SMGroup

SM Journal of Nephrology and Kidney Diseases

Research Article

Serum Glycoprotein Chondrex (YKL-40) and High Sensitivity C- Reactive Protein (hscrp) in Type 2 Diabetic Patients in Relation to Cardiovascular Complications

El-Attar HA[1]*, El –Deeb MM[1] and El-Ghlied LA[2]

[1]*Chemical Pathology Department, University of Alexandria, Egypt*
[3]*Internal Medicine Department, University of Alexandria, Egypt*

Article Information

Received date: Jul 24, 2017
Accepted date: Aug 09, 2017
Published date: Aug 16, 2017

***Corresponding author**

EL-Attar HA, Department of Chemical Pathology, MRI Alexandria University, Egypt, Tel: 01020244286;
Email: hoda.ali55151@yahoo.com

Keywords CRP: C-reactive protein; YKL-40; Human cartilage glycoprotein-39; Breast regression protein- 39; 38-KDa heparin-binding glycoprotein; CHI3L1: Chitinase-3-like-1 protein; Chondrex and 40 KDa mammary gland protein (MGP-40); type 2 diabetes; Atherosclerosis; Cardiovascular complications

Article DOI 10.36876/smjnkd.1003

Abstract

In Type 2 diabetes, C-Reactive Protein (CRP) as an inflammatory marker may be elevated. The glycoprotein Chondrex or YKL-40 is over expressed in many inflammatory conditions. The aim is to study serum hsCRP and YKL-40 in Type 2 diabetic patients in relation to cardiovascular complications.

Methods: Eighty subjects were divided into 3 groups: GROUP 1:16 apparently healthy controls, GROUP 2:16 patients suffering from Type 2 DM without cardiovascular complications and GROUP 3: 48 patients suffering from Type 2 DM with cardiovascular complications. Subjects with acute or chronic inflammation, autoimmune disease or malignancy were excluded. Electrocardiography, Carotid Intima Thikness, Fundus Examination, laboratory investigations: (Complete urine analysis, urinary albumin, Creatinine and calculation of urinary albumin to creatinine ratio, fasting and postprandial glucose, glycated hemoglobin, Creatinine and uric acid, lipid profile, glomerular filtration rate, CRP and YKL-40) were done to all subjects.

Results: High sensitivity CRP levels were significantly elevated in the diabetic group with cardiovascular complications when compared to the diabetic group without cardiovascular complications (p=0.024). YKL-40 was significantly higher in patients with type 2 diabetes mellitus than controls (p=0.017) and cardiovascular complications (p<0.001) contributed to its greater elevation.YKL-40 was positively correlated with triglycerides, systolic and mean blood pressure in the group of diabetic patients without cardiovascular complications and with duration of diabetes and urinary albumin to creatinine ratio in the group with cardiovascular complications. By drawing receiver operating characteristic (ROC) curve between diabetic patients without and with cardiovascular complications the AUC for hsCRP was (0.676, p=0.036) and for YKL-40 was (0.743, p=0.004). By studying the diagnostic performance, YKL-40 had a better specificity and positive predictive value than hsCRP.

Conclusion: YKL-40 has a better specificity and positive predictive value than hsCRP in discriminating between diabetic patients with cardiovascular complications from those without cardiovascular complications.

Introduction

Chondrex or YKL-40 identified in 1989 [1] is related in amino acid sequence to the human glycoprotein chitinase protein family, but YKL-40 has no chitinase activity [2]. The abbreviation YKL-40 is based on 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 [3].

The proteinYKL-40 contains a single polypeptide chain of 383 amino and has several names: “Human cartilage glycoprotein-39 (HC gp39)”, [4] “Breast regressing protein 39 Kd (brp-39)”, [5] “38-KDa heparin-binding glycoprotein (Gp38k)”, [6] “Chitinase-3-like-1 protein (CHI3L1)”, [7] “Chondrex”, [8] and “40 KDa mammary gland protein (MGP-40)” [9].

The YKL-40 can play a role as sentinels that trigger responses to parasites, infections and / or antigen challenge. It attracts eosinophils and T cells to sites of parasitic infections, generates or modulates tissue inflammation and / or remodeling [10].

In normal bone marrow the myelometamyelocytes express YKL-40 protein, and it is stored in the specific granules of neutrophil granulocytes and released from fully activated cells [11].

Previous workers found that, the median serum YKL-40 in healthy subjects, was 43 µg/L (range, 20-184 µg/L; 5-95% interval, 20-124 µg/L), values of YKL-40 increases with age with no difference between men and women [12] and no circadian variability in its level [13].

It is suggested that any change in serum YKL-40 levels more than 20% should be considered to be indicative of significant change [12].

Low grade inflammation and activation of the innate immune system play a role in the common pathogenesis of both insulin resistance and endothelial dysfunction and subsequently

OPEN ACCESS
ISSN: 2576-5450

the development of type 2 diabetes and atherosclerosis. CRP still remains the most validated predictor of cardiovascular events is being supplemented by studies on emerging markers [14]. Dysfunction of the vascular endothelium is considered an important factor in the pathogenesis of diabetic micro- and macroangiopathy [15,16].

A previous study showed that YKL-40 plays a role in endothelial dysfunction in relation to cell migration, reorganization, and tissue remodeling during atherogenesis [16]. YKL-40 promotes chemotaxis, cell attachment, spreading, and migration of vascular endothelial cells, suggesting that YKL-40 promotes the process of atherosclerotic plaque formation, in which vascular smooth muscle cells (VSMCs) are induced to migrate through the intima in response to exogenous signals [3]. YKL-40 also modulates vascular endothelial cell morphology by promoting the formation of branching tubules, indicating a role of YKL-40 in angiogenesis by stimulating the migration and reorganization of VSMCs. Furthermore, YKL-40 is produced and secreted by monocytes during differentiation to macrophages and is also secreted by activated macrophages [17]. Substantial evidence indicates that YKL-40 participates in monocyte differentiation and macrophage activation as part of the endothelial dysfunction and the processes during early stages of atherosclerosis and seems to be of pathogenic importance in the low-grade inflammation that precedes the development of cardiovascular disease [13,17].

Interestingly, macrophages in atherosclerotic plaques express YKL-40 mRNA, particularly macrophages located deep in the lesion, and the highest YKL-40 expression is found in macrophages in the early lesion of atherosclerosis [18].

There is still limited knowledge about YKL-40 in diabetic patients.

Aim

The study of serum C-Reactive Protein (hsCRP) and Chondrex (YKL-40) in Type 2 diabetic patients in relation to cardiovascular complications.

