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CORRELATION BETWEEN HIGH SENSITIVITY C-REACTIVE PROTEIN AND LIPID PROFILE IN YOUNG PATIENTS WITH DIABETES MELLITUS TYPE 1 IN HOMS-SYRIA

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In this study, we evaluated levels of high sensitivity C-reactive protein (hsCRP), as a predictor marker of cardiovascular disease, and lipid profile and studied the relationship between them in young patients with diabetes mellitus type 1 (DMT1). This study was conducted on 71 young with (DMT1), at Al-Arman Healthy Center in Homs- Syria, compared to 25 healthy controls at the same age. Blood samples were collected, and laboratory measurements were performed which included: HbA1c, FBG, TG, LDL-c, HDL-c, TC, hsCRP. Depending on the (HbA1c) values, all study patients had uncontrolled DM, and 58.5% of them had dyslipidemia. DMT1 patients had significantly higher serum concentrations of hsCRP, which indicates the presence of low-grade chronic inflammation. Significant positive correlation was found between (hsCRP) and (HbA1c, TG, LDL-c, TC), and a significant negative correlation with (HDL-c) in DMT 1 group. Conclusions, Atherosclerosis and vascular changes begin from an early age in DMT 1 patients with poor glycaemic control.

Key words: *Type 1 diabetes, atherosclerosis, cardiovascular disease, hsCRP.*

INTRODUCTION

Type 1 diabetes is known as insulin-dependent or juvenile diabetes and it is caused by the immune system destroying beta cells in the pancreas, which can happen at any age but is usually diagnosed in children and young people[1&2]

Type 1 diabetes can lead to other serious complications, especially in uncontrolled cases which include cardiovascular disease, as the cardiovascular mortality rate increases 2-20 times in young patients with DMT 1 due to atherosclerosis that starts from an early age.[3&4]

The term atherosclerosis comes from a Greek origin and means a thickening of the intimal layer of arteries and accumulation of fat. Fats is located in the central core of the plaque, covered by fibrous cap.[5]

It is a very complex process caused by many factors in patients with DMT1 due to dyslipidemia and hyperglycemia.[6] High levels of reactive oxygen species (ROS) and advanced glycation end products (AGEs) increase oxidative stress and reduce the synthesis of Nitric Oxide (NO), in addition to the happening of changes in the structure of actin filaments of endothelial cells (EC).[7&8&9]

Insulin plays a major role in lipids metabolism. It inhibits the hormone-sensitive lipase and vLDL production from the liver. In addition, it increases the activation of LPL (Lipoprotein lipase), which promotes the catabolism of triglyceride-rich lipoproteins.[10]

Insulin resistance is an observed condition in adolescent with DMT1 which is related to an increasing of growth hormone and sex steroids at puberty period, and this may be associated with overweight and family history of type 2 diabetes mellitus (DMT2).[11]

ROS have a direct role in increasing the expression of adhesion molecules, inflammatory factors, and LDL oxidation which leads to the formation of plaques, so any endothelial dysfunction stimulates the

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production of cytokines and inflammatory factors such as IL-6, TNF, VCAM, and CRP.[12]

CRP is an acute-phase protein of the pentraxin family that is produced in the liver in response to an inflammatory state and is elevated in acute infections, chronic immunity diseases and after surgery.[13&14]

hsCRP test is used to detect the smallest concentrations of CRP and is measured by several techniques including turbidimetry, nephelometry and ELISA methods with concentrations starting from 0.01-10 mg/L.[15]

According to latest studies, hsCRP is considered a predictive marker of CVD, so the risk of groups is classified by The American Heart Association and U.S. Centers for Disease Control and Prevention as follows: Low risk: less than 1.0 mg/L, Average risk: 1.0 – 3.0 mg/L, High risk: more than 3.0 mg/L .[16]

In this study, hsCRP test was employed as a predictive indicator of CVD in DMT 1 patients because of its long-term predictive capacity which is likely a reflection of the inflammatory process associated with atherosclerotic risk and it is an inexpensive and easy analysis in the lab.

Therefore, this study was conducted to highlight the significance of macrovascular complications related to hsCRP levels in young patients with DMT1 as most studies in Syria focused on DMT2 patients. Furthermore, we aimed at studying poor glycaemic control in the patients' group that may be attributed to the worsening economic and medical conditions due to the Syrian war.

