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Assessment of SerumYkl-40 and High Sensitivity C-Reactive Protein as Biomarkers of Renal Affection of Children with Type 1 Diabetes

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ABSTRACT

Background: Diabetes describes a group of metabolic disorders characterized and identified by the presence of hyperglycemia in the absence of treatment.

Objective: The aim of this study was early detection of renal affection in children with type 1 diabetes (T1DM) by using serumYkl-40 and high sensitivity C-reactive protein (Hs-CRP) as biomarker.

Patients and methods: This study was a case control study carried out at Pediatric Department, in pediatric endocrine inpatient and outpatient clinic, Zagazig University Hospitals from October 2019 to October 2020. It included 57 participants collected from Pediatric Department in Zagazig University Hospital who were divided into 3 groups; each group included (19) patients.1st group was diabetic group with normoalbuminuria (<30 mg/g creatinine), 2nd group was diabetic group with microalbuminuria (30-299 mg/g creatinine), and the 3rd group was healthy children.

Results : The serumYkl-40 and Hs-CRP were good predictor markers for prediction of renal affection among children with T1DM with (86.8% and 94.7%) ability truly diagnose renal affection, (72.0% and 84.2%) ability to exclude truly negative ones and total (80.7% and 91.2%) accuracy for serumYkl-40 and Hs-CRP respectively.

Conclusion: YKL-40 and Hs-CRP levels could be used as tools to assess the risk of diabetic microangiopathy in the very early stage in T1DM patients.

Keywords: Diabetes mellitus, Diabetic nephropathy (DN), High sensitivity C-reactive protein, SerumYkl-40.

INTRODUCTION

Diabetic nephropathy (DN) is one of the most important complications in patients with diabetes and most common cause of end stage renal disease (ESRD) that is associated with high rates morbidity and mortality. Although microalbuminuria is widely used as an early clinical marker for the detection of diabetic nephropathy, it's limited by the fact that structural damage might precede albumin excretion, this necessitates identifying better biomarkers that diagnose or predict diabetic nephropathy[(1,2)].

The chitinase-like protein family YKL-40, also called cartilage glycoprotein-39 (HC-gp39) and chitinase 3-like-(CHI3L1). It's an inflammatory glycoprotein, its abbreviation is derived from the one letter code for the first three N-terminal amino acids, tyrosine (Y), lysine (K), and leucine (L) and the apparent molecular weight of YKL-40 (40 kD) [(3)]. It is expressed in a variety of cells including macrophage, neutrophils and endothelial cells, and its expression is regulated by various cytokines and hormones[(4)].

YKL-40 has been implicated in diverse biological processes such as extracellular matrix remodeling, fibrosis, angiogenesis and inflammation**,** and elevated circulating or local tissue levels of YKL-40 have been observed in patients with cancers, cardiovascular diseases, infectious diseases, and some autoimmune diseases[(3)].

Several studies reported the associations of YKL-40 and renal diseases. Plasma YKL-40 levels were elevated in patients with adult type 1 or 2 diabetes compared with normal controls and there was a significant positive association between YKI-40 and urinary albumin excretion[(5,6)].

C-reactive protein (CRP) is acute phase protein, whose production in the liver is stimulated by IL-6. These molecules are easy to detect in serum and are secreted in large amounts during infections. In the behavioral literature, IL-6 and CRP are unanimously regarded as inflammatory biomarkers, and both are commonly used to assess the presence and severity of low-grade inflammation[(7)].

High sensitivity C-reactive protein (hs-CRP), which is more sensitive than CRP, gives the opportunity to detect levels of 3 mg/L and less. Several studies demonstrated that hs-CRP was a marker showing low grade chronical inflammation[(8)].

This study aimed to early detection of renal affection in children with type 1 diabetes through using serumYkl-40 and high sensitivity C-reactive protein (Hs-CRP) as biomarker.

PATIENTS AND METHODS

This case control study carried out from October 2019 to October 2020 in pediatric endocrine inpatient and outpatient clinic, at Zagazig University Hospital.

