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Assessment of aquaporin-4 and some biochemical parameters in diabetes mellitus type 2

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Abstract
Background: One of the major causes of end-stage kidney disease and nephropathy is diabetes: it leads to increases in the serum levels of many parameters, such as aquaporin-4 and other biochemical parameters that perform many biological activities throughout the human body. Changes in the plasma and blood levels of these parameters directly relate to an elevated chance of developing type 2 diabetes mellitus (T2DM). However, the potential association between aquaporin-4 and biochemical parameters in cases of T2DM remains to be perfectly understood. Hence, this study is aimed at the assessment of the relationship between the levels of aquaporin-4 and other biochemical parameters and T2DM among Iraqi patients.
Methods: The current study is cross-sectional and included a total of 90 participants (50 with T2DM and 40 healthy without T2DM); all the participants underwent several important routine health examinations. The patients' ages ranged from 18 to 35 years. The samples were collected for the measurement of aquaporin-4 and biochemical parameters via biochemical and clinical methods specified in this study. The association between aquaporin-4 and biochemical parameters in T2DM was determined using statistical analysis methods (SPSS version 24); the level of significance of the identified relationships was determined using Pearson's correlation.
Results: The mean value of glucose, N-terminal pro-b-type natriuretic peptide (NT-proBNP), urea and ferritin for participants with T2DM was significantly higher (P = 0.001), (P = 0.041), (P = 0.038), (P = 0.002), and (P =0.020) compared to the control group. Furthermore, the mean value of uric acid, albumin, myoglobin, and the atherogenic index was higher but not significant in the diabetic group compared to the non-diabetic group. Regarding aquaporin-4 value; it was low in concentration compared with patients at the significant level of P=0.008); aquaporin-4 was found to be negatively correlated with blood glucose levels and NT-proBNP ferritin in T2DM patients.
Conclusions: Elevated levels of blood glucose, urea, NT-proBNP, and ferritin with a low concentration of aquaporin-4 were observed in patients with T2DM; it was also found that there is a correlation between aquaporin-4 and biochemical parameters of T2DM patients. This study recommends testing and screening for aquaporin-4 and other biochemical parameters on a larger scale as it has been shown to be associated with type 2 diabetes.

Keywords: Aquaporin-4, biochemical parameters, type 2 diabetes mellitus, NT-proBNP

Introduction
Diabetes mellitus (DM) is a metabolic syndrome of many etiologies; it is mostly caused by problems in the production, release, and action of insulin, a hormone of the pancreas [1]. DM manifests mainly in severely high levels of serum glucose caused by errors in normal body metabolism of starch, fats, and protein. The result is damage to numerous sensitive body organs such as eyes, kidneys, blood vessels, and heart, nerves [1]. Aquaporins (AQPs) are membrane proteins (24–30 kDa) that derived their nomenclature from their capability to enhance the passage of water molecules across membrane lipid bilayers. There are now thirteen members in the AQP family (AQP 0-12) [2]. Agre *et al.* [3] discovered aquaporin peel in water canals and this discovery solved the long-standing problem of how water exactly marks biological peels and provided molecular-level insight into the critical physiology of water equilibrium, as well as the pathophysiology of diseases related to water equilibrium. AQPs respond to osmotic slopes and variations in hydrostatic stress by being censoriously difficult to maintain ionic and osmotic equilibrium [4]. It is currently unclear how decreased saliva output and altered AQP expressions in diabetic rats relate to one another.

