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Atherogenic Index and Female Gender are Independent Determents of Chronic Subclinical Inflammation in Subjects with Type 2 Diabetes Mellitus

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Abstract

Background: Chronic subclinical inflammatory poses additional risk of cardiovascular diseases in subjects with type 2 diabetes mellitus (T2DM) but its determinants in Bangladeshi population are not fully resolved. The aim of this study was to explore the relationship between marker of chronic subclinical inflammation and gender and atherogenic index (AI) in subjects with T2DM.

Methods: Two hundred and fifty-four subjects with T2DM were included. Demographic and anthropometric variables were estimated. Plasma glucose, serum lipid profile and high sensitivity-C reactive protein (hsCRP) were measured in fasting blood samples using standard methods. AI was calculated as log (concentration of triacylglycerol/high density lipoprotein cholesterol).

Results: The median and interquartile range of age was 51 (43-60) years. Of the total subjects, 47% was female and had higher hsCRP [3.1 (1.7-5.6) *vs* 1.6 (0.84-3.6) mg/L, p<0.0001] but lower AI [0.57 (0.39-0.77) *vs* 0.68 (0.51-0.84), p=0.0015] compared to male. Spearman rank correlation coefficient of hsCRP was significant for BMI (ρ=0.204, p=0.0011) and AI (ρ=0.147, p=0.0195). Logistic regression analysis showed significant positive association of AI (β=1.645, p=0.0078) and female gender (β=1.094, p=0.0002) with subclinical inflammation which remained significant (for AI, β=1.548, p=0.0152; for female gender, β=1.086, p=0.0003) on adjusting other confounders (hypertension, lipid lowering drugs).

Conclusions: Atherogenic index and female gender were found to be independent determinants of chronic subclinical inflammation.

Keywords: Atherogenic index; Chronic subclinical inflammation; C-reactive protein; hsCRP; Obesity; Type 2 diabetes mellitus; Female gender

Introduction

Chronic inflammations due to imbalance of redox status or between pro-inflammatory and anti-inflammatory cytokines are causally related to a wide range of chronic diseases including cancer, hypertension, diabetes mellitus [1]. It plays important role in the pathogenesis of diabetes mellitus (DM) and its complications possibly through its close relation with insulin resistance [2,3], oxidative stress [4], obesity and metabolic syndrome [5]. While obesity is mechanistically involved in chronic subclinical inflammation [5], other factors like physical activity [6], race, gender, socioeconomic status [7,8] and dietary nutritional factors [9] are also critically linked to chronic subclinical inflammation.

High sensitivity C-reactive protein (hsCRP), a proinflammatory cytokine is considered as a potential marker of systemic inflammation [1] and sensitive marker of chronic subclinical inflammation as well [1]. Chronic subclinical inflammation is most prevalent in Bangladeshi population [10], but its determinants are not fully resolved. In this study, we aimed to explore the relationship of two determinants of chronic subclinical inflammation: atherogenic index (AI) and gender with chronic subclinical inflammation as assessed by high-sensitivity C-reactive protein (hsCRP) in a group of type 2 diabetic subjects of Bangladeshi origin.

Methods

Total 254 subjects with type 2 diabetes mellitus according to WHO criteria were included in this cross-sectional study that was conducted in the department of clinical biochemistry, Bangladesh Institute of Health Sciences (BIHS) Hospital, Dhaka, Bangladesh during the period of January 2012 to June 2012. Purposive sampling technique was followed to include study subjects according to inclusion-exclusion criteria. Subjects with comorbid diseases (infection, stroke, myocardial infarction, major surgery, severe allergy, cancer, severe illness, liver abnormalities, chronic kidney disease (CKD), pregnancy, edema, oral contraceptive or anti-inflammatory drugs users and without diabetes mellitus were excluded. Anthropometric data, clinical history of the study subjects were recorded as described elsewhere [10]. Plasma glucose, lipid profiles, hsCRP concentrations were measured by standard methods described elsewhere [10]. Atherogenic index (AI) was calculated as log concentration (triacylglycerol/HDL cholesterol) [11]. hsCRP<1.0 mg/l, 1 mg/l to 3.0 mg/l and >3.0 mg/l were considered as low, medium and high hsCRP [12]. Statistical analysis was performed using MedCalc® statistical software. All data were expressed as median with interquartile range and percentage (%) as appropriate. Spearman rank correlation analysis was used to assess the relationship hsCRP with age, BMI, total cholesterol, HDL cholesterol, LDL cholesterol, triacylglycerol, AI, and plasma glucose. Association of hsCRP was

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analyzed by logistic regression considering hsCRP cutoff value of 3 mg/L and age, gender, body mass index, hypertension, AI, lipid lowering drugs, independent variables.

