using cone beam computed tomography from radiology archive in specialist dental center in Diyala.

Results: The results show condylar head width, condylar head height and condylar head length in sides (right and left), males have noted higher mean value than females. The results show condylar head width and condylar head length in left side, have recorded higher mean value than right side. While, condylar head height in left side, have recorded lower mean value than right side.

Conclusion: Condylar dimensions and sizes may be associated with gender and site. Males have higher condylar dimensions and sizes than females.

Keywords: Condylar head, cone beam computed tomography.

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Introduction

One of the most significant joints of the human body, temporomandibular joint (TMJ) is closely associated to the teeth and oral cavity. The oral structures and connected muscles directly regulate the position and role of the mandibular condylar part of the TMJ [1].

According to nearly definitions, the TMJ is a complicated apparatus in the human body that simplifies a number of functions, such as speaking, eating, and swallowing. It also preserves the mandibular site stable and avoids dislocation carried by infrequent or outside forces [2].

Mandibular condyle, articular eminence, glenoid fossa, and articular disc, which are situated between the glenoid fossa and condylar process. All these, are the essential parts of the temporomandibular joint (TMJ).[3].

Because the morphology, size, and interrelations of the TMJ's constituent tissues can vary importantly, anthropologists are interested in the condyle. Such alteration can

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be critical in the diagnosis of disorders affecting the temporomandibular joint.[4].

The condyle, which is the chief location of growth in the jaw, is replies to continuing stimuli during the remodeling process and is therefore critical to the last dimensions of the adult mandible. Both the final mandibular dimensions and the final relationship between the maxillary and mandibular arches might be associated to size and volume of condyle. Evaluating the anomalies and skeletal variations that influence the TMJ needs a radiographic investigation of the TMJ buildings [5].

Multidirectional or clear views of the TMJ are not likely with conventional radiographic imaging, such as panoramic and cephalometric radiography [6]. For oral and maxillofacial requests, cone-beam computed tomography (CBCT) is beneficial due to its high-resolution images and fast image time. TMJ subjects are one of the many conditions for which CBCT is working.[7,8,9].

Therefore, the aims of this study are to evaluation the variations in the mandibular condylar head dimensions involving condylar head width, length and height in sample of Diyala people using CBCT.

Patients and Methods

The study samples consisted of sixty-five individuals (19 male and 46 female) per age variety from (20-50) years.

Study samples were separated into:

1-Group 1 (males): - Nineteen.

2-Group 2 (females): - Forty-six.

Cone beam computed tomography (CBCT) scanner: A NewTom VGi TM CBCT scanner was used to get the pictures. The scanning parameters were (16 cm x 14 cm) or (24 cm x 19 cm) CBCT imaginings, 110VP, 24 seconds, 5.7mA, and a voxel size of 0.5mm.

The condylar height and length dimensions were determined based on the methods described by Krisjane,[10] height of condylar head lined distance between highest of the condylar head and cross-section line in sagittal plane as in Figure (1); length of condyle line distance between furthermost posterior and anterior point of condylar head in sagittal plane as in Figure (1); while the condylar width measurements were determined based on the methods defined by Hilgers,[11] which is the lined distance between the lateral and medial poles of mandible in the coronal plane as in Figure (2).

One investigator measured the condylar height, width, and length using CBCT pictures.

This study included individuals with normal occlusion, non-edentulous individuals, excluded individuals with (class I-II Kennedy classification, history of trauma, facial asymmetry, fracture and cystic lesion of TMJ).

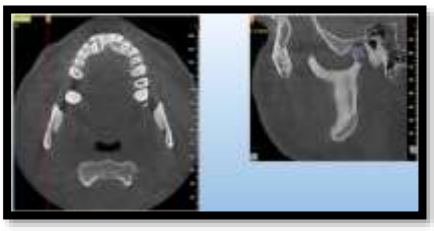

Figure (1): Measurement of condylar length and height in right side of 37 years old male on CBCT in sagittal section.

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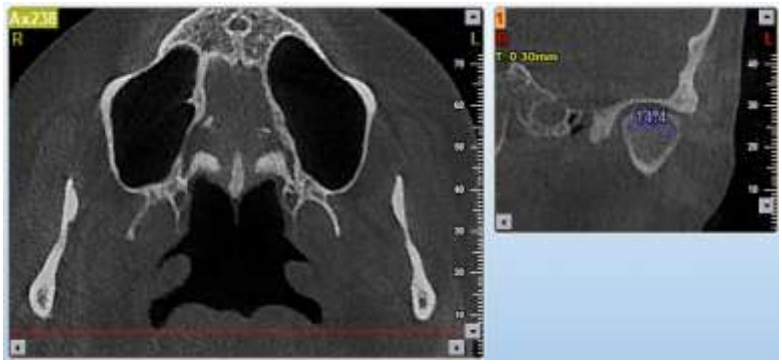

Figure (2): Measurement of condylar width in left side of 22 years old female on CBCT in coronal section.

Statistical Analysis

SAS (2018) -Statistical Analysis System- application was utilized to distinguish the outcome of difference groups (Site and Gender) in study parameters. In this study, the t-test was applied to compare means statistically.

Results

The results illustration condylar head width in sides (right and left), males have documented high mean value (right 15.26 mm, left 16.07 mm) than females (right 14.05mm, left 14.87 mm), with a statistically non-significant relationship as shown in Table (1).

Regarding to condylar head length in sides (right and left), males have documented higher mean value (right 7.48 mm, left 7.26 mm), than females (right 6.99 mm, left 7.23 mm), with a statistically non-significant relationship as shown in Table (2).

Also, condylar head height in sides (right and left), mean value of males (right 3.32 mm, left 2.99 mm) have recorded more than females (right 2.98 mm, left 2.93mm) with a statistically non-significant relationship as revealed in Table (3).

Table (1): Summary data, and t-test (matched paired) for test variances of (condylar width) about (Right and Left) among male and female.

Groups	Site	No.	Mean	SD	SE	MP (t-test)	Df	C.S. (*)
Male	Right	19	15.26	2.62	0.60	1.266	1	0.282 NS
	Left	19	16.07	2.74	0.63			
Female	Right	46	14.05	2.01	0.29	1.051	1	0.469 NS
	Left	46	14.87	2.42	0.35			

* NS: Non-Sig. at P>0.05

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Table (2): Summary data, and t-test (matched paired) for test variances of (condylar length) about (Right and Left) among male and female.

Groups	Site	No.	Mean	SD	SE	MP (t-test)	Df	C.S. (*)
Male	Right	19	7.48	1.19	0.27	0.588	1	0.507 NS
	Left	19	7.26	1.21	0.27			
Female	Right	46	6.99	1.25	0.18	0.602	1	0.244 NS
	Left	46	7.23	1.25	0.18			

* NS: Non-Sig. at P>0.05

Table (3): Summary data, and t-test (matched paired) for test variances of (condylar height) about (Right and Left) among male and female.

Groups	**Site**	**No.**	**Mean**	**SD**	**SE**	**MP (t-test)**	**Df**	**C.S. (*)**
Male	Right	19	3.32	0.68	0.15	0.108	1	0.097 NS
	Left	19	2.99	0.60	0.14			
Female	Right	46	2.98	0.80	0.12	0.391	1	0.745 NS
	Left	46	2.93	0.75	0.11			

* NS: Non-Sig. at P>0.05

Results show condylar head width in left side, have recorded higher mean value (left 15.22 mm), than right side (right 14.41mm), with a statistically non-significant relationship as shown in Table (4).

Regarding to condylar head length in left side, have recorded higher mean value (left 7.24 mm), than right side (right 7.13 mm), with a statistically non-significant relationship as shown in Table (5).

While, condylar head height in left side, have recorded lower mean value (left 2.95 mm), than right side (right 3.08 mm), with a statistically non-significant relationship as shown in Table (6).

Table (4): Effect of Site and Gender in Condylar width.

Measurement	**Gender**	**Mean ± SE**		**T-test (P-value)**
		Right side	**Left side**	
Condylar width	Male	15.26 ±0.60	16.07 ±0.63	1.266 NS (0.282)
	Female	14.05 ±0.2I	14.87 ±0.35	1.051 NS (0.469)
	T-test (P-value)	1.199 * (0.0493)	1.371 NS (0.0855)	---
	Total mean	14.41 ±0.28	15.22 ±0.31	1.22 NS (0.0971)

* S: Sig. at P<0.05, NS: Non-Sig. at P>0.05

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Table (5): Effect of Site and Gender in Condylar length.

Measurement	Gender	Mean ± SE		T-test (P-value)
		Right side	Left side	
Condylar length	Male	7.48 ±0.27	7.26 ±0.27	0.588 NS (0.507)
	Female	6.99 ±0.18	7.23 ±0.18	0.602 NS (0.244)
	T-test (P-value)	0.677 NS (0.219)	0.676 NS (0.471)	---
	Total mean	7.13 ±0.15	7.24 ±0.15	0.510 NS (0.628)

* NS: Non-Sig. at P>0.05

Table (6): Effect of Site and Gender in Condylar height.

Measurement	**Gender**	**Mean ± SE**		**T-test (P-value)**
		Right side	**Left side**	
Condylar height	Male	3.32 ±0.15	2.99 ±0.14	0.108 NS (0.097)
	Female	2.98 ±0.12	2.93 ±0.11	0.391 NS (0.745)
	T-test (P-value)	0.419 NS (0.111)	0.387 NS (0.732)	---
	Total mean	3.08 ±0.09	2.95 ±0.08	0.391 NS (0.655)

* NS: Non-Sig. at P>0.05

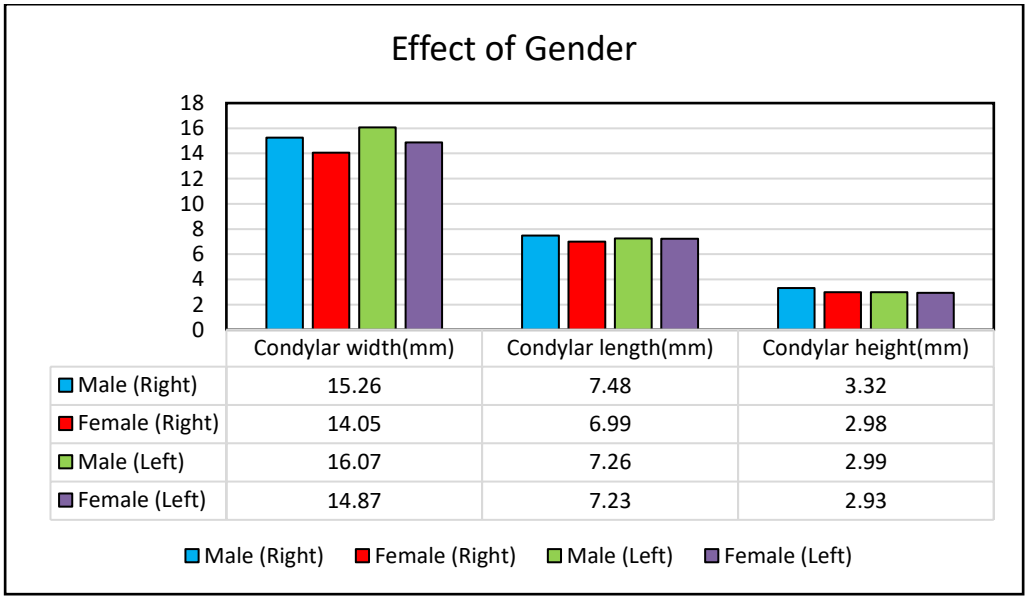

Figure (3): Gathering bar charts of dissimilar parameters among gender in studied groups.

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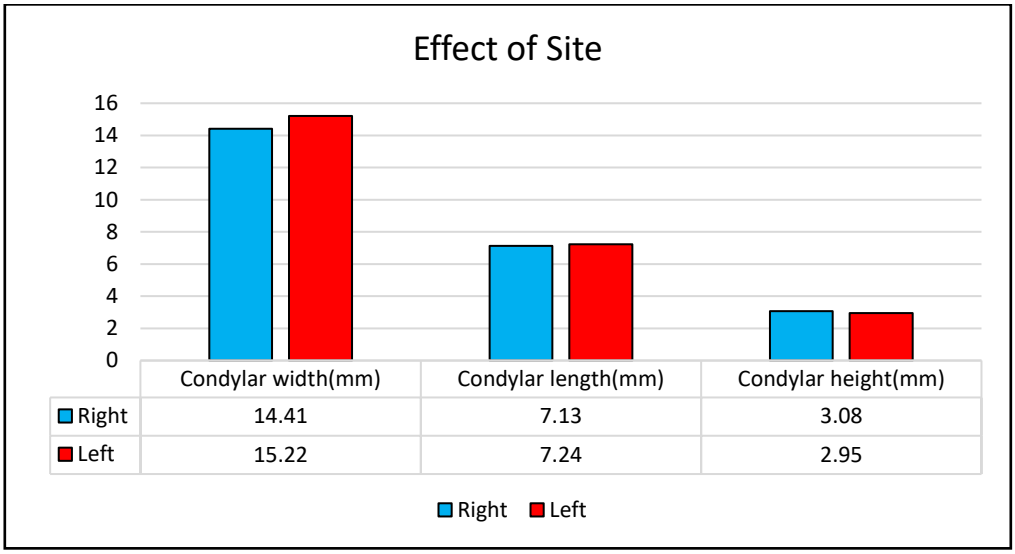

Figure (4): Gathering bar charts of dissimilar parameters among sites in studied groups.

Discussion

Growth of condyle was symmetrical in the age variety less 20 years old, rendering to Neto [12] with variations in front dimension happening during growth.

The presence of the condylar process of mandible may differ from one individual to another and among unlike age groups. A detailed information of the morphology, anatomy and structure is essential in order to differentiate between a normal variation and unusual condyle. Human condyles range in size from 8 to 10 mm antero-posteriorly and from 15 to 20 mm mediolaterally [13].

Compared to computed tomography (conventional), computed tomography (cone beam) exposures patients to fewer radiation and attains high accuracy levels in high-resolution imagery [14].CBCT imagery of TMJ composite, counting the condyle, permits for additional reliable and precise finding of additional delicate bone anomalies in TMJ, which shortens following clinical decisions [15].

Our results show condylar head width in left side and condylar head length have recorded higher mean value than right side. While, condylar head height in left side, have recorded lower mean value (left 2.94 mm), than right side (right 3.08 mm), this may be clarified by the fact that the mandibular condyle is affected by the functional load, occlusal force, kind of malocclusion, and left and right sides. It has understated differences in appearance that are manifest during normal growing or adaptive condylar remodeling to reason for trauma, malocclusion, endocrine diseases, differences in development, and radiation therapy [16,17].

Our results show condylar head length and condylar head height in sides (right and left), males have documented high mean value than females, these results approve with the results of El-Bahnasy,[18] they detailed that no statistically significant variance in the anteroposterior length of the head of condyle

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between males and females. Males had a mean condylar length of 9.20 mm and 9.08 mm on the sides (right and left), respectively more than females which had a mean condylar length of 7.35 mm and 7.24 mm on the sides (right and left), respectively.

These findings matched those of Ishwar Kumar ,[19] they definite that the anteroposterior length of the mandibular condyles was larger in males (9.23 mm and 9.57 mm on the right and left sides, respectively), while the females (8.73 mm and 8.66 mm on the right and left sides, respectively) had lesser values.

Our results show condylar head width in right and left side, males have documented higher mean value than females, this agrees with results of El-Bahnasy,[18] they specified that males had mean mandibular condyle mediolateral width dimensions of 22.17 mm and 22.22 mm on the sides (right and left), respectively; females had mean condylar width measurements of 16.74 mm and 17.03 mm on the sides (right and left), respectively with a statistically significant change.

Similarly, the study of Ishwar Kumar,[19] described that there was no statistically significant change between male and female (the mediolateral width determined on the left side, which was 17.81 mm for females and 18.11 mm for males. On the right side, the condylar width was measured to be 18.10 mm for males and 17.66 mm for females), this may be described by the fact that, the morphologic differences got crossways investigations showed on numerous populations propose that condylar head morphology may vary throughout ethnic groups. It is essential to report and exactly describe all variations. This could aid with the finding of several pathological conditions that affect TMJ [18].

Conclusions

Condylar dimensions and sizes might be linked with gender and site. Males have higher Condylar dimensions and sizes than females.

Recommendations

A new study comprises a larger number of people and compared them to patients suffering from temporomandibular joint disorders.

Source of funding: The current study was funded by our charges with no any other funding sources elsewhere.

Ethical clearance: This study was conducted according to the approval of College of Medicine/ University of Diyala and in accordance with the ethical guidelines of the Declaration of ethical committee of the College (Document no. 2024HMI833).

Conflict of interest: Nil

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تأثير الجنس والموقع على قياسات رأس اللقمة في ديالى

حيدر مهدي عيدان [١]

الملخص

خلفية الدراسة: النتوء اللقمي للفك السفلي عبارة عن نسيج صلب إهليلجي (بنية عظمية) ذو خط عنق رفيع يتصل بفرع الفك السفلي. تُعد النتوءات اللقمية مكونًا تشريحيًا مهمًا للفك السفلي حيث يُعزى تطور عظم الفك السفلي في الاتجاهين السهمي والرأسي من خلال الناتئ القمي.

اهداف الدراسة: لتقييم الشعاعي لقياسات رأس اللقمة حسب الجنس والموقع باستخدام التصوير المقطعي المحوسب بالحزمة المخروطية.

المرضى والطرائق: تكونت عينة الدراسة من خمسة وستين فرداً (١٩ ذكراً و ٤٦ أنثى) تتراوح أعمارهم بين (٢٠-٥٠) سنة. تم قياس عرض الرأس اللقمي وطول الرأس اللقمي وارتفاع الرأس اللقمي في الدراسة باستخدام التصوير المقطعي المحوسب بالحزمة المخروطية من أرشيف الأشعة في مركز طب الأسنان التخصصي في ديالى. تم استخدام تطبيق التحليل الإحصائي SAS (٢٠١٨) – نظام التحليل الإحصائي – لتمييز نتائج مجموعات الاختلاف (الموقع والجنس) في معايير الدراسة.

النتائج: أظهرت النتائج عرض رأس اللقمة، ارتفاع رأس اللقمة وطول رأس اللقمة في الجانبين (الأيمن والأيسر)، وقد لاحظ الذكور قيمة متوسطة أعلى من الإناث. أظهرت النتائج أن عرض رأس اللقمة وطول رأس اللقمة في الجانب الأيسر، قد سجلا قيمة متوسطة أعلى من الجانب الأيمن. بينما سجل ارتفاع رأس اللقمة في الجانب الأيسر قيمة متوسطة أقل من الجانب الايمن.

الاستنتاجات: قد ترتبط أبعاد وأحجام اللقمات بالجنس والموقع. الذكور لديهم أبعاد وأحجام لقمية أعلى من الاناث.

الكلمات المفتاحية: رأس اللقمة , التصوير المقطعي المحوسب بالحزمة المخروطية

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Frequency and Associated Factors of Mask-Induced Acne among Healthcare Workers

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Abstract

Background: Mask-induced acne, also known as maskne, is a skin condition that has become increasingly prevalent during the COVID-19 pandemic. The prolonged use of facial masks has been found to cause skin irritation, inflammation, and the development of acne. Healthcare workers are at an increased risk due to their prolonged and consistent use of facial masks during their work.

Objective: To investigate the occurrence and identify risk factors of mask induced acne among health care workers.

Patients and Methods: This cross-sectional study included 115 healthcare workers at Al_Imamain Al_Kadhumain Medical city who wore the mask daily. Collected data include demographic characteristics (age, sex, and occupation), mask-wearing data include the type of mask worn, the pattern of mask use (disposable or reusable mask), time spent wearing masks over the years, the daily duration of mask usage, and specifics regarding participants' acne, encompassing the type and facial location of the acne, as well as accompanying symptoms (itching, dryness, oiliness, moisture, warmth, and excessive facial sweating), and factors that exacerbate the condition, were all considered in the study.

Results: Out of 115 included subjects 37 (32.17%) were suffering from new-onset mask induce acne. There were 10 men and 27 women. The mean age was 35.5±7.3 years (range: 24-47). The vast majority of the included participants (81.08%) were wearing surgical masks. The duration of mask use in about three-fourths of patients was ≥ one year. About three-fourth of patients were using reusable mask. Pustules were the most common lesion, accounting for two-thirds of the participants, followed by comedones (37.83%). The most common site was cheeks (75.67%), followed by the chin (48.65%). Stress was the most common aggravating factor occurred in 37.84% of the participants, followed by high-glycemic diet and hot weather (27.03% each).

Conclusion: Female, prolonged duration of mask use and wearing reusable masks could be associated with the development of maskne. Stress and a glycemic diet could aggravate the lesion associated with maskne.

Keywords: Maskne, acne lesion, aggravating factors.

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Introduction

Acne is considered to be the third-commonest skin pathology. It is defined by pilosebaceous unit impediment and/or inflammation. Clinically, it represents as

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whiteheads, blackheads, or pimples [1]. Acne pathogenesis involves the interaction of four main pathogenic factors: sebaceous gland hyper-secretion, aberrant follicular keratinization (resulting in pilo-sebaceous duct block), increased follicular establishment of the commensal, anaerobic bacteria Cutibacterium acnes (C. acnes), and host inflammatory response [2,3].

During the COVID-19 pandemic and thereafter, wearing a face mask became a traditional behavior, whether among health workers or public. Although, the COVID-19 pandemic subsided, the recurrent emergence of new variants of the virus induces ongoing precautions, among them wearing a face mask. This is especially evident among health workers, because they expose more people than other populations to the imminent risk. Although such a measure is crucial, it not come without disadvantages.

Masks induce mechanical stress on the skin, manifesting as pressure, friction, and rubbing. This stress triggers keratinocyte proliferation, resulting in subsequent hyperkeratosis characterized by alterations in the stratum corneum, reduced water content, irritation, and a compromised skin barrier [4]. Moreover, the pressure from masks may prompt the occlusion of pilo-sebaceous ducts [5]. Additionally, both pressure and friction have the potential to mechanically rupture comedones, leading to subsequent inflammation [6].

The reported prevalence of acne stemming from prolonged mask usage ranges widely, from 1.3% to 53.1%. This broad spectrum in mask-induced acne prevalence may be attributed to various factors, including the participants' professions, sample sizes, genetic predispositions, environmental influences, duration of mask-wearing, types of masks used, and prior facial skin conditions [7].

In Iraq, there is no previous study that addresses the effect of wearing a mask on acne. Thus, the study aimed to investigate the incidence, demographic, and clinical profile of acne following mask wearing among health workers at Al-Imamain Al-Kadhumain Medical city/ Baghdad.