It included 57 children divided into 3 groups; each group included (19) patients; 1st group was diabetic group with normoalbuminuria (<30 mg/g creatinine) with their age ranged from (3-13), years, 2nd group was diabetic group with microalbuminuria (30-299 mg/g creatinine) with their age ranged from (3-14) years and the 3rd group was control group with their age ranged from (3.5-13) years.

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Ethical approval:

Written informed consent was obtained from all participants parents and the study was approved by the Research Ethical Committee of Faculty of Medicine, Zagazig University. The work was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion criteria: All patients were T1DM (under the age of 18 years, no history of medication other than insulin), diagnosed according to the criteria for diagnosis of diabetes [9]: HbA1c ≥ 6.5%, or FPG ≥ 126 mg/dl (7 mmol/l) or 2-h plasma glucose ≥ 200 mg/dl (11.1 mmol/l), in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dl (11.1 mmol/l).

Exclusion criteria: Neoplasm, liver dysfunction, autoimmune disease, acute inflammation and cardiovascular disease, other renal disease or urological complication and using other drugs.

All patients were subjected to full history taking, full clinical examination. Laboratory investigations (Fasting plasma glucose (FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h). HbA1c by using BioSystems S.A. Costa Brava 30. 08030 BARCELONA. SPAIN. Serum lipid profile VLDL, HDL, LDL, triglycerides and cholesterol.

LDL and VLDL were measured using the following formulas: LDL=cholesterol result– (HDL+VLDL) and VLDL= (TG result)/5.

Serum creatinine and BUN: was assayed using Roche/Hitachi cobas c systems.

Estimated glomerular filtration rate: by Schwartz Formula (0.413×height (in cm)/ serum creatinine (mg/dl)).

Measuring of serum YKL-40:

This human chitinase 3-like 1 ELISA Kit is based on standard sandwich enzyme-linked immunosorbent assay technology. Human chitinase 3-like 1 specific antibody was precoated onto 96-well plate. The test samples and the biotinylated human chitinase 3-like 1 specific detection antibody were added to the wells subsequently and then followed by washing the plate. Streptavidin HRP is added and unbound conjugates are washed away with wash buffer. Horseradish Peroxidase (HRP) substrate tetramethylbenzidine (TMB) is used to visualize HRP enzymatic reaction. TMB is catalyzed by HRP to produce a blue color product that changes into yellow after adding acidic stop solution. The density of yellow is proportional to the human chitinase 3-like 1 amount of sample captured in plate.

Hs-CRP (C - reactive protein):

This CRP test is based upon the reactions between C reactive protein (CRP) and latex covalently bound antibodies against human CRP. CRP values are determined turbid metrically.

Statistical Analysis

Collected data were recorded then presented and analyzed statistically by computer using SPSS version 22 (SPSS Inc. Chicago, IL, U.S.A). Data were summarized and presented in tables and graphs and summarized as mean ± standard deviation (SD), and range for quantitative variables and as number and percentage for qualitative variables. Data were handled using appropriate statistical tests such as: Shapiro-Wilk's test was applied for checking the normality assumption of continuous variables. Chi-square test and Fisher's exact test, wherever appropriate, were used for qualitative data analysis. Kruskal Wallis test was used for comparing the quantitative data. P value equal to or less than 0.05 was considered statistically significant

RESULTS

There was statistically significant difference between the studied groups regarding age. But regarding sex distribution, there was no statistically significant difference between the studied groups (Table 1).