Methods

This case-control study was done in accordance to ethical standards of Medical Research Institute based on Helsinki Declaration revised in 2000.Eighty subjects, recruited consecutively from February to July 2014, after taking their consents, from the diabetes clinic of MRI, were divided as: **Group 1:** 16 apparently healthy volunteers, **Group 2:** 16 patients suffering from type 2 DM without clinically evident cardiovascular complications and **Group 3:** 48 patients suffering from type 2 DM with cardiovascular complications. All subjects were of comparable age and sex. Subjects with acute or chronic inflammation, autoimmune disease or malignancy were excluded.

To all subjects the following was done: Complete physical Examination, B mode ultrasonography for CIMT and fundus examination. Complete urine analysis, urinary albumin, creatinine and calculation of urinary albumin to creatinine ratio. Fasting and postprandial glucose, glycated hemoglobin, creatinine and uric acid, Alanine Aminotransferase (ALT) activities, lipid profile, estimated glomerular filtration rate, also hCRP and YKL-40 [19]. Statistical analysis done using SPSS program version 20 (Statistical Package of social sciences, Chicago, USA) [20].

For quantitative variables

Klomogrov - Smirnov test for normality was used to test for the degree of deviation from normal distribution across all variables. The data of the variables were summarized in the form of: the mean as a measure of central tendency and the Standard Deviation (SD) as a measure of dispersion for normally distributed and as median and range for abnormally distributed. Pearson' and Spearman correlation coefficients were used to calculate correlation between variables. $P<0.05$ is considered significant. ROC curve was drawn by sensitivity on y-axis and 1-specificity on the x-axis. The highest Youden's index calculated gave the best cutoff. The greater the area under the curve was the best curve.

Results

Table 1 shows statistical significance of some clinical findings of the studied groups.

Table 2 shows statistical significance of levels of some studied parameters in the studied groups.

The median value of hsCRP was significantly higher in the group of diabetic patients without cardiovascular complications (group 2) when compared to the control group (group 1), and its median value was significantly increased in the group of diabetic patients with cardiovascular complications (group 3) when compared to both the control group (group 1) and the group of diabetic patients without cardiovascular complications (group 2) (Table 2).

Table 3: shows significant correlations of the studied groups.

Table 4: shows clinical (sensitivity, specificity, positive predictive value, negative predictive value and efficiency) for hsCRP and YKL-40 in the studied groups.

Table 5: shows clinical (sensitivity, specificity, positive predictive value, negative predictive value and efficiency) for hsCRP and YKL-40 in diabetic patients.

YKL-40 had a better sensitivity, negative predictive value and efficiency than hsCRP in discriminating between diabetic patients and controls. However, it had a better specificity and positive predictive value than hsCRP in discriminating between diabetic patients without cardiovascular complications from those with cardiovascular complications. (Table 4&5).

Figure 1: Bar chart showing YKL-40 levels in both diabetic groups in relation to the control group.

Figure1 revealed that level of serum YKL-40 in the group of diabetic patients without cardiovascular complications (group 2) was significantly increased when compared to the control group (group 1). Also the level of serum YKL-40 in the group of diabetic patients with cardiovascular complications (group 3) was significantly higher when compared to both the control group (group 1) and the group of diabetic patients without cardiovascular complications (group 2).

Figure 2 shows ROC curve for hsCRP and YKL-40 between controls and diabetics.

Figure 3 shows that YKL-40 had a bigger area under the Receiver Operating Characteristic (ROC) curve than hsCRP indicating that YKL-40 was better than hsCRP in discriminating between diabetic patients without and with cardiovascular complications.

Table 1: Statistical significance of some clinical findings of the studied groups.

Item		Group 1 (n=16)	Group 2 (n=16)	Group 3 (n=48)
Age (years)	Mean	44.06	48.38	54.96
	SD	±11.82	±8.11	±9.32
	P		NS	0.001*
	p1			NS
Sex	Males	2 (12.5%)	5 (31.3%)	11(22.9%)
	Females	14 (87.5%)	11 (68.8%)	37(77.1%)
	FE p		NS	NS
	FE p1			NS
Weight (kg)	Mean	69.94	88.56	98.04
	SD	±11.13	±14.00	±22.91
	P		0.026*	0.000**
	p1			NS
Systolic BP (mmHg)	Mean	118.75	125	135.21
	SD	±7.19	±11.55	±15.29
	P		NS	0.000**
	p1			0.035*
Diastolic BP (mmHg)	Mean	77.81	83.44	86.91
	SD	±5.15	±8.7	±12.49
	P		NS	0.008*
	p1			NS
Mean BP (mmHg)	Mean	91.44	97.28	102.98
	SD	±5.70	±9.38	±12.94
	P		NS	0.003*
	p1			NS
CIMT (mm)	Mean	0.55	0.67	0.99
	SD	±0.16	±0.13	±0.40
	P		NS	0.000**
	p1			0.003*
Duration of diabetes(years)	Median	-	1.0	12
	Min-max	-	0.10-17.0	4.0-40.0
	P			
	p1			0.000*

n: number of subjects.

p: statistical significance from control group.

p1: statistical significance from group of diabetic patients without cardiovascular complications.

*p-value < 0.05 was considered statistically significant.

**p-value < 0.001 was considered highly significant.

Group1: control group.

Group2: group of diabetic patients without cardiovascular complications.

Group3: group of diabetic patients with cardiovascular complications.

SD: standard deviation. **Min-Max:** minimum-maximum.

Table 2: Statistical significance of levels of some studied parameters in the studied groups.

Item		Group 1 (n=16)	Group 2 (n=16)	Group 3 (n=48)
FSG (mg/dl)	Mean	92	167.56	209.83
	SD	±9.18	±79.7	±88.35
	P		0.022*	0.000**
	p1			NS
PPG (mg/dl)	Mean	105.38	244.31	291.67
	SD	±11.63	±95.25	±109.95
	P		0.000**	0.000**
	p1			NS
HbA1C (%)	Mean	5.31	7.72	9.25
	SD	±0.37	±1.26	±2.09
	P		0.001*	0.000**
	p1			0.010*
Creatinine (mg/dl)	Median	0.9	1.0	1.15
	Min-Max	0.7-1.1	0.7-1.2	0.7-5.3
	P		NS	0.000**
	p1			0.014*
Uric acid (mg/dl)	Mean	3.89	4.81	6.21
	SD	±0.82	±1.12	±2.53
	P		NS	0.001*
	p1			NS
ALT (U/L)	Mean	13.5	20.56	20.08
	SD	±4.07	±8.47	±8.38
	P		0.035*	0.013*
	p1			NS
TC (mg/dl)	Mean	182.12	211.44	203.04
	SD	±19.6	±37.27	±64.8
	P		NS	NS
	p1			NS
HDL-C (mg/dl)	Mean	61.06	43.14	43.65
	SD	±12.33	±7.32	±11.56
	P		0.000**	0.000**
	p1			NS
LDL-C (mg/dl)	Mean	104.7	140.16	123.79
	SD	±19.27	±33.14	±55.99
	P		0.047*	NS
	p1			NS

