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DISSOCIAÇÃO METABÓLICA E PREDITORES DE RISCO DA DOENÇA ÚLCERA PÉPTICA: UMA ANÁLISE CLÍNICA E BIOQUÍMICA

METABOLIC DYSREGULATION AND RISK PREDICTORS OF PEPTIC ULCER DISEASE: A CLINICAL AND BIOCHEMICAL ANALYSIS

اختلال التمثيل الغذائي وعوامل الخطر لمرض القرحة الهضمية: تحليل سريري كيموحيوي

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RESUMO

Introdução: As úlceras pépticas são erosões dolorosas do revestimento do estômago ou do intestino, podendo causar sangramentos e desconforto prolongado, entre outros riscos graves à saúde. **Objetivo**: O objetivo deste estudo foi identificar fatores de risco preditores e indicadores bioquímicos associados ao aumento da prevalência da doença ulcerosa péptica (DUP) em adultos iraquianos. **Métodos**: O estudo incluiu 110 participantes (idade média: 39 anos) submetidos à endoscopia gastrointestinal, dos quais 40 eram controles saudáveis e 70 apresentavam DUP. Foram avaliadas características demográficas e níveis de enzimas hepáticas e pancreáticas. O estudo foi conduzido de julho a outubro de 2024 no Hospital Universitário Marjan e em clínicas gastrointestinais afiliadas. **Resultados**: Os pacientes com DUP apresentaram níveis significativamente mais altos de colesterol, triglicerídeos e LDL, além de níveis mais baixos de HDL. A deficiência de vitamina D (< 20 ng/mL) foi identificada como um importante fator de risco, com os pacientes ulcerosos exibindo níveis significativamente mais baixos (15 vs. 26 ng/mL) e um risco seis vezes maior de desenvolvimento de úlcera. Os pacientes também apresentaram elevações na amilase pancreática (94 vs. 82 U/L), enquanto as enzimas hepáticas estavam ligeiramente mais baixas. Além disso, o risco de DUP foi fortemente associado à infecção por H. pylori (OR 4,24, p = 0,001) e ao tabagismo atual (OR 3,96, p = 0,001). **Discussão**: A deficiência de vitamina D emergiu como o fator de risco mais forte para DUP, influenciando negativamente a integridade da mucosa intestinal e a regulação do estresse oxidativo. A deficiência de vitamina D também afeta as proteínas das junções celulares, aumentando a translocação bacteriana e o dano mucoso. Além disso, a hipercolesterolemia e o tabagismo foram associados a um risco maior de úlcera, ressaltando a necessidade de intervenções metabólicas e mudanças no estilo de vida. **Conclusões**: A conclusão destaca o impacto da deficiência de vitamina D, dislipidemia e alterações nas enzimas pancreáticas no agravamento do estresse oxidativo e na comprometimento da integridade da mucosa intestinal em pacientes com DUP.

Palavras-chave: Enzimas hepatopancreáticas, Doença Ulcerosa Péptica, H. pylori, Deficiência de Vitamina D3

ABSTRACT

Background: Peptic ulcers are excruciating erosions of the stomach or intestinal lining that can cause bleeding and long-term discomfort, among other major health risks. **Aim**: The purpose of this study was to identify predictors, risk factors, and biochemical indicators associated with increased peptic ulcer disease (PUD) in adult Iraqis. **Methods**: The study involved 110 participants (mean age: 39 years) who underwent gastrointestinal endoscopy, consisting of 40 healthy controls and 70 patients with peptic ulcer disease (PUD). Demographic characteristics and hepatopancreatic enzyme levels were assessed. The study was conducted from July to October 2024 at Marjan Teaching Hospital and affiliated gastrointestinal clinics. **Results**: PUD patients showed higher cholesterol, triglycerides, and LDL levels, along with lower HDL. Vitamin D deficiency (<20 ng/mL) was a

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major risk factor, with ulcer patients exhibiting significantly lower levels (15 vs. 26 ng/mL) and a sixfold increase in ulcer risk. Elevated pancreatic amylase (94 vs. 82 U/L), while slightly lower than liver enzymes. Additionally, PUD risk was strongly associated with H. pylori infection (OR 4.24, p = 0.001) and current smoking (OR 3.96, p = 0.001). **Discussion**: Vitamin D deficiency emerged as the strongest PUD risk factor, impacting gut mucosal integrity and oxidative stress regulation. It also affects tight junction proteins, reducing bacterial translocation and mucosal damage. Additionally, hypercholesterolemia and smoking were linked to higher ulcer risk, underscoring metabolic and lifestyle intervention needs. **Conclusions**: The conclusion underscores the impact of vitamin D deficiency, dyslipidemia, and pancreatic enzyme changes in exacerbating oxidative stress and compromising gut mucosal integrity in PUD.

Keywords: Hepatopancreatic enzymes, Peptic Ulcer Disease, H. pylori, and Vitamin D3 deficiency.

الخلاصة

الخلفية :القرحة الهضمية هي تآكلات مؤلمة في بطانة المعدة أو الأمعاء يمكن أن تسبب نزيفًا وانزعاجًا طويل الأمد، بالإضافة إلى مخاطر صحية كبيرة أخرى. **الهدف** :كان الهدف من هذه الدراسة تحديد العوامل المسببة للمخاطر والعوامل الحيوية الكيميائية المرتبطة بزيادة مرض القرحة الهضمية (PUD) لدى البالغين العراقيين. **الطرق** :شملت الدراسة 110 مشاركًا (بمتوسط عمر 39 سنة) خضعوا لتنظير الجهاز الهضمي، ويتكونون من 40 شاهدًا صحيًا و70 مريضًا يعانون من مرض القرحة الهضمية .(PUD) تم تقييم الخصائص الديموغرافية ومستويات إنزيمات الكبد والبنكرياس. أُجريت الدراسة من حزيران إلى تشرين الاول 2024 في مستشفى مرجان التعليمي والعيادات التابعة له. **النتائج** :أظهر مرضى القرحة الهضمية مستويات مرتفعة من الكوليسترول والدهون الثلاثية وLDL، بالإضافة إلى انخفاض .HDL كان نقص فيتامين د 20>) نانوغرام/مل) عامل خطر رئيسي، حيث أظهر المرضى المصابون بالقرحة مستويات أقل بشكل ملحوظ (15 مقابل 26 نانوغرام/مل) مع زيادة خطر القرحة بمقدار ستة أضعاف. تم العثور على زيادة في الأميليز البنكرياسي (94 مقابل 82 وحدة/لتر)، بينما كانت إنزيمات الكبد منخفضة قليلاً. بالإضافة إلى ذلك، كان خطر مرض القرحة الهضمية مرتبطًا بشدة بوجود عدوى الملوية البوابية = p ,4.24 OR) (0.001، 0.001 = p والتدخين الحالي 3.96 OR) ، **المناقشة** :ظهر نقص فيتامين د كأقوى عامل خطر لمرض القرحة الهضمية، حيث يؤثر على تكامل الغشاء المخاطي في الأمعاء وتنظيم الإجهاد التأكسدي. كما يؤثر على بروتينات الالتصاق السطحية، مما يقلل من الانتقال البكتيري وتلف الغشاء المخاطي. علاوة على ذلك، كانت فرط الكوليسترول والتدخين مرتبطين بزيادة خطر القرحة، مما يبرز الحاجة إلى تدخلات في العوامل الأيضية ونمط الحياة. **الاستنتاجات** :يؤكد الاستنتاج على تأثير نقص فيتامين د، والاختلالات الدهنية، وتغيرات إنزيمات البنكرياس في تفاقم الإجهاد التأكسدي والتأثير على تكامل الغشاء المخاطي في مرض القرحة الهضمية.

