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ORIGINAL ARTICLE

Correlation between serum YKL-40 and carotid intima media thickness in type 1 diabetics

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Abstract It has been suggested that elevated serum level of YKL-40 could be a risk factor as well as early marker of both type 2 and type 1 diabetes mellitus (T1D) and their complications. We investigated the correlation between serum level of YKL-40 and carotid intima media thickness (cIMT) as well as urinary albumin/creatinine ratio (UACR) in type 1 diabetic patients. A total of 49 patients with T1D and 43 healthy controls underwent the assessment of serum level of YKL-40 (by

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ELISA) and cIMT measurement (by Doppler ultrasonography). Fasting blood and urine samples were also taken to measure the levels of hemoglobin A1C, lipid profile, CBC, serum and urine creatinine, and urine albumin. Serum levels of YKL-40, cIMT, and UACR were significantly higher in diabetic patients compared to those in healthy people ($P<0.001$). Serum levels of YKL-40 had a significant correlation with cIMT, and duration of diabetes. We report that YKL-40 may be a good prognostic as well as diagnostic marker of early macrovascular complications in T1D.

Keywords Type 1 diabetes mellitus · YKL-40 · Intima media thickness · Diabetic nephropathy

Introduction

Diabetes type 1 (T1D) is an important risk factor of cardiovascular diseases (CVD) and atherosclerosis [1]. It increases the risk of subsequent CVD [2] and stroke [3] 2- to 4- and about 1.8- to 6-folds, respectively. Considering the fact that atherosclerosis is a process beginning in childhood [4], T1D may be a special risk factor of early cardiovascular disease [1, 4].

Increased carotid intima media thickness (cIMT), measured by ultrasound, is an early and strong predictor of atherosclerotic changes leading to future vascular events [5]. Considering diabetes as the main risk factor of atherosclerosis [6], a few studies have indicated that children [7–10], adolescents, and adults [6, 11–16] with T1D have significantly higher cIMT than the healthy people whereas some other studies have not indicated such difference in adults, adolescents [17, 18], and children [19].

YKL-40, a 40-kDa heparin- and chitin-binding glycoprotein, also known as human cartilage glycoprotein 39 (HCgp39) [20], is a new inflammatory marker of acute and chronic inflammation as well as cancer [21]. It is secreted from a variety of human cells [21–23] such as vascular smooth muscle cells [21], macrophages during late stages of differentiation [21], and activated macrophages of atherosclerotic plaques [24]. Having a significant role in endothelial dysfunction and atherosclerosis [21], YKL-40 promotes migration of vascular endothelial and smooth muscle cells through the intima [25] and differentiation of monocytes to lipid-laden macrophages [26]. In this way, YKL-40 could be associated with coronary atherosclerosis [26] as well as stable [27] and progressive [28] CAD.

Albuminuria is a well-established independent predictor of diabetic nephropathy as well as cardiovascular morbidity and mortality in both type 1 and type 2 diabetic patients [29]. YKL-40 is excreted by the kidney, and thus, it also may be a predictive of impaired kidney function [29]. Actually in both type 1 and type 2 diabetic patients, increased levels of YKL-40, which is known to be a risk factor as well as an early marker of cardiovascular diseases [30–32] by itself, have been accompanied with increasing levels of albuminuria [29, 31], and in this way, YKL-40 and low-grade albuminuria have synergistically been predictors of CVD mortality [31].

In T1D patients, high serum levels of YKL-40 could be a risk factor of CVD [30–32]. Considering cIMT as a marker of diabetic atherosclerosis and vascular events [5] and UACR as an independent marker of diabetic nephropathy [29, 31], we aimed to evaluate the correlation between serum levels of YKL-40 and cIMT as well as UACR to introduce whether YKL-40 could be a diagnostic as well as prognostic marker of atherosclerosis and nephropathy in T1D patients. Just one recently published study has done such evaluation almost at the same time as us [33].

