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ORIGINAL ARTICLE

Use of Alpha-1-Acid Glycoprotein as a Best Biomarker to Predict Diabetic Nephropathy in Type 2 Diabetic Patient

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ABSTRACT

Diabetic nephropathy (DN) is one of the most complications of diabetes. It is brought on by the harmful consequences of long-term high blood sugar on the kidneys. The aim of this work finds the relationship between alpha-1-acid glycoprotein (α1-AGP) and diabetic nephropathy and determined the level of the α1-AGP in the different stage of this pathogenesis. The study included 30 apparently healthy subjects and 90 T2DM patients: 30 without nephropathy, 60 with diabetic nephropathy divided into micro- and macroalbuminuria. Serum α1-AGP levels were determined using an ELISA kit. This study found a significant difference between the levels of α1-AGP and kidney function in diabetic nephropathy patients than in healthy subjects, across different stages of the pathogenesis. Also, this study found a strong positive correlation between α1-AGP and the level of blood creatinine, urea & ACR, and a negative correlation with GFR. The results suggested that α1-AGP may be linked to disease progression, a promising marker for Diabetic Nephropathy.

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1- INTRODUCTION

The prevalence of diabetes mellitus (DM) is estimated to increase to 10.2% (five hundred seventy-eight million) worldwide by 2030 and 10.9% (seven hundred million) by 2045. The rate of spread is higher in high-income countries (10.4%) than in low-income countries (4.0%) and in urban regions (10.8%) than in rural areas (7.2%). 50.1% of individuals with diabetes are unaware that they have the disease [1]. Type 1 diabetes (T1DM) mellitus and type 2 diabetes mellitus (T2DM) are the two types of DM, distinguished by etiology [2, 3]. In contrast to T2DM, which is caused by a relative insulin lack in the context of insulin resistance, T1DM mellitus is caused by autoimmune β-cell death and typically results in an absolute insulin deficiency [3]. A large proportion of the health burden associated with diabetes can be attributed to macrovascular and microvascular problems related to diabetes, including coronary heart disease, stroke, peripheral artery disease, heart failure, diabetic retinopathy, renal disease, and cardiac autonomic neuropathy [4]. One of the most complications side effects of diabetes mellitus is diabetic nephropathy (DN). It is brought on by the harmful consequences of long-term high blood sugar on the kidneys [5, 6]. Certain pathological structural and functional alterations in the kidney caused by DN, result in proteinuria, hypertension, and a gradual deterioration in renal function. Alongside this, the glomerular filtration rate (GFR) gradually decreases [6, 7]. The primary cause of end-stage renal disease is now DN, surpassing other serious illnesses [8] is a kind of kidney disease brought on by diabetes that results in poor renal function and spontaneous protein excretion. Additionally, thickening of glomerular basement membrane and mesangial expansion [9]. A rise

in albuminuria or perhaps an initially low GFR that declined in the middle to end stages are indicators of diabetic kidney disease, which is frequently linked to hypertension [10]. Orosomucoid, another name for alpha-1-acid glycoprotein (α1-AGP), is a 41–43 kDa glycoprotein with a pI of 2.8–3.8 [11]. The human peptide moiety consists of a single chain of 183 amino acids with two disulfide bridges [12, 13]. Carbohydrates make up about 45% of the molecular weight and are joined by 5-6 highly sialylated complex-type N-linked glycans [14]. Concentrations of α1-AGP have been associated with a number of conditions, including diabetes, sepsis, heart failure in men, myocardial infraction and stroke risk, and carotid plaque volume (15). Furthermore, it was demonstrated that, in comparison to overweight/obese women with healthy metabolisms, α1-AGP is a biomarker associated with metabolic syndrome [16]. Individuals with T2DM often have elevated serum α1-AGP concentrations. In these individuals, urine α1-AGP excretion has been shown to be an independent predictor of cardiovascular death [17]. Experimental studies employing mice have shown that elevated α1-AGP levels maintain metabolic homeostasis by lowering inflammation [18]. The scientists claim that α1-AGP reduces inflammation in human adipose tissue. El-Beblawy *et al*., [19] however, discovered that α1-AGP is a separate predictor of diabetic microvascular problems in kids and adolescents with T1DM and that its urine level increased with overt nephropathy.

The aim of this study is to measure the level of α1-AGP in the different stages of diabetic nephropathy and whether it could be a diagnostic biomarker.

