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Maternal Risk Factors for Autism Spectrum Disorder

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Abstract

Background: Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder characterized by deficits in social communication, restricted interests, and repetitive behaviors. The etiology of ASD is multifactorial, involving genetic, environmental, and maternal factors. Recent studies have suggested maternal factors, such as advanced maternal age, high BMI, smoking, and depression during pregnancy, as significant risk factors for ASD.

Objective: This study aims to investigate the maternal risk factors that contribute to ASD in children at Diyala, Iraq.

Patients and Methods: This case-control study was conducted on 150 children, comprising 75 children diagnosed with ASD and 75 healthy children as a control group. The study was carried out from August 2023 to May 2024 in Diyala, Iraq. Data collection included comprehensive demographic, social, obstetric, and maternal health histories. ASD diagnosis was confirmed using the Childhood Autism Rating Scale 2 (CARS-2). A logistic regression analysis was performed to assess the association between maternal risk factors and ASD.

Results: The study revealed several significant maternal risk factors for ASD. Advanced maternal age at pregnancy (mean age 28.1 years in cases vs. 22.9 years in controls, p=0.001), high maternal BMI (mean BMI 26.9 in cases vs. 24.4 in controls, p=0.0001), maternal smoking (6.7% in cases vs. 0% in controls, p=0.023), and maternal depression during pregnancy (22.7% in cases vs. 0% in controls, p=0.0001) were all significantly associated with an increased risk of ASD. The use of stimulating hormones before pregnancy also showed a significant association (21.3% in cases vs. 4% in controls, p=0.001). Parity, particularly having 1-2 pregnancies, was also a significant risk factor (p=0.002).

Conclusion: This study identifies advanced maternal age, high BMI, smoking, depression, and the use of stimulating hormones before pregnancy as significant maternal risk factors for ASD in children.

Keywords: Autism, ASD, maternal age and autism, maternal illness and autism.

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Introduction

Autism spectrum disorder (ASD) is a term referring to a constellation of early-appearing deficits in social, emotional, and nonverbal communications in addition to strict or repetitive behaviors. The disorder, which has a global prevalence of 0.5% to 2%, results in a substantial social and

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economic burden (1). These children with ASD become distressed when their surroundings change because their adaptive abilities are limited, the symptoms appear in early childhood and impair daily functioning. Since early diagnosis and behavioral intervention in ASD could effectively improve prognosis, detecting ASD risk factors to identify at-risk children should be encouraged (2). Several prenatal risk factors, including maternal age, interpregnancy_ interval, immune issues (such as autoimmune diseases and infections that occur during pregnancy), medication use (particularly antidepressants, anti–asthmatics, and anti-epileptics), maternal metabolic conditions (like hypertension and diabetes), and maternal fever during pregnancy is a risk factor for ASD in offspring (3,4). Maternal exposure to smoking and pollutants during pregnancy is a risk factor for ASD. Additionally, maternal exposure to stressful life events during pregnancy is a potential risk factor for ASD (4,5,6). The presenting symptoms of ASD depend on age, language levels (from nonverbal to fully fluent), cognitive abilities, and sex. In the first 2 years of life, common features include poor acquisition of or declines in language skills and communicative gestures or failure to learn or adopt these skills. ASD is also characterized by diminished responsiveness in social interactions and presence of repetitive behaviors, such as no response to name when called, hand flapping, and lining up toys in a particular way. Savant abilities are exceptional abilities that appear to be beyond the normal range of human ability, and they are more common in people with ASD. These abilities frequently show up in domains such as memory, creativity, music, mental math, and calendar skills, which include the ability to determine the day of the week for any historical date (7). Behavioral or cognitive rigidity (e.g., insisting that routines are precisely followed or that others adhere to specific verbal scripts), lack of interest in socializing, restricted interests, and lack of imaginative play typically become more apparent as a child develops. Children with visual and/or hearing impairment may have delays in attaining developmental milestones (eg, deficits in nonverbal communication due to blindness) compared with those without sensory impairment and exhibit behaviors that overlap with ASD symptoms (eg, stereotyped, repetitive motor movements), requiring careful assessment to determine whether behaviors these children exhibit are part of the symptoms of ASD (8). The American Academy of Pediatrics recommends screening all children for ASD at 18 and 24 months of age, on the other hand, the US Preventive Services Task Force concluded in 2016 that there was insufficient data to suggest routine screening for young children in the absence of parental concerns. The Modified Checklist for Autism in Toddlers Revised (M–CHAT–R) is a widely Used 20 items screening tool in primary care to identify children ((aged 16 to 30 months)) who may be at risk for ASD. In order to improve the specificity of the tool, a total score of more than two denotes a risk and prompts medical professionals to inquire further about the items the child failed (9).

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Patients and Methods

Study design: A case-control study that included 150 individuals divided in to two groups; case group and control group, each contains 75 population categorized as Autistic and healthy children, respectively. Case group taken from the Institutions for Autistic Children in Diyala from 1st of August 2023 to 31st of May 2024.

Study population: Seventy-five (75) children with ASD considered as case group along with 75 healthy children included as control group.

Inclusion Criteria: The study included patients with following criteria:

1- Patients diagnosed with ASD.
2- Live mothers.

Exclusion criteria:

• Mothers who refused to participate in the study.

• Mothers who were not able to remember.

ASD diagnosis

The diagnosis of ASD was made based on CARS-2 (Childhood Autism Rating Scale -2) (10).

Statistical Analysis

The statistical package for social sciences (SPSS) software version 23 had been used for data entry and analysis. In the descriptive statistics for socio-demographic characteristics, the means, standard deviations, min, max values were used for continuous data. Numbers and percentage values were used for countable data. Chi-square test; or Fisher-Exact test for small frequency cells; was performed for comparison between categorical variables. Independent T-test of the two means was used for comparison between quantitative parameters. A logistic regression analysis has been used for factors that showed a significant association with ASD in univariate analysis to assess its' as confounder for ASD child. P-values ≤ 0.05 were considered statistically significant.

Results

The study included 150 individuals divided into two groups; group A, which included 75 children diagnosed with autism spectrum disorder, and group B, which included healthy children as a control group.

Demographic characteristics

The maternal age is significantly higher in the case group, with a mean of 28.1 years (± 6.6) compared to 22.9 years (± 5.4) in the control group (p=0.001). The distribution of residency shows no significant difference, with 30.7% of cases and 28.0% of controls residing in rural areas (p=0.85). Regarding the education of mothers, there are no significant differences, though the distribution varies slightly across categories: 16.0% of cases and 17.3% of controls have no formal education; 28.0% of cases and 40.0% of controls have primary education; 28.0% of cases and 22.7% of controls have high school education; and 28.0% of cases and 20.0% of controls have higher education (p=0.34). It was found that 22.7% of mothers in the case group are employed compared to 12.0% in the control group (p=0.084), while 77.3% of mothers in the case group are housewives compared to 88.0% in the control group as found in Table 1.

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Table (1): Demographic criteria of cases and control groups.

Variables		Cases N=75	Control N=75	P value
Age of Mother	Mean ± SD	28.1 ± 6.6	22.9 ± 5.4	**0.001**
	Range	26	23	
Residency	Rural	23 (30.7%)	21 (28.0%)	0.85
	Urban	52 (69.3%)	54 (72.0%)	
Education of mother	No Formal	12 (16.0%)	13 (17.3%)	0.34
	Primary	21 (28.0%)	30 (40.0%)	
	High school	21 (28.0%)	17 (22.7%)	
	Higher	21 (28.0%)	15 (20.0%)	
Occupation of mother	Employee	17 (22.7%)	9 (12.0%)	0.084
	Housewife	58 (77.3%)	66 (88.0%)	
Parent consanguinity	Yes	35 (46.7%)	37 (49.3%)	0.74
	No	40 (53.3%)	38 (50.7%)	

Social history

The comparison between cases and controls reveals significant differences in maternal BMI and smoking habits. The mean BMI of mothers in the case group is significantly higher at 26.9 (± 4) compared to 24.4 (± 3.3) in the control group (p=0.0001). The range of BMI values is also broader in the case group (18) than in the control group (16). There is a significant difference in smoking habits, with 6.7% of mothers in the case group subject to passive smoking, while none in the control group face such exposure (p=0.023). Animal contact shows no significant difference, with 14.7% of cases and 12% of controls having animal contact, while 85.3% of cases and 88% of controls have no animal contact (p=0.63), as found in Table 2.

Table (2): Maternal social history of cases and control groups.

Variables		Cases N=75	Control N=75	p value
BMI of mother	Mean ± SD	26.9 ± 4	24.4 ± 3.3	**0.0001**
	Range	18	16	
Smoking	Passive	5 (6.7%)	0	0.023
	No	70 (93.3%)	75 (100%)	
Animal contact	Yes	11 (14.7%)	9 (12%)	0.63
	No	64 (85.3%)	66 (88%)	

* BMI; Body Mass Index.

Obstetric history

Parity showed a notable distinction, with a higher proportion of mothers in the case group having 1-2 pregnancies (48% vs. 24%) and a lower proportion having 3-4 pregnancies (32% vs. 49.3%) compared to the control group (p=0.009). There is no significant difference in the history of abortion, with

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42.7% of cases and 41.3% of controls reporting abortion history (p=0.89). Similarly, twin pregnancies do not significantly differ, with 2.7% of cases and 6.7% of controls having twin pregnancies (p=0.26). Normal conception rates are nearly identical, with 100% of cases and 97.3% of controls reporting normal conception (p=0.15). The type of delivery shows no significant difference, with 62.7% of cases and 54.7% of controls having caesarean sections, and 37.3% of cases and 45.3% of controls having normal vaginal deliveries (p=0.32). A slightly higher, but not statistically significant, percentage of cases experienced delayed labor (4% vs. 0%, p=0.08). Both groups report no birth trauma. Antenatal care quality is similar, with 96% of cases and 98.7% of controls receiving good antenatal care (p=0.31). Close spacing between pregnancies shows no significant difference, with 6.7% of cases and 12% of controls having closely spaced pregnancies (p=0.26), as found in Table 3.

Table (3): Obstetric history of cases and control groups.

Variables		Cases N=75	Control N=75	p value
Abortion history	Yes	32 (42.7%)	31 (41.3%)	0.89
	No	43 (57.3%)	44 (58.7%)	
Parity	1-2	36 (48%)	18 (24%)	**0.009**
	3-4	24 (32%)	37 (49.3%)	
	≥ 5	15 (20%)	20 (26.7%)	
Twin pregnancy	Single	73 (97.3%)	70 (93.3%)	0.26
	Twin	2 (2.7%)	5 (6.7%)	
Normal conception	Yes	75 (100%)	73 (97.3%)	0.15
	No	0	2 (2.7%)	
Type of Delivery	C/S	47 (62.7%)	41 (54.7%)	0.32
	NVD	28 (37.3%)	34 (45.3%)	
Delay of labor	Yes	3 (4%)	0	0.08
	No	72 (96%)	75 (100%)	
Birth trauma	No	75 (100%)	75 (100%)	----
Antenatal care	Poor	3 (4%)	1 (1.3%)	0.31
	Good	72 (96%)	74 (98.7%)	
Close space between pregnancy	Yes	5 (6.7%)	9 (12%)	0.26
	No	70 (93.3%)	66 (88%)	

*C/S; caesarean sections, NVD; Normal Vaginal Delivery

Maternal illness during pregnancy

Gestational diabetes mellitus is equally prevalent in both groups, with 2.7% in each group having it (p=0.99). Similarly, the prevalence of gestational hypertension (HTN) shows no significant difference, with 12% of cases and 10.7% of controls having it (p=0.79). A notable difference is observed in the incidence of mood disorders during pregnancy. A significant proportion of mothers in the case group (22.7%) reported

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depression, compared to none in the control group (p=0.0001). Regarding TORCH infections, there were 2 cases (2.7%) of rubella infection in the case group and no one in the control group (p=0.15), as found in Table 4.

Table (4): Maternal illness during pregnancy for cases and control groups.

Variable		Cases N=75	Control N=75	p value
Gestational DM	Yes	2 (2.7%)	2 (2.7%)	0.99
	No	73 (97.3%)	73 (97.3%)	
Gestational HTN	Yes	9 (12%)	8 (10.7%)	0.79
	No	66 (88%)	67 (89.3%)	
Depression	Yes	17 (22.7%)	0	**0.0001**
	No	58 (77.3%)	75 (100%)	
TORCH	Yes	2 (2.7%)	0	0.15
	No	73 (97.3%)	75 (100%)	

* DM; Diabetics Miletus, HTN; Hypertension, TORCH; (Toxoplasmosis, Other, Rubella, Cytomegalovirus, and Herpes simplex virus)

Drugs before and during pregnancy

The use of contraceptive pills (combined oral contraceptive pills) shows no significant difference, with 12% of cases and 6.7% of controls using them (p=0.15). There is a significant difference in the use of ovulation-stimulating hormones, with 21.3% of cases using them compared to only 4% of controls (p=0.001). The use of folic acid is higher among cases, with 89.3% of cases taking folic acid compared to 70.7% of controls (p=0.058). Acetaminophen use is very similar between the groups, with 1.3% of cases and 2.7% of controls using it (p=0.31). There are no cases of anti-epileptic or anti-depressant drug use in either group. The use of tonics (multivitamins) is identical in both groups, with 2.7% of cases and controls using them (p=0.99) Table 5.

Table (5): Drugs before and during pregnancy of cases and control groups.

Variables		Cases N=75	Control N=75	p value
Contraceptive pills	Yes	9 (12%)	5 (6.7%)	0.15
	No	66 (88%)	70 (93.3%)	
Ovulation-stimulating hormones	Yes	16 (21.3%)	3 (4%)	**0.001**
	No	59 (78.7%)	72 (96%)	
Folic acid	Yes	67 (89.3%)	53 (70.7%)	0.058
	No	8 (10.7%)	22 (29.3%)	
Acetaminophen	Yes	1 (1.3%)	2 (2.7%)	0.31
	No	74 (98.7%)	73 (97.3%)	
Anti-Epileptics	No	75 (100%)	75 (100%)	----
Anti-Depressant	No	75 (100%)	75 (100%)	----
Tonics	Yes	2 (2.7%)	2 (2.7%)	0.99
	No	73 (97.3%)	73 (97.3%)	

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Discussion

The study indicates that the mean maternal age is significantly higher in the case group compared to the control group (28.1 years vs. 22.9 years, p=0.001). In a large meta-analysis study by Wu S et al. (11), they found that an increase in the mother's age is associated with an increased risk of autism in the offspring. There were no significant differences in maternal education, although a higher percentage of mothers in the case group were employed. This contrasts with other studies suggesting lower maternal education levels associated with increased ASD risk in which in study from Egypt by Arafa A et al (12). The study showed, no significant role for parental consanguinity between the case and control groups, this finding is consistent with some studies, like a study from Qatar by Alshaban FA et al (13). The mean BMI of mothers in the case group was significantly higher compared to the control group (26.9 vs. 24.4, p=0.0001) a study by Krakowiak et al (14). It was shown that maternal obesity is associated with a higher risk of ASD. The study reports that 6.7% of mothers in the case group were exposed to passive smoking, while none in the control group were exposed (p=0.023). This suggests that passive smoking during pregnancy is a significant risk factor for ASD. A study by Visser JC et al. (15) found that maternal smoking during pregnancy was associated with a higher risk of ASD in children. The study shows no significant difference in animal contact between the groups. Parity showed a significant difference between the groups, with a higher proportion of mothers in the case group having 1-2 pregnancies (48% vs. 24%) and a lower proportion having 3-4 pregnancies (32% vs. 49.3%) compared to the control group (p=0.009). This was in line with previous study by Cheslack-Postava K et al. (16) that should decrease risk of ASD with increasing parity. Also, another study Burstyn I et al. (17) showed that ASDs decreased with increasing parity. Twin pregnancies did not show a significant difference between the groups in this study (p=0.26) while a study from Egypt by Arafa A et al (2). found that multiple pregnancy is a risk factor for ASD. The history of abortion was similar between groups (p=0.89), as were the rates of normal conception (p=0.15). The mode of delivery, whether a cesarean section or normal vaginal delivery, did not significantly differ between the groups (p=0.32), nor did the quality of antenatal care received (p=0.31). Additionally, close spacing between pregnancies (p=0.26) and the presence of birth trauma (both groups reported none) were also not significantly different. A notable difference was observed in the incidence of depression during pregnancy, with 22.7% of mothers in the case group reporting depression compared to none in the control group (p=0.0001). Studies, such as those of Caparros Gonzalez RA et al. (18). It was concluded that exposure to high levels of stress during pregnancy is associated with ASD. Another study by Ayano G et al (19). It was shown that depressive disorders increased the risk of ASD in offspring. Some studies suggest a modest increase in ASD risk associated with gestational diabetes; other studies, including this one, have not found a significant association (20). For instance, a large cohort study by Shao W et al. (21) found that gestational diabetes was associated with a

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higher risk of ASD. Furthermore, congenital heart disease may increase the risk of autism (22). Existing literature on gestational hypertension and ASD risk is limited, but some studies suggest a potential link, like a study by Wang LW et al. (23). TORCH infections are known to cause severe congenital abnormalities and neurodevelopmental disorders, including ASD (24). However, the low detection rate of rubella (n=2, 2.7%) in this study limits the ability to detect a significant association. Studies have suggested that the use of ovulation-stimulating hormones may be associated with an increased risk of ASD this study and a study by Robinson SL et al. (25) reported that assisted reproductive technologies, including ovulation-stimulating drugs, could be linked to a higher ASD risk. The use of contraceptive pills was similar among the groups in a study by Hargreave M et al. (26). It was shown that maternal use of hormonal contraception may be associated with ASD risk in children. The use of folic acid was higher among cases but not significantly different (89.3% vs. 70.7%, p=0.058), suggesting widespread adherence to prenatal guidelines. In a study by Surén P et al (27). It was found that prenatal folic acid supplements around the time of conception were associated with a lower risk of ASD. Acetaminophen use was also similar (1.3% vs. 2.7%, p=0.31), reflecting the low prevalence and possibly limited impact of occasional use on ASD risk. There were no reported cases of anti-epileptic or antidepressant drug use in both groups. Moreover, maternal intrahepatic cholestasis of pregnancy (ICP) is associated with children's risk of autism (28,29).

Conclusions

Based on the study results, we concluded the following:

Advanced Maternal Age, Maternal BMI, Smoking, Depression, use of Stimulating hormones before pregnancy, and Parity are all factors that are significantly associated with an increased risk of ASD.

Recommendations

Based on study results, we recommended the following: Provide comprehensive preconception counseling to older women planning to conceive, Implement nutritional and lifestyle interventions for women of childbearing age to manage BMI and promote healthy weight. Strengthen smoking cessation programs targeting pregnant women and their families to reduce exposure to secondhand smoke. Integrate mental health screenings and support into prenatal care to identify and treat depression and other mood disorders early in pregnancy. Closely monitor and evaluate the use of stimulating hormones and other fertility treatments, considering potential risks and benefits.

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

Ethical Clearance: Official approval has been obtained to use data, and data were analyzed without the names to protect privacy. This study was conducted according to the approval of the College of Medicine/ University of Diyala and in accordance with the ethical guidelines of the Declaration of Ethical Committee of the College (Document no. 2024NAM890).

Conflict of Interest: Non

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عوامل الخطورة عند الامهات لاضطرابات طيف التوحد

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الملخص

خلفية الدراسة: اضطراب طيف التوحد هو اضطراب تطوري عصبي معقد يتميز بعيوب في التواصل الاجتماعي واهتمامات محدودة وسلوكيات متكررة. تعتبر مسببات اضطراب طيف التوحد متعددة العوامل، حيث تشمل العوامل الوراثية والبيئية والأمومية. أشارت الدراسات الحديثة إلى أن العوامل الأمومية مثل تقدم عمر الأم، ارتفاع مؤشر كتلة الجسم، التدخين والاكتئاب أثناء الحمل، هي عوامل خطر مهمة لتطور اضطراب طيف التوحد. تهدف هذه الدراسة إلى التحقيق في عوامل الخطر الأمومية المساهمة في المرض لدى الأطفال في ديالى، العراق.

اهداف الدراسة: ان الهدف من هذه الدراسة هو معرفة عوامل الخطورة عند الامهات المسببة لمرض اضطراب طيف التوحد.

المرضى والطرائق: اجريت هذه الدراسة من نوع الحالات والشواهد على ١٥٠ طفلًا، شملت ٧٥ طفلًا تم تشخيصهم باضطراب طيف التوحد و٧٥ طفلًا كمجموعة سليمة. بدأت الدراسة من شهر آب ٢٠٢٣ إلى شهر آيار ٢٠٢٤ في محافظة ديالى، العراق. حيث شمل جمع البيانات تاريخ شامل ديموغرافي، اجتماعي، توليدي، وصحي للأمهات. تم تأكيد تشخيص المرض باستخدام مقياس تقييم التوحد في مرحلة الطفولة ٢ (CARS-2) وتم إجراء تحليل الانحدار اللوجستي لتقييم العلاقة بين عوامل الخطر الأمومية واضطراب طيف التوحد.

النتائج: كشفت الدراسة عن عدة عوامل خطر أمومية مهمة للمرض، حيث كان عمر الأم المتقدم أثناء الحمل (متوسط العمر ٢٨,١ سنة) في مجموعة الحالات مقابل (٢٢,٩ سنة) في المجموعة السليمة(p=0.001) ، و متوسط ارتفاع مؤشر كتلة الجسم للأم (٢٦,٩ كغم/م^{٢}) في مجموعة الحالات مقابل (٢٤,٤ كغم/م^{٢}) في المجموعة السليمة (p=0.0001) والتدخين بين الأمهات (٦,٧٪) في الحالات، مقابل (٠٪) في المجموعة السليمة، (p=0.023)، والاكتئاب أثناء الحمل (٢٢,٧٪) في الحالات مقابل (٠٪) في المجموعة السليمة، (p=0.0001) كلها عوامل مرتبطة بشكل كبير بزيادة خطر حدوث المرض. كما أظهر استخدام الهرمونات المحفزة قبل الحمل ارتباطًا كبيرًا حيث بلغت النسبة (٢١,٣٪) في الحالات مقابل (٤٪) في المجموعة السليمة، (p=0.001).وكانت نسبة الولادات لها تأثير، خصوصا عند الأمهات اللاتي حملن مرة أو مرتين فقط، عامل خطر كبير أيضًا (p=0.002).

الاستنتاجات: تبين من خلال هذه الدراسة ان (العمر المتقدم للأم، ارتفاع مؤشر كتلة الجسم ، التدخين، الاكتئاب وعدد الولادات عند الامهات اللاتي حملن مرة او مرتين وايضا استخدام الهرمونات المحفزة قبل الحمل) جميعها تعتبر عوامل خطر عند الامهات لتطور مرض اضطراب طيف التوحد عند الأطفال.

الكلمات المفتاحية: التوحد، اضطراب طيف التوحد، عمر الأم وعلاقته بالتوحد، مرض الأم وعلاقته بالتوحد.

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Effect of Dietary Intake of Lutein Rich Foods on the Retina and its Associated with Retinopathy Among Diabetic Patients

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Abstract

Background: Diabetic retinopathy (DR) is a common micro-vascular consequence of diabetes mellitus that affects the eyes. If untreated, DR cause damage to the retinal blood vessels and result in blindness or visual loss Hyperglycemia over long period of time results in increases inflammatory oxidative stress and protein kinase C pathways that eventually retinal capillary endothelial damage and pericyte loss occurred. Lutein is a carotenoid with anti-inflammatory and antioxidant properties.

Objective: To determine the protection roles of dietary intake of lutein rich foods on the retina and it's associated with retinopathy among diabetic patients.

Patients and Methods: A cross-sectional study was conducted in the Ophthalmology Department of Imamein Kadhimein Medical City, Baghdad, Iraq, from July to November 2023, involving a total of 100 diabetic patients. Questionnaire list was used which consist of sociodemographic information, socioeconomic status, dietary sources of lutein, anthropometric measures and ophthalmic examination and investigations which include optical coherence tomography for macular assessment and HbA1c assessment.

Results: The current study showed that 64% of the diabetic patients had retinopathy and 36% had normal retina. The study showed that 91.7% of diabetic patients with normal retina were consume 3-7 serving/week tomato, 75% were consume 7-35 serving/week egg, 75% were consume 1-7 serving/week zucchini, 72% were consume 1-3 serving/week spinach, 63.9% were consume 3-7 serving/week green pepper, 63.9% were consume 3-7 serving/week basil, 61% were consume 3-7 serving/week parsley, 58% were consume 3-7 serving/week leek, 52.8% were consume 3-7 serving/week lettuce, 41.7% were consume 1-2 serving/week nut and 30.6% were consume 1-2 serving/week pistachio with significant p-value.

Conclusion: Patients with diabetes can avoid retinal damage by consuming the recommended weekly servings of lutein-rich foods especially tomato, eggs, zucchini, spinach, green pepper, basil, parsley, leek, lettuce, nut and pistachio.

Keywords: Diabetic retinopathy, lutein, visual impairment.

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Introduction

The eye is an important organ that need special care (1). Diabetes and its consequences are growing more prevalent worldwide (2). By 2030, it is anticipated that over 191 million individuals globally will suffer from diabetic retinopathy, with over 55 million of them experiencing visual impairment (2). There are 1.4 million type 2 diabetics in Iraq, where the disease affects 8.5% to 13.9% of the population (3). In Iraq, the prevalence of diabetic retinopathy ranged from 28.1% to 32.8%, with proliferative alterations observed in 11.27% of cases (4). Globally, 22.27% of people had DR (5). Diabetic retinopathy is a microvascular disorder that destroys retinal blood vessels and can lead to blindness or visual loss if untreated (6 – 8). Hyperglycemia over long period of time results in increases inflammatory oxidative stress and protein kinase C pathways that eventually retinal capillary endothelial damage and pericyte loss were occurred. Retinal capillary changes causing capillary occlusion, retinal non perfusion and endothelial barrier decompensation which leads to serum leakage and retinal edema (macular edema). These changes occur in both superficial and deep retinal capillary vessels and worsen in more sever diabetic retinopathy. Retinal neovascularization may develop due to increase level of intravascular endothelial growth factor (VEGF) from ischemic retinal tissue (7, 8). Diabetic retinopathy (DR) is a leading cause of vision loss globally, ranking sixth in terms of preventable blindness and fifth in terms of moderate-to-severe visual impairment between 1990 and 2020 (9). A third of individuals with diabetes mellitus have vision-threatening retinopathy, which is characterized by either proliferative or severe non-proliferative DR or the presence of diabetic macular edema (7, 8, 10). Approximately one in three individuals with diabetes mellitus have DR (11). DR is estimated to be the most frequent cause of new cases of blindness among adults 20-74 years of age (12). Studies had been demonstrated that daily ingestion of a multi-component formula combining antioxidants and xanthophyll pigments improves perimetry, color discrimination, macular pigment optical density, and contrast sensitivity in diabetic individuals with and without retinopathy (13). Lutein and zeaxanthin are carotenoids that have anti-inflammatory, antioxidant (14-16) and neuroprotective effects (17). Unique carotenoids that are concentrated in the human macula (center of retina) are: lutein, zeaxanthin, and meso-zeaxanthin (16-19). Lutein and zeaxanthin are obtained from dietary sources such as green leafy vegetables and orange and yellow fruits and vegetables, while meso-zeaxanthin is rarely found in diet and is believed to be formed at the macula by metabolic transformations of ingested carotenoids (17, 19). Several studies have proved that lutein and zeaxanthin are an essential element for eye health (1, 14 – 21). Elevated levels of the food-dependent plasma carotenoids lutein and zeaxanthin are thought to offer protection against diabetic retinopathy (13 – 15). Consuming lutein and zeaxanthin has been shown to help diabetic patients with non-proliferative retinopathy, macular edema and improve their contrast sensitivity and visual acuity (13 – 15). Lutein and zeaxanthin may have protective effect for macula in

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patients with DR because of their biochemical structure and function that neutralize reactive oxygen species and prevent oxidative damage to the retina (biological antioxidants), neuroprotective and anti-inflammatory function in the retina, its position in the center of retina (macula), and its ability to absorb oxidative blue light (2, 14 – 17). Carotenoids that are present in large quantities in egg yolks, orange and yellow fruits, and dark green vegetables (Leek, Parsley, Lettuce, green pepper), tomato and nut are lutein and zeaxanthin (18, 20-22). It is also one of just two carotenoids that are present in the human eye, where it serves to shield the retina from damaging light and oxidation (18). Dietary factors have a significant impact on DR risk modification, as evidenced by the protective effects of a Mediterranean diet, high consumption of fruits, vegetables, and fish, and low calorie intake (22 – 24). Depending on a fact that lutein has antioxidant, anti-inflammatory and neuroprotective effects. Hence, the objective of this study was to determine the protection roles of dietary intake of lutein rich foods on the retina and it's associated with retinopathy among diabetic patients.

Patients and Methods

The Department of Ophthalmology of Imamein Kadhimein Medical City, Baghdad, Iraq was the site for data collection of the current cross-sectional study, for five months duration from the 1st of July to 1st of December 2023. One-hundred diabetic patients were collected from outpatient in ophthalmology department of this hospital; Patients were only included if they met the inclusion criteria which are all diabetic patients aged between 35- 90 years.

Questionnaire list was used in current study and consist of sociodemographic information, socioeconomic status, and dietary sources of lutein, anthropometric measures and ophthalmic examination.

1. Sociodemographic information consist of age, sex, education, occupation and marital status.

2. Socioeconomic status was determined based on standard equation: Education + Occupation + house ownership ×0.5 +car ownership × 0.1 (25).