الكلمات المفتاحية: إنزيمات الكبد والبنكرياس، مرض القرحة الهضمية، الملوية البوابية، ونقص فيتامين

1. INTRODUCTION:

Peptic ulcer disease (PUD), characterized by the development of open sores in the gastric or duodenal mucosa, remains a prevalent gastrointestinal disorder associated with significant morbidity and healthcare costs worldwide. The pathogenesis of PUD is complex and multifactorial, involving interactions between gastric acid secretion, mucosal defense mechanisms, and Helicobacter pylori (H. pylori) infection (Sheneni *et al*., 2023). While the primary etiological factors include H. pylori infection, the use of non-steroidal anti-inflammatory drugs (NSAIDs), and smoking, emerging evidence has highlighted the role of metabolic factors such as dyslipidemia and vitamin D deficiency in the progression of peptic ulcers (Yang *et al.,* 2023).
The formation of peptic ulcers is driven by an imbalance between protective mechanisms of the gastric mucosa, including mucin secretion, bicarbonate production, and antioxidant defenses, and aggressive factors such as acid and pepsin secretion (Lemos *et al.,* 2012). Chronic infection with H. pylori remains a major risk factor, particularly among middle-aged individuals under 50, and is associated with an increased risk of gastric adenocarcinoma (Yang *et al.,* 2023).

Recent studies have underscored the significance of vitamin D deficiency as a potential contributing factor in PUD pathogenesis. Vitamin D, recognized for its immunomodulatory and anti-inflammatory properties, plays a critical role in maintaining mucosal integrity of the mucosal barrier by indirectly enhancing the expression of junctional proteins that constitute tight junctions (TJs) and adherens junctions (AJs) (Aggeletopoulou *et al.,* 2023). A deficiency in these junctional components can weaken the gut epithelial barrier, increasing permeability to pathogens and immunogenic substances. (Vemulapalli and Shirwaikar, 2025).

It has been shown to influence the expression of antimicrobial peptides, such as cathelicidin and defensins, which may limit H. pylori colonization and reduce inflammation in the gastric mucosa (Zhao *et al*., 2023). Moreover, vitamin D deficiency has been associated with increased oxidative stress and impaired mucosal repair mechanisms, potentially exacerbating the severity of ulcerative lesions (Tan *et al.,* 2022).

Furthermore, vitamin D is implicated in lipid metabolism, and its deficiency has been correlated with dyslipidemia, characterized by elevated triglycerides, LDL-C, and reduced HDL-

C levels (Lemos *et al*., 2012). Dyslipidemia may exacerbate oxidative stress and endothelial dysfunction, further compromising gastric mucosal defenses and increasing the risk of ulcer formation. Consequently, the interplay between vitamin D deficiency, dyslipidemia, and PUD suggests that metabolic factors may act as potential predictors of ulcer risk and severity.

Given the complex pathophysiology of PUD and the potential influence of metabolic and nutritional factors, the present study aims to investigate the predictive value of biochemical markers, lipid profiles, and vitamin D levels in assessing the risk and severity of peptic ulcer disease. Identifying these predictors may provide valuable insights for developing targeted therapeutic strategies and preventive measures for high-risk populations.

2. MATERIALS AND METHODS:

2.1. Materials

2.1.1. Study Population and Clinical Assessment:

A cross-sectional study was conducted between March and October 2024, involving 110 participants (aged 20–65) who presented for upper gastrointestinal endoscopy at the Gastroenterology Center within the Morgan Teaching Hospitals and an external Gastroenterology Clinic in Babylon province, Iraq. Endoscopy, a procedure involving the insertion of a flexible camera-equipped tube through the mouth to visualize the stomach and duodenum (Figure 1), served as the diagnostic method for peptic ulcers. Based on the endoscopic findings, participants were divided into two groups: a control group of 40 individuals without peptic ulcers and a study group of 70 individuals with peptic ulcers. Comprehensive demographic information, including body mass index (BMI), age, smoking habits, PDU history, and sex, was collected from each participant using standardized questionnaires and a review of their medical records. Participants with a history of chronic liver or kidney disease, autoimmune disorders, metabolic disorders, cancer, prior gastric surgery, or those who had used vitamin D supplements in the preceding were excluded from the study.

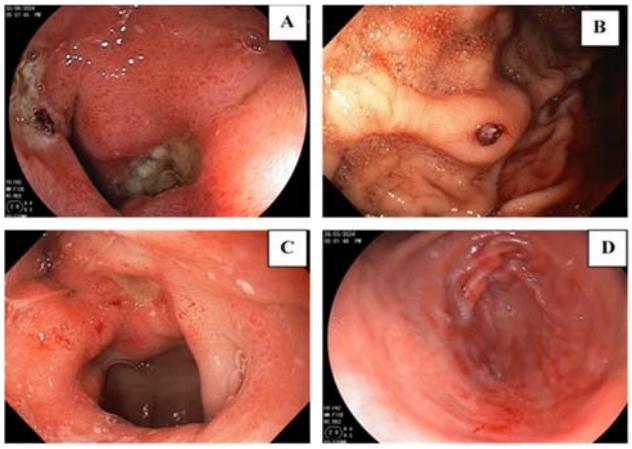

Figure 1: Peptic Ulcer in the stomach and duodenum under Endoscope. (Abd-Alameer & Sharba, 2024).

The endoscopic images reveal reddened and inflamed areas of the stomach lining, indicative of gastritis. Several images (A, B, and C) show mucosal defects or craters, some with exudates, suggestive of peptic ulcers. The tissue around these potential ulcers appears erythematous and inflamed. In contrast, image D presents a normal gastric mucosa without signs of ulceration.

2.1.2. Biochemical Reagents and Analytical Equipment

Biochemical analyses were performed using the Cobas c111 clinical chemistry analyzer (Roche Diagnostics), a fully automated system designed for precise enzyme measurement. The Cobas c111 was employed for the quantification of various enzymes, utilizing specific Roche reagents as follows: ALT (Cat. No. 20764911), AST (Cat. No. 20764920), ALP (Cat. No. 20764937), amylase (Cat. No. 20764982), and lipase (Cat. No. 20764999). Calibration of the analyzer was achieved using PreciControl ClinChem Multi 1 and 2, along with the Calibrator f.a.s. (Roche Diagnostics). Quality control protocols included the verification of test results against established control values to ensure data integrity and analytical precision. The analyzer's automated system minimized manual intervention, thereby enhancing reproducibility and reducing potential measurement bias.

2.2. Methods

A five-milliliter venous blood sample was obtained from each participant. Serum was separated by centrifugation at 3,000 rpm for 10

minutes and then stored at -20 °C until further analysis.

2.2.1. Serum Vitamin D3 Concentrations

Serum concentrations of vitamin D3 were measured using enzyme-linked immunosorbent assay (ELISA) kits provided by Bioassay Technology Laboratory (China, CAT No. E1546Hu). The assay was performed in accordance with the manufacturer's instructions. Briefly, serum samples, calibrators, and controls were added to the pre-coated microplate wells and incubated with a specific antibody against vitamin D3. Following the addition of substrate solution, the absorbance of each well was determined spectrophotometrically. The concentration of vitamin D3 was calculated by generating a standard curve using known calibrator concentrations, thereby enabling quantitative assessment.