Materials and methods

Study population

A total of 49 people suffering from T1D at least 5 years with no yet-known diabetic complications from Kashan Diabetes Center in Iran and 43 sex- and age-matched healthy controls were enrolled. To define the required number of participants, a statistical power of 80 % and $\alpha=0.05$ was considered. Control subjects with no family history of diabetes were recruited from a local blood donation organization. The diagnosis of T1D was based on the American Diabetes Association's criteria. Exclusion criteria were liver, kidney, rheumatoid, endocrine, cardiovascular, and metabolic diseases; familial cardiovascular diseases; cancer; and a history of using antihypertensive or lipid-lowering medications as well as smoking.

The protocol was approved by the local Committee of Ethics and was in accordance with the Helsinki Declaration. Written informed consent was obtained from all participants older than 16 years and in the case of younger ones, from their parents/guardians.

Sampling protocol and measurements

Blood and urine samples were drawn at 8 a.m. to 10 in the morning after 12 h overnight fasting. CBC as well as serum levels of YKL-40, HbA1c, creatinine, lipids (total cholesterol, LDL cholesterol, HDL cholesterol, VLDL cholesterol, and triglycerides), and urinary concentration of albumin and creatinine were evaluated using standard laboratory methods. An automatic cell counter Sysmex K4500 (Japan) counted blood cells, and an immunoturbidometric method of Bayer Diagnostics Europe Ltd. (Ireland) protocol measured HbA1c levels. Lipid profile was assessed using end-point enzymatic methods through Beckman Instruments, Fullerton, CA's protocol. Urine albumin and urine/serum creatinine were measured by enzymatic immunoassay and Jaffe's methods, respectively. In order to define albuminuria through albumin/creatinine ratio measurement, three urine samples were obtained. Serum

YKL-40 was analyzed with a commercial, sandwich-type ELISA kit (Quidel, San Diego, CA, USA) according to its instructions. Arterial blood pressure was measured once using an appropriate-sized cuff after at least 10 min rest at 8–10 a.m. Height and weight were measured using a wall-mounted stadiometer to the nearest 0.1 cm and an electric digital scale to the nearest 0.1 kg, respectively.

Ultrasonography

Having left all participants in supine position for at least 10 min in a quiet room at 22 °C, An unaware reader of the subject's clinical details performed ultrasonography according to standardized scanning protocol for the right and left common carotid arteries using a Medison v20 equipped with a linear 11 MHz transducer (Medison/Samsung Medicine System GmbH, South Korea). On each common carotid artery, a 2-cm segment proximal to the bulb region on the far wall of the carotid was scanned by at least 100 points. All images were taken at end-diastole and then stored digitally for subsequent off-line analysis. Computer software analyzed the IMT distance automatically via arithmetically calculating a mean of the thickenings of the two abovementioned segments.

Table 1 Basic and clinical characteristics of the patients and control group

Variants			Healthy controls (n=43)	T1D (n=49)	P value
Age (years)			10.95±3.83	12.20±3.86	0.12
Gender (male/female)			21/22	22/27	0.7
Duration of diabetes (months)			–	73.22±5.9	–
BMI (kg/m^2)			21.02±4.25	21.23±4.6	0.826
Systolic BP (mmHg)			114.33±9.08	112.73±10.37	0.439
Diastolic BP (mmHg)			75.02±8.96	71.53±8.59	0.06
HbA1c (%)			4.73±0.73	7.34±1.24	<0.001
RBC (Mil/μl)			5±0.52	5.18±1.4	0.421
Hemoglobin (g/dl)			14.36±1.36	13.63±1.16	0.007
Hematocrit (%)			43.32±3.62	41.18±3.09	0.003
Total cholesterol (mg/dl)			159.6±25.2	169.3±23.1	0.059
Triglyceride (mg/dl)			75.91±27.76	77.73±28.4	0.758
HDL (mg/dl)			37.67±6.27	40.61±7.09	0.039
VLDL (mg/dl)			15.86±5.33	15.16±5.87	0.555
LDL (mg/dl)			106.26±19.6	113.24±17.43	0.074
Creatinine (mg/dl)			1.07±0.2	0.87±0.14	<0.001
YKL-40 (ng/ml)	Sex	Male	28.44±2.37	110.54±10.46	<0.001
		Female	28.34±1.92	107.53±10.11	<0.001
		P value	0.97	0.84	–
	Age	≤12 years (n)	27.03±2.6 (10)	113.34±9.20 (28)	<0.001
		>12 years (n)	28.86±1.82 (28)	102.94±11.67 (21)	<0.001
		P value	0.6	0.48	–
		Total	28.39±9.84	108.88±50.53	<0.001
eGFR (ml/min/1.73 m^2)			87.1±34.4	90.6±27.8	0.64
UACR (mg/g Cr)			3.95±0.43	12.16±1.53	<0.001
Urine protein (mg/dl)			2.01±2.17	1.69±1.52	0.538
Urine creatinine (mg/dl)			265.73±158.60	136.58±57.97	<0.001
Mean intima media thickness (mm)	Sex	Male	0.4±0.008	0.46±0.01	0.001
		Female	0.39±0.008	0.46±0.01	<0.001
		P value	0.43	0.97	–
	Age	≤12 years (n)	0.39±0.01	0.46±0.01	0.008
		>12 years (n)	0.38±0.006	0.45±0.01	0.001
		P value	0.48	0.53	–
		Total	0.392±0.006	0.457±0.009	<0.001