3. Dietary sources of lutein: Serving size is used for detecting the dietary sources of lutein. It is a standardized amount of food and used to quantify recommended amounts of food groups, or represent quantities that people typically consume on a Nutrition Facts label. One serving size is equal to: one medium sized egg, one cup of cooked spinach, one large green pepper and one cup of raw (tomato, leek, parsley and lettuce), one medium sized orange and one third cup or handful nuts (12). Recommended level for eye health: 10 milligrams (mg)/day for lutein and 2 mg/day for zeaxanthin (26). The lutein contents of one cup of Spinach, one egg yolk, half cup of parsley and one ounce of pistachios are containing about 20.4 mg (26), 0.1, 1.2 mg and 1.4 mg respectively (1, 27, 28).

4. Anthropometric measures (body weight, height) were measured by stadiometer, and the formula used to determine body mass index (BMI) was weight in kilograms divided by square height in meters. Class I obesity (BMI 30-34.9), class II obesity (BMI 35-39.9), class III obesity (BMI ≥ 40), underweight (BMI < 18.5), normal weight (BMI = 18.5 -24.9), and overweight (BMI = 25-29.9) were the BMI classifications assigned to the patients (29-

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32). Mid upper arm circumference was measured by tape measure (MUAC). Normal MUAC for adult are >23 cm for male and >22cm for women (33).

5. Ophthalmic examination: All patients were examined of visual acuity and intraocular pressure and senior ophthalmologist was examined posterior segment (vitreous and retina) using slit-lamp biomicroscopy.

6. Optical coherence tomography (OCT) for macular assessment: Is a non-invasive test that provides color-coded, cross sectional images of the retina to enable early detection and treatment of ocular disease that may develop without any noticeable symptoms. The OCT scan uses a low- coherence light to obtain higher resolution images of the layers of the retina and optic nerve. The color-coded images provide a wealth of information to measure the thickness of the retina and identify any optic nerve abnormalities (7).

7. Measurement of the level of glycosylated hemoglobin (HbA1c): was tested in laboratory of Imamein Kadhimein Medical City. The hemoglobin A1C (glycated hemoglobin, glycosylated hemoglobin, HbA1c) test is used to assess glucose control levels and diagnose diabetes. It is an average of the blood sugar level over for previous three months and represented in a percentage. Hemoglobin is a protein which only found in red blood cells. The main job of hemoglobin is to carry oxygen from the lungs to all the cells of the body. Hemoglobin becomes glycated or coated with glucose from the bloodstream. The amount of glucose that is present in the blood will attach to the hemoglobin protein, and increased glucose levels will reflect on the surface of the hemoglobin protein, thereby making a higher HbA1c level (34). HbA1c test below 5.7 % classify as normal, or in the non-diabetic range, HbA1c value of 5.7 % to 6.4 % is considered to be pre-diabetic, while HbA1c of 6.5% or higher can be diagnosed as diabetes (35).

Statistical Analysis

Data input and analysis were performed using the Statistical Package for Social Sciences, version 24 (SPSS 24) program. Simple frequency and percentage measures were used to display the data. The chi square test was used to determine the significance of the association between the variables, and Z test which is used for testing the significance of association between two proportions. A p value of 0.05 or less was deemed statistically significant.

Results

1- Age distribution:

This study showed 36% of diabetic patient had normal retina and 64% of them had diabetic retinopathy. Sex distribution was 41% male and 59% female. 50% of patients were with age 40-60 years and 49% were with age more than 60 years (Table 1).

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Table (1): Frequency distribution of age of diabetic patients.

Age (year)	No.	%
< 40	1	1.0
40-60	50	50.0
> 60	49	49.0
Total	100	100.0

2- Body mass index of diabetic patients:

Thirtyeight percent of patients were with class I obesity, 12% with class II and 7% with class III. While 24% of patients were with normal weight and 19% with overweight (Table 2).

Table (2): Frequency distribution of body mass index (BMI) of diabetic patients.

BMI	No.	%
Normal weight	24	24.0
Over weight	19	19.0
Obesity class I	38	38.0
Obesity class II	12	12.0
Obesity class III	7	7.0
Total	100	100.0

3- Diabetic retinal lesions and lutein rich diet consumption:

It is about 49% of diabetic patients had diabetic macular edema, 10% with non-proliferative diabetic retinopathy, 5% with proliferative diabetic retinopathy and 36% of patients had normal retina (Table 3).

Table (3): Frequency distribution of diabetic retinal lesions in diabetic patients.

Retinal lesion	No.	%
Normal retina	36	36.0
Non proliferative diabetic retinopathy	10	10.0
Diabetic macular edema	49	49.0
Proliferative diabetic retinopathy	5	5.0
Total	100	100.0

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The proportion of diabetic patients with normal retina which consume tomato, egg, green pepper, basil, spinach, parsley, leek, lettuce, orange and nut were 91.7%, 75%, 63.9%, 63.9%, 61.1%, 61.1%, 58.3, 52.8%, 30.6%, 33.3% respectively from total number of patients with normal retina, while the proportion of diabetic patients with retinopathy which consume tomato, egg, green pepper, basil, spinach, parsley, leek, lettuce, orange and nut were 76.6%, 46.9%, 32.8%, 9.4%, 28.1%, 20.3%, 7.8%, 4.7%, 14%, 10.9 respectively with significant p-values (0.004, 0.005, 0.003, 0.0001, 0.001, 0.0001, 0.0001, 0.0001, 0.04, 0.007) respectively. The proportion of diabetic patients with normal retina that consume 1-2 serving/week and 3-7 serving/week pistachio are 30.6% and 25% respectively, while the proportion of diabetic patients with retinopathy which consume 1-2 serving/week and 3-7 serving/week pistachio are 3.1% and 9.4% with significant p-value (0.0001, 0.03) respectively (Table 4).

Table (4): Proportion of lutein rich diet consumption among diabetic patients.

Type of Food	No. of serving/wee	Normal retina, n=36		Diabetic retinopathy, n=64		P value	Total
		No.	Proportion	No.	Proportion		
Egg	7-35	27	75	30	46.9	0.005*	100
Spinach	1-2	22	61.1	18	28.1	0.001*	
Green pepper	3-7	23	63.9	21	32.8	0.003*	
Tomato	3-7	33	91.7	49	76.6	0.004*	
Leek	3-7	21	58.3	5	7.8	0.0001*	
Parsley	3-7	22	61.1	13	20.3	0.0001*	
Lettuce	3-7	19	52.8	3	4.7	0.0001*	
Basil	3-7	23	63.9	6	9.4	0.0001*	
Orange	3-7	11	30.6	9	14	0.04*	
Nut	3-7	12	33.3	7	10.9	0.007*	
Pistachio	1-2	11	30.6	2	3.1	0.0001*	
	3-7	9	25	6	9.4	0.03*	

It is about 91.7% of diabetic patients with normal retina were consume 3-7 serving/week tomato, 75% were consume 7-35 serving/week egg, 75% were consume 1-7 serving/week zucchini, 72% were consume 1-3 serving/week spinach, 63.9% were consume 3-7 serving/week green pepper, 63.9% were consume 3-7 serving/week basil, 61% were consume 3-7 serving/week parsley, 58% were consume 3-7 serving/week leek, 52.8% were consume 3-7 serving/week lettuce, 41.7% were consume 1-2 serving/week nut and 30.6% were consume 1-2 serving/week pistachio, while 76.6% of diabetic patients with retinopathy were consume 3-7 serving/week tomato, 40.9% were consume 7-35 serving/week egg, 51.6% were consume 1-7 serving/week zucchini, 31% were consume 1-3 serving/week spinach, 40.6% were consume 1-2 serving/week green pepper, 14% were consume 1-2 serving/week basil, 29.7% were consume 1-2 serving/week parsley,

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12.5% were consume 1-2 serving/week leek, 17% were consume 1-2 serving/week lettuce, 21.9% were consume 1-2 serving/week nut and 3% were consume 1-2 serving/week pistachio with significant p-value (0.01, 0.006, 0.02, 0,0001, 0.005, 0.0001, 0.0001, 0,0001, 0.0001, 0.0001, 0.0001) respectively (Table 5).

Table 5: Frequency distribution of lutein rich diet consumption among diabetic patients.

Type of Food	Normal retina, n=36				Diabetic retinopathy, n=64				P value	Total
	No serving	Serving			No serving	Serving				
		Serving /week	No.	%		Serving /week	No.	%		
Egg	4	1-6	5	13.9	8	1-6	26	40.6	0.006*	100
		7-35	27	75		7-35	30	40.9		
Spinach	10	1-3	26	72	44	1-3	20	31	0.0001*	
Zucchini	9	1-7	27	75	31	1-7	33	51.6	0.02*	
Green pepper	5	1-2	8	22	17	1-2	26	40.6	0.005*	
		3-7	23	63.9		3-7	21	32.8		
Tomato	1	1-2	2	5.6	5	1-2	10	15.6	0.01*	
		3-7	33	91.7		3-7	49	76.6		
Leek	6	1-2	9	25	51	1-2	8	12.5	0.0001*	
		3-7	21	58		3-7	5	7.8		
Parsley	6	1-2	8	22	32	1-2	19	29.7	0.0001*	
		3-7	22	61		3-7	13	20		
Lettuce	5	1-2	12	33	50	1-2	11	17	0.0001*	
		3-7	19	52.8		3-7	3	4.7		
Basil	6	1-2	7	19	49	1-2	9	14	0.0001*	
		3-7	23	63.9		3-7	6	9.4		
Nut	9	1-2	15	41.7	43	1-2	14	21.9	0.0001*	
		3-7	12	33		3-7	7	10.9		
Pistachio	16	1-2	11	30.6	56	1-2	2	3	0.0001*	
		3-7	9	25		3-7	6	9.3		

Discussion

Diabetes mellitus is a group of metabolic diseases that all have a hyperglycemic phenotype, and may associated with obesity which is a major public health problem worldwide (36- 38). Visual impairment is a global issue, particularly in developing nations and among the most common causes of avoidable blindness and moderate-to-severe visual impairment from 1990 to 2020, diabetic retinopathy ranks fifth globally. It is also one of the main causes of vision loss (9, 39). Common carotenoid pigments include lutein and zeaxanthin, which are present in high concentrations in egg yolks, orange and yellow fruits, and dark green vegetables. Because of its antioxidant qualities, position inside the retina, and capacity to absorb oxidative blue light, lutein may offer protection against DR (2). Age-related macular degeneration (AMD) and DR are treated and prevented with dietary and lifestyle changes (40). The current study showed that 75% of diabetes individuals with normal retinas consume 7–35 servings of eggs per week, and this intake was substantially correlated with normal retinal exams in these patients. Previous studies showed that egg

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lutein content has been linked to eye health, the egg yolk provides an excellent dietary source of lutein and zeaxanthin because the bioavailability from the yolk matrix is much higher than from the leaves of green vegetables. The high bioavailability of a fat-soluble nutrient such as zeaxanthin from the egg is due to the rich lipid matrix of the yolk. Egg yolk is a good dietary source of both zeaxanthin and lutein, particularly as part of a typical western diet, which is poor in vegetables and fruits. A high intake of lutein can also increase the macular content of meso-zeaxanthin because the lutein can convert to meso-zeaxanthin in the central retina (1, 26, 27). In the current study consuming spinach, zucchini, green pepper, tomato, leek, parsley, lettuce, basil, oranges, nuts, and pistachios is significantly linked to normal retina function. A weekly consumption of 1-2 serving\week (1-2 cups) of cooked spinach was reported by 61.1% of patients with normal retinal examinations. Previous studies showed that lutein and zeaxanthin are the most common xanthophylls in green leafy vegetables like spinach which had important role in eye health (1). In this study, 63.9% of patients consumed 3-7 servings (one and a half cups) of chopped green pepper or one large bell pepper were with normal retina. Peppers are one of the most widely consumed foods throughout the world owing to their attractive colors and strong flavor, green peppers get their unique yellow and orange hue from lutein, a chemical substance that's abundant in them. Research has demonstrated that lutein, an antioxidant, enhances eye health (41, 42). Carotenoids act as antioxidants and deactivating free radicals. Nutritional supply of carotenoids with ocular health benefits such as lutein and zeaxanthin, with potential health benefits for humans (41, 42). Each week, about 91.7% of people consumed three to seven servings (one cup) of chopped or sliced fresh tomatoes. Lutein is becoming increasingly important in preventive medicine due to its possible role in maintaining good vision. Research has demonstrated that a unique pigment found in tomatoes called lutein serves as a filter to shield the eyes from harmful light and oxygen which showed higher antioxidant capacity that protect the retina and lens against ultraviolet and blue spectrum light. Study in Panama City at 2017 showed that the most consumed lutein and zeaxanthin food sources in the study population were tomatoes, egg yolks and green peppers. Lutein and zeaxanthin, both oxygen-containing carotenoids in tomatoes and tomato-based food products are considered to play vital roles in promoting ocular development and maintaining eye health (28, 43- 45). Among the study group of diabetes patients, those who consumed 3-7 servings (one cup) of raw leek per week accounted for 58% of normal retinal tissue. Previous studies showed significant eye problems can be avoided and maintained with the use of leafy green vegetables like leek. Lutein and zeaxanthin are dietary carotenoids derived from dark green leafy vegetables, orange and yellow fruits that form the macular pigment of the human eyes. It was assumed that they protect against visual disorders such as hypoxia induced retinopathy and diabetic retinopathy. The mechanism by which they are involved in the prevention of eye diseases may be due their local antioxidant activity and physical blue light filtration properties which are the direct biological effects of lutein and also improve normal ocular function by

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enhancing contrast sensitivity and by reducing glare disability which is the photophobia and discomfort when intense light enters the eye (45- 50). Approximately 61.1% of diabetes patients with normal retinal function consumed three to seven servings (one cup of three-quarters bunch or one tablespoon of freshly chopped parsley) of parsley each week. Several studied documented that consumption of dark green leafy vegetables had a protective role against eye diseases. Parsley is an important culinary herb originated from the Mediterranean region. Its main constituent's carotenoids, flavonoids and it has anti oxidative activity (1, 51- 53).

Five to seven servings (two cups of raw chopped lettuce) were consumed weekly by 52.8% of the diabetic individuals in this study with normal retinal results. Numerous studies have identified lutein and zeaxanthin to be essential components for eye health, they constitute the main pigments found in the yellow spot of the human retina which protect the macula from damage by blue light, improve visual acuity and remove harmful reactive oxygen species. Parsley and lettuce are rich in antioxidants, lutein and zeaxanthin, which help shield the surface of the eyes and prevent eye diseases. A study in the US showed that a higher dietary intake of carotenoids, specifically lutein is associated with reduced eye diseases (1, 51- 53). In the current study, a weekly consumption of 3–7 servings (one cup fresh or 2 tablespoons chopped) of basil was reported by about 63.9% of normal retinal examinations. Basil supports eye health, and fights free radicals through its antioxidant and anti-inflammatory properties which is high in beta carotene, lutein and zeaxanthin (54- 57). About 30.6% of diabetic individuals with normal retinal examinations consumed oranges, consuming three to seven servings (one medium-sized piece) per week. Nutrition plays a vital role in human health with no exception to the eye. Healthy eyes provide good vision, which is essential for an enjoyable and productive lifestyle. Numerous studies have identified lutein and zeaxanthin to be essential components for eye health. Consumption of orange have protective effect on the retina. Orange is rich with lutein and zeaxanthin which have a strong antioxidant content (1, 18). Approximately 33.3% of diabetes patients with normal retinal examinations consumed 3–7 servings (equivalent to 1/3 of a cup or one handful) of nuts each week. In diabetes individuals, around 30.6% of normal retina were consumed in 1-2 servings (one handful or ten pieces) per week, while 25% consumed 3-7 servings per week. Of all nuts, pistachios contain the highest concentrations of zeaxanthin and lutein. These nutrients guard your eyes against macular degeneration, an eye condition that can cause vision loss as you age, and blue light damage (19, 21).

Other foods high in lutein, such as kale, which is not available in Iraq, collard greens, squash, broccoli, peas, orange pepper, corn, persimmon, tangerines, carrots, kiwis, grapes, and bananas, were not significantly associated with a protective effect on the retina. This could be because our patients did not have access to these foods or because their prices made them difficult to purchase in addition to their poor dentation.

Conclusions

Patients with diabetes can avoid retinal damage by consuming the recommended weekly servings of lutein-rich foods

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especially tomato, eggs, zucchini, spinach, green pepper, basil, parsley, leek, lettuce, nut and pistachio.

Recommendations

1. Suggested daily consumption of lutein rich foods for diabetic patients.
2. Encourage weight reduction.
3. Increase knowledge about types of lutein rich foods.
4. Routine ophthalmic examination.

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Ethical Clearance: Imamein Kadhimein Medical City and the Arabic Council of Medical Specialization had granted their official approval. After informing the patients about the purpose and goals of the study, assuring their privacy, and ensuring that the questionnaires were completed anonymously, the patients gave their informed consent. (Document no. 2024HRS872).

Conflict of Interest: Non

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تأثير تناول الأطعمة الغنية باللوتين على الشبكية وارتباطه باعتلال الشبكية لدى مرضى السكري

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الملخص

خلفية الدراسة: اعتلال الشبكية السكري هو نتيجة شائعة للأوعية الدموية الدقيقة لمرض السكري الذي يؤثر على العينين. إذا لم يتم علاجه، يتسبب اعتلال الشبكية السكري في تلف الأوعية الدموية في شبكية العين ويؤدي إلى العمى أو فقدان البصر. يؤدي ارتفاع السكر في الدم على مدى فترة طويلة من الزمن إلى زيادة الإجهاد التأكسدي الالتهابي ومسارات بروتين كيناز C التي تؤدي في النهاية إلى تلف بطانة الأوعية الدموية في شبكية العين وفقدان الحويصلة. اللوتين عبارة عن كاروتين ذو خصائص مضادة للالتهابات ومضادة للأكسدة.

اهداف الدراسة: لتحديد الأدوار الوقائية للتناول الغذائي للأطعمة الغنية باللوتين على شبكية العين وارتباطها باعتلال الشبكية لدى مرضى السكري.

الحالات و المنهجية: أجريت دراسة مقطعية في قسم طب العيون في مدينة الإمامين الكاظمين الطبية، بغداد، العراق، في الفترة من يوليو إلى نوفمبر ٢٠٢٣، وشملت ما مجموعه ١٠٠ مريض بالسكري. تم استخدام قائمة الاستبيانات التي تتكون من المعلومات الاجتماعية والديموغرافية والحالة الاجتماعية والاقتصادية والمصادر الغذائية للوتين والقياسات البشرية وفحص العيون والتحقيقات التي تشمل التصوير المقطعي التوافقي البصري لتقييم البقعة الصفراء وتقييم نسبة HbA1c.

النتائج: أظهرت الدراسة الحالية أن ٦٤٪ من مرضى السكري يعانون من اعتلال الشبكية و٣٦٪ لديهم شبكية طبيعية. أظهرت الدراسة أن ٩١,٧٪ من مرضى السكري ذوي الشبكية الطبيعية كانوا يتناولون ٣-٧ حصص/أسبوع من الطماطم، و٧٥٪ كانوا يستهلكون ٧-٣٥ حصة/أسبوع من البيض، و٧٥٪ كانوا يستهلكون ١-٧ حصص/أسبوع من الكوسا، و٧٢٪ كانوا يستهلكون ١-٣ حصص/أسبوع من السبانخ، ٦٣,٩٪ يستهلكون ٣-٧ حصص/أسبوع من الفلفل الأخضر، ٦٣,٩٪ يستهلكون ٣-٧ حصص/أسبوع من الريحان، ٦١٪ كانوا يستهلكون ٣-٧ حصص/أسبوع من البقدونس، ٥٨٪ يستهلكون ٣-٧ حصص/أسبوع من الكراث، ٥٢,٨٪ يستهلكون ٣-٧ حصص/أسبوع من الخس,٤١,٧٪ يستهلكون ١-٢ حصة/أسبوع من المكسرات و٣٠,٦٪ يستهلكون ١-٢ حصة/أسبوع من الفستق مع القيمة الاحتمالية المعتد بها احصائيا.

الاستنتاجات: يمكن لمرضى السكري تجنب تلف الشبكية عن طريق تناول الحصص الأسبوعية الموصى بها من الأطعمة الغنية باللوتين وخاصة الطماطم والبيض والكوسا والسبانخ والفلفل الأخضر والريحان والبقدونس والكراث والخس والمكسرات والفستق.

الكلمات المفتاحية: اعتلال الشبكية السكري، اللوتين، ضعف البصر.

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Correlation Between Lipid Profile and Liver Function in Patients With Non-Alcoholic Fatty Liver

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is a metabolic liver disease characterized by a broad range of liver pathology, including simple steatosis, steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocarcinoma. NAFLD has emerged as a public health concern in the world within the last 20 years, it is linked to metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), obesity, and dyslipidemia. Increased visceral adipose tissue in obese people can cause insulin resistance (IR) and hyperinsulinemia, which will speed up the lipolysis of adipose tissue, Lipo-toxicity-related chronic low-grade inflammation is involved in the development of NAFLD.

Objective: Determine the correlation between lipid profile and liver function in patients with NAFLD.

Patients and Methods: A study was conducted at Tikrit Teaching Hospital from 28 November to 28 December 2023. The study involved 90 participants, 60 with NAFLD and 30 healthy subjects. The study used a spectrophotometer (Model NO. HV-2800EX**)** and a colorimetric kit from Spain linear chemicals to determine various parameters, such as Aspartate aminotransferase (AST), Alanine aminotransferase(ALT), Gamma-glutamyl transferase(GGT), High-density lipoprotein(HDL), Low-density lipoprotein(LDL), Very low-density lipoprotein(VLDL), Triglyceride(TG), and cholesterol.

Results: The mean age of patients in the group was 40.93 years, with ages ranging from 20 to 50 years. Serum levels of liver function enzymes (GGT, AST, ALT) and lipid profile (TG, HDL, LDL, VLDL, cholesterol) were measured and compared to the control groups. Patients with NAFLD had significantly higher serum liver function enzymes and increased serum lipid profile (TG, VLDL, LDL, and cholesterol) while showing a significant decrease in HDL concentration when compared to the control group.

Conclusion: The patients showed an increase in liver function enzymes (AST, ALT, GGT) and lipid profile (LDL, VLDL, TG, cholesterol) with reduced HDL as compared to healthy individuals.

Keywords: Nonalcoholic fatty liver, liver function enzymes, lipid profile.

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Introduction

The metabolic liver disorder known as non-alcoholic fatty liver disease (NAFLD) is characterized by a wide spectrum of liver pathology, from simple steatosis to steatohepatitis (NASH) and fibrosis. Hepatocarcinoma and cirrhosis may result in the end. Since NAFLD is currently the most common cause of chronic liver disease worldwide, it carries a heavy socioeconomic cost. Its prevalence is rising, and it is rising at the same time that obesity and metabolic syndrome are rising. There is a high correlation between obesity and NAFLD, with over 80% of individuals having obesity. In particular, a greater incidence of fibrosis and cirrhosis is thought to be associated with morbid obesity (1). NAFLD has emerged as a significant public health concern in industrialized nations within the last 20 years. It has been connected to metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), and obesity, however, it can also occur in people who are not obese. Rather than dying from chronic liver disease, people with NAFLD typically have an increased chance of dying from cardiovascular illness. Hepatic iron overload has surfaced as a potential novel component involved in both NAFLD and insulin resistance, and it is well-known that there is a close correlation between the two conditions (2). Evidence of hepatic steatosis, as determined by imaging or histology, is necessary for the diagnosis of NAFLD. Additionally, secondary causes of hepatic fat accumulation, such as the use of steatogenic medications (corticosteroids, amiodarone, methotrexate), hereditary disorders (Wilson's disease, alpha-1 antitrypsin deficiency), or viral infections (hepatitis C infection), must be ruled out. Furthermore, the daily limit for alcohol consumption for males and women is 20 g and 30 g, respectively (3). Most NAFLD patients don't have any symptoms, and the condition may go unnoticed until it develops into cirrhosis. Right upper quadrant pain and fatigue are the most often reported symptoms among people with NAFLD at the time of first diagnosis. Affected individuals may exhibit liver fat based on an incident imaging test or as part of a diagnosis for right upper quadrant pain, or they may have an echogenic liver on ultrasonography. Serum tests relating to the liver usually show an elevation of hepatocellular enzymes, with serum alanine aminotransferase (ALT) being greater than serum aspartate aminotransferase (AST) (4).

Within days after consuming a high-fat diet (HFD), hepatic steatosis occurs (5). A recent study found that eating a diet full of saturated fat was a greater risk than eating a diet filled with free sugars for raising intrahepatic TG levels in overweight people (6). These findings support the notion that lipo-toxicity is a key factor in NAFLD. Studies on marker levels in obese individuals have demonstrated that around 60% of the total triglyceride (TG) content in the liver is made up of free fatty acids (FFAs) from adipose tissue (7). Obese individuals who have more visceral adipose tissue may experience insulin resistance (IR) and hyperinsulinemia, which will accelerate the adipose tissue's lipolysis (8). The development of NAFLD is associated with persistent low-grade inflammation caused by lipid toxicity. The level of inflammation as determined by IL-6 and TNF-α in obese individuals has been demonstrated to be significantly and dose-dependently correlated

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with the severity of NAFLD (9). The term "metabolic dyslipidemia" has been used recently to describe the type of dyslipidemia that results from the combined effects of obesity and insulin resistance. The modern world's obesity pandemic is closely linked to dyslipidemia, mostly caused by pro-inflammatory adipokines and insulin resistance. However according to new research, obesity-induced dyslipidemia is not a single pathophysiological entity; rather, it has a variety of characteristics that depend on a wide range of individual circumstances. Accordingly, dyslipidemia is either less pronounced or nonexistent in a subset of metabolically healthy obese (MHO) persons (10). Increased levels of triglycerides (TGs), low-density lipoprotein (LDL), total cholesterol, and low-density lipoprotein (HDL) concentrations, either separately or in combination, are considered dyslipidemia (11). Hepatocytes store excess fat as lipid droplets covered with a variety of structural proteins, which may have a role in the pathogenesis of liver disorders. Intrahepatic lipid buildup in non-alcoholic fatty liver disease (NAFLD) is caused by anomalies in lipid metabolism, including reduced triglyceride (TG) export, increased liver free fatty acid (FFA) intake, increased whole-body lipolysis, and increased synthesis of very low-density lipoprotein (VLDL). These changes in lipid metabolism are associated with abnormal synthesis of adipokines (such as leptin, adiponectin, resisting, vastatin, and retinol-binding protein-4) that impact signaling pathways, as well as an elevation of inflammation and oxidative stress (12). It has been demonstrated that liver dysfunction markers like ALT, AST, and γ-glutamyl-transferase (GGT) are useful measures of liver function and are connected to hepatic insulin resistance. ALT is thought to be a particular marker for liver injury and is mostly seen in the liver, While GGT is present on various cell surfaces and is highly active in the liver, pancreas, and kidney. GGT is involved in the uptake of glutathione and is also assumed to have a role in oxidative stress and chronic inflammation, the two main processes that lead to the development of type 2 diabetes. Thus, the biological markers that underlie the association between liver illness and type 2 diabetes may be hepatic enzymes (13). Reducing aggravating variables and changing one's lifestyle are the goals of early NAFLD treatment, which has received substantial support from the literature. Reducing body weight, performing physical activity, and preventing excessive alcohol consumption have been demonstrated time and time again to greatly improve disease signs and in certain instances, even undo early fibrosis. Only NASH patients with severe fibrosis are often eligible for pharmacologic therapy in NAFLD. For NAFLD patients who are unable to reach their weight loss objectives, bariatric surgery is a viable option. Research has demonstrated that this procedure can effectively reverse NAFLD and lower the risk of HCC (14) .

Aim and objectives: estimate serum levels of lipid profile (cholesterol, HDL, VLDL, LDL, TG) and liver enzyme (AST, ALT, GGT) and compare with healthy subjects in nonalcoholic fatty liver disease.

Patients and Methods

patients: Ninety people, ages ranging from 20 to 50, were examined in this study: 60 patients and 30 controls. A liver examination by

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ultrasound that was acquired for both groups was used to make the diagnosis of NAFLD. The patients were referred to the Tikrit Teaching Hospital's major facilities between November 28, 2023, and December 28, 2023. Using a brief questionnaire, clinical history data, demographics (age, height, weight, and weight), smoking, chronic illnesses, and the treatment plan were gathered. For each case, 5 ml of venous blood was drawn using a sterile disposable syringe, put into gel tubes, and allowed to clot at room temperature for 20 minutes. The serum was removed from each sample and split into two Eppendorf tubes after centrifuging in a centrifuge (Hettich, Germany) for 15 minutes at 3000 rpm. After that, the tubes were kept at -30 C until the biochemical analysis, which included AST, ALT, GGT, TG, VLDL, LDL, HDL, and Cholesterol.

All parameters were measured by spectrophotometric (Double beam Microprocessor ultraviolet-visible spectroscopy Spectrophotometer with software (Model NO. HV-2800EX**)**, and Liner Chemicals Spain kit.

Statistical Analysis

Using SPSS, the data analysis was carried out. P-values < 0.05 are regarded as significant. A P-value > 0.05 was considered non-significant.

Results

90 participants, 30 of whom were aberrantly healthy controls and 60 of whom were\ NAFLD patients, were involved in this study. The study groups were divided into smaller groups according to age, gender, and BMI, and these subgroups are displayed in Table (1). (21.66%) The age range of precipitant was (21-30) years old, (45%) of the patients were within (31-40) years, while (33.34%) of the patients were within the age range (41-50) years.

Table (1): Descriptive of the demographic characteristics of the study population (N=90).