This study's objective was to investigate the alterations in AQP1, AQP5, and AQP8 expression in SMGs of diabetic rats. This information may assist to clarify the molecular process underlying the lower saliva secretion in these cells. A study was recently conducted on the role of AQPs in fetal cell membranes using a few diabetes patients [5], but the regulation of insulin in these tissues is yet to be studied. However, we are aware that insulin controls the expression of aquaglyceroporins in various tissues, including fat and liver tissues, and that this control is lost in T2DM [6]. As it has been shown that AQP4 is a significant factor in Alzheimer's disease and Parkinson's disease [7], it is a potential target in metabolic disorders. To maintain a healthy energy metabolism like obesity, insulin resistance, T2DM, etc., tissues respond to environmental changes. This adaption process may be significantly impacted by the intracellular and intercellular coordination of AQPs. Depending on the circumstance or the resurgence of the disease, AQP may work as a means of communication between the cells and tissues, enabling them to respond to stimuli in the organism in a coordinated manner. The various functions that the various aquaporins perform in both adipocytes and hepatocytes underline the importance of these proteins in insulin resistance and T2DM [8].

The "N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), which is advised by the current practice recommendations, is by far the most researched for the confirmation of the DM diagnosis [9] as a greater risk of T2DM was linked to higher levels of NT-proBNP. The further discovery of a strong interaction between sex, NT-proBNP, and the chance of developing diabetes confounded this association, making the connection between elevated NT-proBNP and raised diabetes risk difficult to interpret [10]. A good indication for diabetics in certain studies is an elevated level of ferritin in the serum [11] Increased ferritin level has been reported to induce diabetes via several means, including the reduced liver ability to extract insulin from the liver, oxidative damage to beta cells of the pancreas, and interference with insulin's ability to regulate hepatic glucose synthesis [12]. Skeletal muscle and human cardiac tissues were shown to contain serum myoglobin (Mb), a 17 kDa monomeric hemoglobin14 that aids in the transport of oxygen from the blood to the mitochondria of body cells [13]. In comparison to T2DM patients without metabolic syndrome, patients with T2DM also exhibit a higher Atherogenic Index [14]. The risk of developing hypertension is higher in cases of elevated serum uric acid levels (SUA). Diabetes patients with high SUA have a poor prognosis." One of the main contributors to the burden of chronic kidney disease (CKD) on the global population is diabetes. Diabetes is primarily a manifestation of an inflammatory process that compromises the endothelium. SUA plays a crucial role in this inflammatory process. Therefore, elevated SUA level is thought to increase the risk of renal damage in T2DM patients [15]. One of the defining characteristics of inappropriate renal function is abnormal levels of serum urea and macro albuminuria. Uncontrolled diabetes may have hyperglycemia-related abnormal blood urea increases. Therefore, the two key indicators to identify any abnormality in the kidney are urea [16]. Plasma albumin levels are influenced by things like nutrition, lifestyle, inflammation, illness, medicines, etc. "Diabetes causes an insulin shortage, which reduces albumin synthesis and secretion. Thus, it is anticipated that albumin levels will fall in people with diabetes and may have an impact on plasma protein glycation. Glycosylated hemoglobin (HbA1c), a marker of high glucose levels, may also be affected" [17].

Materials and Methods

Study Design and Participants

The current study is a prospective, cross-sectional, and observational study. The total participants were 193 eligible individuals all of whom underwent medical examinations. Of the 193 participants, 107 were excluded because their laboratory data were incomplete and they did not meet the inclusion criteria. The study included 90 randomly selected participants who all underwent several important routine health check-ups. This study included 50 patients with confirmed T2DM (24 males and 26 females) and 40 healthy individuals free of diabetes, which is known as the control group. The age of male participants ranged from 18 to 35 years, and the age of the females ranged from 18 to 35 years. Also, the control group included participants who m*et all* inclusion criteria. The patients' ages ranged from 18 to 35 years. The current study was conducted during the period starting from January 8 to May 1, 2022, at Kirkuk General Hospital.

Inclusion and Exclusion Criteria

Inclusion Criteria

Cases were adults within the aforementioned age groups without diabetic complications.

Exclusion Criteria

Diabetic complications: heart disease, myocardial infarction, unstable angina, stable angina, heart failure, diabetic neuropathy, problems with feet, oral health, diabetic retinopathy, hearing, and gestational diabetes.