Statistics

The results were expressed as mean±SD. The groups were compared by independent *t* tests, and differences in proportions were tested using chi-square and Fisher's exact tests. Normality test was performed for the examined variables. The Pearson and Spearman rho coefficients were determined to correlate between the variables with normal and non-normal distribution, respectively. Multivariate linear regression analysis with forward method was used to adjust the effect of probable confounding variables on YKL-40. $P<0.05$ was considered statistically significant. All analyses were made by the SPSS package (version 16; Statistical Package for the Social Sciences, SPSS Inc., Chicago, IL, USA).

Results

Basic and clinical characteristics of the study groups are shown in Table 1. Serum YKL-40 levels were significantly higher in the diabetic group compared to those in the control group ($P<0.001$) (Fig. 1). Among T1D patients, 83.7 % ($n=41$) had a concentration of serum YKL-40 above the 90 % percentile of the healthy control subjects (42.68 μg/ml). Serum YKL-40 levels were also significantly higher in diabetic males and females compared to those in sex-matched nondiabetic ones ($P<0.001$). Moreover, we found elevated YKL-40 concentration in children (≤12 years, $n=28$) and older ones ($n=21$) with T1D compared to that in age-matched control subjects ($P<0.001$). We did not find any correlations between the serum levels of YKL-40 with different parameters of sex, age, BMI, Hb, Hct, HbA1c value, blood pressure, lipid profile, UACR, and serum as well as urine creatinine in the diabetic group (Table 2). Otherwise, it *did* show strong positive correlations only with cIMT ($P<0.001$) and duration of the disease ($P<0.001$) in diabetics (Table 2) (Fig. 2).

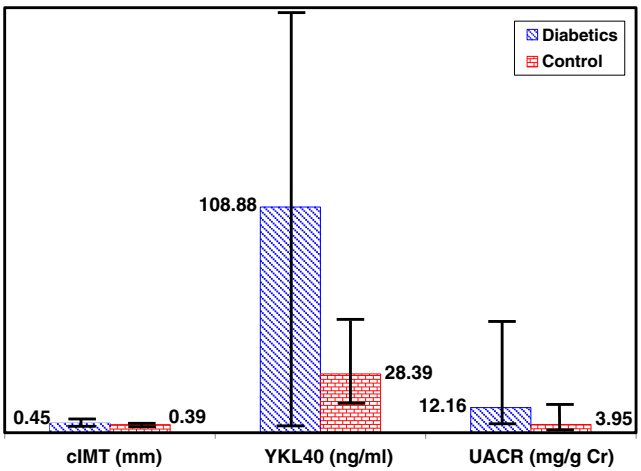

Fig. 1 Comparison of serum YKL-40 levels, cIMT, and UACR ratio between T1D patients and healthy controls ($P<0.001$ in three comparisons). Data are as median levels, 95 % CI

Table 2 Correlation of serum levels of YKL-40 and different parameters in two groups