Variable	Groups	Patient N=60	Control N=30
Age. Groups	21-30 Years	8	10
	31-40 Years	15	10
	41-50 Years	37	10
BMI. Groups	Normal weight	5	13
	Overweight	15	12
	Obesity	40	5
Gender	Male	30	15
	Female	30	15

Lipid Profile

Lipids and lipoproteins metabolisms are altered in nonalcoholic fatty liver. In particular, the plasma concentrations of cholesterol, TG, VLDL, and LDL were all elevated in NAFLD but HDL decreased. Results indicated a significant difference (P < 0.01) in all Lipid profiles in the fatty liver group compared to the control as shown in Table (2).

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Table (2): The mean difference in lipid profile for fatty liver disease to the patients and control groups.

Lipid profile	Patient Mean±SD N=60	Control Mean±SD N=30	P value
TG (mg\dL)	215.99±15.44	189.75±9.16	<0.001[S]
Cholesterol (mg\dL)	198.34±25.09	162.74±6.50	<0.001[S]
HDL(mg\dL)	31.43±7.22	41.58±6.15	<0.001[S]
LDL(mg\dL)	125.47±24.53	83.99±9.58	<0.001[S]
VLDL (mg\dL)	43.19±3.09	37.95±1.83	<0.001[S]
T-test was *: significant at p ≤ 0.05, SD: standard deviation; S: significant; NS= Non-significant.			

Liver Function Enzymes

Comparing patients with NAFLD to healthy control groups, it was seen that the range levels of (GGT, AST, and ALT) U\L increased. The mean and standard deviation values of GGT, AST, and ALT in the patient group were (296.28±75.60), (45.52±7.01), and (45.13±6.63) U\L, respectively. These values were significantly higher than those in the control group (175.93±47.06), (33.01±2.53), and (35.86±1.47) U\L, respectively (p ≤ 0.001). Table (3) displays the distribution of GGT, AST, and ALT serum values in the patients vs the healthy control group.

Table (3): The mean difference in Liver function for fatty liver disease in the patients and control groups.

Liver function	Patient Mean±SD N=60	Control Mean±SD N=30	P value
GGT (U\L)	296.28±75.60	175.93±47.06	<0.001[S]
AST (U\L)	45.52±7.01	33.01±2.53	<0.001[S]
ALT(U\L)	45.13±6.63	35.86±1.47	<0.001[S]
T-test was *: significant at p ≤ 0.05 SD: standard deviation; S: significant; NS= Non-significant.			

The effect of gender on the measured lipid profile according to the patient and control groups. Dyslipidaemia might have a greater influence on fatty liver in males than in females, Therefore, this study also examined the lipid profile panel based on gender groups. Results indicated that cholesterol, TG, and LDL were increased significantly in both male and female adults compared to healthy

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control, p-value <0.001. as presented in Figure (1)

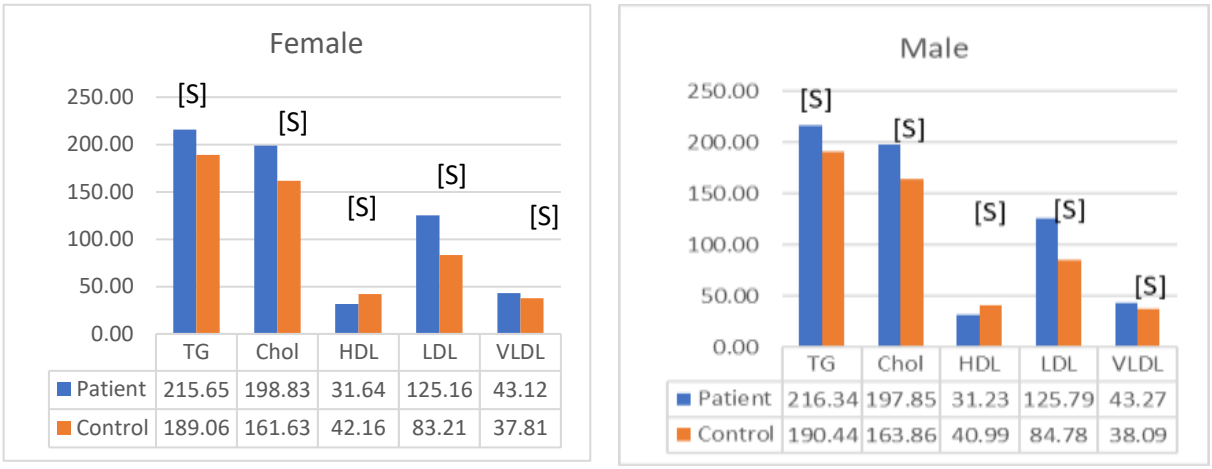

Figure (1): The effect of gender on the lipid profile parameters according to the patients and control groups.

The effect of gender on the measured liver function according to the patient and control groups.

Figure (2) illustrates the mean level of the biochemical in the patients and control groups according to gender. Results showed that male and female patients showed a highly statistically significant increase in the mean levels of GGT, AST, and ALT compared to the control, with p-values were <0.05

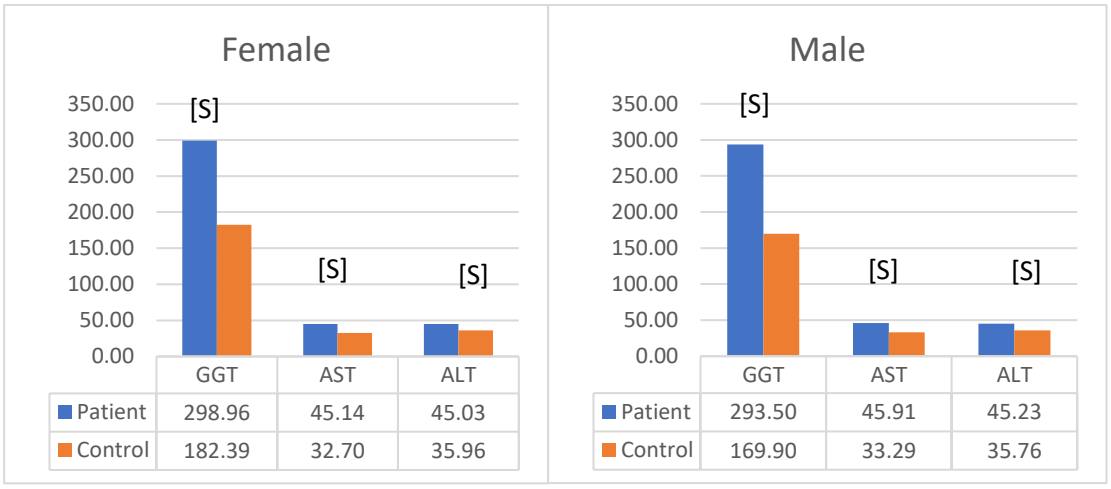

Figure (2): The effect of gender on the liver function parameters according to the patients and control groups.

Results of the receiver operating curve (ROC) and area under curve (AUC) analysis for the GGT, AST, and ALT as diagnostic parameters were done. GGT, AST, and ALT showed good performance for predicting fatty liver disease compared to the control group GGT levels:

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(sensitivity = 98.3 %, specificity 96.6%) at a level = 92.1, For AST levels: (sensitivity = 98.3 %, specificity 96.6%) at a level = 99.7, For ALT levels: (sensitivity = 98.3 %, specificity 96.6%) at a level = 99.5, the p-values of the AUC were <0.05 and highly statistically significant. The p-values of the AUC were <0.05 and statistically significant. Youden's J statistics of the. parameters in Figure 3 confirm these results for GGT, AST, and ALT.

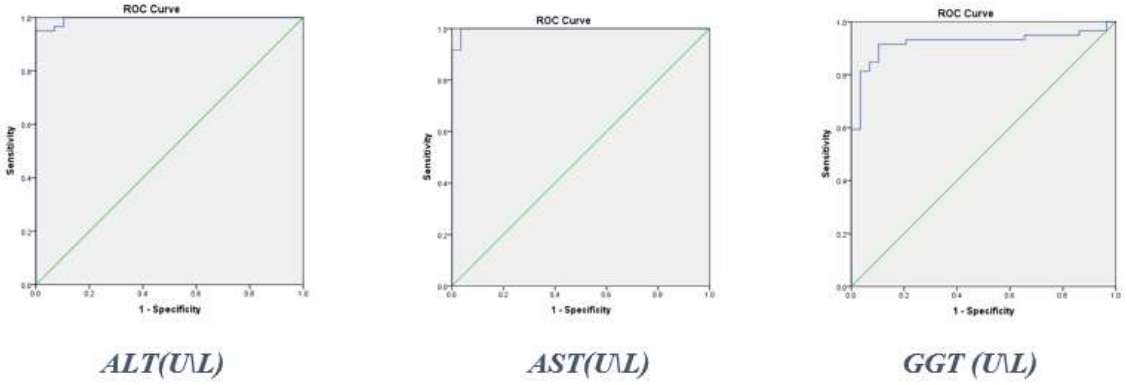

Figure 3: ROC curves for GGT, AST, and ALT in patients.

Discussion

Worldwide, the most prevalent cause of chronic liver disease in developed nations is NAFLD. It's thought that NAFLD represents the metabolic syndrome's hepatic expression. It can progress from simple fatty liver to steatohepatitis (15).

This present study shows a significant increase in serum concentration of lipid profile (LDL, VLDL, TG, cholesterol) and decreased serum concentration of HDL as compared with healthy individuals. This study supports the findings of Han and Ji Men's population study, which found that patients with NAFLD had lower concentrations of HDL-C and higher levels of TG, TC, and LDL-C in their serum compared to normal individuals. The study also found that the associations between fatty liver and dyslipidemia varied depending on the degree of hepatic steatosis. The degree of hepatic fat accumulation influenced the connection between dyslipidemia and fatty liver, with those who had fatty livers having more probability than those who did not. Fatty liver is a hallmark of the metabolic syndrome's hepatic presentation. In addition to other metabolic risk factors such as diabetes, obesity, and hypertension, dyslipidemia is commonly observed in patients with fatty liver disease (16). As a result of the fact that a larger proportion of our patients are obese, Khan and Reenam reported that obese NAFLD patients had more lipolysis in their adipose tissue, which may account for 60–70% of the fat that accumulates in the liver. Together with the excessive lipolysis of adipose tissue, adipocytes produce hormones abnormally (e.g., decreased adiponectin production),

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which exacerbates adipose tissue inflammation (e.g., pro-inflammatory cytokines are released). The enhancement of insulin resistance (IR), which results in ectopic fat deposition, is facilitated by all of these variables (17).

From another point of view, Méndez-Sánchez and Nahum reported in fundamental studies that cholesterol crystals, which are lipid droplets possessing a significant birefringence under polarized light, are exclusively found in NASH models and not in cases of simple steatosis. These circumstances cause activated Kupffer cells (KCs) to gather around cholesterol crystals to form "crown-like structures," which are closely linked to the growth of foam cells and, consequently, atherosclerosis (18). Reduced plasma HDL levels are typically associated with insulin-resistant states. This relationship can be explained by the following mechanism: In the presence of normal cholesteryl ester transfer protein activity and increased plasma VLDL concentrations, VLDL TG can be substituted for HDL cholesterol. In this mechanism, an HDL cholesteryl ester molecule is exchanged for a TG molecule by a VLDL particle with an HDL particle. An atherogenic, cholesterol-rich VLDL remnant particle and an HDL particle with a high TG content but a low cholesterol content are produced by this process (19). The TG-rich HDL particle will subsequently undergo additional changes, such as the hydrolysis of its TG, which will cause the apoA-1 protein to disassociate. As a result, because free apoA-1 leaves the plasma more quickly than apoA-1 bound to HDL particles, there will be a decrease in the amount of circulating apoA-1, HDL cholesterol, and HDL particle count (20).

The present study shows elevated levels of liver function enzymes (AST, ALT, GGT) as compared to control groups this agrees with Xie, Ruijie, and Mingjiang Liu (21) and Fontes-Cal and Tereza who reported AST, ALT, and GGT values in liver enzyme tests were considerably higher in NAFL and NASH patients than in the control group. A 64,5% prevalence of individuals with altered liver enzyme profiles were classified as NAFL or NASH, with the NASH category having a higher prevalence (80%) (22).

Conclusions

Compared to healthy individuals, the patient group in this study showed abnormally high liver enzyme and lipid profiles and significantly lower HDL. Moreover, AST, ALT, and GGT were highly sensitive and specific in predicting NAFLD.

Recommendations

It is recommended to increase the number of participants to obtain accurate results, and assess insulin resistance and evaluate the relationship between it and the incidence of NAFLD. In addition, it is important to determine the role of the drugs on the advancement of NFLAD.

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

Ethical Clearance: Official approval has been obtained to use data and data were analyzed without the names to protect privacy. 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. 2024AHJ838).

Conflict of Interest: Non

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العلاقة بين مستوى الدهون وانزيمات وظائف الكبد لدى مرضى الكبد الدهني الغير كحولي

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الملخص

خلفية الدراسة: مرض الكبد الدهني غير الكحولي هو مرض الكبد الأيضي الذي يتميز بمجموعة واسعة من أمراض الكبد، بما في ذلك التليف والتهاب الكبد الدهني والتنكس الدهني البسيط ويمكن أن يؤدي إلى تليف الكبد وسرطان الكبد. لقد برز مرض الكبد الدهني غير الكحولي باعتباره مصدر قلق للصحة العامة في الدول خلال العشرين عامًا الماضية، وقد تم ربطه بمتلازمة التمثيل الغذائي، داء السكري من النوع ٢، والسمنة واضطراب شحميات الدم. زيادة الأنسجة الدهنية الحشوية لدى الأشخاص الذين يعانون من السمنة المفرطة يمكن أن تسبب مقاومة الأنسولين وفرط أنسولين الدم، مما يؤدي إلى تسريع تحلل الدهون في الأنسجة الدهنية. ويشارك الالتهاب المزمن منخفض الدرجة المرتبط بالسمية الدهنية في تطور المرض الكبد الدهني الغير الكحولي.

اهداف الدراسة: تحديد العلاقة بين مستوى الدهون وانزيمات وضائف الكبد لدى المرضى الذين يعانون من مرض الكبد الدهني الغير الكحولي.

المرضى والطرائق: أجريت دراسة في مستشفى تكريت التعليمي في الفترة ما بين ٢٨ تشرين الثاني (نوفمبر) ٢٠٢٣ و٢٨ كانون الأول (ديسمبر) ٢٠٢٣. وشملت الدراسة ٩٠ مشاركاً، تم تشخيص ٦٠ منهم بمرض الكبد الهني لبغير الكحولي وكان ٣٠ منهم بصحة جيدة. استخدمت الدراسة مقياس الطيف الضوئي ومجموعة قياس الألوان من المواد الكيميائية الخطية الإسبانية لتحديد المعلمات المختلفة، مثل AST وALT وGGT وHDL وLDL وVLDL وTG والكوليسترول.

النتائج: كان متوسط عمر المرضى في المجموعة ٤٠,٩٣ سنة، وتتراوح أعمارهم بين ٢٠ إلى ٥٠ سنة. تم قياس ومقارنة مستويات إنزيمات وظائف الكبد (GGT، AST، ALT) ومستويات الدهون (TG. HDL، LDL. VLDL، الكوليسترول) مع أفراد السيطرة. كان لدى المرضى الذين يعانون من الكبد الدهني الغير كحولي ارتفاع ملحوظ في إنزيمات وظائف الكبد في الدم وزيادة في مستوى الدهون في الدم (TG، VLDL، LDL، والكوليسترول) بينما أظهروا انخفاضًا ملحوظًا في تركيز HDL لدى الأفراد الأصحاء. عند مقارنتها بالمجموعة الضابطة.

الاستنتاجات: أظهر المرضى زيادة غير طبيعية في مستويات إنزيمات الكبد ومستوى الدهون (LDL، VLDL، TG، الكوليسترول) مع انخفاض HDL مقارنة بالأصحاء.

الكلمات المفتاحية: الكبد الدهني الغير الكحولي، انزيمات وضائف الكبد، الملف الدهني.

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The Effect of Osteocalcin in Middle-Age Women With and Without Type2 Diabetes Mellitus

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Abstract

Background: Diabetes mellitus is a chronic disease that affects people of all ages. It's caused by deficiencies in insulin action and secretion, leading to long-term hyperglycemia. This can harm key organs such as the kidneys, heart, eyes, nerves, and blood vessels. Managing diabetes requires significant lifestyle changes and can impact both the patient and their family. Small and bone-specific, osteocalcin (OCN) is a non-collagen protein that is mostly present in bone. It is a sensitive marker of bone formation and primarily attaches to the extracellular matrix of bone after being carboxylated. Small amounts of OCN are also released into the bloodstream, where it aids in glucose and fat metabolism.

Objective: Our study aimed to examine the effect of Osteocalcin, Parathyroid hormone, Estrogen and HbA1c on middle-aged women who had type 2 diabetes compared to those who did not.

Patients and Methods: The study involved 90 middle-aged women, including 60 with type 2 diabetes, and 30 healthy women. The Sandwich enzyme-linked immunosorbent assay was used to measure OCN, PTH, and E2 hormone levels in women with and without type 2 diabetes. HbA1c levels were measured using the Cobos system. The statistical analysis was performed using SPSS software.

Results: In T2DM women, serum OCN, PTH, E2, and HbA1c levels were compared with non-diabetic women. T2DM women had significantly lower levels of serum OCN and PTH, and significantly higher levels of HbA1c than healthy women. Serum E2 levels were also significantly lower in T2DM women. OCN had a positive correlation with HbA1c and negative correlations with PTH and E2.

Conclusion: Significant change was detected in this study in the level of OCN, PTH and E2 between patients and controls. Investigations of serum OCN can be participated in the future as predictive marker for osteoporosis in diabetic women.

Keywords: Osteocalcin, parathyroid hormone, estrogen, Type2 diabetes mellitus.

Introduction

Elevated blood glucose levels are an indication of diabetes mellitus (DM), a long-term metabolic disorder that affects the kidneys, heart, eyes, nerves, and blood vessels gradually. The primary causes of the condition are either abnormal insulin production, insulin

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resistance, or most frequently both (1). Diabetes mellitus type 2(T2DM), also known as adult-onset diabetes, can affect individuals of any age, even children. Conversely, older and middle-aged adults are more likely to have T2DM. Obese and sedentary individuals are more likely to develop T2DM (2). The pathophysiology involves a complex interaction between environmental and genetic factors that results in the development of insulin resistance and β-cell failure (3). The molecular processes involved in the synthesis and release of insulin, as well as the insulin response in tissues, must be tightly controlled for insulin release and action to accurately correspond to the metabolic demand. Consequently, abnormalities in any of the underlying mechanisms may result in a metabolic imbalance and the development of T2DM (4). As the disease progresses, insulin secretion is unable to maintain glucose homeostasis, which results in hyperglycemia. Hyperglycemia is related to cellular oxidative stress through the production of advanced glycation end products, insulin resistance, dyslipidemia, and chronic inflammation (5) . Untreated hyperglycemia can cause serious, life-threatening complications such as kidney damage, eye damage, nerve damage, heart disease, and peripheral vascular disease (6). Hyperglycemia and the accumulation of advanced glycation end products are likely significant factors in the development of reduced bone strength, similar to other diabetic complications (7). To varying degrees, T2DM can affect osteocyte function and bone resorption, remodeling, and formation (8). Research has shown that prolonged high blood sugar levels can increase the levels of advanced glycation end products (AGEs) in bone collagen. This can affect osteoblasts' ability to bind to the collagen matrix, develop, and perform their regular functions (9).

Osteocalcin (OCN), or bone γ-carboxyglutamic acid (Gla) protein, is a circulating protein produced by osteoblasts. It contains three γ-carboxyglutamic acid residues at positions 13, 17, and 20 (10). OCN, which is derived from bone, controls parasympathetic tone, muscle mass, brain development and functions, testosterone synthesis, and glucose metabolism (11). Osteoblasts produce OCN, which is non-collagenous, exists in two forms: the carboxylated form, which binds calcium, and the uncarboxylated form, which is a circulating hormone, this hormone has been shown to improve beta-cell function, insulin responsiveness, and the secretion of adiponectin and insulin (12). The majority of OCN remains in bone tissue where it contributes to bone matrix formation, modifies hydroxyapatite and bone mineralization and binds to calcium and hydroxyapatite in the bone matrix (13). It has been demonstrated that OCN enhances insulin sensitivity in adipocytes by promoting adipocyte expression of adiponectin and increasing insulin synthesis in pancreatic β-cells from Langerhans islets (14). Low levels of OCN have been repeatedly associated with T2DM, elevated blood glucose, and insulin resistance, while higher levels have been linked to improved glucose tolerance and insulin sensitivity (15). OCN helps to increase the uptake and breakdown of glucose and fatty acids in muscles during exercise, promoting adaptation to physical activity, this can improve insulin secretion and sensitivity,

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which helps prevent diabetes, according to studies done on animal models. OCN triggers the activation of GPCR6A, a member of the G protein-coupled receptor family, which then functions on β-cells and muscles. Osteoblasts, which produce and release OCN and have insulin receptors, are directly influenced by insulin (16).

The concentration of OCN in the blood changes with age as bone turnover changes (17), during infancy and adolescence, bone growth requires the highest activity of osteoblasts and a high rate of bone remodeling. Consequently, during these periods, the serum levels of OCN are higher. In adults, a meta-analysis revealed significant differences in total OCN serum concentrations between healthy subjects and those with T2DM (18).

The parathyroid gland secretes a hormone called parathyroid hormone (PTH) when the levels of calcium ions in the blood become low. When PTH binds to its receptor, PTHR1, which is mainly expressed in osteoblasts, it activates a G protein-family coupled receptor (GPCR) resulting in increased bone turnover, ultimately restoring the levels of calcium ions in the blood to normal (19). The unique effects of PTH on bone metabolism are due to its mechanism for regulating the balance of calcium and phosphorus. PTH can cause bone resorption when it is continuously stimulated, but it can also promote bone formation when the stimulation is intermittent, as per certain research findings (20). PTH plays a crucial role in regulating bone turnover by facilitating OCN production. The low bone turnover seen in T2DM patients may be due to the suppression of PTH, which impedes both bone formation and OCN production (21). The effect of OCN on middle-aged women with and without T2DM will be covered in this study, along with any relationships between PTH and E2 levels and whether OCN levels can be used as a predictor of osteoporosis in diabetic women

Patients and Methods

A case-control study at the Endocrinology and Diabetic Center and Al Mahmudyia General Hospital involved ninety Iraqi women in their 40s to 50s. Thirty of the ninety participants were healthy controls, and sixty of the women had been diagnosed with T2DM. All patient data, including height, weight, age, medical history, and any complications from diabetes, were recorded for the study. The research was conducted from November 29, 2023, to December 30, 2023.

For ten minutes, the blood samples were centrifuged at 4000 rpm. An ELISA (Enzyme Linked Immunoassay Analysis) analyzer was used to examine the serum sample of OCN, PTH and E2. OCN, PTH, and E2 were determined using human USA kits while HbA1c wsa estimated Roche\Germany kit using the Cobos C111 system.

ELISA Principle

ELISAs (Enzyme-Linked Immunosorbent Assays) are typically conducted in 96-well polystyrene plates. In this process, serum samples of (OCN, PTH or E2) are incubated in each well, with each well containing a different serum sample. Among the 96 samples, one well is reserved for a positive control serum, and another for a negative control serum. Antibodies or antigens present in the serum are captured by corresponding antigens or antibodies that are coated onto the solid surface of the wells.

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After the incubation period, the plate is washed to remove unbound serum, antibodies, or antigens using a series of wash buffers. To detect the bound antibodies or antigens, secondary antibodies that are conjugated to enzymes, such as peroxidase or alkaline phosphatase, are added to each well. Following another incubation period, any unbound secondary antibodies are washed away. Finally, a suitable substrate is added, and the enzyme reacts with it to produce a color change. This color change can be measured, providing a quantitative assessment of the antigens or antibodies present in the sample. The intensity of the color, measured at 450 nm, indicates the amount of antigen or antibody present.sent in serum are captured by corresponding antigen or antibody coated on to the solid surface. After some time, the plate is washed to remove serum and unbound antibodies or antigens with a series of wash buffer. To detect the bound antibodies or antigens, a secondary antibodies that are attached to an enzyme such as peroxidase or alkaline phosphatase are added to each well. After an incubation period, the unbound secondary antibodies are washed off. When a suitable substrate is added, the enzyme reacts with it to produce a color. This color produced is measurable as a function or quantity of antigens or antibodies present in the given sample. The intensity of color/ optical density is measured at 450nm. The intensity of the color gives an indication of the amount of antigen or antibody.

Statistical Analysis

Using SPSS, the data analysis was carried out. P-values <0.05 are regarded as significant, and P-value > 0.05 is considered non-significant.

Results

Demographic and clinical characteristics

This study involved a total of 90 participants, with 60 of them being patients and 30 controls. The study groups were carefully classified into subgroups based on age, duration of disease, and BMI, and the findings have been presented in Table 1. The results indicate that 46.6% of participants were aged between 48 and 50, while 26.7% of patients were aged between 40-43 and 44-47, and it is worth noting that the participants' BMI range was higher in comparison to other groups, at 61.67. As shown in Table 1, the majority of patients (52%) have been suffering from the disease for one to five years.

Table (1): Descriptive of the demographic characteristics of the study population (N=90).

Variable	Groups	Patient N=60	Control N=30
Age. Groups	40-43 Years	16%	13%
	44-47 Years	16%	8%
	48-50 Years	28%	9%
BMI. Groups	Normal weight	3%	15%
	Over weight	20%	10%
	Obesity	37%	5%
Duration of disease	Less than one years	5%	/
	1-5 Years	31%	/
	More than 5 Years	24%	/

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Examination the level of OCN in women with T2DM group compared to the control group.

Type 2 diabetes patients have lower OCN levels than healthy individuals, as per the results shown in Figure 1. The mean levels of OCN in patients were (4.29 ± 1.13) ng/ml, significantly lower than the Control group (8.21 ± 2.23) ng/ml, with a p-value of ≤ 0.001. Control group (8.21 ± 2.23) ng/ml, with a p-value of ≤ 0.001.

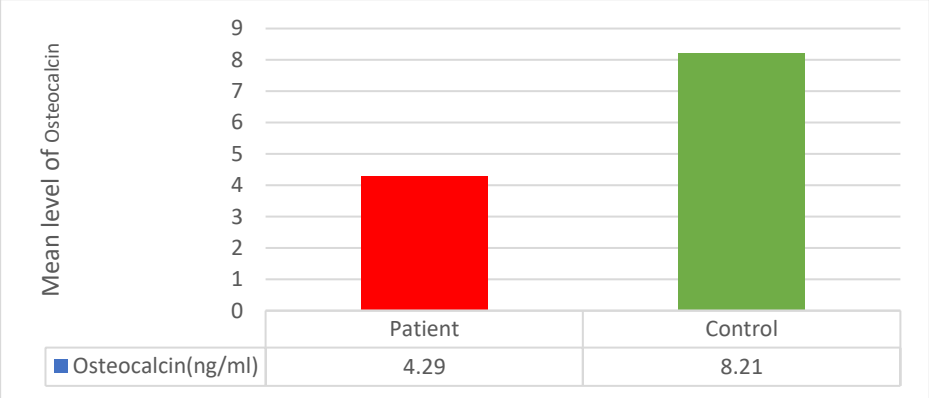

Figure (1): Results of the analysis of OCN in women with T2DM compared to control groups.

Examination the level of supporting parameters indices in women with T2DM for patients with control groups

In this study, we compared the T2DM indices of patients to healthy controls. HbA1c levels in the patient group were significantly higher than in the control group, while PTH and E2 levels were lower. All parameters showed high statistical significance (p<0.001) as seen in Figure 2.

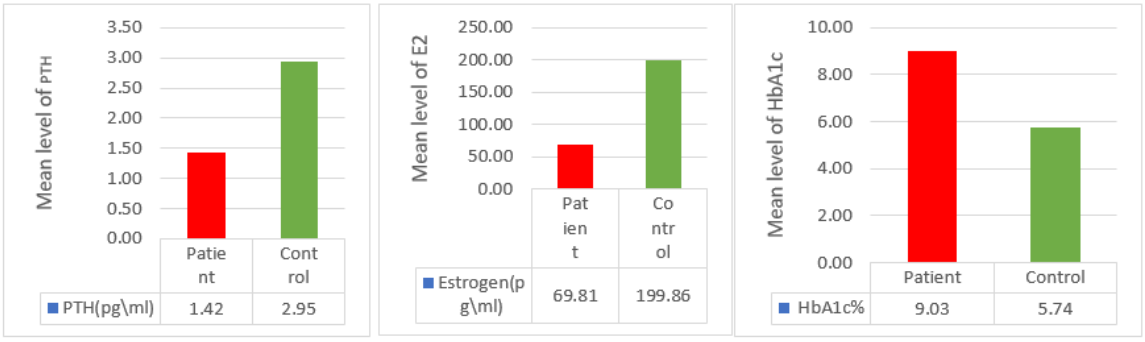

Figure (2): Results of the analysis of supporting parameters in women with T2DM compared to control.

Correlation

The correlation coefficient was used for determining linear relationships with OCN for E2, PTH and HbA1c in women Patients with T2DM.

The results showed that there was a highly statistically significant correlation between OCN and others (p = <0.001), as shown in Figure (3).

