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(A Correlation of Osteonectin with Zinc and Some Biochemical Parameters in Iraqi Type II Diabetic Patients

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Abstract

Background: Chronic hyperglycemia, also known as high blood glucose, is a metabolic disorder that develops when the body cannot produce enough insulin or when its insulin response is compromised. Insulin is a crucial hormone that plays a vital role in carbohydrate, lipid, and protein metabolism. The current study aimed to investigate the potential associations between osteonectin with zinc ions (Zn^{+2}), sodium ions (Na^{+}), potassium ions (K^{+}), chloride ions (Cl^{-}), systolic blood pressure (SBP), blood pressure during diastole (DBP) and glucose levels in the blood while fasting in people who have type 2 diabetes mellitus (T2DM).

Materials and Methods: This research involved 42 patients from Al-Ramadi Teaching Hospital, along with 42 seems healthy controls (HCs). Zn^{+2} and osteonectin levels in the serum were measured using the enzyme-linked immunosorbent assay (ELISA). Serum levels of $Na^{+,}$ K^{+} and Cl^{-} levels were estimated using the C4000 device.

Results: Serum osteonectin (µg/mL) in T2DM patients was higher than in controls ($P < 0.0001$), while Zn^{+2}, K^{+}, Cl^{-}, SBP, DBP in T2DM patents were lower than controls.

A significant positive correlation was detected between osteonectin with K^{+} but, a non-significant positive correlation of osteonectin with $Na^{+,}$ SBP, DBP, and mean arterial blood pressure (MAP) was detected, osteonectin showed a strong inverse relationship with Cl- and Zn^{+2}, according to the findings.

The Rreceiver operating characteristic (ROC) curve indicates that osteonectin was a weaker sensitive marker in diagnosis of T2DM. in addition, SBP, MAP are intermediate markers, while osteonectin, Na^{+}, K^{+}, Cl^{-}, Zn^{+2}, and DBP were markers with poor predictive values, with area under curve (AUC) gave less than 0.6.

Conclusion : Patients' serum osteonectin levels were greater than those of healthy controls. osteonectin also showed weak correlations with zinc and the other variables studied, and the

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best correlation for osteonectin was with sodium ions.

Keywords

fasting serum glucose, sodium ions, potassium ions, chloride ions, blood pressure.

Introduction

A central element in the pathogenesis of T2DM is impaired insulin secretion. [1] T2DM is a prevalent metabolic disorder on a global scale, affecting approximately 500 million individuals. This condition is linked to substantial risks of both morbidity and mortality. [2,3]

When cells in the body, including those in the liver, muscles, and fat, develop an insulin resistance, it leads to type 2 diabetes. To overcome this resistance, the beta cells in the pancreas increase in number and secretion of insulin. However, there comes a point where this compensatory mechanism is overwhelmed, leading to exhaustion and eventual apoptosis of the beta cells. This results in a partial deficiency of insulin and subsequent high levels of glucose in the blood, known as hyperglycemia. [4]

Osteonectin, or Secreted protein acidic and rich in cysteine (SPARC), is an essential component of healthy skeletal tissue that connects collagen with bone mineral components. It also has involvement in initiating active mineralization. Osteonectin is also thought to bind to actin in regenerated myofibers, which may affect the maintenance of muscle function. It helps keep muscles working properly since it's a major regulator of the actin cytoskeleton. [5,6] Previous studies exhibited osteonectin was associated with early kidney damage in patients with T2DM. [7]

A recent study discovered that SPARC enhances the migration of prostate cancer cells. [9] Deng et al. demonstrated that reducing the expression of SPARC inhibited the growth and movement of cholangiocarcinoma cells. [10] Bone growth, maintenance, and healing are among the many functions of SPARC outside of malignancies. [11]

Secreated protein acidic and rich in cysteine, levels are also increased in individuals suffering from acute liver failure or acute severe alcoholic hepatitis. In conditions such as T2DM and gestational diabetes, higher levels of SPARC are linked with elevated serum glucose levels and insulin resistance. [12,13]