Patients and Methods

The Study Population

This is a cross-sectional descriptive study that included a total of 115 healthcare workers at Al-Imamain Al-Kadhumain Medical city whose work usually requires using a mask. The study was performed during the period from November 2022 to April 2023. Subjects with any previous history of acne before using the mask and those with known allergies were excluded from the study. The diagnosis of acne was based on clinical examinations conducted by a specialist dermatologist. The approval of the study was obtained from Institutional Review Board, College of Medicine, Al-Nahrain University.

Prior to data collection, explicit written consent was secured from each participant, accompanied by a thorough explanation of the study's objectives. Participants were granted unrestricted autonomy to withdraw from the study at any point. The confidentiality of all data throughout the study was assured, and participants were given the guarantee that the collected data would be solely utilized for research purposes.

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Data Collection

The aata were collected through a self-structured questionnaire. These data involving demographic characteristic (age, sex and occupation), details regarding mask wearing which involve the type of mask worn, pattern of mask use (disposable or reusable), the duration of mask wearing through the years, the duration of mask wearing per day, and details of participants' acne, including the type and site of acne on the face, escorted symptoms (itching, dry skin, greasy skin, moisture, heat, and excess facial sweating), and aggravating factors.

Statistical Analysis

A descriptive statistic was used to analyze the data. Numerical data were expressed as the mean and standard deviation. Categorical variables were expressed as numbers and percentages. All statistical analyses were performed with performed with SPSS software.

Results

The prevalence of acne

Out of 115 healthcare workers with daily use of the mask rolled in the study, 37(32.17%) were suffering from new-onset mask induce acne Figure (1). Of those 10 men (27.0%) and 27 women (73%). The male-to-female ratio was 1:2.7. The mean age of the participants was 35.5±7.3 years (range: 24-47). Twenty-one cases (56.76%) were doctors, 8(21.62%), were pharmacist, 5 (13.51%) nurses, and only three (8.11%) were analysts Table (1).

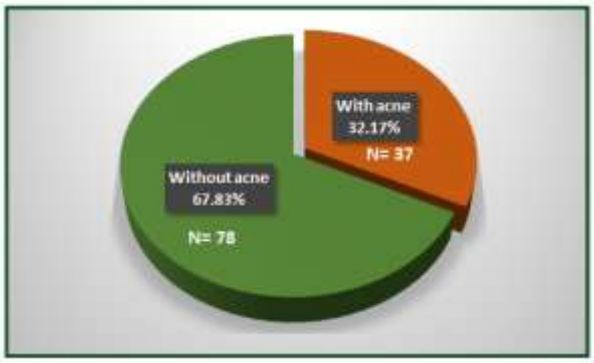

Figure (1): The prevalence of maskne among health workers with maskne.

Table (1): Demographic characteristics of the health workers with maskne (n=37).

Variables	Value
Age, years	
Mean±SD	35.5±7.3
Range	24-47
Sex	
Male	10(27%)
Female	27(73%)
Occupations	
Doctors	21(56.76%)
Pharmacists	8(21.62%)
Nurses	5(13.51%)
Analysts	3(8.11%)

* SD: standard deviation

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The Impact of mask type and duration

The vast majority of the included participants (81.08%) were wearing surgical masks. The duration of mask use in about three-fourths of patients was ≥ one year. The duration of wearing per day was less than 6 hrs in 37.84% and as needed in 43.24%. About three-fourths of patients were using reusable masks. However, one-fourth were using reusable masks Table (2).

Table (2): The impact of mask type and duration in health workers with maskne (n=37).

Variables	No.(%)
Mask type	
KN95	7(18.92%)
Surgical mask	30(81.08%)
Duration of mask using	
Less than one years	10(27%)
≥One years	27(73%)
Duration of wearing/day	
As needed	16(43.24%)
Less than 6 hrs	14(37.84%)
≥ 6 hrs	7(18.92%)
Pattern of mask use	
On time (disposable)	9(24.32%)
Reusable	28(75.68%)

Type of Lesion

Pustules were the most common lesion, accounting for two-thirds of the participants, followed by comedones (37.83%) and papules (32.44%). The least common lesion was nodulocytic lesion, accounting for 8.11% of the total lesion Figure (2). Of note, there were 17 participants with a mixed lesion.

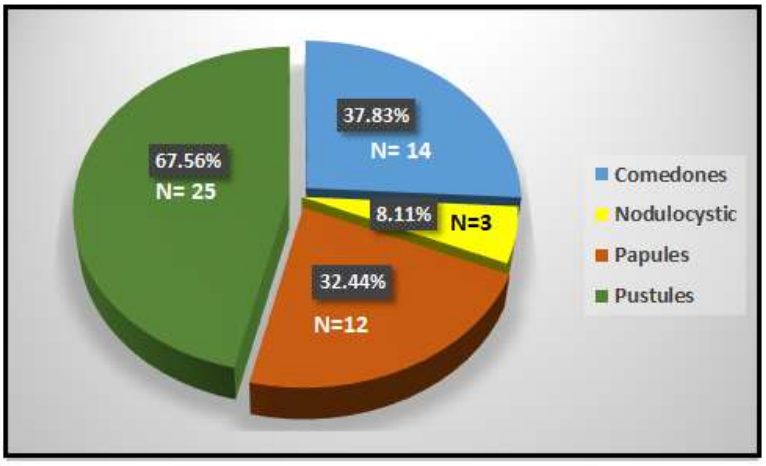

Figure (2): Types of acne lesions in health workers with maskne.

Area of distribution

Table (3) shows the area of distribution of the lesion, in which cheeks were the most common site (75%.67%) followed by the chin (48.65%), the mandibular region (16.22%), the forehead and bridge of the nose (13.51% each), and the least is the temple (2.7%).

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Table (3): Area of distribution of acne in in health workers with maskne (n=37).

Area of distribution	No(%)
Cheek	28(75.67%)
Chin	18(48.65%)
Mandibular region	6(16.22%)
Bridge of nose	5(13.51%)
Forehead	5(13.51%)
Temple	1(2.7%)

Aggravating Factors

Stress was the most common aggravating factor, occurred in 37.84% of the participants, followed by a high glycemic diet and hot weather (27.03% each), premenstrual flares and cosmetics product use (24.32% each), any medical problems (10.81%), obesity (5.41%), and finally smoking, hirsutism, and drug history (2.70% each), as shown in Table (4).

Table (4): Aggravating factors in in health workers with maskne 9n=37).

Aggravating factor	Frequency	percentage
Stress	14	37.84
High glycemic food or fast food	10	27.03
Premenstural flare	9	24.32
Smoking	1	2.70
Hot weathers	10	27.03
Cosmetic products	9	24.32
Medical conditions	4	10.81
Obesity	2	5.41
Hirsutism	1	2.70
Drug use	1	2.70

Discussion

The present study aimed to investigate the incidence, demographic, and clinical profile of acne following mask wearing among health workers.

According to the study's findings, the prevalence of maskne was 32.17%. Within the studies searching for maskne during the COVID-19 pandemic among healthcare personnel, Aravamuthan and Arumugam [8] reported the greatest rate of acne as 62.3%, whereas Shubhanshu and Singh [9] reported the lowest rate as 12%. According to other research [10-12], this percentage is 39.9%, 53.1%, and 56.0%, respectively. The new-onset acne percentages were calculated to be 31.2% and 17.8%, respectively. The survey method has been used in the majority of studies looking into the relationship between mask use and face dermatoses. Before enrolling in our study, all individuals were dermatologically evaluated.

In the current study, females were the dominant sex in 27 (72.9%) of the participants. The majority of cases (65%) were between the ages of 24 and 30. These findings were consistent with those of prior investigations. In research conducted in

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Indonesia, Christopher demonstrated that females outnumbered males by 134 (67%) to 114 (57%), with a predominant age group of less than 25 years. [13]. Hayat et al. [14] found a similar female majority of 102 (67.66%) with an average age of 30.5 years in another investigation in Lahore. This is best explained by the fact that women and adults in this age range are more concerned with their skin and are more likely to seek medical treatment for it.

In this study, surgical masks were the most commonly utilized form of mask, with reusable masks accounting for the vast majority of cases (30 (81%). This is understandable given the ease and low cost of surgical masks. On the other side, 7 (18.9%) people donned KN95 masks. Similar results were obtained by Techasatian et al. in a survey conducted in Thailand, where surgical masks accounted for 526 (63.15%) [12], however in studies conducted in Lahore [14] and New York [8] the KN95 and N95 were the most commonly used types of masks.

In the current study, 37.84% of participants used their masks for less than 6 hours per day, and 43.24% wore them as needed, with the vast majority of participants wearing reusable masks. Techasatian et al. discovered that using a face mask for >4 hours per day increased the likelihood of unwanted skin reactions over the face when compared with wearing a face mask for <4 hours per day in their study [12]. Ozkesici found that 122 (88.4%) of their subjects (health workers) wore masks for >6 hours in a Turkish study [15].

This high prevalence could be attributed to the fact that the study was accomplished during the COVID-19 outbreak, when masks were required. Han et al. reported 5 patients from the public who had their first acne infection as a result of using a mask for an extended period of time. Participants who applied the same mask repeatedly were more likely to acquire new acne or have their existing acne flare up [16]. Repeat use the same mask may cause residue buildup and raise the likelihood of sebaceous gland blockage, which leads to the etiology of mechanical acne [12].

In the current investigation, the predominant acne lesions were identified as pustules and comedones located on the cheeks and chin. This contrasts with another study where the predominant lesions were comedones and papules observed in mask-covered areas such as the chin, cheeks, and nose. Among our participants, 28 individuals (75%) experienced acne primarily on their cheeks, diverging from a study by Hayat [14], where the chin was the most affected area in 73 participants (75.6%).

The study revealed that stress, hot weather, and the consumption of high-glycemic foods were the most prevalent aggravating factors, aligning with findings in a study conducted in India by Aravamuthan and Arumugam [8], where stress was the predominant aggravating factor in 61 cases. Cordain et al. [17] proposed that high glycemic diets might significantly contribute to the elevated prevalence of acne in Western countries. The hypothesis that milk and dairy products contain hormones and bioactive molecules capable of exacerbating acne was also considered. Khunger and Kumar [18] noted that only 40 patients (22%) out of 176 using cosmetics experienced aggravation, while in our study, 24.32% reported worsened lesions

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after using cosmetics, with 27 individuals (24.5%) specifically attributing aggravation to skin-lightening agents.

Conclusions

Female gender, prolonged duration of mask use, and wearing reusable masks could be associated with the development of maskne. The most affected areas of maskne are cheeks and chin. Stress and a glycemic diet could aggravate the lesions associated with maskne.

Recommendations

An effective skincare routine involves employing a gentle facial cleanser, a lightweight moisturizer, and a non-comedogenic sunscreen to minimize irritation and friction, thus preventing acne. It is advisable to refrain from using makeup and other comedogenic products while wearing masks. Additionally, taking breaks from mask-wearing every four hours, when it is safe to do so, is recommended. For those using surgical masks, opting for a new one each day is advised to avoid prolonged reuse. In the case of fabric-reusable masks, regular washing is essential to eliminate any irritating or blocking residues.

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Ethical clearance: This study was conducted according to the approval of College of Medicine/ University of Diyala and in accordance with the ethical guidelines of the Declaration of ethical committee of the College (Document no. 2023KAA802).

Conflict of interest: Nil

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نسبة حدوث حب الشباب الناجم عن الكمامة بين العاملين في مجال الرعاية الصحية وعوامل الخطر المرتبطة به

خلود عباس علي[1]، زينب مجيد صكبان[2]

الملخص

خلفية الدراسة: حب الشباب الناجم عن الكمامة، والمعروف أيضًا باسم حب شباب الكمامة، هو حالة جلدية منتشرة بشكل متزايد خلال جائحة كوفيد-١٩. تبين أن الاستخدام المطول لكمامة الوجه يسبب تهيج الجلد والتهابه وتطور حب الشباب. يتعرض العاملون في مجال الرعاية الصحية لخطر متزايد بسبب استخدامهم المطول والمستمر لكمامات الوجه أثناء عملهم.

اهداف الدراسة: لتحديد نسبة حدوث حب الشباب الناجم عن الكمامة بين العاملين في مجال الرعاية الصحية وعوامل الخطر المرتبطة به.

المرضى والطرائق: شملت هذه الدراسة المقطعية ١١٥ من العاملين في مجال الرعاية الصحية في مدينة الإمامين الكاظمين الطبية الذين كانوا يرتدون الكمامة يوميا. جمعت البيانات الديموغرافية (العمر والجنس والمهنة)، وتفاصيل ارتداء الكمامة بما في ذلك نوع الكمامة التي يم ارتداؤها، ونمط استخدام الكمامة (كمامة يمكن التخلص منها أو يمكن إعادة استخدامها)، والوقت الذي يقضيه العاملون في ارتداء الكمامة على مر السنين، والمدة اليومية لاستخدام الكمامة، و تم أخذ التفاصيل المتعلقة بحب الشباب لدى المشاركين، بما في ذلك نوع حب الشباب وموقعه على الوجه، بالإضافة إلى الأعراض المصاحبة له (الحكة والجفاف والدهون والرطوبة والدفء والتعرق الزائد في الوجه)، والعوامل التي تؤدي إلى تفاقم الحالة.

النتائج: من أصل ١١٥ مشارك ، ٣٧ (٣٢,١٧٪) ظهرت لديهم اعراض حب شباب الكمامة. كان هناك ١٠ رجال و٢٧ امرأة. وبلغ متوسط العمر ٣٥,٥ ± ٧,٣ سنة (المدى = ٢٤-٤٧). ان الغالبية العظمى من المشاركين (٨١,٠٨٪) يستخدمون الكمامة الجراحية. كانت مدة استخدام الكمامة في حوالي ثلاثة أرباع المرضى ≤ سنة واحدة.، فيما كلن حوالي ثلاثة أرباع المرضى يستخدمون أقنعة قابلة لإعادة الاستخدام. البثرات هي الآفة الأكثر شيوعًا والتي ظهرت في ثلثي المشاركين، تليها الكوميدونات (٣٧,٨٣٪). وكان الموقع الأكثر شيوعاً هو الخدود (٧٥,٦٧٪) يليه الذقن (٤٨,٦٥٪). الإجهاد هو العامل الأكثر شيوعًا في التسبب في تفاقم الحالة والذي ظهر في ٣٧,٨٤٪ من المشاركين، يليه اتباع نظام غذائي عالي السكريات والطقس الحار (٢٧,٠٣٪ لكل منهما).

الاستنتاجات: يمكن أن ترتبط المدة الطويلة لاستخدام وارتداء الكمامة القابل لإعادة الاستخدام لدى الإناث بتطور حب شباب الكمامة. ويمكن أن يؤدي الاجهاد والنظام الغذائي عالي السكريات الى تفاقم الآفة المرتبطة بحب شباب الكمامة.

الكلمات المفتاحية: حب الشباب، آفة ارتداء الكمامة، عوامل الخطر

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Evaluation the Efficacy of NB-UVB Treatment Alone in Comparison with Combination Therapy of NB-UVB and Oral Prednisolone in Treatment of Vitiligo

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Abstract

Background: The treatment landscape for vitiligo has witnessed diverse approaches yielding variable outcomes.

Objective: To discern the optimal approach in terms of both tolerability and efficacy by comparing Narrow Band Ultraviolet B (NB-UVB) phototherapy with adjunctive oral mini pulse (OMP) prednisolone tablets.

Patients and Methods: A total of eighty-seven individuals with progressive vitiligo were enrolled in a one-year study, with participants allocated randomly across three study groups through a continuous selection method. Group 1 received a combination of NB-UVB and OMP prednisolone tablets, group 2 underwent NB-UVB treatment only, and group 3 received OMP prednisolone tablets alone. Clinical assessments were conducted at three- and six-month intervals, and statistical analyses were performed utilizing descriptive and bivariate techniques, including the chi-square test, to gauge the significance of differences between the various groups.

Results: In Group 1 (NB-UVB + OMP), substantial improvement was observed in 41.4%, accompanied by moderate improvement in 44.8% of patients. Group 2 (NB-UVB) demonstrated marked improvement in 31.0% and moderate improvement in 38.0%. In Group 3 (OMP), a lower proportion experienced marked (13.8%) or moderate (3.4%) improvement. Chi-square test findings indicated that the combination of NB-UVB and OMP correlated significantly with marked and moderate improvement in contrast to OMP alone, with respective values of $\chi^2 = 6.434$ ($p = 0.001$) and $\chi^2 = 7.831$ ($p = 0.015$) after a six-month follow-up.

Conclusion: Through a comprehensive evaluation of three treatment modalities in vitiligo patients, it was established that the sole application of oral mini pulse steroids (OMP) held an adjunctive value, lacking substantial efficacy on its own. Remarkably, the amalgamation of Narrow Band UVB and OMP presented a clear advantage over either treatment administered independently.

Keywords: Vitiligo, NB-UVB, OMP, Prednisolone.

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Introduction

Vitiligo is a chronic skin disorder characterized by the loss of pigmentation in patches, resulting from the destruction of melanocytes in the skin. Vitiligo is a commonly occurring disorder whose origins remain unidentified, displaying distinct clinical features such as the emergence of white macules on the skin's surface [1]. The condition can cause significant emotional distress and affect the patient's quality of life [2]. The global occurrence of vitiligo has been estimated at around 0.5–2% of the total population, underscoring its widespread impact [3]. One of the primary goals of treatment for active vitiligo is to halt or slow down the progression of depigmentation and induce repigmentation in the affected areas. A range of therapeutic approaches have been explored to address this condition, yielding varying degrees of success [4]. Among the various treatment options available, narrowband ultraviolet B (NB-UVB) phototherapy and combined therapy with oral mini-pulse prednisolone have shown promising results [5]. Narrowband Ultraviolet B (NB-UVB) phototherapy involves exposing the affected skin to a specific wavelength of UVB light. This treatment is considered a first-line therapy for vitiligo due to its effectiveness and relatively low side effects [5, 6]. NB-UVB is thought to stimulate melanocytes' activity and migration to the depigmented areas, leading to re-pigmentation [5, 6].

Clinical studies have demonstrated positive outcomes with NB-UVB treatment for active vitiligo [6]. Oral mini pulse (OMP) prednisolone is a corticosteroid medication that can suppress the immune system's activity and control the inflammatory response that may contribute to the destruction of melanocytes. By reducing inflammation, which is believed to play a role in vitiligo progression, it can create a more favorable environment for re-pigmentation [7]. However, it's essential to acknowledge that long-term use of oral steroids carries potential risks and side effects [7,8]. While complete re-pigmentation might not be attained in all cases, a consistent achievement of 50–75% re-pigmentation can be anticipated, particularly in cases of vitiligo that have recently developed [9]. It's important to acknowledge that a significant subset of patients may only attain partial repigmentation even when subjected to the most advanced therapeutic methods available [10]. As a strategic approach, practitioners might choose to rotate or combine therapies in order to enhance overall re-pigmentation rates while simultaneously minimizing any adverse effects associated with treatment [11]. This underscores the complex nature of vitiligo management, where the primary objectives encompass not only facilitating re-pigmentation but also curbing the progression of the disease. The variability in the severity of vitiligo is closely tied to two key factors. Firstly, the extent of the affected area plays a pivotal role, ranging from localized focal depigmented patches to more widespread lesions that span the body. Secondly, the stability of the disease further shapes its presentation, with some cases remaining relatively stable over time, while others might exhibit fluctuations or progression [12, 13]. This study aims to compare the impact of using NB-UVB phototherapy alone or in

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combination with oral mini pulse prednisolone tablets in the treatment of vitiligo.

Patients and Methods

Study Design

A one-year prospective study was designed to compare the data of vitiligo patients who have undergone treatment from June 2022 to May 2023 at the dermatology outpatient clinic, Baquba Teaching Hospital, Diyala, Iraq. The study adhered to the principles of the Declaration of Helsinki. The approval of the study was guaranteed by the ethical committee at the College of Medicine, University of Diyala, Iraq (Reference number 2023/219).

Inclusion and exclusion criteria

All patients diagnosed with active vitiligo and generalized vitiligo, aged 10 years and older, both genders, and willing to participate in the study have been included. However, cases of stable vitiligo, focal vitiligo, and segmental vitiligo, patients with comorbidities such as high blood pressure, diabetes mellitus, a history of photodermatitis or photosensitivity, lactating and pregnant women, and those unwilling to participate have been excluded from the study.

Sample size calculation

According to previous studies [14, 15], researchers assumed a fifty-percentage reduction in the control group (topical steroid) at a seven-percentage level of significance and a power of eighty to calculate a sample size of eighty-four. A dropout of ten percent was allowed. The total population was ninety-two people, with vitiligo included in the study. Fife patients have been excluded due to exclusion criteria, resulting in 87 patients in the final sample.

Procedure and protocol of treatment

During the study period, all patients underwent a comprehensive assessment that included a thorough clinical history, photographic documentation, general clinical examinations, and complete dermatological evaluation. The medical history of each patient was recorded, encompassing socio-demographic variables, vitiligo onset, course, and duration. Specific details were collected regarding any previous vitiligo-like lesions, such as their number, location, duration, prior treatments administered, and any observed side effects. Family history, systemic diseases, and medication intake were also documented. Clinical and dermatological examinations were performed, involving a comprehensive assessment of the skin, hair, nails, and thyroid gland. For assessing the severity and characteristics of vitiligo lesions, the Vitiligo Extent Score was employed. This scoring system helped determine the extent, site, size, center, and margins of the depigmented lesions. Baseline images of the vitiligo-affected areas were captured for all patients using a digital camera under standardized lighting conditions before initiating any therapy. These images served as reference points for subsequent visits and for the final documentation at the end of the study. Before starting the intervention, patients were explicitly instructed to discontinue any topical and systemic vitiligo treatments for at least three weeks. Moreover, patients were prohibited from using any other vitiligo therapies during the study period unless they first consulted the designated researcher. This measure aimed to ensure accurate evaluation and avoid any

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interference from other treatments during the study.

Therapeutic modalities used to treat vitiligo in this study:A total of 87 eligible patients with active vitiligo were equally assigned into three different groups (G 1, G 2, G 3) as follows;

Group 1: has 29 patients who were receiving both oral mini pulse prednisolone tablets and narrow band UVB (NB-UVB) therapy. The dose of OMP oral mini pulse prednisolone tablets was 40 mg/day given on two consecutive days per week for 8 weeks. The initial dose of NB-UVB administered to these patients was 0.3 J/cm², and the dosage was increased in increments of 0.1 J/cm² with each dose. The maximum dosage of NB-UVB that was administered to these patients was 3 J/cm² given twice weekly in two days interval for up to 30 sessions.

Group 2: Patients who treated by only NB-UVB therapy given twice weekly in two days interval for up to 30 sessions.

Group 3: Patients who treated only by oral mini pulse prednisolone tablets (40 mg/day on two consecutive days per week for 8 weeks).

