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High Sensitivity C-Reactive Protein Level In Sera Of Pre-Diabetic And Newly Diagnosed Type 2 Diabetic Patients

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Abstract: Hs-CRP Inflammatory biomarker may provide means for early detection of metabolic syndrome. **Objective**: to assess the value of high-sensitivity CRP in serum of pre-diabetic and recently diagnosed clients with type 2 diabetes mellitus. **Subject and methods**: This trial was carried out on 180 individuals coming to the medical outpatient clinic of Fayoum University Hospital. The aged ranged from 20-60 years. They were classified into three groups. The **control group I**: was consisted of 60 non-obese, non-diabetic healthy volunteers, .Two study groups were involved in this investigation: **group II** was consisted of 60 newly diagnosed patients with type 2 DM and **group III**: was consisted of 60 pre-diabetic patients coincided for age and gender. All patients involving the control were exposed to clinical history taking, a clinical examination for the recording of body mass index (BMI) and (WC). Tests were conducted for fasting blood glucose, fasting serum insulin, insulin resistance (IR), HbA1C, the lipid patterns, liver and kidney function tests were carried out, serum albumin, a complete blood count (CBC) and serum high-sensitivity C-reactive protein (hs-CRP). **Results:** the current data showed that pre- diabetic patients and new diagnosed diabetic patients have higher levels of hs-CRP titre and HOMA-IR than normal healthy control. This difference was statistically significant difference. **Conclusion**: Hs-CRP was significantly elevated in obese pre diabetics and newly diagnosed type2 diabetics. Since hs-CRP is an important clinical parameter for assessment of the low grade inflammation occurring in metabolic syndrome and diabetes, therefore sequential rise of this inflammatory biomarker could assist in the early recognized of obese type 2 diabetic clients at high cardio metabolic risk.

Summary:

- Obesity is a main risk factor for various chronic diseases, Involving insulin resistance and type 2 diabetes.
- Hs-CRP is an acute-phase protein, its serum level is enhanced in response to inflammation in the body. It is synthesized by the liver in response to factors released by macrophages and adipocytes.
- This work aimed to assess the value of high-sensitivity CRP in serum of pre diabetics and newly diagnosed patients with type 2diabetes
- This work showed a statistically significant difference of hs-CR in pre diabetics and recently diagnosed diabetics in comparison to normal population.
- Serial rise of hs-CRP denotes a deterioration of the inflammatory status in the body and there by a worsening of endothelial function thus increasing possibility of complication.

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Key words: hs-CRP, insulin resistance, HOMA-IR, Prediabetic, new diagnosed patient with type 2 diabetes

1. Introduction

The spread of Type 2 diabetes mellitus (T2DM) is enhancing worldwide. Conventional understanding of the pathogenesis of type 2 diabetes suggests that insulin resistance is an initiating factor which leads to beta-cell hyperfunction subsequently leading to beta-cell failure and therefore overt diabetes [1]. C-reactive protein (CRP) is an acute-phase protein established elevated in blood in response to inflammation in the body. It is synthesized by the liver in response to factors released by macrophages and adipocytes. Chronic inflammation can keep CRP levels elevated, which can increase the risk of diabetes, hypertension, and cardiovascular diseases [2]. Low-grade systemic inflammation is frequently accomplice with insulin resistance and deteriorate insulin secretion, the two key mechanisms implicit the pathophysiology of type 2 diabetes. Raised levels of acute-phase proteins, such

as high-sensitivity C-reactive protein (hs-CRP) and tumor necrosis factor-alpha are frequently previously present in those with prediabetes and are predictive of future type 2 diabetes and cardiovascular disease (CVD) events [3].

Objective:

To assess the value of high-sensitivity CRP in serum of pre-diabetic and recently diagnosed clients with type 2 diabetes mellitus (T2DM).

