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The Potential Role of Polyol Pathway in the Development and Detection of Diabetic Nephropathy

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is the major type of diabetes around the world with a diabetic nephropathy (DN) is the most common complication of this illness. Several pathways involving pro-inflammatory and polyol are activated through the course of T2DM. The current study aims to evaluate the role of sorbitol dehydrogenase (SDH), zinc, fructose and glycosyl phosphatidyl inositol high density lipoprotein binding protein 1 (GPIHBP1) in development of DN in T2DM Iraqi patients. This is a nested case control study, involved 122 patients with DN (72 patients with microalbuminuria (MA) and 50 patients with normoalbuminuria (NA)) and other age- and gender-matched 58 apparently healthy subjects. The SDH activity, fructose and Zn+2 concentration were determined using spectrophotometric assays, while enzyme linked immunosorbent assay (ELISA) was used to measure serum level of GPIHBP1. Other parameters including lipid profile, fasting blood sugar (FBS), glycated hemoglobin (HbA1c) and renal function tests were measured with standard biochemical methods. The mean serum level of SDH activity in MA and NA was 22.26±9.91U/L and 26.39±10.58 U/L, respectively with no significant difference. However, both groups differed significantly from controls (48.39±24.43 U/L). Similarly, fructose level was comparable between MA and NA groups (6.1±1.5 mg/dl and 6.75±1.54 mg/dl, respectively) and significantly lower than that of controls (10.0±2.0 mg/dl). The median level of GPIHBP1 in MA patients was (878.2 pg/ml) which was higher than that of NA group (1014.05pg/ml) and controls (1189.5 pg/ml) with significant differences. In the context of discrimination between MA and healthy control, the area under the curve (AUC) for SDH and fructose was 0.904, 95%CI= 0.853-0.954, p <0.00 and 0.931, 95%CI= 0.886-0.976, p <0.001, respectively, while in the context of discrimination between NA and healthy controls, it was 0.841, 95%CI= 0.767-0.915, p <0.001, and 0.903, 95%CI= 0.848-0.958, p <0.001, respectively. For GPIHBP1, the AUC in the context of discrimination between MA and healthy controls 0.846, 95%CI= 0.776-0.916, p <0.001; between MA and NA controls 0.773, 95%CI= 0.688-0.857, p <0.001, and between NA and healthy controls 0.762, 95%CI= 0.616-0.837, p <0.001. Diabetic nephropathy (whether normo- or microalbuminuria) is associated with elevated serum levels of TG and vLDL compared with healthy subjects. Serum level of GPIHBP1 is not only decreased in patients with DN, but

also inversely associated with the severity of the disease, and can differentiate between normo- and microalbuminuria with a good sensitivity and specificity.

1. Introduction

Type 2 diabetes mellitus (T2DM) is the major type of diabetes around the world. It is caused by the body's ineffective use of insulin added to a slow progressive loss of pancreatic β-cells [1]. Acute hyperglycemia can lead to life-threatening diabetic ketoacidosis, whereas chronic hyperglycemia is linked to macrovascular problems including myocardial infarction, stroke, and microvascular diseases like diabetic nephropathy (DN), retinopathy, and neuropathy [2].

Diabetic nephropathy is one of the most common micro vascular complications which represents the main cause of end-stage renal disease (ESRD) in patients with DM. It is defined as elevated urine albumin excretion (more than 300 mg per 24 hours) coupled with increasing blood pressure leading to reduced glomerular filtration rate (GFR) and eventually ESKD [3]. Because T2DM is a multi-factorial disease, several pathways involving pro-inflammatory, polyol, and others, are activated through the course of the disease. Polyol pathway is an alternative glucose metabolic route which becomes prominent in hyperglycemic condition. It is a two-step process in which glucose is reduced to sorbitol and then sorbitol is converted to fructose. Two enzymes are involved in the polyol pathway, namely aldose reductase and sorbitol dehydrogenase [4]. Since the process cannot proceed without these two enzymes, any entity that is able to inhibit their activities will reduce the flux of this undesirable pathway, and consequently ameliorate diabetic complications [5].