Biochemical and Clinical measurements

Blood samples were drawn from all participants after 15 minutes of rest and a ten-hour fast. Blood samples were kept at 10 °C until centrifugation. All blood samples were homogenized and centrifuged for 10 min at 4000 g and 28°C temperature. Plasma was withdrawn and separated from blood samples immediately for aquaporin-4 assessment, then stored at −80 °C until aquaporin-4 measurement. Plasma aquaporin-4 was measured and determined by an enzyme-linked immunosorbent assay (ELISA, Elabscience company, USA). Plasma concentrations of aquaporin-4 were measured and analyzed using (BIO-TEK INSTRUMENTS, INC, USA). Biochemical parameters that included blood glucose, urea, uric acid and albumin were measured by biometrics. Blood glucose (BG) levels, or blood glucose were assessed by the Trinder reagent test using the GOD-PAP method (BIOLABO company, France). Urea was estimated by the colorimetric direct method (BIOLABO Company, France), uric acid by the uricase method (BIOLABO Company, France), myoglobin estimated by particle enhanced immuno-turbidimetric test (DiaSys diagnostic systems GmbH), while Atherogenic index was estimated by using the following equation

Atherogenic index AI = log (TG/HDL-C) [18]

Serum NT-proBNP and Ferritin were determined by an enzyme-linked immunosorbent assay (ELISA) Elab science

(Technique Inc. kit, USA) and this analysis was performed using (BIO-TEK INSTRUMENTS, INC, USA).

Statistical analysis

SPSS "version 24 was used to perform the statistical analyses. The value of $P < 0.05$ was taken and determined to indicate statistical significance. Quantitative data are expressed as mean ± standard error (SE), which is also referred to as standard deviation ± (SD) of the samples. Pearson's correlation was used to find the correlations between" patients' biochemical parameters and aquaporin-4.

Results

In the current study, a total of 90 participants were enrolled. Among them were 50 (56%) participants with T2DM and 40 (44%) without diabetes (control). The ages of the participants with T2DM were recorded and the minimum and maximum ages were 31 and 60 years. Males constituted 24 (48%) of the T2DM participants and females 26 (52%). The mean value of glucose (225.126 mg/dl) for participants with T2DM was significantly higher ($P = 0.001$) compared to the control whose mean glucose value was (86.201 mg/dl) as shown in Table 1. It is also clear from the obtained results that the mean values of urea and uric acid were 40.240 mg/dl, 6.401 mg/dl for participants with T2DM, respectively, while the mean values were 25.160 mg/dl, 4.560 mg/dl for the control, respectively. Moreover, the level of urea of participants with T2DM and their levels for the control were significantly different ($P = 0.041$) (Table 1), but the uric acid level was not "significant ($P=0.064$). The results of the NT-proBNP and ferritin indicated that the levels were elevated in participants with T2DM, where the mean values were 675.600 pg/ml and 225.274 ng/ml respectively, compared to participants in the control group, where the mean values of NT-proBNP and ferritin were 12.680 pg/ml and 86.200 ng/ml, respectively. Based on these results, the mean values of NT-proBNP and ferritin in participants with T2DM were found to be significantly higher than in the control group ($P = 0.002$) and ($P = 0.020$) respectively, as shown in Table 1. Regarding uric acid, albumin, myoglobin, and the atherogenic index, the results showed that the mean value (6.401 mg dl, 5.108 g/dl, 45.334 ng/ml, and 3.468 mg/dl respectively) for participants with T2DM was significantly lower ($P=0.064$), ($P=0.097$), ($P=0.161$) and ($P=0.275$) respectively compared to the control whose mean values were 4.560 mg/dl, 4.054 g/dl, 43.766 ng/ml, and 2.560 mg/dl, respectively. In addition, the results related to biochemical parameters" were further illustrated in Figure 1, which showed the comparison of these parameters between participants with T2DM and the healthy participants (control group).