2. Patients and Methods:

This cross-sectional study was conducted on 180 subjects; 120 patients recruited from diabetes and internal medicine outpatient clinics of Fayoum University Hospital and 60 healthy nonsmokers age and sex matched volunteers as a control group in the duration time from January 2017 to January 2018 after the approval of the local ethics committee. All participants signed a written consent to participate in the study. They were divided into three groups; Group 1:60 healthy volunteers as a control group, Group II : sixty clients with recently diagnosed type 2 diabetes mellitus (within one month of diagnosis) and Group III: 60 prediabetic patients (increased risk for diabetes) diagnosed by fasting blood glucose (FPG) 100 to 125 mg/dL (reduced fasting glucose, IFG), two-hour post-load glucose (2h pp BG) on the 75 g oral glucose tolerance test (OGTT) 140 to 199 mg/dL (reduced glucose tolerance; IGT) or glycated hemoglobin (HbA1C) 5.7 to 6.4%[4]. All patients aged 20-60 years, within one month of diagnosis of T2DM and those who diagnosed to be prediabetic were included in this study. Exclusion criteria were age less than 20 or more than 60 years, smokers, pregnant or lactating females, patients with history of cardiovascular, cerebrovascular, chronic hepatic, renal or pulmonary diseases. Patients with acute or chronic infection, inflammatory, malignant illness and those on statins or anti-inflammatory medications were also excluded. All subjects were submitted to full clinical history including age, sex, symptoms of diabetes as thirst, polyurea, polyphagia, loss of weight, thorough clinical examination including anthropometric records (body height and weight with calculation of body mass index (BMI), waist circumference (WC), blood pressure and temperature). Fasting morning blood was drawn for FBG, Complete blood count (CBC), liver and renal function tests, erythrocyte sedimentation rate (ESR), lipid profile {serum total cholesterol, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c) and triglycerides (TGs) levels}, HbA1C and serum fasting insulin level. 2h pp BG was done. Serum High-sensitivity C-reactive protein (hs-CRP) level was determined by ELISA kit brought by DRG® International Inc. (EIA-3954), USA with normal range in adults from 0.068 to 8.2 mg/l. Insulin resistance (IR) was estimated on the basis of the homeostasis model evaluation of IR (HOMA-IR), employing the following formulae: HOMA-IR= [fasting insulin (mU/l) ×fasting glucose (mg/l)/405]. Fasting insulin was measured by ELISA kit for the quantitative determination of insulin levels in human serum by Kites supplied by DRG International, Inc ((EIA-2935), USA. HOMA-IR index value; "normal" if <3 and "insulin resistant" if ≥ 3[5].

Statistical Analysis

Results were taken, coded and insides into Microsoft Access and results analysis was carried out employing SPSS software version 18 in windows 7 employing the following tests: Student t test, Chi-square test, ANOVA, Bonferroni Post-HOC, Bivariate Pearson relation test, Sensitivity and specificity test for testing a new test with ROC curve "Receiver Operating Characteristic". $P > 0.05$ was believed no significant, $P < 0.05$ was believed significant $P < 0.001$ was believed highly significant.

For quantitative parametric results one way ANOVA test in comparing more than two independent groups of quantitative data with benferroni Post-HOC to test significance between each two groups.

Bivariate Pearson relation test to test association between variables

For qualitative data Chi square test to compare two of more than two qualitative groups.

Sensitivity and specificity test for testing a new test with ROC curve "Receiver Operating Characteristic".

3. Results:

This study included 180 subjects divided to 3 study groups each included 60 participants; 27 participants (45%) of the control group (group I) were males while 33(55%) were females, their mean age was 41.4±4 years. 26(43.3%) of 60 newly diagnosed T2DM patients (group II) were males while 34(56.7%) were females their mean age was 42.9±4.3 years. 24(40%) of the 60 patients of group III (with pre-diabetes) were males while 36(60%) were females their mean age was 42.5±4.2. Our results revealed that there was marked increase in hs-CRP and HOMA-IR levels in newly diagnosed T2DM patients and pre-diabetics (group II and III) compared to controls (group I) and this difference was statistically significant. As shown in Table (1).

Table (2) shows that there is statistically significant difference with p-value <0.05 between diseased groups and control as regards anthropometric measures (waist circumference, and body mass index)

with **low** mean among group I, however there is no significant difference between group II, and group III.

Table (3) shows that there is statistically significant difference with p-value <0.05 between tested groups as regards HOMA-IR, and hS-CRP level between group I, and each of group II, and group III with **high** mean among group II, and III, with no difference between group II, and III.

