Original article

Visceral adiposity in young patients with coronary artery disease—a case control study

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KEY WORDS

Coronary artery disease
Obesity
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A B S T R A C T

Aim: Central obesity is associated with an increased cardiovascular risk. We carried out a hospital based case control study in young patients with coronary artery disease (CAD) to assess the importance of visceral fat.

Methods: Coronary artery disease was established by coronary angiogram in all cases. Controls were age- and sex-matched subjects with normal coronary angiogram. Computed tomography scan performed at the level of the umbilicus to measure subcutaneous and visceral fat area (VFA).

Results: Cases and controls were well matched in height, weight, and body mass index (BMI). Visceral fat area was significantly higher (122.58 ± 37.59 vs. 88.4 ± 36.95 cm²; $P=0.003$) in cases whereas subcutaneous fat area was similar in cases and controls. Visceral fat area was an excellent predictor of cardiovascular risk (area under receiver operating characteristics curve 0.915 cm²). Visceral fat area correlated with BMI, waist hip ratio, blood sugar, triglycerides, and C-reactive protein significantly.

Conclusion: Visceral adiposity is associated with an increased risk of CAD and it correlated with anthropometric, metabolic, and inflammatory markers.

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Introduction

Coronary artery disease (CAD) is increasing in both young and old in an alarming proportion globally in general and developing Asian countries like India¹ in particular many epidemiological studies^{2–4} have reported a constant association between obesity and mortality due to cardiovascular diseases (CVD). Traditionally, anthropometric measurements such as body mass index (BMI) or waist circumference (WC) have been used to quantify overall adiposity.⁵ However, regional fat depots may be of greater importance than overall adiposity.⁶ Body mass index is a very crude indicator of adiposity and has shown an inconstant relationship with the cardiovascular risk. Although, waist hip ratio (WHR) is a simple and convenient tool for epidemiological studies, it does not distinguish between accumulations of visceral and subcutaneous

abdominal fat. By means of advanced imaging techniques like computed tomography (CT) and magnetic resonance imaging (MRI) scans,⁷ the accurate estimation of subcutaneous and visceral fat compartments is possible without much radiation hazard. Association between CAD risk factors and amount of visceral adipose tissue, measured directly with CT or MRI, are stronger than association observed with indirect measures of visceral adipose tissue, such as waist and WHR.^{8,9} We carried out a hospital based case control study in young patients with CAD to assess the relative importance of visceral fat and its correlation with cardiovascular risk

Methods

This was a hospital based case control study. The younger age for CAD was defined as <55-years for males and 65-years for females. Cases were enrolled from patients admitted in cardiology department with acute myocardial infarction (AMI).

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Coronary artery disease was established by coronary angiogram in all cases. Age- and sex-matched subjects without any history of myocardial infarction, were enrolled as controls when they had normal coronary angiogram. Patients with chronic congestive heart failure (CHF), chronic liver disease, chronic renal failure, collagen vascular diseases, and malignancy were excluded. Informed consent was taken from all patients after explaining the methods.

Anthropometric measurements

Height in centimetres and weight in kilograms (using the same standard weighing machine) were measured and BMI was calculated. Waist girth was measured at the midpoint between lower thoracic cage and iliac crest (usually at the level of umbilicus in the standing position) and hip girth was measured at the inter-trochanteric level (usually the widest diameter around the buttocks)² in the standing position, to the nearest 1 cm using a non-stretchable elastic tape with patients wearing loose clothes.

Biochemical measurements

Blood samples were taken from all study patients after 8 hours of fasting for measurement of fasting blood sugar (FBS), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), triglycerides (TG), and C-reactive protein (CRP).

Estimation of abdominal fat by computed tomography scan

Regional fat distribution was measured by CT performed at the level of the umbilicus to measure the abdominal subcutaneous fat area (SFA) and visceral fat area (VFA). Patients were imaged on Bright speed 16 slice CT scanner (GE medical systems). An un-enhanced axial section was taken at the level of umbilicus with the following parameters (120 Kvp; 250 mAs, and slice thickness 5 mm). The subjects were examined in a supine position with their arms stretched above their heads. The area of visceral adipose tissue and abdominal subcutaneous tissue expressed in square centimetres was calculated by manually outlining the fat containing tissues. The ratio between visceral and subcutaneous adipose tissue was calculated. The radiologist who performed the CT fat measurements was kept blinded to the patient profile.