Citation: El-Attar HA, El –Deeb MM and El-Ghlied LA. Serum Glycoprotein Chondrex (YKL-40) and High Sensitivity C- Reactive Protein (hscrp) in Type 2 Diabetic Patients in Relation to Cardiovascular Complications. J Nephrol Kidney Dis. 2017; 1(1): 1003.
https://dx.doi.org/10.36876/smjnkd.1003

TG (mg/dl)	Median	79	182	158.5
	Min-Max	38-143	71-332	46-1031
	P		0.000**	0.000**
	p1			NS
Urine albumin (mg/l)	Median	11.2	10.55	71.6
	Min-Max	1.4-28.2	3.3-32.4	2.8-3014.8
	P		NS	0.000**
	p1			0.001*
Urine creatinine (mg/dl)	Median	128	123.7	77.9
	Min-Max	40-212	40.5-315.5	17.8-201.5
	P		NS	0.003*
	p1			NS
Alb/cr ratio (mg/g)	Median	10.54	12.73	93.8
	Min-Max	1.6-28.5	2.28-29.6	3.3-8025.7
	P		NS	0.000**
	p1			0.000**
eGFR (ml/min/1.73m2)	Mean	91.13	108.26	84.61
	SD	±10.85	±32.60	±47.10
	P		NS	NS
	p1			NS
hsCRP (mg/L)	Median	0.875	3.58	9.79
	Min-Max	0.16-2.73	0.38-17.2	0.3-92.9
	p		0.000**	0.000**
	p1			0.024*
YKL-40 (ng/mL)	Mean	56.64	165.34	266.62
	SD	±48.21	±122.74	±116.62
	p		0.017*	0.000**
	p1			0.005*

n: number of subjects.

p: statistical significance from control group.

p1: statistical significance from group of diabetic patients without cardiovascular complications.

*p-value < 0.05 was considered statistically significant.

**p-value < 0.001 was considered highly significant.

Group1: control group.

Group2: group of diabetic patients without cardiovascular complications.

Group3: group of diabetic patients with cardiovascular complications.

SD: standard deviation. **Min-Max:** minimum-maximum.

FSG=fasting serum glucose, PPG=post prandial glucose, HbA1C=glycated hemoglobin A1C

ALT=alanine aminotransferase, TC=total cholesterol, HDL-C=high density lipoprotein cholesterol, LDL-C=low density lipoprotein cholesterol, TG=triglycerides, Alb/Cr=albumin /creatinine ratio, eGFR=estimated glomerular filtration rate, hsCRP=high sensitivity C-reactive protein, YKL-40=Chondrex.

Citation: El-Attar HA, El –Deeb MM and El-Ghlied LA. Serum Glycoprotein Chondrex (YKL-40) and High Sensitivity C- Reactive Protein (hscrp) in Type 2 Diabetic Patients in Relation to Cardiovascular Complications. J Nephrol Kidney Dis. 2017; 1(1): 1003.
https://dx.doi.org/10.36876/smjnkd.1003

Table 3: Significant correlations of the studied groups.

Item	Correlation coefficient (r)	Significance (p- value)
Significant correlations of the control group (Group 1):		
YKL-40 and age	0.526	0.037
YKL-40 and TG*	0.559	0.025
YKL-40 and micro-albumin*	-0.500	0.048
hsCRP and uric acid*	0.572	0.021
hsCRP and SBP*	0.504	0.047
hsCRP and MBP*	0.527	0.036
Significant correlations of the group of diabetic patients without cardiovascular complications (Group 2):		
CIMT and HbA1C	0.551	0.027
CIMT and DBP	0.573	0.020
CIMT and MBP	0.547	0.028
YKL-40 and TG*	0.603	0.013
YKL-40 and SBP	0.668	0.005
YKL-40 and MBP	0.521	0.038
hsCRP and age*	-0.555	0.026
hsCRP and FSG*	0.703	0.002
Significant correlations of the group of diabetic patients with cardiovascular complications (Group 3):		
CIMT and age	0.291	0.045
CIMT and weight	-0.286	0.049
CIMT and PPG	0.307	0.034
CIMT and uric acid	0.322	0.026
CIMT and eGFR	-0.325	0.024
CIMT and DBP	0.295	0.042
CIMT and MBP	0.286	0.049
YKL-40 and age	0.362	0.011
YKL-40 and creatinine*	0.395	0.005
YKL-40 and microalbumin*	0.302	0.037
YKL-40 and alb/ cr ratio*	0.386	0.007
YKL-40 and eGFR	-0.366	0.011
YKL-40 and duration of DM	0.371	0.009
hsCRP and LDL*	0.287	0.048

*Spearman correlation.

Table 4: Clinical (sensitivity, specificity, positive predictive value, negative predictive value and efficiency) for hsCRP and YKL-40 in the studied groups.

		Controls	Diabetics	Sensitivity %	Specificity %	PPV %	NPV %	Efficiency %
HsCRP	**≤2.73**	16	14	78.13	100.0	100.0	53.33	82.50
	>2.73	0	50					
YKL-40	**≤91.78**	14	11	82.81	87.50	96.36	56.0	83.75
	>91.78	2	53					

Citation: El-Attar HA, El –Deeb MM and El-Ghlied LA. Serum Glycoprotein Chondrex (YKL-40) and High Sensitivity C- Reactive Protein (hscrp) in Type 2 Diabetic Patients in Relation to Cardiovascular Complications. J Nephrol Kidney Dis. 2017; 1(1): 1003. https://dx.doi.org/10.36876/smjnkd.1003

Table 5: Clinical (sensitivity, specificity, positive predictive value, negative predictive value and efficiency) for hsCRP and YKL-40 in diabetic patients.