Table (1): Comparing sociodemographic characteristics among the studied groups

Variables	T1DM with normoalbuminuria (NO.=19)	T1DM with microalbuminuria (NO.=19)	Control (NO.=19)	F test	p-value
Age (years) mean ± SD Range	9.2±3.1 (3-13)	10.1±3.1 (3-14)	8.1±2.2 (3.5-13)	5.8	**0.005***
Variable	**NO. (%)**	**NO. (%)**	**NO. (%)**	**χ^2**	**p-value**
Sex: Male (35) Female(22)	12 (63.2%) 7 (36.8%)	8 (42.1%) 11 (57.9%)	15 (78.9%) 4 (21.1%)	5.5	0.064

*Statistically significant difference (P ≤ 0.05), **F= ANOVA test,

There was significant difference in diastolic blood pressure between both T1DM groups and control group. There was significant difference in systolic blood pressure, between T1DM with normoalbuminuria and microalbuminuria and between T1DM with normoalbuminuria control, and a highly significant difference between T1DM with microalbuminuria and control (Table 2).

Table (2): Comparing blood pressure, both T1DM and control group

Variables	T1DM with normo-albuminuria (NO.=19)	T1DM with Microalbuminuria (NO.=19)	Control (NO.=19)	F test	p-value	LSD
Diastolic blood Pressure (mmhg) Mean ± SD Range	77.9±8.8 (63-95)	81.1±8.1 (65-90)	66.9±7.1 (63-80)	4.5 16.346	**<0.001****	0.4 (1) **0.005* (2)** **0.02*(3)**
Systolic blood pressure (mmhg) Mean ± SD Range	112.5±10.7 (90-125)	130±3.3 (100-135)	105.2±5.4 (100-115)	7.9 45.985	**<0.001****	**0.02* (1)** **0.01*(2)** **0.001**(3)**

1) T1DM with normoalbuminuria versus T1DM with microalbuminuria.
2) T1DM with normoalbuminuria versus control
3) T1DM with microalbuminuria versus control.

*Statistically significant difference (P ≤ 0.05), **Statistically highly significant difference (P ≤ 0.001), F= ANOVA test, LSD=least significant difference

There was significant difference in FBG between both T1DM groups, and a highly significant difference in FBG between both T1DM groups and control group. There was significant difference in HbA1c (Figure 1), HDL, LDL and total cholesterol between both T1DM groups and control group, with lower HDL in T1DM with microalbuminuria. But there was no significant difference in triglycerides levels between all groups.