Prior to commencing NB-UVB therapy, each patient was given a thorough explanation and guided tour around the phototherapy units. During this counseling session, they were educated about the safety profile of the treatment, emphasizing the significance of adherence and compliance to the prescribed regimen. Additionally, the limitations and potential outcomes of the therapy were discussed to ensure the patients had a comprehensive understanding of the procedure. Aftercare: Follow up every 12 weeks to detect efficacy and complications and for subsequent injections.

Outcome

At the end of three and six months, a clinical assessment was conducted. The degree of improvement was classified into distinct categories: significant improvement (> 75% re-pigmentation), moderate improvement (50–75% re-pigmentation), slight improvement (25–50% re-pigmentation), and limited or no improvement (< 25% re-pigmentation). Comprehensive documentation of any observed side effects was recorded for each case.

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 23. Numerical data were summarized using means and standard deviations. Categorical data were summarized as numbers and percentages. For categorical variables, differences were analyzed with the chi-square test. A statistically significant is considered to be less than 0.05.

Results

Eighty-seven patients were involved in this study, with a mean age (SD) of 19 (SD 7.3) years and a range of 10-38 years. More than half of them were female (51.7%), aged 20–29 (44.8%), and unemployed (56.3%) Table (1). The demographic features look comparable in the three groups, as shown in Table (1). Table (2) presents some of the clinical characteristics of the participants. About two-thirds of them (63.2%) have a disease history of less than one year; three patients had a positive family history of vitiligo; and 29.9% had a history of comorbidities.

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Table (1): Sociodemographic characteristics of patients (n=87).

Variables	Categories	Total	Group 1 n=29	Group 2 n=29	Group 3 n=29	p-value
Gender	Male	42(48.3)	13(44.8)	14(48.3)	12(41.4)	0.237
	Female	45(51.7)	16(55.2)	15(51.7)	17(58.6)	
Age	10-19	35(40.2)	11(37.9)	10(34.5)	13(44.8)	0.201
	20-29	39(44.8)	12(41.4)	12(41.4)	11(37.9)	
	30 and more	13(15.0)	6(20.7)	7(24.1)	5(17.3)	
Occupation	Employed	38(43.7)	13(44.8)	12(41.4)	14(48.3)	0.071
	Unemployed	49(56.3)	16(55.2)	17(58.6)	15(51.7)	

* G 1: Combined NB-UVB + OMP prednisolone tablets. G 2: only NB-UVB; G 3: only OMP prednisolone tablets

Table (2): Clinical features of patients (n=78).

Variables	Categories	Total n=87	Group 1 n=29	Group 2 n=29	Group 3 n=29	p-value
Duration (years)	< 1	55(63.2)	16(61.5)	17(65.4)	20(77.0)	0.365
	1-5	18(20.7)	6(23.1)	7(26.9)	5(19.2)	
	> 5	14(16.1)	4(15.4)	2(7.7)	1(3.8)	
History of Comorbidities	Hypertension	7(8.1)	2(6.9)	3(10.3	2(6.9)	0.327
	Diabetes millets	4(4.6)	2(6.9)	1(3.5)	1(3.5)	
Family history	Vitiligo	3(3.5)	0(0.0)	1(3.5)	2(6.9)	0.292

* G 1: Combined NB-UVB + OMP prednisolone tablets. G 2: only NB-UVB; G 3: only OMP prednisolone tablets

Response to treatment

Table (3) presents the assessment of patients' responses at the end of the first three months. In group 1 (NB-UVB + OMP), six patients (20.9%) achieved remarkable improvement (> 75%). Moderate improvement (50–75%) was reported among twelve patients (41.4%). Nine patients (31.0%) have mild improvement, and two patients have less than 25.0% improvement.

Twelve patients (41.4%) and ten patients (34.5%) showed mild and moderate improvement in group 2 (NB-UUVB), respectively, compared to three patients (10.3%) who showed marked improvement. However, there were four patients who had less than 25% improvement. In Group 3 (only OMP prednisolone tablets), most of the patients (69.0%) showed a poor response. Seven patients (24.1%) reported a mild response, and two patients (6.9%) had moderate improvement; however, none of them had marked improvement Table (3).

Table (3): Evaluation of re-pigmentation among three groups at the end of three months (n=87).

Protocol of treatment	< 25%	25-50%	50-75%	> 75%
G 1 (OMP+NB-UVB)	2 (6.9)	9 (31.0)	12 (41.4)	6 (20.9)
G 2 (NB-UVB)	4 (13.8)	12 (41.4)	10 (34.5)	3 (10.3)
G 3 (OMP)	20(69.0)	7 (24.1)	2 (6.9)	0 (0.0)

* G 1: Combined NB-UVB + OMP prednisolone tablets. G 2: only NB-UVB; G 3: only OMP prednisolone tablets

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Factors associated with three months re-pigmentation outcome in bivariate analysis

Table (4) shows the cross-tabulation to indicate the association with marked improvement (> 75%) and moderate improvement (50–75%). Patients in G1 (chi-square test ($\chi 2$) = 3.535, p = 0.004) and ($\chi 2$) = 5.624, p = 0.025) were significantly associated with the marked and moderate improvement compared to G 3 at three months, respectively. There was also a significant association between G 1 and G 2 at the same period ($\chi 2$ = 2.074, p = 0.033), and ($\chi 2$) = 1.536, p = 0.041), respectively.

Table (4): Factors associated with marked and moderate improvement at three months(N=78).

Improvement at three months	G 1 (n=29)	G 2 (n=29)	G 3 (n=29	$\chi 2$*	p-value	$\chi 2$**	p-value
(> 75%)	6/29 (20.9)	3/29 (10.3)	0 (0.0)	2.074	0.033	3.535	0.004
(50-75%)	12/29 (41.4)	10/29 (34.5)	2/29 (6.9)	1.536	0.041	5.624	0.025

* G 1: Combined NB-UVB + OMP prednisolone tablets. G 2: only NB-UVB; G 3: only OMP prednisolone tablets; *(G1 ve G2); **(G1 ve G 3)

After six months of study, the highest percentage of patients in group 1 (NB-UVB + OMP) had moderate 13 (44.8%) and marked (41.4%) improvement. None of the patients had poor improvement; however, four patients (13.8%) achieved mild improvement.

In Group 2, nine patients (31.0%) had marked improvement, and eleven patients (38.0%) showed moderate improvement, respectively. Mild and poor responses have been seen among seven (24.1%) and two (6.9%) patients, respectively .

In Group 3, only one patient (3.4%) achieved more than 75.0% re-pigmentation, and 4 patients (13.8%) showed moderate improvement, compared to 82.8% who showed either mild or poor improvement Table (5).

Table (5): Evaluation of re-pigmentation among three groups at the end of six months (n=87).

Protocol of treatment	< 25%	25-50%	50-75%	> 75%
G 1 (NB-UVB+OMP)	0 (0.0)	4 (13.8)	13 (44.8)	12 (41.4)
G 2 (NB-UVB)	2 (6.9)	7 (24.1)	11 (38.0)	9 (31.0)
G 3 (OMP)	14 (48.3)	10 (34.5)	4 (13.8)	1(3.4)

Factors associated with six months re-pigmentation outcome in bivariate analysis

Table (6) shows the cross-tabulation to indicate the association with marked improvement (> 75%) and moderate improvement (50–75%). Patients in G 1 (chi-square test ($\chi 2$) = 6.434, p = 0.001) and ($\chi 2$) = 7.831, p = 0.015) were significantly associated with the marked and moderate improvement compared to G 3 at three months, respectively. However, there was no significant association between G 1 and G 2 at the same period ($\chi 2$ = 3.870, p = 0.076), and ($\chi 2$) = 5.752, p = 0.064), respectively.

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Table (6): Factors associated with marked and moderate improvement at six months (N=78).

Improvement at three months	G 1 (n=29)	G 2 (n=29)	G 3 (n=29	*χ2	p-value	**χ2	p-value
(> 75%)	12/29 (41.4)	9/29 (31.0)	1/29 (3.4)	3.870	0.076	6.434	0.001
(50-75%)	13/29 (44.8)	11/29 (38.0)	4/29(13.8)	5.752	0.064	7.831	0.015

* G 1: Combined NB-UVB + OMP prednisolone tablets. G 2: only NB-UVB; G 3: only OMP prednisolone tablets; *(G1 ve G2); **(G1 ve G 3)

Discussion

In the present investigation, notable progress was observed among the participants. Specifically, six patients in group 1, constituting 20.9% of the cohort, exhibited marked improvement, while an additional twelve patients (41.4%) demonstrated moderate improvement. This improvement was witnessed over a three-month period during which narrowband UVB treatment was combined with OMP (oral mini pulse) prednisolone tablets. Nonetheless, the precise underlying mechanism of pigmentation that is triggered by UVB radiation remains shrouded in mystery. A hypothesis proposes the involvement of endothelin and tyrosinase, which are expressed by keratinocytes and may potentially contribute to the pigmentation response [16].

A distinct facet of our study emerged after the initial three months. Among the patients receiving narrow-band UVB treatment, a noteworthy 44.8% exhibited both marked and moderate improvement. In contrast, the percentage of patients displaying moderate improvement with OMP prednisolone tablets was considerably lower, at 6.9%. This divergence underscores the disparate impact of the two treatment approaches. Noteworthy research by Njoo et al. [17] delved into an open study involving 51 children grappling with generalized vitiligo. Over the course of a year, they employed narrow-band UVB therapy, resulting in the impressive finding that more than 75% re-pigmentation was achieved in a significant 53% of their patients [17].

This trend persisted in recent studies as well. Kanwar and colleagues tracked 26 children with generalized vitiligo who underwent narrow-band UVB treatment, revealing that more than 75% re-pigmentation was once again achieved. Further investigation encompassed a retrospective cohort of 109 patients. This particular analysis juxtaposed twice-weekly NB-UVB therapy with a more intensive three-weekly regimen, combined with topical fluticasone propionate and/or tacrolimus. Surprisingly, both treatment arms yielded analogous results, with the combined treatment showing a swifter onset of repigmentation [18]. Impressively, a randomized controlled trial involving 517 patients emphasized the effectiveness of combination therapy involving NB-UVB therapy through a hand-held unit and mometasone. This combination outperformed the use of corticosteroids alone, with a response rate observed in one-fourth of patients, particularly favoring those with vitiliginous lesions situated on the head and neck [19]. Recent systematic reviews further fortified the case for combination therapy. Specifically, the combination of topical tacrolimus and NB-UVB treatment emerged as superior to the application of NB-UVB

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alone [20, 22]. Nonetheless, it's important to highlight the findings of another meta-analysis, which showed no significant distinction between NB-UVB monotherapy and the combination of NB-UVB with calcineurin inhibitors [23]. This complexity underscores the multifaceted nature of treatment responses in vitiligo management.

After six months, our observations unveiled a noteworthy trend. Patients treated with a combined treatment of narrow-band UVB and OMP (oral mini pulse) therapy showed 86.2% moderate to marked improvement. Similarly, those who were treated with narrow-band UVB showed a commendable 69.0% rate of moderate to marked improvement. In stark contrast, merely 14.2% of those treated with OMP prednisolone tablets displayed comparable levels of improvement. While narrow-band UVB therapy spurred faster re-pigmentation, the combination of narrow-band UVB and OMP prednisolone tablets yielded synergistic effects surpassing the outcomes of either treatment employed individually.

Supporting our findings, a recent retrospective review encompassing 58 patients subjected to NB-UVB therapy showcased a consistent re-pigmentation of the skin, with 80% of patients sustaining this improvement one year after treatment. This was particularly significant in cases primarily characterized by non-segmental vitiligo [24].

The endeavor to explore alternative treatments was also evident in the work of Pasricha and Khaitan back in 1993. They experimented with oral mini-pulses of betamethasone and reported varying degrees of repigmentation in their patients. Specifically, 25% of patients experienced a 26–50% re-pigmentation, 7.5% achieved 51–75% re-pigmentation, and an encouraging 15% accomplished over 75% re-pigmentation [25]. In contrast, in our own study, the implementation of oral mini pulse (OMP) prednisolone yielded different outcomes. Only one patient (3.4%) exhibited marked improvement, whereas four patients (13.8%) demonstrated moderate improvement. Regrettably, mild and poor improvement was witnessed in 24 patients (82.8%).

Highlighting the significance of our findings, it's noteworthy that the group of patients receiving combined treatment (Group 1: NB-UVB + OMP) achieved improvement exceeding 75%. This outcome held statistical significance at the 5% level when compared with the group receiving only OMP treatment (Group 3) after three and six months. Employing statistical analysis through SPSS-23 and the Chi-square test, our investigations established that the statistically significant difference between Group 1 and Group 2 was present only at the three-month mark. This further underscored the fact that OMP therapy, among the three modalities examined, functioned primarily as an adjunct, helping to halt disease progression without providing significant inherent re-pigmenting efficacy. Nevertheless, it is important to acknowledge the presence of side effects experienced by our patients. These included tanning and erythema due to ultraviolet therapy, as well as bloating and weight gain attributed to oral steroid usage. These side effects align with those reported in earlier studies, underscoring the consistency of these observations across different research endeavors [17, 26, 27].

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Conclusions

In our study on progressive vitiligo, we made a significant discovery. Patients who underwent a combined treatment approach involving Narrow Band Ultraviolet B (NB-UVB) phototherapy along with oral mini-pulse (OMP) prednisolone tablets experienced substantial improvements in their condition. This combined therapy showed a clear and statistically significant advantage over using NB-UVB phototherapy or OMP prednisolone alone. Interestingly, when OMP prednisolone was used on its own, only one patient showed marked improvement, highlighting its limited efficacy as a standalone treatment. This suggests that OMP plays a supportive role and is most effective when combined with other treatments. These findings emphasize the importance of a holistic treatment strategy for progressive vitiligo. The synergistic effects of NB-UVB phototherapy and OMP prednisolone tablets offer a promising avenue for achieving better outcomes in patient care. Tailored and multifaceted approaches like these are crucial for managing progressive vitiligo effectively.

Recommendations

Further research and data are required to assess the incidence of vitiligo and any associated factors. Continued exploration through both basic and clinical research is essential to enhance our comprehension of vitiligo's underlying pathogenesis and to identify fresh avenues for therapeutic intervention. The landscape is rife with a multitude of promising forthcoming treatments, many of which are currently documented primarily through case reports and series. To ensure a more robust assessment of their effectiveness, however, a greater emphasis on conducting randomized controlled trials is imperative. These trials are pivotal in providing a more comprehensive and unbiased evaluation of the efficacy of these emerging therapeutic approaches.

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Ethical clearance: This study was conducted according to the approval of College of Medicine/ University of Diyala and in accordance with the ethical guidelines of the Declaration of ethical committee of the College (Document no. 2023YAK782).

Conflict of interest: Nil

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تقييم فعالية العلاج بالأشعة فوق البنفسجية ضيقة النطاق وحده بالمقارنة مع العلاج المركب من العلاج بالأشعة فوق البنفسجية ضيقة النطاق و البريدنيزولون عن طريق الفم في علاج البهاق

ياسر عبد الله خميس[1]

الملخص

خلفية الدراسة: شهد المشهد العلاجي للبهاق طرقًا متنوعة تؤدي إلى نتائج متغيرة.
اهداف الدراسة: تسعى هذه الدراسة إلى تمييز النهج الأمثل من حيث التحمل والفعالية من خلال مقارنة العلاج بالأشعة فوق البنفسجية ضيقة النطاق مع جرع مخفضة من أقراص البريدنيزولون عن طريق الفم.
المرضى والطرائق: تم تسجيل ما مجموعه سبعة وثمانون من الأفراد الذين يعانون من البهاق التدريجي في دراسة لمدة عام واحد ، مع توزيع المشاركين بشكل عشوائي الى ثلاث مجموعات دراسة باستخدام طريقة اختيار مستمرة. تلقت المجموعة الاولى مزيجًا من الأشعة فوق البنفسجية ضيقة النطاق مع جرع مخفضة من أقراص البريدنيزولون عن طريق الفم, وخضعت المجموعة الثانية للأشعة فوق البنفسجية ضيقة النطاق فقط، وتلقى المجموعة الثالثة جرع مخفضة من أقراص بريدنيزولون عن طريق الفم فقط. وأجريت التقييمات السريرية على فترة ثلاث اشهر وستة أشهر، وأجريت التحليلات الإحصائية باستخدام تقنيات وصفية وثيقة المتغير، بما في ذلك اختبار مربع كاي لقياس أهمية الاختلافات بين المجموعات المختلفة.
النتائج: في المجموعة الاولى، لوحظ تحسن كبير بنسبة ٤١,٤ ٪ ، مصحوبة بتحسن معتدل بنسبة ٤٤,٨ ٪ من المرضى. أظهرت المجموعة الثانية تحسنا كبيربنسبة ٣١,٠ ٪ والتحسن المعتدل بنسبة ٣٨,٠ ٪. في المجموعة الثالثة ،كانت نسبة التحسن الكبيرأقل بنسبة ٣,٤٪, والتحسن المعتدل بنسبة ١٣,٨٪. أشارت نتائج اختبار مربع كاي إلى أن استخدام مزيجًا من الأشعة فوق البنفسجية ضيقة النطاق مع جرع مخفضة من أقراص البريدنيزولون عن طريق الفم بعد ستة أشهر متابعة يرتبط بشكل كبيرمع التحسن الملحوظ والمعتدل على النقيض من استخدام جرع مخفضة من أقراص بريدنيزولون عن طريق الفم فقط, والقيم ذات الصلة هي [مربع كاي ٦,٤٣٤ (P= 0.001) و نربع كاي ٧,٨٣١ (P= 0.015)]
الاستنتاجات: من خلال تقييم شامل لثلاث طرائق علاجية في مرضى البهاق ، ثبت أن التطبيق الوحيد للجرع المخفضة للبريدنيزولون يحمل قيمة مساعدة، ويفتقر إلى فعالية كبيرة من تلقاء نفسها. ومن اللافت للنظر أن دمج العلاج بالأشعة فوق البنفسجية الضيقة النطاق مع الجرع المخفضة للبريدنيزولون عن طرق الفم قدم ميزة واضحة وحتلا يمكن ان يتعامل بها و تدار بشكل مستقل.

الكلمات المفتاحية: البهاق, الأشعة فوق البنفسجية ضيقة النطاق، جرع مخفضة من أقراص بريدنيزولون عن طريق الفم

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Histological and Histomorphometric illustration the endochondral ossification of the mandibular angle defect repair in rats after oral stimulation with bisphosphonate treatment (an in vivo study)

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Abstract

Background: Bio-phosphonates can be used to lower the risk of hip and spine fractures. Additionally, they can be used to treat Paget's disease of the bones in a variety of dosages. In the procedure that replace hyaline cartilage to bone, this procedure i.e. called endochondral ossification. It starts when mesenchymal cells from the mesoderm develop into chondrocytes. Chondrocytes multiply quickly and release an extracellular matrix to create the cartilage that serves as the model for bone.

Objective: To histomorphometric illustration the endochondral ossification of the mandibular angle defect repair in rats after- oral stimulation with bisphosphonate treatment.

Patients and Methods: 20 rats were used in this work and the animals were divided into the following groups: 10 Rats from the control group. The bone defect was healed naturally without medicament and 10 rats were used in the experiment, and taking the biophosphonate medication helped mend the bone defect. Every single group was studied in 7 and 14 day (5 rats for each healing period) and the surgical procedure was performed for histological and Histomorphometrically examination. The data analysis with spss statistic measure & with P vale ($P \leq 0.05$).

Results: Active effect of the bio-phosphate medicament in the endochondral ossification and the cell that responsible for the cartilage formation and accelerated the healing of the mandibular defect with inhibition of the bone resoption and finally decrease the time that need to full healing.

Conclusion: The chemical medicament that represented by bio-phosphonate accelerated the endochondral ossification in a short time and replacement with bone in the site of the defect.

Keywords: Bio-phosphonates, Cartilage, Chondrocytes, endochondral ossification.

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Introduction

One of the two crucial processes during fetal development of the mammalian skeletal system through which bone tissue is formed is endochondral ossification. Callus, is a type of cartilage that frequently develops during fracture repair, Through the process of endochondral ossification, this cartilage eventually transforms into new bone tissue. Recent research has demonstrated that biomimetic bone, such as apatite, suppresses bone formation by hyper-stimulating the extracellular calcium detecting receptors (CaSR) [1]. In this procedure, hyaline cartilage is switched out for bone. Beginning with the differentiation of mesenchymal cells coming from mesoderm into chondrocytes. To create the cartilage that serves as the model for bone, chondrocytes multiply quickly and release an extracellular matrix [2].

Bone has a highly specialized and intricate structure and function [3]. The hard compartment of the skull, which is well known for its pliability, hardness, and capacity to provide protection to the underlying tissues [4], protects and supports the soft compartment of the skull, which is composed of highly active, mineralized, and vascular connective tissue Figure (1) [5].

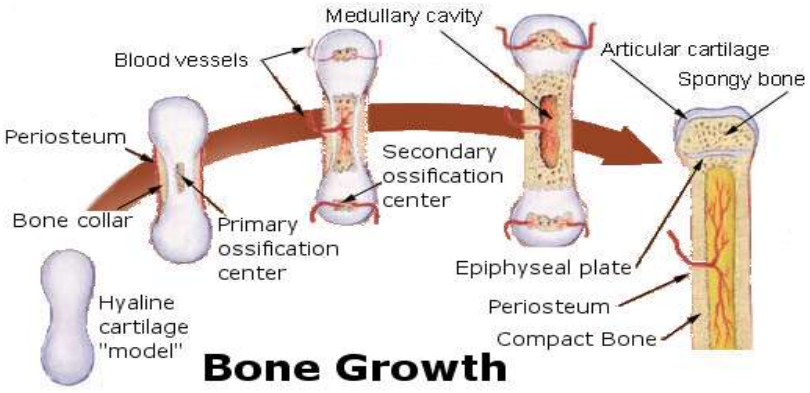

Figure (1): Endochondral ossification [5].

Bone's composite composition gives it special mechanical properties. An organic matrix (mostly Type I collagen) and a mineral matrix (hydroxyapatite crystals embedded in collagen fibers) are the two primary building blocks of bone. The organic matrix is primarily responsible for bone toughness and plastic deformation, despite the fact that the mineral component of bones contributes significantly to bone strength [6]. Multiple anatomical, biomechanical, and biochemical systems work in concert to heal bones. In contrast to many other tissues, skeletal healing may completely restore the biochemical and mechanical characteristics of the wounded tissue[7]. The healing process of bone injuries included the healing of soft and hard tissues. The chemical medicament is widely used in the healing of different wounds topically and systematically [3].