MATERIALS AND METHODS

This study included 96 children and adolescents who were classified into 2 groups: 71 patients (32 boys) who were diagnosed as diabetic patients with type 1 and had regular follow-ups at the Diabetes clinic, Al-Arman Healthy Center; their mean age was (14.69 ±2.78); and 25 control group (12 boys) with the same age group (14.24 ±2.83) were classified as group II (Table 1). The duration of sample collection was between June 2021 and September 2021, after obtaining ethical approval No: 2444 on 13/1/2021.

The inclusion criteria for the patients' group: age ranged from 10 to 19 years, diabetes duration between 1-16 years (4.89 ±3.19) (Table 1).

The exclusion criteria were: severe infection in the last 72 hrs, recent surgical procedure, diabetics with other autoimmune or malignant diseases, patients having hsCRP> 10 mg/L ,and for the last reason 4 patients were excluded from this study.

Measurements of blood pressure, height, and weight were performed. Body mass index (BMI) was defined as weight in (Kg)/(height in meter)^2. Laboratory data included: HbA1c (boditech kit/ cat. No. CFPC-38/ Koria) was measured by an I-chroma (boditech/ RS232/ Koria) using the immunofluorescence technique, (FBG) was determined by a (Biosystem/ cat. No. 11503/ Spain) kit. We used the enzymatic method for measuring TC (Biosystem/ cat. No. 11505/ Spain), TG (Biosystem/ cat. No. 11528/ Spain), LDL-c (Biosystem/ cat. No. 11585/ Spain) and HDL-c (Biosytem/ cat. N0. 11557/ Spain) using Spectrophotometer (340096/ Japan). Also, (hsCRP) was determined by the nephelometry method which is based on agglutination between serum CRP and latex particles coated with specific anti-human CRP antibodies (Biosystem/ cat. No. 31927/ Spain).

All statistical analyses were performed using the Statistical Package for Social Science (SPSS) version 24.0, differences in the means were determined using the Student's *t* test and the results were expressed as mean ± SD. Pearson's test and Spearman's test were used to analyse correlations between variables. The correlation was considered significant if the *p*-value < 0.05.

RESULTS AND DISCUSSION

Results

No differences were observed in systolic and diastolic blood pressure between the two groups **(Table 1)**, there was 48 patients who had family history of DM and CVD **(Table 2)**. We found a significant increase in HbA1c and FBG in patients compared to the control group, so most study patients had uncontrolled DM according to ADA standards **(Table 3)**.

Table 1: Descriptive data of the study group.

Variables	Diabetic group (n=71)	Control group (n=25)	p-value
Age (years)	14.69 ±2.78	14.24 ±2.83	0.24
Sex (F/M)	39/32	13/12	0.8
DM Duration (years)	4.89 ±3.19	-	-
BMI (Kg/m2)	19.34 ±3.55	18.47 ±1.90	0.13
Mean systolic BP (mm Hg)	115 ±7.2	112 ±6.1	0.34
Mean diastolic BP(mm Hg)	77.8 ±4.5	75 ±5.3	0.22

DM, Diabetes Mellitus; BMI, Body Mass Index; BP, Blood Pressure.

Table 2: Descriptive data of the study group.

Chi-square	Diabetic group (n=71)	Control group (n=25)	p-value
Positive family history of DM and CVD (%)	48/71 (67.6%)	(0%)	<0.001

CVD, Cardiovascular Disease; DM, Diabetes Mellitus.

Table 3: Descriptive variables of the study groups.

Variables	Diabetic group (n=71)	Control group (n=25)	p-value
Age (years)	14.69±2.78	14.24 ±2.83	0.24
HbA1c (%)	11.95±2.31	5.67±0.37	<0.001
FBG (mg/dl)	217.53±79.2	84.98±10.15	<0.001
LDL-c (mg/dl)	159.0±30.21	89.58±8.87	<0.001
TG (mg/dl)	197.86±70.83	109.86±19.01	<0.001
HDL-c (mg/dl)	33.07±3.76	53.18±8.31	<0.001
TC (mg/dl)	232.05±49.36	168.74±16.63	<0.001
hsCRP (mg/l)	3.00±2.59	0.46±0.35	<0.001

HbA1c, glycated hemoglobin; FBG, Fasting blood glucose; LDL-c, Low-density lipoprotein cholesterol; TG, Triglycerides; HDL-c, High-density lipoprotein` cholesterol; TC, Total Cholesterol; hsCRP, high sensitivity C-reactive protein.

