Effect of Obesity and Family History of Cardiovascular Diseases and Diabetes Mellitus on Levels of C-Reactive Protein in Young Male

Syed Najamuddin Farooq, Ammad Ahmed, Abdul Halim S Serafi, Saeed H Halawani, Muhammad Amir Mustafa, Muhammad Irfan Safi Rizvi

Abstract

Objective: Objective of the current study was to investigate the effect of obesity and positive family history of Cardiovascular Disease (CVD), Diabetes Mellitus (DM) on plasma C reactive protein (CRP) levels in apparently healthy young individuals.

Methods: Young male Saudi students were interviewed for their personal medical and family history of Cardiovascular Disease (CVD) and Diabetes Mellitus (DM). Anthropometric parameters, height, weight, waist and hip circumference were measured. In-addition they answered perceived stress scale(PSS-14) questionnaire; Finally, Plasma C-reactive protein level were examined in all participants.

Results: Results showed that majority of our participants are overweight with mean BMI 27.113 ± 0.343 Kg/m^2; but are non-stressed (24 ± 0.29). Around fifty four percent of participants have positive family history of Cardiovascular Disease (CVD), Diabetes Mellitus (DM). Average Plasma CRP level were (0.267 ± 0.016 mg/dl) with 26.75% of the participants in high-risk category. Moreover, participants that are overweight/obese and with positive family history of Cardiovascular Disease (CVD), Diabetes Mellitus (DM) showed Significantly (P<0.0001) higher levels of Plasma hs-CRP, compared to the normal weight and with negative family history. A significant correlation was also observed between hs-CRP and BMI and WC. However, stress scores were not significantly different among different groups.

Conclusion: Obesity particularly in association with positive family history of Cardiovascular Disease (CVD), Diabetes Mellitus (DM) or one of the two diseases is a strong predictor of low-grade systemic inflammation indicated by high plasma hs-CRP level.

Keywords: C-reactive protein; family history; cardiovascular; diabetes mellitus

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Introduction

Cardiovascular diseases (CVD), and diabetes mellitus (DM) are serious health threats and the leading causes of mortality and morbidity all over the world. According to WHO, CVD is responsible for 31% of all deaths[1]. However, various studies revealed that the prevalence of CVD is declining in the developed countries while accelerating in the developing areas of the world at an alarming rate. This difference was because of, better preventive strategy based on change in the life style, reduced smoking, control of other modifiable risk factors and adopting healthy diet, along with improved medical facilities in developed areas, compared to increasing urbanization, sedentary life style and scarcity of health facilities in the developing world[2].

Well recognized risk factor diabetes mellitus particularly type 2 diabetes is found to have a specific association with CVD. It is a known fact that diabetics have 2-4-fold increased risk of developing

[1,3,5,6]Department of Physiology,
Faculty of Medicine. Umm-al-Qura University
[2,4]Department of Haematology and Immunology,
Faculty of Medicine. Umm-al-Qura University

Correspondence: Dr. Ammad Ahmed
Department of Haematology and Immunology,
Faculty of Medicine, Umm-al-Qura University,
Email: aamanan@uqu.edu.sa
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CVD compared to non-diabetics and 65-70% of diabetics died because of CVD.

However, large number of CVD victims are apparently healthy and with none or few known risk factors. Further, it is established that, socio-economics, race and ethnicity are important factors that determines the prevalence and outcomes of CVD[3].

Inflammation is given due consideration because of its reported pathogenic contribution in the initiation and progression of atherosclerosis leading to CVD[4]. Diabetes on the other-hand is also found to be the result of a state of chronic, low-level inflammation[5]. An association has been observed between inflammatory markers, Interlukin-6(IL-6) and C reactive protein (CRP) with hyperglycaemia, insulin resistance and overt type 2 DM[6]. The inflammatory markers IL-6 and CRP are also known to predict CVD in healthy population[7]. In many patients, inflammation-mediated link between CVD and DM is reported to be the result of obesity central in particular[8]. Further, CRP is not only a predictor of CVD but is reported to be an important predictor for DM as well[8-9].

Additionally, CRP levels are found to strengthen the predictive rate of conventional factors like cholesterol and blood pressure in evaluating the risk for coronary events[9].