The heart, brain, kidney, pancreas, and skeletal muscle are among the tissues that release an acidic protein that is rich in cysteine, a glycoprotein linked to the extracellular matrix. In humans, the majority of circulating SPARC originates from differentiated subcutaneous

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adipose tissue. While previous research has mainly focused on the association between SPARC and tumors due to its involvement in angiogenesis and tissue repair, Its role in the development of obesity, insulin resistance, type 2 diabetes mellitus (T2DM) and its complications, such as diabetic retinopathy, diabetic nephropathy, and gestational diabetes, has recently been illuminated by new study. In addition to being a risk factor for cardiovascular disease on its own, type 2 diabetes also has a number of risk variables in common with cardiovascular disease. Therefore, the close relationship between SPARC and T2DM and its complications suggests a potential link between osteonectin and the development of coronary heart disease.[14]

This research found that certain risk factors for diabetes were exacerbated by elevated blood zinc levels, which in turn increased the chance of diabetes. Furthermore, other metabolic markers may have acted as mediators between zinc levels in the blood and the likelihood of acquiring diabetes. [15]

Electrolyte imbalances are common in people with diabetes and can be due to abnormal distribution of electrolytes in the body. These imbalances are often caused by high blood levels (hyperglycemia) leading to fluid shifts or by overall deficits in the body caused by excessive urination (osmotic diuresis). [16] Minerals such as sodium, potassium, and chloride are essential for many bodily functions, including metabolism and enzyme activity. [17]

In many Iraqi studies have examined the relationship between inflammatory variables and various diseases, [18,19] but this study is the first study to the relationship of Osteonectin in T2DM in Iraqi patients.

The primary objective of this study was to determine the levels of osteonectin and to examine the relationship between biochemical markers and zinc ions in Iraqi patients with type 2 diabetes mellitus (T2DM).

Materials and Methods:

FSG testing performed after a minimum of eight hours of fasting confirmed the presence of type 2 diabetes in 42 out of 84 participants in this research. Forty-two healthy controls were recruited for the research; they were matched with type 2 diabetes patients according to age, gender, and ethnicity. All of the responders were in the 35-65 age bracket. The sample will take done from August 2023 to December 2023 at Al-Ramadi Teaching Hospital. By using enzyme-linked immunosorbent assays (ELISAs) developed by BT LAB Inc. of China

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and LTA S.r.l. of Via Milano 15/F 20041 Bussero (MI) Italy, respectively, measurements were made of the samples' osteonectin and zinc concentrations.

When the weight was divided by the square of the height, the resulting number was the body mass index (BMI). Serum levels of sodium, potassium, and chloride ions were determined using the Abbott Architect c4000 device (Architect c4000, Abbott Laboratories, IL, USA) by the calorimetric method and commercial kits. SBP (in mmHg) and DBP (in mmHg) were determined

The mean arterial blood pressure (MAP) was calculated from the equation below:

MAP = [(2 x DBP) + SBP] / 3

Sample Collection and Analysis

Ramadi Teaching Hospital was the site of the sample collection. In this research, participants fasted for eight hours before venous blood was drawn. To isolate the serum, the blood was spun at 1500 x g for a duration of 10 minutes. The serum was stored in Eppendorf tubes at -20 °C until analysis.

The osteonectin and zinc levels in each subject's serum were measured using an ELISA microplate reader. The kits used for the analysis were obtained from (BT LAB/China) and (Headquarters of LTA S.r.l. are located in Via Milano 15/F, 20041 Bussero (MI), Italy) (Architect c4000, Abbott Laboratories, IL, USA). FSG, Na^+, K^+ and Cl^- serum levels of each sample were determined by the Abbott Architect c4000 device (Architect c4000, Abbott Laboratories, IL, USA) using the calorimetric method and commercial kits.

Statistics Analysis:

A Graph Pad Prism version 8.02 (Graph Pad Software, La Jolla, CA, USA). Was used to the statistical investigations of these results, Consequences are stated as the mean, standard deviation (SD) and standard error of the mean (SEM). Using a t-test to confirm that the interpersonal differences were statistically significant, we were able to distinguish between HCs and T2DM patients by calculating their area under the receiver operating characteristic (ROC) curve. A value of $P<0.05$ was considered statistically significant. Sensitivity, specificity, and cutoff values were established.

