Diagnostic value of serum C-reactive protein as biomarker of cardiovascular risk in patients with type 2 diabetes

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Abstract. Diabetes mellitus (DM) remains the epidemic of the century and has a major impact on mortality from all-cause and cardiovascular disease (CVD). The systemic inflammatory pathway provides the common pathogenetic link in such comorbidity. To define serum high- sensitivity C-reactive protein (hs-CRP) levels, as a marker of systemic inflammation, in patients with diabetes mellitus type 2 and to relate this to presence of CVD.The study consisted of 118 subjects with type 2 diabetes. Anthropometric characteristics were measured and blood was collected for the evaluation fasting blood sugar (FBS) level, HbAlc, and serum high-sensitivity C-reactive protein (hs-CRP levels). Several clinical and biochemical characteristics were significantly different among the study group: triglyceride (TG) ($p<0.05$), low-density lipoprotein cholesterol (LDL-C) ($p<0.05$), high-density lipoprotein cholesterol (HDL-C) ($p<0.05$). Mean age, body mass index (BMI) and waist circumference of subjects were 60.80 (12.12) years; 72.93 (5.84)kg/m(2) and 22.63 (2.95) cm. Hs-CRP levels were positively correlated with BMI, HDL-C. No relationship was seen between Hs-CRP levels and systolic blood pressure (SBP), FBS level, HbAlc, Cholesterol, TGandLDL-C. Some cardiovascular risk factors (including gender, age, smoking, obesity, dyslipidemia and hypertension) did not show correlation with serum hs-CRP levels, while presence of proteinuria showed. Participants with cholesterol target levels had the statistically significant difference with hs-CRP concentration. The association between hs-CRP and high cardiovascular risk is unlikely to be causal, but hs-CRP might be a predictor for incidence of CVD in diabetic patients with comorbid obesity.

Key words: Hs-CRP; diabetes mellitus; CVD, lipid profile; chronic inflammation

INTRODUCTION

Diabetes, a major lifestyle disorder, has become a global burden, and the prevalence in adolescents and young adults is dramatically increasing (World Health Organization, 2016). Furthermore, evidence is accumulating that young-onset type 2 diabetes mellitus (T2DM) has a more aggressive disease phenotype, leading to premature development of complications, with adverse effects on quality of life and unfavorable effects on long-term outcomes, raising the possibility of a future public health catastrophe (Lascar et al., 2018). Cardiovascular disease (CVD) remains the leading cause of mortality in people with diabetes mellitus (DM), yet a significant proportion of the disease burden cannot be accounted for by conventional cardiovascular risk factors. Moreover, in people with diabetes, the cell types which maintain integrity of the vascular wall in the macrocirculation are more prone to damage, which are evident in the pre-diabetic and pre-hypertensive stages, raising the possibility of a vascular pathology (Strain and Paldanius, 2018). Currently, the chronic systemic inflammation as a common pathogenetic link between DM and cardiovascular disease (CVD) appears to be firmly established (Nguyen et al., 2016; Diabetes Control and Complications, 2016; Ilyas et al., 2017). High-sensitivity C-reactive protein (hs-CRP) appears to contribute to the identification of people at risk of developing CVD; current knowledge, suggests that the CRP concentration might reflect the vulnerability of the atheromatous lesion and the likelihood of a plaque to rupture however, the evaluation of hs-CRP has not yet been widely recommended in guidelines (Rashad et al., 2018; Sparkes et al., 2016). Result from the study may add new evidence of the diagnostic value of hs-CRP as CVD predictor in patients withDM.

MATERIALS AND METHODS

This study was a hospital-based cross-sectional study conducted at 175 Military Hospital from April 2018 to March 2019 and included a total of 118 subjects between the ages of 18 and 65. Study participants were recruited using a random sampling method based on the selection criteria, which included presence or TDM2 based by the standards of American Diabetes Association in 2014. Individuals with known stroke, cancer and decompensated chronic diseases were excluded from this study. Pregnant and lactating women and individuals who were taking drugs that affect hs-CRP levels were also excluded. Informed written consent was obtained from all subjects. The study was approved by the institutional review boards and independent ethics committee.