		Diabetic without cardio vascular complications	Diabetic with cardio vascular complications	Sensitivity %	Specificity %	PPV %	NPV %	Efficiency %
HsCRP	**≤3.93**	10	11	77.08	62.50	86.05	47.62	73.44
	>3.93	6	37					
YKL-40	**≤211.42**	12	15	68.75	75.0	89.19	44.44	70.31
	>211.42	4	33					

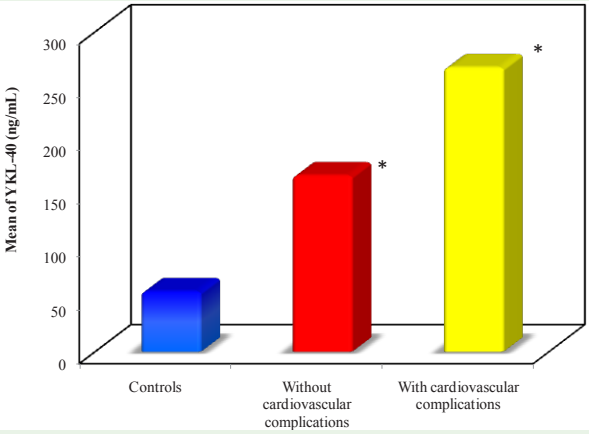
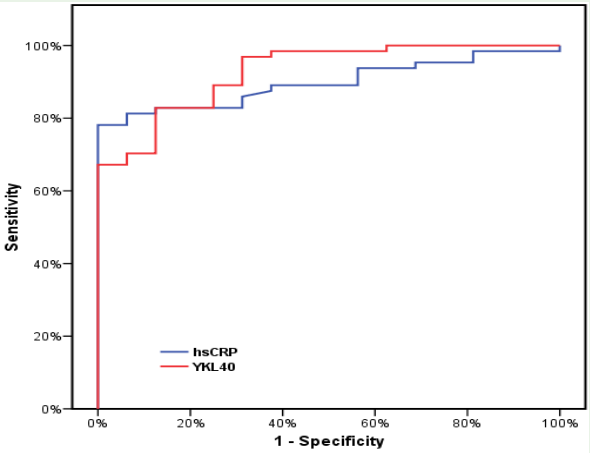


Figure 1: Bar chart showing YKL-40 levels in both diabetic groups in relation to the control group.

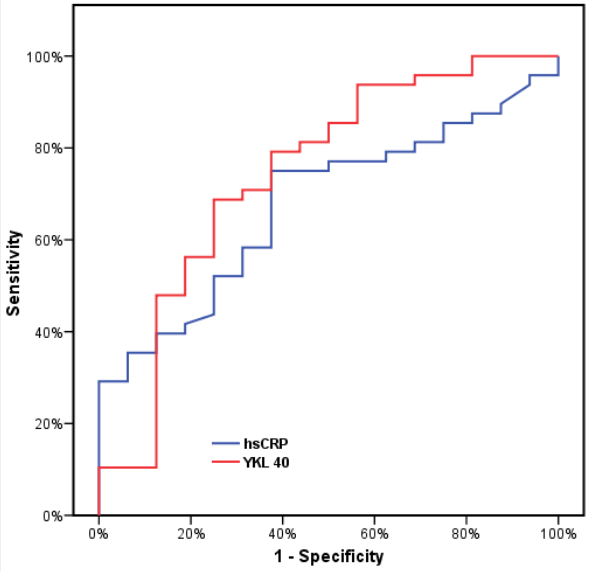
* Statistical significance from controls.

● Statistical significance from the group of diabetic patients without cardiovascular complication.



	AUC	p
hsCRP	0.897*	<0.001
YKL-40	0.927*	<0.001

Figure 2: ROC curve for hsCRP and YKL-40 between controls and diabetics



	AUC	p
hsCRP	0.676*	0.036
YKL-40	0.743*	0.004

Figure 3: ROC curve for hsCRP and YKL-40 between diabetic patients without and with cardiovascular complications.

Discussion

Worldwide, it is estimated that 366 million people have diabetes and half of them are not aware that they have the disease [21].

Subclinical systemic inflammation and abnormalities of a wide variety of systemic inflammatory markers, including CRP, have been reported in type 2 DM [22,23]. Furthermore it induces endothelial dysfunction which appears to be the earliest event in atherogenesis, and plays a pivotal role in all phases of atherosclerosis from the initiation of the fatty streak to plaque rupture with culmination in acute coronary syndrome [24].

Citation: El-Attar HA, El –Deeb MM and El-Ghlied LA. Serum Glycoprotein Chondrex (YKL-40) and High Sensitivity C- Reactive Protein (hscrp) in Type 2 Diabetic Patients in Relation to Cardiovascular Complications. J Nephrol Kidney Dis. 2017; 1(1): 1003.
https://dx.doi.org/10.36876/smjnkd.1003

YKL-40 is expressed and secreted by several cell types of the innate immune system and by differentiated vascular endothelial and smooth muscle cells. A substantial body of evidence indicates that YKL-40 acts not only as an inflammatory marker in relation to both acute and chronic inflammation but also as a growth factor with involvement in extracellular matrix remodeling and angiogenesis. In this regard, YKL-40 was found to be associated with various inflammatory conditions and in early stages of atherosclerosis [25].

Cardiovascular Diseases (CVD) are a major concern considering that the risk of cardiovascular death in patients with T2DM is double the risk of individuals without diabetes [26].

The aim of this work is to study serum human Chondrex (YKL-40) in type 2 diabetic patients in relation to cardiovascular complications.

The present study included eighty subjects divided into three groups. The control group (group 1) included sixteen apparently healthy volunteers (2 males and 14 females); their mean age was 44.06±11.82 years. The group of diabetic patients without cardiovascular complications (group 2) included sixteen patients suffering from type 2 diabetes mellitus without cardiovascular complications (5 males and 11 females); their mean age was 48.38±8.11 years. The group of diabetic patients with cardiovascular complications (group 3) included forty eight patients (11 males and 37 females); suffering from type 2 diabetes mellitus with cardiovascular complications in the form of coronary artery disease (100%), stroke (8.3%) and peripheral artery disease (4.16%) their mean age was 54.96±9.32 years. (Table 1).

Chondrex or YKL-40 is a glycoprotein involved in inflammation and endothelial dysfunction. It is a growth factor for various cell types and has an important role in extracellular matrix remodeling and angiogenesis [27].

In this study the mean of serum YKL-40 in the control group, the group of diabetic patients without cardiovascular complications and the group of diabetic patients with cardiovascular complications was 56.64±48.21, 165.34±122.74 and 266.62±116.62 ng/mL respectively. The YKL-40 level was significantly higher in both the diabetic groups without and with cardiovascular complications when compared to the control group (p=0.017, 0.000) respectively. Also the level of YKL-40 was significantly higher in the group of diabetic patients with cardiovascular complications when compared to the group of diabetic patients without cardiovascular complications (p=0.005). (Table 2)(Figure1).

These results were not in agreement with the work of Kido and colleagues in (2015) [28] but was in accordance with previous results [27,29-31] which stated that YKL-40 level was significantly higher in type 2 diabetes mellitus patients when compared to healthy controls. Also this was consistent with Kim et al, (2012) [31] who stated that the level of serum YKL-40 was markedly increased in type 2 diabetic patients with suspected CAD, compared to those with no evidence of CAD.

Also other studies have demonstrated that serum YKL-40 is increased in patients with acute Myocardial Infarction (MI), [32-34] and in patients with stable chronic CAD [33,35-37].