CRP as a subclinical marker of inflammation has following advantages over others: it has an independent predictive potential called high-sensitivity CRP (detecting CRP concentrations <5 mg/L).

Positive family history (FH) for chronic diseases including CVD and type2 DM is an important non-modifiable risk factor[10]. It is reported that, history of premature coronary artery disease (CAD) (before 55 years of age) in a first-degree relative increases 10-fold risk of the disease to other family members[10].

People with history of myocardial Infarction (MI) in first degree relatives represents higher levels of plasma CRP compared to subjects without such history. Family history has been poorly used as a tool in public health to evaluate health risk, initiate interventions and motivate behavioural changes although, it is an important screening tool for the early detection and prevention of chronic diseases like CVD and DM among apparently healthy population. According to WHO 2015, 42% of all deaths in Saudi Arabia are because of CVDs. In another study Jafree et al reported (5-6%) prevalence of CVD in KSA[11]. Therefore, we designed this study with the aim to assess the occurrence of family history of DM and CVD in young Saudi medical students. In addition, we aim to establish any relationship between plasma hs-CRP in subjects with family history of CVD and DM. Moreover, to determine any association between obesity and stress and family history of CVD and DM with plasma hs-CRP levels.

Subjects and Methods

In this cross-sectional study, we investigated 415 young healthy Saudi medical students, 19-20 years of age. All participants are from Makkah region. The study was carried out between January-April 2017. Subjects with history or evidence of any inflammatory disease during one month prior to the study or having any haematological, autoimmune, renal or hepatic disorder were excluded. University ethical committee approved the study and participants signed a written consent. All participants were interviewed about their personal medical and family history and completed PSS14 questionnaire for stress. Anthropometric parameters and venous blood sample for hs-CRP measurement were taken using standardized protocols.

In this study a positive family history for CVD was considered if first degree relatives, aunt, cousins had been diagnosed with angina, myocardial infarction, angioplasty, or had undergone coronary artery bypass surgery. Similarly, the presence or absence of diabetes in father, mother, siblings, and children was considered as a positive or a negative family history of diabetes. On the basis of positive and negative family history for CVD and DM we

stratified our sample in four groups: Participants with; Positive family history for CVD., Positive family history for DM, Positive family history for both CVD and DM, Negative family history for both CVD and DM.

Anthropometric parameters such as height, waist, hip circumference and body weight were measured using standard clinical protocol. Waist Hip Ratio (WHR) was calculated as an indicator of abdominal visceral fat, by dividing waist circumference (WC) by the hip circumference (HC).

Perceived stress of the participants was also measured by using the perceived stress scale 14 (PSS-14). It consists of 14 questions each with five options from never to very often. To make the questionnaire easily understandable; it was presented with an Arabic version to the participants. The stress score was stratified as Non-stressed (<28) and stressed ($\geq$28).

In-addition venous blood samples (5 ml) collected under aseptic conditions were centrifuged to obtain plasma. High-sensitivity CRP was then measured by latex-enhanced Immunonephlometry (Dade Behring, New York, DE, USA). Both within and between assays quality control was maintained. It can measure a minimal value of 0.01 mg/dl and values below it was described undetectable.

Data collected is expressed as mean ± SE. High sensitivity CRP as a continuous variable was logarithmically transformed for statistical analysis to improve its skewness. The geometric mean of hs-CRP and its geometric mean standard error were used for tabular and graphical presentations. Unpaired student t test was used for continuous normally distributed variables and P value < 0.05 is reported significant. To compare PSS-14 scores of subjects from different groups, Mann-Whitney U test was used. All statistical analysis was performed using graph-pad prism (Graph-Pad 6 software, lajolla CA, USA).

Results

Around four hundred and fifteen young Saudi medical students with a mean age of 19 years from Makkah region participated in this study. They were investigated for the potential risk of cardiovascular diseases (CVD) as well as the frequency of obesity and stress. Information was collected from the participants regarding any family history of CVD and DM. Moreover, plasma hs-CRP level and BMI were measured. BMI is most commonly used method of identifying obesity in various epidemiological studies, when measured in our study group; a mean value of 27.113 ± 0.343 Kg/m^2 was seen (Table 1B). According to WHO criteria, majority of our participants belongs to overweight category. However, it is believed that, BMI cannot distinguish between fat mass and lean body mass. However, waist circumference (WC) and waist hip ratio (WHR) are better indicators of central or abdominal fat. Thus, mean values of WC (90.46 ± 0.88) and WHR (0.942 ± 0.01) were also recorded (Table 1A). Furthermore, mean and median values of hs-CRP (0.267 ± 0.016) and perceived stress score (24 ± 0.29) respectively for the study sample were also established (Table 1B).