Results

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Figure 1 showed Common results for both the control and patient groups include means, standard deviations, and standard error of the mean (SEM). Patients' average age was 50.619 years, while healthcare providers' average age was 50.3571 years, with a p-value greater than 0.05 based on the criteria shown in Table 1, Serum osteonectin (µg/mL) and MAP in DM patients were greater than in controls ($P < 0.0001$), while Zn^{+2}, K^{+}, Cl^{+}, SBP, DBP were lower in T2DM patients than controls.

Table 1: Comparisons of Parameters between Two Studied groups

Parameter	Healthy Controls			T2DM Patients			p-value
	Mean	SD	SEM	Mean	SD	SEM	
Age years	50.36	7.854	0.985	50.619	8.438	1.073	0.345
Osteonectin µg/mL	1.891	0.5121	0.0790	2.193	0.5755	0.0899	0.0132
F.S.G mg/dL	92.62	7.902	1.219	206.2	55.19	8.516	<0.0001
Na Ions mmol/L	140.2	1.656	0.2556	139.3	2.525	0.3896	0.0694
K Ions mmol/L	4.319	0.4324	0.0667	4.405	0.3642	0.0562	0.3287
Cl Ions mmol/L	102.8	2.335	0.3604	103.5	2.680	0.4135	0.2116
Zinc µg/mL	92.17	14.40	2.222	82.88	13.91	2.147	0.0035
SBP mmHg	125.2	8.269	1.276	141.2	16.26	2.509	<0.0001
DBP mmHg	81.90	4.878	0.7527	87.10	8.078	1.247	0.0006
MAP mmHg	96.35	4.727	0.7294	105.1	9.883	1.525	<0.0001

A significant positive correlation was detected between osteonectin with K^{+}, a non-significant positive correlation between osteonectin with Na^{+}, SBP, DBP, and MAP, The findings demonstrated a strong inverse relationship between osteonectin and Cl- and Zn+2, as shown in **:**

Table 2: Osteonectin's Relationship with the Examined Parameters

Parameter	r (Osteonectin µg/mL)	p-value
Osteonectin µg/mL	1	0.000
"F.S.G. mg/dL"	0.176	0.111
"Na mmol/L"	0.188	0.088
"K mmol/L"	0.270	0.013
"Cl mmol/L"	-0.144	0.193

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Zn µg/dL	-0.071	0.524
SBP mmHg	0.167	0.131
DBP mmHg	0.013	0.909
MAP mmHg	0.102	0.361

To determine which biomarkers were most appropriate for FSG screening in patients with type 2 diabetes, curve analysis of the receiver operating characteristic was used (ROC) [AUC: 1, P: <0.0001, Positive if COV: >115.0, Sen: 1.00, Spec: 1.00] (Fig. 1-A) (Table 3). Researchers have discovered osteonectin as a type 2 diabetes patient biomarker [AUC: 0.6495 ,Positive if COV: > 2.125, Sen %:0.5854, Spec%: 0.5952, Likelihood Ratio (LHR): 1.446] , **(Fig. 1-B)**. demonstrates good discriminatory efficacy of SBP and MAP between healthy persons and T2DM patients. SBP [AUC:0.7939, Positive if COV> 129.5, Sen%: 0.7857, Spec%: 0.6429, LHR:2.200]**.** MAP [AUC; 0.7619, Positive if COV; > 98.33, Sen%:0.6667, Spec. %: 0.6667, LHR: 2.000] **(Fig. 1-C).**

While Na^+ [AUC; 0.5876, Positive if COV; < 139.5, Sen %;0.4762, Spec %; 0.5952, LHR; 1.333]**,** K^+ [AUC; 0.5479, Positive if COV; > 4.350, Sen %; 0.5000, Spec %; 0.5000, LHR; 1.000], Cl^+ [AUC; 0.5802, Positive if COV; > 103.5, Sen %; 0.5238, Spec %; 0.4762, LHR; 1.000], Zn^+ [AUC; 0.6834, Positive if COV; < 86.00, Sen %; 0.5952, Spec %; 0.5952, LHR; 1.471]**,** finally DBP [AUC; 0.6825, Positive if COV; < 82.50, Sen %; 0.6190, Spec %; 0.5714, LHR; 1.444], performed poorly as diagnostic biomarkers.