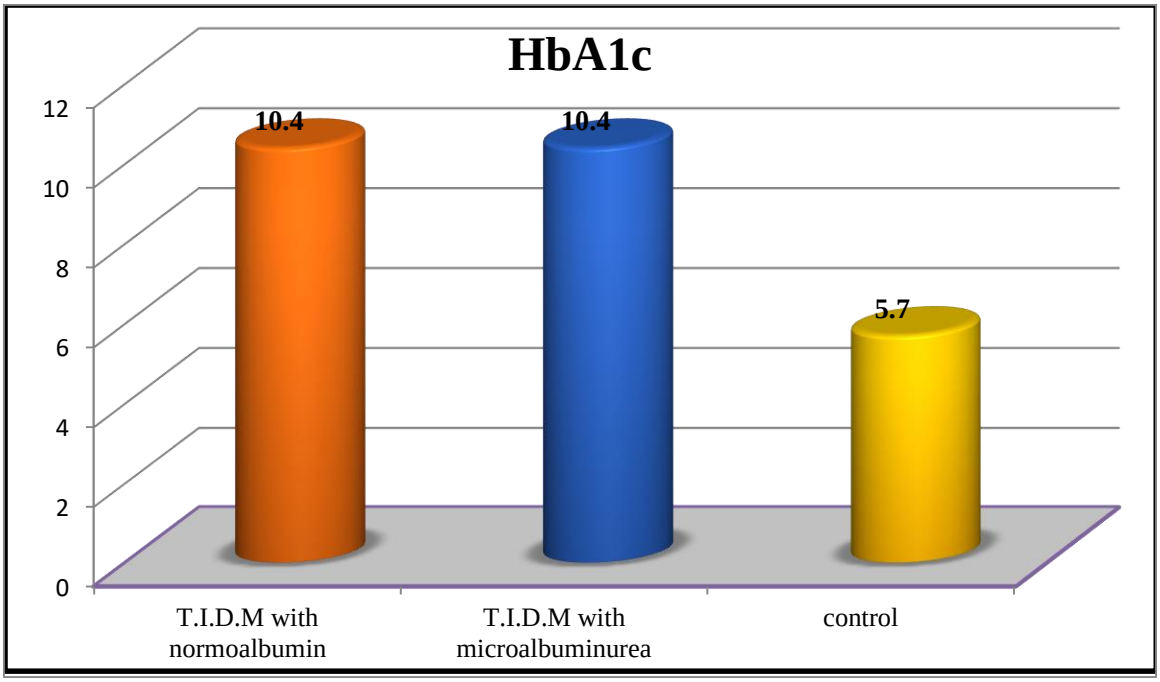

Fig (1): Bar chart for HbA1c among the studied groups

There was statistically significant difference in serum and urinary creatinine, urinary albumin/creatinine ratio, eGFR and urinary albumin between T1DM with microalbuminuria and T1DM with normoalbuminuria and between both T1DM groups and control group. There was statistically significant higher BUN, in both T1DM groups than control group. eGFR was statistically significantly higher among control than normoalbuminuria than microalbuminuria T1DM groups (Figure 2).