Levels of TC, LDL-c, and TG were higher in diabetics than in controls, while levels of HDL-c were significantly lower in diabetics than in controls. Also, type 1 diabetic patients had higher mean serum concentrations of hsCRP than control subjects.

Table 4 shows comparisons between the means of variables according to the duration of disease, significant differences were found in the means of TG and TC levels between the (<5 years) group and (≥5 years) group.

Fig (1, 2) and Table 5 indicate the presence of significant positive correlations between hsCRP and (HbA1c, LDL, TG, TC) and a significant negative correlation with (HDL) and it was noted the presence of significant positive correlations of hsCRP and the 2 groups of duration of disease and family history of DM and CVD **(Table 6)**.

Table 4: Descriptive variables according to the duration of disease.

Parameters	<5 years group (n=34)	≥5 years group (n=37)	p-value
HbA1c (%)	11.84±2.42	12.01±2.23	0.708
FBG (mg/dl)	192.43±80.72	205.74±94.14	0.526
LDL-c (mg/dl)	153.04±32.32	164.48±27.44	0.112
TG (mg/dl)	175.91±61.31	218.03±73.72	0.011
HDL-c (mg/dl)	33.80±3.73	32.41±3.71	0.118
TC (mg/dl)	217.35±43.06	245.57±51.44	0.015
hsCRP (mg/l)	2.41±2.64	3.54±2.45	0.066

HbA1c, glycated hemoglobin; FBG, Fasting blood glucose; LDL-c, Low-density lipoprotein cholesterol; TG, Triglycerides; HDL-c, High-density lipoprotein` cholesterol; TC, Total Cholesterol; hsCRP, high sensitivity C-reactive protein.

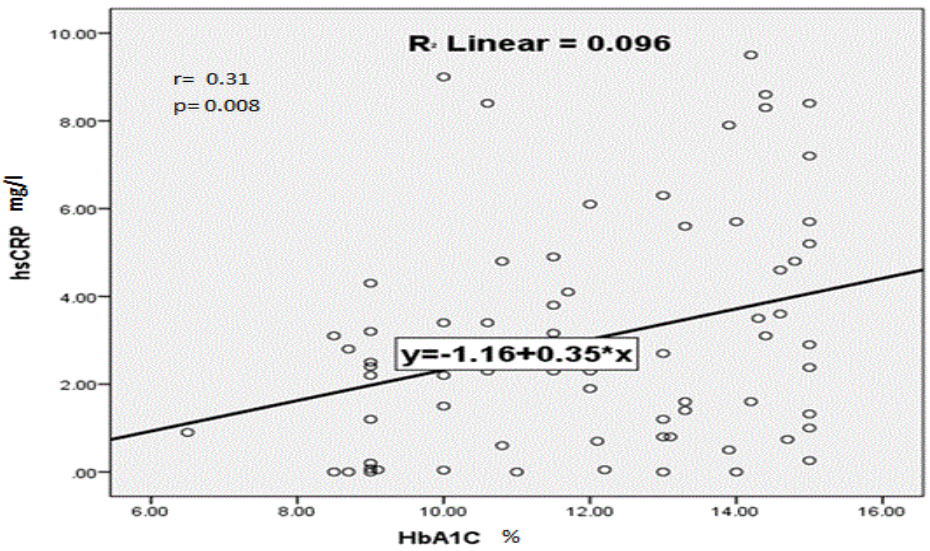

Fig. 1: Correlation of hsCRP and HbA1c in type 1 diabetic patients.