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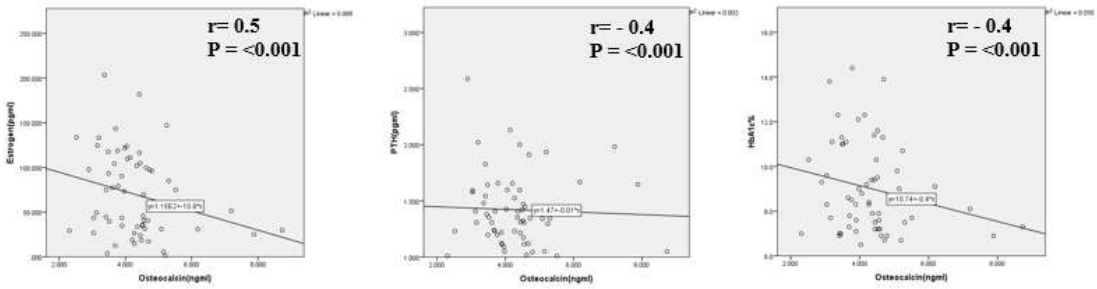

Figure (3): Simple linear regression between OCN and supporting parameters in women with T2DM.

Receiver Operating Characteristic Analysis

Results of the receiver operating curve (ROC) curve and area under curve (AUC) analysis for the OCN as diagnostic parameters were done OCN showed a good performance in predicting T2DM compared to the control group; data are presented in Table (2). For OCN levels: (sensitivity = 93.3 %, specificity 91.7%) at a level = 5.3595, the p-values of the AUC were <0.001 and highly statistically significant, as shown in table (2). The p-values of the AUC were <0.001 and statistically significant. Youden's J statistics for the parameters in Figure (4) confirm these results.

Table (2): The AUC, threshold, sensitivity, and specificity were determined using ROC curves in the study population.

Variable(s)	AUC	Sensitivity %	Specificity %	Youden index	Cut-off points	CI (95%)	PPV	NPV	P value
OCN (ng\ml)	91.70 %	93.30%	91.70%	0.85	5.3595	0.830-1.000	90%	88%	<0.001[S]

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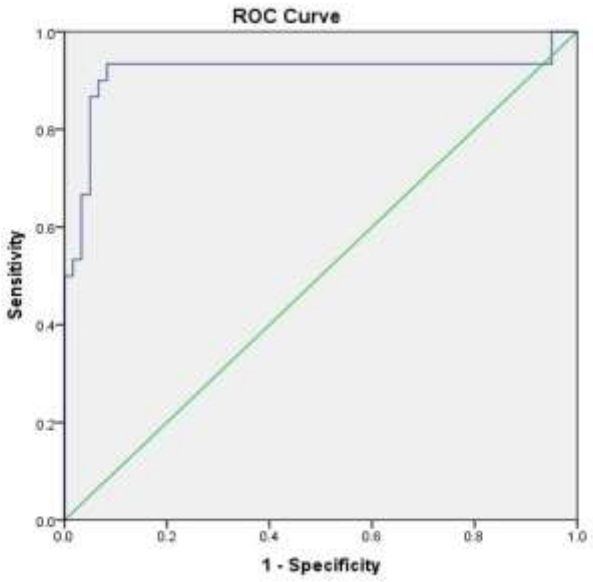

Figure (4): ROC curves for OCN in women with T2DM compared to the control group.

Discussion

The presented case-control study included 60 women (40-50) years of age with T2DM compared to 30 healthy control women. The serum OCN level was highly significantly decreased in patients compared to control women ($p<0.001$). The study findings indicate that osteocalcin (OCN) is associated with the glycemic state in patients with type 2 diabetes mellitus (T2DM). This aligns with previous research that revealed a negative correlation between OCN levels and the progression of T2DM as well as glycosylated hemoglobin (HbA1c) (22) .

Our research indicated that the average HbA1c levels measured in the patient group were significantly higher than those of the healthy control group, and that there was a strong statistical correlation between OCN and HbA1c ($r=-0.4$, $p<0.001$), This is consistent with earlier studies showing that higher HbA1c levels correlate with lower serum vitamin D3 and OCN concentrations (23). This suggests that poor glucose management negatively affects bone growth, leading to an imbalance in bone metabolism which results in increased resorption and a higher risk of osteoporosis. Previous study revealed that patients with poorly controlled blood glucose levels had lower levels of OCN compared to those with well-controlled blood glucose levels (24). The presented study also revealed a significant negative correlation between OCN and HbA1c, indicating a relationship between worsening glucose metabolism and lower OCN levels. This aligns with previous research, revealed that the level of OCN did not show any significant difference between the pre-diabetes and normal glucose tolerance (NGT) groups, however, the pre-diabetes group had a slightly higher level of OCN than the NGT group, suggesting that the plasma OCN levels remain unchanged until diabetes develops (25). During the pre-diabetes state, when more insulin is initially secreted in pancreatic β-cells, osteoblasts may secrete more OCN to overcome a given level of insulin resistance.

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However, when insulin resistance becomes more severe, the osteoblast is unable to release enough OCN, which ultimately leads to the development of diabetes as insulin secretion decreases. Previous study demonstrated that elevated OCN levels enhance insulin sensitivity and glucose homeostasis through their effect on beta-pancreatic cells (26). Bone turnover is a significant factor affecting bone quality, and it can be identified through bone metabolic markers. Studies have revealed that individuals with T2DM have lower levels of OCN, a biochemical marker of bone formation, in their serum as compared to those without T2DM, this suggests that bone formation is suppressed in T2DM patients in comparison to non-T2DM controls (27). A previous study observed low bone turnover in patients with T2DM, which could be attributed to low levels of PTH, responsible for the production of OCN and bone formation (21). Our study also supports these findings as we observed a significant decrease in both OCN and PTH levels. PTH plays a vital role in regulating bone turnover by supporting OCN production. Previous studies have shown that individuals who have T2DM and poor glycaemic control tend to have lower levels of PTH in their serum, which can negatively impact the activity of osteoblasts and lead to demineralization of bones (28). This suggests that there is a correlation between HbA1c levels and PTH levels in diabetic patients. There is a relationship between T2DM and the hormone called 17β-estradiol (estradiol), which is E2 hormone. Estradiol helps to protect β-pancreatic cells from apoptosis during hormone reproduction, which in turn helps to prevent insulin insufficiency. As a result, women have a lower incidence of diabetes because female sex steroids, rather than male hormones, protect against pancreatic β-cell injury. A previous study found that women over 46 years old had higher levels of estradiol compared to those under 45 (29). According to the presented study, women with T2DM have significantly lower levels of E2 than healthy women ($p<0.001$), this finding aligns with prior research, indicating that reduced levels of estradiol due to aging are a significant contributor to osteoporosis in older women (30). Since E2 deficiency can lead to bone loss, which is the primary cause of osteoporosis, hormone therapy has been considered an optional treatment for postmenopausal women to prevent osteoporosis.

E2 plays a crucial role in regulating the expression of hormones that affect bone metabolism. This includes increasing the secretion of calcitonin and enhancing the levels of vitamin D_3 (due to increased renal 1 alpha-hydroxylase and 25-hydroxylase activity). Additionally, E2 can prevent the secretion of PTH by lowering the level at which it responds to blood calcium. Any malfunctions in these regulatory factors can lead to abnormal mineralization or bone structure, which may result in conditions like osteoporosis or fractures (31). The presented study shows a significant correlation ($r=0.5$, $p<0.001$) between OCN and E2 levels. This can be attributed to the impact of low E2 on OCN-secreting bone osteoblasts. It was

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previously thought that while androgens promote bone formation, E2 inhibit it, giving men a higher bone density than women. Because E2 regulates the expression of its receptors, T2DM is associated with a decrease in E2 receptors (ERs), which may lead to impaired bone metabolism. Research has indicated that postmenopausal women may experience gradual deterioration of glucose tolerance, a decline in bone mass density, and an increase in bone turnover due to E2 deficiency (32).

Conclusions

It has been found that middle-aged women with T2DM are more prone to developing osteoporosis as compared to healthy women. This is because of lower levels of OCN, E2, and PTH, all of which have a significant impact on bone health. T2DM leads to a decrease in circulating OCN concentration due to a negative correlation between HbA1c and OCN. This suggests that patients with T2DM have less bone turnover and remodeling.

Recommendations

It was recommended to measure OCN levels of women in various stages of life, such as pre-menopause, menopause, and post-menopause, and measure the level of adiponectin. In addition, it is important for the future study to be done on a larger sample size to give results that are more accurate.

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Ethical Clearance: Official approval has been obtained to use data and data were analyzed without the names to protect privacy. 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. 2024HIJ837).

Conflict of Interest: Non

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تأثير الاوستيوكالسين في النساء متوسطات العمر المصابات وغير المصابات بالسكري النوع الثاني

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الملخص

خلفية الدراسة: مرض السكري هو مرض مزمن يصيب الاشخاص في جميع الاعمار وينجم عن قصور في عمل الانسولين و افرازه مما يؤدي الى ارتفاع السكر في الدم على المدى الطويل. مرض السكري ممكن يضر الاعضاء الرئيسية مثل الكلى والقلب والعينين والاوعية الدموية. تتطلب السيطرة على مرض السكري تغييرات كبيرة في نمط الحياة وممن ان تؤثر على المرض وعائلته. الاوستيوكالسين هو بروتين غير كلايكوجيني صغير مختص بالعظم ويوجد غالبا فيها.وهو علامة حساسة لتكوين العظام ويرتبط بشكل اساسي بالمصفوفة الخارجية لخلايا العظم بعد كاربوكسليته, كما يتم اطلاق كميات صغيرة من هذا البروتين في الدم حيت يساعد في ايض السكريات والدهون.

اهداف الدراسة: هدفت دراستنا إلى فحص تأثير Osteocalcin و Parathyroid hormone و Estrogen و HbA1cعلى النساء في منتصف العمر المصابات بداء السكري من النوع ٢ مقارنة بأولئك اللاتي لم يعانين منه.

المرضى والطرائق: أجريت دراسة الحالات والشواهد على تسعين امرأة في منتصف العمر (٤٠-٥٠) وستين امرأة مصابة بداء السكري من النوع ٢ (ن = ٦٠)، وثلاثين امرأة صحية (ن = ٣٠) ليس لديهن مرض السكري من النوع ٢ ، ٤٥,٨٨ كان المستوى المتوسط لعمر المشارك في هذه الدراسة. بالمقارنة مع النساء الأصحاء وغير المصابات بالسكري، قامت الدراسة بقياس مستويات OCN و PTHو E2لدى النساء في منتصف العمر المصابات أو غير المصابات بداء السكري من النوع ٢. تم تقدير مستوى OCN و PTHو E2في المصل بواسطة مقايسة الامتصاص المناعي المرتبط بإنزيم ساندويتش بينما تم تقدير HbAlc بواسطة نظام Cobos C111 .تم إجراء الفحص الإحصائي بواسطة برنامجSPSS

النتائج: في النساء المصابات بمرض السكري النوع الثاني, تمت مقارنة مستويات OCN و PTHوE2 و HbA1c في الدم مع النساء الاصحاء غير المصابات بالسكري. كان لدى النساء المصابات بالسكري النوع الثاني مستويات قليلة من OCN وPTH وE2 في الدم, ومستويات عالية من HbA1c مقارنة بالنساء الاصحاء. كان لل OCNعلاقة ايجابية مع HbA1c وارتباطات سلبية مع PTH و E2.

الاستنتاجات: تم الكشف عن تغير كبير في هذه الدراسة في مستوى OCN، PTH وE2 بين المرضى والمجموعة الضابطة. يمكن المشاركة في تحقيقات مصل OCN في المستقبل كعلامة تنبؤية لهشاشة العظام لدى النساء المصابات بالسكريز

الكلمات المفتاحية: الاوستيوكالسين, هرمون الغدة الجارادرقية, الاستروجين, مرض السكري النوع الثاني

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Comparative Study of Cardiac Radiation Dose With Different Types of Surgery in Breast Cancer Patients

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Abstract

Background: It has been demonstrated that radiation therapy lowers both the death rate from breast cancer and its recurrence. Precise calculation of the radiation dose is crucial for treating the target site as well as protecting vital organs like the heart since large doses of radiation therapy significantly increase patient morbidity and death.

Objective: To compare the mean heart dose of radiation in breast cancer patients between breast-conserving surgery versus mastectomy, between different radiotherapy doses and fractionation schedules, and between right and left breast cancer irradiation.

Patients and Methods: This is a cross-sectional descriptive retrospective comparative study that was conducted in Baghdad Radiotherapy Center from January 2018 to June 2018, carried on 174 breast cancer patients of different age groups selected randomly and their mean heart dose data collected from their files and database in Baghdad Radiotherapy Center.

Results: The overall average of the mean dose was 372 cGy (range from 76.4 to 716.2). The greatest difference in the mean heart dose was between (BCS) patients who received 5000 cGy with regional nodal irradiation and (BCS) patients who received 4005 cGy also with regional nodal irradiation (difference in the mean is 639.8, the P – value <0.001). Regarding the side of breast cancer, the greatest difference in mean heart dose was seen between left and right breast cancer patients who did the same type of surgery (MRM) and received the same dose of radiotherapy (4256 cGy) (difference in the mean is 565cGy and the P – value <0.001). No statistically significant difference in the mean dose between breast-conserving surgery and mastectomy was recorded.

Conclusion: The mean heart dose of radiotherapy is significantly increased in left-sided breast cancer irradiation as compared to the right side. A dose of 5000 cGy has the greatest effect on the dose received by the heart, especially in left breast cancer. The type of surgery whether breast-conserving surgery or mastectomy did not affect the mean dose received by the heart.

Keywords: Breast cancer, cardiac radiation dose, breast cancer surgery, breast cancer treatment.

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Introduction

A modified radical mastectomy typically includes an axillary node dissection in addition to the removal of the entire breast, nipple, and areola (1). Following breast-conserving surgery (BCS), adjuvant whole-breast radiotherapy (RT) is usual and has been demonstrated to decrease the incidence of local recurrence among all subgroups of women (2). Given that multiple single trials have demonstrated a survival benefit for post-mastectomy radiation therapy (RT), women who are at high risk of local recurrence (T3–T4, > 4 positive lymph nodes, and excision margin < 1 mm) should be routinely administered RT following mastectomy (3). The standard modern technique for definitive radiation therapy for early-stage breast cancer is three-dimensional radiation therapy (3D CRT) with appropriate compensation using an intensity-modulated radiation therapy (IMRT) or field-in-field technique to provide a homogeneous dose to the breast tissue. It was shown that all breast tissue should be included in these fields, which should be collimated to run parallel to the chest wall. Angles of the gantry, collimation, and Cerrobend blocks or the multileaf collimator (MLC) are the greatest ways to treat breast tissue without damaging the heart or lungs. Wedges are a compensatory tool used by some centers (4). Breath-hold is a technique that is being used more frequently for patients with left-sided breast cancer. It involves the patient taking a deep breath and holding it for a brief period (30 to 1 minute). This technique allows the heart to be moved away from the chest wall, which frequently results in better cardiac sparing and better breast/chest wall coverage (5). The internal organs at Cerrobend blocks or the multileaf collimator (MLC) are the greatest ways to treat breast tissue without damaging the heart or lungs. The heart and lungs are at risk (OAR; treatment is limited to the left side). Within the START and FAST-Forward studies, dose limitations for the heart and lung have been established (6). The use of dose-volume histogram (DVH) criteria to assess treatment plans is still being studied. The mean cardiac dosage and the risk of cardiac events have a linear, no-threshold relationship, which is supported by population-based data. This suggests that the cardiac dose should be kept as low as is practical (7). For women with tumors in the left breast, the estimated mean doses of radiation to the heart were 6.6 Gy on average, 2.9 Gy for those with tumors in the right breast, and 4.9 Gy overall. For every 1 Gy increase in the mean radiation dose administered to the heart (95% CI, 2.9 to 14.5; P<0.001), the rate of major coronary events increased by 7.4%. (7, 8). There is less evidence of cardiac toxicity from more recent trials that used methods to restrict exposure to normal cardiac and pulmonary tissues (9). Pericarditis was the most frequent symptom, and it became a serious issue when extensive areas of the heart, or the pericardium, were exposed to doses greater than 40 Gy (10). Very few incidences of coronary artery disease that could be linked to radiation were found in the initial research. But radiation-induced heart disease (RIHD) is the umbrella term for a variety of conditions that can be brought on by radiation exposure; these conditions include arrhythmias, pericarditis, cardiomyopathy, coronary artery disease, pericardial effusions or constriction, and

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valvular illness (11). It can impact any one of the heart's anatomical structures. Pericarditis with effusion in the pericardium has been reported, either in conjunction with or apart from constrictive pericarditis. Due to fibrosis and macroangiopathy in the myocardium, cardiomyopathy may develop, which will ultimately result in heart failure. Radiation therapy to the arteries may hasten atherosclerosis and result in carotid and coronary artery disease, which raises the risk of ischemic stroke and IHD, respectively (12, 13). The EBCTCG meta-analyses and the early randomized radiation trials demonstrated a decline in breast cancer deaths that was offset by an increase in cardiovascular mortality (14). Compared to right-sided breast cancer, left-sided breast cancer has been linked to a greater mortality rate from IHD (14, 6, 15). The purpose of this study was to examine the mean cardiac dose of radiation from two distinct types of breast cancer operations, namely mastectomy and breast-conserving surgery, as well as the various radiation dosages utilized in the treatment of breast cancer and the distinction between radiation treatment for left and right breast cancer.

Patients and Methods

This is a cross-sectional retrospective descriptive comparative study that was conducted in Baghdad Radiotherapy Center from January 2018 to June 2018, carried on 174 breast cancer patients of different age groups, and their data was collected from their files and database in Baghdad Radiotherapy Center. The patients enrolled in this study have already been diagnosed with breast cancer and received radiotherapy in our center, the majority of patients were females 170 and only 4 males, their ages ranged from 18 to 77 years old with a mean age of 47.5 years. All the data are obtained from the patient file database in our center and the radiation data from the MOSAIQ system for the mean heart radiation dose for each patient. The patients in this study underwent full staging to exclude secondary metastasis before starting the treatment and then managed by neoadjuvant chemotherapy at the start or surgery either breast-conserving surgery or with modified radical mastectomy both with axillary lymph node sampling or dissection, then followed by adjuvant chemotherapy if indicated for each case with or without hormonal treatment, and radiotherapy is given for them according to their indication to the chest wall with or without axillary irradiation.

Patients excluded from the study are those with:

- Recurrent disease
- Bilateral disease
- Those with bolus used

Those with boost to tumor bed (if the patient has boost then the heart dose is taken with the boost dose). The 174 patients are divided into two groups:

Breast-conserving surgery: 81 patients further divided into two different radiation doses and two different sides (right and left):

- 5000 cGy includes 50 patients subdivided into: the right side with lymph node irradiation 18, without lymph node irradiation 10, and the left side with lymph node irradiation 9, without lymph node irradiation 13.
- 4005 cGy includes 31 patients subdivided into: the right side with lymph node irradiation 12, without lymph node irradiation 6, and the

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left side with lymph node irradiation 7, without lymph node irradiation 6.

Modified radical mastectomy and axillary dissection: 93 patients further divided into two radiation doses and two different sides (right and left):

- 4256 cGy include 50 patients, all with lymphatic irradiation subdivided into: right side 20 and left side 30.
- 4005 cGy includes 43 patients, all with lymphatic irradiation, also subdivided into right side 23 and left side 20.

Concerning the distribution of the patients in the study, (46.5%) of patients did BCS, and (53.5%) did MRM. For the sides of breast cancer, they were almost equally distributed between the right and left sides (51%) and (49%), respectively.

Statistical Analysis

All the data was analyzed using the Statistical Package for Social Sciences (SPSS) version 16, and all the quantitative variables were presented as mean and standard deviation, while qualitative variables were presented as frequency and percentages. One Way ANOVA test is used to evaluate the statistical difference and compare different groups. A P-value <0.05 was considered significant.

Results

Demographical data

In this study, 174 breast cancer patients were included, with their ages ranging from (18 to 77) years. The highest incidence of breast cancer was seen in the 6th decade (50 – 59) years, and their percentage (29.3%) was followed by the 5th and 7th decades equally (23.5%). whereas the lowest incidence is seen in young patients (3rd decade), as shown in Figure (1).

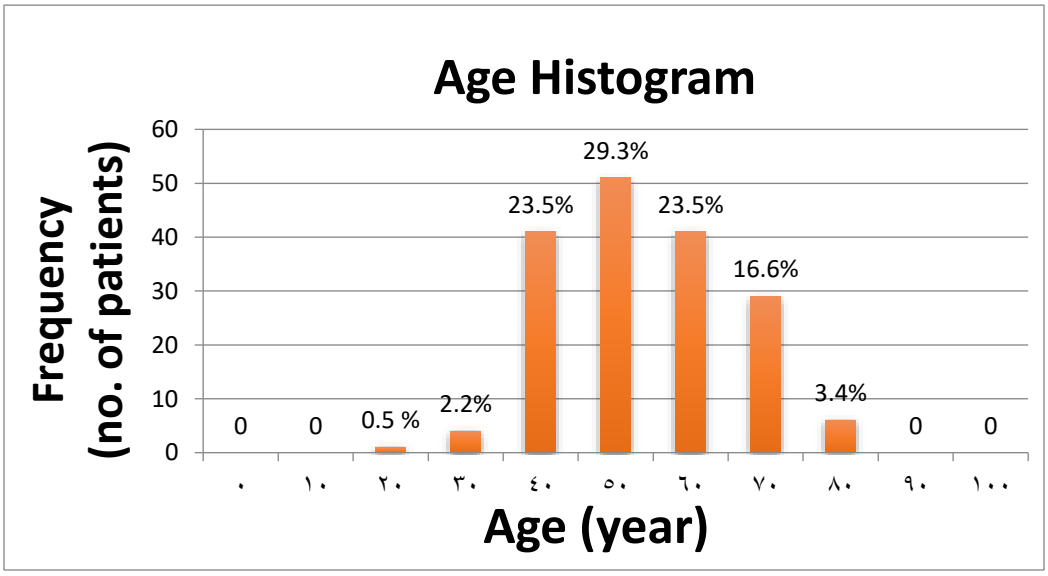

Figure (1): Age distribution in the studied breast cancer patients.

Regarding the staging of breast cancer and according to the most commonly used staging system, the American Joint Committee on Cancer (AJCC) we found that the most frequent stage regardless of the type of

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surgery was stage IIIA (T2N2M0) making about (19%) of our patients studied to be followed by stage IIIB (T2N3M0) about patients had early breast cancer, while the remaining had advanced disease. further details can be seen in Figure (2).

(15%). only a few patients (3%) had non-invasive disease (DCIS). About (30%) of

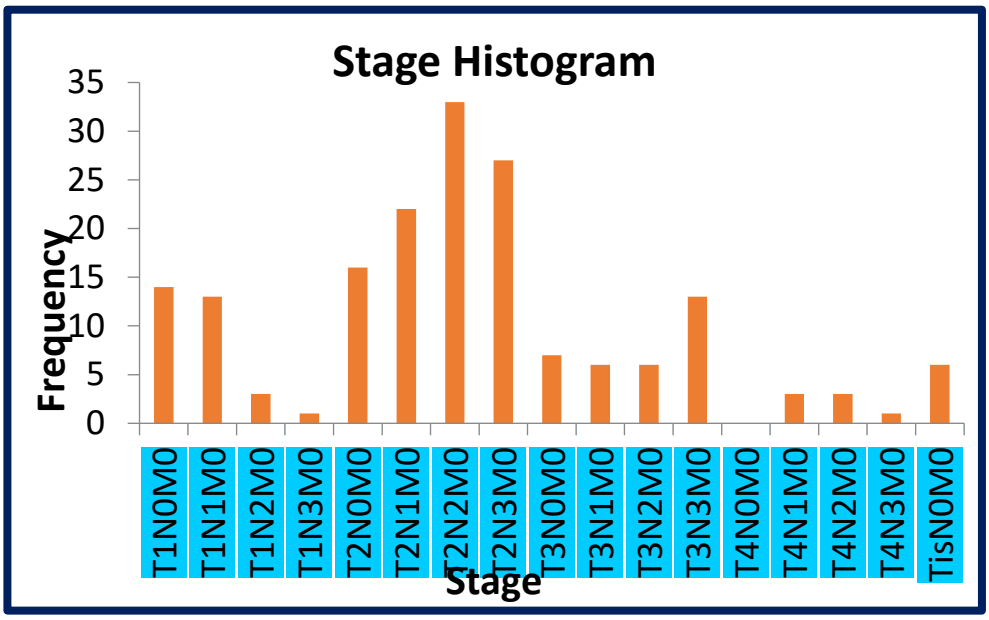

Figure (2): Stage distribution in breast cancer patients in our data collected.

Heart mean dose data

This study involved two main groups of breast cancer patients: those with breast-conserving surgery (BCS) and modified radical mastectomy (MRM); each group is further subdivided according to the dose of radiotherapy, whether regional nodal irradiation given or not and also according to the sidedness of breast cancer (right and left). The mean heart dose was calculated and compared between the different groups. In Table (1) below we see that patients with left-sided breast cancer who underwent breast-conserving surgery (BCS) and received a dose of 5000 cGy with nodal irradiation have the highest mean heart dose (716 cGy) with standard deviation (± SD 275) and confidence interval of the mean (C.I. 211), followed by patients with left-sided disease with modified radical mastectomy (MRM) who received 4256 cGy with nodal irradiation in which the mean heart dose was (658 cGy) with (± SD 199 and C.I. of mean 74). The lowest mean heart dose was seen in patients with right-sided breast cancer who did (MRM) and received a dose of 4005 cGy with nodal irradiation (mean heart dose 76 cGy with ± SD 27 and C.I. of mean 17). The overall average of the mean dose was 372 cGy (range from 76 to 716). The average mean heart dose on the left side was 627 cGy (range from 551 to 716). While the average mean heart of the right side was 117 cGy (range from 76 to 158).

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Table (1): different study groups with mean heart doses and standard deviation. BCS: breast-conserving surgery, MRM: modified radical mastectomy, YES: means L.N. irradiation, NO: without L.N. irradiation, all MRM received L.N. irradiation, RT: right, LT: left.

Column	Number of patients	Mean dose(cGy)	Std. Dev.	C.I. of Mean
BCS-4005-Yes-RT	12	76	27	17
BCS-5000-Yes-LT	9	716	275	211
BCS-5000-No-LT	13	620	262	158
MRM-4005-RT	23	130	131	56
MRM-4005-LT	20	653	231	108
MRM-4256-RT	20	93	30	14
MRM-4256-LT	30	658	199	74

* BCS: breast-conserving surgery, MRM: modified radical mastectomy, YES: means L.N. irradiation, NO: without L.N. irradiation, all MRM received L.N. irradiation, RT: right, LT: left.

The one-way analysis of the variance (one-way ANOVA) was used for testing the difference in the values of the mean heart dose and its significance, which shows that the differences in the mean values among the study groups are greater than would be expected by chance. There is a statistically significant difference (P = <0.001). Power of performed test with alpha = 0.050: 1.000. All Pairwise Multiple Comparison Procedures (Tukey Test) were used for testing the difference in the mean heart dose and its significance by comparing each group with the others and the comparison of each effective possible factor such as the type of surgery, side of breast cancer, radiotherapy dose and the lymph node irradiation. In the table (table 2) below, the test shows the greatest difference in the mean heart dose was between (BCS) patients who received 5000 cGy with nodal irradiation and (BCS) patients who received 4005 cGy also with nodal irradiation (difference in the mean is 639 cGy, the P – value <0.001). Regarding the side of breast cancer, the greatest difference in mean heart dose was seen between left and right breast cancer patients who did the same type of surgery (MRM) and received the same dose of radiotherapy (4256 cGy) (difference in the mean is 565 cGy and the P – value <0.001). The difference in the mean dose between breast-conserving surgery and mastectomy was not significant.

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Table 2: Comparison of mean heart dose for different study groups and its significance.

Comparison	Difference of Means(cGy)	number	P value	P<0.050
BCS-5000-Yes vs. BCS-4005-Yes	639	12	<0.001	Yes
BCS-5000-Yes vs. BCS-4005-No-	557	12	<0.001	Yes
MRM-4256-LT vs. MRM-4256-RT	565	12	<0.001	Yes
MRM-4256-LT vs. MRM-4005-RT	528	12	<0.001	Yes
MRM-4005-LT vs. MRM-4005-RT	523	12	<0.001	Yes
MRM-4005-LT vs. BCS-4005-No-RT	495	12	<0.001	Yes
MRM-4005-LT vs. BCS-4005-No-LT	102	12	0.983	Do Not Test
BCS-5000-No- vs. BCS-5000-Yes	503	12	<0.001	Yes
BCS-5000-No- vs. BCS-4005-No-	461	12	<0.001	Yes
BCS-4005-Yes vs. BCS-4005-No-	408	12	0.001	Yes
BCS-4005-No-LT vs. MRM-4005-RT	421	12	<0.001	Yes
BCS-4005-No-RT vs. MRM-4005-RT	28	12	1.000	Do Not Test

* BCS: breast-conserving surgery, MRM: modified radical mastectomy, YES: means L.N. irradiation, NO: without L.N. irradiation, all MRM received L.N. irradiation, RT: right, LT: left.

A result of the "Do Not Test" occurs for a comparison when no significant difference is found between two means that enclose that comparison. Also, not testing the enclosed means is a procedural rule, and a result of the Do Not Test should be treated as if there is no significant difference between the means, even though one may appear to exist.