In the initiation and progression of atherosclerosis, activated macrophages take up lipids and then these lipid-rich macrophages secrete inflammatory mediators that stimulate VSMC migration and proliferation, resulting in atherosclerosis. It is known that YKL-40 is secreted by activated macrophages and neutrophils in different tissues with inflammation, and vascular smooth muscle cells (VSMC). In this regard, YKL-40 may be involved in the early stage of atherosclerosis and CAD [31].

When diabetes is accompanied by other major cardiovascular risk factors such as hypertension, dyslipidemia, and smoking the incidence of atherosclerosis is markedly increased. The atherosclerosis process in diabetes is indistinguishable from that of the non diabetic population, but it begins earlier and is often more extensive and more severe [38].

Dyslipidemia, an established risk factor for Cardiovascular Disease (CVD), is strikingly common in patients with type 2 diabetes, affecting almost 50% of this population [39].

In the current study, the mean HDL-Cholesterol level in both diabetic groups (group 2 and 3) was significantly lower than the control group (p=0.000 for both). Also the median of triglycerides level was significantly higher in both diabetic groups (group 2 and 3) when compared to the control group (p=0.000 for both). The mean LDL-Cholesterol level was significantly higher in the group of diabetic patients without cardiovascular complications (group2) when compared to the control group (group 1) (p=0.047) (Table 2).

YKL-40 was positively correlated with triglycerides in the group of diabetic patients without cardiovascular complications (r=0.603, p=0.013), (Table 3) similar to the findings of Røndbjerg et al, (2011) [27] Rathcke et al, (2012) [40] and Kim et al (2012) [31].

Carotid-wall intima–media thickness is a surrogate measure of atherosclerosis associated with cardiovascular risk factors and with cardiovascular outcomes [41].

In this study, the mean of the Carotid Intima Media Thickness (CIMT) in the control group, the group of diabetic patients without cardiovascular complications and the group of diabetic patients with cardiovascular complications was 0.55±0.16, 0.67±0.13 and 0.99±0.40 mm respectively. The CIMT was significantly higher in the group of diabetic patients with cardiovascular complications when compared to both the control group and the group of diabetic patients without cardiovascular complications (p=0.000, 0.003) respectively (Table 1).

In vitro studies showed that YKL-40 promotes chemotaxis, cell attachment, spreading and migration of vascular endothelial cells which suggest a role of YKL-40 in the atherosclerotic plaque formation. These in vitro studies are supported by immunohistochemical analysis which has shown in vivo protein expression of YKL-40 in human smooth muscle cells in atherosclerotic plaques [6].

In agreement with a previous study done by Ito et al, (2010) [42] who stated that eGFR is negatively associated with CIMT in type 2 diabetic patients we found that the CIMT was negatively correlated with eGFR in the group of diabetic patients with cardiovascular complications (group 3) (r=-0.325, *p*=0.024) (Table 3). Also this comes in agreement with another study done by Cho et al, (2011) [43] who stated that CIMT may be a predictor of diabetic nephropathy progression in patients with type 2 diabetes.

In the present study, a significant positive correlation was found between YKL-40 and systolic blood pressure in the group of diabetic

patients without cardiovascular complications (r=0.668, p=0.005). (Table 3), this came in agreement with previous studies [27,31]. In contrast Rathcke et al, (2009) [35] found a significant positive correlation between YKL-40 and diastolic blood pressure not the systolic.

Regarding the duration of diabetes, it was 0.1-17 years, median 1 year for group 2 patients and 4-40 years, median 12 years in group 3 patients. There was a significant increase in the duration of diabetes in the diabetic patients with cardiovascular complications when compared to those without (p=0.000) (Table 1). This goes with the longer duration of diabetes, the more the predisposition to cardiovascular complications being exposed to more risk factors and the pathology of diabetes on the blood vessels.

In the current study, there was a significant positive correlation between YKL-40 and duration of DM in the group of diabetic patients with cardiovascular complications. (r=0.371, p=0.009) (Table 3). This was in agreement with Røndbjerg et al, (2011) [27].

Glycemic control reduces the incidence of cardiovascular events in T2DM [44].

A prospective epidemiological analysis based on the Heart Outcome Prevention Evaluation (HOPE) study also identified a significant relationship between glycemic level and incident cardiovascular events [45]. HbA1c is also the accepted measure of long-term glycemia in the long-term follow-up study to the Diabetes Control and Complications Trial (DCCT), [46] which have found a lower risk for macrovascular complications with improved glycemia [47]. It was suggested that poor glycemic control is associated with structural changes in the carotid artery that are consistent with early atherosclerosis [48].

In the present work, there was a significant positive correlation between HbA1c and CIMT (r = 0.551, p = 0.027) in the group of diabetic patients without cardiovascular complications (Table 3).

Uric acid, the final oxidation product of purine catabolism, can act as a prooxidant, [49,50] but it may also have a therapeutic role as an antioxidant [51]. Hyperuricemia has been found to be associated with obesity and insulin resistance, and consequently with type 2 diabetes [52,53]. It relates to endothelial dysfunction by inducing antiproliferative effects on endothelium and impairing nitric oxide production and inflammation, e.g., through increased C-reactive protein expression [53,54]. Finally, uric acid may play a role in immune activation with subsequent increased chemokine and cytokine expression [55,56].

In the present study, uric acid level was significantly higher in the group of diabetic patients with cardiovascular complications when compared to the control group (p=0.001) (Table2), which was the case with Ito et al (2011) [57] who stated that hyperuricemia was associated with diabetic micro- and macroangiopathies. Furthermore, the incidence of coronary heart disease was significantly higher in the patients with hyperuricemia than in those without. Also Rathmann *et al (1993) [58]* reported that hyperuricemia was associated with coronary heart disease in 4,047 patients with type 2 diabetes mellitus according to a cross-sectional study.

In the present work, serum uric acid level was positively correlated with CIMT in the group of diabetic patients with cardiovascular complications (group 3) (r=0.322, p=0.026) (Table 3). Which was in agreement with a previous study [58].

Increased serum level of uric acid is an independent risk factor for cardiovascular disease. Accumulation of free radicals in the presence of hyperuricemia stimulates lipid peroxidation, which may be responsible for increased CIMT. Moreover it increases platelet adhesiveness and vascular smooth muscle proliferation [59].

Clinical hallmarks of diabetic nephropathy include a progressive increase in urinary albumin excretion and late decline of glomerular filtration rate, which occurs in association with an increase in blood pressure, ultimately leading to end stage renal failure [60]

In the present study, Alb/cr ratio was significantly higher in the group of diabetic patients with cardiovascular complications (group 3) when compared to both the control group (group 1) and the group of diabetic patients without cardiovascular complications (group 2), (P=0.000 for both) (Table 2).