2.2.2. Lipid Profile, Liver Enzyme, and Pancreatic Enzymes

The lipid profile, encompassing total cholesterol (CHO), high-density lipoprotein (HDL), and triglycerides (TG), alongside the liver and pancreatic enzymes amylase and lipase, were determined using automated biochemical analyzers following established laboratory protocols (Cobas c 111 analyzers). Fasting venous blood samples were collected in plain or serum-separating tubes (SST). Following collection, samples were centrifuged at 3,000–3,500 rpm for 10 minutes to separate the serum. The resulting serum samples were then loaded onto the analyzer's sample rack, and the Cobas c 111 system automatically processed the samples by aspirating and mixing them with the appropriate reagents, followed by photometric measurement of absorbance. Serum analyte concentrations were determined using Equation 1, but the Calculation of LDL-C and VLDL-C was performed using the Friedewald equations (Martin *et al*., 2013) as Equation 2:

[Analyte] (mg/dl) = (Absorbance of Sample/ Absorbance of Standard) ×[Standard] (mg/dl) (Eq.1)

[LDL-C] (mg/dl) = [Total Cholesterol] - ([Triglycerides] / 5) - [HDL Cholesterol]; [VLDL-C] (mg/dl) = [Triglycerides] / 5 (Eq.2)

2.2.3. Investigation of Helicobacter pylori

The assessment of Helicobacter pylori (H. pylori) infection was conducted using two diagnostic techniques: the urea breath test and the stool antigen test, each selected to provide complementary diagnostic accuracy. In the urea breath test, the Heliprobe® system (manufactured in Sweden) was employed to detect H. pylori infection through the measurement of urease activity. Participants were instructed to fast for 6 to 7 hours prior to the procedure to ensure optimal test sensitivity. Initially, a baseline breath sample was obtained by having the patient exhale into a balloon-like container or tube. Subsequently, the patient ingested a urea solution labeled with a carbon isotope, either radioactive or non-radioactive, designed to react with urease produced by H. pylori. After a waiting period of 10–30 minutes, a second breath sample was collected. The two breath samples were then analyzed and compared to detect the presence of labeled carbon dioxide, indicative of urease-mediated hydrolysis of urea by H. pylori. This stepwise approach allowed for the precise detection of H. pylori infection with high sensitivity and specificity.

For the stool antigen test, stool samples were collected and subjected to enzymatic immunoassay analysis using a commercial diagnostic kit developed explicitly for H. pylori antigen detection. The enzyme immunoassay utilized monoclonal antibodies to identify H. pylori antigens, providing a non-invasive diagnostic alternative that complements the urea breath test. The combined use of both diagnostic methods was intended to enhance overall diagnostic accuracy and mitigate the risk of false-negative results, thereby ensuring a more comprehensive assessment of H. pylori infection status.

2.3. Statistical Analysis

Statistical analysis was performed using IBM SPSS 28 (IBM Corp., Chicago, Illinois, USA). The normality of continuous data was assessed using the Kolmogorov-Smirnov test, and normally distributed data were presented as mean ± standard deviation (SD). Categorical data were summarized as frequencies and percentages, and group comparisons were conducted using chi-square tests. Differences between groups for continuous variables were evaluated using independent t-tests. Logistic regression was employed to identify independent risk factors for peptic ulcers. A p-value of less than 0.05 was considered statistically significant for all analyses.

3. RESULTS AND DISCUSSION:

3.1. Results

3.1.1. Demographics Distribution of Risk Factors in Peptic Ulcer Disease Versus Controls

The age distribution varied by category (χ^2=9.71, p=0.021), and the two groups (40 Ctrl, 70 PUD) differed considerably (χ^2=8.18, p=0.004) in our cohort of 110 participants (Table 1). PUD cases were overrepresented in the 30–39 and ≥ 50-year age categories. A non-significant correlation was found between smoking status and PUD (48.2% smokers vs. 51.8% non-smokers; χ^2=0.15, p=0.703), whereas sex proportions were similar (χ^2=2.95, p=0.086). The undefined history variable (χ^2=1.31, p=0.253) and BMI categories did not exhibit any significant effects (χ^2=4.38, p=0.112). PUD was more likely to have a vitamin D insufficiency (< 20 ng/mL) (χ^2=4.40, p=0.036), with a mean of 18.83 ± 9.45 ng/mL.

Despite the non-random distribution of ulceration types (non, duodenal, and gastric; χ^2=10.95, p=0.012), which favored stomach ulcers, H. pylori status did not change (χ^2=0.58, p=0.446).

3.1.2. Biochemical Profiles in Peptic Ulcer Disease and Controls

Comprehensive biochemical analysis revealed notable differences between PUD patients and healthy controls across multiple parameters (Table 2).

Total cholesterol levels averaged 175.99 ± 47.17 mg/dL across all participants, with a significantly higher prevalence of hypercholesterolemia (≥ 200 mg/dL) among PUD patients (χ^2 = 10.51, p = 0.001). Similarly, the mean triglyceride concentration was 171.36 ± 66.89 mg/dL, with elevated triglyceride levels (≥ 150 mg/dL) strongly associated with PUD status (χ^2 = 55.31, p < 0.001).

Mean LDL cholesterol concentration (103.57 ± 37.36 mg/dL) did not significantly differ between groups (χ^2 = 0.33, p = 0.567). Average HDL cholesterol was 34.04 ± 8.79 mg/dL, while VLDL cholesterol averaged 34.27 ± 13.38 mg/dL across all participants.

Regarding hepatic enzymes, mean ALT and AST activities were 11.74 ± 4.21 U/L and 16.67 ± 4.98 U/L, respectively. Mean ALP activity was 51.73 ± 10.80 U/L, and total serum bilirubin averaged 0.35 ± 0.11 mg/dL.

Pancreatic enzymes analysis revealed a mean amylase activity of 89.50 ± 20.96 U/L and a mean lipase activity of 41.60 ± 14.38 U/L across the study population.

3.1.2. Categorical Distribution and Logistic Regression of Risk Factors for PUD

Multivariate logistic regression analysis identified several strong independent predictors of peptic ulcer disease (Table 3). Prior history of PUD emerged as a significant risk factor (OR 5.66, 95% CI 2.28–14.04; p < 0.001), increasing the odds of current PUD nearly six-fold. Similarly, vitamin D deficiency (< 20 ng/mL) demonstrated the strongest association with PUD development (OR 6.48, 95% CI 2.75–15.27; p < 0.001), conferring more than six times greater risk. Hypercholesterolemia (total cholesterol ≥ 200 mg/dL) also substantially increased PUD risk (OR 6.35, 95% CI 2.37–17.04; p < 0.001).

Helicobacter pylori infection represented another significant risk factor (OR 4.24, 95% CI 1.80–10.02; p = 0.001), as did current smoking status (OR 3.96, 95% CI 1.70–9.19; p = 0.001). Both factors increased PUD risk approximately fourfold. Additional metabolic parameters associated with elevated PUD risk included hypertriglyceridemia (≥ 150 mg/dL: OR 2.88, 95% CI 1.29–6.41; p = 0.010) and elevated LDL cholesterol (≥ 100 mg/dL: OR 2.25, 95% CI 1.02–4.97; p = 0.045), both approximately doubling the risk of disease. However, no sex nor age group reached significance: > 50 years was completely neutral (OR 1.20, p = 0.770), while 30–39 years (OR 0.41, p = 0.090) and 40–49 years (OR 0.27, p = 0.056) displayed a non-significant tendency toward decreased risk compared to 20–29 years. Similarly, there was no difference between male and female sex (OR 0.53, p = 0.120). The BMI subgroups showed conflicting results: overweight/obesity (OR 0.27, p = 0.007), less than underweight trended toward increased risk (OR 3.65, p = 0.073) (Figure 2).