Discussion

Increasing age is an important established risk factor for breast cancer development. In this study, 174 breast cancer patients were included with their ages ranging from (18 to 77) years, the highest incidence of breast cancer seen in the 6th decade (50 – 59) years and their percentage (29.3%) followed by the 5th and 7th decades equally (23.5%) (18). In this study, the lowest incidence was seen in young patients (3rd decade), similar to many epidemiological data, which state that sporadic breast cancer is relatively uncommon among women younger than 40 years but increases significantly thereafter (19). Due to increased screening, the majority of patients present with early-stage breast cancer, which was inconsistent with the results of this study in which the most frequent stage, regardless of the type of surgery, was stage IIIA (T2N2M0), making about (19%) of our patients studied to be followed by stage IIIB (T2N3M0) about (15%) and only about (30%) of patients had early breast cancer, while the remaining had advanced disease. The distribution of the patients in the study, (46.5%) of patients did BCS and (53.5%) did MRM, and for the doses of radiotherapy, those who received doses of (5000 cGY, 4260 cGY) were (28.8%) for each, and (42.5%) of patients received a dose of (4005 cGY). For the sides of breast cancer, they were equally distributed between the

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right and left sides (51%) and (49%), respectively. The majority of patients received lymph node irradiation (80%), and those who did not (20%) according to the stage of the disease. All the doses and fractionations of radiotherapy used in our study were the standard doses and fractionations used in many centers worldwide after publications of the randomized trials (16, 17, 18). LAD is considered to be a more important vessel at risk due to its implication in the pathogenesis of ischemic heart disease. Rates of major coronary events increased linearly with the mean dose to the heart by 7.4% per gray, with no apparent threshold. The increase started within the first 5 years after radiotherapy and continues for at least 20 years after radiotherapy. In this study, the overall average mean dose of the heart was 372 cGy (3.7Gy) (range from 76 cGy to 716 cGy), and this is considered acceptable as compared with a population-based case-control study conducted in 2168 women who underwent radiotherapy for breast cancer between 1958 and 2001 in Sweden and Denmark. Individual patient information was obtained from hospital records. For each woman, the mean radiation doses to the whole heart and the left anterior descending coronary artery were estimated from her radiotherapy chart. The overall average of the mean doses to the whole heart was 4.9 Gy (range, 0.03 to 27.72) (20). In our study we see that patients with left sided breast cancer who underwent breast conserving surgery (BCS) and received a dose of 5000 cGy with nodal irradiation have the highest mean heart dose (716) with standard deviation (± SD 275) and confidence interval of mean (C.I. 211), followed by patients with left sided disease with modified radical mastectomy (MRM) who received 4256 cGy with nodal irradiation in which the mean heart dose was (658) with (± SD 199 and C.I. of mean 74). the greatest difference in the mean heart dose was between (BCS) patients who received 5000 cGy with nodal irradiation and (BCS) patients who received 4005 cGy also with nodal irradiation (difference in the mean is 639 , the P – value <0.001) these findings are consistent with the results of prospective randomized trial conducted in Egypt at Kasr AL-ainy center of clinical oncology and nuclear medicine (NEMROCK) to assess cardiac toxicity in left sided breast cancer patients with different fractionations in two arms ; one arm using conventional fractionation (5000 cGy / 25fx / 5wks) and the other arm using hypofractionation (4256 cGy / 16fx / 3 ½ wks) 5 years after 3D conformal radiotherapy using the same planning technique that is used in our center (the breast or chest wall was treated isocentrically using 2 tangential beams with selective multileaf blocking to protect the organs at risk “heart and lung”) and the volume of the heart that received 40Gy (V40) was not allowed to exceed 30% . The results showed that cardiac dysfunction developed more in the conventional arm and concluded that hypo-fractionated radiotherapy decreased cardiac toxicity though not statistically significant (21). There are possible factors that have led to the high mean dose of the heart in left-sided breast irradiation in our study: if the distance of the heart from the chest wall is too small for some women, it was not the breath hold or respiratory gating technique or those who require internal mammary irradiation, in which the mean dose may be around 10 Gy as confirmed in many studies in which cardiac

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dose and toxicity increased with internal mammary nodal irradiation. (22). In comparison between the right and left breast cancer mean heart dose, our study showed that the average mean dose on the right side was 1.1 Gy (range from 0.7 to 1.5), and The average mean heart dose on the left side was 6.2 Gy (range from 5.5 to 7.1) which was also consistent with the population-based data which state that The mean cardiac dose from irradiation of left-sided breast cancer can be two or three times that for a right-sided breast cancer, and the Current mean doses of radiation to the heart from radiotherapy for breast cancer are typically about 1 or 2Gy for the disease of the right breast and 6.6 for the left side and the risk of cardiovascular events was greater with left breast cancer radiotherapy when compared with the right. (23,24). In our study, there was no statistically significant difference in mean heart dose between patients who underwent breast-conserving surgery and mastectomy, which was incomparable with a study evaluating cardiac radiation exposure in patients after mastectomy and after breast-conserving surgery, which showed that the mean heart dose after BCS was 141 cGy (SD 61.8) and 234 cGy (107.5) after mastectomy indicating that the type of surgery affects the heart dose of radiotherapy (25,26).

Conclusion

The mean dose of radiotherapy received by the heart is greatly affected by the side of breast cancer, with a dose two to three times more in left-sided treatment. The mean heart dose was highest in a dose of 5000 cGy compared to the other doses. In addition, the type of surgery has no significant effect on the mean heart dose.

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Recommendations

The use of new techniques such as breath holding deep inspiration technique and advanced planning systems such as IMRT in left-sided breast cancer radiotherapy especially if pre-existing cardiac disease is present or in young patients with long life expectancy is recommended to keep the mean heart dose as low as possible. In addition, the introduction of intraoperative IORT in selected cases of breast cancer may be beneficial in decreasing the heart dose.

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Ethical Clearance: Official approval has been obtained to use data and data were analyzed without the names to protect privacy. 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. 2024SAK860).

Conflict of Interest: Non

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دراسة مقارنة للجرعة الإشعاعية القلبية بأنواع مختلفة من العمليات الجراحية لمرضى سرطان الثدي

سجاد عباس خيرالله المالكي [١], علاء حسن مصطاف [٢], يحيى علي دشر الحيدري [٣]

الملخص

خلفية الدراسة: لقد ثبت أن العلاج الإشعاعي يقلل من عودة سرطان الثدي وكذلك الحد من وفيات سرطان الثدي. إن جرعة الإشعاع مهم ان يتم حسابها بدقة لكل من الموقع المراد معالجته وكذلك لحماية الأعضاء الحيوية مثل القلب حيث يكون له تأثير كبير على المرضى والوفيات على المرضى إذا تلقوا جرعة عالية من العلاج الإشعاعي.

اهداف الدراسة: للمقارنة بين متوسط جرعة القلب من الإشعاع لدى مرضى سرطان الثدي بين ما يلي: جراحة الحفاظ على الثدي واستئصال الثدي، وجرعات العلاج الإشعاعي المختلفة وجداول التجزئة وكذلك بين جهة اليمين واليسار عند العلاج الشعاعي لسرطان الثدي.

المرضى والطرائق: هذه دراسة مقارنة وصفية مقطعية أجريت في بغداد مركز للعلاج الإشعاعي في الفترة من يناير ٢٠١٨ إلى يونيو ٢٠١٨، ونفذت على ١٧٤ مريضا بسرطان الثدي من مختلف الفئات العمرية حيث ان بيانات جرعة القلب التي تم جمعها من ملفاتهم ومن قاعدة بياناتهم في مركز العلاج الإشعاعي في بغداد. ينقسم المرضى إلى مجموعتين: جراحة الحفاظ على الثدي واستئصال الثدي الجذري المعدل. كل مجموعة يتم تقسيمها إضافيا حسب جرعة العلاج الإشعاعي وجهة سرطان الثدي المصابة.

النتائج: كان المتوسط العام لجرعة القلب من الاشعاع ٣٧٢ cGy (يتراوح من ٧٦,٤ إلى ٧١٦,٢). أكبر فارق في متوسط جرعة القلب كان بين مرضى (جراحة الحفاظ على الثدي) الذين تلقوا ٥٠٠٠ cGy مع اشعاع العقد اللمفاوية ومرضى (جراحة الحفاظ على الثدي) الذين تلقوا ٤٠٠٥ cGy أيضا مع الإشعاع للعقد اللمفاوية (الفرق في المتوسط هو ٦٣٩,٨، P - القيمة <٠,٠٠١).
فيما يتعلق بجانب سرطان الثدي، فإن أكبر فارق في متوسط الجرعة المستلمة بين مرضى سرطان الثدي جانبي اليسار واليمين الذين قاموا بنفس النوع من الجراحة (استئصال الثدي الجذري المعدل) وتلقوا نفس الجرعة من العلاج الإشعاعي (٤٢٥٦ cGy) (الاختلاف في المتوسط هو ٥٦٥cGy وP - القيمة <٠,٠٠١).
لا يوجد فروق ذات دلالة إحصائية في معدل جرعة القلب من الاشعاع بين جراحة الحفاظ على الثدي واستئصال الثدي.

الاستنتاجات: ان معدل جرعة القلب من العلاج الإشعاعي زادت بشكل ملحوظ في تشعيع الجانب الايسر لسرطان الثدي بالمقارنة مع الجانب الأيمن. جرعة من ٥٠٠٠ cGy له التأثير الاكبر على الجرعة التي يتلقاها القلب خاصة في سرطان الثدي الأيسر. لا يؤثر نوع الجراحة، سواء كانت جراحة الحفاظ على الثدي أو استئصال الثدي، على معدل الجرعة التي يتلقاها القلب.

الكلمات المفتاحية: سرطان الثدي، جرعة الإشعاع القلبي، جراحة سرطان الثدي، علاج سرطان الثدي.

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Ligasure Hemorrhoidectomy Versus Milligan Morgan Hemorrhoidectomy Prospective Randomized Study

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Abstract

Background: Hemorrhoidectomy is a frequently performed surgical procedure associated with postoperative pain. The use of Ligasure could result in a decreased incidence of pain and bleeding, as coagulation with high-frequency currency has minimal thermal spread and limited tissue damage.

Objective: The research compares Ligasure pile excision with surgical diathermy excision for the treatment of III-IV-grade piles.

Patients and Methods: Eighty patients with pile III or IV degrees were randomized into two groups: Group one (LS) and group two (diathermy). The study evaluates the mean postoperative pain, intraoperative bleeding, and intraoperative time requirement, early and late complications. All patients were followed up for of 10-12 months.

Results: The operating time is considerably shortened in Ligasure group (LS); postoperative pain disappears earlier in LS than in diathermy. Additionally, there was less intraoperative bleeding in LS, and short duration hospital stay as compared to diathermy group.

Conclusion: LS is an efficient procedure in degree III or IV pile excision. Therefore, the procedure enhances the use of LS as one of the acceptable modality surgical options for grade III–IV pile.

Keywords: Hemorrhoidectomy, ligasure™ vessel sealing system, milligan morgan technique.

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Introduction

Hemorrhoids, also known as piles, are swollen and symptomatic anal cushions (1). These cushions consist of dense submucosal tissue and are rich in blood vessels. They are a common concern seen in general surgery clinics, as they account for a significant portion of patients and their associated symptoms. Despite their prevalence, the exact cause of hemorrhoids remains unidentified (2,3), common cause for hemorrhoids as general is constipation and may be upper gastrointestinal disorder[16]. Typically, these piles are found at the 3, 7, and 11 o'clock positions when the patient is in a lithotomy position, and additional smaller hemorrhoids may be observed between the main piles Surgical intervention, known as hemorrhoidectomy, is recommended for third and fourth-degree hemorrhoids. It is also considered when second-degree hemorrhoids do not respond to non-operative treatments. Hemorrhoidectomy can be performed using two primary techniques: the open technique, commonly known as the Milligan Morgan operation, and the closed technique, known as the Ferguson technique, which is more

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popular in the USA. Both methods involve ligating and excising the hemorrhoids. In the open technique, the anal mucosa and skin are left open to heal by secondary intention, while in the closed technique, the wound is closed primarily The primary concern associated with hemorrhoidectomy is the pain experienced during the postoperative period (1,4-7) The major factors contributing to this discomfort include the incisions and anal packing made during the surgery, the application of sutures, cauterization, and the potential risk of surgical site infection.(5)To address these challenges, numerous techniques have been employed with the aim of reducing postoperative pain, minimizing bleeding, and mitigating the development of strictures.one of the complication of postoperative surgical excision of haemorrhoids is peri anal fistulae. (15). The Ligasure™ Vessel Sealing System is a bipolar electrothermal hemostatic device designed primarily for use in abdominal surgery. (6, 7). Using a combination of pressure and electrical energy, it ensures complete coagulation of vessels up to 7 mm in diameter. The Ligasure™ system is completely automated and incorporates intelligent sensors that ensure complete coagulation with minimal thermal spread to adjacent tissue (calculated at approximately 0.5–2 mm).7 Several randomized studies have been performed to compare Ligasure™ hemorrhoidectomy with various types of conventional hemorrhoidectomies, and the results suggested that Ligasure™ hemorrhoidectomy is a safe, fast, and simple procedure. (8-13). The Ligasure™ Vessel Sealing System is an advanced bipolar electrothermal hemostatic device primarily designed for abdominal surgery. (5, 6) by utilizing a combination of pressure and electrical energy, it effectively coagulates vessels up to 7 mm in diameter. The system's automation and intelligent sensors ensure thorough coagulation while minimizing thermal spread to surrounding tissue, approximately ranging from 0.5 to 2 mm. Numerous randomized studies have compared Ligasure™ hemorrhoidectomy with conventional techniques, and the results consistently indicate that Ligasure™ hemorrhoidectomy is a safe, efficient, and straightforward procedure. (8-13) Building on these findings, this prospective, randomized study aims to compare the surgical outcomes of hemorrhoidectomy performed using Ligasure™ with conventional diathermy techniques. Other techniques for treating hemorrhoids include the following:

Stapled hemorrhoidopexy (Procedure for Prolapse and Hemorrhoids PPH), Bipolar coagulation, Doppler Guided Hemorrhoidal Artery Ligation (DG-HAL) ,Hemorrhoidolysis ,Laser surgery for hemorrhoids ,Photocoagulation , and Atomizing Hemorrhoids. These various methods offer a range of options for managing hemorrhoids, and each may be suitable based on individual patient needs and the surgeon's expertise. The main objectives include comparing the levels of postoperative pain, the duration of the surgical procedure, the extent of bleeding, and the occurrence of postoperative complications between the two techniques. By conducting this investigation, we aim to shed light on the potential advantages and benefits of utilizing the Ligasure device in hemorrhoid surgery.

Patients and Methods

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The research was conducted at Shaqlawa Teaching Hospital and Welfare Private Hospital in Hawler city, focusing on patients with grade III and IV hemorrhoids. A total of 80 patients were admitted and enrolled in the study, and they were divided into two groups, each includes of 40 patients. Prior to the operation, all patients were admitted one day in advance and started on a laxative regimen. The surgical procedures were performed under either general or spinal anesthesia, as determined by the anesthetist, with the patients positioned in lithotomy. In the first group, the hemorrhoidectomy was carried out using the Ligasure Device, leaving the mucosal defect open. Conversely, the second group underwent hemorrhoidectomy through the Milligan Morgan technique, involving scissors and the application of 2/0 vicrylR sutures to secure the hemorrhoidal pedicle, with bleeding controlled using monopolar cautery. The study was conducted from April 2022 to April 2023, and its objective was to compare the outcomes of these two different techniques, offering insights into the potential advantages of using the Ligasure Device in hemorrhoidectomy procedures. Patients who had complicated hemorrhoids, previous perianal operations, or other perianal pathologies in addition to hemorrhoids, as well as those with bleeding disorders, were excluded from the study. Data for the study was gathered through patient histories, clinical examinations, including per rectal examinations, and direct interviews conducted during the operation. Information on operation time and blood loss was recorded during the surgical procedure. The patients were further interviewed on the third day and the second week following the operation. To collect the data effectively, a well-designed questionnaire was used, which included fields such as patient's name, age, sex, history of hypertension and diabetes mellitus, operation duration, volume of blood loss,and any postoperative complications encountered. After the surgery, postoperative pain relief was administered using Tramadol hydrochloride injection at a dose of 50mg IV once daily, followed by maintenance through oral intake of 100mg Diclofenac Sodium (olfen capsule) twice daily. To assess and monitor the pain levels, a visual analogue scale (VAS) was utilized, where patients rated their pain on a scale from 0 (no pain) to 10 (maximum pain), and the results were daily recorded.

Statistical Analysis

The statistical analysis involved presenting clinical data using measures such as means, medians, and proportions. For comparing the two groups, Student t-test and Chi-square test of association were employed. Probability values below 0.05 were considered statistically significant, while values below 0.01 were deemed highly significant. These statistical methods were used to determine the significance of the results, enabling meaningful interpretations and conclusions to be drawn from the data.

Results

Ligasure device for advanced and prolapsed symptomatic hemorrhoids patients (Third and Fourth-degree haemorrhoids)

This study included a total of 80 patients with grade III and IV hemorrhoids who underwent hemorrhoidectomy using the Ligasure device (LS) or the Milligan Morgan technique (MMH) at Shaqlawa Teaching Hospital and

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Welfare Private Hospitals from April 2022 to April 2023.

Among the patients, 56 were male, and 24 were female, resulting in a male-to-female ratio of approximately 2.3:1. The age of the participants ranged from 20 years to 71 years.

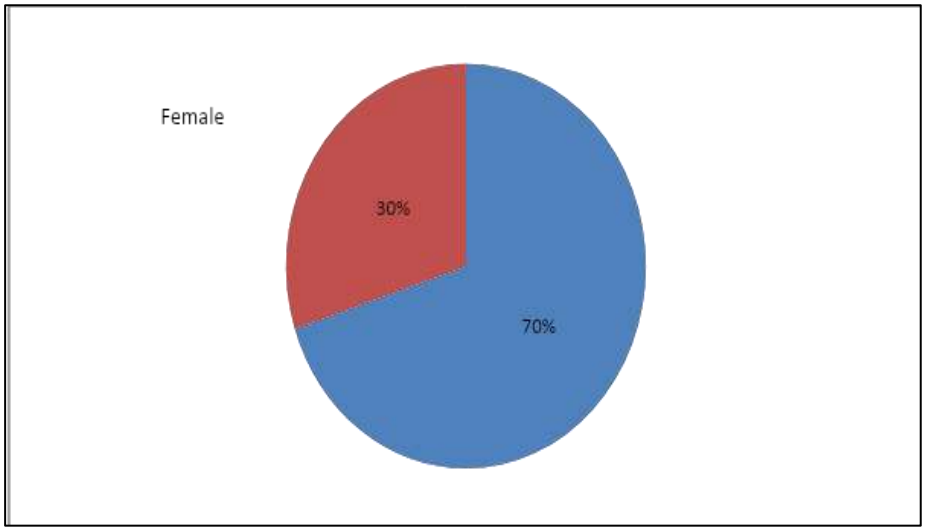

Figure (1): Sex distribution of the studied patients.

Table (1). Clinical characteristics of the studied patients.

	LS group (n=40)	MMH group (n=40)	P value
Age: (years)			
Range	23-70	20-71	0.634
Mean ± SD	39 ± 9.1	38 ± 11.7	NS
Sex			
Male	29	27	0.499
Female	11	13	NS
Grade			
III	25	28	0.300
IV	15	12	NS

Main symptoms of the patients leading to hemorrhoidectomy were bleeding (40%) followed by prolapse (27.5%), pain (25%), pruritus (5%) and discharge (2.5%) (Figure 2).

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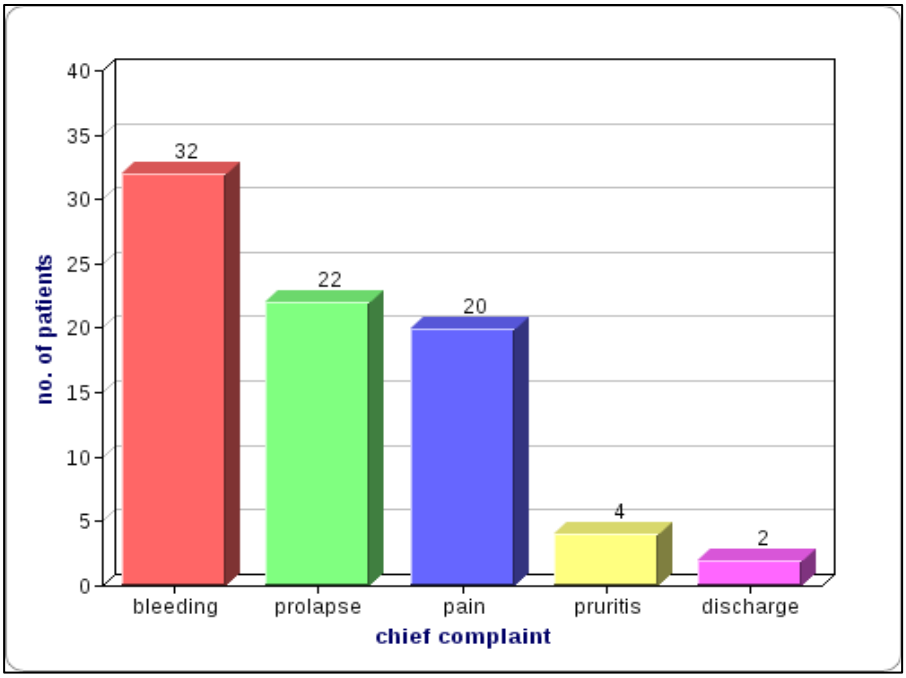

Figure (2): Presentation of the patients.

The duration of the surgical procedure in the LS group was shorter compared to the MMH group, although this difference was not statistically significant. However, the amount of blood loss during the operation was significantly lower in the LS group compared to the MMH group. Regarding postoperative complications, there was no statistically significant difference between the two groups. (Table 2, Figure 3). The severity of pain was evaluated using a visual analogue scale, and it was found that the LS group experienced significantly lower pain scores during the first 14 days post-surgery. Moreover, the intensity of pain gradually decreased over time in this group. (Table 3, Figure 4).

Table (2): Operative time, intraoperative blood loss and complications.

	LS group	MMH group	P value
Operative time: (minutes)			
Range	5 - 27	8 - 30	1.636
Mean ± SD	15 ± 5.8	17 ± 5.7	(NS)
Blood loss: (milliliter)			
Range	2 - 15	5 - 60	<0.001
Mean ± SD	5 ± 3.2	21 ± 12.4	(S)
Complications:			
Urinary retention	1	2	(NS)
Stenosis	1	0	(NS)

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Table (3): Pain score (VAS) in the first two weeks in both groups.

LS group	MMH group	P value	
Day 1			
Range	4 - 6	7 - 9	< 0.001
Mean ± SD	4.8 ± 0.8	8.1 ± 0.7	(S)
Day ++3			
Range	3 - 6	6 - 8	< 0.001
Mean ± SD	4.3 ± 1.0	7.2 ± 0.6	(S)
Day 14			
Range	0 – 2	2 – 4	< 0.001
Mean ± SD	1.5 ± 0.5	3.3 ± 0.7	(S)

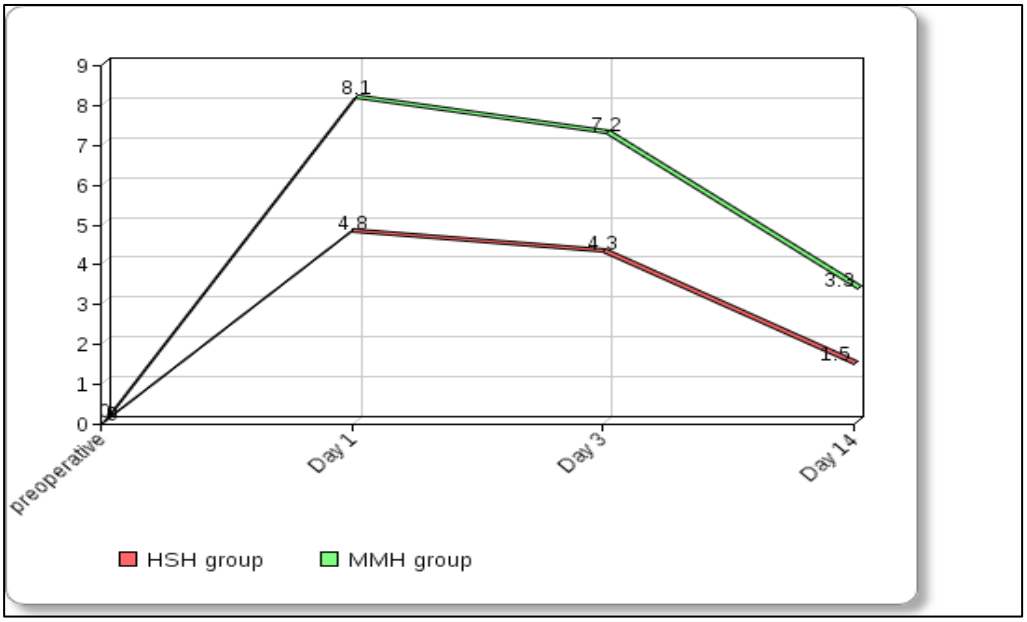

Figure (3): Mean VAS pain scoring among studied groups.

Ligasure device in third degree haemorrhoids patients

Among 53 patients diagnosed as third degree haemrrhoids ,25 patients treated by using ligasue device (LS) and 28 patients treated by Milligan Morgan open approach (MM), 12 patients treated by (LS) they returned back to work at first week post operative, as compared

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by (MM) group returned back to work around 3 weeks post operative, 13 patients treated by LS, returned to work around 10 days postoperative. 20 patients in LS group, they noted mild bleeding at the first 4 day post operatively, 5 patients by LS, no any bleeding, 22 patients treated by MM suffered mild to modertae bleeding at first week post operative.as showed in figure 4 ,6 patients treated by MM noted mild bleeding postoperative at first week day.

After 6 months follow up ,18 patients in MM group diognosed as anal stenosis required revision surgery for anal stenosis, and only 5 patients in LS group diagnosed as anal stenosis, they reqiured simple anal dilatation.

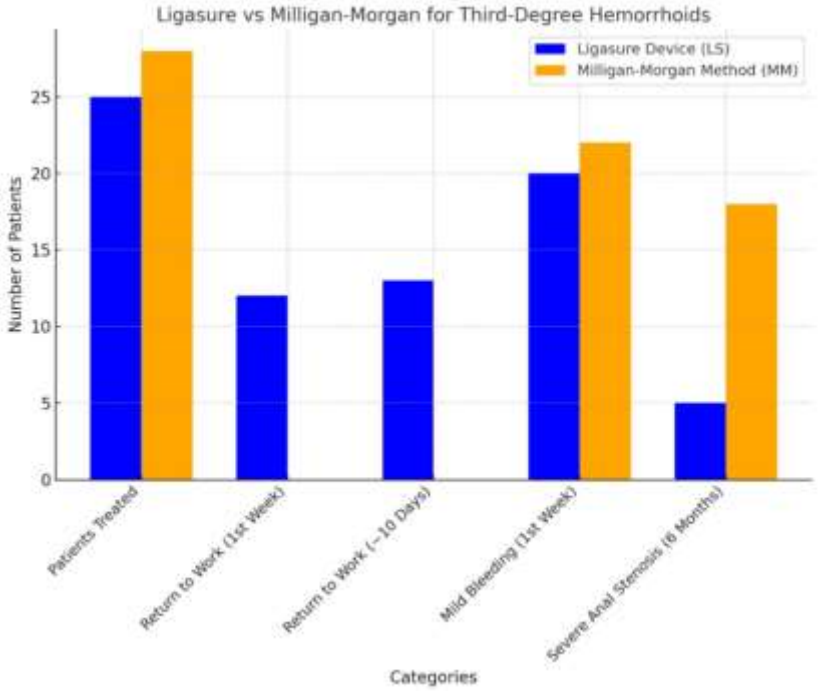

Figure (4): Ligasure versus milligan-morgan for third degree haemorrhoids patients.

Ligasure device for fourth degree haemorrhoids

Among 27 patients diagnosed as fourth degree haemorrhoids,15 patients treated by Ligasure device (LS),12 Patients treated by Milligan Morgan method (M M), 10 patients in LS group ,returned back to work 7 days post operative,as compared by MM group returned back to work around 3 weeks post operative. Only 2 patients in LS group noted post operative bleeding in first week post operatively. Around 4 patients treated by MM method, noted bleeding post opertively reqiured intervention.as showed in figure 5

After 6 month follow up , 5 patients in LS group and 7 patients in MM group noted severe anal stenosis, required surgical intervention.

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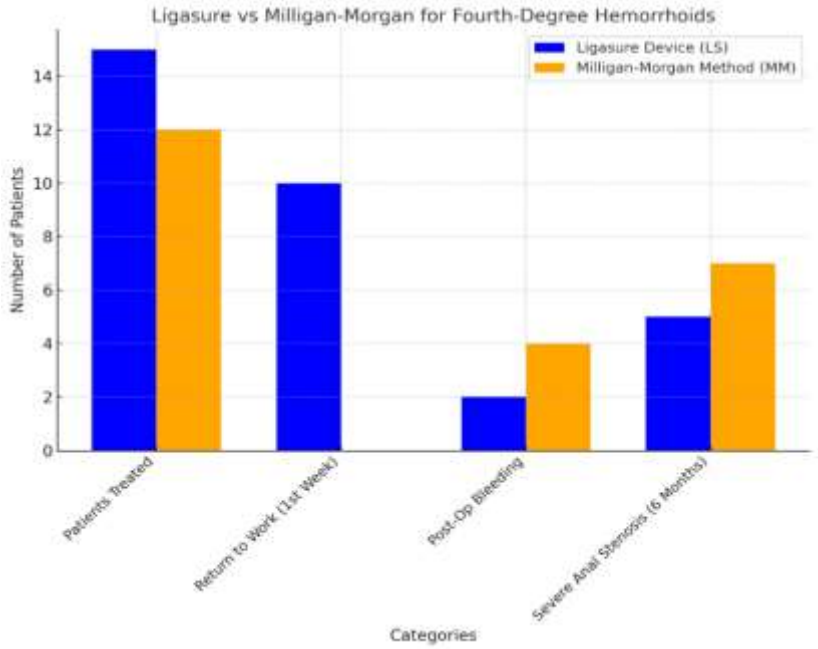

Figure (5): Ligasure versus milligan-morgan for fourth degree haemorrhoids patients.

