SERUM HIGH SENSITIVITY C-REACTIVE PROTEIN AND NON-HIGH DENSITY LIPOPROTEIN CHOLESTEROL LEVELS AS CARDIOVASCULAR RISK FACTORS IN PATIENTS WITH TYPE 2 DIABETES

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ABSTRACT: Type 2 diabetes mellitus is associated with increased cardiovascular risk. Two markers of cardiovascular risk assessment are high sensitivity C- reactive protein (hs-CRP) and non-high density lipoprotein cholesterol (non-HDL cholesterol). This case-control study attempted to compare levels of hs-CRP and non-HDL cholesterol between type 2 diabetic patients and non-diabetic individuals and investigate patients at high risk for cardiovascular disease, and analyze the association of hs-CRP levels with other cardiovascular risk factor in type 2 diabetes. A total of 123 type 2 diabetic patients [35 males and 88 females; median and (interquartile range) age of 57.0 (51.8-64.2) years; mean ± SE body mass index of 26.4 ± 0.4 kg/m^2, disease duration 5.7 ± 0.5 years; and median and (interquartile range) hemoglobin A1C of 7.8 (6.7-9.4)%] and 92 non-diabetics [27 males and 65 females; median (interquartile range) age of 51.0 (45.0-59.0) years; mean ± SE body mass index of 24.8 ± 0.3 kg/m^2] were studied. All subjects were interviewed by using the questionnaires included about lifestyle and medication used. Physical examinations and an over-night fasting blood collection were performed. Glucose, hemoglobin A1c, lipid profile, and hs-CRP levels were analyzed. The results indicate that serum levels of hs-CRP and non-HDL cholesterol in patients with type 2 diabetes were significantly higher than those in non-diabetics. Stratification into cardiovascular risk groups according to hs-CRP levels in combination with non-HDL cholesterol levels revealed that 72.4 percent of patients had high risk, 27.6 percent had intermediate risk, but none had low risk. However, an increased risk for CVD resulting in elevated hs-CRP (> 3 mg/l) of type 2 diabetes was significantly different from non-diabetes (odds ratio 1.95, 95% Confidence Interval 1.06-3.59, p-value 0.04). In type 2 DM, hs-CRP levels were significantly positive correlated with body mass index and fasting plasma glucose, inversely correlated with duration of diabetes. There were no significant correlation between hs-CRP and gender, age, waist circumference, blood pressure, lipid levels and hemoglobin A1C. In conclusion indicates that serum hs-CRP and non-HDL cholesterol levels in patient with type 2 diabetes are significantly higher than those in non-diabetics. The measurement of serum hs-CRP level as an adjunct to non-HDL cholesterol level may be useful for identifying cardiovascular risk in type 2 diabetes and should be evaluated in further prospective study.

Keywords: high sensitivity C-reactive protein, non-HDL cholesterol, cardiovascular risk factor, type 2 diabetes

INTRODUCTION

Type 2 diabetes mellitus is an important public health problem worldwide because of its high prevalence and complications [1]. Cardiovascular disease (CVD), are the most prevalent cause of death in these patients [2]. Dyslipidemia, characterized by decreased levels of high density lipoprotein cholesterol (HDL-C), elevated levels of low density lipoprotein cholesterol (LDL-C) and triglyceride (TG), is very common in type 2 diabetes with vascular complication [3]. The estimation of LDL-C level becomes progressively less accurate as plasma triglyceride concentration increases. The measurement of non-high density lipoprotein cholesterol (non-HDL cholesterol), which derived from the difference of total cholesterol and HDL-C, is more potential for identifying dyslipoproteinemias, and for CVD risk assessment than LDL-C [4-6]. In addition, non-HDL cholesterol was also recommended as a secondary target for therapy in patients with triglyceride (TG) more than 200 mg/dl, especially those with diabetes and metabolic syndrome [7].

Furthermore, many evidence and findings from clinical and population studies suggest that an inflammation is important in atherosclerosis, process in which fatty deposits build up in the inner lining of arteries, which causes for CVD development. High sensitivity C reactive protein

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(hs-CRP) is one of the acute phase proteins that increase during systemic inflammation and can be used as biomarker of inflammation process. Level of hs-CRP is useful for a CVD risk predictor in general population and diabetes mellitus [8-10]. With regard to present medication use, hs-CRP level is also used for stratification of CVD risk [11]. Therefore, the aims of this study are to compare levels of hs-CRP and non-HDL cholesterol between patients with type 2 diabetes and non-diabetic controls, and indicate patients at high risk for CVD, and investigate the association between serum hs-CRP and other traditional CVD risk factors in type 2 DM.