Date of diabetes diagnosis, age, sex, height, weight, and use of cardiac medications (anticoagulants, ace inhibitors and statins) were abstracted from the medical records at each study visit. Body mass index (BMI, kg/m2) was computed from height and weight measurements, and baseline diabetes duration was calculated based on date of diagnosis. HbA1c was assessed at baseline and at the end of the study

using a laboratory assay standardized to the Diabetes Control and Complications Trial. Serum concentrations of triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were assessed. Systolic and diastolic blood pressure (SBP and DBP) were abstracted from medical records at each visit. Patients examined in this study were categorized and assessed based on the classification of chronic kidney disease(Sparkes et al., 2016).

The collected data were analyzed statistically to determine the significance of different parameters by the SPSS program (v. 14.0). Normal distribution of variables was assessed by Kolmogorov–Smirnov test. The values among groups are compared using one-way ANOVA. Nonparametric Mann–Whitney tests was used for quantity variables that were not normally distributed. A P-value <0.05 was considered as statistically significant. Regression analysis was used to study association among parameters.

RESULTS

Baseline characteristics of the study participants

Baseline demographic characteristics for study participants are shown in Table 1. There were no differences in age and gender between studied subjects. Mean age of the participants was 60.8 years (SD: 12.1) in subjects. At baseline, more than a half of participants were confirmed by presence of several modified cardiovascular risk factors (physical inactivity, overweight and obesity, hypertension, dyslipidemia). However, the mean body mass index (BMI) and waist circumference (WC) value were not elevated.

Table 1. Baseline demographic and diet characteristics of studied patients with type 2 diabetes

Parameter		p-Value
Age (years) male female	 57,77± 13,71 63,26 ± 10,1	 >0,05
Age groups ≤ 40 40-50 50-60 60-70 > 70	 6(5,1) 18(15,3) 36(30,5) 31(26,3) 27(22,9)	
Gender Women Men	 53 (44,9) 65 (55,1)	

Average BMI (kg/m^2) male female general	 22,17 ± 2,71 23,01 ± 3,11 22,63 ± 2,95	 >0,05
Waist circumference (cm) male female general	 73,47 ± 6,28 72,48 ± 5,46 72,93 ± 5,84	 >0,05
Smoke	13(11)	
heavy drinking	4(3,4)	
Little physical activity	78(66,1)	
Overweight and obesity (BMI>23)	54(45,8)	
Hypertension	80(67,8)	
Dyslipidemia	87(73,7)	

Data are expressed as mean ± SD, median and interquartile range, or percentage of frequency [%], as appropriate.

The studied group was characterized by hyperglycemia and elevated glycated hemoglobin: fasting serum glucose level was 11,35 mmol/l (SD: 6,15) and HbA1c was 8,07 % (SD:2,40). The corresponding mean time of diabetic history was 3,12 years (SD: 2,29).

Among the 118 patients with T2DM, the prevalence of microalbuminuria and macroalbiminuria were 5.22 % and 7, 83 % respectively.

Mean values of lipid profile parameters did not fit treatment goals recommended by 2019 ESC/EAS Guidelines for the management of dyslipidaemias: (Mach et al., 2020) (Table 2).

Table 2. Baseline characteristics of lipids profile of studied patients with type2 diabetes

Index	Min – Max	Mean	Compare with good control value	One sample T-test
Cholesterol (mmol/l)	1,3 – 10,24	5,07 ± 1,44	< 4,5	>0,05
Triglyceride (mmol/l)	0,52 – 12,87	2,64 ± 2,07	< 1,5	<0,05
LDL-C (mmol/l)	0,15 – 6,44	2,97 ± 1,08	< 2,5	<0,05
HDL-C (mmol/l)	0,22 – 4,54	1,28 ± 0,64	> 1,1	<0,05

Data are expressed as mean ± SD, median and interquartile range.