On the basis of family history for CVD and DM, study group was classified into CVD history positive 6.02% (25/415), DM history positive 31.81% (132/415), CVD and DM history positive 15.90% (66/415) and CVD and DM history negative 46.27% (192/415) groups (Table.1B) which indicates that, 53.73% of our total subjects have both CVD and DM or one of them in their families.

Although, CVD history positive group represents least number of participants; however, their mean hs-CRP results are highest (0.36 ± 0.077) of the four identified groups (Table 2). It is also important to note that, on the basis of hs-CRP results, participants with positive family history for CVD fall in high-risk category according to AHA standards while the others showed medium risk (Table 5).

Furthermore,the groups with positive family history for CVD, DM, and both diseases are found to

have 50%, 17% and 17% respectively, higher values of plasma hs-CRP than the normal participants. Statistically this difference in the hs-CRP level between groups with family history positive for CVD, DM or one of the two diseases vs. group with family history negative for CVD, DM or one of the two diseases is significant (P<0.00001) (Table 2). Additionally, anthropometric parameters BMI, WC, HC and WHR measured during this study were also observed to be significantly higher among participants with positive family history compared to their negative family history counterparts (Table 2).

Family history is believed to be a non-modifiable risk factor for CVD and DM. where-ashs-CRP as an important indicator of acute inflammation. In the present study we noticed higher values of hs-CRP in participants from all positive family history groups compared to the negative family history. Inorder to explore this finding we regrouped our participant in normal weight and overweight-obese categories on the basis of their BMI and examined their hs-CRP levels. Surprisingly, we found that, there is a significant difference between normal weight individuals vs.over weight/obese; irrespective of their family history (Fig 1).

However, in overweight-Obese group participants with negative family history were found to have lesser values of hs-CRP compared to participants with positive family history. Moreover, all group of overweight-obese subjects represented significantly higher results for hs-CRP when compared with the normal weight subjects from all groups (Fig 1). Our participants with family history of CVD and DM or one of the two diseases seems to play less effective role to produce much increase in plasma hs-CRP levels and the significant elevation observed possibly represent a combined effect of positive family history and obesity.

Considering the role of obesity in increasing plasma hs-CRP we further examined if an association exists between hs-CRP and anthropometric variables. All four groups based on family history showed positive and significant (P<0.00001) correlation of Plasma hs-CRP levels with BMI and WC. Furthermore, CVD and DM history positive groups showed significant correlation of hs-CRP with WHR and HC respectively as well. The strongest correlation (r 0.704) was observed between hs-CRP and BMI in CVD positive group while the weakest (r 0.035) between hs-CRP and WHR in DM positive group (Table 3). No correlation was observed between plasma hs-CRP and stress in any family history based group (Table 3).

Results of current study also represents significantly (P<0.0001) higher values of plasma hs-CRP in overweight-Obese group compared to the normal weight participants (Table 4) irrespective of their family history. Further, overweight-obese participants represent significantly (P<0.00001) higher values of BMI, WC, HC and WHR compared to the normal weight individuals (Table 4) thus, demonstrating a positive association between anthropometric parameters and plasma hs-CRP level.

Stress is reported to be one of the factors involved in the etiology of CVD and DM. In the present study we assessed the stress level of our participants and its effect on their plasma hs-CRP level. According to the results however, we did not find any significant difference in the stress scores between positive family history compared to negative family history group.

However, to identify any contribution of stress in the higher hs-CRP results obtained from positive family history participants, we divide all four groups in non-stressed and stressed classes on the basis of their stress score.

Furthermore hs-CRP values obtained from non-stressed vs. stressed subjects were found to be non-significant. We observed; higher stress is not associated with a positive family history of CVD or DM to enhance plasma hs-CRP level. Pearson correlation demonstrated a negative and non-significant correlation between hs-CRP and Stress in all the groups.