MATERIALS AND METHODS

A total of 123 type 2 diabetic patients without vascular complications who attended the Bangkhayeang Community Medical Unit, Pathumthani Province and 92 non-diabetics who were apparently healthy and had normal blood biochemical testing were recruited in this case-control study that was conducted between June and July 2009. Each participant was given a questionnaire which included information concerning lifestyle behavior (smoking, alcohol consumption, and exercise), past medical history and present medical used by an interview. All participants underwent complete physical examination including body weight, height, waist circumference, and blood pressure, Body mass index was calculated as weight in kilograms divided by height in squared meters. An over-night fasting venous blood sample was collected in the early morning and immediately transported on ice to the laboratory. Diagnosis of diabetes was established if the patient had: 1) prior diagnosis of type 2 diabetes mellitus; 2) fasting plasma glucose ≥ 126 mg/dl; and/or if taking oral hypoglycemic agents [12]. Hypertension was defined as blood pressure of 140/90 mmHg or higher and/or use of antihypertensive drug [13]. Individual having a markedly elevated hs-CRP (greater than 10 mg/l), diabetic patients treated with insulin, pregnant women, postmenopausal women receiving hormone replacement or having contraceptives were excluded. All participants gave their informed consents before participating in this study.

Laboratory analyses

Plasma and serum were separated by centrifugation at 3,000 r.p.m. for 10 minutes. Hemoglobin A1c in EDTA blood was measured by high performance liquid chromatography method on the HLC 723G7 (Tosoh corporation, Chuo-ku, Tokyo). Plasma glucose was determined by hexokinase method [14]. Serum total cholesterol and triglyceride were measured by enzymatic methods [15, 16] Serum HDL-C were measured by direct homogeneous assay [17]. LDL-C were calculated from the Freidewald's equation [18]. Non-HDL cholesterol levels were calculated from the difference between total cholesterol and HDL-C. High sensitivity CRP levels were measured using an particle enhanced immunoturbidimetric method. All reagents, calibrators and control materials used were the products of DiaSys Diagnostic Systems GmbH, Holzheim, Germany and the tests were preformed on an automatic analyzer (Merck, MEGA, Germany). The intra-and inter-assay coefficient variations for hs-CRP were 5.3%, and 3.6% at concentration of 0.91 and 1.80 mg/l, respectively. The inter-assay CVs for other tests were less than 5%.

Statistical analyses

The statistical analyses were performed by using SPSS version 16. (Thailand) for Window. The data were expressed and mean ± S.E. (standard error of mean) for normal distribution variables and as median (interquartile range) for non-normal distribution variables, and percentages for discrete variables. Where appropriate, data were log-transformed to achieve a normal distribution. The difference of the means, medians, and proportions between the study group were tested by unpaired *t* test, median test, and $\underline{K^2}$ test, respectively. The frequencies for increased hs-CRP levels (> 3 mg/l) among patients and controls were compared by the odd ratio. Pearson and Spearman correlation were used to determine the association between hs-CRP and other variables. A p-value less than 0.05 was considered statistically significant.

RESULTS

The characteristics of the study group are given in Table 1. There were no significant differences between gender and HDL-C among the two groups. There were significant differences between patients and controls with respect to age, waist circumference, BMI, blood pressure, glucose, HbA1c, TC, TG and LDL-C.

High sensitivity C reactive protein and non-HDL cholesterol levels were significantly higher in the patients with type 2 DM when compared to non-diabetic group (mean ± SE: 2.83 ± 0.23 mg/l vs 2.00 ± 0.21 mg/l, p = 0.004 and mean ± SE: 185.2 ± 3.5 mg/dl vs 159.0 ± 3.2 mg/dl, p = 0.048), respectively as depicted in Figure 1.

Table 2 showed the stratification of the patients into the cardiovascular risk groups by using hs-CRP in combination with non-HDL cholesterol. According the CDC-AHA and NCEP ATP III guidelines, the cardiovascular risk in diabetic patients was stratificed [11, 12]. The results revealed that 36.6% and 35.8% has high risk (high hs-CRP + high non-HDL cholesterol and intermediate hs-CRP + high non-HDL cholesterol), respectively. Of 0.8% and 26.8% has intermediate risk (intermediate hs-CRP + low non-HDL cholesterol and low hs-CRP + high non-HDL cholesterol), respectively. None has low risk (low hs-CRP + low non-HDL cholesterol).