There was a significant positive correlation between YKL-40 and albumin to creatinine ratio in the group of diabetic patients with cardiovascular complications (r=0.386, p=0.007) (Table 3). These results support the assumption proposed by Røndbjerg et al, (2011) who stated that the association found between YKL-40 and albuminuria in both T1D and T2D could reflect common determinants, such as inflammation, or a causal link where inflammation leads to increase in YKL-40, and subsequent generalized vascular damage reflected by albuminuria [27].

A significant negative correlation was found between YKL-40 and eGFR in the group of diabetic patients with cardiovascular complications (r=-0.366, p=0.011) (Table 3). This was similar to Catalan et al, (2011) [59] In contrast, other results [27,35] stated that increasing YKL-40 levels were not predicted by a decline in eGFR. Also there was a significant positive correlation between YKL-40 and serum creatinine in the group of diabetic patients with cardiovascular complications (r=0.395, p=0.005) (Table 3). This result was in accordance with Rathcke et al, (2009) [35], Catalan et al, (2011) [25].

In the present study the median level of YKL-40 in diabetic patients without retinopathy (n=15) was 237.1 (85.15-340.85 ng/ml) and in complicated diabetic patients with retinopathy (n=33) was 287.49 (60.12-511.54 ng/ml) showing a significantly higher levels than in uncomplicated diabetic patients (p=0.048, 0.003) respectively (Table not shown).

The median level of YKL-40 in complicated diabetic patients without nephropathy (n=16) was 234.76 (60.12-479.33 ng/ml). In complicated diabetic patients with nephropathy (n=32) it was 287.16 (60.79-511.54 ng/ml) showing a significantly higher levels than in uncomplicated diabetic patients (p= 0.003) (Table not shown).

The inflammatory processes play a pivotal role in all stages of the development of both acute and chronic atherosclerosis [61].

C-reactive protein, an acute phase reactant synthesized in the liver in response to the cytokine interleukin-6, is a factor in the development of atherosclerotic plaque. Although CRP was initially believed to be only a marker of vascular inflammation, further researches indicates that it also plays an active role in atherogenesis [62].

In addition to YKL-40 the underlying inflammatory process was also demonstrated by the significantly higher hsCRP values in all patient groups compared to the control group (p=0.000). In the present study hsCRP values ranged from 0.16 to 2.73 mg/L with a median of 0.875 mg/L in the control group, from 0.38 to 17.2 mg/L with a median of 3.58 mg/L in the group of diabetic patients without cardiovascular complications, while in the group of diabetic patients with cardiovascular complications it ranged from 0.3 to 92.9 mg/L with a median of 9.79 mg/L (Table 2). Also hsCRP was significantly higher in the group of diabetic patients with cardiovascular complications when compared to the group of diabetic patients without cardiovascular complications (p=0.024), (Table 2).

In the present study there was no correlation between hsCRP and YKL-40 which came in agreement with Thomsen et al, (2010) [30] Catalan et al, (2011) [25] Kim et al, (2012) [31] implying that YKL-40 and hsCRP are produced and secreted independently of each other.

Although hsCRP was used as a predictor of cardiovascular risk [62]. Recently it has been evaluated as a prognostic biomarker in patients with IHD. As hsCRP is mainly produced in the liver, it is likely that biomarkers as YKL-40 secreted from inflammatory cells within the atherosclerotic plaque could be superior prognostic biomarker [61].

Using the upper limit of control hsCRP value as a cutoff 2.73 mg/L, the sensitivity, specificity, positive predictive value, negative predictive value and efficiency of hsCRP were 78.3%, 100%, 100%, 53.33% and 82.50% in diabetic patients while using the best cutoff of 91.78 ng/ml YKL-40 sensitivity, specificity, positive predictive value, negative predictive value and efficiency were 82.81%, 87.50%, 96.36%, 56.0% and 83.75%. YKL-40 had a better sensitivity, negative predictive value and efficiency than hsCRP in discriminating between controls and diabetics (Table 4).

Using the best cutoff of 3.93 mg/L the sensitivity, specificity, positive predictive value, negative predictive value and efficiency of hsCRP were 77.08%, 62.50%, 86.05%, 47.62% and 73.44% while using the best cutoff of 211.42 ng/ml, YKL-40 sensitivity, specificity, positive predictive value, negative predictive value and efficiency were 68.75%, 75.0%, 89.19%, 44.44% and 70.31%. From the previous results it can be noticed that YKL-40 had a better specificity and positive predictive value than hsCRP in discriminating between diabetic patients without and with cardiovascular complications (Table 5).

In the present work, by drawing receiver operating characteristic (ROC) curve between controls and diabetic, the Area Under the Curve (AUC) for hsCRP was 0.897, p<0.001 and for YKL-40 was 0.927, p<0.001 (Figure 2). Whereas in the curve between diabetic patients without and with cardiovascular complications the AUC for hsCRP was 0.676, p=0.036 and for YKL-40 was 0.743, p=0.004. (Figure 3) This indicates that YKL-40 was better than hsCRP in discriminating total diabetic patients from controls and diabetic patients with cardiovascular complications from those without.

Conclusion

The inflammatory YKL-40 was significantly higher in patients with type 2 diabetes mellitus than controls and cardiovascular complications contributed to its greater elevation. YKL-40 was positively correlated with several cardiovascular risk factors such as triglycerides, systolic blood pressure and mean blood pressure in the group of diabetic patients without cardiovascular complications and in the group of diabetic patients with cardiovascular complications, with duration of diabetes mellitus and urinary albumin to creatinine ratio denoting that longer duration of inflammation leads to increased YKL-40 levels with subsequent generalized vascular damage reflected by albuminuria.

There was no correlation between both inflammatory markers YKL-40 and hsCRP implying that they are produced and secreted independently of each other. YKL-40 had a better specificity and positive predictive value than hsCRP in discriminating between diabetic patients without cardiovascular complications from those with cardiovascular complications.