According to the American heart association recommended cut off values of plasma hs-CRP 26.75% of the total participants (Table 1A) of our

study group (111/415) presents high risk while among participants with positive history for CVD, DMor both 28.7% and 29.15% of them are found to be in the high and medium risk category respectively (Table 5) for developing CVD or DM in future. Furthermore, among the individuals with negative family history of CVD or DM) 24.7% and 36.8% are high and medium risk candidates respectively for the future risk of CVD and DM (Table 5).

Table 1A. Characteristics of participants

Parameter	Mean ± SD (n= 415)
Age	19.05 ± 0.026
hs CRP (mg/dl)	0.267 ± 0.016
PSS 14 score	24 ± 0.29
BMI	27.113 ± 0.343
Waist Circumference (cm)	90.46 ± 0.88
WHR	0.942 ± 0.01

CRP, C-reactive protein; PSS-14, Perceived stress scale. Variables are expressed as mean ± SD.

Table 1B. Classification of participants into different categories

Categories	Parameter	Percentage
BMI	Normal Weight	n= 200 (48%)
based categories	Over Weight& Obese	n= 215 (52%)
Family history	CVD family history positive	n= 25 (6.0%)
based categories	DM family history positive	n= 132 (31.8%)
	CVD+DM family history positive	n= 66 (15.9%)
	CVD+DM family history negative	n= 192 (46.2%)
PSS 14 stress	Normal	n= 192 (46.2%)
score-based	Stressed (PSS14)	n= 124 (29.8%)
categories		

Table 3. Correlation of hs-CRP with anthropometric parameters

Correlation	CVD & DM Neg (n= 192)	CVD Pos (n= 25)	DM Pos (n= 132)	CVD & DM Pos (n= 66)
CRP vs.	0.704	0.415)	0.617	0.401
BMI*	P<0.05	P<0.00001	P<0.00001	P<0.00001
CRP vs.	0.519	0.284	0.309	0.296
WC*	P<0.05	P<0.05	P<0.05	P<0.05
CRP vs.	0.064	0.242	0.120 NS	0.249
HC*	NS	P<0.05	NS	P<0.05
CRP vs.	0.435	0.035	0.215	0.053
WHR	P<0.05	NS	NS	NS
CRP vs.	0.084	0.137	-0.167	-0.072
Stress	NS	NS	NS	NS

hs-CRP, high sensitivity C-reactive protein;CVD Neg; family history of cardiovascular disease negative; DM neg, diabetes mellitus family history negative; CVD pos, cardiovascular disease family history positive; DM pos, diabetes mellitus family history positive; NS, not significant. *All independent variables that showed a significant difference (p<0.05)

Table 4. Comparison of Normal vs. Overweight & Obese

Parameter	Normal weight n= 200	Overweight & Obese n= 214	P-Value
hs-CRP (mg/dl)*	0.153 + 0.221	0.358 + 0.026	P<0.0001
PSS-14 Stress	23 + 0.519	25 + 0.404	NS
BMI*	21.75 + 0.138	31.78 + 0.434	P<0.0001
Waist circumference (cm)*	80.48 + 0.793	99.28 + 1.226	P<0.00001
Hip circumference (cm)*	91.91 + 0.89	103.56 +1.39	P<0.00001
Waist hip ratio *	0.889 + 0.01	0.985 + 0.016	P<0.00001

NS, not significant.Variables are expressed as mean ± SD. *All independent variables that showed a significant difference (p<0.05).