Table 1 Clinical and metabolic characteristics of subjects.

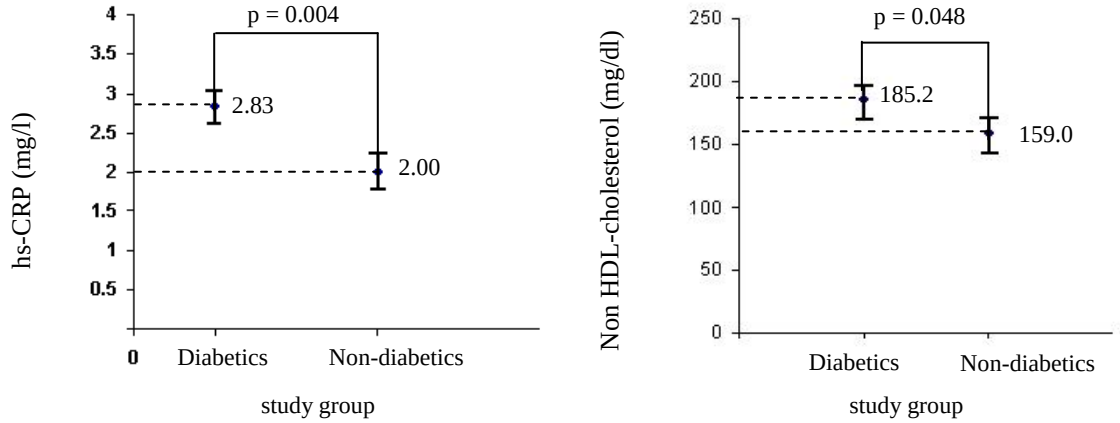
Variables	Diabetics	Non-diabetics	p-value
N	123	92	
Gender (male/female)	35/88	27/65	0.800
Age* (years)	57.0 (51.8-64.2)	51.0 (45.0-59.0)	< 0.001
Waist circumference* (inches)	35.0 (32.9-37.1)	33.0 (31.0-34.0)	< 0.001
BMI**(kg/m^2)	26.4 ± 0.4	24.8 ± 0.3	0.005
Systolic BP* (mm Hg)	130 (122-142)	120 (112-124)	< 0.001
Diastolic BP* (mm Hg)	80 (74-90)	77 (70-82)	0.021
Duration of diabetes** (year)	5.7 ± 0.5		
Hypertension (%)	28.4	2.4	
Smoking (%)	9.8	9.8	1.000
Alcohol consumption (%)	10.6	16.3	0.995
Exercise (%)	57.7	59.8	0.542
Glucose* (mg/dl)	137.0 (112.3-155.3)	93.0 (86.0-99.0)	< 0.001
HbA1c* (%)	7.8 (6.7-9.4)	6.1 (5.8-6.4)	< 0.001
Total cholesterol* (mg/dl)	239.5 (212.5-272.0)	226.0 (196.0-240.0)	0.001
Triglyceride** (mg/dl)	207.9 ± 12.2	118.3 ± 5.9	< 0.001
LDL cholesterol** (mg/dl)	147.8 ± 3.2	135.4 ± 1.2	0.035
HDL cholesterol** (mg/dl)	55.7 ± 1.0	60.9 ± 1.2	0.384

* Data are presented as median (interquartile range)
** Data are presented as mean ± SE
p-value significant at < 0.05

Table 2 CVD risk stratification in diabetics, using hs-CRP in combination with non-HDL cholesterol.

Cardiovascular Risk		number of diabetics	percentage
High Risk			
High hs-CRP (>3 mg/l) +	High non - HDL cholesterol (>100 mg/dl)	45	36.6
or	Low non - HDL cholesterol (<100 mg/dl)	0	0.0
Intermediate hs-CRP (1 -3 mg/l) +	High non - HDL cholesterol (>100 mg/dl)	44	35.8
Intermediate Risk			
Intermediate hs-CRP (1 -3 mg/l) +	Low non - HDL cholesterol (<100 mg/dl)	1	0.8
Low hs-CRP (< 1 mg/l) +	High non - HDL cholesterol (>100 mg/dl)	33	26.8
Low Risk			
Low hs-CRP (< 1 mg/l) +	Low non - HDL cholesterol (<100 mg/dl)	0	0.00

Figure 1 High-sensitivity C reactive protein and Non-HDL cholesterol levels of the study group. The data are shown as the mean ± SE.