Discussion

Typically, grade I and grade II hemorrhoids are managed using medical therapy or procedures such as rubber band ligation, which induces tissue fibrosis. These less invasive approaches generally lead to reduced pain, quicker recovery, and the convenience of being performed in a clinic setting, allowing patients to resume their normal daily activities sooner (1). On the other hand, for grade III and grade IV hemorrhoids, hemorrhoidectomy is considered the most appropriate and preferred treatment option. This surgical procedure is well-suited for addressing more advanced hemorrhoids and achieving effective results. The current study focused solely on grade III and IV hemorrhoids, deliberately avoiding the variability introduced by operating on lower grades. Additionally, patients with coexisting anorectal conditions like fissures or fistulas, as well as those who had previous perineal operations, were excluded to ensure homogeneity in both groups. Interestingly, the male-to-female ratio in the study was 2.3:1. This higher number of male patients was attributed to the fact that many female patients declined surgery conducted by male doctors. The surgical operation duration was observed to be shorter in the LD group compared to the MMH group, although this difference did not reach statistical significance. It is believed that the reduced need for achieving hemostasis in the LD group contributed to a quicker procedure. By maintaining a consistent study focus and considering potential confounding factors, this research offers valuable insights into the effectiveness of the treatment options for grade III and IV hemorrhoids. The Ligasure Device provides an exceptional approach to achieving bloodless dissection of vascular tissue. Its remarkable hemostatic capabilities enable efficient excision of hemorrhoidal tissue without the requirement

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to manage bleeding from numerous sites. While the Ligasure Device may take slightly longer than electrocautery to divide the hemorrhoidal tissue, it is crucial to avoid any undue traction on the surgical cut margins to prevent bleeding. The key to success lies in the careful application of the device, ensuring minimal tissue tension during the procedure. The primary drawback of surgical hemorrhoidectomy is the postoperative pain, which can be attributed to various factors such as the incision made during the procedure, sutures application, cauterization, and the potential risk of surgical site infection. The Ligasure device presents an ideal solution for hemorrhoidectomy due to its localized coagulation capability with minimal lateral thermal injury, extending only up to 2 mm deep. In comparison, studies examining thermal injuries caused by other methods revealed that monopolar electrocautery induced lateral thermal damage up to 15 mm deep, bipolar electrocautery resulted in injuries up to 9 mm deep, and CO2 laser caused injuries up to 4 mm deep. By utilizing the Ligasure device, surgeons can achieve effective hemostasis while minimizing tissue damage, offering a promising approach to mitigate postoperative pain and improve patient outcomes. In this study, there was a notable reduction in postoperative pain among patients in the LD group, validating the initial concept that avoiding lateral thermal injury significantly translates to lower postoperative pain. Furthermore, the absence of sutures in the LD group may also contribute to the decreased pain experienced by patients. Several previous studies have examined the impact of LD and other surgical techniques on postoperative pain. Rowsell et al. found that LD resulted in less postoperative pain and intraoperative blood loss compared to bipolar scissor hemorrhoidectomy and scissor excision. (13) Sayfan et al. compared the same surgical procedures as Thorbeck et al. and concluded that LD is an effective method for hemorrhoidectomy, with no significant difference in postoperative pain and operation time when compared to other approaches (5,8). Additionally, Franklin et al. compared LD and electrocautery hemorrhoidectomy using the closed technique in all patients, and they observed that LD offered quicker operating times, less blood loss, and reduced postoperative pain (10). The study did not find any significant difference in the incidence of postoperative complications between the two groups. However, one patient with circumferential hemorrhoids developed anal stenosis after LD, requiring surgical correction under general anesthesia by the third week after the initial operation. Fortunately, the patient reported near-complete resolution of their condition later on. Despite its benefits, the significant drawback of the Ligasure Device, like many new technologies, is the additional expense incurred. The disposable handpiece of the coagulating shears model alone costs approximately $100, representing a direct addition to the procedure's cost. Additionally, the generators used in the process are relatively expensive, costing approximately $10,000 each.

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Conclusions

The results of this study support the use of the Ligasure device for hemorrhoidectomy, as it has been demonstrated to be an easy, safe, Patients who underwent the LD group experienced a highly significant reduction in postoperative pain compared to those in the MMH group, indicating its potential to enhance the post-surgical recovery experience. Additionally, the LD group showed significantly less blood loss during the operation.

Recommendations

Based on the favorable outcomes observed in this study, we recommend the adoption of the Ligasure device for hemorrhoidectomy procedures, especially in cases where minimizing postoperative pain and reducing blood loss are essential goals. Surgeons and medical staff should receive proper training and education to ensure proficiency in using the Ligasure device effectively and safely. However, considering the high cost associated with the LD procedure, it is advisable for healthcare institutions to carefully assess the economic feasibility and benefits before incorporating this technology into routine practice. Comparative cost-effectiveness studies may provide valuable insights to guide decision-making. Future research should also focus on long-term patient outcomes and quality of life assessments to further validate the benefits of using the Ligasure device in hemorrhoid surgery**.**

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

Ethical Clearance: The patient selection and data-gathering methods were authorized by the Ethical Committee of Hawler Medical University's College of Medicine. The patients provided written informed permission for the surgical operation, research participation, and publishing of the results and any accompanying photos. The study adhered to the ethical criteria set by the institutional and national research committees, as well as the 1964 Helsinki Declaration. (Document no. 2024AMA813).

Conflict of Interest: Non

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استئصال البواسير بطريقة ليجاشور مقابل استئصال البواسير بطريقة ميليجان مورجان
دراسة عشوائية مستقبلية

أحمد مصطفى أحمد[١]

الملخص

خلفية الدراسة: العملية استئصال البواسير بشكل شائع كإجراء جراحي مصاحب لآلام ما بعد العملية. يمكن أن يؤدي استخدام جهاز Ligasure إلى تقليل حدوث الألم والنزيف نتيجة تسديد الأوعية بواسطة تردد العالي، مما يسفر عن انتشار حراري ضئيل وتحد من التحجر النسيجي.

اهداف الدراسة: يقوم البحث بمقارنة استئصال البواسير باستخدام جهاز Ligasure مع استئصالها بواسطة الانقاذ الجراحي لعلاج البواسير من الدرجة الثالثة او الرابعة.

المرضى والطرائق: تم اختيار ثمانون مريضاً يعانون من بواسير من الدرجة الثالثة او الرابعة إلى مجموعتين: المجموعة الأولى باستخدام Ligasure والمجموعة الثانية باستخدام الحث الجراحي. يقوم الدراسة بتقييم المتوسط للألم بعد العملية ونزيف أثناء العملية والوقت اللازم للعملية والمضاعفات المبكرة والمتأخرة. تم متابعة جميع المرضى لفترة تتراوح بين (١٠-١٢) شهرًا.

النتائج: تمت عملية الجراحية أربعين مريضًا باستخدام الحث الجراحي، وأربعين مريضًا باستخدام Ligasure. تقلصت الوقت اللازم للعملية بشكل كبير في Ligasure، واختفى الألم بعد العملية في وقت أبكر في Ligasure مقارنة بالحث الجراحي. بالإضافة إلى ذلك، كان هناك أقل نزيف أثناء العملية في Ligasure.

الاستنتاجات: الاستنتاجات Ligasure هو إجراء فعال في استئصال البواسير من الدرجة الثالثة او الرابعة لذا، يعزز الإجراء استخدام Ligasure كإحدى الخيارات الجراحية المقبولة للبواسير من الدرجة الثالثة او الرابعة، على الرغم من أنه أكثر تكلفة من العملية الانقاذ الجراحي.

الكلمات المفتاحية: استئصال البواسير، نظام إغلاق الأوعية الدموية Ligasure™، تقنية Milligan Morgan

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Histological and Histomorphomitrical Evaluation of Rabbit Oral Cavity Wound Healing by Feeding Absorbable Amino Acid

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Abstract

Background: Traumatic oral ulcer is well-circumscribed, depressed lesion with an epithelial defect that is covered by a fibrin clot, resulting in a yellow-white appearance, occurs due to chemical, mechanical or thermal injury to oral mucosal end with painful erosion. Amino acids are necessary for wound healing because they promote the growth of connective tissue as well as the activation and proliferation of fibroblasts.

Objective: evaluation the effect of systemic application of amino acid collection (oral intake) in treatment of traumatic oral ulceration over selected time by histological and histomorophometric assessment of soft tissue healing.

Patients and Methods: 20 adult male rabbits that weight about 700-900 Kg and age about (6-8) months where used in this experimental study. The traumatic ulcer created with (8mm) diameter, and (1mm) by surgical round diamond bur in the right cheek mucosa, then divided the groups in two groups,10 rabbits for control group that left healed normally , and 10 rabbits for experimental group that daily used mixture of amino acids systemically through mixing with water for one month. The animals were sacrificed along 3 and 7 days healing periods and the species examined histologically after histological preparation of the traumatic ulcer.

Results: Histological and histomorphometeric findings showed decreased inflammation, accelerated reepithelization of ulcer surface, better angiogenesis, and promoted remodeling of the extracellular matrix resulting with enhanced tissue maturation and complete healing in all
study groups than in the control group.

Conclusion: the chemical medicament that represented by systemic application of amino acid effective in accelerating the healing of traumatized ulcers in experimental group than that in control group by accelerated cell proliferation and mucosa reepithelization.

Keywords: Traumatic ulcers, amino acid, reepithelization.

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Introduction

The mucous membrane lining the interior of the mouth is called the oral mucosa. It consists of a layer of stratified squamous epithelium known as "oral epithelium" and the lamina propria, a connective tissue beneath it (1). The mouth cavity has occasionally been seen as a mirror that reflects a person's overall health (2). The oral mucosa, which lines the inside of

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the mouth, can change to indicate systemic disorders like diabetes or vitamin deficiencies, as well as the local impacts of long-term alcohol or tobacco use (3). When compared to the skin, the oral mucosa often heals more quickly and leaves fewer scars behind (4,5, 6). According to histology and function, the oral mucosa can be categorized into three primary groups: Lining mucosa, which is non-keratinized; the alveolar mucosa, which lines the space between the buccal and labial mucosae (7, 8). Ocular epithelial cells are frequently replaced by cells every 14 to 21 days (9). This is because there is a continuous turnover due to the high functional demands placed on the mouth cavity (10,11). The oral epithelium was specialized cells referred to as non-keratinocyte cells in addition to keratinocytes cells, which include melanocytes, Langerhan cells, and Merkel cells. (12-13). Dendritic cells obtained from the bone marrow, known as Langerhans cells, settle in the stratum spinosum. The function of these cells is phagocytosis in the epithelium (14-15,16). Langerhans cells serve as the connecting factor between the immune system and the oral mucosa (17,18). In addition to fibroblasts, macrophages, mast cells, and inflammatory cell fibers, which is present as the lamina propria. The epithelium consists of the superficial papillary layer and the deeper reticular layer (19,20). Because of their strong bond with the bone, these fibrous attachments, known as mucoperiosteum, give the oral mucosa the ability to withstand compression and shear (21). The fibroblast is the main cell type that performs vital tasks in the lamina propria. It takes part in the synthesis and replenishment of the amorphous substance and connective fibers, as well as in the process of wound healing, when an increase in fibroblasts occurs (22). The function of mucosa represented by Protective Function: The mechanical, chemical and biological stressors of daily life continuously test the mouth cavity's environment (6). Nonetheless, new research indicates that it might be related to immunity (23, 24). To diagnose the oral epithelial should use tissue preparation Once properly prepared, an oral mucosa biopsy sample may be examined under a microscope. Specimen preparation techniques include suitable dehydration and tissue preservation, cleaning, paraffin infiltration, sectioning, and staining—most frequently with hematoxylin and eosin (H&E) (25-26). Organic substances have both amino and carboxylic acid functional groups are known as amino acids (27). Despite the fact that nature contains more than 500 amino acids (28). The amino acids arginine, cysteine, glutamine, tyrosine, glycine, proline, and serine are among those that are conditionally necessary for oral health (29). A-aminoglutaric acid is glutamate. One amino acid that is needed to make proteins is glutamic acid. It transforms into glutamate throughout the body. This substance facilitates the transmission and reception of information between brain nerve cells (30). It is important for Brain Functioning by providing the brain with the high energy needed for great functioning and boosting mental preparedness (31). Heart Function: One type of glutamic acid that helps to improve cardiac function is monosodium glutamate. It also lessens the discomfort in the chest brought on by coronary heart disease. Prostate Health**:** Glutamic acid supports the prostate's regular operation. Glutamic acid is naturally present in large concentrations in the prostate.

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Immune system support and detoxification: The elimination of harmful metabolic waste products generated by the human body depends on glutamic acid (31). Aspartic acid aminosuccinic acid produced when proteins are hydrolyzed is aspartic acid. According to certain athletes, aspartic acid increases stamina. Your immune system strengthened by it. (32,33). The development of neural tissue and neurotransmission involves the production of proteins, asparagine, arginine, nucleotides, and various other chemicals, all of which are mediated by L-asp. Leucine, isoleucine, and valine are among the branched-chain amino acids (BCAAs), which are vital nutrients. Dairy products, beef, and legumes all contain them. BCAAs may lessen muscle breakdown by promoting the production of new muscular tissue (34,35,36) In conclusion, it appears that a dietary approach centered on BCAA supplementation that aims to lessen or avoid muscle damage brought on by intense exercise is not very effective (37). A semi-essential amino acid that called L-arginine essential for smooth muscle cell relaxation and blood pressure reduction (38) According to the meta-analyses L-arginine helps hypertensive adults reduce their systolic and diastolic blood pressure in a meaningful way, lowering the diastolic blood pressure of expectant mothers with gestational hypertension and shortening surgical patients' hospital stays; two of the three meta-analyses revealed a 40% decrease in the frequency of hospital-acquired infections (39).

Patients and Methods

Study design and protocol: The experiment was done at Diyala province- Baqubah from 1st November 2023, and all parts of the work (surgical and histological work and writing the paper) on 1st March 2024. The 20 male rabbits were randomly assigned and used in the work into two groups consisting of 10 animals each: the experimental group and the control group. Each group was divided into two groups according to healing periods to 3 days and 7-day healing intervals (5 rabbits to each interval). The intramuscular (IM) injection of xylazine 2% (0.08 ml/kg B.W.) and ketamine 10% (3 mg/kg B.W.) was used to provide the general anesthetic solution. All surgical tools and towels were autoclaved for 30 minutes at 121°C and 15 bar/cm2 of pressure prior to the procedure as found in Figure 1.

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Figure (1): surgical instruments.

A bur stopper was put on the surgical bur once the necessary ulcer size was ascertained using the digital vernia. Using a round diamond bur at 15,000 revolutions per minute (rpm), an 8 mm traumatic ulcer was created on the mucosa of the right cheek as found in Figure 2.

Figure (2): trumatic ulcer.

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Ten milliliters of sterile distilled water were administered as a single dosage once a day to treat the ulcer (Control Group). An amino acid (40) single dosage of 0·3 g/kg/day was used to treat the ulcer. Animals were killed with an excess of general anesthesia at the conclusion of the three and seven-day healing periods after ulceration in order to obtain ulcer samples for histological and histochemical analysis. In order to create slides, the specimens were embedded in paraffin, fixed in 10% formalin solution, and sectioned into thin 5 m slices. Hematoxylin and eosin (H&E) staining was done under a light microscope for histological evaluation (41, 42).

Statistical Analysis: Data analysis from clinical and microscopically investigated studies was conducted in the current study using the computer statistical program SPSS (statistical package of social science software, version 23). The statistical analysis was used:

1. Descriptive Data Analysis includes Mean, Standard Deviation, and Standard Error.
2. Inferential Data Analysis -Independent T-test for comparison between the control and study groups and between two different variables of the same group and ANOVA test to show the significant differences between different groups in all durations and between different durations of each group of the variables to be measured. The level of significance was used in statistics as Highly significant at $P < 0.001$, Significant at $P < 0.05$, and non-significant at $P > 0.05$ (43).

Results

All rabbits recovered clinically after induced ulceration in buccal mucosa without complications or interference with normal daily activities, with no changes in body weight of the rabbits at all healing periods. In all study groups, After the third day of ulceration, the ulcers were noticeably smaller in diameter, did not produce any exudate, had uneven borders, and had shallow depths that were covered in yellow or white pseudomembrane. On the seventh day, the ulcers had lessened in size, with a white halo surrounding them and a slight redness. However, in control, the ulcer on the 3rd day formed with bleeding and exudate formation with minimal reduction of ulcer diameters and size. On the seventh day, the ulcer had clearly shrunk in size, and there was redness surrounding the wounded area, encircled by a white halo.

Histological Finding

histologically, on the third day, the keratinocytes in the study groups demonstrated active epithelial growth moving toward the core defect from the ulcer's edge, accompanied by a noticeable decrease in the ulcer area due to the approximate proximity of two ulcer margins. A study group's moderate infiltration of inflammatory cells, a large number of blood vessels, a profusion of fibroblast cells, and the presence of new collagen fibrils dispersed randomly across all study groups were all revealed by the lamina properia, which also displayed early immature granulation tissue formation with inflammatory cell infiltration figure 3. Upon light microscope examination, the third control group revealed limited epithelium regeneration from the ulcer margin toward the central defect. Additionally the lamina propria show heavy infiltration of both acute and chronic inflammatory cells in the central area of the ulcer, which was associated with necrotic tissue. Few fibroblast cells were also

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visible, along with sparse and thin blood vessels below the necrotic area (see figure 4)
At 7th day the histological picture of the ulcer of the study group show new well-defined keratinized squamous epithelium with well-defined rete ridge. Closed approximation at wound edges with strong epithelial activity and high maturity of epithelial cell layers in all study groups (Figure 5). Lamina properia showed transition of mature granulation tissue into fibrotic connective tissue in all study groups that characterized by signs of collagen fibers remodeling, copious amount of numerous blood vessels, increase of fibroblast cells number and reduction in the inflammatory cells infiltration (absent of inflammatory cells in study group) while the histological picture of control group reveal the lamina properia, which has recently developed thin epithelium in the ulcer region, with granulation tissue development, a moderate to severe amount of inflammatory cells, few blood vessels, and few collagen fibers (Figure 6).

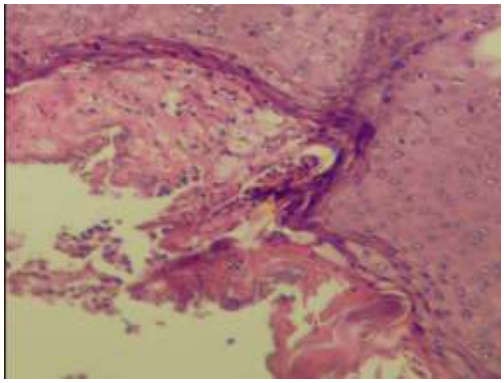

Figure (3): The study group on the 3rd day showed inflammatory cell proliferation and collagen fiber H&E stained slide (x10).

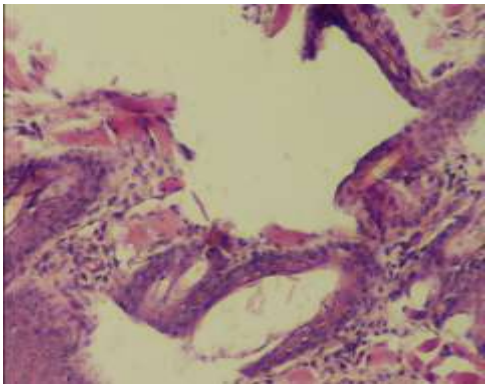

Figure (4): The control group on 3rd day showed mild inflammatory cell proliferation and absence of collagen.

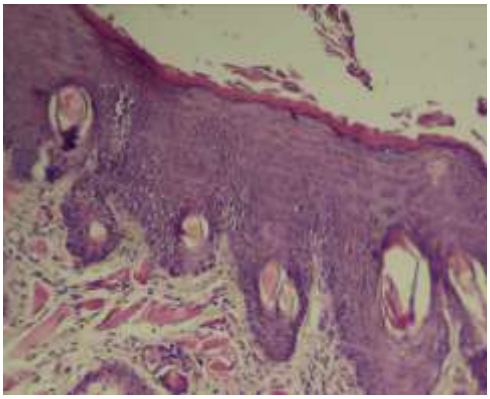

Figure (5): The study group at 7th days showed new well-defined keratinized squamous epithelium with well-defined rete ridge H&E stained slide (x10).

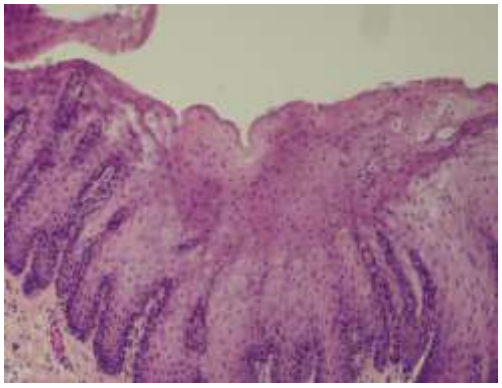

Figure (6): The control group at 7th days showed newly formed thin epithelium in the ulcer area H&E stained slide (x10).

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Ulcer size results

Both the control and research groups displayed a reduction in ulcer size (mm2) beginning from the 3 rd day and the lowest mean value (mm2) for final ulcer size was seen at them the 7 th day.(Control and study groups showed highly significant differences at all healing periods by using T-test, the mean of ulcer size was highly significantly higher ($p<0.001$) in control group than in study groups (Table 1).

Table (1): ANOVA test for the defiance in the size of the ulcers.

Day	Subgroups	Mean ±S.D	T-test	P- value
3 day	Study group	97.13 ± 1.45	37.52	0.00** HS
	Control group	150.73± 3.02	35.57	0.00** HS
7 day	Study group	31.47 ± 2.19	49.03	0.00** HS
	Control group	128.68 ± 1.25	83.27	0.00** HS

Inflammatory score results

The results of the study showed a lower mean inflammatory score in the study groups than the mean inflammatory score of the control group. Using the Mann-Whitney U test, the inflammatory score showed a high significant difference between the control and study groups at all periods, which means the inflammatory score was lower in the study groups than in the control group during all durations (Table 2). The ANOVA test showed a substantial difference between the research and control groups, as found in Table 3.

Table (2): Descriptive statistics of the inflammatory score with the comparison between all groups and healing periods.

Day	Subgroups	N0	Min	Max	Mean
3 day	Study group	5	6	3	5
	Control group	5	4	4	4
7 day	Study group	5	1	2	1.33
	Control group	5	3	4	3.66

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Table (3): Inflammatory scores between control and study groups in all durations by ANOVA test.

Day	Subgroups	Mean ±S.D	T-test	P- value
3 day	Study group	17.7± 3.02	14.13	0.00** HS
	Control group	9.13 ± 1.45	1.84	0.00** HS
7 day	Study group	31.47 ± 2.19	23.3	0.00** HS
	Control group	19.68 ± 1.25	5.2	0.00** HS

Blood vessel results

Over time, the research and control groups' mean blood vessel counts grew, with increase in the mean values in the study groups than in the control group table 4.

Table (4): Descriptive statistic of blood vessel count with comparison between all groups and healing periods.

Day	Subgroups	N0	Min	Max	Mean
3 day	Study group	5	2	3	3
	Control group	5	4	6	5
7 day	Study group	5	7	9	8
	Control group	5	4	7	6

The results showed highly significant differences ($p<0.001$) in number of blood vessel between durations for control and study groups using ANOVA test showed high significant difference between the group at 3 and 7 days table5.

Table (5): blood vessel count difference between control and study groups in all durations by ANOVA test.

Day	Subgroups	Mean ±S.D	T-test	P- value
3 day	Study group	17.7± 3.02	14.13	0.00** HS
	Control group	9.13 ± 1.45	1.84	0.00** HS
7 day	Study group	31.47 ± 2.19	23.3	0.00** HS
	Control group	19.68 ± 1.25	5.2	0.00** HS

Discussion

The adult New Zealand white rabbit was selected for this investigation because it fulfills a number of the desired requirements. This is partly because of its size and simplicity of handling. The rabbits are also useful because, at six months of age, they acquire skeletal maturity and serve as a useful model for humans (44-45). Rabbits were used as the animal models in the current study's experimental protocols. The majority of clinical studies pertaining to the healing of wounds on the oral mucosa have favored

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using rabbits as experimental models due to their well-known morphology and physiology of the oral cavity, as well as the similarities between their oral mucosa and that of humans, which is composed of subjacent connective tissue and surface epithelial tissues (45).

The results of present study demonstrated reduced ulcer size with treatment of amino acids mixture at all period of study (3rd, and 7th days) post wound than control group, which revealed highly significant differences in ulcer size between study groups and control group at 3rd, and 7th days. This result agree with {46} who found a significant reduction of excisional wound size treated with avocado oil, by topical application of the semisolid formulation of avocado oil (SSFAO 50%) or in natural avocado oil on the skin wound of rat, influenced the time for excisional wound closure. On the fifth day of treatment, an observed significant increase wound contraction in groups treated with SSFAO and in natural avocado oil when compared to the control. The results of this study demonstrated the role of amino acids as anti-inflammatory agent to decrease the inflammatory process at three period 3rd, and 7th days of study groups in comparing these periods with control group, the results showed significant differences in inflammatory score between study and control groups at all healing periods. The results of this study agree with (46). who reported topical application of the SSFAO 50% or in natural avocado oil on the skin wound of rat decreased the inflammatory process (reduce number of inflammatory cells) at the 3rd and 7th days of treatment. And agree with (47) Which used avocado oil in the healing the traumatic ulcer and showed modulate inflammatory response through high availability of oleic acid present in the SSFAO, and competes with linoleic and linolenic acids that inhibited cyclooxigenases and lipooxigenases pathway. The results of this study showed adding of curcumin to avocado oil increase newly blood vessels formation through granulation tissue, there were significant difference between mean of new blood vessels of this group in compare with the mean in control group, especially at the 7th days post wound. This results agree with (48). that reported adding of polyphenol compound from curcumin to saturated fatty acid and polyunsaturated fatty acid (PUFA), administrated to enhance gingival wound healing in dog, showed potent angiogenesis effect that promote granulation tissue formation rich with new blood vessel that provided nourishment and eliminated the waist products from wound bed, in which additive effect induce endothelial cells activation, migration and proliferation with adequate secretion of angiogenesis growth factors.

Conclusion

Mixed amino acid was more effective in treatment of oral ulceration .systemic consumption of different amino acid was showed a reduction in ulcer size and increase percentage of ulcer healing with limited periods through increase wound contraction by activation of myofibroblast and reepithelialization by approximation of ulcer edge. Also the amino acids that used in treatment of oral ulcer cause enhancing reepitheliazations, increase angiogenesis and reduce inflammatory reaction in the ulcer site. Which reduce both acute and chronic inflammatory cells infiltration in ulcer during early periods, activating mucosal keratinocyte

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migration, proliferation to restore epithelial defect, enhancing endothelial cells to promote new blood vessels.

Recommendations

The worldwide utilization of amino acid since the use of medicine has greatly expanded. In order to ascertain the different characteristics, potencies, and configurations of these amino acids, as well as their adverse effects and toxicity, additional research is required. Other elements that must be taken into account include the type, size, and position of the wound as well as the vascular supply, infection, and other issues that could prevent the healing process.. This study indicated that systemic intake of amino acids with a controlled and low concentration could expedite healing as a supplement to or replacement for existing therapies.

Source of Funding: This research did not qualify for any kind of financial support of any kind

Ethical Clearance: This study was approved by the Ethics Committee of the College of Medicine, University of Diyala, and according to the ethical approval. (Document no. 2024MAH827).

Conflict of Interest: Non

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التقييم النسيجي والنسيجي لشفاء جروح تجويف الفم لدى الأرانب عن طريق تغذية الأحماض الأمينية القابلة للامتصاص

منار عبد الرزاق حسن[1]

الملخص

خلفية الدراسة: قرحة الفم المؤلمة هي آفة منخفضة ومحدودة بشكل جيد مع خلل ظهاري مغطى بجلطة الفيبرين، مما يؤدي إلى مظهر أصفر-أبيض، يحدث بسبب إصابة كيميائية أو ميكانيكية أو حرارية للغشاء المخاطي للفم مع تآكل مؤلم. الأحماض الأمينية ضرورية لشفاء الجروح لأنها تعزز نمو النسيج الضام وكذلك تنشيط وتكاثر الخلايا الليفية.

اهداف الدراسة: تقييم تأثير التطبيق المنهجي لجمع الأحماض الأمينية (تناول الفم) في علاج تقرح الفم المؤلم خلال فترة زمنية محددة عن طريق التقييم النسيجي والنسيجي لشفاء الأنسجة الرخوة.

المرضى والطرائق: تم استخدام ٢٠ ذكر أرنب بالغ بوزن حوالي ٧٠٠-٩٠٠ كغم وأعمار حوالي (٦-٨) أشهر حيث تم استخدامها في هذه الدراسة التجريبية. تم إنشاء القرحة المؤلمة بقطر (٨ مم)، و(١ مم) بواسطة مثقاب ماسي دائري جراحي في الغشاء المخاطي للخد الأيمن، ثم تم تقسيم المجموعات إلى مجموعتين، ١٠ أرانب للمجموعة الضابطة التي تركت تلتئم بشكل طبيعي، و١٠ أرانب للمجموعة التجريبية التي يستخدم يومياً خليط من الأحماض الأمينية نظامياً من خلال خلطه مع الماء لمدة شهر. تمت التضحية بالحيوانات خلال فترات شفاء مدتها ٣ و7 أيام وتم فحص الأنواع تشريحيا بعد التحضير النسيجي للقرحة المؤلمة.