Studying the elements of polyol pathways can give a better insight for the mechanisms by which DN develop. Furthermore, some markers could be utilized in early detection of DN in T2DM patients. Therefore, the present study aimed to evaluate the role of SDH, Zn^{+2}, fructose and GPIHBP1 in the development and progression of DN in Iraqi patients with T2DM.

2. Material and Methods

The current study was designed as nested case control study. It included 122 patients with DN. clinic in Al-Imamain Alkadhimain Medical City, from January 2021 to August 2021. The medical history of each patient was taken regarding age, gender, history of renal disease, history of any other diseases, and smoking condition. Measurements of their height and weight were done to calculate their body mass index (BMI).

Patients were classified into two groups on the basis of albumin creatinine ratio (ACR) in urine the first group include 50 patients with ACR less than (30 mg/g) (normoalbuminuria), the second group72 patients with ACR (30-300 mg/g) (microalbuminuria), while the control group includes 58 healthy subjects. Patient with chronic liver disease, patients diagnosed with T1DM, kidney failure for causes other than T2DM, cardiovascular diseases including coronary artery disease, peripheral vascular disease, stroke, the infections and emergency patients were excluded from the study.

Other 58 age-and gender matched apparently healthy subjects were included as control group. The study was approved by the Institutional Board Review, College of Medicine, Al-Nahrain University. A written

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consent from each participant was obtained prior to data collection after explaining the aim of study. Each patient was given the complete unconditioned choice to withdraw anytime. The confidentiality of data throughout the study was guaranteed and the patients were assured that data will be used for research purpose only.

Blood samples were collected in the morning after the participant had fasted for at least 8 hours. About 5 ml of venous blood were collected in plain tube. Serum was separated and used for measurement of SDH activity, lipid profile, FBS, Zn^{+2}, fructose and GPIHBP1.

The urine sample was taken at the first morning in a sterile, detergent-free vial. Five milliliters of mid-urine were taken from each participant and centrifuged at 1000x g for around 10 minutes to remove the solid contents.

2.1 Methods

The fasting blood sugar, glycated hemoglobin, serum creatinine, urea, lipid profile, SDH, Zn^{+2} and fructose were measured by standard laboratory methods in a certified laboratory by using commercial kits. The glomerular filtration rate (GFR) was estimated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation as follows: eGFR = 186.33 (serum creatinine)_1.154 3age-0.2033 (0.742 for women). Chronic kidney disease (CKD) was defined as eGFR less than 60 mL/min/1.73m^2 [6].

2.2 Statistical Analysis

Statistical analyses were performed by using SPSS software version 25.0 (SPSS, Chicago). Continuous data were subjected to normality test (Shapiro Wilk test), Data with normally distribution were presented as mean and standard deviation, and analyzed with Student t-test (for two group comparison) or analysis of variance (ANOVA) (for three group comparison). Receiver operating characteristic curve (ROC) was used to evaluate sorbitol, and fructose in the context of discrimination between different groups. Pearson's correlation test was used to explore the possible correlation of sorbitol, fructose and Zn^{+2} with other numerical variables. A p- value less than 0.05 was considered to indicate a statistically significant difference.

3. Result

The mean age of the patients with MA, NA and controls was 51.13±10.77 years, 54.02±9.90 years and 51.13±8.71years, respectively with no significant differences between the three groups. Females were more frequent in NA group (55.1%) than either MA group (38.89%) or controls (46.43%) with no significant differences. Furthermore, the three groups were comparable in terms of weight, height and BMI with no significant difference as shown in table (1).