References

1. Zhang W, Murao K, Zhang X, Matsumoto K, Diah S, Okada M, et al. Resveratrol represses YKL-40 expression in human glioma U87 cells. BMC Cancer 2010; 10: 593.
2. Scully S, Yan W, Bentley B, Cao QJ, Shao R. Inhibitory activity of YKL-40 in mammary epithelial cell differentiation and polarization induced by lactogenic hormones: a role in mammary tissue involution. Plos One. 2011; 6: 25819.
3. Kazakova MH, Sarafian VS. YKL-40 a novel biomarker in clinical practice? Folia Med 2009; 51: 5-14.
4. Hakala BE, White C, Recklies AD. Human cartilage gp-39, a major secretory product of articular chondrocytes and synovial cells, is a mammalian member of a chitinase protein family. J Biol Chem. 1993; 268: 25803-10.
5. Johansen JS, Jensen BV, Roslind A, Nielsen D, Price PA. Serum YKL-40, a new prognostic biomarker in cancer patients? Cancer Epidemiol Biomarkers Prev. 2006; 15: 194-202.
6. Rathcke CN, Vestergaard H. YKL-40 an emerging biomarker in cardiovascular diseases and diabetes. Cardiovasc Diabetol. 2009; 8: 61.
7. Johansen JS, Williamson MK, Rice JS, Price PA. Identification of proteins secreted by human osteoblastic cells in culture. J Bone Miner Res. 1992; 7: 501-512.
8. Lee CG, Elias JA. Role of breast regression protein-39/YKL-40 in asthma and allergic responses. Allergy Asthma Immunol Res. 2010; 2: 20-27.
9. Shackelton LM, Mann DM, Millis AJT. Identification of a 38-kDa heparin-binding glycoprotein (gp38k) in differentiating vascular smooth muscle cells as a member of a group of proteins associated with tissue remodeling. J Biol Chem. 1995; 270: 13076-13083.
10. Rehli M, Krause SW, Andreesen R. Molecular characterization of the gene for human cartilage gp-39 (CHI3L1), a member of the chitinase protein family and marker for late stages of macrophage differentiation. Genomics. 1997; 43: 221-225.
11. Harvey S, Weisman M, O'Dell J, Scott T, Krusemeier M, Visor J, et al. Chondrex: new marker of joint disease. Clin Chem. 1998; 44: 509-16.
12. Mohanty AK, Singh G, Paramasivam M, Saravanan K, Jabeen T, Sharma S, et al. Crystal structure of a novel regulatory 40-kDa mammary gland protein (MGP-40) secreted during involution. J Biol Chem. 2003; 278: 14451-14460.
13. Johansen JS. Studies on serum YKL-40 as a biomarker in diseases with inflammation, tissue remodeling, fibroses and cancer. Dan Med Bull. 2006; 53: 172-209.
14. Chupp GL, Lee CG, Jarjour N, Shim YM, Holm CT, He S, et al. A chitinase-like protein in the lung and circulation of patients with severe asthma. N Engl J Med. 2007; 357: 2016-27.
15. Koller B, Muller-Weifel A, Rupec R, Korting HC, Ruzicka T. Chitin modulates innate immune responses to keratinocytes. Plos One. 2011; 6: 16594.

Citation: El-Attar HA, El –Deeb MM and El-Ghlied LA. Serum Glycoprotein Chondrex (YKL-40) and High Sensitivity C- Reactive Protein (hscrp) in Type 2 Diabetic Patients in Relation to Cardiovascular Complications. J Nephrol Kidney Dis. 2017; 1(1): 1003.
https://dx.doi.org/10.36876/smjnkd.1003

16. Shibata Y, Fosrer LA, Bradfield JF, Myrvik QN. Oral administration of chitin down regulates serum IgE levels and lung eosinophilia in the allergic mouse. J Immunol. 2000; 164: 1314-21.

17. Da Silva CA, Chalouni C, Williams A, Hartl D, Lee CG, Elias JA. Chitin is a size-dependent regulator of macrophage TNF and IL-10 production. J Immunol. 2009; 182: 3573-3582.

18. Lee CG, Da Silva CA, Lee J-Y, Hartl D, Elias JA. Chitin regulation of immune responses: An old molecule with new roles. Curr Opin Immunol 2008; 20: 684-649.

19. Burtis CA, Ashwood ER, Bruns DE. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 4th Ed. Elsevier Saunders Company, St Louis 2006, pp. 808-12 (Urine analysis), 887-8(Urinary albumin), 887(albumin creatinine ratio), 881-4(HbA1C), 822-3(eGFR).

20. Puri BK. SPSS in practice: an illustrated guide. 2nd Ed. London; New York: Arnold; 2002.

21. Boutayeb A, Lamlili MEN, Boutayeb W, Maamri A, Ziyyat A, Ramdani N. The rise of diabetes prevalence in the Arab region. Open Journal of Epidemiology. 2012; 2: 55-60.

22. Deshpande AD, Hayes MH, Schootman M. Epidemiology of diabetes and diabetes related complications. Phys Ther. 2008; 88: 1254-1264.

23. Rathcke CN, Johansen JS, Vestergaard H. YKL-40, a biomarker of inflammation, is elevated in patients with type 2 diabetes and is related to insulin resistance. Inflamm Res. 2006; 55: 53-9.

24. Rathcke CN, Vestergaard H. YKL-40, a new inflammatory marker with relation to insulin resistance and with a role in endothelial dysfunction and atherosclerosis. Inflamm Res. 2006; 55: 221-227.

25. Catalán V, Gómez-Ambrosi J, Rodríguez A, Ramírez B, Rotellar F, Valentí V, et al. Increased circulating and visceral adipose tissue expression levels of YKL-40 in obesity-associated Type 2 diabetes are related to inflammation: impact of conventional weight loss and gastric bypass. The Journal of Clinical Endocrinology & Metabolism. 2011; 96: 200-9.

26. Fu AZ, Qiu Y, Radican L, Yin DD, Mavros P. Pre-existing cardiovascular diseases and glycemic control in patients with type 2 diabetes mellitus in Europe: a matched cohort study. Cardiovascular Diabetology. 2010; 9:15.

27. Røndbjerg AK, Omerovic E, Vestergaard H. YKL-40 levels are independently associated with albuminuria in type 2 diabetes. Cardiovascular Diabetology. 2011; 10: 54.

28. Kido J, Bando Y, Bando M, Kajiura Y, Hiroshima Y, Ingaki Y, et al.YKL-40 level in gingival crevicular fluid from patients with periodontitis and type 2 diabetes. Oral Dis. 2015; 21: 667-673.

29. Nielsen AR, Erikstrup C, Johansen JS, Fischer CP, Plomgaard P, Krogh-Madsen R, et al. Plasma YKL-40 A BMI-independent marker of type 2 diabetes. Diabetes 2008; 57: 3078–82.

30. Thomsen SB, Rathcke CN, Zerahn B, Vestergaard H. Increased levels of the calcification marker Matrix Gla Protein and the inflammatory markers YKL-40 and CRP in patients with type 2 diabetes and ischemic heart disease. Cardiovascular Diabetology. 2010; 9: 86.

31. Kim HM, Lee BW, Song YM, Kim WJ, Chang HJ, Choi DH, et al. Potential association between coronary artery disease and the inflammatory biomarker YKL-40 in asymptomatic patients with type 2 diabetes mellitus. Cardiovascular Diabetology. 2012; 11: 84.

32. Nojgaard C, Host NB, Christensen IJ, Poulsen SH, Egstrup K, Price PA, et al. Serum levels of YKL-40 increases in patients with acute myocardial infarction. Coron Artery Dis. 2008; 19: 257- 263.