Results

Characteristics of the study subjects

Two hundred fifty-four subjects with type 2 DM (135 male and 119 female) were included. The median and interquartile ranges of age and BMI were 51 (43-60) years and 26.2 (23.5-28.4) kg/m^2 respectively. Of the total subjects, 91 (35.8%) had BMI >27.5 kg/m^2. Table 1 represents the characteristics of the study subjects. Sixty-three subjects (%) had total cholesterol above 200 mg/dl, 156 (%) had low HDL cholesterol (<35 mg/dl for male and <40 mg/dl for male), 128 (%) had TAG above 150 mg/dl and 138 (%) had LDL cholesterol above 100 mg/dl.

Comparison of variables between BMI and gender groups

Only hsCRP showed statistically significant difference between BMI groups (p<0.01). Obese subjects had significantly higher hsCRP compared to non-obese subjects. BMI, HDL cholesterol and hsCRP were significantly higher in female and AI was significantly lower in female compared to male (Table 2).

Relationship of hsCRP with measured variables

The Spearman rank correlation coefficients of hsCRP for age, BMI, total cholesterol, HDL cholesterol, LDL cholesterol, triacylglycerol, atherogenic index and fasting plasma glucose were presented in Table 3. hsCRP showed significant correlation with BMI (p<0.0001).

Variables	Number (%) or Median (Interquartile range)
Gender (Male/Female)	135 (53%)/119 (47%)
Age (years)	51 (43-60)
BMI kg/m^2	26.2 (23.5-28.4)
Fasting plasma glucose (mmol/L)	6.9 (5.8-8.8)
2 hours plasma glucose (mmol/L)	10.1 (8.3-13.2)
Total cholesterol (mg/dL)	171 (147-200)
HDL cholesterol (mg/dL)	35 (29-40)
LDL cholesterol (mg/dL)	104 (84-130)
TAG (mg/dL)	151 (107-219)
AI	0.65 (0.47-0.80)
hsCRP (mg/L)	2.24 (0.97-4.3)
Hypertension (%)	145 (56.9%)
Antilipidemic drugs (%)	151 (59.4%)
Smoker (%)	29 (11.4%)
BMI, Body mass index; TAG, Triacylglycerol; AI, Atherogenic index	

Table 1: Characteristics of the study subjects.

Logistic regression analysis

Logistic regression analyses considering hsCRP (cutoff value of 3 mg/L) as dependent variable and age, AI, gender, BMI as independent variable showed significant positive association of AI (β=1.645, p=0.0078) and female gender (β=1.094, p=0.0002) with high hsCRP which remained significant (for AI, β=1.548, p=0.0152; for female gender, β=1.086, p=0.0003) on adjusting other confounders (hypertension, lipid lowering drugs) (Table 4).

Discussion

High-sensitivity C-reactive protein (hsCRP) is a potent marker of subclinical chronic inflammation as well as better predictor of cardiovascular diseases (CVD) [13,14]. Considerable ethnic, socioeconomic, demographic, lifestyle and gender variation in hsCRP has been reported by several studies [7,8]. Dyslipidemia and gender have found to be associated with chronic subclinical inflammation in different population [7,8], however its contribution to chronic subclinical inflammation remains to be evaluated in Bangladeshi population. In this study, we aimed to explore the association of chronic subclinical inflammation with atherogenic index and gender in a group of type 2 diabetic subjects of Bangladeshi origin.

In this study, we observed a significant difference in hsCRP between obese and non-obese subjects and between male and female gender by group comparison. A positive relation between hsCRP and BMI has also been explored by Spearman rank correlation which disappeared in logistic regression analysis. Chronic subclinical inflammation showed significant positive association with female gender and atherogenic index (adjusted for age, BMI, hypertension and anti-lipidemic drugs).

In this population, lipid abnormality, particularly low HDL cholesterol has found to be significantly associated with hsCRP [10,15,16]. While Rehnuma et al. [16] and Ferdousi et al. [15] observed no significant association between subclinical inflammation and BMI in apparently healthy or hospital based middle-aged Bangladeshi population, Siddique et al. [10] found positive association of hsCRP with BMI in a large hospital based middle-aged population. In this study, positive trend of association between hsCRP and BMI was observed. Diabetes mellitus is a well-recognized inflammatory condition that was affirmed in previous studies in this population [17]. A graded relation of CRP and glycemic status in established type 2 diabetic subjects has previously been explored in Bangladeshi population [18]. Female subjects in most of the previous studies were found to have higher hsCRP or lower antioxidant status [10,15,18] and thus reflecting a positive association of subclinical inflammation with female gender