Statistical analysis

Descriptive statistical analysis has been carried out in the present study. Continuous variables are presented as mean $\pm$ standard deviation (min–max) and categorical variables are presented in number (%). Significance is assessed at 5% level of significance. Student *t* test (two-tailed, independent) has

been used to find the significance of study parameters on continuous scale between two groups (inter-group analysis). Receiver operating characteristics (ROC) curve has been used to find the discriminate capacity of various adiposity measurements like BMI, WHR, SFA, and VFA for cardiovascular risk. Pearson correlation was used to find the correlation of VFA with various parameters.

Results

A total of 50 patients (20 cases and 30 controls) were studied. Cases and controls were well matched with respect to age (43.00 ± 11.44 vs. 40.83 ± 9.29 years; $P=0.458$), gender (males 75% vs. 76.7%) and prevalence of co-morbidities like diabetes mellitus (DM) (45% vs. 40%), hypertension (HTN) (45% vs. 43.3%), dyslipidaemia (50% vs. 33.3%), smoking (55% vs. 36.7%), and family history of CAD (15% vs. 6.7%) (Table 1). Majority of the subjects were male in both cases and controls, being true to the higher incidence of CAD in young males compared to females. The mean height and weight of the cases and controls were comparable and the BMI didn't show any significant difference between the two groups (25.47 ± 2.65 vs. 23.92 ± 3.00 ; $P=0.067$). Body mass index was within normal range for majority of patients in cases and controls taking the cut-off value of 25 kg/m^2 as the upper limit of normal. Waist circumference was significantly higher in cases compared with controls (94.90 ± 6.68 vs. 88.17 ± 8.17 cm; $P=0.004$). Waist hip ratio also remained significantly higher in cases (1.00 ± 0.05 vs. 0.92 ± 0.05 ; $P<0.005$). Of the intra-abdominal adiposity measures, SFA did not vary much between cases and controls (201.02 ± 69.88 vs. 206.82 ± 76.66 ; $P=0.787$). Visceral fat area was significantly higher in cases in comparison to the control population (122.6 ± 37.59 vs. $88.40 \pm 36.95 \text{ cm}^2$, $P<0.005$). The ratio of VFA to SFA (VFA/SFA ratio) was also found to be significantly higher in cases. Among the metabolic parameters, FBS (145.25 ± 57.08 vs. 97.77 ± 13.04 , $P<0.001$) and TG (193.75 ± 45.38 vs. 128.60 ± 50.86 ; $P=0.009$) were significantly higher in cases compared to controls. C-reactive protein, the inflammatory marker, also showed a significantly higher value in cases compared to controls (0.58 ± 0.37 vs. 0.28 ± 0.26 , $P=0.002$) (Table 2 and Figure 1).

Receiver operating characteristics curve analysis was carried out with different measures of obesity like BMI, WC, WHR, SFA, VFA, and VFA by SFA ratio (VFA/SFA). Visceral fat area as measured by CT scan was found to be an excellent

Table 1
Baseline characteristics.

	Control (n=30)	Cases (n=20)	P value
Age (yr)	40.83 ± 9.29	43 ± 11.44	0.81
Male (%)	23 (76.7)	15 (75)	0.89
Diabetes mellitus (%)	12 (40)	9 (45)	0.58
Hypertension (%)	13 (43.3)	9 (45)	0.85
Dyslipidaemia (%)	10 (33.3)	10 (50)	0.06
Smoking (%)	11 (36.7)	11 (55)	0.06
Family history of CAD (%)	2 (6.7)	3 (15)	0.07

CAD: coronary artery disease.

Table 2

Comparison of study variables in controls and cases.