2- MATERIALS AND METHODS

2.1 Studied Groups

Ninety patients, 30 with T2DM and 60 with DN, between the ages of 30 and 60 years, who Visited Mustansiriyah University's National Center For Diabetes Treatment And Research are included in this study. The patients were divided into 3 main groups according to the albumin-creatinine ratio (ACR): 30 diabetic patients with an ACR of 30 mg/g T2DM without nephropathy (G1), 30 patients with an ACR between (30-300) mg/g microalbuminuria group (G2), and 30 patients with an ACR greater than 300 mg/g macroalbuminuria group (G3). This study included 30 healthy volunteers (aged 30 to 60) that are served as controls. Subjects who met the exclusion criteria included T1DM, were pregnant, and had hepatic or end stage renal dieses.

2.2 Samples of Blood and Urine

The morning following an eight-hour fast, urine and blood samples were collected. While urine samples were examined immediately, the serum was separated from blood samples by centrifuging them for 15 minutes at 1500 rpm. The serum was then kept at -20°C for analysis.

2.3 Experimental Section

Alpha-1-acid glycoprotein concentration was measured using an ELISA kit from Cloud-Clone Crope in the United States. Fasting blood glucose (FBG), urea, and creatinine were measured enzymatically. Albumin and creatinine concentrations were calculated with the collected urine samples. The microalbumin level was measured using urine test strips. This test is based on the 'protein error.' (The indicator's "protein error" concept, which is brought on by the presence of albumin, is the foundation of the test. The sensitivity of sulfonephthalein to albumin is quite high) Creatinine was measured in urine by a reaction with 3,5-dinitrobenzoic acid in an alkaline environment. The albumin-creatinine ratio was determined by dividing the microalbumin level by the urine creatinine level.

2.4 Statistical Analysis

The data was examined using IBM SPSS for Windows, Version 21.0. First, a one-way analysis of variance (ANOVA) was used to assess whether the mean changes across the four distinct groups were statistically significant. Next, a Pearson correlation analysis was performed to determine the correlation coefficient (r). Finally, ROC curve analysis was conducted to assess each marker's ability to identify illnesses.

3- RESULTS AND DISCUSSION

The baseline characteristics of the T2DM patients (n = 90) and controls (n = 30) were displayed in Tables 1 and 2 as mean ± SD. Between the patient group and the healthy controls, there were no differences in age (p=0.537). Between the three patient groups, there are a highly significant difference in the disease duration values (p=0.000). Between patient groups and control groups, FBS values likewise demonstrated a highly significant difference (p=0.000). The patient groups with G2 and G3 exhibited greater significant differences (p<0.001) in creatinine and

urea levels when compared to patients with G1 and the control group. G2 and G3 showed a highly significant decline in GFR but no significant difference between the control and G1. The ACR values across the three patient groups show a highly significant difference ($p<0.001$). Between the control and patient groups, the lipid profile showed significant differences.

Table (1): Baseline characteristics of the Studied Groups

Parameters	Control Group (n=30)	Patient groups			
		G1 (n=30)	G2 (n=30)	G3 (n=30)	*P* value
Age (year)	52.10±8.65[a]	54.73 ±6.30[a]	53.40 ±6.91[a]	53.67 ±5.54[a]	0.537
Duration of disease (years)	-------	4.20±1.21[a]	8.83±2.85[b]	12.80±0.96[c]	0.001
BMI (Kg/m^2)	23.34±2.59[a]	29.84±6.99[b]	28.53±4.29[b]	29.99±4.56[b]	0.001
FBG (mg/dl)	105.32±8.76[a]	181.20±79.11[b]	191.63±79.13[b]	219.20±103.21[b]	0.001
B. urea (mg/dl)	16.89±3.25[a]	18.53±3.01[a]	41.63±9.07[b]	70.33±14.35[c]	0.001
S.creatinine (mg/dl)	0.65±0.12[a]	0.81±0.19[a]	1.52±0.14[b]	2.16±0.57[c]	0.001
GFR(mL/min/1.73m)	106.55±6.11[a]	87.67±13.91[a]	46.90±6.48[b]	25.78±8.15[c]	0.001
ACR (mg/g)	-----	16.37±3.46[a]	116.65±45.70[b]	681.04±217.78[c]	0.001

BMI: body mass index
Different superscript letters indicate significant differences between groups ($p<0.05$);
Identical small letters indicate non-significant differences between two groups;
***P*<0.05 is considered significant.**