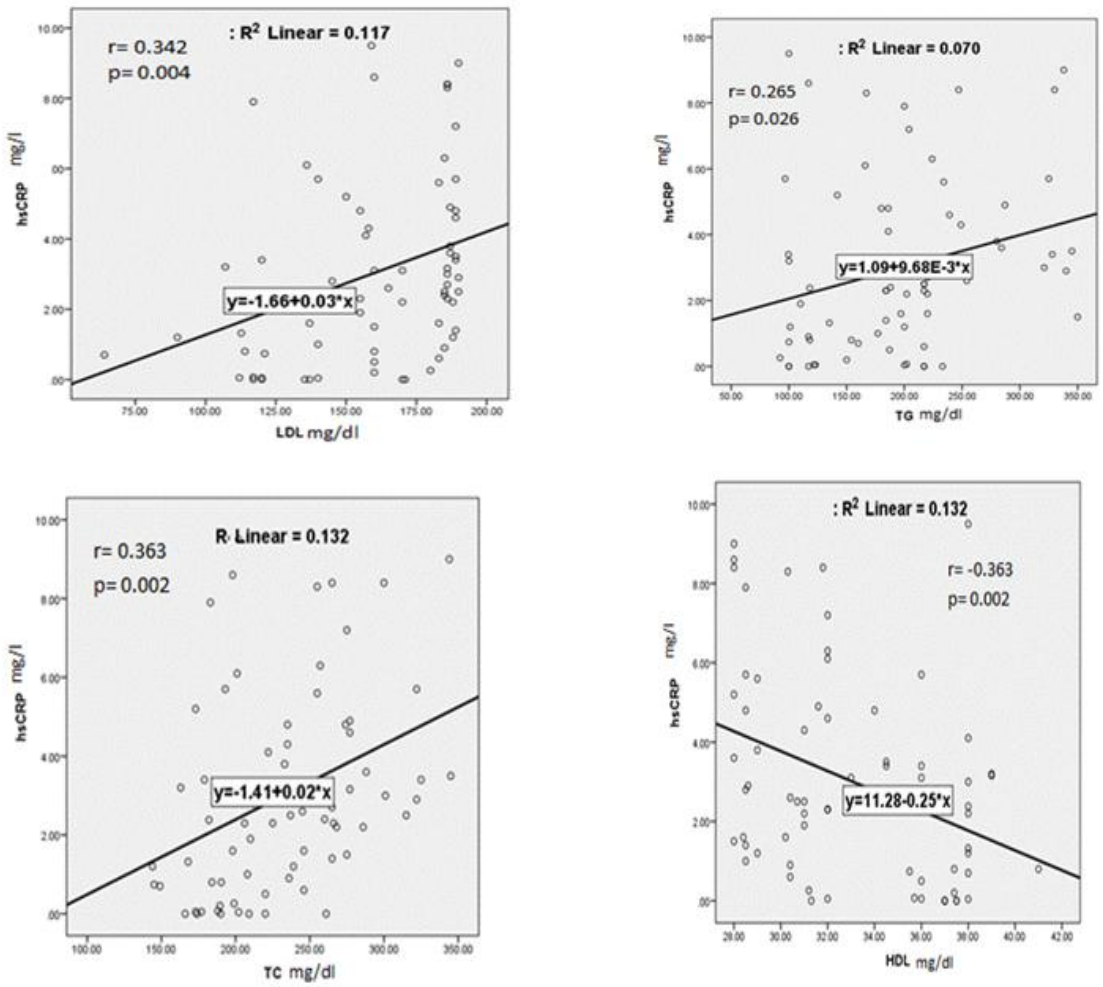

Fig. 2: Correlations of hsCRP and lipids profile in type 1 diabetic patients.

Table 5: Correlation of hsCRP and other variables.

	Pearson correlation (r)	p-value
hsCRP	-	-
HbA1C	0.310*	0.008
FBG	0.147	0.274
LDL-c	0.342**	0.004
TG	0.265*	0.026
HDL-c	-0.363**	0.002
TC	0.363**	0.002
age	0.072	0.551

hsCRP, high sensitivity C-reactive protein; HbA1c, glycated hemoglobin; FBG, Fasting blood glucose; LDL-c, Low-density lipoprotein cholesterol; TG, Triglycerides; HDL-c, High-density lipoprotein` cholesterol; TC, Total Cholesterol.

Table 6: Correlation of hsCRP and other variables.

	Spearman correlation	p-value
hsCRP		
Groups of Duration of disease	0.277	0.020
Family history of DM and CVD	0.407	<0.001

hsCRP, high sensitivity C-reactive protein; DM, Diabetes Mellitus; CVD, Cardiovascular Disease.