Figure (3): Mean HOMA-IR and hS-CRP level in different study groups Showing increased in HOMA-IR and hs-CRP level among diabetics and prediabetics

Table (4) shows that there is no statistically significant relation with p-value >0.05 between each of HOMA-IR, and hs-CRP and any of age, waist circumference, BMI, and HbA1C %, among newly diagnosed diabetic group which indicated no association between any of these variables with HOMA-IR, or hs-CRP level among newly diagnosed diabetic group.

Table (5) shows that there is no statistically significant relation with p-value >0.05 between each of HOMA-IR, and hs-CRP and any of age, waist circumference, BMI, and HbA1C %, among pre-diabetic group which indicated no association between any of these variables with HOMA-IR, or hs-CRP level among pre-diabetic group.

Table (1): Comparisons between different clinical and laboratory results among the three tested groups.

Variables	Group I (n=60)	Group II (n=60)	Group III (n=60)	p-value	Sig.
	Mean± SD	Mean± SD	Mean± SD		
WC (cm)	82.8±9.1	122.7±3.7	122.4±3.4	<0.001[a,b]* 0.9[c]	HS NS
BMI (kg/m^2)	21.7±1.4	33.3±1.5	33.1±1.7	<0.001[a], [b]* 0.9[c]	HS NS
HB (g/dl)	12.6±1.01	12.6±1.1	12.7±0.99	0.8	NS
WBCs (10^9/L)	5.1±0.58	5.3±0.6	5.5±0.66	0.4[a], 0.3[b], 0.2[c]	NS
PLT	296.1±55.6	309.8±63.1	311.7±50	0.1[a], 0. 2[b], 0.9[c]	NS
ESR	13.8±2.8	13.6±2.9	13.6±2.8	0.9	NS
AST (IU/l)	26.7±4.2	29.2±2.6	27.2±4.2	0.001[a]* 0.9[b] 0.01[c]*	HS NS S
ALT (IU/l)	34.5±2.1	36.5±1.4	36.3±1.6	<0.001[a,b]* 0.9[c]	HS NS
Albumin (mg/dL)	3.9±0.15	3.87±0.14	3.84±0.16	0.3	NS
Creatinine (mg/dL)	0.86±0.12	0.85±0.13	0.86±0.14	0.9	NS
Urea (mg/dL)	34.6±1.8	35.2±1.6	34.6±1.6	0.1	NS
Total cholesterol (mg/dl)	92.8±9.4	104.6±8.9	103.4±9.4	<0.001[a,b]* 0.9[c]	HS NS
Triglyceride (mg/dl)	53.02±8.2	156.9±19.8	154.6±18.1	<0.001[a,b]* 0.3[c]	HS NS
LDL-c (mg/dl)	50.3±5.1	50.2±4	49.8±3.9	0.9	NS
HDL-c (mg/dl)	52.4±5.5	43.3±5.6	41.4±5.3	<0.001[a,b]* 0.2[c]	HS NS
FBG (mg/dl)	84.4±4.9	154.6±28.6	118.6±2.9	<0.001[a,b,c]*	HS
2Hpp BG (mg/dl)	122.8±8.2	367.03±54.9	177.1±13.1	<0.001[a,b,c]*	HS
HbA1c %	4.9±0.22	8.72±0.95	6.03±0.15	<0.001[a,b,c]*	HS
HOMA-IR	1.96±1.2	6.51±5.2	5.72±4.4	<0.001[a,b]* 0.8[c]	HS NS
hS-CRP (mg/L)	4.4±2.4	13.5±3.1	13.2±2.4	<0.001[a,b]* 0.9[c]	HS NS

a:significance difference between GI, and G II. b:significance difference between GI, and G III c:significance difference between G II, and G III

Table (2): Comparisons of anthropometric measures between different study groups.

Variables	Group I (n=60)	Group II (n=60)	Group III (n=60)	p-value	Sig.
	Mean± SD	Mean± SD	Mean± SD		
WC (cm)	**82.8±9.1**	122.7±3.7	122.4±3.4	**<0.001**[a,b]* 0.9[c]	**HS** NS
BMI (kg/m^2)	**21.7±1.4**	33.3±1.5	33.1±1.7	**<0.001**[a, b]* 0.9[c]	**HS** NS

a:P value between GI, and G2 <0.001(HS); b:P value between GI, and G3 <0.001 (HS)
c:P value between G2, and G3 (NS)