Table 3: ROC curve area for each parameter examined in T2DM

Parameter	AUC	Positive if COV	Sensitivity	Specificity	Likelihood Ratio
Osteonectin µg/mL	0.6495	> 2.125	0.5854	0.5952	1.446
F.S.G mg/dL	1.000	> 115.0	1.000	1.000	
Na Ions mmol/L	0.5876	< 139.5	0.4762	0.6429	1.333
K Ions mmol/L	0.5479	> 4.350	0.5000	0.5000	1.000
Cl Ions mmol/L	0.5802	> 103.5	0.5238	0.4762	1.000
Zinc µg/mL	0.6834	< 86.00	0.5952	0.5952	1.471
SBP mmHg	0.7939	> 129.5	0.7857	0.6429	2.200
DBP mmHg	0.6825	> 82.50	0.6190	0.5714	1.444
MAP mmHg	0.7619	> 98.33	0.6667	0.6667	2.000

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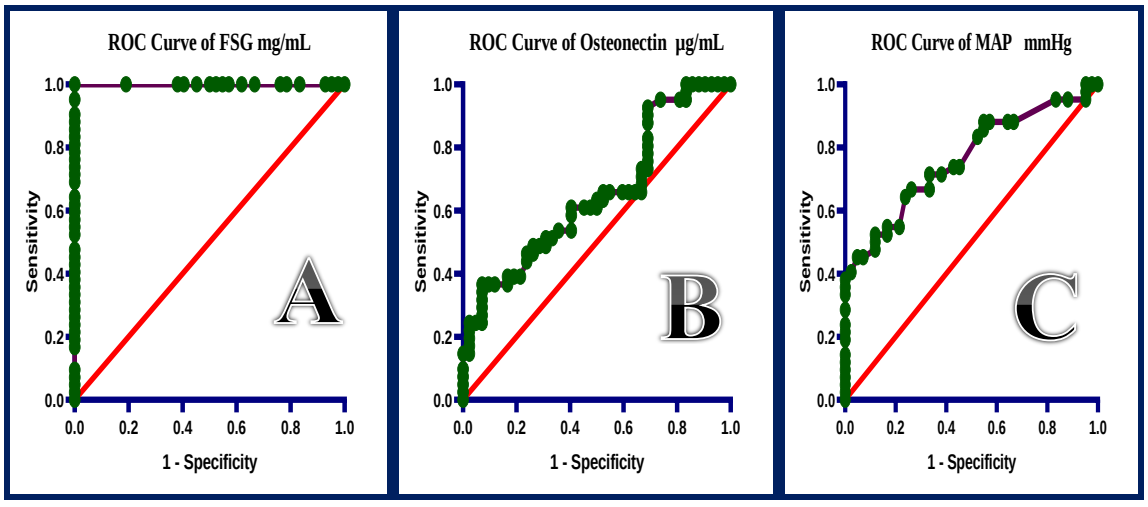

Discussion

Type 2 diabetes mellitus, in which insulin production and activity are impaired, may develop for a variety of causes and manifests as high blood glucose levels. By 2030, it is estimated that the global diabetic population will reach approximately 439 million individuals. Long-term diabetes can lead to organ damage and dysfunction, primarily affecting the eyes, nerves, foot, blood vessels, kidneys, and heart. Prolonged diabetes has also been connected to the emergence of microvascular problems like nephropathy, neuropathy, and retinopathy. [20]

Osteonectin, is an adipokine primarily found in subcutaneous fat. Studies on osteonectin-null mice have demonstrated its involvement in glomerulosclerosis and tubulointerstitial damage caused by high blood glucose levels. [21]