Table (2): Lipid profile of the Studied Groups

Parameters	Control Group (n=30)	Patient groups			*P* value
		G1 (n=30)	G2 (n=30)	G3 (n=30)	
TC (mg/dl)	129.97±16.69[a]	172.73±26.39[b]	179.77±31.52[b]	188.43±26.10[b]	0.001
TGs (mg/dl)	100.96±20.09[a]	171.90±24.50[ab]	177.43±22.42[ab]	191.87±32.26[b]	0.001
VLDL-C (mg/dl)	21.79±5.34[a]	38.27±4.81[b]	40.90±7.39[b]	41.20±11.09[b]	0.001
HDL-C (mg/dl)	55.86±4.77[a]	40.17±7.96[b]	39.77±6.12[b]	36.23±6.97[b]	0.001
LDL-C (mg/dl)	56.46±7.03[a]	90.90±38.11[b]	92.57±40.26[b]	106.50±36.35[b]	0.001

Different little letters indicate significant differences between two groups;
Identical small letters indicate non-significant differences between two groups;
***P*<0.05 is considered significant.**

Table 3 showed the α1-AGP evaluation (mean+SD) for each research group. The patient groups (G3, G2, and G1) and the control group had highly different α1-AGP levels [3.12±0.85, 2.22±0.54, 1.28±0.36, and 0.80±0.089, respectively]. Significant variations were also found in the data between patient groups.

Table (3): Level of the α1-AGP in the groups according to the study

Parameters	Control Group (n=30)	Patient groups			*P* value
		G1 (n=30)	G2 (n=30)	G3 (n=30)	
α1-AGP (mg/mL)	0.80±0.089[a]	1.28±0.36[b]	2.22±0.54[c]	3.12±0.85[d]	0.001

Different little letters indicate significant differences between two groups;
Identical small letters indicate non-significant differences between two groups;
***P*<0.05 is considered significant.**

The findings showed an important negative correlation between α1-AGP level and GFR in the G1, G2, and G3 groups (r=-0.578, p=0.001, r=-0.549, p=0.002, and r=-0.473, p=0.008, respectively). The most current research found a significant positive correlation between α1-AGP level and urea in the groups with G1, G2, and G3 (r=0.465,

p=0.010, r=0.419, p=0.021, r=0.561, p=0.001), respectively. In both the G1 and G2 groups, there was a considerable positive correlation between the level of α1-AGP and creatinine concurrently (r=0.426, p=0.019, r=0.475, p=0.008). In the G2 and G3 groups, respectively, α1-AGP and ACR exhibited a strong positive correlation (r=0.387, p=0.035, r=0.406, p=0.026) (Table 4).

Table (4): Correlation between studied parameters and α1-AGP (mg/mL) levels

Categories	G1		G2		G3	
	r	***P***	**r**	***P***	**r**	***P***
GFR(mL/min/1.73m^2)	-0.578**	0.001	-0.549**	0.002	-0.473**	0.008
urea (mg/dL)	0.465**	0.010	0.419*	0.021	0.561**	0.001
creatinine (mg/dL)	0.426*	0.019	0.475**	0.008	0.358	0.052
ACR (mg/g)	0.351	0.057	0.387*	0.035	0.406*	0.026
**** shows significant correlations at 0.01;** *** indicates significant correlations at 0.05.**						

Receiver Operator Characteristics (ROC) Analysis Curve

Compared with healthy individuals, the ROC analysis showed that α1-AGP had a strong capacity to predict nephropathy in the diabetic group, including patients with G1, G2, and G3. This outcome was achieved through investigations that accounted for the test's sensitivity and specificity, as well as the area under the curve (Figure 1). The area under curve (AUC) (0.977) and *p* value (< 0.001) in the G1 group indicate that α1-AGP can predict DN in individuals without illness (control groups), with a sensitivity of 96.67% and specificity of 100%. This study demonstrated that α1-AGP had a high ability to distinguish between G2 and healthy groups, with higher sensitivity (96.7%) and specificity (86.7%) (AUC = 0.946, $p < 0.001$) in the G2 group.