Variable	Control group (*P* value)	Diabetic group (*P* value)
Age[a]	−0.05 (0.751)	0.046 (0.752)
Duration of diabetes[a]	–	0.789 (<0.001)
BMI (kg/m^2)[b]	−0.144 (0.359)	0.282 (0.05)
Systolic BP (mmHg)[a]	0.094 (0.548)	−0.279 (0.052)
Diastolic BP (mmHg)[a]	0.174 (0.265)	−0.04 (0.783)
Hemoglobin (g/dl)[b]	−0.076 (0.627)	−0.018 (0.902)
Hematocrit (%)[b]	−0.15 (0.336)	−0.032 (0.829)
HbA1c (%)[b]	0.148 (0.344)	0.00 (0.995)
Total cholesterol (mg/dl)[b]	−0.067 (0.668)	0.049 (0.738)
Triglyceride (mg/dl)[a]	−0.027 (0.866)	0.182 (0.211)
HDL (mg/dl)[b]	0.012 (0.94)	−0.12 (0.411)
VLDL (mg/dl)[b]	−0.1 (0.524)	0.19 (0.191)
LDL (mg/dl)[b]	0.11 (0.484)	0.029 (0.841)
Mean intima media thickness[b]	−0.179 (0.282)	0.925 (<0.001)
Creatinine (mg/dl)[b]	−0.366 (0.028)	0.04 (0.787)
Urine albumin (mg/dl)[a]	−0.029 (0.851)	−0.07 (0.628)
Urine creatinine (mg/dl)[b]	0.008 (0.959)	0.11 (0.45)
UACR[a]	−0.088 (0.575)	−0.131 (0.368)

[a] Nonparametric

[b] Parametric

T1D patients had a significantly greater mean cIMT as well as UACR than those in the control group ($P<0.001$) (Fig. 1). Both children (≤12 years) ($P=0.008$) and older ($P=0.001$) diabetics showed higher cIMT than the age-matched nondiabetics. There was also a significant difference in cIMT of diabetic males ($P=0.001$) and females ($P<0.001$) compared to that of sex-matched nondiabetic ones. In T1D group, mean cIMT showed a strong positive correlation to duration of

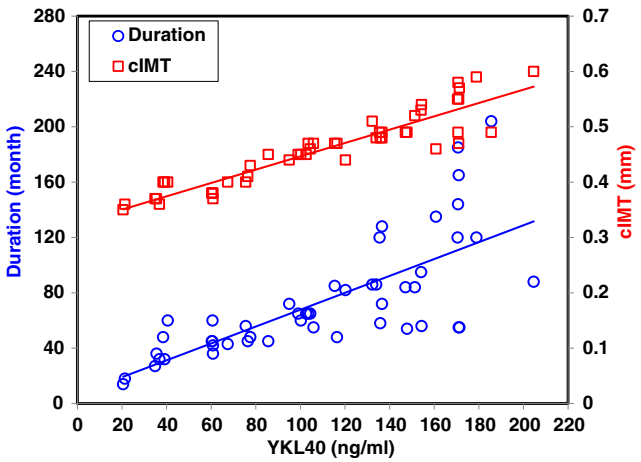

Fig. 2 Correlation of serum levels of YKL-40 with cIMT and duration of diabetes in T1D patients

diabetes (r=0.773, P<0.001), but it did not show any significant correlation with HbA1c, lipid profile, blood pressure, BMI, and UACR (data not shown).

Modeling the effect of variables of sex, age, BMI, duration of diabetes, Hb, Hct, HbA1c value, systolic as well as diastolic blood pressure, lipid profile, serum creatinine, and UACR on the prediction of cIMT values in diabetics through linear multiple regression analysis with forward method, we found the fittest model through Lr-test with variables of age (P value of Lr-test=0.095) and duration of diabetes in addition to YKL-40, in which it could explain cIMT values as 86 % (adjusted R^2=0.8617) (Table 3). The significant level was considered 0.1 in Lr-test.