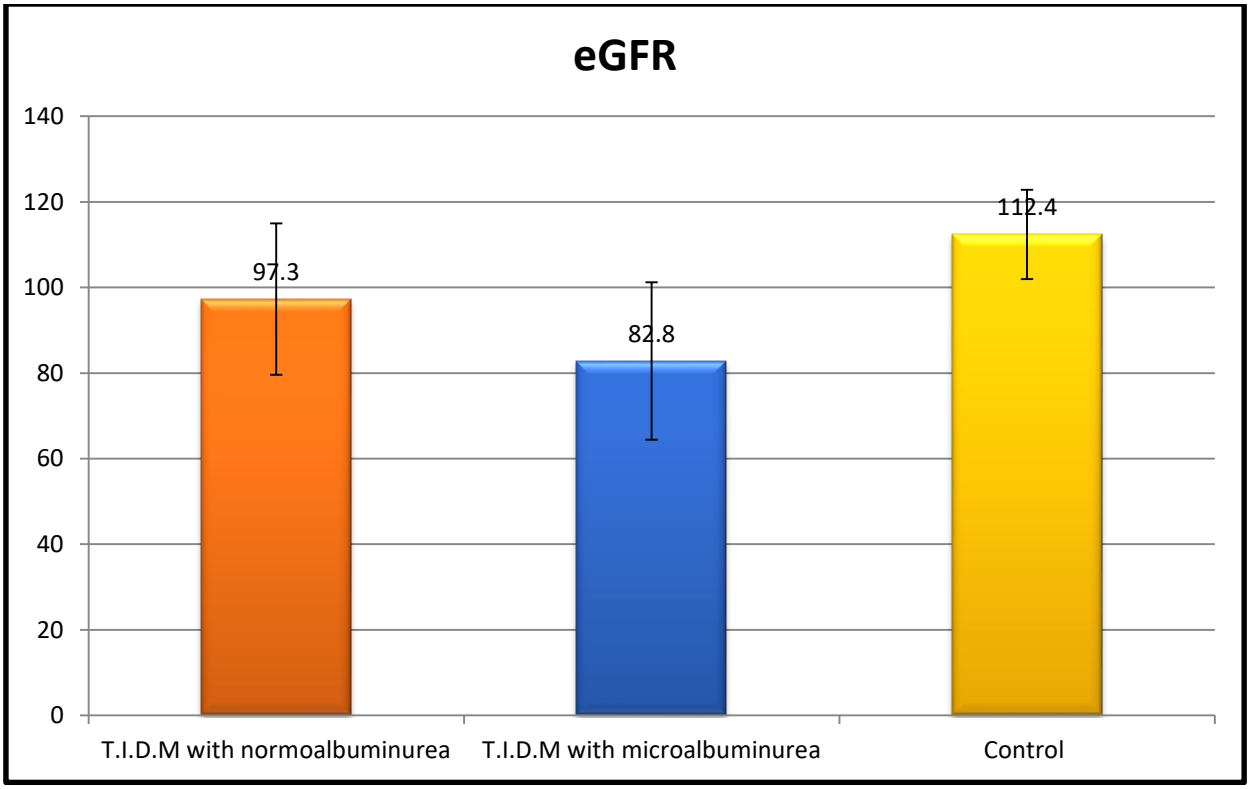

Fig (2): Bar chart for the eGFR among the studied groups

There was statistically significant higher Ykl-40 in T1DM with microalbuminuria than with normoalbuminuria and also in T1DM with normoalbuminuria than control group and there was a highly significant difference between T1DM with microalbuminuria and control (Table 3).

Table (3): Comparison between the studied groups regarding serumYkl-40

The studied groups	Number of patients (57)	SerumYkl-40 (ng/ml) mean ± SD Range	Kruskal Wallis Test	p-value	LSD
T1DM with normoalbuminuria	19	59.7±20.1 (32-100)	18.1	**0.001****	**0.002*(1) 0.01*(2) 0.001** (3)**
T1DM without microalbuminuria	19	82.1±26.8 (46.5-160)			
Control	19	41.9±12.6 (27-74)			

(1) T1DM with normoalbuminuria versus T1DM with microalbuminuria.
(2) T1DM with normoalbuminuria versus control.
(3) T1DM with microalbuminuria versus control.
*Statistically significant difference (P ≤ 0.05), **Statistically highly significant difference (P ≤ 0.001), LSD=least significant difference

There was statistically significant higher Hs-CRP in T1DM with microalbuminuria than with normoalbuminuria, and highly significant difference between both T1DM groups and control (Table 4).

Table (4): Comparison between the studied groups regarding Hs-CRP

The studied groups	Number of patients (57)	**Hs-CRP** (mg/l) mean ± SD Range	Kruskal Wallis Test	p-value	LSD
T1DM with normoalbuminuria	19	1.71±0.51 (1.23-2.92)	19.4	**0.001****	**0.04*(1) 0.001**(2) 0.001** (3)**
T1DM without microalbuminuria	19	2.1±0.63 (1.32-3.52)			
Control	19	0.93±0.62 (0.25-2.7)			

(1)T1DM with normoalbuminuria versus T1DM with microalbuminuria.
(2) T1DM with normoalbuminuria versus control.
(3) T1DM with microalbuminuria versus control.
*Statistically significant difference (P ≤ 0.05), **Statistically highly significant difference (P ≤ 0.001), LSD=least significant difference

Table (5), showed that serumYkl-40 and Hs-CRP are good predictor markers for prediction of renal affection among children with T1DM with (86.8% and 94.7%) ability truly diagnose renal affection, (72.0% and 84.2%) ability to exclude truly negative ones and total (80.7% and 91.2%) accuracy for serumYkl-40 and Hs-CRP respectively.

Table (5); Accuracy of serumYkl_40 and Hs-CRP in detection of renal affection in children with T1DM

Variable	Sensitivity	Specificity	PVP	PVN	Accuracy
SerumYkl-40	86.8%	72.0%	84.6%	72.2%	80.7%
Hs-CRP	94.7%	84.2%	92.3%	88.9%	91.2%
Variable	**Cut off**	**AUC**	**P**	**95% CI**	
SerumYkl-40	>45.7(ng/ml)	0.87	**<0.001****	0.78-0.97	
Hs-CRP	>1.23 (mg/l)	0.89	**<0.001****	0.79-1.00	

There was statistically highly significant difference between the studied groups regarding high serum Ykl-40 where most of the T1DM with microalbuminuria and with normoalbuminuria had high Ykl-40, while only (31.6%) of control group had high Ykl-40 (Table 6).