النتائج: أظهرت النتائج النسيجية والنسيجية انخفاض الالتهاب، وتسريع إعادة تنسج سطح القرحة، وتولد الأوعية الدموية بشكل أفضل، وتعزيز إعادة تشكيل المصفوفة خارج الخلية مما يؤدي إلى تعزيز نضج الأنسجة والشفاء الكامل في جميع الحالات مجموعات الدراسة منها في المجموعة الضابطة.

الاستنتاجات: الدواء الكيميائي الذي يمثله التطبيق الجهازي للأحماض الأمينية فعال في تسريع شفاء القرحة المصابة في المجموعة التجريبية مقارنة بالمجموعة الضابطة عن طريق تكاثر الخلايا المتسارع وإعادة تنسج الغشاء المخاطي.

الكلمات المفتاحية: القرحة المؤلمة، الأحماض الأمينية، إعادة التظاهر.

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Assessment of Language Impairment Management of Post Stroke at Erbil Public Hospitals

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Abstract

Background: Stroke is the most common cause of aphasia which need to be managed because it postpones stroke recovery and causes psychological and social problems for the patients and their families. Researchers have observed that the issue of language disorder in post-stroke patients has been poorly addressed in Kurdistan Region.

Objective: This neurolinguistic study aims at presenting a comprehensive scale study about the demography of stroke and aphasic patients at Rizgary hospital over a period of two months in2024.

Patients and Methods: This cross-sectional study is carried out at Rizgary Public hospital in Erbil-Kurdistan Region. Demographic for all the patients who were registered at Erbil hospitals during the two months in 2024. Then the process of diagnosing aphasia and dysarthria as language impairments are carried out.

Results: Among 234 subjects, the mean age of post stroke patients is 33.4 ± 22.038001years .15.3% of patients were not paralyzed, meanwhile 44.8% got right side body paralysis, followed by left side 38%, and both side 1.7%. The highest risk factor is hypertension (68.8%), followed by diabetes mellitus (41.4%), and ischemic heart disease (21.7%).

Conclusion: Language disorders is about (71.4%) which is a high range among post-stroke patients. Language disorders does not only affect stroke management but it also impair the individual's quality of life. If language impairments are screened earlier in patients, it is possible to intervene in language skills and work through speech therapy.

Keywords: Language impairment, stroke, dysarthria.

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Introduction

One of the vital characteristics of humans is language but when the nervous system is affected for any reason, it will cause language impairment and behavioral problems (1). Moreover, early identification of the phases of stroke is also needed because it is correlated with language recovery process evaluation (2). Thus, stroke phases are identified into acute (the first few hours to days following a stroke), subacute (initial weeks following stroke), and chronic (begins months to years), which are defined according to time from stroke onset (3). One of the common consequences following stroke is cognitive impairment which includes deficits in attention, working memory, and executive functions (4). One of the causes of stroke is atrial fibrillation which rises the risk of

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mortality of stroke patients (5, 6). Obesity as an indirect effect on stroke, since it increases the amount of blood volume, makes filling pressure to be higher, and also increases the sympathetic activation, which ultimately leads to raised stroke volume (7, 8). Aphasia is one of the most prominent disabilities caused by stroke, which is defined as an impairment of language that is caused by brain damage (9). Ferdous and other colleagues refer to the strong correlation between stroke and aphasia and indicate that "sometimes language problems may lead to complicated clinical presentation and poor response to treatment" (p,2) (1). Stroke is not the only cause of aphasia, other causes of aphasia are; traumatic brain injury, neurodegenerative disease, brain tumor, and brain infection (10, 11). However, it is unconditioned for all stroke patients to have aphasia since it is developed in one-third of patients with stroke (12). Aphasia results in disruption of communication, decreased social activity, depression, low job possibility, and severe disability (13). The most common current methods for aphasia treatment are speech and language therapy (SLT), medical therapy, transcranial direct current stimulation, and recurrent low-frequency transcranial magnetic stimulation (14). SLT consists of impairment-based therapies that target the underlying linguistic deficits (phonological, morphological, lexical, semantic, or syntactic level) and aim at improving functional communication (15). In deciding which therapy to be used in the recovery process, combinations of different therapeutic approaches are commonly used by SLT pathologists in an attempt to tailor the language treatment to each patient (16). Relatively, however, whatever approach is used, there is good evidence that patients' receptive, expressive language and their functional communication are improved compared to no SLT (17). Zumbansen and Thiel argue that there is good evidence that SLT benefits patients' functional communication, receptive and expressive language compared to no SLT (18).

Patients and Methods

This cross-sectional study is carried out at Rizgary Public hospital in Erbil-Kurdistan Region. All the public hospitals and centers in Erbil send neurological cases , including stroke patients ,to Rizgary since it is the only public hospital that treats neurological conditions in Erbil. Demographic data, including ; age , gender , hemisphere , paralyzed side , risk factors , and social communication are collected for all the patients who were registered at Erbil hospitals during the TWO months of February and April(We couldn't collect data on March because of administrative regulation of the hospital) in 2024 . A total of 234 stroke patients were included for stroke demographic data collection , after excluding other neurological cases. Meanwhile , only 167 subjects suffered from language impairment and are included for aphasia assessment. The research uses Boston Classification system for aphasia classification . After obtaining consent from the administrative staff of the hospital and the patients or their families , socio-demographic data are obtained , then the collected data are classified, cleared and analyzed. Then the process of diagnosing aphasia and dysarthria as language impairments are carried out.

Statistical Analysis

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Data analysis was performed using SPSS version 25.0. Descriptive statistics were used to summarize sociodemographic characteristics, and clinical manifestations.

Results

Concerning the **(**Demographic Distribution of Stroke Participants **),**a total of 385 patients , with neurological condition ,were transferred from all the public patients in Erbil districts to Rizgari public hospital during February and April of 2024 . On the same day of transferring, Cerebral computed tomography (CT) scan was performed and were re-evaluated by a neuroradiologist with knowledge of the type of aphasia. Magnetic resonance imaging(MRI) is used by radiologist to estimate the volume of the lesion and its location assess the different types of aphasia. After the primary assessment ,non-stroke neurological condition (n=119**)** or clinical status of medically unstable patients (n=32**)** were excluded and totally 234 stroke patients were included. After taking patients' consent or their caregivers' , a special form was designed to collect demographic data about the patients . The demographic data included ; sex, age, stroke lesion, hemiplegic side, and risk factors. The data are presented in Table (1).

Table (1): The Profile of (234) subjects.

1. Demographic information(n=234)		
Age	Frequency (n)	Percentage
21-30	2	0.9
31-40	6	2.6
41-50	24	10.3
51-60	55	23.5
61-70	52	22.2
71-80	61	26.1
>80	34	14.5
Mean ±SD	33.4 ± 22.038001	
b. GENDER	Frequency (n)	Percentage
Male	115	49.1
Female	119	50.9
2.Stroke related information		
A.Paralysis	Frequency (n)	Percentage
1.Right side of the body	105	44.9
2.Left side of the body	89	38.0
3.Both side of the body	4	1.7
4.No weakness	36	15.4
B. Hemisphere affected due to stroke	Frequency (n)	Percentage
1. Right hemispheric lesion	99	42.3
2. Left hemispheric lesion	102	43.6
3. Both hemispheric lesion	33	14.1
3. Risk Factors		
Factors	Frequency (n)	Percentage
1.Diabetes mellitus	97	41.5
2.Hypertension (HTN)	161	68.8
3. Ischemic heart disease (IHD)	51	21.8
4.Smoking	34	14.5

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5.obesity	5	2.1
Mean ±SD	69.6±*54.57*325354	
6. sociolinguistic disorder (Behavior toward family members)n=234		
sociolinguistic disorder	Frequency	Percentage
1.Destructive	176	75.2%
2.Constructive	58	24. 8.%

The results of the collected data in Table (1) indicate that among 234 subjects ,the mean age of post stroke patients is 33.4 ± 22.038001years and males (49.1%) are more prevalent than females (50.8)..15.3% of patients were not paralyzed , meanwhile 44.8% got right side body paralysis, followed by left side 38% , and both side 1.7%. The highest risk factor that caused stroke is Hypertension (68.8%), followed by Diabetes mellitus (41.4%), and Ischemic heart disease (21.7%). Meanwhile , smoking (14.5) and obesity(2.1) are the lowest risk factors consequently. Concerning sociolinguistic disorder , due to stroke, 75.2% showed destructive behavior toward their family members. Concerning Language and Speech Evaluation (Aphasia and Dysarthria),in order to have a comprehensive assessment of aphasia as a language impairment, it was crucial to assess dysarthria since the co-occurrence of dysarthria with aphasia was observed in the majority of aphasic cases.

1.Aphasia

Among the 234 stroke patients, for aphasia classification and assessments, patients with normal language function (n=67) were excluded , so totally 167 subjects are included. The most common classification of Aphasia is Boston Classification system which includes eight types of aphasia ;(1) Broca's, ;(2)Transcortical Motor aphasia ;(3) Global ;(4)Mixed Transcortical;(5) Wernicke's;(6) Transcortical Sensory;(7) Conduction (8), and Anomic. These types are characterized by a specific profile of symptoms based on fluency of verbal expression (i.e., fluent vs. non-fluent speech), language comprehension skills, and repetition abilities . According to the results, only Five types of aphasia were detected ; maximum of patients 82 % with Broca's aphasia ; followed by 61% had Wernick's Aphasia; 26.3% had Conduction Aphasia;13.8% got Global Aphasia ; and 20.4% were observed with Anomic Aphasia . Due to the inability to use language , 56.3%showed destructive and 43.7% constructive behavior toward their family members Table 2

Table (2): aphasia classification based on characteristics (19).

A.Broca's Aphasia (production disorder) (n=16	Frequency	Percentage
1. Expressive Language Disorder(*producing* no fluent speech that has reduced phrase length, impaired melody) .Comprehension of syntactica complex sentences (e.g., passive sentences) is of impaired .	74	44.3%
2. Agramatism (their sentences consist mostly content words with few, if any, function words	37	22.2%
3. Unable to read and write properly	26	15. 6%

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TOTAL	137	82%
B.Wernick's Aphasia(comprehension disorder)		
4.Comprehension is impaired. ,i.e. unable to understand any speech of other people . (Concept Disorder) .	48	28.7%
5.Their speech is fluent but is empty of meanin with a mix of sentence constructions (par agrammatism. Language output contains many aphasias including semantic paraphasia (e.g., say "train" for the target word "bus") and neologism (non words like "fluffertump").	37	22.2%
6. Error awareness is often poor due to limited auditory comprehension.	9	5.4%
7.Reading and writing are frequently significant impaired.	8	4.8%
TOTAL	102	61.1%
C. Conduction Aphasia (repetition disorder)		
8. Repetition skills are disproportionally impaired relative to comprehension a expression. Having fluent speech with phonemic distortions, relatively good comprehension, and mild t moderate naming deficits.	38	22.8%
9.Mild to moderate naming deficits.	6	3.5%
TOTAL	44	26.3%
A. Global Aphasia (production and comprehension)		
10. Comprehension is significantly impaired even the single word level, spoke output is severely limited	17	10.2%
1.Spontaneous speech, nam and repetition are constrained recurring utterances.	6	3.6%
Total.	23	13.8%
E. Anomic Aphasia(naming disorder)		
12.Having difficulty with naming but no other profou comprehensive and expressi deficits.	28	16.8%
13.Speech is fluent with th exception of intermittent pau and hesitations resulting fro word finding difficulties.	6	3.6%

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TOTAL	34	20.4%
2. sociolinguistic disorder (Behavior toward family members)		
sociolinguistic disorder	Frequency	Percentage
1.Destructive	94	56.3%
2.Constructive	73	43.7%

There is no perfect aphasia classification system because aphasic patients do not fit neatly within any of the well-defined neoclassical aphasia syndromes. Besides, patients within the same subtype aphasia may differ quite significantly from other patients who have the same syndrome. This study attempts to assess aphasia focusing on abnormal verbal expression, including, understanding spoken or written language, repetition, naming, reading, and writing and linguistic disorders such as semantic, pragmatic, phonological, or syntactic disorders (table3). During conversation, (44.3%) were unable to accurately produce the correct words or phrases during speech, 32.9%. were unable to understand the speech of others, 26.3 % were unable to repeat words and phrases, and 13.8% got Comprehension and speech production impairments. Meanwhile, linguistic disorder was present in 28.1% of the patients presented: (i) pragmatic disorder (use of language in a specific situation and context); (ii) Agrammatism in 22.2% (grammatical part of the sentences and disorder in the formation of the sentences); (iii) 20.4% could not remember the correct names and numbers of words (Anomia) during speech; (iv) and only 16.2% did not know how to read properly. When viewing the images, 23.4 could not describe the events (Vocabulary and Cognitive Linguistic Disorder).

Table (3): Verbal Linguistics Behavior and Linguistic Impairments of Language (1).

A. Language impairment of verbal abilities (n =167)	**Frequency (n)**	**Percentage**
1.Unable to accurately produce the correct words or phrases during spe (expressive language disorder)	74	44.3
2.Unable to understand any speech of other people (receptive/concept disorder)	55	32.9
3. Unable to repeat words and phrases.	44	26.3
4. Comprehension and speech production are impaired	23	13.8

B. Linguistic Disorder(n=167)	**Frequency**	**percentage**
1. use of language in a specific situation and context (pragmatic disorder)	47	28.1%
2. having disorder of sentence formation or grammar (Agramatism)	37	22.2%
3. Unable to remember the names and numbers of the correct words (Anomia) during speech	34	20.4%
4.Unable to read properly (Phonetics and Phonological Disorder)	27	16.2%
5. When viewing the images unable to describe the events (Vocabulary and Cognitive Linguistic Disorder)	39	23.4%

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Dysarthria is another case of language disorder which is defined as an articulator deficiency Language pathologists (SLPs), clinically, assess dysarthria to measure articulation and speech intelligibility. Since there is no speech-language pathologist (SLP) in Rigzary hospital, the researcher, as a physician, did a physical exam to diagnose dysarthria by checking; patient's ability to coordinate breathing, voice, the quality of voice, the ability to move lips, tongue, jaw and face. Besides, doing MRI and CT scan tests to check abnormality that may affect the speech. This study focused also on Dysarthria since it may co-occur with aphasia in post stroke patients which makes stroke management harder. (table 4):

Table (4) Assessment of dysarthria.

1.Dysarthria(n=234)	Frequency	Percentage
Flaccid	13	5.6
Spastic	10	4.3
Ataxic	27	11.5
Hypokinetic	61	26.1
Mixed	14	5.9
Total	125	53.4
2.No Dysarthria	109	46.6
3.Both dysarthria and aphasia	91	38.9

In this study, (53.4 %) of the subjects got dysarthria; (i) Hypokinetic (26.1 %); Ataxic (11.5%); Mixed (5.9 %); Flaccid (5.6%); and Spastic (4.3 %). Among those patients who got dysarthria, (38.8%) of them suffered from co-occurrence of aphasia, meanwhile, (46.6 %) didn't have dysarthria. Results are presented in Discussion The results of the collected demographic data of atroke patients (table -1) indicate that among 234 subjects, the mean age of post stroke patients is 33.4 ± 22.038001years and males (49.1%) are more prevalent than females (50.8). Concerning the effect of gender on language recovery, there is an assumption about a quicker language recovery by females since their brain activation is more diffuse and involves both the left and right inferior frontal gyrus, meanwhile, only left inferior frontal gyrus is lateralized for brain activities in males (20). However, studies concluded no differences in language recovery between sexes (21, 22). Evidences supporting the theory of gender differences has been found to be weak and further researches need to be conducted (23).15.3% of patients were not paralyzed, meanwhile 44.8% got right side body paralysis, followed by left side 38%, and both side 1.7%. The highest risk factor that caused stroke is Hypertension (68.8%), followed by Diabetes mellitus (41.4%), and ischemic heart disease (21.7%). Meanwhile, smoking (14.5) and obesity (2.1) are the lowest risk factors consequently. Concerning sociolinguistic disorder, due to stroke, 75.2% showed destructive behavior toward their family members. There is no perfect aphasia classification system because aphasic patients do not fit neatly within any of the well-defined

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neoclassical aphasia syndromes. Besides , patients within the same subtype aphasia may differ quite significantly from other patients who have the same syndrome classification patients. For example, one patient with Broca's aphasia may have mild-moderate reading comprehension deficits, while another does not (1). Because of these concerns, Because of these concerns, some researchers (24,25, 26). Gordon, advocate focusing on identifying the precise points of impairment in language processing, such as semantic, morphological, pragmatical, phonological, or syntactic disorders. advocate focusing on identifying the precise points of impairment in language processing, such as semantic, morphological, pragmatical, phonological, or syntactic disorders. Accordingly, (19) state that a comprehensive aphasia assessment includes each component of language (e.g., syntax, semantics, pragmatics---etc.), in every modality (comprehending spoken or written language and expressing spoken language, written language, and gestures) since aphasia manifests almost all verbal abilities, such as, abnormal verbal expression, difficulties in understanding, repetition, naming, reading, and writing. Therefore, Focusing on underlying linguistic deficits (phonological, morphological, lexical semantic or syntactic level) is the target of impairment-based therapies, as SLT method, which uses, for example , morphological decision tasks at the word, sentence or text level to improve morphological deficits (15). This research recommends using assessments, such as The Boston Diagnostic Aphasia Examination, 3rd edition (BDAE) [24], and the Western Aphasia Battery – Revised (WAB-R) (27) are the most common comprehensive aphasia assessments. Comprehensive Aphasia Test (CAT) (28), for diagnosing types of aphasia and also emphasizes on linguistic disorder assessment for ASL management. Dysarthria is another oral communication dysfunction which need to be differentiated from aphasia. Dysarthria is defined as a neurologic motor speech impairment causing the speech musculature to be slow, weak and/or imprecise (29). 20% to 30% of stroke survivors are affected by Dysarthria (28). Accordingly, dysarthria and aphasia may co-occur together Ali and colleagues reported that 29.6% of their stroke patients had both (30).

Conclusions

Language disorders does not only affect stroke management but it also impair the individual's quality of life. If language impairments are screened earlier in patients, along with screening for neurological disorders, it is possible to intervene in language skills and work through speech therapy. Unfortunately, language -speech pathologists are not available in neither in the public nor in the private hospital in Kurdistan Region. Social and economical policy, need to be adopted by the government, in order to improve health care services and providing equitable post-stroke medical care. Generally, it can be concluded that Stroke and language problem in post-stroke patients is significant, but this domain is poorly addressed in Kurdistan Region. This is the first neurolinguistic study investigating the case of post-stroke patients in Erbil District. Large-scale studies are needed to better visualize the extent of the problem. A paucity of good –quality epidemiological studies on stroke and language impairment is needed in Kurdistan region.

Recommendations

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Opening a modern Neurological hospital or Center where Neurologists ,Psychologists ,Radiologists , and Language –Speech Pathologists work as a team. The study also recommends opening special training in LSA for the physiotherapists and trainers at the hospital by professional people in the field from the neighborhood countries (Iran , Turkey , Jordon –etc.). A Long term solution , is putting language and speech pathology in the curriculum of Physiotherapy Department at Polytechnic and Medical Colleges in Kurdistan Region to be taught as a separate subject during the academic years.

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Ethical Clearance: This study was conducted according to the approval of Rizgary hospital –Erbil –Kurdistan Region, Iraq (Document no. 2024AHK887).

Conflict of Interest: Non

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تقييم إدارة ضعف اللغة بعد السكتة الدماغية في مستشفيات أربيل العامة

ازاد حسن خضر[١], نجاة محمد امين مولود [٢]

الملخص

خلفية الدراسة: السكتة الدماغية هي السبب الأكثر شيوعا للحبسة والتي تحتاج إلى علاج لأنها تؤجل الشفاء من السكتة الدماغية وتسبب مشاكل نفسية واجتماعية للمرضى وعائلاتهم. لاحظ الباحثون أن مشكلة اضطراب اللغة لدى مرضى ما بعد السكتة الدماغية لم تتم معالجتها بشكل جيد في إقليم كردستان.

اهداف الدراسة: تهدف هذه الدراسة اللغوية العصبية إلى تقديم دراسة شاملة حول التركيبة السكانية لمرضى السكتة الدماغية وفقدان القدرة على الكلام في مستشفى رزكاري على مدى شهرين في عام ٢٠٢٤. إلى جانب الكشف عن الانتشار والوفيات في المستشفى.

المرضى والطرائق: أجريت هذه الدراسة المقطعية في مستشفى رزكاري العام في أربيل - إقليم كردستان. ديموغرافية لجميع المرضى الذين تم تسجيلهم في مستشفيات أربيل خلال الشهرين في عام ٢٠٢٤. ثم يتم تنفيذ عملية تشخيص فقدان القدرة على الكلام وعسر التلفظ مع ضعف اللغة.

النتائج: من بين ٢٣٤ شخصا، كان متوسط عمر مرضى ما بعد السكتة الدماغية ٣٣,٤ ± ٢٢,٠٣٨٠٠١ سنة .١٥,٣٪ من المرضى لم يصابوا بالشلل، بينما أصيب ٤٤,٨٪ بشلل في الجسم الأيمن، يليه الجانب الأيسر ٣٨٪، وكلا الجانبين ١,٧٪. أعلى عامل خطر هو ارتفاع ضغط الدم (٦٨,٨ ٪)، يليه داء السكري (٤١,٤ ٪)، وأمراض القلب الإقفارية (٢١,٧ ٪).

الاستنتاجات: تبلغ نسبة الاضطرابات اللغوية حوالي (٧١,٤٪) وهي نسبة عالية بين مرضى ما بعد السكتة الدماغية. لا تؤثر اضطرابات اللغة على إدارة السكتة الدماغية فحسب، بل إنها تضعف أيضا نوعية حياة الفرد. إذا تم فحص إعاقات اللغة في وقت مبكر في المرضى، فمن الممكن التدخل في المهارات اللغوية والعمل من خلال علاج النطق.

الكلمات المفتاحية: ضعف اللغة, السكتة الدماغية , عسر التلفظ.

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The Safety and Efficiency of Percutaneous Nephrolithotomy in Managing Renal Stones in A Single Solitary Kidney

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Abstract

Background: Urologists have significant challenges when treating individuals with a solitary functional kidney who have renal stones. Various therapeutic approaches are employed to treat renal stones in people with just one working kidney, such as shock wave lithotripsy, retrograde intrarenal surgery, and percutaneous nephrolithotomy (PCNL).

Objective: To assess the safety and efficiency of PCNL in patients with a solitary kidney.

Patients and Methods: A percutaneous nephrolithotomy (PCNL) procedure was conducted on 20 patients who had a solitary kidney and were experiencing renal stone issues. The upper calyceal route was utilized. Factors such as the duration of the operation, full removal of the stone, presence of any remaining stone fragments, decrease in hemoglobin levels, requirement for a blood transfusion, necessity for any follow-up procedures, and length of hospital stay were all taken into account. Patients were monitored for a period of 6 months after the surgical procedure to identify any potential problems.

Results: The mean age of the patients was 45.45±7.49 years (range: 34–61 years). About two-thirds of the patients (65%) were male. The mean stone size was 3.81 ± 1.57 cm. The mean operative time was 53.3±15.57 min (range: 30-90 min). Secondary puncture was required only in one case (5%). Residual stones were reported in 3 patients. Four patients (20%) needed blood transfusions. The mean duration of hospital stay was 36.3±16.51 hrs. Serum creatinine had dropped from 2.2±0.88 mg/dL preoperation to 1.54±0.31 mg/dL after 6 months postoperation, with a significant difference.

Conclusion: PCNL is a safe and effective method for the removal of renal stones in patients with a solitary kidney, especially when other management options are not feasible. The procedure is associated with acceptable rate of residual stone, blood transfusion and postoperative hospital stay.

Keywords: Solitary functional kidney, percutaneous nephrolithotomy, renal stone.

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Introduction

Large renal calculi pose a significant risk to those who have just one functioning kidney. These factors can potentially result in urinary tract infection (UTI), anuria, renal insufficiency, or sepsis, which can have severe consequences for patients with impaired kidney function (1,2). Consequently, patients with a single kidney require proactive treatment for stones. Managing stones in these individuals continues to be a difficult situation, where completely removing the stone and

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safeguarding renal function through safe surgical therapies is crucial (1,3).

The treatment options available for such renal stones range from medical dissolution therapy through extracorporeal shockwave lithotripsy (ESWL) and open surgery to minimally invasive surgery like percutaneous nephrolithotomy (PCNL). Advances in the ESWL and PCNL over the past several decades have not only revolutionized the treatment of renal stones but also has facilitated the ease with which stones are removed (4). Of note, ESWL is largely depend on the number of sessions an failure at initial treatment is associated with a low success rate for subsequent ESWL (5). Percutaneous nephrolithotomy (PCNL) is a viable choice for treating intricate kidney stones, even in individuals with just one functioning kidney (6). The PCNL was first introduced in 1976 (7). Since then, PCNL has become a commonly used method for renal calculi, especially in cases with staghorn stones or cases in which stones are larger than 2 cm. Currently, endoscopic procedures have advanced significantly, making PCNL a viable choice for complicated kidney stones, even in patients with single kidneys (8), although it was found to be associated with readmission by some authors (9). Despite the technical approach being identical to that of patients with bilateral healthy kidneys, surgery on a single kidney is more difficult due to the danger of problems during and after the procedure, which could lead to the lone renal unit deteriorating. As a result, when performing PCNL on single kidney patients, the surgeon experiences heightened anxiety (10).

Solitary kidney results from various causes, mainly including congenital factors and iatrogenic factors. The prevalence of kidney stones is 8.8% (11), and patients with a solitary functioning kidney are also at a high risk of developing kidney stones; an untreated staghorn stone is likely to destroy the kidney and cause life-threatening sepsis (12). A solitary kidney would compensate for hypertrophy, and its cortex would incrassate, which makes it vulnerable. From this aspect, management of stones in a solitary kidney is intractable for urologists. Despite its potential surgical complications, including infection, severe bleeding and urinary fistula, PCNL providing reasonable SFRs while preserving renal function (13). In order to minimize such deterioration and ensure effective stone clearance, it is imperative to perform the surgical approach with great precision in these patients. Research in the literature indicates that PCNL procedures conducted on kidneys that are working alone have been linked to a higher rate of complications compared to kidneys that are functional on both sides (14). Those with greater thickness of the renal parenchyma due to compensatory hypertrophy are more susceptible to hemorrhage during PCNL treatment compared to those with bilateral kidneys (15). Furthermore, the presence of substantial bleeding in these individuals can lead to the development of acute renal failure. This occurs when blood clots clog the urinary system and the remaining kidney is unable to compensate for the loss of renal function (16). Based on these findings, it seems reasonable to take care of the question of whether the PCNL procedure is safe and effective in aging male patients with a solitary kidney.

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The aim of this study is to evaluate the safety and efficacy of percutaneous nephrolithotomy (PCNL) in individuals who have only one functioning kidney. Given that the majority of data on this topic is derived from the Western population, to the best of my understanding, this study represents the first attempt to investigate this intricate phenomenon in Iraq.

Patients and Methods

This is a prospective descriptive study conducted at a single center. The study included 20 consecutive patients who had a single kidney and were diagnosed with renal stones. These patients were scheduled for percutaneous nephrolithotomy (PCNL) at Al-Nasiriyah Teaching Hospital between 1st of January and 31st of December 2022. The study included patients with pelvic calculus and/or inferior calyceal calculi. However, the study excluded patients who had calyceal diverticula stones, a history of coagulopathy, those who were morbidly obese, and those with congenital UT defects. The study received approval from the local committee of Al-Nasiriyah Teaching Hospital. Following a comprehensive evaluation of the patient's medical history and physical examination, all individuals received a series of diagnostic procedures, including renal ultrasonography, X-ray KUB, non-contrast computed tomography (NCCT), and several blood tests (renal function tests, electrolytes, and blood coagulation). Additionally, urine analysis as well as urine culture were performed. The study was endorsed by the local health committee, and every patient provided their written informed consent.

Surgical Technique

The identical cohort of urologists conducted percutaneous nephrolithotomies (PCNL) on all patients while they were under sedation. The initial procedures involve performing a cystoscopy and inserting a 6Fr ureteral catheter to see the renal collecting system using contrast material.

Patients received treatment using upper calyceal approaches, which were conducted within the space amid the paraspinal and posterior axillary line. The puncture of the upper calyceal supracostal was consistently carried out in the mid-scapular line, namely in the eleventh intercostal gap. The puncture site was located to the lateral side of the mid-scapular line in patients who were fat. The skin and under-skin punctures were conducted throughout the exhalation phase of supracostal punctures, while profound inhalation was employed for punctures in renal parenchyma. The unobstructed flow of urine via the needle and the accurate placement of the Teremo guidewire were used as criteria to determine a fruitful calyceal puncture. The Alken metal dilator device was employed to expand the original tract to a diameter of 24 French units (Fr), followed by the introduction of an amplatz sheath. The stones were fragmented using a Swiss Lithoclast Master, manufactured by Electro Medical Systems in Nyon, Switzerland, along with a rigid nephroscope made by Stortz with a size of 24-26Fr. After the process of breaking the stones into smaller pieces and removing them, direct nephroscopy and fluoroscopy were employed to examine the collecting system for any leftover stones. Both nephrostomy implantation and antegrade Double-J stenting are performed in all cases. During the postoperative phase, patients' chest pain, difficulty breathing, rapid breathing, and limited air entry were thoroughly observed. If

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deemed required, intercostal drainage was planned in response to potential thoracic problems. On the first day after surgery, the patients' hemoglobin levels were tested, and a KUB X-ray was conducted.