Osteonectin levels were greater in the patient HCs than in the HCs themselves, even though the ages of the two groups were same in this research. We found that those with type 2 diabetes had much greater amounts of osteonectin than the control group, which is consistent with previous research. [22]

In agreement with our results observed a significant elevation in the level of SPARC. [14]

Although the vital role of circulating O

A small number of research have looked at the link between soluble osteonectin and insulin resistance, diabetes, and complications from diabetes, however nobody knows for sure what this link is. Individuals who have just been diagnosed with type 2 diabetes or gestational diabetes tend to have greater amounts of osteonectin, which has been linked to metabolic risk

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factors such as obesity, dyslipidemia, and insulin resistance (Xu et al., 2013) . On the other hand, IR patients with polycystic ovarian syndrome have osteonectin expression downregulated (Kaur et al., 2012). Regardless of a greater body mass index, people with type 2 diabetes were shown to have lower amounts of osteonectin mRNA in their main islets when compared to non-diabetic persons (Harries et al., 2013). According to Sireesha et al. (2009), Diabetic nephropathy was associated with a decrease in osteonectin expression in renal biopsies, in contrast to type 2 diabetes, which was associated with an increase. Contrary to expectations, individuals with diabetic nephropathy and tubulointerstitial lesions were found to have higher serum SPARC concentrations (Kanauchi, Nishioka, Kawano, & Dohi, 1997). [23]

Elevated levels of osteonectin in the bloodstream are considered an indicator of increased bone formation. Osteonectin is a key molecule that helps osteoblasts commit, differentiate, and survive. [24]

Recent study was determined serum levels of osteonectin in T2DM patients; compared to healthy persons, there was an increase in osteonectin levels in patients compared to healthy people, this is consistent with the results of our study.[25]

In our investigation, we discovered that patients' zinc levels were lower than those of healthy people. our results were consistent with previous studies that were conducted before by Saharia *et al* [26] and Basaki *et al* (27), found lower zinc levels in the blood of those who had type 2 diabetes. Zn is necessary for proper insulin production, storage, and release in pancreatic β cells. The transport of Zn ions into the secretory granules is facilitated by the ZnT8 transporter (SLC30A8). [29]

Our results show a positive correlation between osteonectin with Na^+, SBP, DBP, and MAP.

Individuals with diabetes often exhibit elevated blood pressure levels compared to those without the condition.[28]one of the primary causes of CVD in individuals with diabetes is hypertension, which is a prevalent symptom of the disease. [30]

Our results show a negative correlation between osteonectin with Cl^-.

The receiver operating characteristic curve is a visual representation of the performance of a binary classifier system as the threshold for classification is adjusted. It plots the true positive rate (TPR), sometimes referred to as sensitivity, in relation to the false positive rate

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(FPR), across various threshold configurations . The ROC curve helps in selecting optimal models and disregarding suboptimal ones regardless of cost context or class distribution. It is widely used in various fields including radiology, mdicine biometrics, and machine learning research. The ROC curve originated during World War II for detecting enemy objects in battlefields and was later adopted in psychology to explain perceptual detection. Its application has since expanded to different domains and continues to be a valuable tool for evaluating and comparing classification models.

According to results of ROC analysis, SBP, MAP were intermediate markers. While osteonectin, Na^{+}, K^{+}, Cl^{-}, Zn^{+2}, Ultimately, DBP are indicators that do not have good predictive value; their AUC is less than 0.6 .

Study limitation:

The main limitation of this study was: This study was conducted in a single center with a small sample size. Therefore, in order to validate and generalize the results of this investigation, larger trials combining several centers are required. Prospective research is required to determine the true relationship between these variables.

Conclusion

The study found that the serum osteonectin level was significantly higher in patients with T2DM in comparison to HCs. Therefore, the results suggest that regular monitoring of serum osteonectin level might be a useful biomarker to predict the risk of T2DM. The study also showed there were no significant correlations for osteonectin with zinc and the other variables that were studied, except potassium ions.

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