Original article

The effects of body fat distribution on coronary and carotid atherosclerosis: An autopsy study

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BACKGROUND: Epidemic levels of obesity and overweight in today's world are leading to a higher number of mortality and morbidity, especially due to cardiovascular diseases (CVDs). Body fat distribution contributes a great amount to atherosclerosis formation and therefore increased CVD incidence. The present study used the autopsy of 40 healthy-appearing adults who died due to non-cardiac causes to explore the association between atherosclerosis and body fat distribution indices including abdominal fat, visceral fat, subcutaneous fat, and pericardial fat. **METHODS:** This cross-sectional study examined the autopsy of 40 individuals of 20 to 50 years old who died due to non-cardiac causes, mostly car accidents, and were sent to the forensic center. Measurement of abdominal fat, visceral fat, subcutaneous fat and heart weight/height ratio as a pericardial fat index in the cadavers was followed by atherosclerosis assessment in the carotid artery, left and right internal and external carotid arteries, as well as right coronary artery (RCA), left anterior descending (LAD) and left circumflex (LCX) coronary arteries based on American Heart Association (AHA) criteria. In order to evaluate the relation between atherosclerosis development and body fat distribution indices, SPSS version 19 was used for multinomial logistic regression analysis in the crude and adjusted models (for age, smoking, LDL-c, HDL-c, HBA1c, and CVD history). The effectiveness of body fat distribution variables along with age, smoking, LDL-c, HDL-c, HBA1c, and CVD history on atherosclerosis was also determined by stepwise forward regression analysis. **RESULTS:** The average age of the subjects was 29.97 ± 9.84 years. Among 40 performed autopsies only 3 were women. Coronary and carotid atherosclerosis were observed in 50% and 85% of the cadavers, respectively. Logistic regression analysis revealed no link between carotid atherosclerosis and body fat distribution indices. Although, the correlation found between heart weight/height ratio and atherosclerosis in the crude model did not remain significant after the adjustment of other indices, stepwise forward regression analysis resulted in OR = 9.461 and confidence interval = 1.199-74.650. **CONCLUSIONS:** Our results indicated a link between coronary atherosclerosis and heart weight/height ratio. Since coronary and carotid atherosclerosis were not found to be correlated with subcutaneous and visceral fat, further investigation is suggested.

KEYWORDS: Obesity, Abdominal Fat, Visceral Fat, Subcutaneous Fat, Pericardial Fat, Atherosclerosis

BACKGROUND

In today's world, the prevalence of obesity and overweight is reaching epidemic levels .[1]More than 50% of American adults are now obese or overweight[2] and the occurrence of the problem has doubled since the 1960s in the country.[3] Obesity and overweight are also common in the Middle East, with Bahrain having the highest rate (29%).[4] The third national non-communicable disease risk factors surveillance report, has reported the obesity prevalence rate to be 22.3% in Iran.[5]

Morbidity and mortality, due to obesity-induced diseases, have increased as a result of high obesity incidence.[6] Some studies do not consider obesity as an independent risk factor for cardiovascular disease (CVD) and indicate increased cardiometabolic disorders and CVD risk factors in obese people responsible for the higher frequency of CVDs.[7,8] A study conducted in 7 European countries revealed low association between obesity and CVD occurrence.[9] Furthermore, recent studies found weight loss treatments in obese people with no accompanying cardiometabolic disorders ineffective in reducing CVD risk.[10] However, other studies, including the one Framingham performed on 5209 American female and male adults for 26 years,[11] demonstrate a direct link between obesity and coronary artery diseases.[12-14]

Obesity type and body fat distribution are important elements in CVD occurrence, and research confirms that CVDs and their risk factors are directly