In patients with T2DM the significant increase of hs-CRP was revealed (Figure 1): mean hs-CRP value was 7,66 mg/L (SD:18,98) ($p<0,05$).

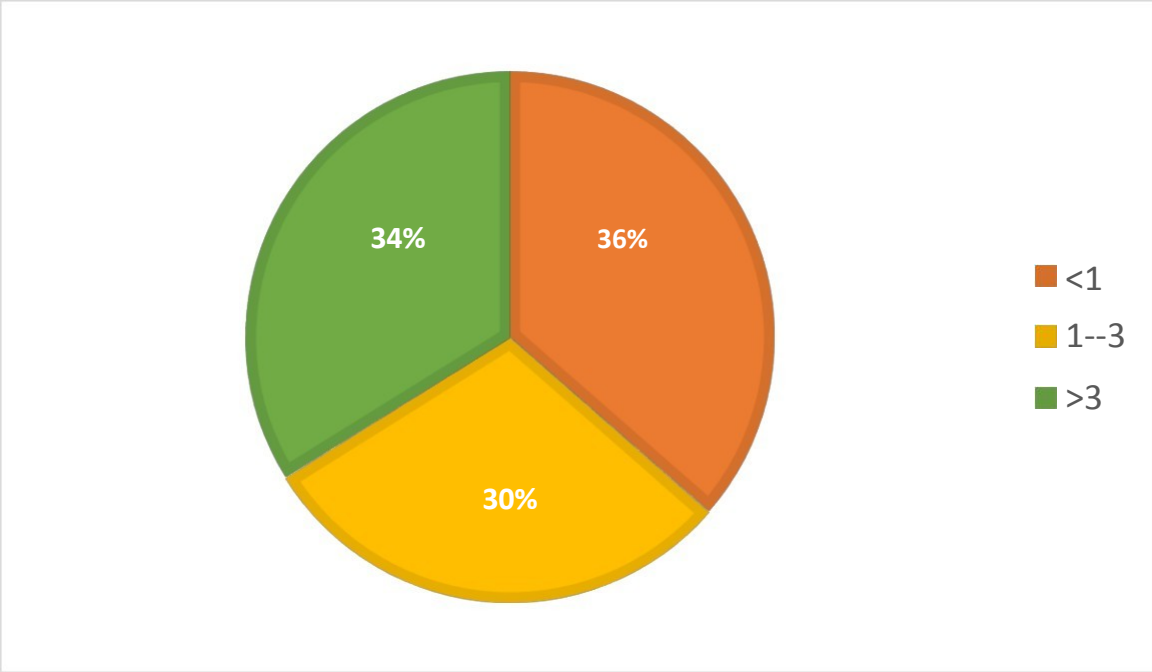

Figure 1. Rate of cardiovascular risk stratification by hs-CRP concentration

Age in years was positively correlated with hs-CRP levels (= 0.2816, < 0.01), while diabetes duration in years was not (= −0.26, > 0.05) (Figure 2).

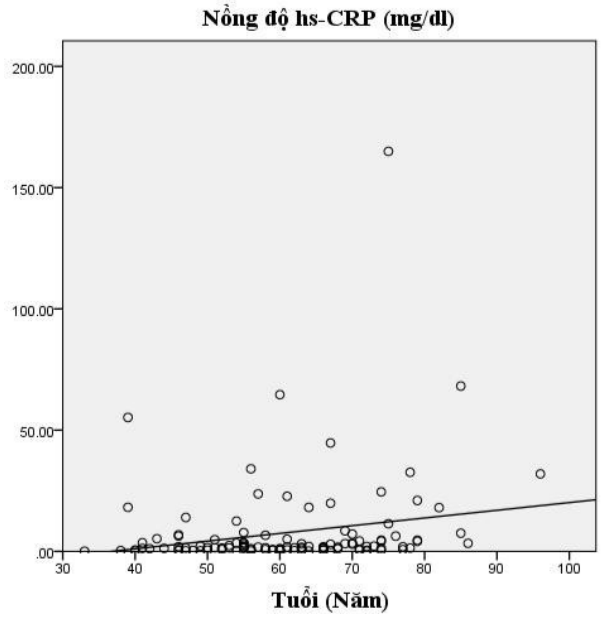

Figure 2. Correlation between hs-CRP and age

No significant association were observed between hs-CRP level and such risk factors as SBP, FBS, HbALC, TC, TG, LDL-C. However, correlation between hs-CRP and BMI (Figure 3), HDL-C (Figure 4) were found: (= 0.233, < 0.05; = 0.29, < 0.01), respectively.