Factors such as the length of the operation, complete removal of the stone, remaining stone fragments, decrease in hemoglobin levels, requirement for a blood transfusion, necessity for additional procedures, and duration of hospital stay were all taken into account. Full clearance was defined as the complete absence of a visible shadow on the X-ray KUB taken after the surgery or a remaining stone size of less than 4 mm as determined by US/CT. A blood transfusion is administered if the hemoglobin level during surgery drops below 8 g/dL. Patients were monitored for a duration of one month following the surgery, during which any complications that occurred after the operation were documented.

Statistical Analysis

The data was tabulated and analyzed using the SPSS version 25 computer program, which is a statistical package for social science. Descriptive analysis was performed for numerical data using the mean and standard deviation, whereas for categorical data, they were calculated using frequency and distribution. The study employed a paired t-test to assess the levels of serum creatinine before and 6 months after the procedure. A p-value of 0.05 was deemed statistically significant.

Results

Preoperative characteristics of the patients: The mean age of the patients was 45.45±7.49 years (range: 34–61 years). About two-thirds of the patients (65%) were male, with a male-to-female ratio of 1.86:1. The left-side kidney was more frequent, accounting for 60% of the patients. The mean stone size was 3.81±1.57 cm (range: 1.5–7.0 cm). The mean serum level of creatinine before operation was 2.2±0.88 mg/dL (range: 1.14–4.4 mg/dL), as shown in Table 1.

Table (1): Preoperative characteristics of the patients.

Variables	Value
Age, years	
Mean±SD	45.45±7.49
Range	34-61
Sex	
Male	13(65%)
Female	7(35%)
Affected side	
Right	8(40%)
Left	12(60%)
Stone size, cm	
Mean±SD	3.81±1.57
Range	1.5-7.0
Preoperative Cr, mg/dL	
Mean±SD	2.2±0.88
Range	1.1-4.0

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Intraoperative characteristics of the patients:

Intraoperative characteristics of the patients are shown in table 2. The mean operative time was 53.3±15.57 min (range: 30-90 min). The vast majority of patients (95%) did not required secondary puncture; however 5% of the patients required such intervention. Residual stones were reported in 3 patients (15%) (2 of whom had 5 mm and the third one had 10 mm residual stone). Four patients (20%) needed blood transfusion (one unit in three patients and 2 units in one patient) as shown in Table 2.

Table (2): Intraoperative characteristics of the patients.

Variables	Value
Operative time, min	
Mean±SD	53.3±15.57
Range	30-90
Secondary puncture required	
No	19(95%)
Yes	1(5%)
Residual stone	
No	17(85%)
Yes	3(15%)
Blood transfusion	
No	16(80%)
Yes	4(20%)

Postoperative characteristics

The mean duration of hospital stay was 36.3±16.51 hrs (range: 16-72 hrs). After six months postoperative, the mean serum creatinine was 1.54±0.31 mg/dL (range=1.0-2.1), as shown in Table 3.

Table 3: postoperative characteristics.

Variables	Value
Hospital stay, hrs	
Mean±SD	36.3±16.51
Range	16-72
Postop serum Cr, mg/dL	
Mean±SD	1.54±0.31
Range	1.0-2.1

Comparison of creatinine before and after surgery

Paired t-test was used to compare serum creatinine level before and six months after surgery. As depicted in figure 1, serum creatinine declined from 2.2±0.88 mg/dl to 1.54±0.71 mg/dl. Statistically, there was a highly significant difference between the two readings.

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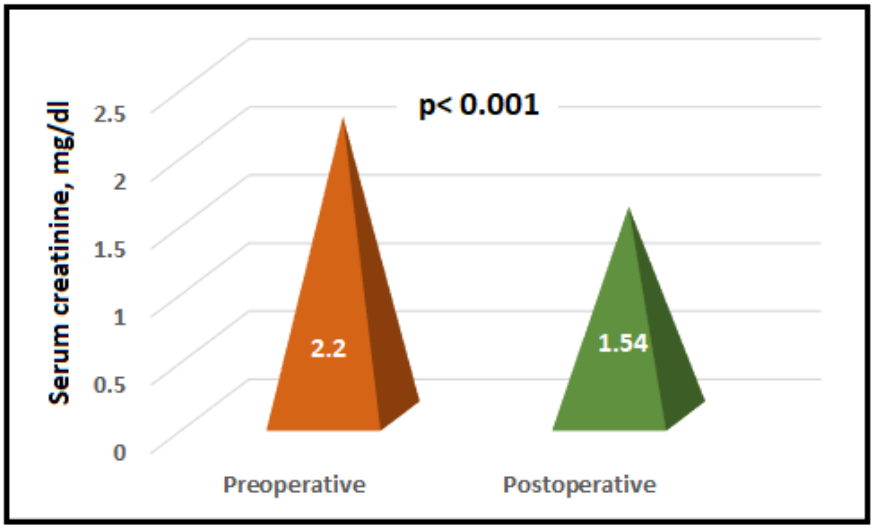

Figure (1): The mean serum level of creatinine in patients with solitary kidney before undergoing PCNL and 6 months after surgery.

Discussion

Currently, the surgical treatment of kidney stones has undergone significant transformation due to remarkable advancements in endoscopic technology. Patients with a solitary kidney are at a higher risk of perioperative problems and renal function impairment after surgery (15). In the current era of minimally invasive surgery, PCNL is a primary surgical method used to remove large renal stones (16). This study included 20 patients with single, solitary kidneys aged 45.45±7.49 years, of whom 65% were males. In China, a study conducted by Bai *et al*. (17) found 73.3% out of 116 consecutive patients with solitary kidneys were males, and the mean age of the patients was 52.22 ± 10.56 years. A very recent study assessed 47 patients; out of them, 32 (68.09%) were males. The mean age was 39.89 ± 15.33 years (18). Another study from the UK conducted by Jones et al. (19) on a total of 116 patients (69 males) with a mean age of 49.6 years The above-mentioned articles share some similarities, like middle age and male predominance. Our investigation revealed that the duration of the operation varied between 30 and 90 minutes, with an average operative time of 53.3±15.57 minutes. A research group from India (20) demonstrated that the operative time varied between 40 and 300 minutes, with an average operative time of 85.1 minutes. According to a study conducted by Jones et al (19), the average duration of a surgical procedure called URS for treating kidney stones in a single kidney was found to be 64.9 minutes, with a range of 18 to 190 minutes. Another study from Brazil conducted by Torricelli et al (21) showed that the mean operative time was 138.3±36.7 minutes. In a study conducted on 16 Turkish patients by Besiroglu et al (10), the total operative time was 85.3 (52–109) minutes. The superiority of the present study over the above-mentioned studies is that the shorter operative time may be due to the experience of the surgical team. In the current study, only one patient (5%) required a second puncture. In their study,

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Torricelli et al (21) from Brazil reported that 25% of their PCNLs were done with two percutaneous accesses. In another study from Pakistan, only two patients (4.26%) required multiple tracts (18).

The study found that the stone-free percentage was 85% which is within the context of international studies. In Torricelli et al.'s study, the rate of patients without stones was 67%. (21), Jones et al. (19) documented the safety of PCNL in patients with a solitary kidney, demonstrating a stone-free rate of 77.3% (defined as the absence of any remaining calculi or pieces measuring ≤2 mm). According to a study conducted in India on 128 patients, the rate of successfully removing kidney stones following the first PCNL procedure was 88.1% in group 1 and 50% in group 2, as determined by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF K/DOQI) (22).

Four individuals (20%) in the current research required blood transfusions. According to a report, the requirement for blood transfusion and the likelihood of experiencing serious bleeding were greater following PCNL in solitary kidneys compared to bilateral kidneys (8). In the study conducted by Jones et al. (19), it was shown that 30.6% of the patients who had PCNL experienced postoperative problems. Among these issues, 5.6% of the patients required a blood transfusion. Hosseini and colleagues (23) conducted PCNL on a cohort of 412 individuals who had a single functioning kidney. Out of these patients, 19 (4.6%) experienced bleeding that necessitated a blood transfusion. Besiroglu et al. (10) found that 18% of the patients in their study, specifically 3 out of 16 patients, experienced hemorrhage that required transfusion during the perioperative period.

Compensatory hypertrophy frequently occurs in solitary kidneys, resulting in an increase in the thickness of the renal parenchyma. There was speculation that accessing such dense renal tissue could potentially raise the danger of bleeding. Some risk factors for significant bleeding include puncturing the upper calix, having a large stone, having many tracts, being operated on by an untrained surgeon, and having just one kidney (14).

The current study found that hospital stays varied from 16 to 72 hours, with an average duration of 36.3±16.51 hours. Torricelli *et al* (21) discovered that the mean length of hospital stay was 5.6±3.9 (ranging from 2 to 16) days. Approximately 55.5% of patients had a hospital stay of little more than 4 days. Only a total of four patients required hospitalization for a duration exceeding one week as a result of surgical complications. Besiroglu et al (10) reported that the hospital stay lasted for an average of 4.7 days, ranging from 3 to 8 days.

Our study detected significant improvement in renal function as measured by the serum level of creatinine, which was 2.2±0.88 (1.1–4.0 mg/dL) preoperatively and 1.54±0.31 (1.0–2.1 mg/dL) postoperatively. Similar to our study, a Turkish study showed that serum creatinine levels were 1.38 (0.7–2.6) preoperatively and 1.20 (0.7–2.2) postoperatively (8). We may speculate that purifying the kidney from the stones leads to improved kidney function.

Mithani et al (18) conducted a study to evaluate the renal function of patients with a solitary kidney before and after undergoing PCNL. The researchers discovered that the average serum creatinine level at the

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beginning of the study was 2.45 mg/dL, but it fell to 2.32 mg/dL after the surgery. Upon additional observation, the patients exhibited an average serum creatinine level of 1.97 mg/dL, which represented a drop of 0.48 mg/dL from the initial measurement.

Conclusions

Overall, our data suggest that percutaneous nephrolithotomy (PCNL) is a secure and efficient technique for patients who have just one functioning kidney. Nevertheless, it is imperative to validate our discoveries through additional well-planned investigations, which should involve a more extensive group of participants.

Recommendations

The study recommends using PCNL as a gold standard for the treatment of renal stones in patients with solitary kidneys when there are no specific contraindications.

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Ethical Clearance: Official approval has been obtained to use data and data were analyzed without the names to protect privacy. 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. 2024FFM864).

Conflict of Interest: Non

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سلامة وكفاءة عملية استئصال حصوات الكلى عن طريق الجلد في علاج حصوات الكلى في الكلية المنفردة

فاقد فرج الموسوي [١]

الملخص

خلفية الدراسة: يواجه أطباء المسالك البولية تحديات كبيرة عند علاج الأفراد الذين يعانون من الكلية الانفرادية والذين لديهم حصوات كلوية. يتم استخدام أساليب علاجية مختلفة لعلاج حصوات الكلى لدى الأشخاص الذين لديهم كلية انفرادية، مثل تفتيت الحصى بموجة الصدمة، والجراحة الرجعية داخل الكلى، واستئصال حصوات الكلى عن طريق الجلد

اهداف الدراسة: تقييم سلامة وكفاءة واستئصال حصوات الكلى عن طريق الجلد في المرضى الذين يعانون من الكلى الانفرادية.

المرضى والطرائق: تم إجراء عملية استئصال حصوات الكلى عن طريق الجل على ٢٠ مريضًا لديهم كلية انفرادية وكانوا يعانون من مشاكل حصوات الكلى. استخدم الطريق الكاليسيلي العلوي لهذا الغرض. سجلت البايات ذات الصلة مثل مدة العملية، والإزالة الكاملة للحصوة، ووجود أي شظايا حصوة متبقية، وانخفاض مستويات الهيموجلوبين، والحاجة إلى نقل الدم، وضرورة أي إجراءات متابعة، ومدة الإقامة في المستشفى.. تمت متابعة المرضى لمدة ٦ أشهر بعد العملية الجراحية لتحديد أي مشاكل محتملة.

النتائج: بلغ متوسط عمر المرضى ٤٥,٤٥ ± ٧,٤٩ سنة (المدى: ٣٤-٦١ سنة). حوالي ثلثي المرضى (٦٥٪) كانوا من الذكور. كان متوسط حجم الحصوة ٣,٨١ ± ١,٥٧ سم، ومتوسط مدة العملية ٥٣,٣ ± ١٥,٥٧ دقيقة (المدى: ٣٠-٩٠ دقيقة). لوحظت الحاجة الى اجرا ثقب ثانوي حالة واحدة فقط (٥٪)، كما تم العثور على بقايا الحصوة في ٣ مرضى (١٥٪). أربعة مرضى (٢٠٪) احتاجوا إلى عمليات نقل دم. وكان متوسط مدة الإقامة في المستشفى ٣٦,٣ ± ١٦,٥١ ساعة. انخفض الكرياتينين في الدم من ٢,٢ ± ٠,٨٨ ملغم / ديسيلتر قبل العملية إلى ١,٥٤ ± ٠,٣١ ملغم / ديسيلتر بعد ٦ أشهر بعد العملية، وبفرق معنوي.

الاستنتاجات: استئصال حصوات الكلى عن طريق الجلد هو وسيلة آمنة وفعالة لإزالة حصوات الكلى لدى المرضى الذين يعانون من كلية منفردة، لاسيما عندما تكون خيارات العلاج الأخرى غير ممكنة.

الكلمات المفتاحية: كلية عاملة منفردة, استخراج حصوات الكلى عن طريق الجلد, حصوات الكلى.

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Successful Laparoscopic Cholecystectomy of Giant Gallstone – A Case Report Study

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Abstract

Background: Gallstone diseases are the most common biliary pathologies. They are very frequent in the Western world, where the approximate incidence is about 10–15%. Laparoscopic cholecystectomy is the method of choice for treating gallstone disease. The conversion rate of laparoscopic to open surgical procedures is estimated to be about 4%- 5%. Gallstone size is important since large/giant gallstones are more liable for technical difficulties during laparoscopic interventions.

Objective: The aim is to present the rare case of a giant gallstone removed laparoscopically.

Case presentation: A female of 53 years old presented to the private clinic for on-and-off signs and symptoms of gallstone diseases throughout the previous 3 years; investigation revealed a large gallbladder stone (4 cm in maximum diameter). Laparoscopic cholecystectomy has been performed for an adhesive gallbladder without the need for conversion to the open classical method and without complications; the gallstone size measured after retrieval was about 4 cm in length.

Conclusion: Giant or large gallstones carry a significant risk of complications. Even in these challenging cases, laparoscopic cholecystectomy is regarded as the preferred treatment option over open cholecystectomy. Highly skilled and experienced laparoscopic surgeons should perform the procedure to ensure successful outcomes. The possibility of converting to an open procedure in case of failure to expose the clear anatomy and any intraoperative technical difficulties should be considered.

Keywords: Giant gallstone, gallstone disease, large gallstone, laparoscopic cholecystectomy.

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Introduction

Gallstone diseases are the most common biliary pathologies. (1) It is very frequent in the Western world (2), where the approximate incidence is about 10–15% (1), and at a time the prevalence in the East is increasing (2). The Caribbean, particularly Trinidad and Tobago, is no exception, as is found at the San Fernando Hospital, where many laparoscopic cholecystectomies are performed annually (3). More than 80% of gallstone cases are asymptomatic, and only about 1–2% of those without symptoms will develop clinical features necessitating surgical interventions. (4) Morang and Achham recorded the peak and minimum prevalence between females and males by a rate of (6.45% vs. 2.44%), respectively (5). The exact etiology of gallstone disease is

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idiopathic, but it is found that defects in lipid metabolism due to supersaturation of bile are the main cause (4).

An abnormality in the normal relationships between the major constituents of bile—bile acids, phospholipids, and cholesterol—resulted in the formation of gallstones. The first step of gallstone formation is saturation, followed by crystallization, and finally, the growth of the stones. Cholesterol-saturated vesicles are formed due to a high index of cholesterol saturation, which will initiate the cholesterol monohydrate crystals nucleation, forming the core of the cholesterol stone, and no studies suggest the difference between the pathogenesis of the formation of giant gallstones and regular-sized cholesterol stones (4). Laparoscopic cholecystectomy is the method of choice for the treatment of gallstone disease (4, 6), which is one of the commonest operations performed by general surgeons worldwide, and it can be performed in up to 96% of the cases; the frequency of conversion from laparoscopic to open cholecystectomy is nearly 4%-5%. Gallstone size is important since giant/large gallstones have more complication risks and technical difficulties during laparoscopic cholecystectomy (6). Gallstones more than 3 cm are known as large gallstones and carry more risks of gallbladder malignancy. Very rarely, gallstones reach a size of more than 5 cm, which are known as giant gallstones (6, 7). Classical open cholecystectomy may even be considered by some surgeons for giant gallstones (6). In the literature, only very few cases with such sizes were reported. (7) In this study, which can be considered as the first case recorded in our city (Erbil, Kurdistan Region, Iraq), we present a case of a large gallstone in which a successful operation was performed for her laparoscopically. For the comparison, a review of the literature has been done too. Therefore, **t**he aim of this case report study is to present the largest gallstone and the first case recorded in the literature retrieved laparoscopically in Erbil city and the Kurdistan region of Iraq.

Case Presentation

A female of 53 years old presented to the private clinic with a 3-year history of intermittent right upper abdominal pain, colicky in nature, aggravated by fatty meals, radiating to the right shoulder area, associated with epigastric fullness and dyspepsia but no jaundice or fever. Symptomatic review of other related systems was insignificant; past medical, past surgical, drug, family, and socioeconomic histories were negative for related conditions apart from the history of CBD stone retrieval by ERCP before one month. Physical examination and vital signs with abdominal examination were normal. Hematological investigations revealed normal CBC, liver function, renal function, and blood sugar tests. Normal gallbladder wall thickness with a single large gallstone measuring about 33 mm was the result of an ultrasound scan of the abdomen and pelvis without clear ultrasound features of acute infections of the gallbladder or CBD stone; hence the case was diagnosed as a symptomatic gallstone. The need for surgery, complications of the operation, and risks of general anesthesia and drugs were discussed with the patient and accompanied personnel in addition to the dangers of neglecting the treatment and particularly surgical intervention. After the decision of the operation, for the aim of

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elective laparoscopic cholecystectomy, consent was taken, and the patient was admitted. After the patient had been fully prepared, general anesthesia was used for the procedure with endotracheal intubation. The patient was put in a supine position, and the Veress needle technique operation started. A 10 mm supra umbilical port for the camera was inserted, and carbon dioxide created pneumoperitoneum. Another 10 mm working epigastric port and two additional 5 mm supporting ports (on the right side of the abdomen) were inserted under camera vision control. After entrance to the intra-abdominal cavity, thick adhesions were observed between the gallbladder (fundus and body) on one side and the greater omentum on the other; adhesiolysis by unipolar electrocautery was performed. Mild distension of gallbladder with an acceptable cystic duct length observed. The gallbladder wall was tough at the neck. It made it difficult to work with non-traumatic grasper forceps and other laparoscopic instruments because the gallstone occupied the infundibulum, neck, and all of Hartmann's pouch area, with most of the lower part of the body of the gallbladder. After obtaining the critical view of safety, the clipping of both the cystic artery and cystic duct was done, the gall bladder was dissected from the cystic plate and its bed, trial of the gall bladder retrieval with its large containing stone was done throughout the epigastric 10 mm port site but failed, For facilitating the stone and gallbladder extraction, the epigastric port incision was enlarged to a size of about 2 cm. With the aid of sponge forceps and finger manipulation, the gallbladder was extracted to the outside. Following taking out of the specimen and good hemostasis, the pneumoperitoneum was evacuated, and then the fascia was closed primarily with a poly filament and absorbable suture, and skin suturing was done via monofilament and non-absorbable suture material. A drain was placed in the gallbladder bed region and fixed, the wounds were closed, and finally, dressing was done after cleaning the area with normal saline. Total operation time was 45 minutes. After the procedure was finished, the gallbladder was opened to assess the gallstone size, and it measured approximately 4 cm in maximum dimension length (Figure 1), but it was not weighted. The patient passed smoothly and had an uneventful recovery and post-operative period as well. The procedure ended without the need to convert to the open method; recovery was uneventful without any intra- or postoperative complications. On the first postoperative day (about 20 hours after the procedure), the patient was discharged from the hospital with instructions for oral fluid intake and medication usage and an appointment for drain removal; two days later, the drain was minimally containing serosanguinous fluid and then removed. One week after the operation, port site stitches were removed, and the wounds were clean.

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Figure (1): giant gall stone removed.

Discussion

The laparoscopic cholecystectomy of the largest gallstone removed, which was 12.8 cm in maximum diameter, was reported by Singh et al. (8); few giant gallstones were reported by other studies. (9,10), a length of 16.8 cm gallstone removed by classical cholecystectomy incision is regarded as the largest gallstone ever removed in the emergency setting (11). Two giant cases of gallstones were reported in Nepal (4*3.3*3 cm and 5*3*2.8 cm) with weights of 23.2 gm. and 24.7 gm., respectively, during June 2021. (12) Meanwhile we did an operation on a giant/large gallstone; the gallstone measured about 4 cm in maximum dimension. Regarding sex incidence of gallstones, it is more common among female populations. (13) Our operated case goes with these criteria since the case was female. One of the presentations of gallstones may be with small bowel obstruction via cholecysto-duodenal fistula formation, causing gallstone ileus, particularly when the stone is large and lodged in the distal ileum. (14) However, the size of the gallbladder stone in this study was large but did not irritate the gallbladder wall to cause necrosis, fistula formation, or migration. The best option for managing symptomatic gallstones is laparoscopic cholecystectomy. However, open cholecystectomy has been mentioned as the procedure of choice by some authors for giant gallstones; the reason behind this idea was the technical difficulties associated with large-sized stones that may cause challenges to the surgeon during the operative procedure of laparoscopic cholecystectomy. (15) In the agreement with others, our opinion is that; for patients with giant/large gallstones, laparoscopic cholecystectomy performed in the experienced hands still is the best initial approach, providing that failure to expose the clear anatomy and technical difficulties necessitates conversion to open classical operation. (9) We followed all the steps necessary for a routine laparoscopic

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cholecystectomy, the removal of the gallbladder from its bed in the fossa done successfully. A study done for 68 cases in Iraq (16) for fundus-first laparoscopic cholecystectomy, because of adhesions and difficulties in Calot triangle identification, mean hospital stay was between more than two days and up to 1 week; this was not in line with our case report study in which only 20 hr. was the time for this stay and the patient was discharged the morning after the surgery; this may be due to fewer adhesions, fewer difficulties facing us, and less bleeding risk in our case in comparison to the study mentioned in which surgeries had been done on difficult cases with obscured Calot triangles. In regards to the operation time for the procedure, it was more than 70 minutes in some cases and up to 2 hr. in other cases recorded by Azhy M. (17). In our view, recording a shorter operation time (45 min.) in our present case is also due to the same reasons mentioned above for shorter hospital stay. The Kocher (classical right subcostal incision) is well known for its relevant complications, particularly splinting on inspiration and increased postoperative pain that results in atelectasis of the base of the lung. That is why, for specimen retrieval, the decision was made to enlarge the epigastric port incision instead of conversion to a classical or minimum subcostal incision to prevent or at least reduce the potential complications of the open incision. This proved more beneficial because the patient had a smooth postoperative period and was discharged from the hospital on the first postoperative day. The size and method of extraction of the gallbladder from the abdomen after cholecystectomy is another consideration. In a recent systematic review regarding the extraction through the epigastric vs. umbilical port, it was found that epigastric port retrieval may be associated with more postoperative pain in patients undergoing laparoscopic cholecystectomy in comparison to the umbilical port retrieval and might also be associated with longer gallbladder retrieval time. (18) However, the gallbladder retrieval in our case was done through the epigastric port site because we had no studies regarding this comparison. Secondly, we think that this short period is not considered important for an operation lasting at least half an hour. In addition, we believe that enlarging and extending the epigastric port has less risk for future port site hernia in comparison to the supra- or infra-umbilical port site incision, and this may be explained by more pressure of the bowel and visceral organs on the peri-umbilical wounds rather than in comparison to the epigastric wounds. Regarding the method of extraction, in our case, the gallbladder was taken out without using an endo bag, which is usually used to prevent spillage of bile and wound infection. Our method is not in line with a recent meta-analysis that showed a lower wound infection rate in patients who underwent gallbladder retrieval by the use of a bag vs. without using the bag (4.2% vs. 5.9%) (19). our explanations for not using the endo bag are, first, the bag is not present in most of the hospitals in our city; on the other hand, this can be regarded as one of the limitations of our study. Secondly, again, we have no local studies or data confirming a higher wound infection rate in those cases with no use of the bag in comparison to those using a bag, and thirdly, usually, we will use such a method for a huge number of small stones to prevent spillage of the stones to

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inside the peritoneal cavity so as not to waste more time for finding and removing small stones for the aim of avoiding micro abscess formation. In addition, we believe that using such bags for large stones is unnecessary. Our study has a strong point since, up to our best information, this is the only giant/large gallstone case reported in the literature in Erbil, Iraq, till now, which was retrieved laparoscopically. However, Xu et al. detailed the laparoscopic retrieval of a 9.5-cm gallstone, and Becerra et al. reported the removal of a 16.8-cm gallstone via classical cholecystectomy incision in the emergency setting (11). From the literature to date, our gallstone appears to be the largest removed laparoscopically; meanwhile, a stone size of 4*3.3*3 cm and 5*3*2.8 cm gallstones were removed laparoscopically in Nepal (20).

Conclusion

This study found that even for giant/large gallstones, laparoscopic cholecystectomy is the best treatment option compared with open cholecystectomy and should be performed by surgeons with valuable experience with laparoscopic surgeries. Any intraoperative technical difficulties, in combination with the possibility of conversion to open cholecystectomy in case of inability to obtain clear anatomy, should be taken into consideration.

Recommendations

In spite of technical difficulties for surgery of giant gallstones, laparoscopic cholecystectomy is feasible.

Ethical Clearance

The Ethical Approval Committee at the college of General Medicine, Koya University, approved this case report study. (Document no. 2024STB818).

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Conflicts of Interest: Non

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نجاح عملية منظاريه لاستئصال كيس صفراء مع حصوة كبيرة, تسجيل حالة نادرة

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الملخص

خلفية الدراسة: أمراض حصوات المرارة هي أكثر أمراض القنوات الصفراوية شيوعًا. وهي شائع جدًا في العالم الغربي حيث تبلغ نسبة الإصابة التقريبية حوالي ١٠-١٥٪ ويتزايد انتشارها في الشرق. استئصال المرارة بالمنظار هو الطريقة المفضلة لعلاج مرض حصوات المرارة والتي تعد واحدة من أكثر العمليات الجراحية شيوعًا التي يقوم بها الجراحون في جميع أنحاء العالم؛ معدل حدوث التحويل من استئصال المرارة بالمنظار إلى استئصال المرارة المفتوحة هو ما يقرب من ٤٪ -٥٪. يعد حجم حصوة المرارة أمرًا مهمًا، نظرًا لأن حصوات المرارة الكبيرة العملاقة تكون أكثر عرضة للصعوبات الفنية أثناء التدخلات بالمنظار.

عرض الحالة: مريضة تبلغ من العمر ٥٣ سنة قدمت إلى العيادة الخارجية الخاصة بشكوى من الاعراض والعلامات أمراض حصوات المرارة طوال ٣ سنوات سابقة، أظهرت الفحوصات وجود حصوات مرارة كبيرة (٤ سم)، وتم إجراء استئصال المرارة بالمنظار دون الحاجة للتحويل لفتح الطريقة الكلاسيكية ودون حدوث اي تعقيدات او مضاعفات.

المرضى والطرائق: مريضة تبلغ من العمر ٥٣ سنة قدمت إلى العيادة الخارجية الخاصة بشكوى من الاعراض والعلامات أمراض حصوات المرارة طوال ٣ سنوات سابقة، أظهرت الفحوصات وجود حصوات مرارة كبيرة (٤ سم)، وتم إجراء استئصال المرارة بالمنظار دون الحاجة للتحويل لفتح الطريقة الكلاسيكية ودون حدوث اي تعقيدات او مضاعفات.

الاستنتاجات: حصوات المرارة الكبيرة أو العملاقة يزيد من خطر حدوث مضاعفات، ومن الضروري استئصال المرارة بالمنظار في المرضى الذين لا يعانون من أعراض. حتى بالنسبة للحصوات المرارية الكبيرة العملاقة، وجد أن استئصال المرارة بالمنظار هو العلاج المفضل بدلاً من استئصال المرارة المفتوحة ويجب إجراؤه بواسطة جراحين بالمنظار ذوي خبرة، مع الأخذ في الاعتبار إمكانية التحويل إلى الفتح في حالة عدم القدرة على كشف التشريح والصورة الواضحة في القنوات الصفراوية المجاورة وأي صعوبات فنية أثناء العملية. حالتنا المذكورة هي أكبر حصوات المرارة من حيث الحجم التي تم الإبلاغ عنها في الأدبيات المسترجعة بالمنظار في مدينة أربيل وإقليم كردستان العراق.

الكلمات المفتاحية: حصوات المرارة العملاقة، مرض حصوات المرارة، حصوات المرارة كبيرة الحجم، استئصال المرارة بالمنظار.

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