Only one diabetic pateint had non-HDL cholesterol within 100 mg/dl. When compared between the two studied groups, the odds ratio for the prediction of CVD risk by using hs-CRP level > 3 mg/l was 1.95 (95% confidence interval 1.06–3.59) and by using of non-HDL cholesterol >100 mg/dl was 4.11 (95% confidence interval 0.42 – 40.19), as shown in Table 3. Among diabetic patients, the hs-CRP levels were significantly correlated positively with BMI (r = 0.255, p = 0.004) and glucose (r = 0.216,

Table 3 The odds ratio of CVD risks among the studied groups.

Parameters	Type 2 diabetes mellitus n =123	Non-diabetes mellitus n = 92	odds ratio (95% confidence interval)
hs-CRP > 3.0 mg/l	45	21	1.95 (1.06 – 3.59)*
hs-CRP ≤ 3.0 mg/l	78	71	-
Non-HDL-C > 100 mg/dl	122	89	4.11 (0.42 – 40.19)
Non-HDL-C ≤ 100 mg/dl	1	3	-

* statistically significant differences (p-value < 0.05).

Table 4 Correlation between serum hs-CRP levels and other cardiovascular risk factors in type 2 diabetes mellitus.

Variables	High sensitivity C reactive protein	
	Correlation coefficients (r)	p-value
Gender	-0.057	0.529
Age	-0.035	0.697
Waist circumference	0.122	0.178
BMI	0.255	0.004
Systolic BP	-0.053	0.563
Diastolic BP	-0.019	0.837
Duration of diabetes	-0.202	0.026
Smoking	0.019	0.832
Alcohol consumption	-0.069	0.451
Exercise	-0.011	0.220
Glucose	0.216	0.016
HbA1c	0.137	0.133
Total cholesterol	0.109	0.229
Triglyceride	0.059	0.513
LDL cholesterol	0.046	0.614
HDL cholesterol	-0.020	0.830
Non-HDL cholesterol	0.123	0.174

p = 0.016) and correlated inversely with duration of diabetes (r = -0.202, p = 0.026). But were not correlated significantly with gender, age, waist circumference, systolic blood pressure and diastolic blood pressure and all lipid levels as shown in Table 4. (r = -0.057, p = 0.529; r = -0.035, p = 0.697; r = 0.122, p = 0.178; r = 0.053, p = 0.563; r = -0.019, p = 0.837)

DISCUSSTION

Chronic low-grade inflammation occurs in type 2 DM as well as those with CVD [19, 20]. In this study, patients have higher hs-CRP levels than those of controls. This main result is in line with previous study [21]. In addition, recent study demonstrated that the mean hs-CRP level in 800 Indian population was 1.87 mg/dl and hs-CRP levels was significantly higher among the diabetic subjects with 4.8 mg/dl, for non-diabetics with 2.5 mg/dl that were higher than our results (2.83 mg/l and 2.00 mg/l, respectively) [22]. Besides this, Limal et al. reported that the type 2 diabetic subjects with high blood pressure had a more active inflammatory state with increased plasma hs-CRP levels than those patients with type 2 DM or normal subjects [23].

A possible mechanism, which type 2 DM may induce inflammation, has received much attention in the present time, particularly due to advanced glycation end products. It may activate macrophages and increase oxidative stress and interleukin-6 synthesis, resulting in the production of CRP [24]. The association of this inflammation which the progress of atherosclerosis in type 2 DM has not been confirmed. However, the bracial-ankle pulse wave velocity which is an index of atherosclerosis is to be reported higher in type 2 DM patients having hs-CRP levels of 3-10 mg/l than in those having hs-CRP less than 3.0 mg/l [25]. Non-HDL cholesterol levels in the type 2 DM group are also found to be increased. It is reasonable to state that the hepatic triglyceride rich lipoprotein (TGRLP) secretion is primarily regulated by insulin and hyperinsulinemia is usually noted in early state of diabetes mellitus (DM) which suggest that higher TGRLP can be found simultaneously [21]. In patients with coronary heart disease equivalent such as DM, non-HDL cholesterol remains an important target of therapy and an optional goal is less than 100 mg/dl [7].