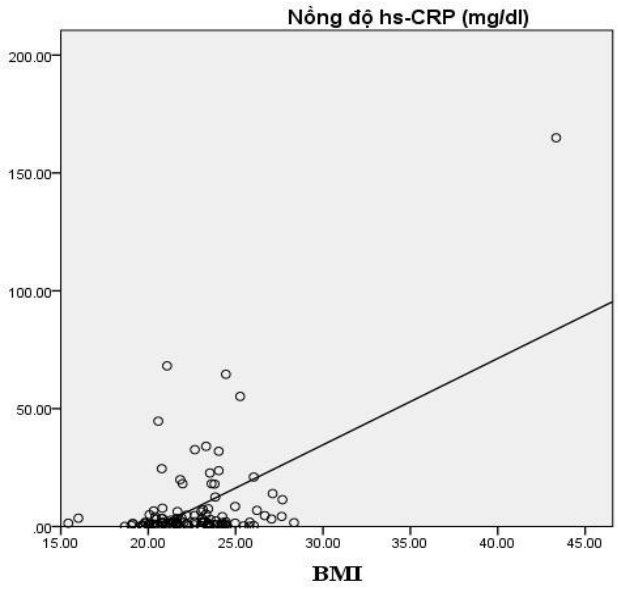

Figure 3. Correlation between hs-CRP and BMI

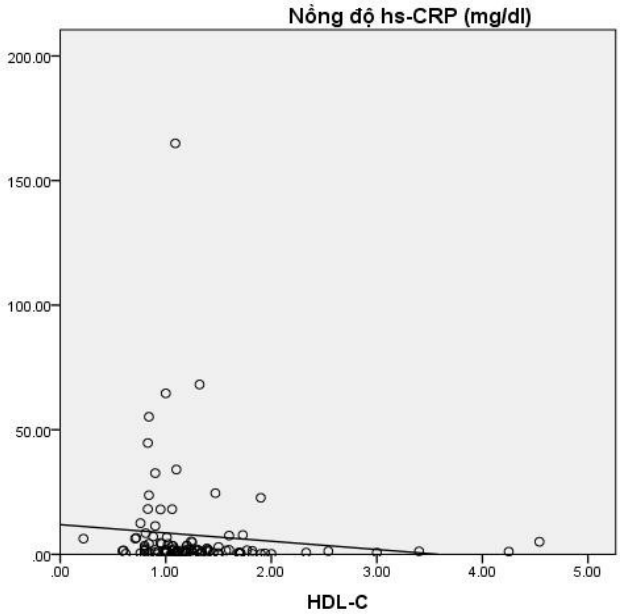

Figure 4. Correlation between hs-CRP and HDL-C

The results of hs-CRP levels depending on diabetes duration in patients with T2DM are shown in Table 3.

Table 3. Average serum hs-CRP concentration depending on diabetes duration

Time (years)	N	
< 1	25	2,15 ± 1,67
1 – 5	79	7,89 ± 21,10
> 5	14	10,05 ± 16,84
p (Anova)	> 0,05	

In subjects with T2DM no significant differences in hs-CRP levels determined by age and gender were found (Table 4). Moreover, no positive association between hs-CRP concentration and following cardiovascular risks: smoking, overweight/obesity, dyslipidemia, hypertension, proteinuria was shown (Table 5).