A group of medications known as bisphosphonates is used to treat osteoporosis and related conditions because they end the loss of bone density. They are the medications for osteoporosis that are most

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frequently administered [8]. Because they contain two phosphonate (PO(OH)2) groups, they are known as bisphosphonates. Diphosphonates (bis- or di- + phosphonate) is another name for them. According to the evidence, they lower the risk of fracture in post-menopausal women who have osteoporosis [9],[10],[11]. Bone resorption can be effectively inhibited by bisphosphonates. Alendronate, Etidronate, Pamidronate, Ibandronate, Risedronate, Clodronate, Tiludronate, and Zoledronate are among the medications in this family that can be used either as free acids or as sodium salts. In addition to treating hypercalcemia of malignancy and Paget's disease of the bones, they are widely employed in the treatment and prevention of bone loss caused by glucocorticoid medication, post-menopausal estrogen loss, or malignant illness. The medications are pyrophosphate analogs, which have been demonstrated to limit calcium phosphate dissolution in vitro but not in vivo over a long period of time Fleisch (2002)[12].

For a long time, the molecular basis of how bisphosphonates work was poorly known (Figure 2) [13]. Etidronate and clodronate, the first researched bisphosphonate compounds, were later shown to produce lethal non-hydrolyzable analogs of adenosine triphosphate (ATP) that interfere with ATP-dependent intracellular functions. These substances may have interfered with mitochondrial ATP translocases, which is why osteoclast cells died following therapy. [14].The more powerful compounds, which are nitrogen-containing bisphosphonates, are not converted to ATP analogs. Instead, they work to impede the mevalonate/cholesterol biosynthesis pathway enzyme farnesyl pyrophosphate synthase (FPPS). Farnesyl diphosphate and geranyl geranyl diphosphate, in particular, are not biosynthesized when FPPS is inhibited[16],[15].

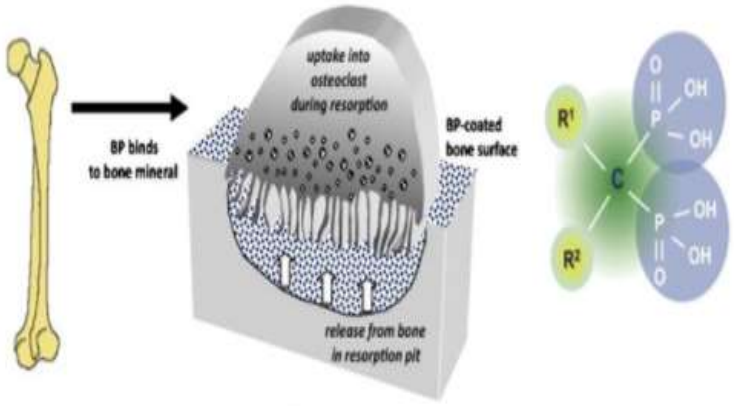

Figure (2): Work of bisphosphonate[13].

Osteoblasts build bone, and osteoclasts break it down, keeping bone tissue constantly remodeling and in balance (homeostasis). By inducing osteoclasts to go through apoptosis, or cell death, bisphosphonates slow down bone loss by preventing the digestion of bone. The uses of bisphosphonates include the prevention and treatment of osteoporosis, Paget's disease of bone, bone metastasis (with or without hypercalcemia), multiple myeloma, primary hyperparathyroidism, osteogenesis imperfecta, fibrous dysplasia,

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and other conditions that exhibit bone fragility [17].

The mandible is a complicated structure in terms of its makeup, place in developmental history, and purpose. The ramus, the coronoid, the condylar and angular processes, and the alveolar components—where the teeth erupt—are among the anatomical units that make up this structure[18].

The presence of bony trabeculae wrapped in a cartilaginous cap can be used to assess the angle of the mandible, which histologically contains the protein osteocalcin (OC). Histologically, OC should be distinguished from osteoma, which is made up of hard, dense, and compact lamellar bone, benign osteoblastoma, which is made up of well-vascularized connective tissue stroma and widely dilated capillaries and actively produces osteoid and woven bone, chondroma, which is made up of lobules of hyaline cartilage with chondrocytes within well-formed lacunae[19][20].

Patients and Methods

All experimental methods were completed in conformity with the moral guidelines for using animals in research, and all work and data will be collected according to ethical approval from diyala university, college of medicine with ID(2023MAH758) . Twenty albino rats, weighing between 300 and 400 grams and being between 6 and 8 months old, were used in this experiment. The medial side of the mandible's angle was operated on surgically on the animals. The animals were divided into following groups:

1-10 rats from the control group. The bone defect was allowed to naturally mend on its own then divided in to two healing periods:

a-5 rats are taken after one week(7 days)

b-5 rats are taken after two week(14 days)

2-10 rats were used in the experiment, and taking the bisphosphonate medication helped the bone defect which mend then divided in to two healing periods:

a-5 rats are taken after one week(7 days)

b-5 rats are taken after two week(14 days)

All surgical tools have been sterilized in the oven at 150 °C for 1 hour to ensure maximum sterilization. The instruments were then wrapped in aluminum foil and sterilized in the autoclave at 150 °C and 15 bar/cm2 for 1 hour [21] Figure (3).

Figure (3): Surgical tools.

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The procedure was performed using a skillful surgical technique and under very sterile settings. After shaving the animal's skin, it was cleansed and disinfected using a piece of cotton dipped in 96 % alcohol and iodine. A skin incision was made with a sharp blade (no.10), and the skin and fascia flap were reflected.

The rotational speed used for bone penetration was 1500 rpm. A bone defect hole of 1.8mm was performed with a small round bur[20]. After the hole was prepared, the drilling site was cleaned using a saline solution to get rid of any drilling debris. On the mandibular angle bone, a defect was formed Figure (4).

Figure (4): The rotational speed used for bone penetration.

After the operation, wash the area with normal saline. The muscle was sutured with a 3/0 absorbable (catgut) suture, and skin was sutured with 3/0 silk suture. The period was carried with 2.5 mg/day dose (one time take in the day) of oral bisphosphonate medicament supported the healing process[21]. Using overdose anesthesia, after the animals were scarified at intervals of the surgical location, skin, fascia, and muscles were removed. After that, bone specimens were produced by removing around 5 mm of bone from the area surrounding the surgery site, irrigating the area continuously with saline to prevent bone injury, and dissecting the fragment and fixing it in 10% buffered formalin. Tissue Processing and Staining for histological examination were done and stained with H&E stain for slide were preparation and histological examination and examined under 10 X magnification to determined the effect of the medicament histologically and Histomorphometrically.

Statistical analysis

Statistically according to Table (1) showed the cells in difference of the study group in the count of cells in each every healing periods (7 & 14 days), the table showed higher significant difference of both chondroblast & chondrocytes cell between the experimental and control group at 7 days of healing period.

Results

After producing a H&E slide and examined under a light microscope with10 X magnification power. The microarchitectures

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were measured by counting the chondroblasts. Chondrocyte, Osteoblast ,Osteocyte and Osteoclast cell number / mm^2 in 7 and 14 days healing periods.

At 7 days duration: the histological slide of rats that were treated with bisphosphonate medicament Figure (5) showed new cartilage cells (chondroblast) at the region of active ossification and filled the area of the defect with the presence of iso-group number of chondrocytes embedded in the perichondrium , little inflammatory cell, fat cells and blood vessel adjacent to progenitor cells. In addition to the cartilage we showed bright red spongy bone fragments are encircled by a long row of osteoblasts the number of the bone building cell less than the cartilage building cell.Osteocytes, which are the osteoblasts that were previously imprisoned in their own matrix deposits, are found in lacunae within the spicule this cell showed in little account in contrast with bone building cell and showed lesser number of osteoclast cell in contrast with other cells at 7 day healing periods. In contrast with the control group Figure (6) that showed low number of chondroblast that form the cartilage matrix with high number of inflammatory cells, while the bone building cells showed low account number with absences of the chondrocyte and osteocyte and osteoclast Figure (7).

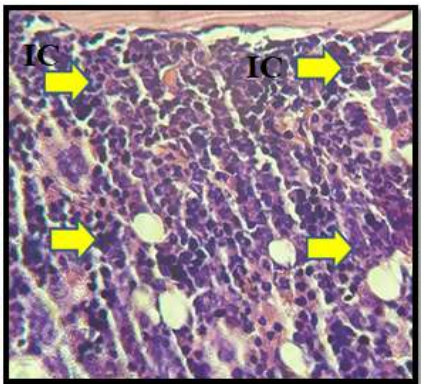

Figure (6): control group at 7 days that showed high count number of inflammatory cell (IC) at defect area.

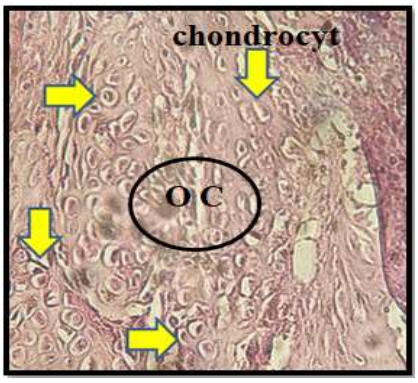

Figure (5): experimental group at 7 days showed high number of cartilage cell (both chondrocyte and chondroblast) that related to endochondral in ossification center (OC) ossifications.

In Figure (7) represented mean number of cell at 7 days healing period showed high count number of chondrocytes and condroblasts number of experimantal group when we compaired with control group showed large differences in count number of same cell but in control group, and shoewd higher count of bone building cells rather than control group. The control group in 7 days healing period showed lower number of osteoclast and osteocytes cell than the count of same cells but in experimantal group and other different cells in the feiled.

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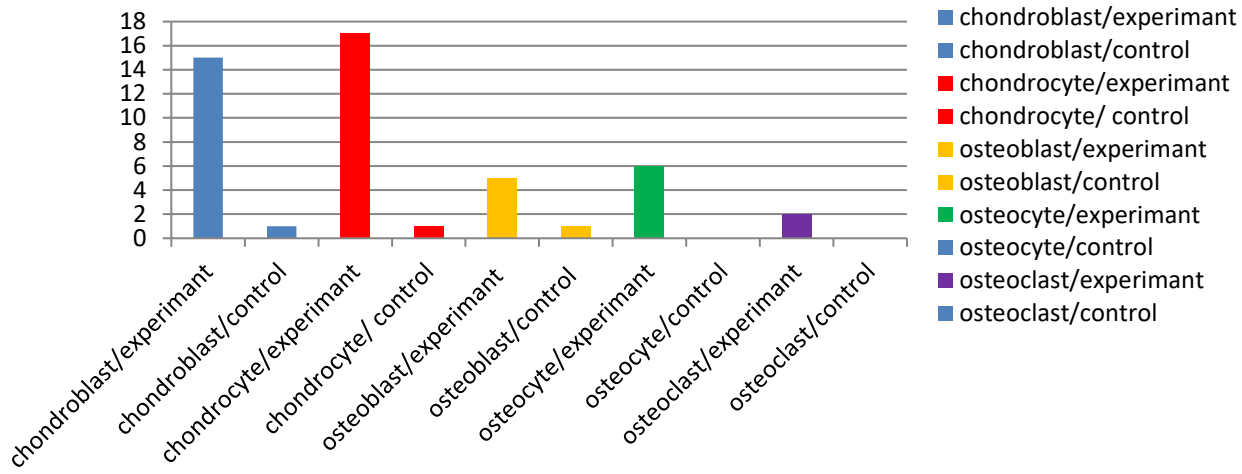

Figure (7): Mean of cells at 7 days healing period

At 14 days healing periods, the experimantal group showed rappid bone lying down with a high number of osteocyte cell in its laqunae incontrast with cartilage cells (chondrocyte and condroblast) showing lower count in the slides and precence of the bone building cells (osteoblast) with alow count of osteoclast and large area of bone matrix in contrast with bone marrow Figure (8). In the control group at 14 days healing periods showed specules of bone trabecule with large area of bone marrow among the trabecule in contrast with experimantal group that showed more bone area to bone marrow area with presence of same osteocytes in the center of the bone trabecule and osteoblast cells on the perifery of bone the trabecule Figure (9).

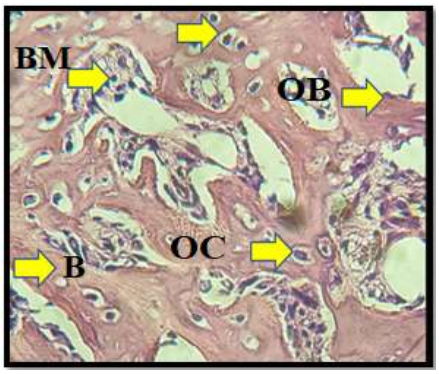

Figure (9): control group at 14 days that showed little number of osteocyte (OC) in little bone area and high bone marrow area (BM).

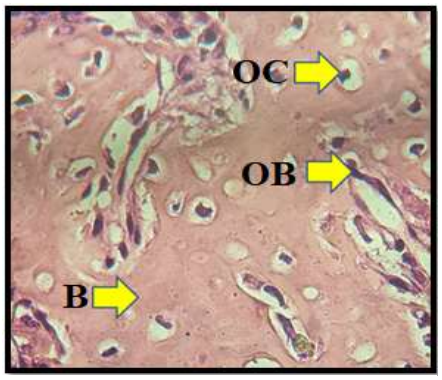

Figure (8): Experimental group at 14 days showed high number osteocytes (OC) and large area of bone (B) rather than bone marrow area.

In Figure (10) represented mean number of cell at 14 days healing period showed high count number of osteocytes cell number of experimantal group when we compaired with control group showed large differences in count number of same cell but in control group, and shoewd higher count of bone building cells rather than control group and showed lower count of cartilage cells.

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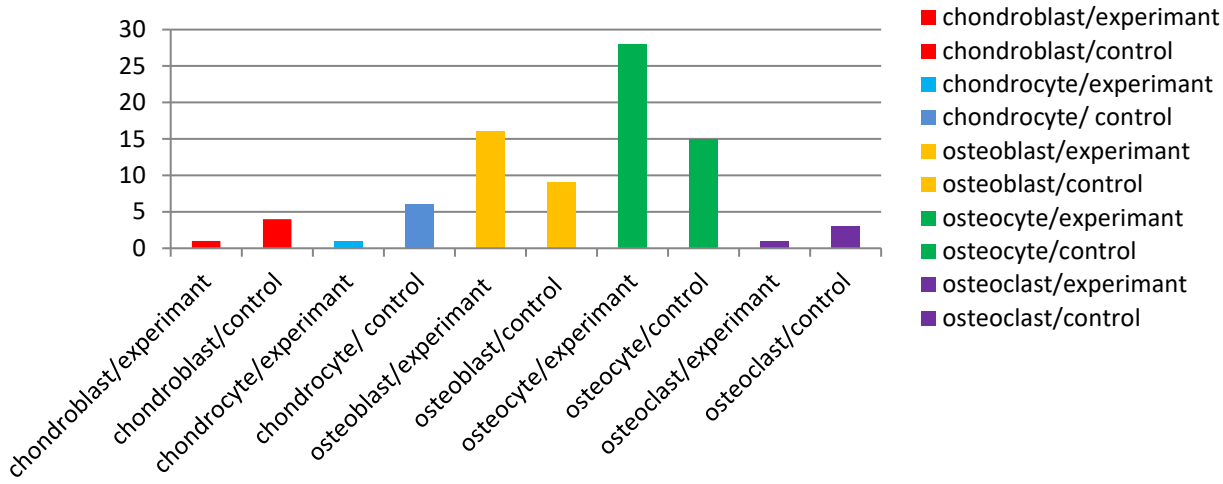

Figure (10): Mean of cells at 14 days healing period.

While these cells at 14 days showing non-significant difference between the study groups. The bone building cells (osteoblast shoed at7 days significant difference while showed a non-significant difference at 14 days healing period. In both 7& 14 day showed a significant difference between the groups in the osteocyte cells count and showed non-significant difference in the count of osteoclast in all study groups.

Table (1): Descriptive statistics of the cells count (H&E) and groups' difference in each duration (ANOVA test).

The cell	duration	group	Descriptive statistics	Group difference	
			S D	P value	Description of p value
Chondroblast	7 days	Experimental	1.386	0.000	HS
		control	0.587		
	14 days	Experimental	0.432	0.666	NS
		control	0.654		
Chondrocytes	7 days	Experimental	1.337	0.004	HS
		control	0.778		
	14 days	Experimental	0.32	0.123	NS
		control	0.54		
Osteoblast	7 days	Experimental	1.5	0.014	S
		control	1.04		
	14 days	Experimental	0.430	0.632	NS
		control	0.431		
Osteocytes	7 days	Experimental	0.802	0.012	S
		control	0.1274		
	14 days	Experimental	0.816	0.045	S
		control	1.164		
Osteoclast	7 days	Experimental	0.230	0.453	NS
		control	0.301		
	14 days	Experimental	0.345	0.332	NS
		control	0.321		

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Statistically according to Table (2) showed the difference of duration in cells in all the study group (experimental and control group) the table represented high significant difference of both chondroblast & chondrocytes cell in 7 days healing time in expeimantal group, while this cell showed non-significant difference in 14 days healing periods in the control group. The osteoblast cells showed significant difference in the experimental group but showed non-significant difference in control group in both healing periods. The statistic result represented high significant difference in the osteocytes cell in experimental group between the 7&14 days healing periods, while showed non-significant difference in control group. The osteoclast cell showed non-significant difference in each healing periods and the study group.

Table (2): Descriptive statistics of the cells count (H&E) and durations' difference in each group.

The cell	group	duration	Descriptive statistics	Group difference	
			S D	P value	Description of p value
Chondroblast	Experimental	7 days	0.611	0.000	HS
		14 days	0.951		
	control	7 days	0.200	0.088	NS
		14 days	0.202		
Chondrocytes	Experimental	7 days	0.306	0.002	HS
		14 days	0.445		
	control	7 days	0.520	0.451	NS
		14 days	0.550		
Osteoblast	Experimental	7 days	1.8	0.18	S
		14 days	0.976		
	control	7 days	0.801	0.306	NS
		14 days	1.060		
Osteocytes	Experimental	7 days	0.654	0.001	HS
		14 days	0.307		
	control	7 days	0.501	0.33	S
		14 days	0.432		
Osteoclast	Experimental	7 days	0.34	0.270	NS
		14 days	0.3		
	control	7 days	0.234	0.231	NS
		14 days	0.254		

Discussion

The pharmaceutical industry now views traditional medicine as a source for identifying bioactive molecules that may be employed in the creation of synthetic medications. Chemical medicines (bisphosphonate medicament) have always been a significant part of the healthcare system [22]. The inorganic pyrophosphate is a naturally occurring polyphosphate present

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in sera and urine [23]. In our study used bisphosphonates as an initiator for endochondral ossification due to their strong affinity for the hydroxyapatite on the surface of bones in areas of bone production or bone remodeling agree with [24] when included the bisphosphonate to retained bone trabeculae with osteoid development among the malignant cells. Due to bisphosphonates used to accelerate the healing by inactivation of clastic cells' (resorptive activity), and calcified cartilage fragments remained embedded inside the produced bone trabeculae at the mandible of young rats agree with [25] when used the alendronate-administrated as a treated to formed trabeculae during the endochondral ossification of the mandibular condyle.

Complex interactions among cells of the cartilage lineage and the mesenchymal bone cell and inflammatory cell lineage play a major role in the pathophysiology of bone healing. The current study depicts an inflammatory response and formation of the cartilage and replacement with bone in experimental groups and at various stages (7, 14 days) of the bone healing process [7]. The progression of bone healing as indicated by matrix deposition by activation the ossification center to synthesized cartilage cells and synthesis of osteoblasts during the first week (7 days) and bone trabeculae formation within newly formed bone as shown in histological sections that increased in number and width throughout the 14 days intervals. The presence of resorptive cell represented by osteoclast that retain in residing Howship lacunae indicates remodeling process during the healing periods, with high significant activation and increase in count of the cartilage cells and replacement the cartilage matrix with bone matrix and precipitation the inorganic substance to enhance the time that required to heal the defect area after used the bisphosphonate as an initiator this histological changes was detected by histomorphometry analysis. These findings of experimental group is agreed with [26] stated that osteoporosis female Wistar rats was fed their food daily with L. sativum seeds.

Regarding results of histomorphometrical analysis have shown that the nonequivalence of count difference of examined cartilage parameters and recorded microarchitecture between control and experimental groups, clarified a high avalue in experimental groups than those of control groups in different intervals time especially in 7 days healing period due to active endochondral ossification at site of bone defect, with show bone trabeculae filled a proximately the whole defect in comparison to histologic views for control group after 14 days healing period. this agree with [7] that used herbal material that represented by Symphytum officinale oil when applied locally on generated bone defect healing in rat tibia and shown it was very effective in healing the bone defect.

Conclusions

The endochondral ossification of the mandibular angle defect was considerably changed in young rats treated with bisphosphonates. However, they remained dormant and could remodel the calcified cartilage/primary bone trabeculae into the spongy bone at the mandibular angle. It did not prevent the recruitment and fusion of

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cartilage cells and bone cells during the ossification of the defect area with deposited matrix, which were abundant at the ossification areas. The current findings highlight the risk of impairing maxillofacial growth in young patients who receive bisphosphonate therapy, which is recommended for the treatment of bone disorders in childhood such as osteogenesis imperfecta, juvenile Paget's disease, and secondary osteoporosis related to anorexia nervosa, cerebral palsy, and post-renal transplants.

Recommendations

One of the most important medicaments that has been scientifically proven (laboratory and histologically) to be one of the effective medicaments in treating osteoporosis and bone fractures and repairing them in a good standard period in order to increase the efficiency of bone-building cells and cells that maintain the skeleton of the bone.

Source of funding: The current study was funded by our charges with no any other funding sources elsewhere.

Ethical clearance: This study was conducted according to the approval of College of Medicine/ University of Diyala and in accordance with the ethical guidelines of the Declaration of ethical committee of the College (Document no. 2023MAH798).

Conflict of interest: Nil

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رسم توضيحي نسيجي ونسيجي للتعظم الغضروفي لإصلاح عيب زاوية الفك السفلي في الجرذان بعد التحفيز الفموي باستخدام علاج البايفوسفونيت (دراسة في الجسم الحي)

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الملخص

خلفية الدراسة: يمكن استخدام الفوسفونات الحيوية لتقليل خطر الإصابة بكسور الورك والعمود الفقري. بالإضافة إلى ذلك، يمكن استخدامها لعلاج مرض باجيت الذي يصيب العظام بجرعات متنوعة. في الإجراء الذي يتم فيه استبدال الغضروف الزجاجي بالعظام، يسمى هذا الإجراء التعظم الغضروفي. يبدأ عندما تتطور الخلايا الوسيطة من الأديم المتوسط إلى خلايا غضروفية. تتكاثر الخلايا الغضروفية بسرعة وتطلق مصفوفة خارج الخلية لتكوين الغضروف الذي يعمل كنموذج للعظام.