3.1.3. Dyslipidemia, Hepatopancreatic Enzyme Alterations, and Vitamin D3 Associated with Peptic Ulcer Disease

In this cohort, peptic ulcer disease (PUD) patients differed significantly from healthy controls across multiple biochemical parameters.

Liver enzymes exhibited modest but significant reductions in PUD patients compared to controls. ALT levels were lower in PUD patients

(10.82 ± 3.97 vs. 13.37 ± 4.18 U/L, p = 0.002, Figure 3A), as were AST (15.83 ± 4.68 vs. 18.13 ± 5.21 U/L, p = 0.024) and ALP (49.83 ± 10.19 vs. 55.05 ± 11.14 U/L, p = 0.017, Figure 3B). Total serum bilirubin concentrations remained comparable between groups (0.33 ± 0.09 vs. 0.37 ± 0.13 mg/dL, p = 0.122, Figure 3C).

PUD patients demonstrated a pro-atherogenic lipid profile characterized by significantly elevated levels of total cholesterol (193.15 ± 55.07 vs. 157.96 ± 33.59 mg/dL, p = 0.001, Figure 3A), triglycerides (185.80 ± 71.17 vs. 147.71 ± 52.69 mg/dL, p = 0.004, Figure 3B), LDL (110.32 ± 39.08 vs. 91.78 ± 31.20 mg/dL, p = 0.008, Figure 3E), and VLDL (36.97 ± 14.13 vs. 29.54 ± 10.54 mg/dL, p = 0.002, Figure 3D). Conversely, HDL levels were significantly lower in PUD patients (32.55 ± 6.92 vs. 36.64 ± 10.96 mg/dL, p = 0.037, Figure 3C).

Regarding pancreatic enzymes, serum amylase was significantly higher in PUD patients (93.53 ± 24.18 vs. 82.46 ± 10.67 U/L, p = 0.001), while lipase activity showed no significant difference between groups (43.12 ± 14.76 vs. 38.95 ± 13.47 U/L, p = 0.145, Figure 4A-B).

Notably, vitamin D levels were markedly lower in PUD patients compared to controls (14.61 ± 6.74 vs. 26.22 ± 9.00 ng/mL, p < 0.001, Figure 5), representing a 44% reduction in this essential nutrient.

3.2. Discussion

The results of this investigation identify several key predictors of peptic ulcer disease (PUD), notably emphasizing the significant roles of vitamin D deficiency, hypercholesterolemia, H. pylori infection, and smoking status. Vitamin D deficiency exhibited the highest odds ratio among the analyzed factors, indicating a strong association with increased PUD risk. This finding corroborates existing literature that highlights vitamin D's function in preserving gastrointestinal mucosal integrity and modulating oxidative stress pathways (Wang *et al.,* 2024; Fekete *et al.,* 2025). Specifically, vitamin D influences the expression of tight junction proteins, which helps prevent bacterial translocation and subsequent mucosal injury (Kellermann *et al.,* 2020; Sharba & Wajid, 2024).

Hypercholesterolemia was also identified as a notable predictor, suggesting that elevated cholesterol levels may contribute to heightened oxidative stress and inflammatory processes within the gastric mucosa, thereby facilitating ulcer development. The relationship between dyslipidemia and PUD is supported by evidence indicating that lipid peroxidation can compromise the mucosal barrier. Elevated levels of triglycerides and low-density lipoprotein (LDL) cholesterol were associated with increased risk, reflecting underlying metabolic disturbances in affected individuals (Temesgen *et al.,* 2022).

The lipid profile observed in PUD patients tends to be pro-atherogenic, characterized by increased total cholesterol, triglycerides, LDL, and very low-density lipoprotein (VLDL). Such dyslipidemia may promote mucosal injury through mechanisms involving oxidative stress and endothelial dysfunction. Elevated LDL may contribute to foam cell formation in the gastric microvasculature, akin to processes involved in atherosclerosis. At the same time, hypertriglyceridemia can increase reactive oxygen species (ROS), impairing mucosal defenses by degrading prostaglandins. These mechanisms are supported by animal models demonstrating that high-fat diets accelerate ulcer formation via activation of inflammatory pathways like TLR4/NF-κB (Li *et al*., 2022). However, some studies have reported no significant lipid-PUD association in individuals with well-controlled metabolic syndromes, suggesting that dyslipidemia's contribution may be secondary to systemic inflammation. Additionally, reduced HDL cholesterol levels in PUD patients (p = 0.037) further emphasize its anti-inflammatory role, as HDL inhibits monocyte adhesion to endothelial cells, a process vital to preventing mucosal injury (Wu *et al.,* 2022; Wu *et al.,* 2023).

According to this study, H. pylori infection is a significant risk factor for PUD, which is consistent with a large body of research that emphasizes the pathogen's role in causing mucosal inflammation and ulcer development (Bashir & Khan, 2023). Helicobacter pylori's pathogenicity is driven by key virulence factors such as cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A VacA, which disrupt epithelial integrity, induce apoptosis, and promote chronic inflammation (Hundt *et al.,* 2023). The bacterium uses its flagella to penetrate the mucous layer and adheres to gastric epithelial cells via adhesins like blood group antigen-binding adhesin (BabA) and sialic acid-binding adhesin (SabA), facilitating colonization and immune evasion (Yang *et al.,* 2023). Its urease enzyme neutralizes gastric acid by converting urea into ammonia, enabling its survival in the acidic stomach environment (Shaikh *et al.,* 2023).

Additionally, smoking was found to be a significant risk factor, most likely because of mechanisms like delayed ulcer healing, impaired mucosal blood flow, and increased stomach acid output. Cigarette smoke is a significant risk factor for peptic ulcer disease (PUD), primarily due to its high concentration of free radicals. These reactive species include aldehydes, quinones, benzo(a)pyrene, epoxides, and peroxides (Marcilla *et al*., 2012), which generate reactive oxygen species (ROS). Inadequate neutralization of ROS by antioxidants results in oxidative stress, contributing to mucosal damage and ulcer formation. Moreover, cigarette smoke exacerbates PUD by impairing the gastric mucosal defense mechanisms and delaying ulcer healing, likely due to the toxic effects of its chemical constituents. Smoking has also been associated with increased colonization of Helicobacter pylori, a major etiological factor in PUD. The oxidative environment created by ROS can disrupt the gastric mucosa, facilitating H. pylori adhesion and proliferation, thereby amplifying the ulcerogenic effect (Kim *et al.,* 2017; Berkowitz *et al*., 2018

However, in this cohort, neither sex nor age showed any discernible prognostic effect. This result deviates from some earlier studies that found an increased risk of PUD as people age (Collatuzzo *et al*., 2022; Liu *et al*., 2024).

The findings regarding BMI revealed that underweight individuals exhibited a higher risk of PUD, while those who were overweight or obese appeared to have a protective effect. This aligns with Akbulut *et al.* (2021), who identified decreased BMI and older age as independent risk factors for PUP. In the current study, both low BMI and advanced age emerged as significant predictors of PUP in multivariate analysis, which is consistent with Akbulut's findings. Although some studies have reported conflicting data on the relationship between obesity and PUD (Kim *et al*., 2017), the association between low BMI and increased PUP risk has not been previously emphasized, highlighting the need for further investigation. Additionally, older age was also associated with higher PUP risk and increased mortality in other studies, with a higher prevalence of comorbidities, NSAID use, and larger ulcer sizes (>1 cm) in the elderly group (Kim *et al*., 2017). This pattern may reflect differences in metabolic status, inflammatory responses, or nutritional reserves.

