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Comparative Study of Serum Angiopoietin like Protein-8 and Hyaluronic Acid in Iraqi Hemodialysis Patients with and without T2DM

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Abstract

The current work was designed to investigate serum angiopoietin like protein-8 and hyaluronic acid among Iraqi hemodialysis patients with and without type 2 diabetes mellitus, and to find relationship between them, as well as if these patients are at risk of kidney fibrosis. ***Subjects & Methods*:** in this study, serum samples were obtained from (60) Iraqis patients with end stage renal diseases (ESRD)on hemodialysis (HD) (30 patients with T2DM (G2) and 30 patients withoutT2DM (G3)) in addition to (30) healthy individuals as a control group (G1), their ages ranged from (35-65) years. The patients attended the Al-Yarmouk Teaching Hospital, Baghdad. ***Results**:* the results in this study showed a highly a significant elevation inserum angiopoietin like protein-8 (ANGPTL8) and hyaluronic acid (HA) levels in G2 and G3 comparing with G1, Also,a no significant elevation in ANGPTL8 level, and a highly significant decrease in HA level were found in G3 comparing to G2. Additionally, a highly significant correlation for ANGPTL8 with FSG, HbA1C%, urea, creatinine, and HA in G1, G2, and G3.***Conclusions*:** This study was the first in estimation of the serum ANGPTL8 level and proved a relationship between ANGPTL8 and end stage renal diseases. There are an increase in serum ANGLP8 and HA levels in patients with end stage renal diseases on hemodialysis, and this suggests that the ANGPTL8 and HA possibly will be using as a potential markers predicting kidney fibrosis in hemodialysis patients with and without T2DM, and then these patients may be at risk of renal fibrosis.

Keywords: *End stage renal failure, Hemodialysis, kidney fibrosis, Angiopoietin like protein-8,Hyaluronic acid*

Introduction

End-stage renal failure is a progressive condition that has an important negative influence on patients' health-related type of life, owing to the accompanying disability or imposed restrictions in nearly every aspect of their everyday lives [1], also it can be defined as an irreparable fall in renal function when renal replacement treatment (RRT) is required for patients' survival. Dialysis and kidney transplantation considered the main types of renal replacement therapy [2]. Hemodialysis is a complicated process for patients that necessitates regular hospital or dialysis center visits, usually three times per week, suggesting significant changes in the patients' normal way of life [3].Hemodialysis's main purpose is to reestablish the intracellular and extracellular fluid environment that is typical of normal kidney function. This is achieved by the transmission of urea from the blood to the dialysate, as well the bicarbonate was transferred from the dialysate

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to the blood [4].End-stage renal disease (ESRD) is caused by a variety of factors, the most common of which is type 2 diabetes mellitus (30–50%) [5]. Mohammad K et al concluded in their analysis that previous diabetes-related awareness in hemodialysis patients with diabetes was considerably influenced by residency and household income, but not by informative level.According to the findings of this report, a significant part of diabetic patients on maintenance hemodialysis had impaired glycemic control [6].Angiopoietin-like proteins (ANGPTLs) are a type of secreted glycoprotein that has a helix domain at the N-terminus and a fibrinogen-like C-terminus. Angiogenesis, stem cell dilation, inflammation, tissue reformation, and lipid metabolism are all common functions of ANGPTLs [7].ANGPTL members' proteins influence not only endothelial cell proliferation and motility, but also inflammation and tumor cell activity. Inflammatory processes, counting mechanisms of start, development, propagation, invasion, angiogenic switch, and metastasis, play a critical role in carcinogenesis [8].Angiopoietin like protein-8 (ANGPTL8), also called as betatrophin, TD26, re-feeding mediated fat and liver (RIFL), lipasin, C19, or f80, is a new protein that is primarily expressed in the human liver [9]. It is linked to glucose and lipid metabolism, as well the incidence of insulin resistance [10]. It differs from other of the ANGPTL family memberships in that it lacks a fibrinogen-like domain, glycosylation sites, and amino acids for disulfide bond formation. ANGPTL8 was first identified as a tumor-associated antigen [11], but subsequent research revealed that it regulates plasma triglyceride levels and plays a job in the lipid metabolism [12].One of the mainingredients of extracellular matrix (ECM) in the connective tissues and other organs is hyaluronic acid (HA), a large non-sulfated glycosaminoglycan [13]. HA, which has been shown to be elevated in chronic kidney disease, is one of the direct indicators of fibrosis (CKD). N-acetyl glucosamine and glucuronic acid units make up HA, a high molecular weight protein [14]. Hyaluronic acid plays a significant function in fibrosis, which has only recently been recognized. However, a growing number of publications have emerged that indicate HA plays a mainfunction in the fibrotic process, especially in the fibrotic lung and kidney disease [15].Renal fibrosis is the end-stage morbid mechanism of any chronic renal damage or maladaptive healing. It is the underlying morbid mechanism of chronic kidney disease (CKD), which affects more than 10% of the world's populace and has limited treatment decisions. Excessive deposition of extracellular matrix (EM) causes renal fibrosis, which disrupts and replaces the functional parenchyma, resulting in kidney failure [16].