Table (6): Relation between renal affection and SerumYkl-40 according to the cut off value between diabetic patients and control group

Serum Ykl-40	T1DM with normoalbuminuria		T1DM with Microalbuminuria		Control		χ^2	p-value
	No (19)	%	No (19)	%	No (19)	%		
>45.7(ng/ml)	14	73.7%	19	100.0%	6	31.6%	**20.9**	**0.001****
<45.7(ng/ml)	5	26.3%	0.0	0.00%	13	68.4%		

** Statistically highly significant difference (P ≤ 0.001)

There was statistically highly significant difference between the studied groups regarding high Hs-CRP where (100.0% and 89.5%) of the T1DM with microalbuminuria and with normoalbuminuria had high Hs-CRP, while only (15.8%) of control group had high Hs-CRP (Table 7).

Table (7): Relation between renal affection and Hs-CRP according to the cut off value between diabetic patients and control group

Hs-CRP	T1DM with Normoalbuminuria		T1DM with Microalbuminuria		Control		χ^2	p-value
	No (19)	%	No (19)	%	No (19)	%		
>1.23 (mg/l)	17	89.5%	19	100.0%	3	15.8%	37.1	**0.001****
<1.23 (mg/l)	2	10.5%	0.0	0.00%	16	84.2%		

** Statistically highly significant difference (P ≤ 0.001)

DISCUSSION

The present study showed that there was statistically significant difference between the studied groups regarding age with older age among T1DM with microalbuminuria than with normoalbuminuria and in both than controls. But regarding sex distribution, there was no statistically significant difference between the studied groups. This demographic data was in consistence with **Suh *et al.*** [3], they found that subjects in the T1DM groups were statistically significant older than subjects in the control group (11.91±3.61 years for the control group vs. 16.52±4.11 years for the patient groups (16.35±3.51 for T1DM with normoalbuminuria versus with microalbuminuria 16.89±5.44, p=0.001**) with no significance difference regarding sex with male to female ratios were (3/6 versus 9/11 versus 13/19, p=0.8) and these demographic data was opposite to that of **MacKenzie *et al.*** [9]**.**

In this study we found that there was significant difference in diastolic blood pressure between both T1DM groups and control group. There was significant difference in systolic blood pressure, between T1DM with normoalbuminuria and microalbuminuria and between T1DM with normoalbuminuria and control, and a highly significant difference between T1DM with microalbuminuria and control.

There was non-significant difference in HbA1C, HDL, LDL, total cholesterol and BUN between T1DM with normoalbuminuria and T1DM with microalbuminuria, but they were significantly different between both diabetic groups and controls. There was a statically significant difference in FBG, serum and urine creatinine, urinary albumin/creatinine ratio, eGFR and urinary albumin between T1DM with normoalbuminuria and T1DM with microalbuminuria, and between both T1DM groups and controls. There was non-significant difference in triglycerides between the study groups. These results were the same finding of **Hussein *et al.*** [10] which showed a statistically significant increase in the mean of FPG, HbA1c, microalbumin in urine, ACR levels in diabetic group compared to control group. There was a statistically significant increase in the mean of LDL, triglycerides, serum creatinine and urinary creatinine levels in diabetic groups compared to control group. While the mean of HDL and eGFR levels showed a highly statistically significant decrease in diabetic groups compared to control group (P < 0.01). But no statistically significant difference was detected in the mean of total cholesterol levels in diabetic group compared to control group. The significant difference in FBG and HbA1C as we found, explain the progression of diabetic nephropathy by glucose induced tissue injury in diabetic patients.

In the current study, there was statistically significant higher serum Ykl-40 among T1DM with microalbuminuria than with normoalbuminuria and also between T1DM with normoalbuminuria and control group and highly significant difference between T1DM with microalbuminuria and control. Also (100.0%) of the T1DM with microalbuminuria and (73.7%) of the T1DM with normoalbuminuria had high Ykl-40, while only (31.6%) of control group had high Ykl-40**.** This was in agreement with **Sakamoto *et al.*** [11] who found significantly higher serum YKL-40 levels in T1DM patients than healthy controls (52.3 ranged from (21.4 to 274.1 ng/mL) versus 46.4 ranged from (20.3 to 136.7 ng/ml) respectively. Finally **Shiasi *et al.*** [12] was in agreement with our results and found that serum level of YKL-40 were significantly higher in T1DM patients compared to control subjects, 83.7% (n = 41). Serum YKL-40 levels were also significantly higher in diabetics according to sex and age compared to those in sex- and age-matched non-diabetics.