Lower ALT and AST levels in PUD patients go counter to traditional models of hepatobiliary disease, but they are similar to findings in chronic inflammatory conditions such as rheumatoid arthritis, where systemic cytokines inhibit the production of hepatic enzymes (McConaghy *et al*., 2023). This could be an energy-saving compensation strategy during protracted inflammation. As suspected in autoimmune pancreatitis, elevated serum amylase ($p = 0.001$) is consistent with autoantibody cross-reactivity or pancreatic duct obstruction caused by H. pylori (Giroux *et al*., 20243. In contrast to studies that link H. pylori to pancreatic exocrine dysfunction, the absence of lipase significance ($p = 0.145$) may be the result of differing enzyme stability or timing of the sampling (Kapoor *et al.,* 2021; Lin *et al*., 2021).

As a predictor of PUD, vitamin D insufficiency (<20 ng/mL) is strongly supported by its involvement in modifying innate immunity (OR 6.48; $p < 0.001$). Vitamin D may influence the development and progression of peptic ulcer disease through several mechanisms, primarily involving its effects on gastric physiology, immune response, and cellular health. The following sections outline these potential mechanisms. Vitamin D has been shown to exert gastroprotective effects, as evidenced by studies where vitamin D3 treatment reduced gastric acidity and ulcer indices in animal models. This protection is attributed to the inhibition of oxidative stress and stimulation of mucus production, which are crucial for maintaining gastric mucosal integrity (Oghogho and Uwaifoh, 2021; Abd-Alameer & Sharba, 2024).

Vitamin D plays a significant role in modulating the immune response within the gastrointestinal tract. It interacts with the mucosal immune system, potentially influencing inflammatory conditions that can exacerbate ulcer formation (Peppelenbosch *et al.,* 2017; *Nabavi et al.,* 2022). Adequate vitamin D levels may help in reducing inflammation, thereby lowering the risk of ulcer development. Deficiency in vitamin D has been linked to impaired gastric epithelial cell proliferation and altered gastric gland function. Studies indicate that vitamin D deficiency can stimulate acid secretion and disrupt normal cell lineage differentiation in gastric tissues, which may contribute to ulcer formation (Sirajudeen *et al.*, 2019; Sirajudeen *et al.,* 2023).

4. CONCLUSIONS:

The study highlights several critical risk factors associated with peptic ulcer disease (PUD), with vitamin D deficiency emerging as a prominent contributor due to its role in maintaining

gut mucosal integrity and reducing oxidative stress. Additionally, dyslipidemia, characterized by elevated LDL and triglycerides alongside reduced HDL, was identified as a significant risk factor, likely exacerbating oxidative damage to the gastric mucosa. Elevated pancreatic amylase levels further suggest a possible link between pancreatic dysfunction and ulcer development. Moreover, lifestyle factors such as smoking and hypercholesterolemia were strongly associated with increased PUD risk, indicating a complex interplay of metabolic and inflammatory pathways. These findings suggest that targeted interventions addressing vitamin D supplementation, lipid management, and pancreatic enzyme regulation may be strategic in mitigating PUD risk and preventing ulcer recurrence.

5. DECLARATIONS

5.1. Study Limitations

The study had several limitations that should be considered when interpreting the findings. First, the relatively small sample size (110 participants) could limit the statistical power and generalizability of the results to larger populations or different demographics. The cross-sectional design of the study further restricts the ability to establish causal relationships between the variables, as it only captures data at a single point in time. Additionally, the study was conducted at a single center, which may limit the external validity of the findings, as the results may not be applicable to other settings with different patient populations or healthcare systems. Furthermore, the study focused on a limited set of biomarkers, which may not comprehensively reflect the full spectrum of potential factors influencing the outcomes. Expanding the range of biomarkers in future studies could provide a more holistic understanding of the underlying mechanisms.

5.2. Acknowledgements

The authors would like to express their profound gratitude to the consultant physicians and dedicated staff members at the Digestive System Center, whose invaluable support and expertise significantly contributed to the successful completion of this study. Their unwavering commitment to patient care and research excellence facilitated the comprehensive data collection and clinical assessments essential to this investigation. The authors also extend their heartfelt appreciation to all participants, whose cooperation and willingness to share their medical histories and undergo diagnostic procedures made this research possible. Their participation was instrumental in advancing the understanding of the underlying biochemical and clinical factors associated with peptic ulcer disease.

5.3. Funding source

The authors funded this research. In accordance with the ethical guidelines of the Periódico Tchê Química, which do not allow donations from authors with manuscripts under evaluation (even when research funds are available), or in cases of authors' financial constraints, publication costs were fully absorbed by the journal under our Platinum Open Access policy, through the support of the Araucária Scientific Association (https://acaria.org/). This policy aims to ensure complete independence between the editorial process and any financial aspects, reinforcing our commitment to scientific integrity and equity in knowledge dissemination.

5.4. Competing Interests

The authors declare that they have no competing interests or conflicts of interest that could have influenced the work presented in this manuscript. This includes, but is not limited to, financial relationships, personal affiliations, intellectual property considerations, or other potential sources of bias. All authors have reviewed and approved this declaration, ensuring transparency and maintaining scientific integrity in the reporting of this research.

5.5. Open Access

5.6. Use of AI

The manuscript was written directly in English, with all sections carefully crafted to ensure clarity, accuracy, and precision in scientific communication. We employed AI tools to assist in refining the language and ensuring the correctness of technical terms and methodology descriptions. These translation tools were specifically used to translate the abstract into Portuguese, and the editors revised it. Following the AI-assisted editing, the authors thoroughly reviewed the manuscript to ensure all scientific content was accurate and the terminology used was appropriate. The authors are responsible for the accuracy and integrity of all content, and the AI tools were used solely to enhance the language for effective international dissemination of the research.

6. HUMAN AND ANIMAL-RELATED STUDIES

6.1. Ethical Approval

The study protocol was meticulously designed to adhere to the ethical principles delineated in the Declaration of Helsinki, emphasizing the safeguarding of participants' rights, dignity, and welfare. The protocol received formal approval from the Medical Ethics Committee of the University of Kufa in May 2024, following a comprehensive ethical review to ensure scientific validity and participant protection.

6.2. Informed Consent

Informed consent was rigorously obtained from all participants through a dual process involving both verbal and written documentation. Each participant was provided with a detailed explanation of the study's objectives, potential risks, benefits, and the right to withdraw without repercussions. Written consent was documented through participant signatures, thereby affirming their voluntary and informed participation. To maintain strict confidentiality, all data were anonymized and securely stored, accessible only to authorized researchers, thus aligning with data protection protocols. Additionally, explicit consent was obtained from both participants and researchers for the publication of research findings. This consent extended to the dissemination of de-identified data to ensure privacy and uphold the principles of transparency and ethical research dissemination.