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associated with increased abdominal fat accumulation and obesity.[15,16] In addition, metabolic disorders such as hypertension, diabetes mellitus, and lipid disorders have been observed in subjects with normal Body Mass Index (BMI) but having abdominal obesity.[17] Several studies show body fat distribution relating with not only CVD incidences, but also angiographic changes.[18,19] Another cause of CVDs is pericardial fat that has been presented by some studies to have an independent role in CVD occurrence and even atherosclerosis.[20-23] Atherosclerosis and its gradual development into atheroma plaque lead to clinical symptoms and CVD. Coronary fatty streak formation starts during the second decade of life.[24] The pathobiological determinants of atherosclerosis in youth (PDAY) research group reported that the atherosclerosis process begins throughout the second and third decades of life in many Americans. They also found abnormal coronary intimal thickness in one out of every six American teenagers.[25] During the initial phases of atherosclerosis, the condition cannot be diagnosed through usual paraclinical methods. Therefore, conducting autopsies for artery examination is the best method of assessing the microscopic atherosclerosis. Studies on autopsies confirmed the correlation between the intensity of coronary fatty streak and traditional risk factors.[26]

At present, there is growing prevalence of obesity in Iran and insufficient research to determine fat distribution indices of atherosclerosis and CVD incidences in the Iranian society. Therefore, we investigated atherosclerosis rate in the autopsy of people who appeared to be healthy and died due to non-cardiac problems. Moreover, we correlated this rate with anthropometric indices and body fat distribution including abdominal, visceral, subcutaneous fat and heart weight/ height ratio as a pericardial fat index.

METHODS

The present cross-sectional study investigated the data obtained from the autopsy of 40 subjects, aging 20 to 50, who died due to non-cardiac reasons and were sent to the forensic center. The bodies, with no obvious changes in body weight or form, serious injuries or contusion, were kept in a temperature of 4°C and studied in less than 24 hours. An identification form containing demographic information, cardiovascular disease, diabetes, hypertension and smoking history was completed for each subject. Since, asking the associates of the deceased about the exact amount of smoking was impossible, the question was to determine whether or not they smoked. At arrival, a 10cc blood sample was taken from each cadaver's heart, and the serum was separated in order to measure high density lipoprotein cholesterol (HDL-c) and low density lipoprotein cholesterol (LDL-c) to identify the presence of lipid disorders. Glycohemoglobin (HBA1C) was also measured to examine diabetes. Since increased levels of lipids and blood sugar can affect atherosclerosis incidence, these variables were adjusted in order to eliminate such effects.

Anthropometric measurements including height, hip, and abdominal circumferences were conducted by trained technicians and under the supervision of an experienced general physician. Three indices, namely visceral abdominal fat (VAF), subcutaneous abdominal fat (SAF), and pericardial fat (PF) were used in determining body fat distribution. However, heart weight was considered as PF representative index since it is directly linked with pericardial fat.[27] In order to measure heart weight, it was removed by cutting through the aorta as it left the pericardium. Knowing the direct relation between heart weight and body size indices,[28] heart weight (g)/ height (cm) ratio was utilized to better describe the effect of pericardial fat. The thickness of subcutaneous abdominal fat was measured at the internal rectus sheath, midway between xiphoid and umbilicus. In order to measure VAF, the omentum was first separated from intra-abdominal organs and removed from the abdomen. Fat was then removed from the omentum and weighed immediately.

In this study, careful examination of atherosclerosis was performed based on the American Heart Association (AHA) criteria.[29] Macroscopic analysis of stenosis in coronary, common carotid, internal, and external carotid arteries was also carried out. In order to evaluate atherosclerosis in the right coronary artery (RCA), left anterior descending (LAD) and left circumflex (LCX) arteries, the hearts were cut and after macroscopic study of stenosis, multiple right-angle incisions were made 3 centimeters from artery origin. Afterwards, slides and staining (Hematoxylin and Eosin (H&E) and Masson Trichrome) were prepared and were sent to the laboratory to recognize collagen precisely and determine the exact stage of atherosclerosis. Removal of bilateral carotid arteries including left and right common carotid arteries, and internal and external carotid arteries have been followed by macroscopic study of stenosis. Then, tissue samples of proximal common carotid arteries at their branching point, and proximal internal and external carotid arteries (3cm from artery origin) were sent to the lab to be used in stained slides. Stenosis was recorded in macroscopic form and as the percentage of plaque area to vessel cross-sectional area. After preparation and staining,

tissue samples were examined by a pathologist to determine probable atherosclerosis development in the mentioned arteries based on distribution pattern of fat cells, fibrous tissue and collagen.

