Original Article

Relations of high sensitive C-reactive protein (hs-CRP) with microalbuminuria as a useful predictor of cardiovascular risk among type 1 diabetes mellitus patients

Abeer J. Hassan* **BSc, PhD**

Abstract:

Background: Inflammation and more specifically inflammatory cytokines are determinant in the development of microvascular diabetic complications, including neuropathy, retinopathy and nephropathy.
Objective: The aim of present study is to evaluate the relationships between high sensitive C-reactive protein, microalbuminuria and risk factors for cardiovascular disease.
Subjects and methods: the study involved (30) patients with type 1 diabetic mellitus compared to (30) healthy control. A fasting blood sample was drawn from all subjects after an overnight fasting to measure the biochemical parameters which including glycated hemoglobin, lipid profile, atherogenic index of plasma and high sensitive C-reactive protein concentration in blood of all subjects, also evaluating microalbuminuria, creatinine, urea level in urine of type 1 diabetic mellitus patients and healthy control.
Results: results revealed a significant increase in the level of glycated hemoglobin, total cholesterol, triglyceride, low density lipoprotein, high sensitive C-reactive protein, microalbuminuria, urea and atherogenic index of plasma. While a significant decrease in high density lipoprotein level in patients group compared with control group. Also, there were a highly significant positive correlation between high sensitive C-reactive protein and glycated hemoglobin, atherogenic index of plasma and microalbuminuria.
Conclusions: the results of this study suggests that high sensitive C-reactive protein can be use with microalbuminuria as a biochemical marker to predict the early stage of cardiovascular disease in children and adolescents with type 1 diabetic mellitus.
Key words: hs-CRP, microalbuminuria, type 1 diabetic mellitus, cardiovascular risk.

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Introduction:

Diabetes mellitus is one of the most frequent chronic diseases in childhood; patients with long standing diabetes may develop complication affecting the eyes, kidneys, nerves or major arteries. Approximately 30– 40% of people with type one diabetes develop renal failure(1).

Diabetic nephropathy is the single most common cause of end stage renal disease (ESRD) in the western countries (2). An increased urinary albumin excretion rate of 20 – 200 mg/ 24 hours is called microalbuminuria (MU) can be detected and constitutes an early stage of nephropathy. Microalbuminuria was originally established as predictor of renal failure in patients with diabetes mellitus (3).

Inflammation and more specifically inflammatory cytokines are determinant in the development of microvascular diabetic complications, including neuropathy, retinopathy and nephropathy (4). High sensitivity C-reactive protein (hs-CRP) production is part of the nonspecific acute-phase response to most forms of inflammation, infection and tissue damage. Hs-CRP is produced predominantly in hypatocytes as a pentamer of identical subunit in response to several cytokines such as Interleukin-6 (IL-6) (5). Hs-CRP has been shown to be increased in individuals with coronary artery disease. CRP directly binds highly atherogenic oxidized low- density lipoprotein cholesterol (LDL-C) and is present within lipid-laden plaques (6). Also hs-CRP is sensitive marker for diabetic nephropathy in type 1 diabetics (7) and recently, microalbuminuria has become a prognostic marker for cardiovascular disease (CVD) in diabetic patients and it is associated with an increased risk for all cause of cardiovascular mortality and cardiac abnormalities (8). So that, the aim of this study was to determine the relation between hs-CRP with microalbuminuria and considered as risk factors for cardiovascular disease among type 1 diabetic patient.

**Dept. of Community Health/ Institute of Medical Technology-Baghdad / Middle Technical University.*
Email: a2a11s@yahoo.com

Materials and Methods

A total of 60 subjects were enrolled to National Diabetic Center (NDC) of Al-Mustansiriya University from October to December 2014. They were divided into two groups 30 patients with type 1 diabetes the mean age (16 ±0.31) years and 30 healthy subjects as a control group with mean age (17± 0.57) years. Patients with urinary tract infection, hypertension, renal failure and heart failure of any stage were excluded.

A fasting blood sample was drawn from all subjects after an

overnight fasting to measure glycated hemoglobin HbA1c (Axis-shield POC AS kit) (9), plasma glucose level determined by using kit supply from Randox, UK (10), total cholesterol was measured using enzymatic method with Biolab SA France kit (11), triglyceride (Biolab SA France kit) (12), high-density lipoprotein cholesterol (HDL-c) (Biolab SA France kit) (13). Also, hs-CRP was determined by using enzyme-linked immune sorbent assay (ELISA) method (DRG kit, Germany) (14). First morning urine samples were collected to estimation urinary albumin (Randox, UK kit) (15), urinary creatinine (SYRLAB kit) (16) and urea (SYRLAB kit) (17). Also atherogenic index of plasma (AIP) was calculated from the formula [log (TG/HDL-c)] (18).

Statistical analysis: to compare the significance of the difference in the mean values of two groups, student's T-test was applied and the results were expressed as mean ± SD and P≤0.05 was considered significant. The correlation coefficient (r) test is used to describe the association between the different studied parameters.