From Table 2, the mean value of aquaporin-4 is 1.434 ng/ml for participants with T2DM which is significantly lower ($P = 0.008$) compared to the control value (2.593 ng/ml). Moreover, the results related to aquaporin-4 were further illustrated in Figure 2, which shows the comparison of aquaporin-4 levels between the participants with T2DM and the healthy participants (control group). It was evident that the aquaporin-4 levels of the patients were lower than that of the control group.

Table 1: Comparison of biochemical parameters in T2DM patients and healthy participants (control), (N = 90)

Parameters	Control Mean ± SE (N=40)	Patients Mean ± SE (N=50)	P-Value
Glucose mg/dl	86.201±1.685	225.126±2.416**	0.001
Urea mg/dl	25.160±3.053	40.240±2.497*	0.041
Uric acid mg/dl	4.560±0.273	6.401±0.656	0.064
Albumin g/dl	5.054±0.139	4.182±0.214	0.097
Myoglobin ng/ml	43.766±2.145	45.334±3.624	0.161
Atheroginic mg/dl	2.560±0.595	3.468±1.303	0.275
NT-proBNP pg/ml	12.680±2.376	675.600±5.817**	0.002
Ferritin ng/ml	106.200±1.685	325.274±3.447*	0.020

(NT-proBNP) N-terminal pro-b-type natriuretic peptide

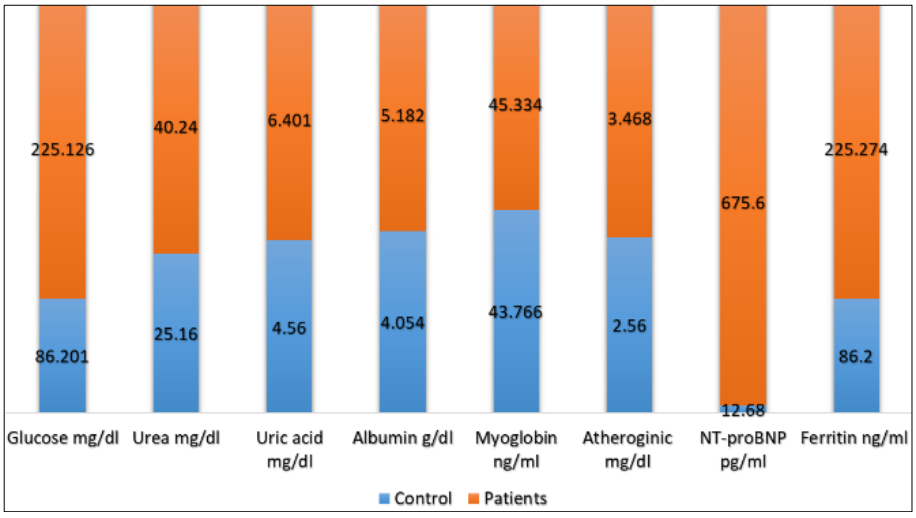

Fig 1: Comparison of biochemical parameters among T2DM participants and healthy participants (control).

Table 2: Comparing Aquaporin 4 levels in T2DM patients and healthy participants (control).

Parameters	Control Mean ± SE (N=40)	Patients Mean ± SE (N=50)	P-Value
Aquaporin 4 ng/ml	2.593±0.203	1.434±0.079**	0.008

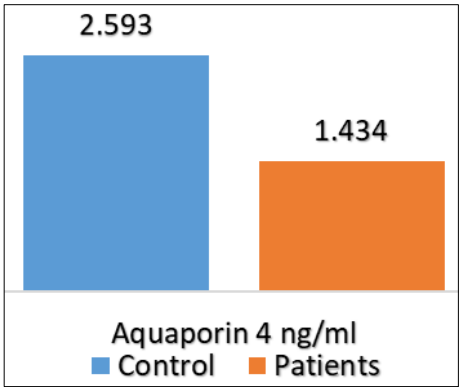

Fig 2: Comparison of aquaporin-4 levels between T2DM patients and the control.