اهداف الدراسة: لتوضيح نسيجي وهستومورفومتري لعملية التعظم الغضروفي لإصلاح عيب الزاوية السفلية في الفئران بعد التحفيز الفموي باستخدام علاج البيسفوسفونات.

المرضى والطرائق: تم استخدام ٢٠ فأراً في هذا العمل وتم تقسيم الحيوانات إلى المجموعات التالية: ١٠ فئران من المجموعة الضابطة. وتم شفاء العيب العظمي بشكل طبيعي دون دواء وتم استخدام ١٠ فئران في التجربة، كما ساعد تناول دواء البيوفوسفونات في إصلاح العيب العظمي. تمت دراسة كل مجموعة خلال ٧ و ١٤ يوم (٥ فئران لكل فترة شفاء) وتم إجراء العملية الجراحية للفحص النسيجي والنسيجي. تم تحليل البيانات باستخدام المقياس الإحصائي spss وبقيمة ($P \geq 0.05$) P.

النتائج: تأثير فعال لدواء الفوسفات الحيوي في التعظم الغضروفي والخلية المسؤولة عن تكوين الغضروف وتسريع شفاء عيب الفك السفلي مع تثبيط إعادة العظام وأخيرًا تقليل الوقت اللازم للشفاء الكامل.

الاستنتاجات: الدواء الكيميائي المتمثل بالبيوفوسفونات يسرع عملية التعظّم الغضروفي في وقت قصير واستبداله بالعظم في مكان الخلل.

الكلمات المفتاحية: الفوسفونات الحيوية, الغضروف، الخلايا الغضروفية، التعظم الغضروفي

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Dyslipidemia in insulin dependent diabetic children

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Abstract

Background: Children and adolescents with insulin-dependent diabetes mellitus (IDDM) are at high risk of metabolic disorders that may interfere with lipid metabolism and predispose to dyslipidemia.
Objective: To detect the incidence of dyslipidemia and associated factors in children with IDDM in Diyala.
Patients and Methods: This was a case-control study that included a total of 100 children with type 1 diabetes mellitus(T1DM) and 100 age- and gender-matched non-diabetic children who presented to the Pediatric Department/Al-Batool Teaching Hospital during the period from April 2022 to April 2023. Demographic data included the child's age, gender, weight, mother's educational level, mother's job, child's educational level, school attendance, and physical activity. Clinical data included systolic and diastolic blood pressure, HbA1c, family history of illness, disease duration, type of insulin, and insulin dose. Fasting lipid profile and hemoglobin A1c investigations were done for the study groups, and the data were statistically analyzed.
Results: The overall dyslipidemia in IDDM children and controls was 46% and 8%, respectively, with a highly significant difference. The mean age and weight in diabetic patients with dyslipidemia were 8.23±3.63 years and 28.96±13.31 kg, respectively, which was higher than that of normolipidemic diabetic patients (10.72±3.23 years and 34.22±12.14 kg, respectively) with significant differences. Furthermore, 28.26% of mothers of dyslipidemia-.diabetic patients were employed, compared with only 11.11% of normolipidemic-diabetic patients, a significant difference. A family history of DM was reported in 47.83% and 27.78% of dyslipidemic and normolipidemic diabetic patients, respectively, with a significant difference.
Conclusion: The incidence of dyslipidemia among diabetic children in Diyala is 46%. Older age, increased body weight, and a mother's job as an employer are significantly associated with the development of dyslipidemia in insulin-dependent diabetes mellitus patients.
Keywords: Dyslipidemia, Diabetes mellitus, Children, Diyala.

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Introduction

The prevalence of dyslipidemia (DLP) in the general population, including diabetic children, has recently increased [1].The increased prevalence of DLP may be attributed to lifestyle changes such as sedentarism and high-carbohydrate and fat diets [2]. Dyslipidemia is not a mandatory component of type 1 diabetes, and in well-

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controlled cases, the lipid profile is often normal [3]. Poorly controlled T1DM often presents atherogenic lipid abnormalities, including elevated triglycerides, low HDL-C levels, and an increased prevalence of small, dense low-density lipoprotein particles [4]. VLDL levels can be influenced by increased liver VLDL production, reduced catabolism, or both [5]. Insulin resistance causes unchecked lipolysis of triglycerides in adipocytes and myocytes, causing a flood of fatty acids to return to the liver [6] .The liver's production of VLDL increases due to the increased return of fatty acids [7]. Insulin inhibits hormone-sensitive lipase in adipose tissue, reducing free fatty acid secretion. Postprandial, enterocytes produce large lipoproteins, chylomicrons, which are hydrolyzed by lipoprotein lipase (LPL) in the circulation. Insulin influences postprandial lipid metabolism by reducing chylomicron production, increasing LPL activity, and enhancing chylomicron-remnant catabolism [8].Insulin increases LDL-receptor expression and activity, promoting LDL catabolism by binding to the plasma membrane of hepatic or other tissues [9]. Patients with type 1 diabetes mellitus and diabetic ketoacidosis often exhibit quantitative lipid abnormalities due to insulin deficiency [8]. Insulin deficiency reduced triglyceride-rich lipoprotein catebolism, leading to hypertriglyceridemia and reduced LDL-cholesterol levels. The results are low HDL cholesterol levels,which resolve rapidly after adequate insulin therapy [9]. Epidemiological studies have shown quantitative lipid disorders such as hypertriglyceridemia and elevated LDL-cholesterol and non-HDL cholesterol levels in patients with suboptimal glycemic controls [10,11]. Aim of the study to detect the incidence of dyslipidemia and associated factors in children with type 1 DM in Diyala.

Patients and Methods

This was a case-control study that included a total of 100 children with T1DM and 100 age- and gender-matched non-diabetic children who presented to the Pediatric Department/Al-Batool Teaching Hospital during the period from April 2022 to April 2023. It included children with IDDM from 3 to 15 years old, excluding those with chronic diseases and nutritional problems. An interview questionnaire was used to collect information from the child's parents. A written consent from each child's parent was obtained prior to data collection after explaining the aim of study. The confidentiality of data throughout the study was guaranteed and the parents were assured that data will be used for research purpose only. Demographic data included the child's age, gender, weight, mother's educational level, mother's job, child's educational level, school attendance, and physical activity. Clinical data included systolic and diastolic blood pressure, HbA1c, family history of illness, disease duration, type of insulin, and insulin dose. Blood samples were collected after an eight-hour fasting period and analyzed by Erba XL-200 German using standard methods. Total cholesterol (TC), triglycerides (TG), and HDL-C levels were measured. LDL-C levels were calculated by the Friedewald formula LDL-C=(TC)-(HDL-C)-(TG/5) using the available lipid data. Hemoglobin A1c (A1c) measurement was performed using the Erba XL-200 German. Dyslipidemia was defined by the American

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Diabetes Association (ADA) as having LDL-C >100 mg/dl, HDL-C < 40 mg/dl (males) and<50 mg/dl (females), TC ≥200 mg/dl, and TG ≥150 mg/dl, and dyslipidemia was considered present if one or more of these lipid or lipoprotein levels are abnormal [28].

Statistical Analysis

The data were analyzed using IBM SPSS version 25 (SPSS Inc., Chicago, Illinois, USA). The descriptive data was reported in number and percentage form for categorical data and mean and standard deviation (SD) for continuous data. Differences were evaluated using the Student's t test for continuous parametric data and the Pearson chi-squared test for categorical data. Pearson's correlation test was used to explore the possible correlation between the lipid profile and other variables. A P value of ≤ 0.05 was considered statistically significant.

Results

Demographic characteristics of the study population

Table (1) shows the demographic characteristics of the study population. The mean age of patients was 9.37±3.65 years compared with 9.73±2.28 years for control, with no significant difference. Likewise, there were no significant differences between the two groups in terms of gender, weight, mother's educational level, mother's job, child's educational level, and child's physical activity. However, first and second consanguinity were more frequent among patients (35% and 8%, respectively) than controls (19% and 3%, respectively), with a highly significant difference.

Table (1): Demographic characteristics of the studied group.

Demographic characteristics	Patients (n=100)	Controls (n=100)	*p*-value
Age, years			
Mean ±SD	9.37±3.65	9.73±2.28	0.471
Range	3.0-15	3.0-15	
Gender			
Male	48(48%)	54(54%)	0.396
Female	52(52%)	46(46%)	
Weight, kg			
Mean ±SD	31.38±13.0	28.54±11.92	0.113
Range	12.5-60	12-60	
Consanguinity			
None	57(57%)	78(78%)	**0.006**
1st relative	35(35%)	19(19%)	**
2nd relative	8(8%)	3(3%)	
Mother educational level			
Illiterate	30(30%)	26(26%)	
Primary	37(37%)	32(32%)	0.626
Secondary	21(21%)	26(26%)	
Higher	12(12%)	16(16%)	
Mother job			
House wife	81(81%)	82(82%)	0.856
Employee	19(19%)	18(18%)	
Child educational level			
Illutrant	13(13%)	7(7%)	
Kindergarten	12(12%)	14(14%)	0.261
Primary	50(50%)	44(44%)	
Secondary	25(25%)	35(35%)	

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School attendance			
Regular	71(71%)	78(78%)	
Interrupted	18(18%)	16(16%)	0.654
Stopped	11(11%)	6(6%)	
Physical activity			
Active	90(90%)	93(93%)	0.613
Non-active	10(10%)	7(7%)	

P value: significant , high significant** , very high significant

Clinical Characteristics of the studied group Both SBP and DBP were comparable between patients and controls, with no significant differences. On the other hand, HbA1c, as a marker for diabetes, was much higher in patients than controls (10.86%±2.37 and 5.71%±0.54), respectively, with a highly statistically significant difference. Furthermore, 37% of patients who had a family history of DM compared with 23% of controls with such a history showed a significant difference. The mean duration of T1DM was 3.02±2.71 years (range: 2–12 years). In the majority of patients (86%), soluble lente was the mode of treatment. The mean insulin dose was 25.15±14.39 Table (2).

Table (2): Clinical characteristics of the studied group.

Clinical characteristics	**Patients (n=100)**	**Controls (n=100)**	***p*-value**
Systolic blood pressure, mmHg			
Mean ±SD	103.3±9.32	105.46±10.46	0.124
Range	80-120	90-120	
Diastolic blood pressure, mmHg			
Mean ±SD	66.0±8.4	76.8±8.94	0.146
Range	50-90	50-90	
HbA1c, %			
Mean ±SD	10.86±2.37	5.71±0.54	**<0.001**
Range	4.6-16.9	3.8-6.1	***
Family history of illness			
Diabets mellitus	37(37%)	23(23%)	**0.031***
Hypertention	17(17%)	9(9%)	0.093
Congenital heart disease	5(5%)	4(4%)	0.733
Disease duration, years			
Mean ±SD	3.02±2.71	--------	-----
Range	0.2-12		
Type of insulin			
Soluble-lente	86(86%)	--------	-----
Mixture	14(14%)		
Insulin dose, Unit			
Mean ±SD	25.15±14.39		
Range	7.0-80		

* P value: significant* , high significant** , very high significant

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Lipid Profile

The mean serum level of total cholesterol TC in patients was 4.31±1.3 mmol/l, which was higher than that of controls (3.97±1.0 mmol/l) with a significant difference. Borderline and high levels of TC were reported in 18% and 8% of patients, respectively, compared with 13% and 0% in controls, respectively, with a significant difference. Similarly, the mean serum level of triglyceride TG was higher in patients than controls (1.46±0.83 mmol/l vs. 1.26±0.5 mmol/l). Furthermore, 16% and zero of patients and controls had a high level of TC, with a highly significant difference. Likewise, the mean LDL-c in patients was 3.0±0.93 mmol/l, which showed a higher level than that of controls (2.54±0.5 mmol/l) with a highly significant difference, while 35% vs. 8% of patients and controls had a higher level of LDL-c with a highly significant difference. Finally, patients demonstrated a lower serum level of HDL-c than controls (1.4±0.6 mmo/l vs. 1.62±0.28 mmol/l), with a highly significant difference. Interestingly, normal HDL-c was reported in only 29% of patients compared with 81% of controls, with a highly significant difference. The overall incidence of dyslipidemia was 46% among cases and 8% among controls Figure (1).

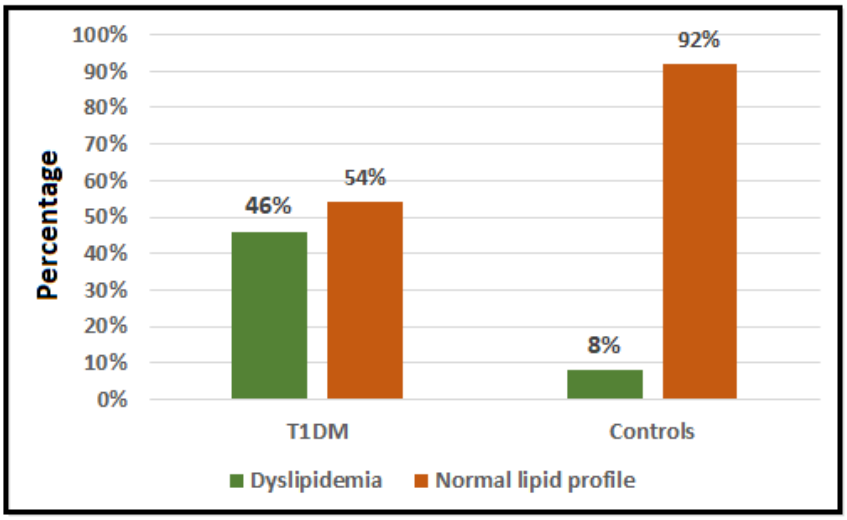

Figure (1): The incidence of dyslipidemia in T1DM patients and controls.

The overall dyslipidemia of T1DM patients and controls was 46% and 8%, respectively, with a highly significant difference Table (3).

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Table (3): Lipid profile and dyslipidemia rate in T1DM patients and controls.

Lipid profile	Patients (n=100)	Controls (n=100)	*p*-value
Total cholesterol, mmol/l			
Mean ±SD	4.31±1.3	3.97±1.04	**0.41**
Range	1.15-8.05	120-340	
Normal	74(74%)	87(87%)	
Borderline	18(18%)	13(13%)	**0.007****
High	8(8%)	0(0%)	
Triglycerides, mmol/l			
Mean ±SD	1.46±0.83	1.26±0.5	**0.043***
Range	0.2-4.1	0.52-2.2	
Normal	69(69%)	74(74%)	**<0.001 *****
Borderline	15(15%)	26(26%)	
High	16(16%)	0(0%)	
LDL-c, mmol/l			
Mean ±SD	3.0±0.93	2.54±0.5	**<0.001 *****
Range	0.9-5.37	0.2-3.9	
Normal	36(36%)	64(64%)	
Borderline	29(29%)	28(28%)	
High	35(35%)	8(8%)	**<0.001 *****
HDL-c, mmol/l			
Mean ±SD	1.4±0.6	1.62±0.28	**0.001 *****
Range	0.2-4.02	1.0-1.98	
Normal	29(29%)	81(81%)	
Borderline	71(71%)	19(19%)	**<0.001 *****
Overall dyslipidemia	46(46%)	8(8%)	**<0.001 *****

P value: significant , high significant** , very high significant

Association of Demographic Factors with Dyslipidemia in T1DM Patients

Three demographic factors were significantly associated with dyslipidemia in T1DM patients. The mean age and weight in patients with dyslipidemia were 8.23±3.63 years and 28.96±13.31 kg, respectively, which was higher than that of normolipidemic patients (10.72±3.23 years and 34.22±12.14 kg, respectively) with significant differences. Furthermore, 28.26% of mothers of dyslipidemia patients were employed compared with only 11.11% of normolipidemic patients, with a significant difference Table (4).

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Table (4): Association of demographic factor with dyslipidemia in T1DM patients.

Variables	Normolipidemia (N=54)	Dyslipidemia (N=46)	p-value
Age, years			
Mean ±SD	8.23±3.63	10.72±3.23	**0.001**
Range	3.0-14.0	3.0-15.0	***
Gender			
Male	26(48.15%)	22(47.83%)	0.974
Female	28(51.85%)	24(52.17%)	
Weight, kg			
Mean ±SD	28.96±13.31	34.22±12.14	**0.043**
Range	13.0-59.0	12.5-60.0	*
Consanguinity			
None	32(59.26%)	25(54.35%)	0.686
1st relative	17(31.48%)	18(39.13%)	
2nd relative	5(9.26%)	3(6.52%)	
Mother educational level			
Illiterate	16(29.63%)	14(30.43%)	
Primary	23(42.59%)	14(30.43%)	0.358
Secondary	8(14.81%)	13(28.26%)	
Higher	7(12.96%)	5(10.87%)	
Mother job			
House wife	48(88.89%)	33(71.72%)	**0.029**
Employee	6(11.11%)	13(28.26%)	*
Child educational level			
Not educated	9(16.67%)	4(8.7%)	
Kindergarten	9(16.67%)	3(6.52%)	0.145
Primary	26(48.15%)	24(52.17%)	
Secondary	10(18.52%)	15(32.61%)	
School attendance			
Regular	9(16.67%)	4(8.7%)	
Interrupted	31(57.41%)	35(76.09%)	0.315
Stopped	3(5.56%)	4(8.7%)	
Physical activity			
Active	6(11.11%)	4(8.7%)	0.688
Non-active	48(88.89%)	42(91.3%)	

* P value: significant* , high significant** , very high significant

Association of Clinical Factors with Dyslipidemia in T1DM Patients

Three clinical factors demonstrated a significant association with dyslipidemia in patients with T1DM. Family history of DM was reported in 47.83% and 27.78% of dyslipidemic and normolipidemic patients, respectively with a significant difference. Dyslipidemic patients had longer disease duration than normolipidemic patients (4.14±1.25 years vs. 2.06±1.67 years) with a significant difference. Finally, the mean insulin dose in dyslipidemic and normolipidemic patients was 29.26±15.4 U and 21.65±12.58 U, respectively, with a significant difference Table (5).

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Table (5): Association of clinical factors with dyslipidemia in 100 patients with T1DM.

Clinical factors	Normolipidemia (N=54)	Dyslipidemia (N=46)	*p*-value
Systolic blood pressure, mmHg			
Mean ±SD	101.85±8.92	105.0±9.6	0.093
Range	80-120	90-120	
Diastolic blood pressure, mmHg			
Mean ±SD	65.0±8.18	67.17±8.6	0.199
Range	50-80	50-90	
HbA1c, %			
Mean ±SD	10.03±2.28	10.37±2.48	0.474
Range	6.0-14	4.6-16.9	
Family history of illness			
Diabetes mellitus	15(27.78%)	22(47.83%)	**0.038***
Hypertension	10(18.52%)	7(15.22%)	0.661
Congenital heart disease	3(5.56%)	2(4.35%)	0.782
Disease duration, years			
Mean ±SD	2.06±1.67	4.14±1.25	**<0.001 *** **
Range	0.2-7.0	0.25-12.0	
Type of insulin			
Soluble-lente	46(85.19%)	40(86.96%)	0.799
Mixture	8(14.81%)	6(13.04%)	
Insulin dose, Unit			
Mean ±SD	21.65±12.58	29.26±15.4	**0.008 ** **
Range	7.0-80	10-72	

* P value: significant* , high significant** , very high significant

Incidence of Dyslipidemia

Correlation of lipid profile with other factors in T1DM patients

Pearson's correlation was used to explore the possible correlation of lipid profile with other variables in patients. Total cholesterol had a significant positive correlation with each of age (r= 0.340, p= 0.001) and weight (r= 0.289, p= 0.004), disease duration (r= 0.377, p<0.001) and insulin dose (r= 0.328, p= 0.001). On the other hand, TG demonstrated a significant positive correlation with each of age (r= 0.355, p<0.001), weight (r= 0.251, p= 0.012), disease duration (r= 0.249, p= 0.012), DBP (r= 0.239, p= 0.017) and insulin dose (r= 0.435, p<0.001). Finally, LDL-c displayed a significant positive correlation with DBP (r= 0.215, p= 0.031) as shown in Table (6).

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Table (6): Correlation of lipid profile with other factors in T1DM patients.

Factors	TC		TG		LDL-c		HDL-c	
	R	p-value	R	p-value	R	p-value	R	p-value
Age	**0.340**	**0.001 *****	**0.355**	**<0.001 *****	0.174	0.083	0.100	0.323
Weight	**0.289**	**0.004****	**0.251**	**0.012***	0.054	0.591	0.181	0.072
Duration	**0.377**	**<0.001 *****	**0.249**	**0.012***	0.155	0.122	0.058	0.567
HbA1c	0.176	0.080	0.143	0.155	0.011	0.914	0.162	0.108
SBP	0.146	0.148	0.119	0.238	0.137	0.175	0.134	0.184
DBP	0.127	0.208	**0.239**	**0.017***	**0.215**	**0.031**	0.114	0.261
Ins. Dose	**0.328**	**0.001 *****	**0.435**	**<0.001 *****	0.100	0.324	0.002	0.985

* P value: significant* , high significant** , very high significant

Association of Lipid Profile with Categorical Variables in T1DM Patients

Serum concentrations of different components of the lipid profile were comparable between different categories of consanguinity, mother's educational level, mother's job, school attendance, physical activity, family history of hypertension, family history of CHD, and insulin dose, with no significant differences. However, females had a higher level of TG than males (1.63±0.97 mmol\l vs. 1.27±0.61 mmol\l) with significant differences. Furthermore, children with secondary school levels had a higher mean of TC (5.09±1.2 mmol/l) than other levels, with a significant difference. Additionally, the presence of a family history of DM is associated with higher levels of TG, LDL-c (1.71±0.89 mmol/l and 3.82±0.86 mmol/l, respectively), and a low level of HDL-c (1.29±0.40 mmol/l) than those without such a history (1.31±0.77 mmol/l, 2.8±0.93 mmol/l, and 1.57±0.82 mmol/l, respectively) with significant differences Table (7).

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Table (7): Association of lipid profile with the binomial variables in 100 patients with T1DM.