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Table 1. *Distribution of Risk Factors and Biochemical Profiles in Peptic Ulcer Disease Versus Controls*

Demographics criteria		**Total N=110**		**Chi-Square p-value**
		N	**%**	
Groups	Healthy Controls (Ctrl)	40	36.4%	8.18 0.004*
	Peptic Ulcer Disease (PDU)	70	63.6%	
Age (year)	Mean ± SD	39.36±14.78		
	20-29 yr.	30	27.3%	9.71 0.021*
	30-39 yr.	36	32.7%	
	40-49 yr.	14	12.7%	
	≥ 50 yr.	30	27.3%	
Sex	Male	46	41.8%	2.95 0.086 Ns
	Female	64	58.2%	
Smoking	Smoker	53	48.2%	0.15 0.703 Ns
	Non-Smoker	57	51.8%	
BMI (kg/m^2)	Mean ± SD	23.57±4.23		
	Underweight	31	28.2%	4.38 0.112 Ns
	Normal weight	32	29.1%	
	Overweight & Obese	47	42.7%	
History of PUD	Yes	49	44.5%	1.31 0.253 Ns
	No	61	55.5%	
Vitamin D3 (ng/ml)	Mean ± SD	18.83±9.45		
	Vt. D <20	66	60.0%	4.40 0.036*
	Vt. D ≥ 20	44	40.0%	
H. pylori test	Ve+	51	46.4%	0.58 0.446 Ns
	Ve-	59	53.6%	
Ulceration Types	Non	40	36.4%	10.95 0.012*
	Duodenal ulcer	25	22.7%	
	Gastric ulcer	45	40.9%	

Significant differences at *p-value ≤0.05, **<0.01. SD: Standard Division. NS: Non-significant

Table 2. *Assessment of Dyslipidemia and Enzyme Alterations in All Peptic Ulcer Patients and Controls*

Biochemical Profile		**Total N=110**		**Chi-Square p-value**
T. Chol. (mg/dl)	Mean ± SD	175.99±47.17		
	< 200 mg/dl	72	65.5%	10.51
	> 200 mg/dl	38	34.5%	0.001*
T.G	Mean ± SD	171.36±66.89		
	< 150 mg/dl	94	85.5%	55.31
	> 150 mg/dl	16	14.5%	0.0001**
LDL	Mean ± SD	103.57±37.36		
	< 100 mg/dl	52	47.3%	0.33
	> 100 mg/dl	58	52.7%	0.567 Ns
HDL (mg/dL)	Mean ± SD	34.04±8.79		
VLDL (mg/dL)	Mean ± SD	34.27±13.38		
ALT (U/L)	Mean ± SD	11.74±4.21		
AST (U/L)	Mean ± SD	16.67±4.98		
ALP (U/L)	Mean ± SD	51.73±10.80		
T.S.B (mg/dL)	Mean ± SD	0.35±0.11		
Amylase (U/L)	Mean ± SD	89.50±20.96		
Lipase (U/L)	Mean ± SD	41.60±14.38		

Significant differences at *p-value ≤0.05, **<0.01. SD: Standard Division. NS: Non-significant

Table 3. *Categorical Distribution and Logistic Regression of Risk Factors for PUD*

Variable	Category in PDU (vs. reference)	PUD n (%)	Ctrl n (%)	OR	95 % CI	p-value
Age (year)	20–29 (ref.)	22 (31.4 %)	8 (20.0 %)	1.00	–	–
	30–39	19 (27.1 %)	17 (42.5 %)	0.41	0.14–1.15	0.090
	40–49	6 (8.6 %)	8 (20.0 %)	0.27	0.07–1.03	0.056
	≥ 50	23 (32.9 %)	7 (17.5 %)	1.20	0.37–3.85	0.770
Sex	Female (ref.)	39 (55.7 %)	16 (40.0 %)	1.00	–	–
	Male	31 (44.3 %)	24 (60.0 %)	0.53	0.24–1.17	0.120
History	No (ref.)	29 (41.4 %)	32 (80.0 %)	1.00	–	–
	Yes	41 (58.6 %)	8 (20.0 %)	5.66	2.28–14.04	<0.001**
Smoking	Non-smoker (ref.)	28 (40.0 %)	29 (72.5 %)	1.00	–	–
	Smoker	42 (60.0 %)	11 (27.5 %)	3.96	1.70–9.19	0.001**
BMI (kg/m^2)	Normal weight (ref.)	23 (32.9 %)	9 (22.5 %)	1.00	–	–
	Underweight	28 (40.0 %)	3 (7.5 %)	3.65	0.88–15.08	0.073
	Overweight & Obese	19 (27.1 %)	28 (70.0 %)	0.27	0.10–0.70	0.007*
Vit D3	≥ 20 ng/mL (ref.)	17 (24.3 %)	27 (67.5 %)	1.00	–	–
	< 20 ng/mL	53 (75.7 %)	13 (32.5 %)	6.48	2.75–15.27	<0.001**
H. pylori	Negative (ref.)	29 (41.4 %)	30 (75.0 %)	1.00	–	–
	Positive	41 (58.6 %)	10 (25.0 %)	4.24	1.80–10.02	0.001*
Total Cholesterol	< 200 mg/dL (ref.)	33 (47.1 %)	34 (85.0 %)	1.00	–	–
	≥ 200 mg/dL	37 (52.9 %)	6 (15.0 %)	6.35	2.37–17.04	<0.001**
Triglycerides	< 150 mg/dL (ref.)	24 (34.3 %)	24 (60.0 %)	1.00	–	–
	≥ 150 mg/dL	46 (65.7 %)	16 (40.0 %)	2.88	1.29–6.41	0.010*
LDL	< 100 mg/dL (ref.)	28 (40.0 %)	24 (60.0 %)	1.00	–	–
	≥ 100 mg/dL	42 (60.0 %)	16 (40.0 %)	2.25	1.02–4.97	0.045*

Significant differences at p-value*<0.05, **<0.01. OR: odds ratio. CI: confidence interval.BMI categories: underweight (< 18.5), normal (18.5–24.9), overweight/obese (≥ 25 kg/m²). Vit D: deficient (< 20 ng/mL) vs. sufficient (≥ 20 ng/mL). H. pylori: Ve^+ vs. Ve^-