The results showed that the mean values of aquaporin-4 were 1.357 ng/ml and 1.511 ng/ml for male and female participants with T2DM, respectively. However, the aquaporin-4 level of participants based on gender was not significantly associated (P = 0.074) (Table 3). Figure 3 showed that the levels of aquaporin based on the mean values were slightly higher for males with T2DM than for females with the same disease.

Table 3: Comparing aquaporin 4 levels between males and females.

Parameters	Male Mean ± SE (N=24)	Female Mean ± SE (N=26)	P-Value
Aquaporin 4 ng/ml	1.357±0.140	1.511±0.073	0.074

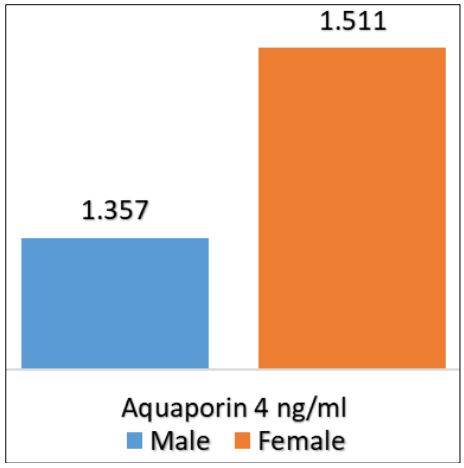

Fig 3: Comparing aquaporin 4 levels between males and females.

The results of the correlation between biochemical parameters and aquaporin -4 for patients with T2DM are shown in Table 4. There was no significant correlation between aquaporin-4 and urea, uric acid, albumin, myoglobin, and atherogenic index (P > 0.05) in patients with T2DM; but there was a significant negative "correlation between aquaporin-4 and glucose (P = 0.05) in T2DM patients. Also, the results showed that there was a significant negative correlation between aquaporin-4 and NT-proBNP and ferritin (P = 0.009) and (P = 0.01) respectively, in T2DM" patients.

Table 4: Correlation between biochemical parameters and aquaporin-4 in T2DM patients.

Correlations Patients Parameters	Glucose	Urea	Uric acid	Albumin	Myoglobin	Atherogenic	NT-proBNP	Ferritin
Aquaporin 4	-0.979*	0.421	-0.083	-0.526	-0.371	-0.214	-0.981**	-0.977**
P-Value	0.05	0.315	0.614	0.071	0.093	0.217	0.009	0.01

*Correlation is significant at the 0.05 level, ** Correlation is significant at the 0.01 level, Positive number = Direct proportion, and Negative number =inverse proportion.

Discussion

In the current study, the blood glucose level was significantly higher in participants with T2DM compared to healthy participants because individuals with T2DM had higher levels of plasma glucose concentration [19]. Also, the reason for the higher glucose levels "in patients with T2DM than normal is that they have insulin resistance and thus results in the abnormality in plasma glucose balance [20]. Currently, many studies have been conducted that are concerned with the level of urea in the blood and its association with T2DM. The results of this study showed that the levels of urea in the blood of patients with T2DM were higher compared to healthy participants. This result is consistent with the results of many recent studies that focused on the relationship between urea levels in the blood and the risk of developing T2DM, where they found that individuals with T2DM have higher urea level that directly associate with T2DM [16]. It certainly points to prolonged hyperglycemia, which causes renal nephrons to permanently deteriorate. Nephrons, the kidneys' tiny cleaning organs, suffer damage as a result of high blood sugar. This normally leads to decreased function of the kidneys since the maintenance of fluid electrolyte balance is the kidney's primary function. an increase in the level of serum urea" is mostly an indication of decreased glomerular filtration rate (GFR) [21].