Aim of study: The current work was designed to investigate serum angiopoietin like protein-8 and hyaluronic acid among Iraqi hemodialysis patients with and without type 2 diabetes mellitus, and to find relationship between them, as well as if these patients are at risk of kidney fibrosis.

Patients& Methods

Patients Selection and Study Protocol:

This study was performed in AL-Yarmouk Teaching Hospital, Baghdad. The study was included 60 hemodialysis patients with chronic kidney failure; 30 patients with DM (G2) and 30 patients without DM (G3), in addition to 30 healthy individuals as control (G1), their ages ranged (35-65) years for all subjects. Excluded criteria included patients with viral hepatitis.

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Laboratory Measurements:

Serum samples, which obtained from all patients and control, were frozen until used to analysis of fasting serum glucose(FSG), urea, creatinine, these were determined using standard biochemical techniques by Hitachi auto-analyzer. Glycated hemoglobin (HbA1c) was assayed by Elisa kit from MyBiosource, which employs the direct competitive inhibition enzyme immunoassay techniquefor the quantitative determination of human glycated hemoglobin A1c (GHbA1c) concentrations in lysate for RBC. Calculation of body mass index (BMI) wasbased on the following equation, weight (kg) divided by the square of height (m2) [17]. Serum Angiopoietin Like Protein 8 (ANGPTL8)was determined by ELISA kit from SUNLONG, No.(SL2465Hu) uses Sandwich-ELISA as the method.Serum hyaluronic acid (HA) was assayed employs the quantitative sandwich enzyme immunoassay technique by ELISA kit from CUSABIO (CSB-E04805h).

Statistical Analysis

The statistical analysis was determined by *Microsoft excel 2016*. Data were expressed as Mean ± SD. The multiple variations between patients and normal groups were tested by using a t-test, *P-value < 0.001*, and *P-value< 0.05* that were reflected to highly significant and significant respectively. The relationship between all studied parameters was explaining by using Pearson's connection coefficient (r).

Results

The clinical parameters of the study groups are shown in table 1. The measurement of BMI, FSG, HbA1C, Urea, and Creatinine levels were detected in hemodialysis patients (HD) with diabetes mellitus (DM) (G2) and without DM (G3) , as well control (G1).The results in the current study display a significant *(P<0.05)* increase in BMI levels in G2 compared with control G1, as well no significant *(P<0.05)* raise in G3 as paralleled to G1, and no significant *(P<0.05)*differences between G2 and G3 in BMI levels.

There were a highly important *(P < 0.001)*elevation in serum HbA1c, urea, and creatinine levels in G2 and G3, while there was a highly important *(P < 0.001)*increase in FSG level in G2 and no significant *(P<0.05)* increasein G3 when compared with control (G1).

The results in this study showed a highly significant *(P < 0.001)* variance in FSG and HbA1c levels , as well no significant *(P<0.05)* variance in urea and creatinine levels between two patients groups (G2 and G3).Data in Table 2 and figure 1 explained a highly important *(P < 0.001)* increase in serum ANGPTL8 and HA levels among patient's groups (G2 and G3) comparing to G1, in addition to no significant *(P<0.05)* differences in ANGPTL8 level, and highly significant *(P < 0.001)* variance in HA level were found between two patient's groups (G2 and G3).

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Table 1. Diagnostic parameters in HD patients with DM (G2) and without DM (G3) , as well control (G1).

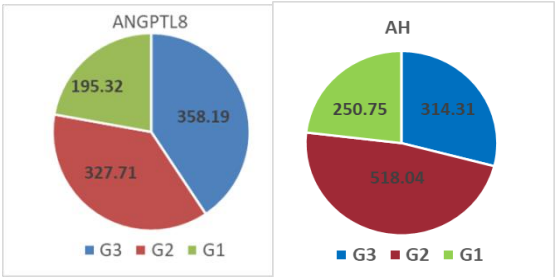
Groups / Parameters	G1 No.(30)	G2 No.(30)	G3 No.(30)
Gender Female/Male	9/21	10/20	14/16
BMI	24.56±1.38	28.66±10.30 a^{*}	26.17±5.91 b^{NS} c^{NS}
FSG mg/dl	85.76±6.98	214.93±59.10 a^{**}	89.26±6.99 b^{NS} c^{**}
HbA1c%	4.92±0.59	8.17±1.23 a^{**}	5.52±0.66 b^{**} c^{**}
Urea mg/dl	20.5±4.71	136.11±46.42 a^{**}	145.94±38.58 b^{**} c^{NS}
Creatinine mg/dl	0.91±0.23	7.07±2.54 a^{**}	7.76±2.10 b^{**} c^{NS}