Discussion

In this study, hsCRP and lipid profile which were considered markers for cardiovascular disease and this is compatible with the American Heart Association (AHA). We found that most patients were uncontrolled diabetics for several reasons including the regression of economic conditions due to the Syrian war, lack of adherence to treatment and diet and possibly due to insulin resistance in patient at puberty especially 9 patients were obese. (58.5%) of study patients had dyslipidemia. Insulin plays a central role in the regulation of lipid metabolism[17] and at the same time iatrogenic hyperinsulinemia caused by insulin resistance leads to lipid disorders.[18] Therefore, dyslipidemia is common among uncontrolled DMT 1 patients.[17,19] These results are in agreement with Shin-Hee Kim et al and Bedowra Zabeen et al studies,[20&21] who concluded that a substantial proportion of adolescents and young adults with DMT 1 had dyslipidemia.

DMT 1 patients had a higher level of hsCRP with a mean of (3 mg/L), which indicates the presence of low-grade inflammation.[22]

We found significant differences of TG and TC between 2 groups (<5 years and ≥ 5 years), it is meaning that development of dyslipidemia occurs as the disease progresses but this study has potential limitation, it is the lack of follow-up of our patients' laboratory values, therefore, we can not define their effect on monitoring the disease progression over time.

Our study showed a positive correlation between hsCRP and HbA1c **(fig.1)**, this could indicate the presence of vascular damage due to increased production of (ROS), which promote oxidative stress,[23] and due to increased formation of (AGEs) products both of which contribute to the pathogenesis of atherosclerosis through the migration of monocytes and release of cytokines which stimulates the release of C-reactive protein from hepatocytes.[24]

In the diabetic group, hsCRP levels were positively correlated with LDL,TG, and TC. However, hsCRP showed a negative correlation with HDL **(fig.2)**.

These results suggest that unfavorable lipids indicators play roles in the mechanism of vascular damage by facilitating the formation of foam cells and increasing the inflammatory

state by increasing the expression of adhesion molecules and releasing inflammatory cytokines as in *Fawas et al* research.[15,25]

Furthermore, we found high levels of hsCRP in young diabetics with a family history of cardiovascular disease (3.98 mg/L) and this is in agreement with recent studies but we still need to conduct more research to determine the genetics of the disease.

In conclusion, these results indicate that atherosclerosis may start in childhood in DMT 1 patients with poor glycaemic control and dyslipidemia, so it is highly recommended to do regular monitoring of lipids profile indicators of patients as well as their glycaemic control and weight.

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نشرة العلوم الصيدلية
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العلاقة بين البروتين المتفاعل C عالي الحساسية والصّيغة الليبيدية عند اليافعين المصابين بداء السّكري من النّمط الأول في حمص – سوريا

ريهام نعيم ديبان – سلاف الوسوف

قسم الكيمياء الحيوية والأحياء الدقيقة ، جامعة البعث ، حمص ، سوريا

في هذه الدّراسة تم تقييم مستويات البروتين المتفاعل C عالي الحساسية والصّيغة الليبيدية عند اليافعين المصابين بداء السّكري من النّمط الأول وتم دراسة علاقة الارتباط بينهما. شملت هذه الدّراسة ٧١ مريض سكري يافع من النّمط الأول و ٢٥ كعينة ضابطة بنفس الفئة العمرية في مركز الأرمن الصحي في مدينة حمص– سوريا. تم أخذ عينات دم وريدي وإجراء التّحاليل المخبرية التّالية: الخضاب السّكري (HbA1c)، سكر الدّم الصّيامي (FBG)، البروتين الشّحمي منخفض الكثافة (LDL-c)، البروتين الشّحمي مرتفع الكثافة (HDL-c)، ثلاثيات الغليسريد (TG)، الكوليسترول الكلي (TC)، البروتين المتفاعل C عالي الحساسية (hsCRP). وجدنا أنّ كل مرضى الدّراسة غير مضبوطي سكر الدّم بالاستناد لقيم HbA1c، و ٥٨.٥% يعانون من اضطراب في الصّيغة الليبيدية. وتمّ ملاحظة ارتفاع مستويات hsCRP عند المرضى وهذا دليل على وجود التهاب مزمن منخفض الدّرجة. لوحظ وجود علاقة ارتباط إيجابية معنوية بين hsCRP وكلاً من (HbA1C, LDL-c, TG, TC) وسلبية معنوية مع (HDL-c).

الخلاصة: يبدأ التّصلب العصيدي والأذية الوعائية عند مرضى داء السّكري من النّمط الأول بعمرمبكر.