Variables	TC, mmol/l	TG, mmol/l	LDL-c, mmol/l	HDL-c, mmol/l
Gender				
Males	4.85±1.27	1.27±0.61	2.92±0.93	1.39±0.62
Females	4.34±1.35	1.63±0.97	3.03±0.94	1.4±0.59
p-value	0.844	**0.028***	0.543	0.978
Consanguinity				
None	4.35±1.36	1.44±0.82	3.07±0.89	1.43±0.6
1st relative	4.25±1.31	1.6±0.87	2.9±1.0	1.37±0.64
2nd relative	4.34±0.9	0.96±0.55	2.7±0.95	1.25±0.54
p-value	0.946	0.155	0.487	0.715
Mother education level				
Illiterate	4.12±1.57	1.45±0.71	3.06±1.03	١.٤±0.37
Primary	4.13±1.21	1.41±0.84	2.72±0.87	1.35±0.35
Secondary	٤.٧٢±1.07	1.6±1.07	3.33±0.61	١.٦6±0.92
Higher	4.01±0.67	1.37±0.66	2.94±1.16	1.52±0.41
p-value	0.١23	0.830	0.111	0.١34
Mother job				
House wife	4.24±1.31	1.42±0.81	2.87±0.91	1.4±0.56
Employee	4.63±1.21	1.62±0.94	3.32±0.92	1.38±0.78
p-value	0.234	0.338	0.068	0.891
Child education level				
Not educated	3.98±0.92	1.65±0.41	2.71±0.90	1.22±0.43
Kindergarten	3.97±1.19	1.38±0.59	2.64±1.05	1.38±0.63
Primary	4.09±1.33	1.49±0.79	3.12±0.89	1.33±0.49
Secondary	5.09±1.2	1.79±1.0	3.0±0.94	1.62±0.81
p-value	**0.006****	0.115	0.290	0.157
School attendance				
Regular	3.95±1.21	1.43±0.75	2.57±0.98	1.44±0.76
Interrupted	4.44±1.4	1.6±0.9	3.1±0.93	1.42±0.61
Stopped	4.54±1.0	1.18±0.46	3.15±0.78	0.27±0.24
p-value	0.458	0.417	0.159	0.826
Physical activity				
Active	3.88±0.98	1.29±0.90	3.04±0.63	1.3±0.65
Non-active	4.36±1.33	1.48±0.83	2.97±0.96	1.41±0.60
p-value	0.269	0.505	0.826	0.602
Family Hx of DM				
No	4.13±1.24	1.31±0.77	2.8±0.93	1.57±0.82
Yes	4.62±1.37	1.71±0.89	3.82±0.86	1.29±0.40
p-value	0.071	**0.022**	**0.012**	**0.026**
Family History of Hypertention	4.34±1.35	1.5±0.88	2.98±0.97	1.93±0.63
No	4.18±1.08	1.25±0.53	2.96±0.75	1.44±0.45
Yes				
p-value	0.658	0.253	0.937	0.734
Family History of CHD				
No	4.3±1.3	1.46±0.83	2.98±0.93	1.41±0.61
Yes	4.5±1.58	1.39±0.96	2.98±1.1	1.19±0.36
p-value	0.773	0.853	0.998	0.436
Type of insulin				
Soluble-lente	4.34±1.29	1.51±0.86	2.96±0.95	1.4±0.63
Mixture	4.11±1.44	1.17±0.62	3.09±0.84	1.38±0.41
p-value	0.541	0.160	0.637	0.934

* P value: significant* , high significant** , very high significant***

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Discussion

The present study aimed to detect the incidence of dyslipidemia and associated factors in children with T1DM in Diyala. Alrasheed [12] looked into the parameters that are related to dyslipidemia and its prevalence among 234 Saudi patients with T1DM. According to the current study, dyslipidemia was present in around half (50%) of the individuals who were included. In a cross-sectional investigation, Abed[13] found that 64% of 129 young people with T1DM had dyslipidemia. Similar findings were made by Mona [14], who examined 60 kids and teens and found that the incidence of dyslipidemia in diabetic patients and controls was, respectively, 65% and 28.2%. In Iraq, 66% of children with T1DM had dyslipidemia, compared to 34% of the non-diabetic control group, according to [15]. In 202 Turkish children and adolescents with T1DM, Bulut [16] assessed the prevalence of dyslipidemia and its correlation with clinical and laboratory results. A relatively low rate (26.2%) of dyslipidemia was reported among those patients. In contrast, a 72.5% rate of dyslipidemia was reported in a Brazilian study including 239 patients with T1DM. The authors attributed the significant prevalence of dyslipidemia to the individuals' wide age range, as well as the rise in sedentary behavior, diets heavy in carbohydrates, and obesity with advancing years. There are a number of reasons why various studies may differ from one another, but the most significant ones are dietary practices, variations in the patients' clinical and demographic features, treatment regimens, and reference ranges for lipid profiles. The increased prevalence rate of dyslipidemia among T1DM patients could be explained by several factors, mainly related to carbohydrate metabolism and insulin deficiency. These factors may cause fat cells to break down from their stored triglyceride forms and result in a greater release of free FA into the circulation. Increased FAs in the plasma lead to increased uptake of these acids by the liver. The liver then synthesizes triglycerides from these FAs. The presence of increased triglycerides stimulates the secretion and assembly of apolipoprotein B and vLDL-C [17]. High LDL-C was the most common kind of dyslipidemia in the current study, accounting for the majority of cases. Within the dyslipidemic group, high LDL-C and low HDL-C were the most common types of dyslipidemia found in the Alakkad study [18]. These were followed by isolated high LDL-C in 6 patients (18.75%), isolated low HDL-C in 5 patients (15.63%), and hypercholesterolemia and high LDL-C in 4 patients (12.50%). According to the study by Mona [14], and Kantoosh [19], hypertriglyceridemia predominated among children with diabetes in Egypt. According to Patiakas [20], among diabetic patients, hypercholesterolemia is the most common form, while hypertriglyceridemia is the least common type. According to Alrabaty [21], the most prevalent dyslipidemia pattern in children and teenagers with T1DM is hypertriglyceridemia. These variations in the types of dyslipidemia between researchers could be attributed to glycemic management, comorbidities, and lifestyle variables. In the present study, older age, increased body weight, and a mother's job as an employee were significantly associated with dyslipidemia in patients with T1DM, while

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there was no significant impact of HbA1c, physical activity, sex, blood pressure, or type of insulin. These results are, at least, partially in accordance with many previous studies. This is consistent with the findings of Moayeri and Oloomi [22], who discovered a significant correlation between lipid concentrations and the length of diabetes. It was shown by Patiakas [20] and Alrabaty [21] that gender had no discernible effect on lipid abnormalities in children and teenagers with type 1 diabetes. Moreover, dyslipidemia did not significantly correlate with age, BMI, the duration of diabetes, or the presence or absence of hypertension, according to Alrasheed [12] .Unlike the current findings, Mona [14] found no significant correlation between dyslipidemia and age or length of diabetes. Nonetheless, they discovered a strong correlation between dyslipidemia and BMI ($P = 0.024$). Marcovecchio [15] also found significant correlations with age ($P < 0.001$), BMI ($P < 0.05$), length of diabetes ($P < 0.001$), and HbA1c ($P < 0.001$), which is similar to the findings of this investigation. In a retrospective analysis of 806 children and adolescents with type 1 diabetes, Soliman and Ibrahim [23] found that higher levels of dyslipidemia (TG, TC, and LDL-c) were substantially correlated with poorer glycemic control, longer diabetes duration, and older age. Abed [13] likewise found a significant ($P < 0.043$) correlation between dyslipidemia and a higher mean HbA1c. It was discovered by Muchacka-Bianga [24] that children with T1DM may have lipid problems regardless of how well their metabolism is controlled. Conversely, Teles and Forne´s [25] as well as Guy [16] discovered a link between elevated blood lipid levels and subpar (inadequate) glycemic management. The absence of a significant impact of glycemic control on dyslipidemia in the present study may be attributed to differences in age and insulin doses between the included patients. According to Alakkad [18], there was no statistically significant difference in the mean duration of diabetes between the dyslipidemic and normolipidemic groups (5.7± 3.1 years and 5.5± 2.60 years, respectively). Similar to the present study, Wiltshire [26] and Ladeia [27] found that serum TG correlates positively with insulin dose in children and adolescents with T1DM. This effect of insulin dose may reflect the hyperglycemic status of patients with dyslipidemia who require a higher dose of insulin. An interesting finding in the present study that was not indicated in the previous studies was that T1DM children of employee women are more prone to dyslipidemia than those of housewife women. This may be explained by two main factors, First, there is more time for the supervision of child lifestyle when the mother is a housewife. Secondly, most employee women use ready-to-eat foods and chunks from the market, which usually have high lipid contents. In contrast, housewives may pay more attention to preparing healthy food for their children.

Conclusions

There is a marked increase in dyslipidemia in patients with T1DM compared with non-diabetic children. Older age, increased body weight, and a mother's job as an employer are significantly associated with the development of dyslipidemia in T1DM patients.

The presence of a family history of DM, longer T1DM duration, and a higher dose of

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insulin could be considered risk factors for dyslipidemia in T1DM patients.

Recommendations

Regular monitoring of blood lipid levels in diabetic patients.Urging parents to commit to nutritional education and follow-up of diabetic patients.Early identification of dyslipidemia in diabetic patients will decrease its consequences.

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Ethical clearance: The study was approved by the Arab Council for Medical Specialization NO.2243 at 16/11/2022.

This study was conducted according to the approval of College of Medicine/ University of Diyala and in accordance with the ethical guidelines of the Declaration of ethical committee of the College (Document no. 2024BNA853).

Conflict of interest: Nil

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عسر شحميات الدم لدى الاطفال المصابين بداء السكري في محافظة ديالى

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الملخص

خلفية الدراسة: الأطفال والمراهقون المصابون بداء السكري من النوع الأول معرضون بشكل كبير لخطر الإصابة باضطراب التمثيل الغذائي الذي قد يتداخل مع استقلاب الدهون ويؤدي إلى الإصابة بعسر شحميات الدم.

اهداف الدراسة: لكشف عن حدوث عسر شحميات الدم والعوامل المرتبطة به لدى الأطفال المصابين بالسكري من النوع الأول في ديالى.

المرضى والطرائق: شملت هذه الدراسة ما مجموعه ١٠٠ طفل مصاب بداء السكري من النوع الأول و١٠٠ طفل سليم مماثل من حيث العمر والجنس. تم جمع البيانات الديموغرافية بما في ذلك عمر الطفل، والجنس، والوزن، والمستوى التعليمي للأم، ووظيفة الأم، والمستوى التعليمي للطفل، والالتحاق بالمدارس، والنشاط البدني، والبيانات السريرية بما في ذلك ضغط الدم الانقباضي والانبساطي، ونسبة السكر التراكمي، والتاريخ العائلي للمرض، ومدة المرض، ونوع الأنسولين وجرعة الأنسولين. تم قياس مستوى الدهون في عينات الدم التي تم جمعها بعد صيام ٨ ساعات.

النتائج: بلغ معدل عسر شحميات الدم في مرضى الداء السكري من النوع الأول مجموعة السيطرة ٤٦٪ و٨٪ على التوالي وبفرق معنوي. وكان متوسط العمر والوزن لدى المرضى الذين يعانون من عسر شحميات الدم ٨,٢٣ ± ٣,٦٣ سنة و ٢٨,٩٦ ± ١٣,٣١ كغم على التوالي وهو أعلى من المرضى الذين لايعانون من عسر شحميات الدم (١٠,٧٢ ± ٣,٢٣ سنة و ٣٤,٢٢ ± ١٢,١٤ كغم على التوالي) وبفروق معنوية. علاوة على ذلك، فإن ٢٨,٢٦٪ من أمهات مرضى عسر شحميات الدم كن موظفات مقارنة بـ ١١,١١٪ فقط من المرضى ذوي شحوم الدم الطبيعية وبفرق معنوي. سجل التاريخ العائلي لمرض السكري في ٤٧,٨٣٪ و٢٧,٧٨٪ من مرضى عسر شحميات الدم والمرضى سويي الشحوم ، على التوالي، وبفرق معنوي. كان لدى مرضى عسر شحميات الدم مدة مرض أطول من المرضى سويي الشحوم (٤,١٤ ± ١,٢٥ سنة مقابل ٢,٠٦ ± ١,٦٧ سنة) وبفرق معنوي. أخيرًا، كان متوسط جرعة الأنسولين لدى مرضى عسر شحميات الدم والمرض سوي الشحوم ٢٩,٢٦ ± ١٥,٤ وحدة و ٢١,٦٥ ± ١٢,٥٨ وحدة على التوالي، وبفرق معنوي.

الاستنتاجات: إن معدل الاصابة بعسر شحميات الدم بين الأطفال والمراهقين في ديالى يقع ضمن سياق الانتشار العالمي لهذا المرض. يرتبط التقدم في السن وزيادة وزن الجسم ووظيفة الأم كموظفة بشكل معنوي بتطور عسر شحميات الدم لدى مرضى الداء السكري من النوع الأول . يمكن اعتبار وجود تاريخ عائلي لمرض السكري، ومدة طويلة للداء السكري من النوع الأول ، وجرعة أعلى من الأنسولين عوامل خطر لعسر شحميات الدم لدى مرضى الداء السكري من النوع الأول .

الكلمات المفتاحية: عسر شحميات الدم، داء السكري، الاطفال، ديالى

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A Comparative Study Between Pemetrexed and Taxanes as First Line Treatment of Metastatic Lung Adenocarcinoma

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Abstract

Background: Adenocarcinoma of the lung is the most common type of lung cancer. Platinum agents in combination with other chemotherapy are currently the cornerstone for chemotherapy of advanced cases with metastasis.

Objective: To compare the response rate of pemetrexed doublets versus taxanes doublets in patients with metastatic lung adenocarcinoma.

Patients and Methods: This a prospective study that included 60 patients with pulmonary adenocarcinoma. Those patients received a platinum based doublet chemotherapy with additional treatment protocol; combined with either pemetrexed or taxanes (paclitaxel or docetaxel) with 30 patients in each arm. Tumor size, response rate and side effects of chemotherapy were evaluated in both arms.

Results: The median reduction in tumor size in pemetrexed and taxan arms were 4.72 cm2 and 6.53 cm2 respectively. Nausea, fatigue, constipation and anorexia were more common in pemetrexed arm, while leukopenia, arthralgia and peripheral neuropathy were more common in taxan arm.

Conclusion: Serious side effects such as leukopenia, and peripheral neuropathy were more common in taxan than pemetrexed arm. Pemetrexed is preferable to use as a fist line treatment for patients with metastatic adenocarcinoma of the lung.

Keywords: Adenocarcinoma, Pemetrexed, Taxanes, metastatic lung cancer.

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Introduction

Adenocarcinoma of the lung, which falls under the category of non-small cell lung cancer (NSCLC) [1], is the prevailing form of lung cancer. The primary cause of this cancer type is cigarette smoking [2]. TNM staging [3] is used to determine the extent of the disease. Adenocarcinoma in situ and minimally invasive adenocarcinoma, although infrequent, constitute only 5% of surgically removed adenocarcinomas [4]. The most frequently encountered invasive adenocarcinoma is categorized based on five distinct histological growth patterns: lepidic, acinar, papillary, micropapillary, or solid [5].

Historically, platinum doublet chemotherapy has served as the established initial treatment for individuals having metastatic lung adenocarcinoma lacking a

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defined mutation [6]. Extensive research has explored various combinations of third-generation drugs alongside platinum agents, such as cisplatin plus paclitaxel and cisplatin plus gemcitabine. These combinations have demonstrated comparable response rates and survival durations in patients with metastatic NSCLC. In cases where patients cannot put up with platinum agents, non-platinum treatments like gemcitabine plus docetaxel or gemcitabine plus vinorelbine may serve as reasonable alternatives [7,8].

It was established that pemetrexed increases survival rate for patients with non-squamous NSCLC as first-line and maintenance chemotherapy [7]. Single-agent immunotherapy such as nivolumab, atezolizumab and pembrolizumab have been found to prolong survival in general [9,10,11]. Extensive research has focused on innovative combination therapies for advanced lung adenocarcinoma, which involve pairing chemotherapy with a checkpoint inhibitor. One notable example is the mixture of pembrolizumab with carboplatin and pemetrexed, which has been studied and approved as a first-line treatment option. Additionally, the combination of two checkpoint inhibitors, namely ipilimumab plus nivolumab, has demonstrated benefits in patients with a high tumor mutational rate (≥10 mutations per mega-base). It is crucial to select an approved targeted therapy as the initial treatment if the tumor harbors an tortious mutation [6]. The assessment of treatment response utilizes the response evaluation criteria in solid tumors (RECIST) criteria and employs a three-dimensional approach [12,13]. The current study aims to compare the response rate to platinum doublets pemetrexed versus platinum doublets taxanes in first line treatment for patients with metastatic NSCLC adenocarcinoma subtype in Iraqi patients.

Patients and Methods

The Study Population

This is a prospective study including patients with metastatic pulmonary adenocarcinoma who were attending Oncology Teaching Hospital in Baghdad during the period from 1 January 2020 to 31 July 2020. Patients with histologically confirmed advanced pulmonary adenocarcinoma by trans-bronchial or trans-thoracic biopsy with metastases to bone, liver and brain, detected by computed tomography (CT) examination, were eligible for the study. The study included Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≤1, adequate hematopoietic, liver and renal functions, age less than 75 and stage IV lung tumor adenocarcinoma subtype. On the other hand, patients having PS 2 or more, patient positive for EGFR, those with incomplete radiological assessment, uncontrolled diabetes mellitus or peripheral neuropathy and renal or hepatic insufficiency were excluded from the study.
Written informed consent following approval of the health authority from all participants was obtained before data collection after explaining the aim of the study.

The Study Groups

History and physical examination including TNM staging were performed for all patient. All patients were given platinum based doublet chemotherapy 4-6 cycles according to national comprehensive cancer network Guidelines [14], with carboplatin AUC 5 i.v over 30 minutes (manufactured by Hospira),

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combined with one of the following drugs :
Group A: 30 patients treated with pemetrexed (manufactured by Lilly Pharma) 500mg/m^2 i.v over 10 minutes
Group B: 30 patients treated with taxanes, paclitaxel (manufactured by Hospira) 175mg/m^2 i.v over 3 hours or docetaxel (manufactured by Pfizer) 75mg/m^2 i.v over 60 minutes.
Treatment has been delayed 1 week for patients in any arm with grades 3–4 neutropenia, thrombocytopenia and anemia with hemoglobin less than 8 g/dl. Treatment discontinued if the patient has experienced decrease in his performance status, complication or progression.
The response of patients was evaluated according to RECIST guidelines. Clinical evaluation and CT scan were performed every 3 treatment cycles.
A patient was considered to have complete response when there is disappearance of all target lesions. A patient had partial response when there is at least 30% decrease in sum of the longest diameters of the target lesion. Stable disease indicates neither a shrinkage sufficient to qualify for partial response nor sufficient increment to qualify for progressive disease.

Statistical Analysis

Data entry was performed using the SPSS software (vesion 24). Continuous data were subjected to normality test. Mean and standard deviation (SD) was used to express the normally distributed data which were analyzed with Student t-test, while median and range were used to present non-normally distributed date. Those data were analyzed with Mann Whitney U test. Categorical variables were expressed as number and percentage, and were analyzed using the Chi-square ($\chi 2$) test. Spearman's correlation test was used to explore the possible correlation of tumor reduction with other continuous variables. Null hypotheses of no difference were rejected if p-values were less than 0.05.

Results

Demographic characteristics of patients

The mean age of pemetrexed arm was 60.35±10.5 years which did not differ significantly from that of taxan arm (58.87±12.29 years). Likewise, the two arms were comparable in terms of weight, height and BMI without significant differences. Males and zero ECOG score were more frequent than females and ECOG 1 score representing 56.67% and 66.67% in pemetrexed and taxan arms, respectively with no significant difference. In contrast, smokers were more frequent in taxan than pemetrexed arms (53.33% versus 26.67%) with a significant difference Table (1).

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Table (1): Demographic characteristics of the patients.

Variables	Pemetrexed(n=30)	Taxan(n=30)	p-value
Age, years			
Mean±SD	60.35±10.5	58.87±12.29	0.703
Range	37-77	34-74	
Gender			
Male	17(56.67%)	20(66.67%)	0.426
Female	13(43.33%)	10(33.33%)	
Weight, kg			
Mean±SD	73.9±11.67	76.8±11.3	0.507
Range	58-105	60-100	
Height, cm			
Mean±SD	168.6±10.55	166.13±11.03	0.244
Range	151-183	148-181	
BMI, kg/m^2			
Mean±SD	26.13±5.0	28.38±6.21	0.332
Range	20.9-44.85	19.6-41.62	
Smoking, pack/year			
Never	22(73.33%)	14(46.67%)	**0.035**
Ex/current smokers	8(26.67%)	16(53.33)	
ECOG			
Zero	17(56.67%)	20(66.67%)	0.426
One	13(43.33%)	10(33.33%)	

Therapeutic and clinical characteristics of the Patients

The most common comorbidity was hypertension (HTN) accounting for 36.67%% and 46.67% of patients in pemetrexed and taxan arms respectively, with no significant differences. Patients in pemetrexed arm had remarkably smaller initial and final tumor size (28.37±28.78 cm^2 and 22.52±36.7 cm^2, respectively) than those in taxan arm (40.52±37.55 cm^2 and 35.83±25.76 cm^2, respectively). However, the differences were significant only in final reading. The vast majority of patients in both arms received 6 cycles treatment Table (2).

Table (2): Therapeutic and clinical characteristics of the patients.

Variables	Pemetrexed (n=30)	Taxan (n=30)	p-value
Comorbidities			
No comorbidity	16(53.33%)	12(40%)	0.301
Hypertension	11(36.67%)	14(46.67%)	0.432
Diabetes mellitus	3(10%)	8(26.67%)	0.095
Others	1(5%)	1(6.67%)	0.916
Initial tumor size, cm^2			
Mean±SD	28.37±28.78	40.52±37.55	0.240*
Range	3.0-132	3-132	

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Final tumor size, cm^2 Mean±SD Range	 22.52±36.7 0-167	 35.83±25.76 1.12-99	**0.023***
Treatment cycles 4 6	 4(13.33%) 26(86.67%)	 4(13.33%) 26(86.67%)	 1.00

* Mann Whitney U test

Reduction in tumor size

The median reduction in tumor size in pemetrexed arm was 4.72 cm^2 (range -66.5-95.22 cm^2) compared with 6.53 cm2 (range -50.0-88.0 cm^2) in taxan arm. Statistically, there was no significant difference between the two arms (p= 0.657) Figure (1).

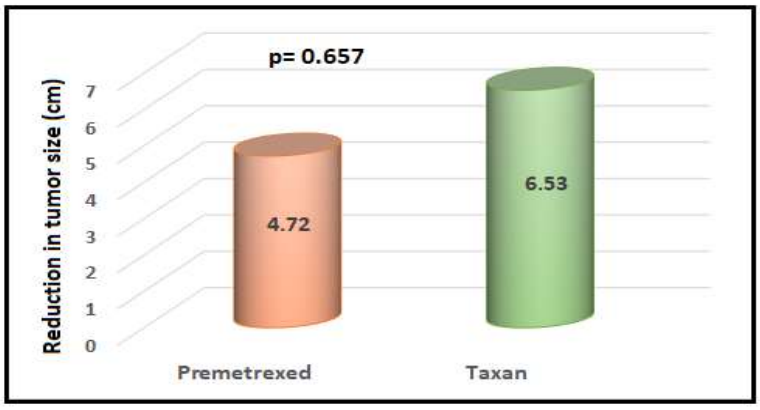

Figure (1): Median reduction in tumor sizes in pemetrexed and taxan treated arms.