Table 2. Effect of family history of CVD, DM and co-morbidity

Parameter	CVD Neg vs. CVD Pos n= 192 n= 25	DM Neg vs. DM Pos n= 192 n= 66	CVD & DM Neg vs. CVD & DM Pos n= 192 n= 132
hs-CRP (mg/dl)*	0.24 ± 0.021 VS 0.36 ± 0.077 P<0.00967	0.24 ± 0.021 VS 0.28 ± 0.03 P<0.00001	0.24 ± 0.021 VS 0.28 ± 0.029 P<0.00001
PSS14 Stress	24 ± 0.384 VS 26 ± 1.546 NS	24 ± 0.38 VS 24 ± 0.57 NS	24 ± 0.38 VS 24 ± 0.5 NS
BMI*	26.65 ± 0.46 VS 26.90 ± 1.286 P<0.00001	26.65 ± 0.46 VS 27.99 ± 0.70 P<0.000089	26.65 ± 0.46 VS 26.81 ± 0.9 0.41355 NS
Waist circumference (cm)*	89.71 ± 1.25 VS 96.36 ± 3.895 P<0.00001	89.71 ± 1.25 VS 90.60 ± 1.57 P<0.00001	89.71 ± 1.25 VS 90.12 ± 1.7 P<0.00001
Hip circumference (cm)*	97.29 ± 1.32 VS 98.94 ± 3.564 P<0.00001	97.29 ± 1.32 VS 97.99 ± 1.59 P<0.00001	97.29 ± 1.32 VS 98.17 ± 1.7 P<0.00001
Waist hip ratio*	0.94 ± 0.012 VS 1.02 ± 0.077 P<0.00001	0.94 ± 0.02 VS 0.94 ± 0.02 P<0.00001	0.94 ± 0.012 VS 0.94 ± 0.03 P<0.00001

CVD Neg; family history of cardiovascular disease negative; DM neg, diabetes mellitus family history negative; CVD pos, cardiovascular disease family history positive; DM pos, diabetes mellitus family history positive;NS, not significant. Variables are expressed as mean ± SD. *All independent variables that showed a significant difference ($p<0.05$)

Table 5. Three main categories based on hs-CRP levels

Low Level	CVD & DM family history negative	n= 73 (38.4%)
	CVD family history positive	n= 7 (28%)
	DM family history positive	n= 59 (44.7%)
	CVD & DM family history positive	n= 28 (42.42%)
Medium Level	CVD & DM family history negative	n= 70 (36.84%)
	CVD family history positive	n= 7 (28%)
	DM family history positive	n= 40 (30.3%)
	CVD & DM family history positive	n= 18 (27.27%)
High Level	CVD & DM family history negative	n= 47 (24.74%)
	CVD family history positive	n= 11 (44%)
	DM family history positive	n= 33 (25%)
	CVD & DM family history Positive	n= 20 (30.3%)

hs-CRP, high sensitivity C-reactive protein; DM, diabetes mellitus; CVD, cardiovascular disease

Discussion

Family history is an important predictor of chronic diseases like CVD and DM[12-13]. In Saudi Arabian society, incidence of CVD is increasing as the risk factors like obesity, diabetes and hypertension are reported to increase on yearly basis[11,14]. Present study showed that, 53.73% of our subjects have CVD, DM or one of the two diseases present in their family. Family history is an important non-modifiable risk factor. Furthermore, current study showed that, majority of the participants are overweight; with higher values of WC (High Risk 46.75%) and WHR (High Risk 69.40%), as well as increased levels of plasma hs-CRP (High Risk 26.75%). This combination of risk factors increases the possibility of our subjects to be a victim of CVD or DM that requires hard-line primary preventive measures. Our results of positive family history are higher compared to only 29.7% response of positive family history of CVD in a study conducted on 22-55 years of age among Saudi women in Riyadh KSA[15].