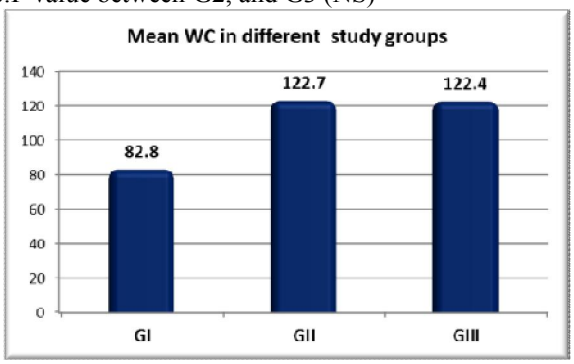

Figure (1) :Mean WC in cm among different study groups showing increased waist circumference among diabetics and prediabetics

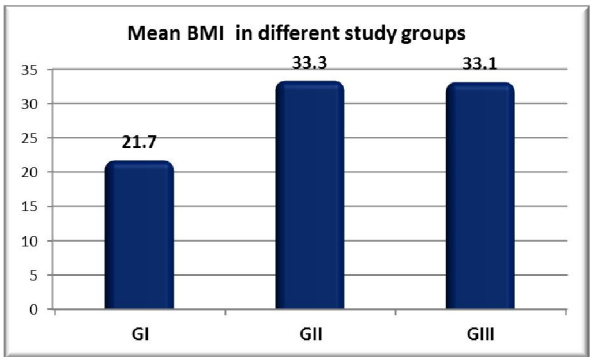

Figure (2):Mean BMI in different study groups showing increased BMI among diabetics and prediabetics

Table (3): Comparisons of insulin resistance and hsCRP level in different study groups.

Variables	Group I (n=60)	Group II (n=60)	Group III (n=60)	p-value	Sig.
	Mean± SD	Mean± SD	Mean± SD		
HOMA-IR	1.96±1.2	6.51±5.2	5.72±4.4	**<0.001**[a,b*] 0.8[c]	**HS** NS
HS-CRP	4.4±2.4	13.5±3.1	13.2±2.4	**<0.001**[a,b*] 0.9[c]	**HS** NS

a: P value between GI, and G2 <0.001(HS) b:P value between GI, and G3 <0.001(HS)
c:P value between G2, and G3 (NS)

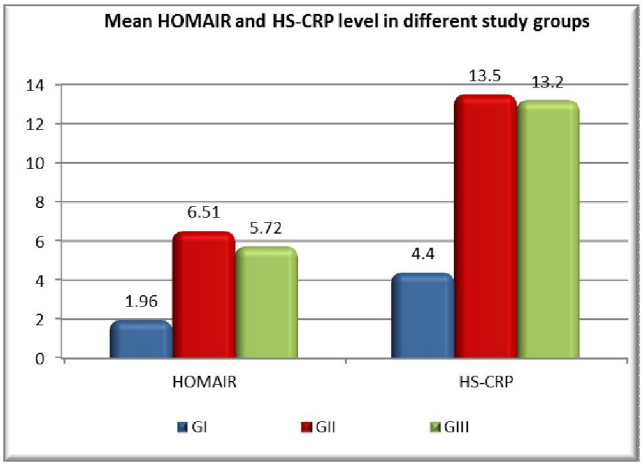

Figure (3): Mean HOMAIR and HS-CRP levels in the different study groups

Table 4. IR, and hs-CRP with study variables among newly diagnosed diabetic patients.

Variables	HOMAIR			HS-CRP		
	r	p-value	Sig.	r	p-value	Sig.
Age (years)	-0.23	0.07	NS	-0.07	0.6	NS
WC(cm)	0.12	0.4	NS	-0.10	0.4	NS
BMI(kg/m^2)	0.13	0.3	NS	0.08	0.6	NS
HbA1c %	0.05	0.7	NS	0.12	0.3	NS
HS-CRP	-0.11	0.4	NS	----	----	----

Table (5): Correlation between HOMA-IR, and hs-CRP with study variables among pre-diabetic patients.

Variables	HOMAIR			HS-CRP		
	r	p-value	Sig.	r	p-value	Sig.
Age (years)	0.17	0.2	NS	-0.08	0.6	NS
WC(cm)	0.03	0.8	NS	0.008	0.9	NS
BMI(kg/m^2)	-0.12	0.4	NS	0.02	0.9	NS
HbA1c %	-0.06	0.7	NS	-0.13	0.3	NS
HS-CRP	-0.12	0.4	NS	----	----	----

Table (6): Sensitivity and specificity of hs-CRP in diagnosis of pre-diabetic patients.