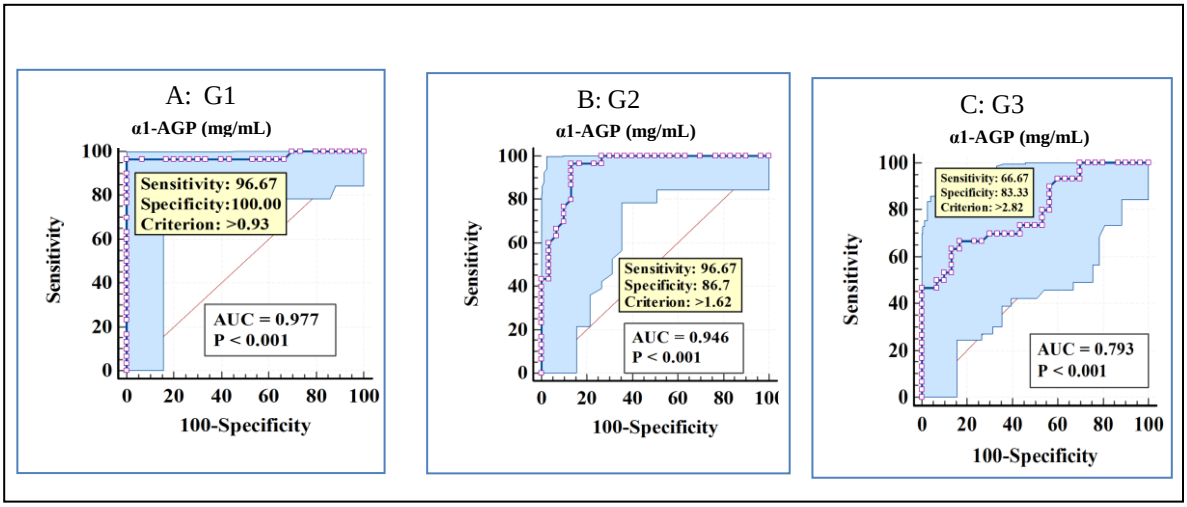

Fig (1): Shows the results of a ROC analysis of the α1-AGP level of patient groups compared to healthy groups (A–C)

Diabetic nephropathy is a clinical illness marked by glomerulosclerosis, leading to severe proteinuria, high blood pressure (BP), and impaired secondary renal function. DN can affect both type 1 and type 2 diabetics. Proteinuria is the main clinical sign and a key risk factor for DN progression [20]. This study found that the patient groups' blood urea and serum creatinine levels were higher in groups with more advanced nephropathy. One useful risk factor for clinical DN is the length of diabetes. Furthermore, individuals with long-term diabetes who have microalbuminuria may acquire a more severe glomerulopathy before their illness can be diagnosed as microalbuminuria. One important factor in determining the severity of the glomerulopathy was the duration of the sickness [9]. Elevated urine albumin excretion and total cholesterol are strongly correlated, according to multiple research studies [21]. People with diabetic kidney disease have been found to have lower levels of HDL-C but higher plasma concentrations of very low density lipoprotein cholesterol, low density lipoprotein cholesterol, total cholesterol, and triglycerides [22]. This was consistent with our findings, which showed that, with the exception of high density lipoprotein, which was the reverse, lipid levels were higher in G3 groups than in G2 groups, which were higher than

normal Recently, dyslipidemia appears to be common in people with diabetes and has been recognized as a significant risk factor for the development of DN [23]. It is known that inflammatory conditions cause the release of the acute-phase protein α1-AGP [24] and has been connected to the development of diabetes [25]. According to the available data, the T2DM group's α1-AGP levels differed significantly statistically from those of the control group, R. Alquoqa *et al*. [26] found that α1-AGP levels were significantly higher in DM patients compared with healthy control individuals. This was explained by the protein's immunomodulatory properties, which protect adipose tissue from excessive inflammation and metabolic dysfunction by lowering hyperglycemia and regulating the immune response [27]. Local study included 200 adults with type 2 diabetes attending primary health care centers in Kurdistan Region of Iraq revealed that diabetes duration, smoking status, and psychosocial determinants including stress, emotional well-being, support systems, and diabetes management confidence emerged as significant predictors of various self-management practices [28].

The results corroborated those of a 2021 investigation on mice carried out in Japan by Watanabe *et al*., [29] which discovered that the plasma alpha-1-acid glycoprotein levels in wild-type mice increased by almost 3.5 times on days 1-2 after renal ischemia-reperfusion. These mice also had increased renal failure, tubular damage, and inflammation. One of the main acute-phase proteins, alpha-1-acid glycoprotein, possesses several anti-inflammatory and anti-oxidative characteristics [30]. Consequently, subclinical atherosclerosis and vascular inflammation have been connected to its high levels in serum and urine. Supporting this, El-Beblawy *et al.* [19] confirmed that patients with and without microvascular complications had significantly higher levels of α1-AGP in both serum and urine compared to controls, with the highest levels observed in patients with complications. Furthermore, patients with G2 had higher serum and urine α1-AGP than those with G1.

4- CONCLUSION

Alpha-1-acid glycoprotein levels were significantly higher in patient groups than in healthy subjects, showing positive correlations with creatinine, urea, and ACR, and a negative correlation with GFR. These results suggest may serve as a diagnostic biomarker for DN presence/progression.

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