Table (1): Demographic characteristics of the study population

Variables	Micro (n=72)	Normo (n=49)	Controls (n=56)	p- value
Age, years				
Mean±SD	54.13±10.77	54.02±9.90	51.13±8.71	0.185
Range	27-75	33-73	37-70	
Gender				
Male	44(61.11%)	22(44.9%)	30(53.57%)	0.212
Female	28(38.89%)	27(55.1%)	28(46.43%)	

WT				
Mean±SD	89.32±27.57	83.56±14.18	85.49±16.54	0.315
Range	49.0-191.0	55.0-115.0	49.0-191.0	
Height				
Mean±SD	165.03±14.11	164.77±7.76	165.45±7.74	0.952
Range	66.0-199.0	150.0-186.0	150.0-180.0	
BMI				
Mean±SD	30.47±5.71	30.70±3.78	31.51±7.19	0.586
Range	19.1-48.4	22.0-39.5	22.3-65.6	

Table (2) shows the lipid profile in patients and controls. Data regarding the components of lipid profile were found to be non-normally distributed. Accordingly, data were mostly expressed as median, and nonparametric Kruskal Wallis test was used to compare between these groups. Median serum level of TC in MA group was 169.5 mg/dl, which did not differ significantly from that of NA group (185.5 mg/dl) or controls (176.1 mg/dl). Likewise, the median level of HDL and LDL in MA, NA and controls was (39.65 mg/dl and 90.5 mg/dl; 42 mg/dl and 96 mg/dl; and 45 mg/dl and 102.57 mg/dl, respectively) with no significant differences. In contrast controls demonstrated lower TG and vLDL levels (123mg/dl and 25.75 mg/dl, respectively) than either MA group (144.5 mg/dl and 34 mg/dl, respectively) or NA group (160 mg/dl and 32.6 mg/dl) with significant differences.

Table (2): Lipid profile in different groups

Variables	**Micro (n=72)**	**Normo (n=49)**	**Controls (n=56)**	**p- value**
TC, mg/dl				
Mean±SD	172.12±53.02	182.48±44.55	179.15±39.49	0.145
Median	169.5	185.5	176.1	
Range	84.0-320.0	25.0-253.0	108.7-285.0	
TG, mg/dl				
Mean±SD	176.64±99.34	192.67±99.03	145.77±72.19	**0.048**
Median	144.5[a]	160[a]	123[b]	
Range	45-432	66-448	43-449	
HDL, mg/dl				
Mean±SD	43.50±14.46	44.76±14.19	44.58±9.25	0.366
Median	39.65	42.0	45.0	
Range	23.3-96.0	22.3-83.2	26.4-71.3	
LDL, mg/dl				
Mean±SD	95.76±38.02	101,82±34.4	106.97±31.85	0.129
Median	90.5	96.0	102.57	
Range	37.8-180	38.7-193.6	33.3-183.8	
vLDL, mg/dl				
Mean±SD	43.33±35.46	40.65±24.11	28.58±13.35	**0.024**
Median	34[a]	32.6[a]	25.75[b]	
Range	.0-198.0	13.2-134.9	8.6-89.7	

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TG: triglycerides, HDL: high density lipoprotein, LDL: low density lipoprotein, vLDL: very low density lipoprotein. Different small letters indicate significant differences

Three markers were investigated for their association with albuminuria. The mean serum level of sorbitol in MA and NA was 22.26±9.91U/L and 26.39±10.58 U/L, respectively with no significant difference. However, both groups differed significantly from controls (48.39±24.43 U/L). Similarly, fructose level was comparable between MA and NA groups (6.1±1.5 mg/dl and 6.75±1.54 mg/dl, respectively) and lower significantly form that of controls (10.0±2.0 mg/dl). Zinc level was very close between the three groups with no significant differences. The median level of GPIHBP1 in controls was (1189.5 pg/ml) which was higher than that of NA group (1014.05pg/ml) MA patients (878.2 pg/ml) with significant differences table (3).