Variables	Non-obese	Obese	Male	Female
Age (years)	52 (44-60)	50 (42-60)^{ns}	52 (43-60)	50 (42-60)^{ns}
FPG (mmol/L)	6.8 (5.6-8.2)	6.9 (6.0-9.4)^{ns}	6.8 (5.7-8.2)	6.9 (5.8-9.3)^{ns}
2HPG (mmol/L)	10.1 (8.4-13.2)	9.9 (8.0-12.7)^{ns}	10.0 (8.2-13.2)	10.1 (8.3-13.0)^{ns}
T-Chol (mg/dL)	172 (149-205)	170 (142-196)^{ns}	171 (143-197)	174 (152-206)^{ns}
HDL-Chol (mg/dL)	35 (30-40)	36 (29-41)^{ns}	33 (27-38)	39 (33-41)***
LDL-Chol (mg/dL)	106 (87-132)	97 (76-122)^{ns}	105 (83-129)	104 (84-130)^{ns}
TAG (mg/dL)	150 (100-209)	157 (114-230)^{ns}	156 (116-227)	148 (99-200)^{ns}
AI	0.65 (0.47-0.81)	0.65 (0.47-0.78)^{ns}	0.68 (0.51-0.84)	0.57 (0.39-0.77)**
hsCRP (mg/L)	1.86 (0.85-3.99)	2.95 (1.24-5.56)*	1.55 (0.84-3.60)	3.08 (1.68-5.60)***
FPG, Fasting plasma glucose; 2HPG, Plasma glucose 2 hours after oral glucose load; T-Chol, Total cholesterol; HDL-Chol, High density lipoprotein cholesterol; LDL-Chol, Low density lipoprotein cholesterol; TAG, Triacylglycerol; AI, Atherogenic index; ns, Not significant; *, p<0.01; **, p<0.001; ***, p<0.0001.				

Table 2: Comparison of variables between obese and non-obese subjects and between male and female.

Variables	Correlation coefficient	p value
Age (years)	-0.064	0.3122
BMI (kg/m^2)	0.237	<0.0001
Total cholesterol (mg/dL)	0.028	0.6516
HDL cholesterol (mg/dL)	0.082	0.1906
LDL cholesterol (mg/dL)	0.011	0.8588
Triacylglycerol (mg/dL)	0.106	0.0914
Atherogenic index (AI)	0.121	0.0543
Fasting plasma glucose (mmol/L)	0.061	0.3964

Table 3: Correlation of hsCRP with anthropometric and biochemical variables.

Variables	Odds ratio	95% CI	Coefficient (β)	p value
Age	1.0033	0.9785 to 1.0288	0.003303	0.7963
Body mass index	1.0417	0.9733 to 1.1149	0.04085	0.2382
Hypertension (No)	0.5728	0.3164 to 1.037	-0.5573	0.0658
Lipid lowering drugs (No)	2.2027	1.2487 to 3.9008	0.7916	0.0064
Atherogenic index	4.6995	1.3466 to 16.4003	1.5475	0.0152
Gender (Female)	2.9614	1.6336 to 5.3684	1.0857	0.0003

Table 4: Association of hsCRP with AI and gender.

which was reaffirmed in this study. Apart from the major determinants, smoking [19], dietary fiber [20], non-alcoholic fatty liver [21] are found to be associated with chronic subclinical inflammation in Bangladeshi population.

From the findings of the present study in type 2 diabetic subjects and based on above discussion, chronic subclinical inflammation is likely to be associated with several factors and seems to be complex. Atherogenic index and female gender are thus to be considered as risk factors for chronic subclinical inflammation in type 2 diabetic subjects of Bangladeshi origin in addition to other potential risk factors. Thus, subjects with high atherogenic index and female gender may facilitate the diagnosis of subclinical chronic inflammation and prediction of cardiovascular diseases. Apart from biochemical factors, epigenetic variations in islets [22] or alteration of DNA methylation are required to be considered for risk prediction in type 2 diabetes mellitus. Recent genome-wide study in islets revealed that a number of type 2 diabetes mellitus (T2DM) associated genes increased the levels of DNA methylation during aging and some of these genes play a role in the insulin secretion and development of T2DM [23]. For instance, it has been found that ZNF518B gene locus is gaining of DNA methylation as individuals are getting older and the higher level of DNA methylation negative correlates with the expression of this gene. Interestingly, as ZNF518B also functions as a mediator of histone methyltransferases G9a and GLP [24] and G9a/GLP complex is essential for the maintenance of genomic imprinting [25], the ectopic expression of ZNF518B may also lead to the aberrant expression of imprinted genes, some of which are strongly associated with the occurrence of diabetes, such as PLAGL1 and HYMAI [26]. Therefore, apart from gender and atherogenic index (AI), it is also interesting to investigate the links between the blood-based epigenetic markers or the levels of epigenetic modifiers and type 2 diabetes mellitus.

Conclusion

Atherogenic index and female gender are independent determinants of chronic subclinical inflammation in middle-aged subjects with type 2 diabetes mellitus.

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