With regard to the NCEP ATP III, hs-CRP is included among the emerging risk factors and non-HDL cholesterol is a secondary target for lipid lowering therapy. Moreover, the risk stratification using hs-CRP in comparison with non-HDL cholesterol reveals that 72.4% of our diabetic patients has high risk, 27.6% has intermediate risk but none has low risk for cardiovascular disease (Table 2). The CDC-AHA guidelines have also recommended that these group may benefit from measurement of hs-CRP with regard to their individual risk prediction. These results show that the atherosclerosis is more accelerated in these patients. In this study, patients with having hs-CRP

more than 10 mg/l are excluded because any recent illness, tissue injury, infection, or other general inflammation will raise the level of hs-CRP and give a falsely elevated estimate risk.

In addition, 28 percent of our patients has hypertension. The associations between hypertension and increased hs-CRP levels have been demonstrated [23, 26]. Chae et al. has explained that high blood pressure increases the risk of atherosclerosis by promoting inflammation activation of the arterial wall. Therefore; hypertension may result in an increased vascular oxidative stress and exert a pro-inflammatory influence on the arterial wall [27]. The clear mechanism by which high blood pressure leads to atherosclerosis remains unclear; however our finding suggests that individual with the two associated diseases had more active inflammatory state. Moreover, our diabetic patients are overweight (mean BMI ± SE; 26.4 ± 0.4 kg/m^2) [28]. There is an evidence that human adipose tissue expresses and releases the pro-inflammatory cytokine interleukin6, potentially inducing low-grade systemic inflammation in persons with excess body fat [29]. Our results suggest that an increased inflammation marker, dyslipidemia, high blood pressure, overweight and smoking in these diabetic patients will increase the CVD risk level.

In order to achieve the hs-CRP and non-HDL cholesterol goal, lifestyte changes (weight reduction, smoking cessation, and regular exercise) are recommended to be the initial approach of therapy [11]. Some pharmacological agents are reported to be effective. Statin may be intensified or combined with ezetimibe or niacin or fibrate or omega-3-fatty acid for lowering non-HDL cholesterol level [30]. Not only these lipid-lowering drugs but also the non-steroidal anti-inflammatory drugs (NSAIDs like aspirin, ibuprofen, and naproxen), anti-hypertensive agents, anti-diabetic agents and vitamin E can also reduce hs-CRP level [31-35].

Regarding the association of hs-CRP levels with other CVD risk factor in type 2 DM, hs-CRP levels correlate positively with BMI and glucose, and correlate inversely with duration of diabetes but do not correlate with gender, age, waist circumference, blood pressure, hemoglobin A1c and all lipid levels. These results agree with others [20, 36]. In contrast, the others have found that hs-CRP levels correlate both positively and inversely with non-HDL cholesterol [31]. In addition, the relation between hs-CRP and HbA1c has been shown in type 2 diabetes [35]. However, in the cohort study hs-CRP is reported to be the strongest predictor of death and cardiovascular death in type 2 DM after 5-year follow up with the relative risk of 3.7 and 5.4, respectively [37]. In addition, the type 2 diabetic patients with hs-CRP more than 3 mg/l have shown higher risk for CVD death than those with hs-CRP less than 3 mg/l [38]. Contrary to the findings of the Strong Heart Study that carry out in an American Indian population with a high prevalence of diabetes have shown that hs-CRP elevations are strongly related to the presence of cardiovascular disease among non-diabetic women but not among diabetics, irrespective of glycemic status. Thus, the predictive value of hs-CRP elevations may vary among subsets of population [39].

The potential limitations of our study merit careful consideration. First, this study is included only the attendant patients with type 2 diabetes from the specific community health center. So it does not represent all diabetics. Second, most of the patients are prior diagnosis of diabetes and they are receiving the hypoglycemic agents and/or lipid-lowering therapy and/or anti-hypertensive drugs. Therefore, it is difficult to investigate the association between hs-CRP and other risk factors without interference from therapy. However,our study indicates that hs-CRP and non-HDL cholesterol levels are significantly higher in patients with type 2 diabetes without vascular complications than those in non-diabetics.The determination of hs-CRP as an adjunct to non-HDL cholesterol may be useful in risk assessment for primary cardiovascular disease prevention in type 2 diabetes and further prospective studies are needed.

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