Table (3): Serum level of sorbitol dehydrogenase activity, fructose, Zn+2 and GPIHBP1 in patients and controls

Variables	Micro (n=72)	Normo (n=49)	Controls (n=56)	p- value
SDH, U/L				
Mean	22.26±9.91[a]	26.39±10.58[a]	48.39±24.43[b]	**<0.001**
Range	5.0-39	7-54	24-135	
Fructose mg/dl				
Mean	6.1±1.5[a]	6.75±1.54[a]	10.0±2.0[b]	**<0.001**
Range	3.0-9.0	4.0-10.0	6.0-15	
Zn^{+2}, mg/dl				
Mean	17.48±0.67	17.56±0.58	17.6±0.48	0.484
Range	15.6-18.67	15.88-18.69	15.8-18.68	
GPIHPB1, pg/ml				
Mean	883.3±103.71	982.2±155.1	1160.1±222.1	**<0.001**
Median	878.2[c]	1014.05[b]	1189.5[a]	
Range	712-1014	668.9-1187.5	722-1799	

3.1 Diagnostic Value of Different Markers

Receiver operating characteristic curve was used to find out the diagnostic values of those markers with significant variation between different groups.

3.2 Patients with Microalbuminuria Vs. Healthy

(Figure 1), (Figure 2) and table (4) show the Diagnostic value of sorbitol, fructose and GPIHPB1in the context of discrimination between Microalbuminuria and Healthy control.

Variables	under the curve (AUC)	Confidence interval (CI)	p- value	cut off value	sensitivity	specificity
SDH, U/L	0.904	0.853-0.954	**<0.001**	28.76	86%	73%

Fructose, mg/dl	0.931	0.886-0.976	**<0.001**	7.71	86%	83%
GPIHPB1, pg/ml	0.846	0.776-0.916	**<0.001**	972.5	80%	68%

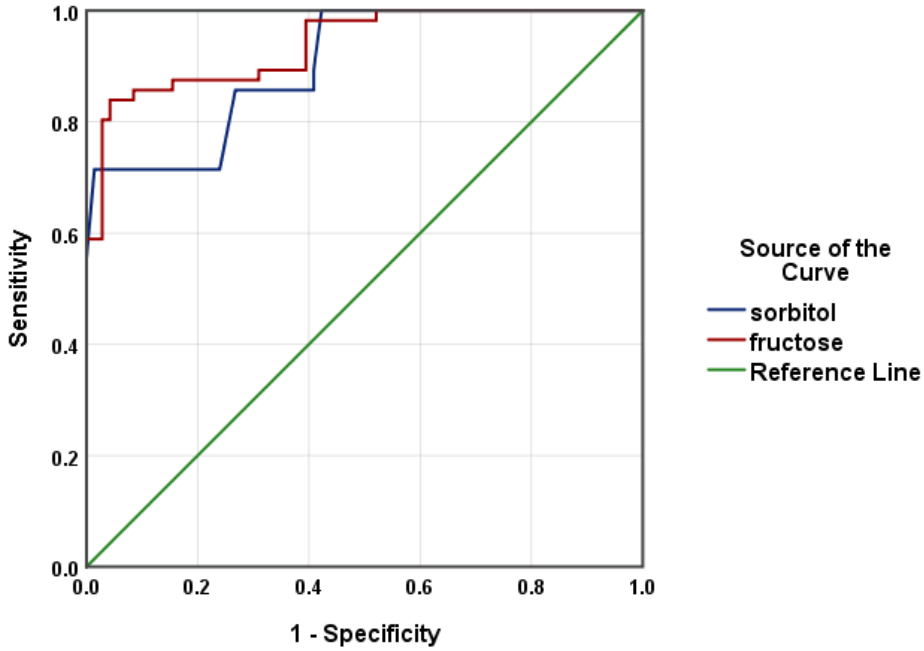

Figure 1: Receiver operating curve for sorbitol dehydrogenase activity and fructose in the context of discrimination microalbuminuria patients and controls