Response to treatment

The response rate was in favors of pemetrexed arm in which there was only 4 (13.33%) non-responders compared to 10 (33.33%) among taxan arm with no significant differences (p= 0.211) (Figure 3-2). Interestingly, there was only one patients with complete remission in taxan Figure (2).

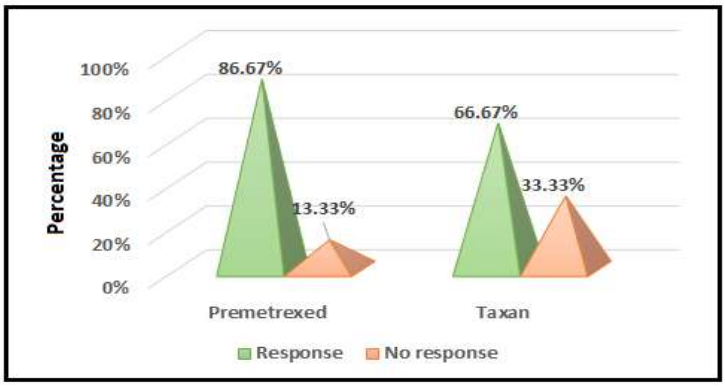

Figure (2): Response rate in the three treatment protocols.

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Correlation of tumor reduction with other variables

Spearman's correlation test was used to explore the possible correlation between tumor reduction and other continuous variables. In general, none of the included variables had a significant correlation with tumor reduction Table (3).

Table (3): Spearman's correlation between tumor reduction with other continuous variables.

Variable	Pemetrexed		Taxan	
	R	p-value	r	p-value
Age	-0.007	0.977	-0.025	0.929
Weight	0.121	0.612	0.445	0.096
Height	0.023	0.923	-0.103	0.715
BMI	0.078	0.744	0.380	0.163
No. of cycles	0.289	0.216	0.085	0.763

Association of tumor reduction with gender, smoking, and co-morbidity

There was no significant effect of gender, smoking habit or the presence of comorbidity on the reduction rate. However, patients with ECOG 0 score in pemetrexed arm had significantly higher reduction size 13.05±35.6 cm^2 than those with ECOG 1 (-4.94±15.25 cm^2) as shown in Table (4).

Table (4): Association of tumor reduction with gender, smoking and comorbidity.

Variables	Pemetrexed	Taxanes
Gender		
Males	4.22±38.89	4.72±22.1
Females	8.29±7.58	4.62±53.85
p-value	0.624	0.859
Smoking		
Yes	6.1±14.66	-5.02±24.79
No	4.42±82.67	11.69±37.48
p- value	0.479	0.121
Comorbidity		
Yes	8.76±36.46	8.03±44.96
No	1.49±17.89	2.47±26.87
p-value	0.625	0.776
ECOG		
0	13.05±35.6	3.67±33.37
1	-4.94±15.25	6.72±38.53
p-value	**0.031**	0.440

* Non-parametric Mann Whitney test was used for comparison

Side effects of the treatment

A total of 12 side effects were reported for the two arms., seven of which differed significantly between arms. Nausea, fatigue, constipation and anorexia were more common in pemetrexed arm ($P<0.05$), while leukopenia, arthralgia, and peripheral neuropathy were more common in taxan arm ($P<0.05$) Table (5).

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Table (5): Side effects of the three treatment arms.

Effects	Pemetrexed (n=30)	Taxan (n=30)	p-value
Leukopenia	0(0%)	18(60%)	**<0.001**
Neutropenia	12(40%)	16(53.33%)	0.433
Nausea	27(90%)	16(53.33%)	**0.004**
Vomiting	18(60%)	18(60%)	1.0
Alopecia	24(80%)	21(70%)	0.265
Diarrhea	7(33.33%)	8(26.67%)	0.599
Arthralgia	0(0%)	16(53.33%)	**<0.001**
Peripheral neuropathy	0(0%)	16(53.33%)	**<0.001**
Anemia	24(80%)	24(80%)	1.0
Fatigue	24(80%)	0(0%)	**<0.001**
Constipation	12(40%)	0(0%)	**<0.001**
Anorexia	24(80%)	0(0%)	**<0.001**

Discussion

Not only does pemetrexed have less toxicity that taxan, but may also it is better than other chemotherapies. In their study, Scagliotti et al. conducted a comparison between the effectiveness of cisplatin/pemetrexed and cisplatin/gemcitabine as first-line treatments for patients with non-small cell lung cancer (NSCLC) [15]. The overall survival (OS) was found to be equal in both treatment arms, with a duration of 10.3 months. However, when analyzing the nonsquamous subgroups, it was observed that survival was significantly extended with cisplatin/pemetrexed. Specifically, in patients with adenocarcinoma, the survival duration was 12.6 months compared to 10.9 months with cisplatin/gemcitabine. In the case of large cell histology, the survival was 10.4 months with cisplatin/pemetrexed, while it was 6.7 months with cisplatin/gemcitabine.

According to the result of the current study, all demographic characteristics were comparable between the pemetrexed and taxan arms with no significant differences, except smoking habit which is more frequent among taxan arm with a significant difference (P=0.035). An American study including 1370 patients with NSCLC demonstrated no prognostic effect of smoking status on treatment response or overall survival rates [16]. Thus, smoking is undoubtly the main risk factor for adenocarcinoma, but may have less important role in the response to chemotherapy.

Clinically, the mean final tumor size in taxan arm was larger than that of pemetrexed arm. However, when the reduction rate in tumor size was calculated, there was no significant differences between the two arms. Interestingly, the response rate in pemetrexed arm was better than that of taxan arm (86.67% versus 66.67%) although the difference was not significant.

Global studies on this matter have yielded contradictory outcomes. In a randomized, multi-centric study, the combination of carboplatin and pemetrexed was compared to carboplatin and docetaxel in patients diagnosed with advanced non-small cell lung cancer (NSCLC). The group of patients

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treated with carboplatin and pemetrexed exhibited a longer median survival without experiencing significant toxicity, as did the patients in the carboplatin and docetaxel group. The median overall survival was comparable between the two groups, along with similar response rates. As a result, the authors concluded that carboplatin and pemetrexed could serve as a suitable first-line treatment regimen for non-squamous NSCLC [17]. Another retrospective analysis of a large multi-centric study comparing pemetrexed to docetaxel revealed overall response rates of 9.1% and 8.8% (P = 0.105), respectively [18].

Based on the result of the current study, reduction in tumor size inversely associated with ECOG in pemetrexed arm. In ECOG 1 group, there was a slight increase in tumor size compared with initial size. In contrast, the tumor size greatly reduced in ECOG 0 group. Thus, the large tumor burden may associate with some signs and symptoms for the disease and affect ECOG score.

Another interesting finding in the present study was that pemetrexed treatment was associated with more frequent nausea (the nausea may be attributed to the cisplatin base), fatigue, constipation and anorexia, while taxane arm was associated with more frequent leukopenia, arthralgia and peripheral neuropathy. In the Hanna's study [19], hematologic toxicity in patients treated with docetaxel was greater than those treated with pemetrexed.

Conclusions

Pemetrexed arm seems to have a better response rate and toxicity profile than taxan arm although the difference was not a significant. In terms of side effect, serious side effects such as leukopenia, and peripheral neuropathy were more common in taxan than pemetrexed with significant differences.

Recommendations

The study recommends using pemetrexed as a fist line treatment for patients with adenocarcinoma unless otherwise a patients had adverse reaction to the drug. Also, it is better to avoid using taxanes in patient with chronic disease due to side effects of taxanes.

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Ethical clearance: This study was conducted according to the approval of College of Medicine/ University of Diyala and in accordance with the ethical guidelines of the Declaration of ethical committee of the College (Document no.2023SQA769).

Conflict of interest: Nil

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دراسة مقارنة بين البيميتريكسيد والتاكسان كعلاج أولي لسرطان الرئة الغدي النقيلي

سرمد قحطان الصالحي [١] , أزهر صبيح الزبيدي [٢]

الملخص

خلفية الدراسة: سرطان الرئة الغدي هو النوع الأكثر شيوعا من سرطان الرئة. تعتبرالادوية البلاتينية مع العلاجات الكيميائية الأخرى حاليًا حجر الزاوية في العلاج الكيميائي للحالات المتقدمة التي تعاني من ورم خبيث.

اهداف الدراسة: لمقارنة معدل استجابة ثنائيات البيميتريكسيد مقابل ثنائيات التاكسان في المرضى الذين يعانون من سرطان الرئة الغدي النقيلي.

المرضى والطرائق: شملت هذه الدراسة الاستطلاعية ٦٠ مريضا يعانون من سرطان غدي رئوي. تلقى هؤلاء المرضى علاجًا كيميائيًا مزدوجًا قائمًا على البلاتين مع بروتوكول علاج إضافي؛ تم دمجه مع البيميتريكسيد أو التاكسان (باكليتاكسيل أو دوسيتاكسيل) مع ٣٠ مريضًا في كل مجموعة. تم تقييم حجم الورم ومعدل الاستجابة والآثار الجانبية للعلاج الكيميائي في كلا االمجموعتين.

النتائج: بلغ متوسط الانخفاض في حجم الورم في مجموعتي البيميتريكسيد والتاكسان ٤,٧٢ سم٢ و٦,٥٣ سم٢ على التوالي. كان الغثيان والتعب والإمساك وفقدان الشهية أكثر شيوعًا في مجموعة البيميتريكسيد، بينما كانت قلة الكريات البيض والألم المفصلي والاعتلال العصبي المحيطي أكثر شيوعًا في مجموعة التاكسان.

الاستنتاجات: ظهرت الآثار الجانبية الخطيرة مثل نقص الكريات البيض، والاعتلال العصبي المحيطي أكثر تواترا في مجموعة التاكسان مقارنة بمجموعة البيميتريكسيد. يفضل استخدام البيميتريكسيد كعلاج خط اول للمرضى الذين يعانون من سرطان غدي منتشر في الرئة.

الكلمات المفتاحية: سرطان الغدة الدرقية , بيميتريكسيد , تاكسانات , سرطان الرئة النقيلي

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Revalence of Molar Incisor Hypomineralization among Primary School Children in Baquba City

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Abstract

Background: Molar incisor hypomineralization is a clinical symptom of general hypomineralization affecting a single or multiple first permanent molars, which is generally accompanied with incisors.

Objective: To determine the prevalence of molar incisor hypomineralization among 12 years students in Baquba city.

Patients and Methods: This study was conducted from middle of January 2022 till the end of May 2022 in Baqubah city/Diyalla Governorate/Iraq. The sample excluded all students who had other enamel defects (fluorosis or hypoplasia, uncooperative students and students who refuse to participate.

Results: Out of 700 participants, 52.43% of them were females and the rest were males. About 13% of the total sample showed a molar incisor hypomineralization, with significant association between gender, in which male were significantly more affected than females. The data showed 13% of the total sample had a demarcated opacities . Also the results showed that the upper centrals were more affected by hypominrlization than other teeth.

Conclusion: However, the study revealed that demarcated opacity was the most common form of defect with a significant correlation, with a frequency of 13%. The upper central tooth was always the most commonly impacted by molar incisor hypomineralization.

Keywords: MIH, hypomineralization, Demarcated opacity.

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Introduction

Molar incisor hypomineralization (MIH) is a significant medical issue encounterd by both adult and children's dentists. Due to the condition manifesting early in childhood, severe morbidity leading to handicapped dentition at a young age, the complexity of the disease as well as its treatment, the poor prognosis of restorations and the need for long-term follow-up, and the associated behavioral problems, children are more likely to seek dental care at a younger age [1].

Tooth hypoplasia is a developmental disorder that affects the quality with the quantity of tooth structure. MIH was lately piqued the curiosity of the pediatric dental society [2]. MIH is a kind of dental hypoplasia known as "systemic hypomineralization of one to four permanent first molars frequently associated with affected incisors" [3].

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Unexplained enamel deficient mineral in permanent first-molar teeth is additionally referred to as idiopathic enamel opacities in permanent first molars. Idiopathic enamel opacities in the first permanent molars, non-fluoride enamel hypomineralization in first permanent molars, and nonendemic mottling of permanent first molar enamel. Suggested term for this medical condition is molar incisor hypomineralization [4].

Molar hypoplasia (MH) is a comparable disorder that demonstrates hypomineralization (loss of minerls) of first permanent molars only without the association of the permanent incisors. MIH and MH are believed to be members of a MIH scope , with MIH being a more severe version of the disorder than MH [5] .

Affected teeth with molar incisor hypomineralization are extremely porous, promoting plaque production and decay vulnerability. Furthermore, these porous teeth are extremely sensitive. Making it challenging to maintain efficient plaque control [6]. Dental caries risk is increased by these conditions [7].

Environmental toxins, pre/peri and postnatal issues, fluoride exposure, frequent childhood diseases, and medically fragile infants have all been proposed as probable reasons by researchers. Regardless of the realization that we are aware of the etiological elements, further evidence is still required to confirm the effect they have. We need to conduct experimental dose/response studies on the molecular basis of ameloblasts to improve our comprehension of the components that are now presumptively involved. Prospective studies are also required to uncover additional variables that may be relevant [8].

Pneumonia, dioxins in mother's milk ,asthma, upper respiratory tract infections , antibiotics, otitis media, children exanthematous fevers and tonsillitis and tonsillectomy all been proposed as probable causes of MIH by different authors [9] .

Others speculated that polychlorinated biphenyl diet, birth and neonatal circumstances, acute or chronic childhood illness/treatment, nursing or fluoride were all influences. Other authors have proposed high fever, hypoxia, hypocalcaemia, antibiotic (amoxicillin) exposure, and dioxin exposure as risk factors [10].

The prevalence of defects ranges from 2.4 to 40.2%. It appears to differ among areas and birth cohorts. Cross-comparison of results from multiple research is challenging due to the use of different indicators and criteria, examination variability, recording techniques, and age groupings. Preterm children had a higher rate of molar incisor hypomineralization than controls (38% vs 16%), as did enamel developmental abnormalities (69.5% vs 51%) [11]. MIH risk increases with low gestational age and birth weight [12]. Also the prevalence of MIH in a group of Iranian children was 20.2 [13]. Furthermore a previous study conducted in university of Baghdad /collage of dentistry reported that the prevalence of MIH in patients attending the pedodontic clinic was about 9.25% of the sample [14].

Patients generally complain about the existence of faulty molars and/or incisors. Due to the fact that the lesions are visually and clinically appers to be similar to cheese in color and stracture/consistency, they are

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commonly referred to as "cheese molars." Evermore, based on the stage of the illness, the age of the etiological agent's contact, and the age of the patient's presentation to the dental clinic, Symptoms include sensitivity to air, cold, warm, and mechanical stimuli; difficulty consuming foodstuff; and decayed dentition and their consequences. In advanced cases, patients have reported being unable to clean their teeth owing to dental pain [15]. Patients may even complain about several or unsuccessful repairs [16].

On examination, one or multiple permanent first molars and incisors may show hypoplasia. Hypoplasia in the maxilla are more common than in the mandible .Usually affected areas are the occlusal surfaces. Enamel with hypominrilaztion is appers to be fragile and porous, and it sometimes breaks down, resulting in atypical nondecayed frank cavities . This fast decay of the teeth frequently necessitates costly restorative operations. Caries can develop fast in MIH molars [17].

There is a need for early identification, planning of therapy, and prediction of hypomineralized first molars. The risk assessment, remineralization and desensitization, prompt diagnosis, caries prevention and posteruption breakdown, restorations and removals and ongoing care steps are defined as a six-step management technique [18].

Risk factor calculation has been created for anthers depanding on the color of enamel opacities. They measured enamel opacities based on white, yellow, and brown color shades, allowing them to determine vulnerability to structural deterioration over time [19]. It was determined that teeth with brown and yellow opacities were more vulnerable than those lighter ones. Findings found to be helpful to assist doctors in developing a risk-based remady plan for MIH suffering childrens. Deciduous molar hypomineralization (DMH) can also be utilized therapeutically as a prospective predictor of MIH. Proper early preparation & intervention may halt the progression of the illness [20].

Thorough treatment for pediatric illnesses has to tackle both emotions and behaviors with the objective of delivering sustained recovery in free of pain environments. Inadequate pain management, complicated cavity designs, and restorative material preference (Repairs for molars with hypominerztion seem to be failing on a regular basis) among the problems. There is no agreement to help clinicians make clinical judgments about cavity design and material selection [21]. Many treatment methods described in various research include restorations by composite, glass ionomer cement, full veneer metal-ceramic crowns, stainless steel crowns, implants and fixed-removable partial dentures [22].

For injured incisors, aesthetic alternatives in younger age groups patients includes porcelain veneer to porcelain crowns or composite and microabasion in minimum cases , while in older patients metal-ceramic full veneer crowns [23]. If teeth cannot be saved, extraction should be thought about. Additionally, in situations of removal, an orthodontic strategy should be established for the management of space and reganing of function in children [24].

The null hypothesis of the present study was that molar incisor hypomenrilization

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would not be significantly different in the prevalence among genders in Iraqi population.

Patients and Methods

This study was an observational cross-sectional analytical design. The moral and ethical clearance board of the Faculty of Dentistry, University of Baghdad, has given their permission (no 556 in 7-4-2022) .To calculate the adequate sample size in the prevalence studies there is a simple formula ($n=Z^2P(1-P)/d^2$), in which n is the number of samples tested, Z is the level of trust statistic, P indicates anticipated prevalence (which can be gathered from comparable investigations or a pilot investigation undertaken by the investigators), & d is precision (equivalent to the effect size).. Performing a pilot study for MIH for 50 subjects with percentage about 20% and Using G power 3.1.9.7, alpha error =0.05 , and calculating the sample according to t so the sample size is 683 students, thus 700 students is enough [25].

Employing EpiTools software to randomly select subjects from each school and splitting the number of males and females from each school on the total number of students in that school and multiplying this percentage with the number of selected students from it to get the number of males and females from that school, 418 males and 282 females are selected from 61 schools, resulting in 418 males and 282 females being selected from 61 schools. Because 85 males refused to participate in the study, only 333 males participated, while the 85 subjects were added to 282 females, for a total of 367 females.

This study was conducted from middle of January 2022 till the end of May 2022 in Baaqubah city/Diyalla Governorate/Iraq .Herein, all patients were evaluated and examined by the researcher, oral examinations were performed according to world health origination guidelines [26].

Each student was examined in an appropriate room in his school, sat in a straight chair with a lofty back on which the student's head could be supported. During the inspection, a portable light was utilized for illumination [27], and the equipment were sanitized in a hot air oven at 160 degrees Celsius for one hour [28]. The criteria used to assess the MIH is the European Academy of Pediatric Dentistry that is scored as 0 ,1,2,3,4 and 5 ,interprtated as Normal, Demarcated opacity, Posteruptive enamel breakdown, A typical restoration and Extraction molar due to MIH and Unerupted molar due to MIH ,respectively [29].Figure (1) showed normal and affected tooth.

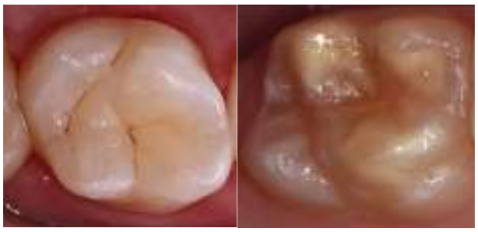

Figure (1): normal and affected molar byMIH.

Statistical Analysis

The Statistical Procedure and Statistics for Social Sciences (SPSS version -22, Chicago, Illinois, USA) was employed during statistical evaluation.

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Results

A total sample of 700 (100%) students were involved in the study, the number and percentage of male students was 333 (47.57%), while the number and percentage of female students was 367 (52.43%).

Table (1): Distribution of the total sample by gender.

Gender	Number	%
Male	333	47.57
Female	367	52.43
Total	700	100

Based on the distribution of the sample, results illustrates the prevalence of MIH in the total sample. It was found that 91(13%) of subjects were affected by MIH, distributed in 52 males and 39 females with significant association between gender and MIH (P<0.05) Table (2).

Table (2): Descriptive and statistical test of Molar incisor hypomineralization among gender.

Gender					Chi squa	P value
	Free		With			
	N.	%	N.	%		
Male	281	46.14	52	57.14	3.842	**0.0499***
Female	328	53.86	39	42.86		
Total	609	87	91	13		

**=significant at p<0.05

Results in Table (3) illustrates Demarcated opacity and Atypical restoration are higher in males than females with significant association for Demarcated opacity (P<0.05), while no significant association for Atypical restoration (P>0.05). On the other hand, Enamel breakdown and Extracted molar due to MIH were higher in females than males but with no significant association (P>0.05).

Table (3): Distribution and statistical test of Molar incisor hypomineralization scores among gender.

Variables	Gender				Statistcs	P value	Total	
	Male		Female					
	N	%	N	%			N	%
Demarcated opacity [a]	52	7.43	39	5.57	3.842	0.049*	91	13.00
Post eruptive enamel breakdow	17	2.43	21	3	0.129	0.719	38	5.43
Atypical restoration[b]	3	0.43	1	0.14	1.214	0.351	4	0.57
Extracted molar due to MIH[b]	1	0.14	2	0.29	0.245	1.00	3	0.43

*=significant at p<0.05

* a=chi square, b=Fisher exact

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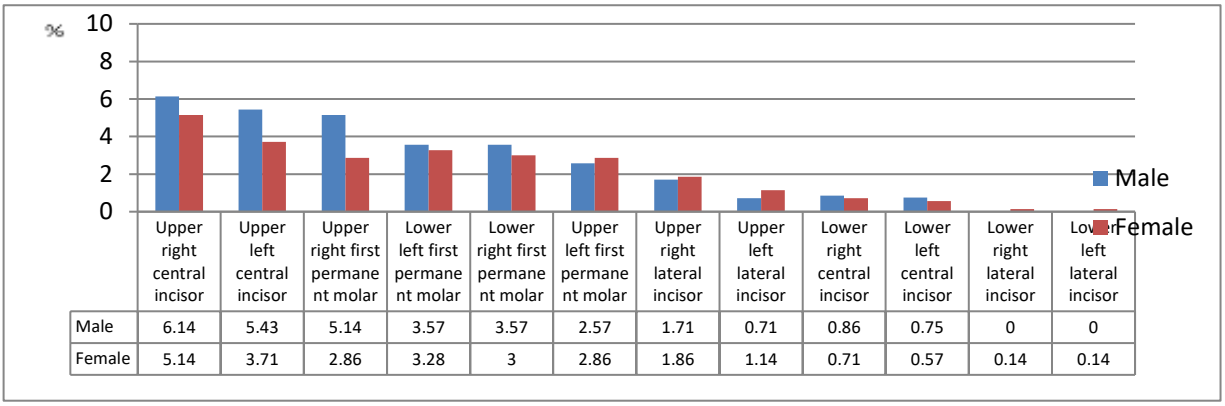
Results in Figure (2) illustrates that in regarding to the gender. Males reports the highest percentage of tooth affected by MIH was (upper right central incisor) and the least affected tooth was (lower left central incisor), while in female the highest percentage of tooth affected by MIH was (upper right central incisor) and the lowest percentage was reported in the lower left lateral incisor.