** (P<0.05), ** (P < 0.001), NS: Non-Significant (P ≥ 0.05).*
a: t-test between G1 and G2, b: t-test between G1 and G3, c: t-test between G2 and G3

Table 2. Mean ± SD for serum ANGPTL8 and HA levels in HD patients with DM (G2)andwithout DM (G3) , as well control (G1).

Groups / Parameters	G1 No.(30)	G2 No.(30)	G3 No.(30)
ANGPTL8 pg/ml	195.32±61.93	328.38±78.93 a^{**}	364.86±108.86 b^{**} c^{NS}
HA ng/ml	250.75±33.28	518.04±80.68 a^{**}	314.31±42.84 b^{**} c^{**}

*** (P < 0.001), NS: Non-Significant (P ≥ 0.05).*
a: t-test between G1 and G2, b: t-test between G1 and G3, c: t-test between G2 and G3



(A) (B)

Figure 1: Distribution of serum ANGPTL8 (A) and HA (B) in G1,G2,and G3.

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Correlation coefficient (r) and *p-value* for ANGPTL8 and others studied parameters were shown in Table 3. There were a highly important*(P < 0.001)* negative association between ANGPTL8 and BMI in G1, G2, and G3. While a highly important*(P < 0.001)* positive association between ANGPTL8 and FSG in G1 and a highly important*(P < 0.001)* negative relationship with FSG in G2 and G3.

ANGPTL8 was correlated positively (by highly significant relation) with urea and creatinine in G1 and G2, as well as a highly significant negative correlation between ANGPTL8 with urea and creatinine was found in G3. There was a highly significant *(P < 0.001)* negative correlation between ANGPTL8 and HA in G1 and G2, in addition to a highly important*(P < 0.001)* positive relationship between them in G3.

Table 3. Correlation coefficient analysis between serum ANGPTL8 with studied parameters in control (G1), HD patients with DM (G2) and without DM (3).

Groups Parameters	ANGLP8		
	r1	r2	r3
BMI	-0.09 **	-0.21**	-0.13 **
FSG	0.1 **	-0.04 **	-0.3 **
HbA1C	-0.24 **	0.04 **	0.08**
Urea	0.009 **	0.25 **	-0.01**
Creatinine	0.25 **	0.04 **	-0.1**
HA	-0.19 **	-0.18**	0.07**

*****: Highly significant(P < 0.001)***

Discussion

Type 2 diabetes mellitus (T2DM) is the more publiclone illness resulting end-stage renal disease (ESRD) which leads to the hemodialysis [18].Patients with and without diabetes had substantial variations in insulin concentrations and only minor but important alterations in plasma glucose levels, glucose kinetic parameters, and extracorporeal glucose elimination after receiving concentrated glucose infusions similar to those used for an intravenous glucose tolerance test throughout hemodialysis [19].Patients with chronic kidney disease (CKD) have higher serum urea and creatinine levels, which can contribute to a variety of other harmful diseases. Haemodialysis resulted in lower serum levels and less load on the kidneys in these patients. [20].

Our findings are consistent with some researches that T2D is a predictor of an raised level of ANGPTL8; its concentration was greater in individuals with T2D, both with morbid obesity and healthy weight than inindividuals without T2D [21, 22]. The findings of the Fenzl et al. study

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point to a possible correlation between elevated ANGPTL8 levels and T2D. However, this association is unclear and does not seem to contain a direct impact on indicators of β -cell activity, which is consistent with a previous study that found no correlation between circulating ANGPTL8 and variables of β-cell job and glucose homeostasis in insulin resistance patients [23].While ANGPTL8 is not involved in cell growth control, its association with endocrine and metabolic diseases such as diabetes mellitus has garnered a lot of attention. In individual sick with long-term type 1 diabetes, Espes et al. discovered an elevation in circulating ANGPTL8 [24]. In type 2 diabetic patients, Fu et al. found an elevation in ANGPTL8 levels [21]. A previous study found that newly diagnosed type 2 diabetic patients' circulating ANGPTL8 levels increased by about twofold [25]. Some previous studies have shown that, in the absence of T2D, morbid obesity is relatedwith lower concentration of ANGPTL8in the blood[26,27].In contrast to the current research, Ebert et al. found that CD patients had substantially lower Angptl8 levels than individual with an eGFR of 50 mL/min/1.73 m2 in their study. These findings indicate that Angptl8 is not likely to be removed by the kidneys. Other adipokines and hepatokines are substantially elevated in end-stage renal disease, in comparison to Angptl8.Interestingly, in a subset of the patients, circulating Angptl8 was significantly raised after as paralleled with prior hemodialysis. These datarecommend that the adipokine/hepatokine is not dialyzable. It is probable that hem-concentration from the elimination of liquid may have contributed to this alteration. Alternatively, Angptl8 excretion may be inproved in tissues as a response to the blood circulation or metabolic alterationscaused by dialysis.Since insulin importantly increases Angptl8 mRNA expression in differentiated 3T3-L1 adipocytes in vitro, it's thinking that a high level of insulin in blood plays a role in the upregulation of the adipokine/hepatokine in T2DM [28]. However, the current study found a highly significant increase in ANGLP8 levels in HD patients, These findings indicate that Angptl8 is most likely removed by the kidneys.