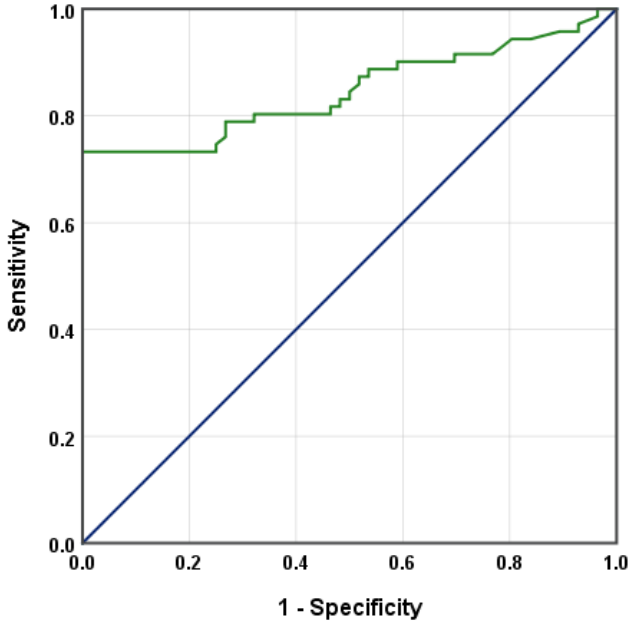

Figure 2: Receiver operating curve for GPIHPB1 in the context of discrimination microalbuminuria

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patients and controls

3.3 Microalbuminuria Vs. Normoalbuminuria

(Figure 3) and table (5) show the Diagnostic value of GPIHPB1in the context of discrimination between Microalbuminuria Vs. Normoalbuminuria

Variables	under the curve (AUC)	Confidence interval (CI)	p- value	cut off value	Sensitivity	Specificity
GPIHPB1, pg/ml	0.773	0.688-0.857	**<0.001**	1097.3	71%	78%

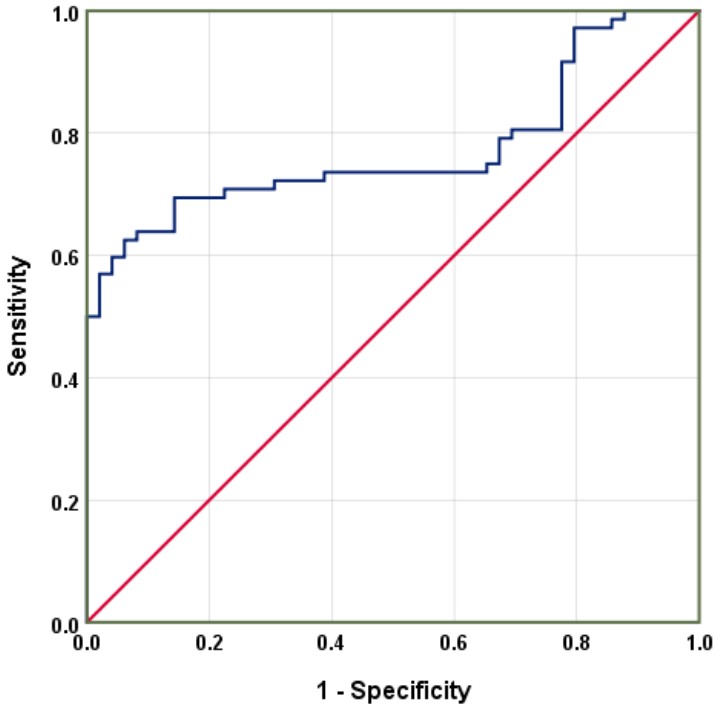

Figure 3: Receiver operating curve for GPIHPB1 in the context of discrimination microalbuminuria patients and normoalbuminuria

3.4 Normoalbuminuria Vs. Healthy

(Figure 4), (Figure 5) and table (6) show the Diagnostic value of sorbitol, fructose and GPIHPB1in the context of discrimination between Normoalbuminuria and Healthy control