Variables	Control (n=30)	Cases (n=20)	Significance
Height (cm)	167.60±8.38	163.2±6.94	$t=1.943$; $P=0.0580$
Weight (kg)	67.37±10.45	67.8±8.95	$t=0.152$; $P=0.880$
Body mass index (kg/m ²)	23.92±3	25.47±2.65	$t=1.871$; $P=0.067$
Waist (cm)	88.17±8.17	94.9±6.68	$t=3.064$; $P=0.004^*$
Hip (cm)	94.52±7.91	93.9±5.42	$t=0.304$; $P=0.762$
Waist hip ratio	0.92±0.05	1±0.05	$t=5.275$; $P<0.001^*$
Subcutaneous fat area (cm ²)	206.82±76.66	201.02±69.88	$t=0.271$; $P=0.787$
Visceral fat area (cm ²)	80.94±30.36	135.79±29.5	$t=6.329$; $P<0.001^*$
Visceral fat area/subcutaneous fat area ratio	0.41±0.14	0.73±0.23	$t=6.188$; $P<0.001^*$
Fasting blood sugar (mg/dL)	97.77±13.04	145.25±57.08	$t=4.408$; $P<0.001^*$
Total cholesterol (mg/dL)	178.67±42.22	193.75±45.38	$t=1.201$; $P=0.236$
Low-density lipoprotein cholesterol (mg/dL)	116.47±32.22	126.9±37.16	$t=1.055$; $P=0.297$
High-density lipoprotein cholesterol (mg/dL)	36.27±10.59	33.25±7.46	$t=1.103$; $P=0.275$
Triglycerides (mg/dL)	128.60±50.86	176.1±73.57	$t=2.703$; $P=0.009^*$
C-reactive protein (mg/dL)	0.28±0.26	0.58±0.37	$t=3.347$; $P=0.002^*$

*P value is highly statistically significant.

Figure 1 Computed tomography section of abdomen at the level of umbilicus to show varying degree of visceral fat area and subcutaneous fat area in two patients with identical body mass index.

predictor of cardiovascular events in the study population. The ROC curve analysis showed, a WHR of 0.95 (sensitivity 85%, specificity 76.67%), and VFA of 110.97 cm² (sensitivity 90%, specificity 86.7%) were found to be the cut-off values above which cardiovascular risk increased in the study population (Table 3 and Figure 2).

Correlations of VFA with anthropometric and metabolic variables were done using the Pearson correlation. Visceral fat area was highly correlated with BMI ($r=0.484$; $P=0.01$) and WHR ($r=0.612$; $P<0.001$). Among the metabolic variables, VFA showed significant correlation with FBS ($r=0.465$; $P=0.001$) and TG ($r=0.384$; $P=0.006$) whereas correlation with TC, LDL, and HDL were very weak and insignificant. Visceral fat area highly correlated with the inflammatory marker CRP significantly ($r=0.450$; $P=0.001$) (Table 4 and Figure 3).

Discussion

In this hospital based case control study, we assessed the relative importance of visceral adiposity in young patients with

Table 3

Receiver operating curve analysis of various measures of obesity.

Predictors of cardiac disease	AUC (cm ²)	Remarks
Body mass index	0.637	Poor test
Waist measurement	0.732	Fair test
Hip measurement	0.468	Failed test
Waist hip ratio	0.882	Good test
SFA	0.471	Failed test
VFA	0.915	Excellent test
VFA/SFA ratio	0.897	Good test

AUC: area under curve, SFA: subcutaneous fat area, VFA: visceral fat area.

CAD. We found that visceral fat is significantly higher in CAD patients. Even though this study does not prove any causal association of visceral fat with CAD, the role of visceral fat in the overall risk profile of such patients is revealed more vividly. In our study, BMI was within the normal range for most of the patients and in general, most Indian patients presenting with acute coronary syndrome have a near normal BMI. The relatively weak association between BMI and CAD has already been proved by many studies especially in south Asians.²

Figure 2 Receiver operating characteristics curve analysis of different measurements of obesity (BMI, waist, WHR, VFA, SFA, VS ratio) as predictor of cardiovascular risk. BMI: body mass index, ROC: receiver operating curve, SFA: subcutaneous fat area, VFA: visceral fat area, WHR: waist hip ratio.

The average WC of the patients with proven CAD (males 95 cm, females 94 cm) was significantly higher compared with patients without CAD (males 89 cm; females 84 cm) which was in turn higher than the upper limits of normal for Indian population (males <90 cm; females <80 cm),¹⁰ emphasising the high prevalence of metabolic syndrome in young Indian population. Likewise, WHR also was higher in patients with CAD (males 1.003; females 1) in comparison to patients without CAD (males 0.94; females 0.87). Pouliot et al.¹¹ has shown threshold values of WHR 0.85 for women and 0.95 for men are associated with metabolic risk. The current study

Table 4

Pearson correlation of visceral fat area with anthropometric and metabolic variables.

Pair	Pearson correlation	P value
VFA vs. body mass index	0.484	0.001*
VFA vs. waist hip ratio	0.612	<0.001*
VFA vs. fasting blood sugar	0.465	0.001*
VFA vs. total cholesterol	0.181	0.208
VFA vs. LDL cholesterol	0.131	0.364
VFA vs. HDL cholesterol	−0.095	0.514
VFA vs. triglycerides	0.384	0.006*
VFA vs. C-reactive protein	0.450	0.001*

*P value is highly statistically significant. HDL: high-density lipoprotein, LDL: low-density lipoprotein, VFA: visceral fat area.