Results

Table (1) shows a non significant increase in age between patient (16± 0.31) years and control group (17± 0.57) years. Also, the mean level of FBG, HbA1c%, total cholesterol (TC), triglyceride (TG) and low density lipoprotein-cholesterol (LDL-c) were significantly higher increased in pataients than in control group. While a highly significant decrease in level of HDL-c of type 1 diabetic group than control group. On the other hand a highly significant difference in AIP index between the two groups. Also, data in table (1) show a significant increase (P<0.05) in microalbuminuria, urea and hs-CRP when comparing patient group with control group.

Table 1 : Descriptive characteristics of the study groups.

Parameters	T1DM group	Control group	P-value
Age (Yrs)	16 ± 0.31	17± 0.57	>0.05
FBG (mg/dl)	178.97 ± 5.28	94.33 ± 1.82	<0.001
HbA1c %	10.84 ± 2.49	5.1 ± 0.3	<0.001
TC (mg/dl)	230.35 ± 8.43	154.5 ± 6.4	<0.001
TG (mg/dl)	188.72 ± 4.07	148.27 ± 7.30	<0.001
HDL-c (mg/dl)	32.52 ± 2.34	40.22 ± 0.31	<0.001
LDL-c (mg/dl)	144.72 ± 4.66	85.81 ± 16.3	<0.001
AIP	0.837 ± 0.01	0.364 ± 0.02	<0.001
MU (mg/dl)	131.77 ± 32.02	16.2 ± 0.41	<0.05
Creatinine (mmol/L)	8.64 ± 2.42	9.21 ± 0.54	<0.05
Urea (mg/dl)	30.49 ± 6.30	18.43 ± 1.39	<0.05
Hs-CRP (µg/dl)	3.28 ± 0.09	1.83 ± 0.65	<0.05

P-values <0.05 was considered statistically significant

Results in table (2) indicate the presence a highly significant positive correlation between HbA1c, microalbuminuria, AIP and hs-CRP in type 1 diabetic group. Also, a highly significant positive correlation between AIP and microalbuminuria level was noticed in patient group.

Table 2 : correlation between hs-CRP and HbA1c, MU, AIP

	R	P-value
HbA1c & hs-CRP	0.283	<0.001
MU & hs-CRP	0.382	<0.001
AIP & hs-CRP	0.623	<0.001
MU & AIP	0.415	<0.001

P-values <0.05 was considered statistically significant

Discussion:

Diabetes mellitus is a group of chronic disease characterized by hyperglycemia which results from the defects in the insulin secretion, insulin action or both. Cardiovascular disease (CVD) is a major cause of morbidity and mortality in patients with type 1 diabetes mellitus (19). In the present study, patients with T1DM group showed significantly higher levels of lipids (TC, TG, LDL-c and VLDL-c) and lipid risk factors atherogenic index of plasma AIP which are well known risk factors for cardiovascular disease and that compatible with 2011 American Diabetes Association (ADA) medical care recommendations and other studies (20,21). Insulin plays a central role in the regulation of lipid metabolism. In T1DM, lipid disorders are observed due to insulin deficiency and that mainly cause of reduce lipoprotein lipase activity and cholesterol ester transport protein. Therefore, dyslipdemia are prevalent in diabetic mellitus patient (22). AIP indicates

a balance between the actual concentration of plasma triglyceride and low density lipoprotein (23). AIP correlates with size of pro-antiatherogenic lipoprotein particles (24). So that, AIP might be a better predictor of incidence of atherogenicity. The finding of the current study demonstrates a higher significant increase in microalbuminuria levels in T1DM group when compared with control group. Although, a statistical significant difference was detected in both urinary creatinine and urea in patients group when compared to that of control. These results are agreement with Razavi et al. whom concluded significant prevalence of microalbuminuria in children and adolescents with diabetes type 1 (25). Polyuria (excessive urine production) is a common symptom in T1DM patients and that causes damage to the glomerular membrane. An early indicator of glomerular dysfunction is the presence of microalbuminuria (26). Studies of patients with diabetes mellitus show that microalbuminuria precedes the nephropathy associated with diabetes particularly in T1DM. Progression from microalbuminuria to clinical nephropathy can be delayed with intensive therapy to normalize blood glucose and blood pressure (27). Some authors suppose that poor glycemic control is the risk factor for proteinuria (28). Also, as the result the concentration of TG, VLDL-c, LDL-c and TC rises with increasing albumin excretion rate in patients with T1DM. Furthermore, recent work demonstrated that AIP correlates positively with microalbuminuria in T1DM patients group. So that, microalbuminuria could be considered risk factor for cardiovascular disease in type 1 diabetic (29).

High sensitive-CRP an inflammatory factor with wide variability among various ages, sexes and ethnicities is modestly associated with CVD (30). CRP was previously reported as a predictor for micro- and macrovascular complications of diabetes (31). As expected, in present results serum hs-CRP levels in patients group were significantly higher than control group and that agree with others (32,33). The elevation in hs-CRP may be related to activation of macrophages and increased oxidative stress. So that, T1DM is now accepted to be a chronic immune-inflammatory disorder (34) and because of that hs-CRP suppose a marker for coronary artery disease (35).Also, a positive correlation was found between HbA1c, MU, AIP and hs-CRP.

Conclusion: this study suggests that hs-CRP can be used with MU as a biochemical marker to predict the early stage of cardiovascular disease in children and adolescents with type 1 diabetic mellitus.

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