Variables	under the curve (AUC)	Confidence interval (CI)	p- value	cut off value	Sensitivity	Specificity
SDH, U/L	0.841	0.767-0.915	**<0.001**	38.41	71%	92%

Fructose, mg/dl	0.903	0.848-0.958	**<0.001**	8.47	80%	70%
GPIHPB1, pg/ml	0.726	0.616-0.837	**<0.001**	965.58	78%	66%

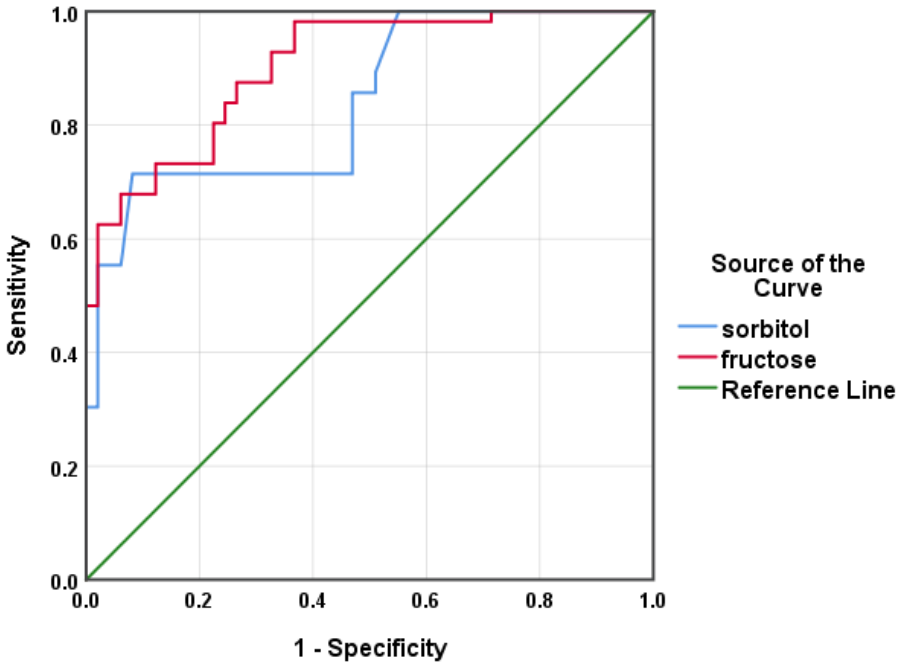

Figure 4: Receiver operating curve for sorbitol dehydrogenase activity and fructose in the context of discrimination normoalbuminuria patients and controls

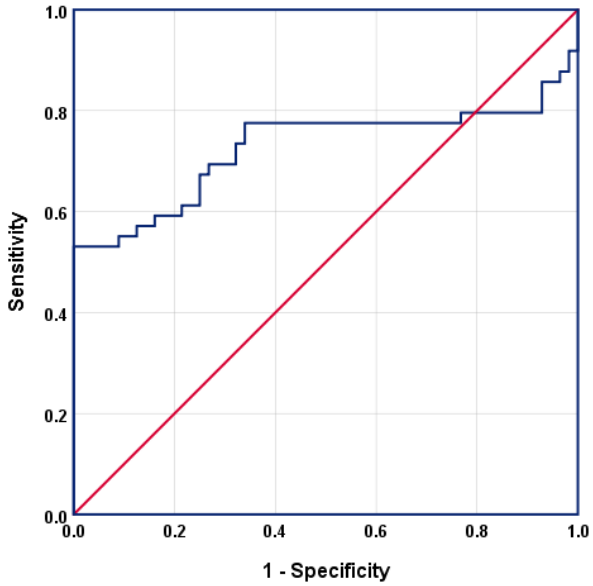

Figure 5: Receiver operating curve for GPIHPB1 in the context of discrimination normoalbuminuria

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patients and normoalbuminuria

4. Discussion

According to the results of the present study, there were no significant difference in most components of lipid profile between the three groups. However, MA and NA groups demonstrated higher levels of TG and vLDL (144.5 mg/dl and 34 mg/dl); and (160 mg/dl and 32.6 mg/dl), respectively than controls (123 mg/dl and 25.75 mg/dl, respectively) with significant differences.