Regarding Hs-CRP, the present study found that there was statistically significant higher Hs-CRP in T1DM with microalbuminuria than with normoalbuminuria and highly significant difference between T1DM with normoalbuminuria and control group and also between T1DM with microalbuminuria and control, also (100.0% and 89.5%) of the T1DM with microalbuminuria and with normoalbuminuria had high Hs-CRP, while only (15.8%) of control group had high Hs-CRP. This was in agreement with **Sakamoto *et al.*** [11] who found that Hs-CRP levels in T1DM patients were significantly higher than control groups (171 ranged from (53 to 7380) versus 321 ranged from (51 to 13000) ng/mL respectively, and in contrary to this, **MacKenzie *et al.*** [9] found that Hs-CRP was not statistically significantly different between control and diabetic groups (0.52 ranged from (0.25 to1.3) versus 0.53 ranged from (0.25 to 0.98).

Atherosclerosis begins in childhood. Measures of endothelial and smooth muscle function as well Hs-CRP are used as subclinical markers of early atherosclerosis and chronic inflammation. Elevated Hs-

CRP is associated with impaired endothelial function in both healthy children and adults. In children and adults with T1DM, inflammatory markers including Hs-CRP are associated with serum markers of endothelial function. Endothelial dysfunction, a fundamental event in the development of atherosclerosis, occurs early in T1DM before clinically detectable atherosclerotic disease and is critical to the pathogenesis of both the microvascular and the macrovascular complications of diabetes[9].

Regarding the diagnostic ability of serum Ykl-40 and Hs-CRP in detection of renal affection in children with T1DM, the current study found that the serum Ykl-40 and Hs-CRP were good predictor markers for prediction of renal affection among children with T1DM with (86.8% and 94.7%) ability truly diagnose renal affection, (72.0% and 84.2%) ability to exclude truly negative ones and total (80.7% and 91.2%) accuracy for serumYkl-40 and Hs-CRP respectively. The cut-off value of urinary YKL-40 for defining renal injury has not been clearly established by other studies. Based on the results of **Suh *et al.*** [3] studies evaluating urinaryYKL-40 as a marker for tubular injury, the levels of urinary YKL-40/Cr in control subjects were very low and on the other hand, the levels in patients having renal injury were markedly elevated. However, to determine whether urinary YKL-40 is a reliable marker for renal injury, further studies are needed, especially in a population of children[3].

To examine a possible involvement of YKL-40 levels in the development of diabetic nephropathy, we evaluated the association between YKL-40 levels with albumin- to-creatinine ratio (UACR) and other renal and metabolic parameters and found that serum Ykl-40 was statistically highly significantly positively correlated with serum and urinary creatinine, urinary albumin and UACR. Also, YKL-40 was statistically significantly positively correlated with disease duration, children age and triglyceride and there was significant negative correlation with eGFR with no statistically significant correlation with other variables. This was in agreement with **Sakamoto *et al.*** [11] who found a significant positive association between YKL-40 levels and UACR, also YKL-40 levels showed significantly positive correlations with diabetes duration.

Rathcke *et al.* [6] did multiple regression analyses and showed correlation of YKL-40 with the urinary albumin- to-creatinine ratio (UACR) in the total group of participants (r= 0.50, P=0.001). No significant correlation was found between YKL-40 and systolic blood pressure, BMI, or total cholesterol, and YKL-40 levels were not predicted by GFR.

CONCLUSION

YKL-40 and Hs-CRP levels could be used as tools to assess the risk of diabetic microangiopathy in the very early stage in T1DM patients. Hs-CRP was the most accurate predictor marker followed by YKL-40 for diabetic nephropathy**.**

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