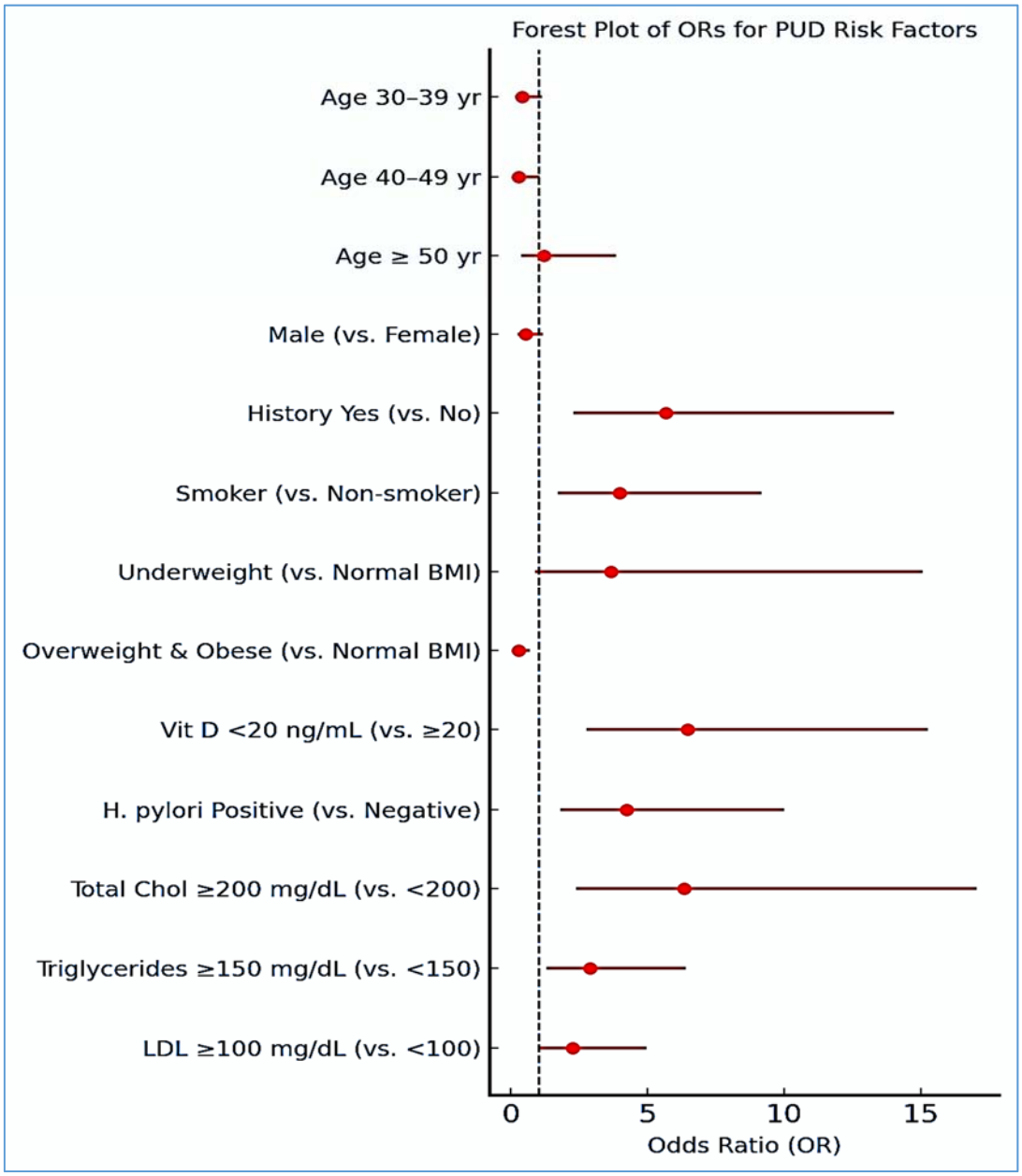

Figure 2. *Forest Plot of Adjusted Odds Ratios for Risk Factors Associated with Peptic Ulcer Disease*

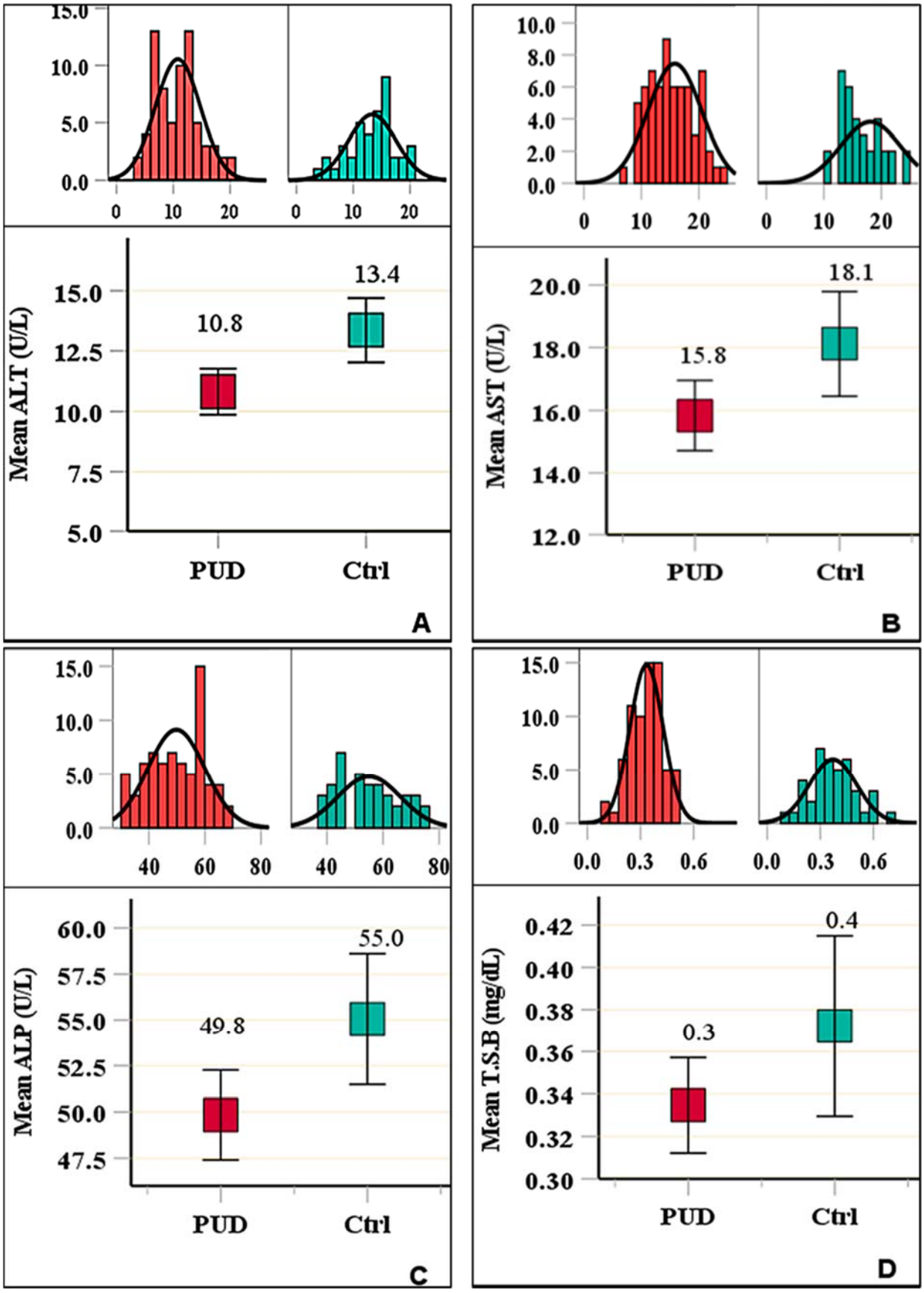

Figure 3. *Liver enzyme and total serum billirubib levels in PUD patients compared with the Healthy controls (A:ALT, B: AST, C: ALP, and D: T.S.B)*