The association of lipid profile with the development of DN in patients with T2DM is a debate issue. Some studies have shown a positive association between a high level of TC and DN in diabetic patients [7]. Others studies found a significant increase in the mean of vLDL in patients under hemodialysis [8- 10]. Another study showed the concentrations of vLDL and TG are elevated in patients with DN compared with those with T2DM [11]. In contrast, other studies have found a lack of significant changes in serum lipid profiles or even an inverse association between TG levels and DN [12].

As patients and controls in the present study are selected to match each other in BMI, this may greatly explain the non-significant differences in most components of lipid profile between the three groups.

However, it can be deduced from other studies that lipid profile does has an impact on the development of DN in patients with T2DM.

The mechanisms by which plasma lipids influence DN have not been fully elucidated, but certain factors may be involved. In glomerulus, there are mesangial foam cells which express scavenger receptors for modified, glycosylated and oxidized LDLC. Accumulation of these substances in the mesangial matrix triggers the activation of monocytes into macrophages [13].

It is believed that the mechanism of renal injury due to dyslipidemia occurs through three stages. First, exposure to oxidized lipoproteins stimulates the mesangial cell (in glomeruli) to secrete chemotactic agents and adhesion molecules which further enhances the recruitment of macrophages. The monocyte infiltration results in glomerulosclerosis and tubular fibrosis. Secondly, the uptake of oxidizing LDL by recruited macrophages stimulates the release of reactive oxygen species (ROS) and the expression of prosclerotic and proliferative cytokines (transforming growth factor [TGF]-β1 and platelet-derived growth factor-AB). Finally, these cytokines stimulate the production of extracellular matrix proteins subsequently promoting mesangial expansion [14].

Other than glomeruli, studies of hyperlipidemic rats showed that the tubular injury was ascribed to interstitial macrophage infiltration and an increase in TGF-β1 gene expression. It is believed that this is mediated via cytokine reactions and ROS. These phenomena are similar to those in vivo studies where the tubular uptake and metabolism of filtered lipoproteins resulted in the expression of cytokines and subsequent local inflammation [15].

In the present study, SDH activity and fructose did not differ significantly between NA and MA. However, both groups had significantly lower levels of these markers compared with controls. Unfortunately, there was no previous similar study in this regard. However, as the SDH catalyzes the oxidization of sorbitol into fructose, the result indicates a reduction in SDH which was accompanied by logical consequence (reduction in fructose). Thus, it can be concluded that there was an accumulation of sorbitol in patients with DN regardless of its stage. In fact, the disorder in sorbitol pathway metabolism has been implicated by many

investigators in the pathogenesis of diabetes-induced vascular and neural dysfunction in animal models of diabetes [16]. Nevertheless, the precise nature of the biochemical imbalances that mediate sorbitol pathway linked functional abnormalities remains unclear. Postulated mechanisms include myo-inositol depletion and associated impaired phosphatidylinositol metabolism [17]; osmotic stress due to accumulation of intracellular sorbitol; decreased availability of NADPH (required for maintenance of reduced glutathione), which is oxidized to NADP+ coupled to reduction of glucose to sorbitol by aldose reductase; and a cascade of metabolic imbalances initiated by an increased cytosolic ratio of free NADH:NAD+ resulting from increased oxidation of sorbitol to fructose by SDH [18].

The accumulation of sorbitol can change cellular membrane osmotic pressure and triggers osmotic stress. This osmotic stress has been thought to be the main underlying been implicated in diabetic kidney dysfunction or mechanism for diabetic nephropathy. Supporting this assumption is the study of [19], [20] who revealed high sorbitol in diabetic patients.