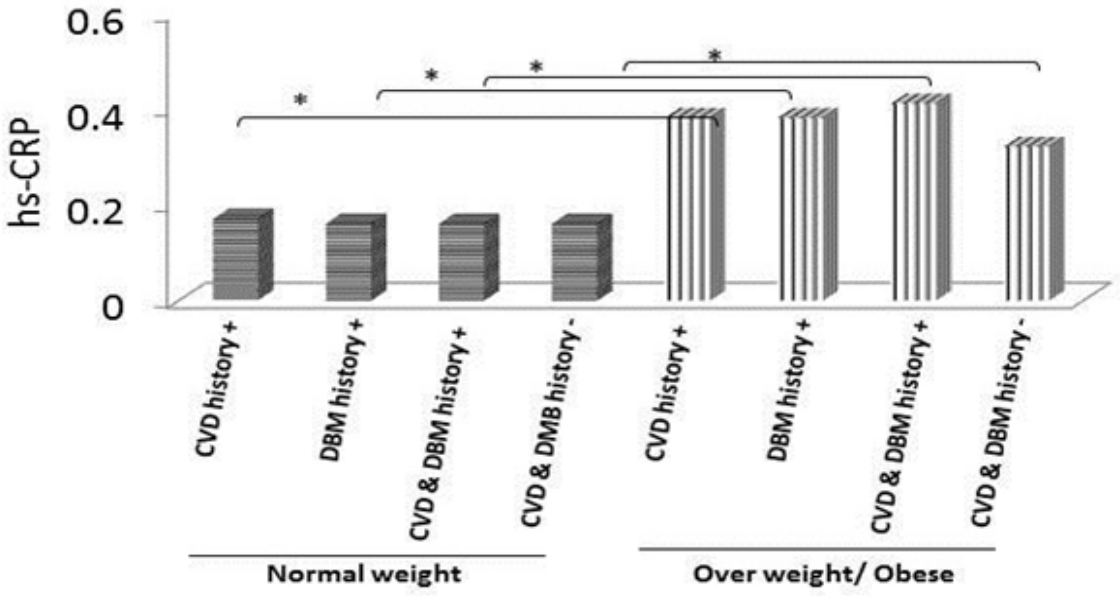

Fig 1. Comparison of hs-CRP levels in normal weight vs. Overweight / obese with different family history

Plasma levels of hs-CRP were measured and participants were classified as normal/ overweight/ Obese on the basis of their BMI. The normal weight individuals irrespective of their family history have significantly less CRP levels as compared to the overweight / Obese individuals. *All independent variables that showed a significant difference ($p<0.05$).

We showed 6.02% positive family history of CVD. This finding is in agreement with the CVD prevalence in KSA reported by most of the earlier studies[11,14]. Our results also showed maximum positive family history rate of 32% for DM, representing the increasing incidence and its possible role in the increasing CVD prevalence in KSA.

We noted significantly higher values of plasma hs CRP in all the groups with positive family history (CVD, DM or one of the two). We can attribute this increased plasma hs-CRP to both genetic and environmental factors.

CRP is not only a predictor of chronic diseases like CVD and DM in apparently healthy people but is reported to contribute in the process of atherosclerosis as well, through its influence on vascular strength[9]. Higher plasma values of CRP, IL-6 and TN are also reported in 5-15 years of age healthy children with positive family history of CAD[16]. Earlier observations of significant association between positive family history of CAD and markers of subclinical atherosclerosis also supports our explanation that, higher hs-CRP values in our subjects with positive history of CVD and DM along with high BMI, WC, HC and WHR possibly leads to the development of inflammatory process of atherosclerosis.

Furthermore, significant association of hs-CRP with BMI and WC was noticed in our participants with positive family history, which might be responsible for low grade systemic inflammation indicated by higher plasma level of acute phase reactant CRP[17]. Higher plasma hs-CRP levels are demonstrated by our participants with positive family history of CVD, DM or one of the two diseases can also be explained on the basis of significantly higher values of BMI and other anthropometric parameters.

Participants included in this study were healthy subjects of 19-20 years with no history of diseases, trauma or infection during the month prior to the study therefore; this reduces the chances of any confounding subclinical disease and possible reasons for raised hs-CRP except over-weight, obesity and stress. Interestingly over weight/obese subjects showed significantly higher values of hs-CRP in all four groups irrespective of the family history of disease compared to the normal weight. This indicates that, the genetic factor is potentiated by increase weight and BMI for enhancing plasma hs-CRP level.

Our results demonstrated that, majority of our participants have substantial risk of developing CVD or DM because they are overweight with higher measurements of WC and WHR. Earlier studies also reported that, among 15-20 years of age Saudis 24% male and 33% female are obese[18].

Conclusion

The combination of positive family history of CVD, DM or one of the two and environmental factors (life style) is possibly responsible for the low-grade systemic inflammation leading to increased level of hs-CRP. Furthermore, it is suggested that,family history should be included as a tool for the identification of subjects at high risk in our society, particularly the youngsters. Strict measures must be taken to reduce the incidence of CVD, DM and the incidence of over-weight and obesity. Efforts are also required to increase public awareness regarding the risk factors associated with these problems as well as the life style.

Conflict of Interests

Authors have no conflict of interests and received no grant/funding from any organization.

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