33. Wang Y, Ripa RS, Johansen JS, Gabrielsen A, Steinbruchel DA, Friis T, et al. YKL-40 a new biomarker in patients with acute coronary syndrome or stable coronary artery disease. Scand Cardiovasc J. 2008; 42: 295-302.

34. Hedegaard A, Ripa RS , Johansen JS, Jorgensen E, Kastrup J. Plasma YKL-40 and recovery of left ventricular function after acute myocardial infarction. Scand J Clin Lab Invest. 2010; 70: 80-86.

35. Rathcke CN, Persson F, Tarnow L, Rossing P, Vestergaard H. YKL-40, a marker of inflammation and endothelial dysfunction, is elevated in patients with type 1 diabetes and increases with levels of albuminuria. Diabetes care. 2009; 32: 323-8.

36. Kastrup J, Johansen JS, Winkel P, Hansen JF, Hildebrandt P, Jensen GB, et al. High serum YKL-40 concentration is associated with cardiovascular and all-cause mortality in patients with stable coronary artery disease. Eur Heart J. 2009; 30: 1066-1072.

37. Kucur M, Isman FK, Karadag B, Vural VA, Tavsanoglu S. Serum YKL-40 levels in patients with coronary artery disease. Coron Artery Dis. 2007; 18: 391-396.

38. Goldman L, Ausiello D .Cecil Medicine . 23rd Ed. Elsevier Saunders Company. Phildelphia 2008; 1748-1759.

39. Vijayaraghavan K. Treatment of dyslipidemia in patients with type 2 diabetes. Lipids in Health and Disease. 2010; 9:144.

40. Rathcke CN, Thomsen SB, Linneberg A, Vestergaard H. Variations of CHI3L1, levels of the encoded glycoprotein YKL-40 and prediction of fatal and non-fatal ischemic stroke. Plos One. 2012; 7: 43498.

41. Ito H, Komatsu Y, Mifune M, Antoku S, Ishida H, Takeuchi Y, et al. The estimated GFR, but not the stage of diabetic nephropathy graded by the urinary albumin excretion, is associated with the carotid intima-media thickness in patients with type 2 diabetes mellitus: a cross-sectional study. Cardiovascular Diabetology. 2010; 9: 18.

42. Cho DH, Chung JO, Chung DJ, Chung MY. Increased carotid intima-media thickness is associated with progression of diabetic nephropathy in patients with type 2 diabetes. Endocrinol Metab 2011; 26: 310-316.

43. Stettler C, Allemann S, Jüni P, Cull CA, Holman RR, Egger M, et al. Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: meta-analysis of randomized trials. Am Heart J. 2006; 152: 27-38.

44. Gerstein HC, Pogue J, Mann JF, Lonn E, Dagenais GR, McQueen M, et al. The relationship between dysglycaemia and cardiovascular and renal risk in diabetic and non-diabetic participants in the HOPE study: a prospective epidemiological analysis. Diabetologia. 2005; 48: 1749-1755.

45. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005; 353: 2643-2653.

46. Saudek CD, Derr RL, Kalyani RR. Assessing glycemia in diabetes using self-monitoring blood glucose and hemoglobin A1c. JAMA 2006; 295:1688-97.

47. Shah AS, Dolan LM, Kimball TR, Gao Z, Khoury PR, Daniels SR, et al. Influence of duration of diabetes, glycemic control, and traditional cardiovascular risk factors on early atherosclerotic vascular changes in adolescents and young adults with type 2 diabetes mellitus. J Clin Endocrinol Metab. 2009; 94: 3740-3745.

48. Becker BF. Towards the physiological function of uric acid. Free Radic Biol Med. 1993; 14: 615-31.

49. Strazzullo P, Puig JG. Uric acid and oxidative stress: relative impact on cardiovascular risk? Nutr Metab Cardiovasc Dis. 2007; 17: 409- 414.

50. Strasak AM, Rapp K, Hilbe W, Oberaigner W, Ruttmann E, Concin H, et al . On behalf of the VHM & PP Study Group. The role of serum uric acid as an antioxidant protecting against cancer: prospective study in more than 28 000 older Austrian women. Ann Oncol. 2007; 18: 1893-1897.

51. Baker JF, Krishnan E, Chen L, Schumacher HR. Serum uric acid and cardiovascular disease: recent developments, and where do they leave us? Am J Med. 2005; 118: 816-826.

52. Kanellis J, Kang DH. Uric acid as a mediator of endothelial dysfunction, inflammation, and vascular disease. Semin Nephrol. 2005; 25: 39- 42.

53. Waring SW, McKnight JA, Webb DJ, Maxwell SR. Uric acid restores endothelial function in patients with type 1 diabetes and regular smokers. Diabetes. 2006; 55: 3127-32.

Citation: El-Attar HA, El –Deeb MM and El-Ghlied LA. Serum Glycoprotein Chondrex (YKL-40) and High Sensitivity C- Reactive Protein (hscrp) in Type 2 Diabetic Patients in Relation to Cardiovascular Complications. J Nephrol Kidney Dis. 2017; 1(1): 1003.
https://dx.doi.org/10.36876/smjnkd.1003

54. Gersch MS, Johnson RJ. Uric acid and the immune response. Nephrol Dial Transplant 2006; 21: 3046-7.

55. Sanchez-Lozada LG, Nakagawa T, Kang DH, Feig DI, Franco M, Johnson RJ, et al. Hormonal and cytokine effects of uric acid. Curr Opin Nephrol Hypertens. 2006; 15: 30-33.

56. Ito H, Abe M, Mifune M, Oshikiri K, Antoku S, Takeuchi Y, et al. Hyperuricemia is independently associated with coronary heart disease and renal dysfunction in patients with type 2 diabetes mellitus. Plos One. 2011; 6: 27817.

57. Rathmann W, Hauner H, Dannehl K, Gries FA. Association of elevated serum uric acid with coronary heart disease in diabetes mellitus. Diabete Metab. 1993; 19: 159-166.

58. Alderman MH. Podagra, uric acid and cardiovascular disease. Circulation 2007; 116: 880-883.

59. Kovacos GL. Diabetic nephropathy. JIFCC 2009; 20: 1.

60. Kastrup J. Can YKL-40 be a new inflammatory biomarker in cardiovascular disease? Immunobiology. 2012; 217: 483-491.

61. Clearfield MB. C-reactive protein: a new risk assessment tool for cardiovascular disease. J Am Osteopath Assoc. 2005; 105: 409-16.

Citation: El-Attar HA, El –Deeb MM and El-Ghlied LA. Serum Glycoprotein Chondrex (YKL-40) and High Sensitivity C- Reactive Protein (hscrp) in Type 2 Diabetic Patients in Relation to Cardiovascular Complications. J Nephrol Kidney Dis. 2017; 1(1): 1003.
https://dx.doi.org/10.36876/smjnkd.1003