Discussion

In line with some previous studies [31, 33], we found a higher serum level of YKL-40 in a group of T1D patients without known diabetic complications. Moreover, according to our knowledge, we report, for the first time, an elevated YKL-40 concentration in a homogenously young population of type 1 diabetics compared to that in matched control subjects. As a role player of endothelial dysfunction [21, 34, 35], it seems that YKL-40 is an important pathogenic factor of diabetic micro- and macroangiopathy complications [36], a concept that has had some reflection in cIMT of type 2 diabetic patients [37]. Several studies have revealed more cIMT in both types 1 [12, 16], like ours, and 2 [33, 38, 39] diabetics. Concerning the duration of diabetes with a small standard deviation (73.22± 5.9 months), the population of our study was very homogenous. Actually, as there is no difference between the cIMT of our diabetic children (≤12 years) and older ones (P= 0.53), it could be supposed that there has been enough time to see the effect of YKL-40 and diabetes on the development of atherosclerosis and increase of cIMT. According to our study and in spite of the recent report of Sakamoto et al. [33], there is a strong correlation between serum levels of YKL-40 and cIMT in type 1 diabetic patients (Fig. 2). Therefore, we *do* recommend serum YKL-40 as a proper diagnostic marker of early macrovascular complications in T1D patients. According to our regression model, in addition to serum levels of YKL-40, the effects of age as well as duration of diabetes were so strong in estimation of cIMT.

Table 3 Linear multiple regression analysis with forward method evaluating the effect of related different demographic and clinical parameters on the correlation of serum level of YKL-40 and cIMT in T1D patients

Variables	Unstandardized coefficients		t	Significance
	B	Standard error		
Gender	0.003	0.007	0.401	0.690
Age	0.001	0.001	0.244	0.808
BMI	−0.001	0.001	−1.294	0.202
Disease duration	0.001	0.001	−1.546	0.129
Systolic blood pressure	0.001	0.001	−0.509	0.614
Diastolic blood pressure	0.001	0.001	−0.5	0.619
LDL	0.001	0.001	0.766	0.447
VLDL	0.005	0.001	0.008	0.993
HDL	0.001	0.001	0.709	0.489
Serum creatinine	−0.019	0.026	−0.699	0.488
HbA1C	0.001	0.003	0.416	0.679
UACR	0.001	0.001	1.07	0.290

Interestingly, both our ±12 years of age diabetics had an increased cIMT compared to that in age-matched nondiabetics. Published data related to cIMT in children with T1D agree [1, 8, 9] and disagree [19, 40] with our study. These inconsistencies may partly be due to firstly, some dissimilarities in the methodology of cIMT measurement, i.e., manual [1] versus utilizing computed automatic analyzing softwares [7, 10, 40], using high [1, 7, 10, 40] versus medium [7] resolution ultrasound systems; secondly, lack of a documented well-standardized method for cIMT measurement [38]; and thirdly, probably different sizes as well as ethnicity of the study populations.

In disagreement with some other studies [31, 33], we found no significant correlation between YKL-40 and UACR in T1D patients. Such discrepancy may thus be plausible considering that our patients were young, and therefore, they had short diabetes duration (about 6 years) not enough for the development of nephropathic complications.

In line [7, 8, 33] and against [16] some other studies, we did not observe a significant correlation between HbA1c and cIMT in our patients. However, it should be considered that chronic hyperglycemia in childhood may also constitute as a separate risk factor of premature and accelerated macroangiopathy [39] and seems to influence atherosclerosis development in the long run [38]. cIMT progression is due to both diabetes per se and other risk factors that be accompanied by diabetes, in particular, systolic arterial hypertension, total cholesterol levels [7], smoking, and high BMI [16, 41]. None of our patients had such risk factors, and therefore, while mean cIMT had a strong positive correlation to duration of diabetes, it did not have any correlation to lipid profile, blood pressure, and BMI. It is likely that significant increase of the cIMT in our patients is a proof of subclinical atherosclerosis, and therefore, it may be reversible through intensive treatment [16].

Our study had some advantages. Firstly, relatively proper sample size and associated standard deviations that yield a proper power to detect differences in subgroup analyses. Secondly, there were no essential factors affecting the comparability of the groups including diabetic complications and large differences in age, duration of diabetes, and length of

treatment. Such uniformity of the patients is seen less in other studies.

The main limitation of our study is the lack of longitudinal data that could be taken through serial samples to monitor the changes of YKL-40 serum levels. This limitation allowed just a cross-sectional analysis of YKL-40 profile of only limited robustness.

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Conflict of interest The authors have no conflicts of interest to declare.

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