The upregulation of Angptl8 in T2DM is a compensative mechanism that helps to border the metabolic effects of insulin resistance and increase glucose tolerance. instead, Angptl8 resistance, like insulin and leptin resistance in obesity, may evolve in T2DM. Many factors influence ANGPTL8 transcription and translation, including glucose, insulin, and GLP-1[29].Inplasma, high concentration of hyaluronic acid has previously been linked to ESRD, and it has been shown that hyaluronic acid levels are linked to hemodialysis period and certain indicators of chronic inflammation, such as dialysis-related amyloid. Connection of the blood with bio-incompatible dialysis membranes has been shown to catalyze cytokine output, and cytokines have been shown to stimulate cytokine production [30].The mechanism that causes serum HA levels to rise in CKD patients is unknown. Uremic toxins, on the other hand, are thought to cause generalized endothelin receptor dysfunction [31]. Hyaluronic acid is also involved in endothelial dysfunction and the progression of arteriosclerosis. Another mechanism for HA rise in uremic patients, in addition to high endothelial receptor dysfunction, is an increase in HA synthesis-stimulating factors. In patients with uremia, prostaglandins, cytokines, or both play a role in HA synthesis [32].Hyaluronic acid (HA), an integral ingredient of the extracellular matrix (ECM) in every tissue in the body that is primarily produced by hepatic stellate cells and break down by sinusoidal endothelial cells, plays a critical function in fibrosis that has only recently been recognized [33].Our previous understanding of HA in the fibrosis was restricted to older article that mainly focused on a connection between elevated HA concentration and

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fibrosis, implying that HA could be used as a biomarker for fibrosis diagnosis. By it is role in fibroblast movement, proliferation, and fibroblast-to-myofibroblast differentiation, HA contributes to fibrosis. Furthermore, fibrosis has been linked to HA receptors, especially CD44 and RHAMM, as well as HA produces and degrading enzymes. This indicates that HA and its regulatory pathways may be new targets for antifibrotic treatments [34].The findings indicate that HA may play an indirect function in the fibrosis progression: HA is known to bind and recruit immune cells, and its aggregation prior to fibrosis indicates increased immune cell recruitment, as seen in individuals' sick with idiopathic pulmonary fibrosis. In return, immune cells liberation a combination of inflammatory mediators and growth factors that have been shown to cause fibroblasts, resulting in fibrosis [35, 36].The creation of scar tissue caused by prolonged irregular wound healing is called fibrosis, which is diagnosed by an important elevation in ECM deposition, also Inflammation is famous, to be a main causal marker to fibrosis. Moderate inflammation ends in the restoration of normal tissue architecture, while extreme and chronic inflammation causes tissues to lose their healing potential. This indorses a fibrogenic repair response, excessive ECM accumulation, and irregular tissue architecture formation. As a result, persistent fibrosis impairs organ function [35, 37].

Conclusions

This study was the first in estimation of the serum ANGPTL8 level and proved a relationship between ANGPTL8 and end stage renal diseases. In the current study, there are an increase inserum ANGLP8 and HA levels in patients with end stage renal failure on hemodialysis that may make these patients at risk of renal fibrosis.The physiological jobs of ANGPTL8 occur by PI3K, Akt, FOXO1 and other signaling pathways [38, 39], these signaling pathways are closely linked to the happening and progress of liver fibrosis. In addition to Hyaluronic acid (HA) mostly produced by hepatic stellate cells and destroyed by sinusoidal endothelial cells, plays a significant function in fibrosis that has been recognized, recently[33]. Serum HA level, which is amarker of fibrosis [40], therefore, the ANGPTL8 and HA possibly will be also using as a potential markers predicting kidney fibrosis in hemodialysis patients with and without T2DM.

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