	Upper right central incisor	Upper left central incisor	Upper right first permanent molar	Lower left first permanent molar	Lower right first permanent molar	Upper left first permanent molar	Upper right lateral incisor	Upper left lateral incisor	Lower right central incisor	Lower left central incisor	Lower right lateral incisor	Lower left lateral incisor
Male	6.14	5.43	5.14	3.57	3.57	2.57	1.71	0.71	0.86	0.75	0	0
Female	5.14	3.71	2.86	3.28	3	2.86	1.86	1.14	0.71	0.57	0.14	0.14

Figure (2): Distribution of Molar incisor hypomineralization by Teeth type.

Discussion

Results of current study revealed , based on total sample level , prevalence of MIH is 13%, this finding seems to agree with the findings of several other study who reported a percentage of MIH in School children varied from 13.6% to 35% [5,30,31,32].Furthermore similar findings were observed in Iran, a prevalence of 12.7% was reported [33], and this may be due to the geographical location of Dayla to Iran ,that influences to form a similar water qualities shared by the underground water supply in that geographical zone. However the findings is higher than a what been reported in a study conducted in 2016 for the same age ,that found prevalence of MIH was 9.7% in the child population residing in Chennai ,India [34] and this is mostly due to the fact that most of the region water floriation is within the optimum level according to a study conducted in that area in 2013 [35].

However the results disagree with findings of a previous Iraqi study conducted in AL Najef government , that reported a prevalence of Molar Incisor Hypo mineralisation of about 22.9%, this might be attributed to differences in mathematical calculation and the age groups included within the study [36].

Gender wise an increase in the percentage of males to females with MIH with a percentage of 57.14 % to 42.86% respectively, with significant association in between gender. Furthermore the findings are agree with findings of other study reported, that MIH was more in males than females [37, 38].However These findings disagree with previous Iraqi study who reported females were higher in the percentage of affected in the MIH [39]. These results may be due to the fact that males are less involved in the oral health care than females and males are less protective for their teeth than females [40].

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Results shows a low percentage of extracted teeth due to MIH and these findings agrees with findings of previous study [41], this is might be related due to the devolving in the process of early detection of the MIH and the management of condition by preventive and conservative techniques . These finding do agree with the findings of previous studies, demarcated opacity were the most commen type of the defect with significant association, [42,43], this might be explained in part by the inclusion of younger children in the present research, since a number of those delineated opacities may break with period of time. This theory is backed by past research findings [44].

Regarding differences in the percentage of tooth mostly affected by MIH results shows males had higher percentage of upper central affected by MIH were higher in both gender than what been reported in lateral incisors and these findings agrees with previous studies that stated central incisors were more affected than the laterals in both jaws , even more upper central incisors founds to be more affected than the lower central incisors [45].These findings may be attributed to the sample selection criteria and the geographical properties of the area of examination .

Conclusions

Molar incisor hypomineralization (MIH) exhibits a substantial prevalence on a global scale, particularly in those under the age of 10. Hence, it is crucial to formulate more suitable dental healthcare methods for the purpose of addressing the needs of these youngsters and discerning the underlying causes of the condition in order to prevent its occurrence.

Recommendations

Molar incisor hypominrliaztion it's an evident problem within the Iraqi population , but this study does not represent the Iraqi population as all due to the differences in the economical levels and living standers between different cities within Iraq , due to this the researchers recommend to run a similar studies on different Iraqi cities and to run different other studies with different age groups and utilizing other parameters to investigate the validity and reliability of each other diagnostic parameter.

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Ethical clearance: This study was conducted according to the approval of College of Medicine/ University of Diyala and in accordance with the ethical guidelines of the Declaration of ethical committee of the College (Document no. 2023SEA781).

Conflict of interest: Nil

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مدى انتشارحالة نقص الاملاح والتمعدن في الاضراس والقواطع الامامية في الاطفال عمر ال ١٢ سنة ضمن مدارس مدينة بعقوبة

سيف عصام عبد الله [١] , بيداء حسين عون [٢]

الملخص

خلفية الدراسة: نقص تمعدن الاضراس والقواطع الامامية هو أحد الأعراض السريرية لنقص التمعدن العام الذي يؤثر على ضرس أو عدة أضراس دائمية أولى، والتي تكون مصحوبة بشكل عام بالقواطع.

اهداف الدراسة: لتحديد مدى انتشار نقص تمعدن الاضراس والقواطع الامامية بين طلاب ١٢ سنة في مدينة بعقوبة.

المرضى والطرائق: أجريت هذه الدراسة من منتصف كانون الثاني ٢٠٢٢ حتى نهاية أيار ٢٠٢٢ في مدينة بعقوبة/ محافظة ديالى/ العراق. استبعدت العينة جميع الطلاب الذين لديهم عيوب أخرى في المينا (التسمم بالفلورايد أو نقص التنسج في طبقه المينا، الطلاب غير المتعاونين والطلاب الذين يرفضون المشاركة في هذه الدراسة.

النتائج: من بين ٧٠٠ مشارك، ٥٢,٤٣٪ منهم إناث والباقي ذكور. حوالي ١٣٪ من إجمالي العينة أظهرت النتائج نقص تمعدن الاضراس والقواطع الامامية مع وجود ارتباط معنوي بين الجنس حيث كان الذكور أكثر تأثراً من الإناث بشكل ملحوظ، وأظهرت البيانات أن ١٣٪ من إجمالي العينة لديهم عتامة محددة، كما أظهرت النتائج أن القواطع العلوية كانت أكثر تأثراً بنقص التمعدن من بقيه الاسنان.

الاستنتاجات: كشفت الدراسة أن العتامة المحددة هي الشكل الأكثر شيوعًا لهذه الحاله (نقص التمعدن) مع وجود ارتباط كبير، بتكرار ١٣٪، وكان السن القاطع العلوي دائمًا هو الأكثر شيوعًا في تأثر نقص تمعدن الاضراس والقواطع.

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Mechanisms of *Helicobacter pylori* Resistance to Antibiotics

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Abstract

Background: *Helicobacter pylori* is the most frequent human bacterial infection worldwide; it is prevalent in approximately half of the world's population. *H.pylori* poses a major health risk because it possesses distinct virulence factors and highly resistant to antibiotics. Multidrug resistance (MDR) and single-drug resistance are two distinct resistance profiles. Chromosome mutations influence antibiotic activity via target-mediated pathways. Inadequate drug absorption, efflux pumps activity, biofilm development, and cocci formation represent supplementary biological mechanisms by which *H.pylori* acquires drug resistance. The overexpression of efflux pumps genes in mutant isolates is readily detectable in post-therapy courses.

Objective: Characterization of the biological and molecular mechanisms contributing to the development of antibiotic resistance in *H.pylori*.

Conclusion: An alarming rate of drug-resistant *H.pylori* is on the rise. Primary and acquired resistance to clarithromycin and metronidazole has increased globally. Bacterial factors including biofilms, efflux pumps, and molecular mechanism are in association with *H.pylori* resistance. It is important to continue to monitor the resistance profiles of *H.pylori* isolates.

Keywords: *Helicobacter pylori*, MDR, Efflux pump, Biofilm, antibiotic resistance.

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Introduction

Helicobacter pylori is a micro-aerobic, curved, Gram-negative bacteria, a fastidious finicky microorganism that demands complex growth media including blood or serum to serve as a supplementary source of nutrients compared to other intestinal microorganisms [1]. *H.pylori* is highly adapted to its role as a gastric pathogen that causes wide infections ranging from asymptomatic gastritis and peptic ulcer disease to gastric malignancy [2]. *H.pylori* is one of the 12 most important antibiotic-resistant organisms to target while developing new medications, according to the WHO [3]. Clarithromycin and metronidazole resistance, both acquired and primary, has increased worldwide in recent years.

Since antibiotic susceptibility testing is not feasible, therapy selection is empirical. The eradication protocol consists of two antibiotics taken as well as proton pump inhibitors (PPIs) to substantially reduce release of gastric acid [4]. Main therapeutic medicines include bismuth, clarithromycin, amoxicillin, tetracycline, and metronidazole;

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first-line conventional regimens comprise PPI, clarithromycin, amoxicillin, or metronidazole [2].

In general, antimicrobial resistance mechanisms can be broadly classified into four categories: drug uptake limitation, drug target modification, drug inactivation through enzyme modification, and active drug efflux pumps. Even *H.pylori* possesses a diverse array of efflux pump types, as do the majority of bacteria. Bacterial efflux pumps can be grouped based on their structure and source of energy into five families: the ABC (ATP-binding cassette) family, the MATE (multidrug and toxic compound extrusion) family, the SMR (small multidrug resistance) family, the MFS (major facilitator superfamily), and the RND (resistance-nodulation-cell division) family [5]. The RND family is the most common, this family has three members: inner membrane efflux proteins (IEPs), periplasmic efflux proteins (PEPs), and outer membrane efflux proteins (OMEPs) [6]. The hefABC, hefDEF, and hefGHI super families of RND efflux systems were identified [7].

Post-therapy detection of efflux pump overexpression in mutant isolates provides confirmation of their roles in the development of drug resistance in pathogenic bacteria [8].

H.pylori Antimicrobial Resistance

Single-Drug Resistance Profiles and Bimolecular Mechanisms

Antimicrobial resistance is significantly higher in developing nations than in industrialized nations [9]. The World Health Organization (WHO) has released a list of the twelve most dangerous bacterial species to the general public as "priority pathogens," classifying them into three priority levels: crucial, elevated, and moderate [10]. The worldwide prevalence of *H.pylori* antibiotic resistance has escalated to concerning degrees, which has a substantial detrimental effect on the effectiveness of empirical treatments. The following antibiotics are used during infection.

Clarithromycin

The macrolide antibiotic clarithromycin (CLR) has bacteriostatic activity. *H.pylori* is effectively treated with clarithromycin owing to its high absorption in gastric mucus and stability in acidic environments [11]. By traversing the bacterial cell wall, it reversibly bonds to domain V of the 23S rRNA located on the 50S subunit of the ribosome. This interaction effectively obstructs the translocation of aminoacyl transfer RNA and the formation of polypeptides [12].

The resistance of *Helicobacter pylori* to clarithromycin is predominantly attributed to point mutations that occur in the V domain of 23S rRNA. These mutations result in a change in ribosome structure that inhibits the attachment of clarithromycin to 23S rRNA, consequently diminishing the efficiency of protein synthesis [13].

Metronidazole

Metronidazole (MET) is an antibiotic that has strong bactericidal activity. It is a member of the nitroimidazole family and is classified as a pro-drug, that becomes active when reduced under the influence of nitro reductase, nitroso derivatives, nitro anion radicals, and hydroxylamines are all products of its nitro group [14]. These byproducts have the potential to disrupt the bacterial DNA helix's structural integrity [15]. The production of nucleic acid is inhibited as a

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result of the interaction between metronidazole and the nitro reductase. It is possible that another nitro reductase produced by *H.pylori* is responsible for activating the biocidal effect of metronidazole [16]. The key mechanism that contributes to the development of metronidazole resistance is the inactivation of nitro reductases, which are responsible for the synthesis of antibacterial metabolites that destroy bacterial DNA [17]. Genomic rearrangements such as insertions, deletions, frameshift mutations, missense mutations, or premature truncations nearly usually cause this inactivation in the *rdx*A gene, which codes for nitro reductase [18]. Another factor that has been linked to *H.pylori* resistance to metronidazole is a point mutation in the flavinreductase A (*frx*A) gene. Metronidazole resistance is multifactorial and has not been definitively proven because it can develop in the absence of inactivation of NADPH nitroreductases *rdx*A and frxA. Furthermore, it has been found that *H.pylori* strains resistant to MTZ have increased expression of two efflux pump genes, *hp1165* and *hef*A, suggesting a connection between the RND family efflux pump system and MTZ resistance which explains the resistance observed in clinical isolates with intact *rdx*A and *frx*A [19].

Levofloxacin

The third-generation fluoroquinolone levofloxacin (LVX) is an antibiotic. Because it blocks DNA gyrase, levofloxacin prevents the replication of chromosomes, making it a bactericide. Point mutations in the *gyr*A and *gyr*B loci, which encode DNA gyrase subunits, have been linked to resistance to levofloxacin in *H.pylori*, at the quinolone-resistance determining region (QRDR) of the *gyr*A gene, mutations at codons 87 and 91 are both the most common and well-studied (20).

Tetracycline

Bacteriostatic tetracycline (TET) reversibly binds to the 30S subunit of *H.pylori* ribosomes that contain 16S rRNA in order to inhibit protein synthesis [21]. Tetracycline-resistant *H.pylori* is unusual,between 2011 and 2021, resistance to TET- was observed in only 0.87 percent of *H.pylori* strains in the United States [22]. Resistance is caused by mutations in the binding site of the medication [23]. The fact that some *H.pylori* isolates are resistant to treatment despite lacking a mutation in the 16*SrRNA* gene is indicative of a multifactorial resistance involving multiple mechanisms. These include a lowered susceptibility to antibiotics due to a tighter membrane, altered ribosomal binding, drug breakdown by enzyme, and an active efflux pump [13].

Amoxicillin

Antibiotic β-lactam amoxicillin (AMX) possesses bactericidal characteristics. Amoxicillin inhibits the synthesis of peptidoglycan, thereby preventing the development of bacterial cell walls. The majority of *H.pylori* resistance to amoxicillin results from mutations in the penicillin-binding proteins PBP1, PBP2, and PBP3[24]. PBPs are a class of proteins that have an affinity for b-lactams, which helps in the creation of the peptidoglycan layer of bacterial cell walls as well as in its maintenance. The most crucial strategy for resistance to amoxicillin has been identified as mutations in PBP1A that reduce its affinity for the drug [25]. PBP1 is a PBP with transglycosylase and transpeptidase activity

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and a high molecular weight, unlike the others [26]. AMX resistance is also contributed to by the creation of beta-lactamase enzyme. The presence of beta-lactamase activity was detected in a highly resistant *H.pylori* strain [27].

Multidrug Resistance Mechanisms and Profiles

Multidrug-resistant (MDR) *Helicobacter pylori* isolates are those that exhibit resistance to two or more classes of antibiotics [28]. MDR is correlated with antibiotic misuse, high antibiotic consumption, treatment failures, and bacterial factors including mutations, efflux pumps, and biofilms [29]. A microorganism's cell membrane is home to a protein-based carrier system called an efflux pump. Typically, they have correlations with multiple drug resistance due to their ability to extrude several kinds of antibiotics in bacteria [30]. Although they are typically encoded by genes located on chromosomes, transposable elements can play a role in their expression in certain bacteria. The regulation of efflux pump gene expression is accomplished through complex and multifaceted mechanisms. These regulators are situated upstream of the operon that encodes these genes in the form of repressors [31] .

Five types of bacterial efflux pumps exist. ATP-binding cassette (ABC) hydrolyzes ATP to generate energy. The proton motive force powers the multidrug and toxin extrusion (MATE) family, which includes the Na+/H+ drug antiport systems, the major facilitator superfamily (MFS), the small multidrug resistance (SMR) family, the resistance-nodulation-cell division (RND) superfamily, and the proteobacterial antimicrobial compound efflux (PACE) family [32]. RND family transporters, which play an essential part in the efflux pump system, are responsible for the efflux of a number of antibiotics, including CLR, AMX, and TET. The RND family features a combined apparatus that is composed of three parts [33]. It consists of a periplasmic membrane-fusion (adaptor) protein, an outer membrane protein channel, and a cytoplasmic-bound trimer membrane pumas, as illustrated in Figure (1). Their energy source is the proton motive force, which they actively use to extrude substrates [34].

A multidrug-resistant strain of *H.pylori* develops when the *hef*A gene is overexpressed, which promotes antibiotic efflux via the efflux pump system. In addition, the variation in MATE family member hp1184 and hp1181 expression levels between MDR and sensitive strains indicates that active efflux may be associated with additional efflux pump families [35].There are three different RND families: hefABC, hefDEF, and hefGHI. The efflux pump's outer membrane protein is encoded by *Tol*C homologs *hef*A, *hef*D, and *hef*G [5].

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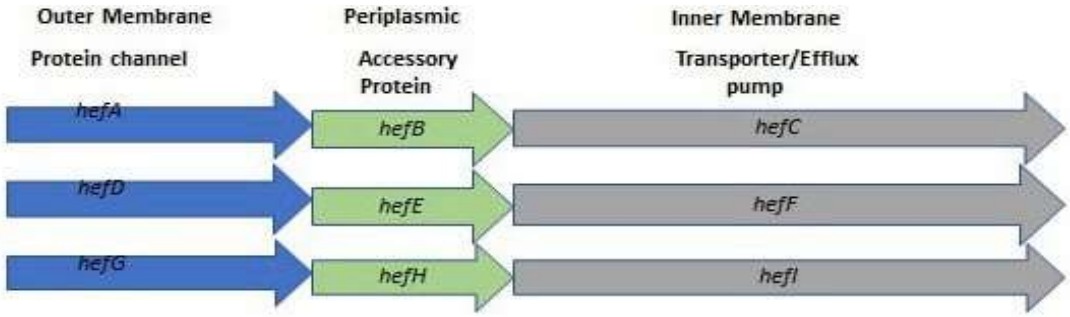

Figure (1): Efflux Pump Operon.

Multi-drug resistance transporters (MDTs) are comprised of certain RND efflux pumps along with other families. Facilitating the movement of molecules from the cytoplasm to the periplasm and outer membrane, these transporters are responsible for extracellular efflux [36]. Certain transporters establish a strong association between the outer membrane protein TolC and the RND subunits AcrB, AcrD, AcrF, and MFS (EmrB) via periplasmic binders AcrA, AcrE, and EmrA [37] as shown in Figure(2). The development of multidrug resistance (MDR) in planktonic cells isattributed to MDTs [38].

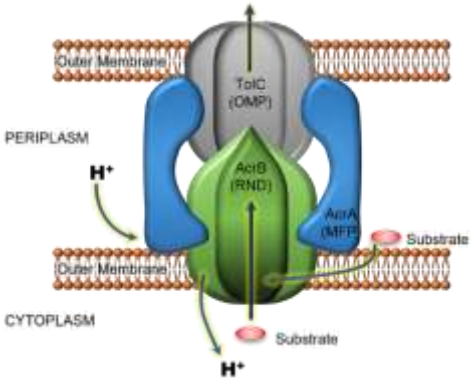

Figure (2): *TOl*C gene structure.

An additional crucial mechanism of MDR is *H.pylori* biofilm formation [39]. Biofilms consist of sessile bacteria that produce a protective matrix, forming complex microbial communities [40]. Attached to the cell surface, this biofilm made *H.pylori* 100-1,000 times more drug-resistant than in the planktonic state [41].

Management of *H.pylori* Infections

The treatment of *Helicobacter pylori* infection faces significant obstacles, Since antibiotic susceptibility testing is not practical, empirical therapy selection is utilized [42]. Hence, an escalation in antibiotic resistance may potentially disrupt the abundance and variety of gastrointestinal microbiota [43]. Combination therapy involving multiple antibiotics is advised due to the ease with which *H.pylori* develops resistance to singular antibiotics. The selection of a first-line treatment regimen is influenced by a number of variables, involving local antibiotic resistance prevalence and patient characteristics like

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age, comorbidities, and medication sensitivities [44]. Bismuth, a proton pump inhibitor, tetracycline, and metronidazole make up the bismuth quadruple treatment, was found to be the best effective treatment after being subjected to a network meta-analysis of numerous first-line treatment regimens. However, in comparison to triple therapy, this treatment has a greater risk of side effects and is more complicated to administer [45].

Conclusions

Clinical eradication therapy has encountered numerous obstacles due to the escalating rates of *H.pylori* resistance in recent decades. *H.pylori* resistance is associated with bacterial factors including biofilms, efflux pumps, and mutations. Mutations in genes associated with nucleic acid synthesis, rRNA coding, and cell wall synthesis are key methods for *H.pylori* in preventing bactericidal effects. Biofilm generation and the efflux pump mechanism both play a role in the emergence of multidrug-resistant bacteria. Given the rising resistance rate of *H.pylori* to conventional antibiotics. Since antibiotic susceptibility testing is not feasible, therapy selection is empirical. Selecting and monitoring medications is crucial for effective clinical eradication treatment. The considerable decline in the effectiveness of *H.pylori* treatments may lead to clinical complications including gastric cancer and peptic ulcers, as infections persist longer.

Recommendations

Screening as well as treatment of *H.pylori* to reducing consequences and antibiotic resistance.

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Conflict of interest: Nil

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آليات مقاومة الملوية البوابية للمضادات الحيوية

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الملخص

خلفية الدراسة: تعد الملوية البوابية العدوى البكتيرية الأكثر شيوعا في العالم، وهي منتشرة فيما يقرب من نصف سكان العالم. تشكل الملوية البوابية خطراً صحياً كبيراً لامتلاكها عوامل ضراوة مميزة ومقاومة عالية للمضادات الحيوية. المقاومة للأدوية المتعددة ومقاومة الدواء الفردي هما نوعان مميزان لمقاومة الملوية البوابية. تؤثر طفرات الكروموسوم على نشاط المضادات الحيوية عبر المسارات المستهدفة وكذلك امتلاكها آليات بيولوجية كالامتصاص الغير كافي للدواء، نشاط مضخات الدفق، تطور الأغشية الحيوية، وتحولها الى الشكل الكروي تكتسب من خلالها المقاومة للأدوية. يمكن اكتشاف الإفراط في التعبير الجيني لمضخات الدفق في العزلات الطافرة بسهولة ما بعد العلاج.

اهداف الدراسة: لتوصيف الآليات البيولوجية والجزيئية التي تساهم في تطوير مقاومة المضادات الحيوية في الملوية البوابية.

الاستنتاجات: إن المعدل المقلق لبكتيريا الملوية البوابية المقاومة للأدوية آخذ في الارتفاع. لقد زادت المقاومة الأولية والمكتسبة لكلاريثروميسين وميترونيدازول على مستوى العالم .ترتبط العوامل البكتيرية بما في ذلك الأغشية الحيوية ومضخات الدفق والآلية الجزيئية بمقاومة بكتيريا الملوية البوابية. من المهم الاستمرار في مراقبة تطور المقاومة لعزلات الملوية البوابية.

الكلمات المفتاحية: الملوية البوابية، مقاومة المضادات الحيوية، مضخة التدفق، الأغشية الحيوية، مقاومة المضادات الحيوية.

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