Table 4. The average plasma concentration of hs-CRP determined by age and gender

Risk factors		hs-CRP (mg/L)	P
Age (years old)	> 60	5,31 ± 11,85	> 0,05
	< 60	10,10 ± 24,10	
Sex	Male	7,26 ± 13,68	> 0,05
	Female	80 ± 22,5	

Table 5. Average plasma hs-CRP concentration with some modified cardiovascular risk factors

Risk factors		hs-CRP (mg/L)	P
Smoking	Yes	6,64 ± 8,09	> 0,05
	No	7,79±19,93	
Overweight and obesity	Yes	10,87 ± 25,06	> 0,05
	No	5,02 ± 11,22	
dyslipidemia	Yes	6,73 ± 19,39	> 0,05
	No	9,55 ± 18,98	
Hypertension	Yes	9,77 ± 22,54	> 0,05
	No	3,22 ± 4,89	
Proteinuria	Yes	12,08 ± 19,1	> 0,05
	No	6,90 ± 19,22	

In patients with T2DM no significant differences in number of cardiovascular risk factors to hs-CRP plasma levels were discovered (Table 6). Moreover, there was no significant correlation between hs-CRP concentration and most known cardiovascular risk factors except proteinuria (CI 95% 1.86 – 25.10) (Table 7).

Table 6. Relationship to hs-CRP plasma levels with a combination of risk factors

Number of risk factors	N	Ratio (%)	hs-CRP
1	14	11,86	2,61 ± 4,68

2	35	29,66	5,20 ± 12,77
3	43	36,44	8,88 ± 14,81
4	25	21,18	12,16 ± 32,85
p (Anova)	>0,05		

Cardiovascular risk factors include: smoking, low physical activity, overweight, obesity, dyslipidemia, hypertension

Table 7. Logistic multivariate regression correlation between hs-CRP and some cardiovascular risk factors

Risk factor	β	p	OR	CI 95%
Age ≥ 60	0,612	>0,05	1,844	0,756 – 4,495
Male	0,096	>0,05	1,101	0,412 – 2,943
Smoke	0,815	>0,05	2,259	0,455 – 11,206
Overweight and obesity	0,636	>0,05	1,888	0,766 – 4,658
Dyslipidemia	-0,13	>0,05	0,878	0,298 – 2,589
Hypertension	-0,526	>0,05	0,591	0,224 – 1,564
Proteinuria (+)	1,924	<0,05	6,849	1,869 – 25,106

According to the data of the study, high hs-CRP concentration (>3mg/L) was negatively associated with FBS levels (CI 95% 0,69-4,04) and HbA1c (CI 95% 0.64-3.47).

There was no significant difference among hs-CRP for mean target FBS levels (p>0.05) (Table 8), HbA1c levels (p>0.05) (Table 9), LDL-C (Table 10) and HDL-C (Table 11) levels using ANOVA. Though, evident difference between hs-CRP levels and target TC levels (Table 12) in patients with T2DM was observed (p>0.05).

Table 8. Relation between hs-CRP levels with fasting blood sugar level reached target in the studied patients

hs-CRP (mg/L) / fasting blood sugar level	Mean (± SD)	P (Anova)
Good (n = 21)	3,2 ± 5,55	>0,05
Permissive (n = 13)	9,24 ± 19,6	
Least (n = 80)	8,79 ± 21,42	

Table 9. Relation between hs-CRP concentration to reached target HbA1c in the studied patients

hs-CRP (mg/L) / Level HbA_1c	Mean (± SD)	P (Anova)
Good (n = 36)	5,25 ± 11,95	>0,05
Permissive (n = 24)	13,35 ± 35,28	

Least (n = 52)	6,8 ± 11,88	

Table 10. Relation between hs-CRP levels to reached targets LDL-c in the studied patients

hs-CRP(mgL) / Level LDL-C	Mean (± SD)	P (Anova)
Good (n = 30)	12,21 ± 31,23	>0,05
Permissive (n = 37)	6,82 ± 15,73	
Least (n = 37)	4,73 ± 8,72	

Table 11. Relation between hs-CRP levels to reached target HDL-c

hs-CRP(mg/L) / Level HDL-C	Mean (± SD)	P (Anova)
Good (n = 52)	3,80 ± 10,19	>0,05
Permissive (n = 31)	12,53 ± 31,44	
Least (n = 21)	9,89 ± 14,71	