Figure 3 Correlation of visceral fat area with various anthropometric and metabolic variables. BMI: body mass index, CRP: C-reactive protein, FBS: fasting blood sugar, HDL: high-density lipoprotein, LDL: low-density lipoprotein, TG: triglycerides, VFA: visceral fat area, WHR: waist hip ratio.

gives a WHR cut-off value of 0.95 above which the CAD risk increases, especially in males. Gupta et al.¹⁰ showed that WHR >0.9 in men and >0.8 in women is associated with a significant increase in multiple risk factors in a study done in Indian urban population. Waist and WHR were significantly different between the patients with or without CAD in both males and females. Many studies^{12,13} have shown waist and WHR as significant predictors of onset of diabetes and CAD. INTERHEART study² showed WHR as the strongest predictor of MI across all ethnic groups and ages.

Even though WHR is a simple and convenient epidemiological tool to measure the regional distribution of body fat, it cannot distinguish between the deep intraperitoneal fat and the subcutaneous fat and it is mentioned as a limitation of many large studies.² To our knowledge, this is the first Indian study done to estimate the adiposity parameters in CAD patients. We used CT scan to measure the abdominal fat because it is the gold standard for adiposity measurements. The radiation exposure is <0.1 mSv. We measured abdominal fat at the level of umbilicus. The choice to perform the scan at the level of the umbilicus was initially proposed by Borkan et al.¹⁴ who found that at the level of the umbilicus there is the highest percentage of body fat, and it best allows differentiation of subcutaneous from intra-abdominal fat. Subcutaneous fat area was comparable in all subjects irrespective of the presence or absence of CAD and other co-morbidities. We observed that SFA was significantly high in females of the control group compared to males ($P=0.05$) but this difference was not evident among the cases. It can be explained that subcutaneous adiposity gives a protective effect associated with large hip in females¹⁵ and it is the main source of good 'cytokines' like adiponectin.¹⁶

Visceral fat area showed a strong association with CAD. Visceral fat area was significantly high in patients with proven CAD. Central obesity has been considered as a risk factor for CVD from earlier days itself. Now studies^{17,18} have shown that it is the visceral fat which adds the risk associated with central obesity. Von Ebyen et al.¹⁹ showed VFA measured by CT scan has a significant association with the AMI in Danish young men. In previous studies done by Fujimoto et al.²⁰ in Japanese-American men and Niklas et al.²¹ in postmenopausal women, visceral adiposity was found to be the most significant predictor of coronary events.

Various populations have shown different thresholds for VFA above which cardio-metabolic complications would be more likely to be observed. This study showed a threshold VFA of 110 cm² as a cut-off value in Indian population to predict the higher risk for cardiovascular complications. Desprès and Lamarche,²² Hunter et al.,²³ and Williams et al.²⁴ studied men and/or women with wide range of body weights in various populations. They found that a value above 110 cm² was associated with an increased risk of coronary heart disease supporting our observation. In another study, performed in Japan by Saito et al.²⁵ in non-obese and obese males and females, fat areas at the umbilicus level as determined by CT had threshold values 100 cm² for men and 90 cm² for women. Korean population was found to have a cut-off value of 103 cm² as found in the study by Kim et al.²⁶

The ratio of visceral fat to the subcutaneous fat (VFA/SFA ratio) was also significantly high in CAD patients. Saito et al.²⁵ has shown that a VFA/SFA ratio of 0.4 has a good discriminatory value to predict the cardiovascular risk.

Visceral fat area showed a significant correlation with FBS, TGL, and CRP whereas SFA did not show any correlation with these metabolic parameters. Similar observations were found in many large studies done with large number of males and females.^{27–29} Visceral fat compartment is a metabolically active endocrine organ, secreting various substances and inflammatory markers like interleukin-6, plasminogen activator inhibitor-1, and CRP, which may contribute to its role in cardio-metabolic and athero-thrombotic risk.³⁰ Hence, the contribution of visceral adiposity to the overall cardiovascular risk in young CAD patients appears to be significant.

Conclusion

In this hospital based case control study, we found that visceral adiposity is associated with an increased risk of CAD and it also correlated with BMI, waist, WHR and increased levels of FBS, STGL, and CRP. Further large studies will clarify the role of visceral fat and its contribution to CVD in Indian population.

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