The results of the current study revealed that there were significantly elevated levels of NT-proBNP and ferritin in participants with T2MD. This occurs in T2MD patients as a result of several reasons, including irregular blood glucose levels and the production of glycation, which leads to oxidative stress, which in turn causes a change in this parameter. This result agrees with many studies on diabetics and NT-proBNP [22]. Additionally, the results of this study showed that diabetic patients' blood ferritin levels are much greater than those of the control group. Ferritin has been recognized as a marker of inflammation as well as a guide for the body's iron supply. Regarding the role of ferritin in type 2 diabetes, there have been some revisions to the concepts; impairment to the liver's ability to remove hepatic insulin "and interference with insulin's ability to inhibit hepatic glucose synthesis are all examples of oxidative damage to pancreatic beta cells [23].

In our study, we sought to assess aquaporin 4 and to understand its pathologic impact on people with T2DM. Additionally, NO leads to oxidative stress and the death of neurons. Intriguingly, another study by Bi *et al.* demonstrated that the removal of oxidative stress suppresses the increase in AQP4 levels in brain astrocytes induced by hydrogen peroxide (H_2O_2) [24]. They also demonstrated that de novo AQP4 synthesis is not necessary for the rise in AQP4 plasma membrane expression caused by H2O2.

These findings suggest that AQP4 and ROS also have a close relationship [25]. Furthermore, these cases were directly related to patients with T2DM. Thus, this association could explain why the concentration of aquaporin-4 is decreased in patients with" T2DM. Our results indicate that the levels of aquaporin-4 were significantly low for those with T2DM than the control group and that there is a close association between low aquaporin-4 concentration and T2DM. There are not many studies evaluating aquaporin-4 levels and their association with T2DM. In view of this, the results obtained in this work were important and consistent with the results of the study conducted by other researchers, where a significantly negative association between aquaporin-4 and T2DM was attributed to the relationship between oxidative stress and aquaporin-4 which encourages the generation of ROS. Aside from causing oxidative damage, ROS may also trigger the upregulation of aquaporin 4 [24]. Regarding gender and its association with aquaporin-4 levels in patients with T2DM, the result showed differences in the relationship of gender (males and females) with type 2 diabetes and levels of aquaporin-4; however, the observed differences in aquaporin-4 between males and females were not significant.

Furthermore, the results of our study regarding the correlation between biochemical parameters and aquaporin-4 for patients with T2DM indicated that aquaporin-4 was correlated with some parameters and there was no association with the rest. But no significant correlation was found between aquaporin-4 and urea, uric acid, atherogenic index, myoglobin, and albumin in patients with T2DM. Also, aquaporin-4 levels negatively correlated with blood glucose levels in T2DM patients. This is explained by the fact that the low concentration of aquaporin-4 in plasma leads to an increase in insulin resistance. Thus, this indicates the correlation between aquaporin-4 and glucose in patients with T2DM [26, 27, 28]. In this study, the correlation between aquaporin-4 and ferritin, and NT-proBNP was evaluated in patients with T2DM. The results showed that aquaporin-4 was negatively correlated with ferritin and NT-proBNP. These results represent one of the strengths of this study, as when looking at previous and recent studies, no study had reported the results of the correlation between aquaporin-4, ferritin, and NT-proBNP. However, the true relationship between aquaporin-4 and biochemical parameters in T2DM requires more research for more accurate predictions.

Conclusion

The "results of the current study showed that the levels of blood glucose, urea, NT-proBNP, and ferritin were significantly higher in T2DM patients than in the control group; these values were also significantly associated with T2DM. The levels of aquaporin-4 in T2DM patients were significantly lower compared to the control group but significantly associated with T2DM. In addition, there was no significant association between gender and aquaporin-4 levels in patients with T2DM. Regarding the aquaporin-4 and biochemical parameters values in T2DM, aquaporin-4 was found to negatively and significantly correlate with blood glucose levels, NT-proBNP, and ferritin while there was no significant correlation between" aquaporin-4 and other parameters in T2DM patients. From the foregoing, it is recommended that tests and examinations of aquaporin-4 and biochemical parameters be conducted more broadly as it has been proven to be associated with type 2 diabetes. This may justify future studies to predict the effect and role of these parameters and aquaporin-4 in the effort to reduce the burden of diabetes.

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