Table 12. Relation between hs-CRP levels and reached target cholesterol

hs-CRP(mg/L) / Level Cholesterol	Mean (± SD)	P (Anova)
Good (n = 37)	4,03 ± 7,77	<0,05
Permissive (n = 25)	4,57 ± 7,12	
Least (n = 53)	14,95 ± 31,03	

DISCUSSION

T2DM, a highly prevalent condition, is heterogeneous with regard to its impact on cardiovascular disease risk, primarily, because of common pathogenetic link, chronic low-grade inflammation (Nguyen et al., 2018). Hs CRP levels have received widespread attention because of a multitude of prospective studies that have shown that is one of the most known sensitive marker of inflammatory process. In this study of diagnostic value of serum CRP as biomarker of cardiovascular risk in type 2 diabetes evaluation, we found that hs-CRP concentration were higher in diabetic patients as compared to healthy patients. Similar reports were published by some researchers (Ebrahimi et al., 2016; Tutuncu et al., 2016; Chuengsamarn et al., 2017), whereas some studies failed to observe this difference among patients with DM and control subjects (Retnakaran, 29017). Ohkumaet al. (2017) found a direct correlation between serum levels of hs-CRP and diabetes duration, whereas our data indicate that diabetes duration does not influence serum hs-CRP.

Carbone et al. (2019) reported the relationship between hs-CRP and SBP in metabolic syndrome, while we revealed negative association among them. Previous studies have reported that FBG, LDL-C, WC and gender are independently associated with serum hs-CRP concentrations (Wang et al., 2016; Zhang et al., 2018; Syauqy et

al., 2018; Parrinello et al., 2015; Nishide et al., 2015; Siddiqui et al., 2019). However, we did not find any significant difference among hs-CRP levels and FBS, HbALC, TC, TG, LDL-C. It has been suggested that this association may be noncausal. As reported, there were no evident association between hs-CRP concentration and history of smoking, whereas Siddiqui et al. (2019) showed that chronic history of smoking patients had significantly increased hs-CRP level. In the present study the hs-CRP values are significantly higher in diabetics who had dyslipidemia signs compared to controls($p<0.05$).

Singh et al. (2019) and Wang et al. (2016) projected similar results in studies done from many parts of the world. Its known that diabetic kidney disease develops in half of genetically predisposed patients with T2DM. Early diagnosis of kidney damage and nephroprotective treatment are the ways of preventing the disease progression (Żyłka et al., 2018). The combination of T2DM and chronic kidney disease not only increases the risk of end stage renal disease but also of cardiovascular events and all-cause mortality, with cardiovascular complications being the main cause of death in these patients. Recent evidence suggests that CRP plays a major role in the pathophysiologic processes and the course of renal injury in patients with T2DM. Similar results were revealed in our study, significant correlation between hs-CRP concentration and proteinuria levels in patients with T2DM (CI 95% 1.86 − 25.10).

According to the criteria of ACCF/AHA (American Diabetes Association, 2016), if CRP concentrations >3 mg/L was with "high risk", no associations with FBS levels (CI 95% 0,69-4,04) and HbA1c (CI 95% 0.64-3.47) were found. There was no significant difference among hs-CRP for mean target FBS levels ($p>0.05$), HbA1c levels ($p>0.05$), LDL-C and HDL-C levels using ANOVA. Studies have shown that intensive LDL-lowering therapy results in a significant reduction in cardiovascular disease risk and improved outcomes (Kumar et al., 2018; Chianeh et al., 2016). Though, no significant difference among hs-CRP concentrations for mean target LDL-C and HDL-C levels were observed in ourstudy.

CONCLUSION

In concussion, results obtained in this study show that association between hs-CRP and high cardiovascular risk is unlikely to be causal.

The current study focuses on the importance of hs-CRP in cardiovascular risk stratification in diabetic patients with comorbid obesity and dyslipidemia.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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