The present results contrast the study of [21] who showed serum fructose was increased in diabetic patients. However, their study included diabetic patients with poorly controlled disease, and the differences in glucose control may at least partially account for the differences in observed serum fructose. Fructose can also be produced in the body by activation of the aldose reductase (AR) in the polyol pathway. A variety of stimuli are known to increase AR expression, including ischemia, hypoxia, hyperglycemia, hyperosmolality, and uric acid [22].

As an enzyme, SDH requires zinc as cofactor. The present study showed that the reduced activity of SDH is not ascribed to deficiency in Zn^{+2} as there were no significant differences between the three group in Zn^{+2} level. This result disagrees with study of [23] who reported that diabetic patients with microalbuminuria and low values of e-GFR had a lower mean serum zinc level than other diabetic nephropathy groups. We also found a significant inverse relationship between serum zinc and microalbuminuria; and a significant positive relationship between serum zinc and e-GFR. This variation between the two studies may be attributed to the variation in sample size.

This result disagreement with study for [24] there showed serum GPIHBP1 levels were significantly higher in patients with T2DM with diabetic retinopathy DR, DN, and microvascular complications than in those without these complications. This result agrees with [25] there data suggest that decreased GPIHBP1 availability in insulin resistant state may hamper peripheral lipolysis capacity.

The endothelium-derived molecule, glycosylphosphatidylinositol-anchored binding protein 1 (GPIHBP1), plays a critical role in LPL metabolism and function by anchoring LPL to the endothelium and binding chylomicrons.

The current study are in accordance with previous studies by Vaziri that indicated a GPIHBP1-deficient humans exhibit severe hypertriglyceridemia and diminished heparinreleasable LPL, pointing to the critical role of GPIHBP1 in regulation of LPL activity. Given its central role in regulation of LPL activity and triglyceride metabolism, we explored the effect of chronic kidney disease (CKD) on GPIHBP1 expression [26].

Also the present study agrees with previous studies by Aruga that indicated increased GPIHBP1 was significantly associated with decreased body fat [27]. Furthermore, [25] suggested that decreased GPIHBP1 availability in insulin resistant state may hamper peripheral lipolysis capacity.

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Several mechanisms have proposed to explain the effect of hypertriglyceridemia on DN. Firstly, triglyceride-rich lipoprotein could stimulate the activation of the transforming growth factor-beta (TGF-β) pathway. TGF-β subsequently promotes the production of ROS, leading to glomerular damage. Activation of TGF-β also increases matrix deposition in the tubulointerstitium and mesangium [28]. Secondly, triglyceride-rich lipoprotein can activate monocytes and disrupt cellular glycocalyx, causing increased permeability in the glomerulus [29]. Oxidized lipoprotein can inhibit nitric oxide-mediated vasodilation, modulate mesangial cell proliferation, and increase monocyte chemoattractant expression, which all contribute to glomerular injury [30].

Collectively, these data indicated the DN (whether normo- or microalbuminuria) is associated with elevated serum levels of TG and vLDL compared with healthy subjects. There is a remarkable reduction in SDH activity in patients with DN accompanied with increased serum level of sorbitol. Serum level of GPIHBP1 is not only decreased in patients with DN, but also inversely associated with the severity of the disease. Sorbitol dehydrogenase and fructose had a moderate-very good diagnostic values in the context of discrimination between DN (whether normo- or microalbuminuria) and healthy controls, while GPIHBP1 can also differentiate between normo- and microalbuminuria with a good sensitivity and specificity.

Thus, patients with T2DM should have a regular check-up for their lipid profile in order to decrease the chance of DN development. Serum SDH activity and fructose concentration could be used as additional diagnostic biomarkers beside ACR for early detection of DN. Serum level of GPIHPB1 could be used to differentiate microalbuminuria from normoalbuminuria in T2DM patients suspected to have DN, especially if there are logistic difficulties in performing ACR.

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