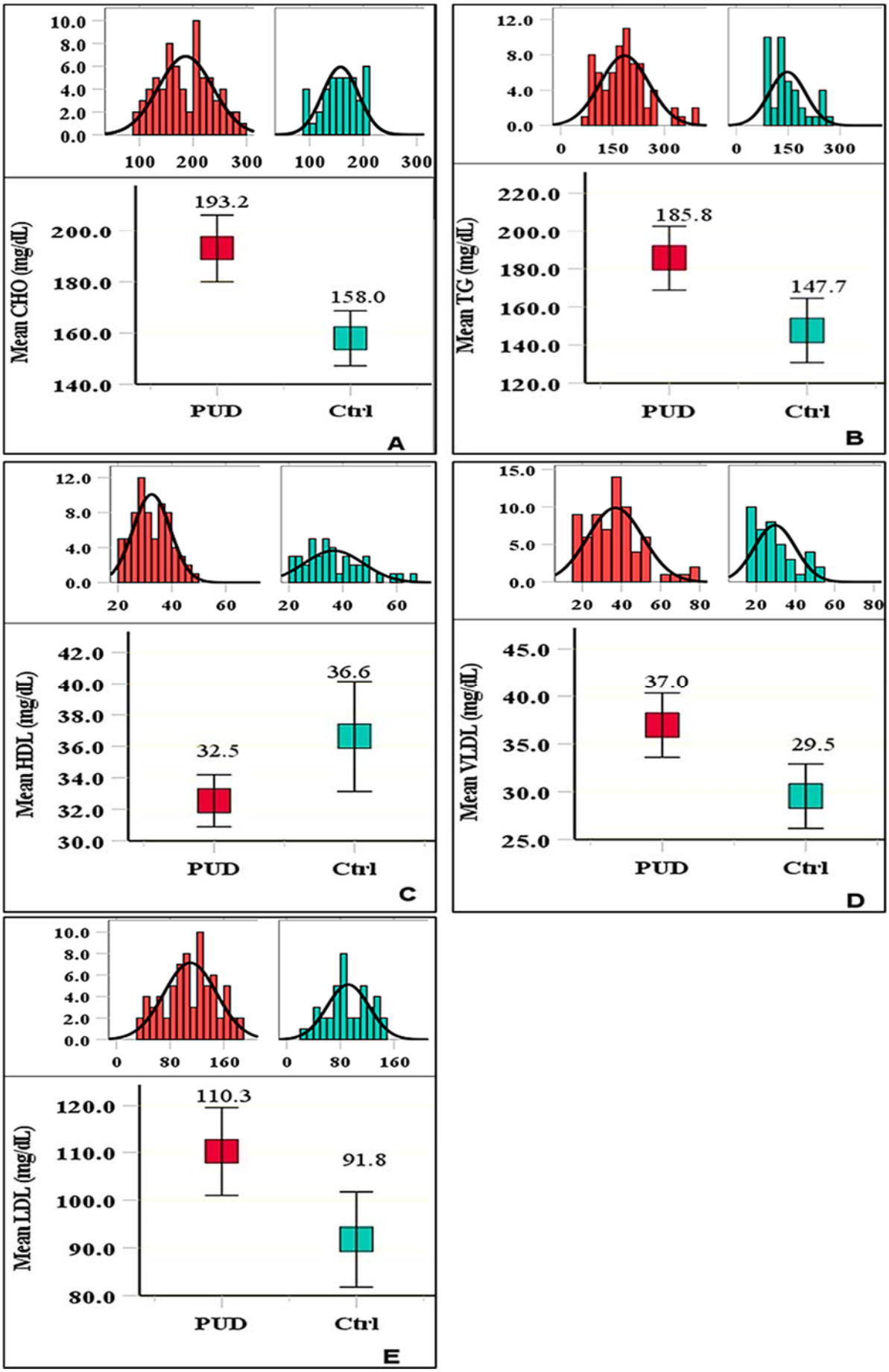

Figure 3. *Lipid profile in PUD patients compared with the Healthy controls (A: T. Cho., B: TG, C:HDL, D: VLDL, E: HDL)*

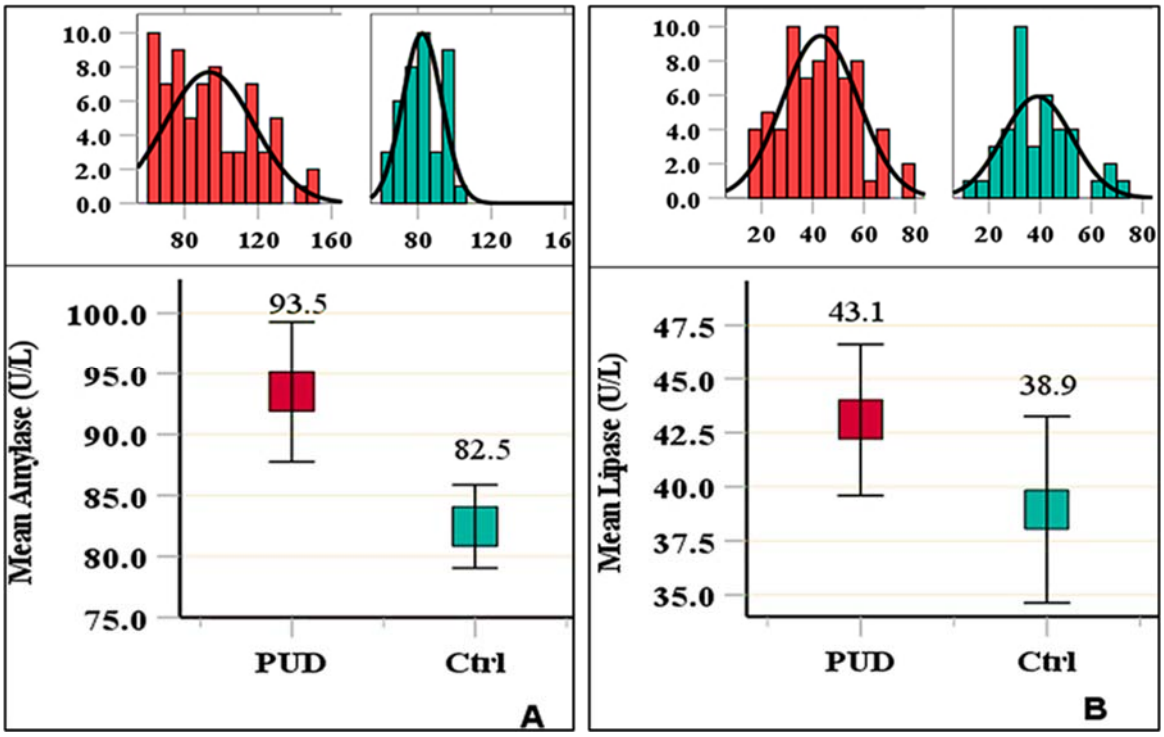

Figure 4. *Pancreatic enzyme in PUD patients compared with the Healthy controls (A: Amylase, and B: Lipase)*

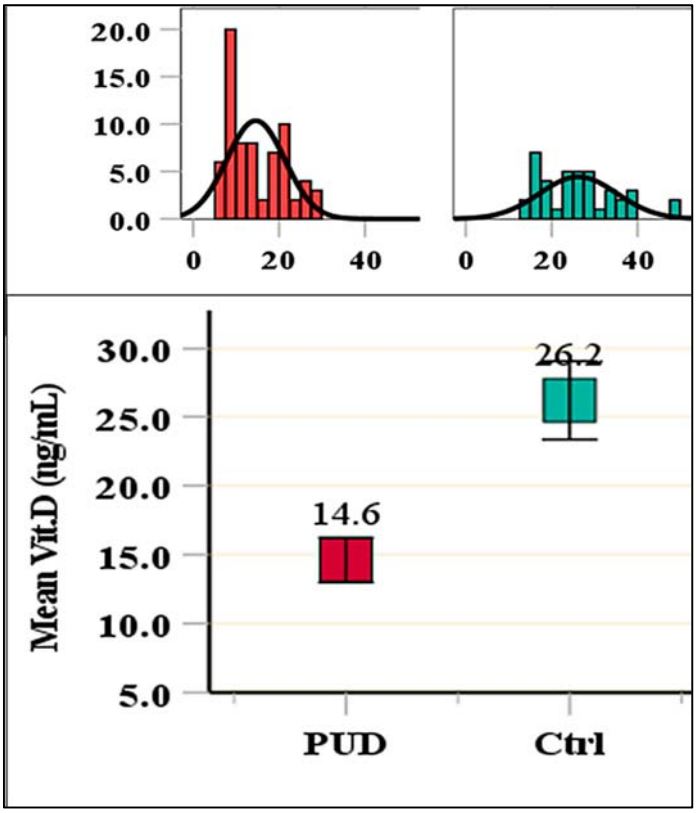

Figure 5*. Vitamin D3 levels in PUD patients compared with Healthy controls*