Variable	Sensitivity	Specificity	AUC	Accuracy	Cut off point
HS-CRP	96.7%	51.7%	71.8%	60.5%	8.57

Sensitivity and specificity test for hs-CRP illustrates probability of being true positive is **(60.5%)** more than being false positive when repeat test 100 times with sensitivity **(96.7%)** and specificity **(51.7%)**at cutoff value of **(8.57).**

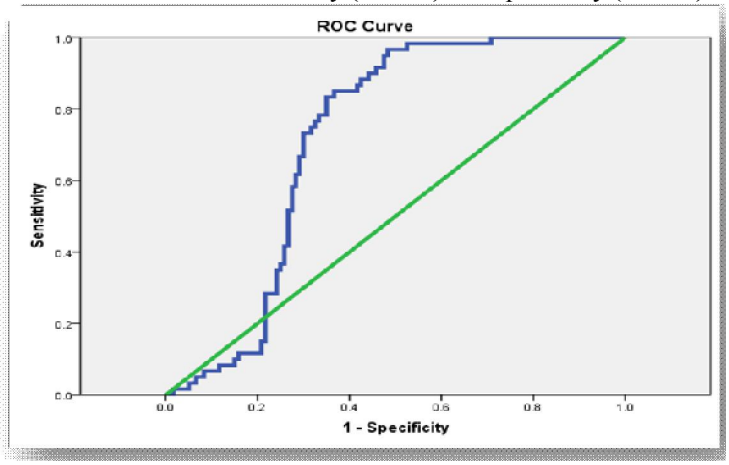

Figure (4) :ROC curve for hs-CRP:

4. Discussion:

In this cross-sectional study, we found higher levels of hs-CRP and HOMA-IR in pre diabetics and early diagnosed T2DM patients compared to controls (within one month). These results emphasized the pivotal role of insulin resistance in the pathophysiology of T2DM development[6] and are in agreement with **Wang et at., (2016)**[7] who showed increased levels of CRP in prediabetes and T2DM subjects compared with normal glucose subjects.

The role of chronic inflammation described by mild elevation in the prevalent levels of the called severe stage proteins in the pathogenesis of T2DM is well recognize [8]. Common techniques included in the link between inflammation and glucose metabolic disturbance involves the activation of nuclear factor-kB and JUN N-terminal kinase, pathways causing the recruitment of the immune system cells in adipose tissue [9]. **Grossmann et al., (2015)**[10] found dynamic changes in inflammatory biomarkers with T2DM development with a significant increase in hs-CRP in prediabetics to normoglycemic subjects and diabetic patients denoting very early immune system activation.

Guerrero-Romero (2014) [11] stated that promoted CRP levels were associated with FPG and 2 h post load glucose in the pateints with IGT, but not in exposes to IFG or normal glucose tolerance. On

contrary to our results **Herder et al., (2016)**[12] in their longitudinal study noticed a significant association between baseline levels of hs-CRP and HbA1C but they denied any significant association between changes in HbA1C and hs-CRP levels. Moreover, In the KORA investigation in Germany, the favorable association between CRP and diabetes disappeared in men after adjustment for BMI, while it continued in women [13] (this is probably due to the fact that CRP is associated with visceral fat while BMI depends on muscles, bones, visceral, and subcutaneous fat). Data from the KORA study documented that baseline hs-CRP significantly predicted change in HbA1c over 7 years following multivariable modification [14].

Conclusion:

Hs-CRP was significantly elevated in obese pre diabetics and newly diagnosed type2 diabetics. Since hs-CRP is an important clinical parameter for assessment of the low grade inflammation occuring in metabolic syndrome and diabetes, therefore sequential rise of this inflammatory biomarker could assist in the early recognition of obese type 2 diabetic clients at high cardio metabolic risk.

Conflict of Interest

Mohamed Abdelhady Mashahit, Eman Mahmoud Ezzat, Ahmed AbdelKawi Hamad, Ghada Mohamed Ezzat, Doaa Gaber Mezar declare that they have no conflict of interest

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