A multinomial logistic regression analysis was performed on all collected data using SPSS version 19 (SPSS Inc., Chicago, IL, USA). In investigating the effect of fat accumulation as an independent factor and considering the link between obesity and metabolic disorders, diabetes mellitus, hyperlipidemia, and smoking were regarded as confounding factors.
It should be mentioned that as stated by the Iranian current law, deaths with an unknown cause were confirmed and the cadavers were legally moved to the forensic center, so no religious or legal obligations existed in studying the subjects. The protocol of this study was reviewed and approved by the Ethical Committee of Isfahan University of Medical Sciences in Isfahan Cardiovascular Research Center (Research project Number: 89125) (The scanned file of approval has been uploaded).

RESULTS

A total of 40 autopsies were performed on subjects averagely aging 29.97 ± 9.84 at the time of death, including 3 women (7.5%). Body fat distribution indexes and smoking history are demonstrated in table 1.

Coronary and carotid artery involvements were observed in 20 (50%) and 34 (85%) cadavers, respectively. As it is seen in table 2, which shows the frequency of microscopic atherosclerosis in the studied coronary and carotid arteries, right external carotid artery is the most involved and the highest frequency of atherosclerosis among coronary arteries is observed in LAD.

Table 3 presents crude (first model) and adjusted (second model) odds ratios (ORs) of investigated factors on atherosclerosis based on logistic regression analysis. Age, sex, smoking, LDL-c, HDL-c, HbA1C and CVD history have been adjusted in the second model. This table reveals no association between visceral fat, subcutaneous fat or waist circumference and carotid or coronary atherosclerosis in crude and adjusted models. In the crude model, heart weight/height ratio was the only index to have a significant effect on coronary atherosclerosis (OR = 11.185, and confidence interval = 1.398-89.468). Although, this index did not have a significant effect in the adjusted model, the effect remained significant after stepwise forward regression analysis (OR = 9.461, and confidence interval = 1.199-74.650).

Table 1. Demographics, medical history and fat distribution characteristics in Study cadavers

Variable	Mean/Frequency
Age (years)*	29.97 ± 9.84
Sex (male)**	37 (92.5)
History of CVD (No)**	40 (100)
Waist (cm)*	79.95 ± 18.85
Hip (cm)*	97.27 ± 18.04
Height (cm)*	172.12 ± 6.08
SAF (cm)*	1.76 ± 1.30
VAF(gr)*	129.00 ± 101.29
Heart weight (gr)*	298.25 ± 67.98
Heart/Height (kg/cm)*	1.72 ± 0.37
Smoking (Yes)**	11 (27.5)
HbA1C (mg/dl)*	5.41 ± 0.75
LDL-c (mg/dl)*	102.45 ± 18.79
HDL -c(mg/dl)*	44.72 ± 7.59
WHR*	0.81 ± 0.06

*: Mean ± SD
**: Number (%)
CVD: Cardiovascular Diseases, SAF: subcutaneous abdominal fat, VAF: visceral abdominal fat, HDL-C: High Density Lipoprotein, LDL: Low Density Lipoprotein, HBA1C: Glycohemoglobin

Table 2. Frequency of microscopic atherosclerosis in coronary and carotid arteries

Variable	Frequency Number (%)
Microscopic atherosclerosis (Yes)	
• LAD	14 (35)
• LCX	11 (27.5)
• RCA	8 (20)
• Right common carotid	16 (40)
• Left common carotid	22 (55)
• Right internal carotid	15 (37.5)
• Left internal carotid	14 (35)
• Right external carotid	23 (57.5)
• Left external carotid	12 (30)
• All coroners	20 (50)
• All carotid	34 (85)

LAD: Left Anterior Descending, LCX: Left Circumflex, RCA: Right Coronary Artery

DISCUSSION

As previously mentioned in the findings, microscopic atherosclerosis in carotid and coronary arteries was observed in 85% and 50% of autopsies, respectively. Among body fat distribution indices only heart weight/ height ratio was proven to be related with coronary atherosclerosis and they remained related after stepwise regression analysis.

Studies have shown diverse findings about how atherosclerosis is linked with body fat distribution indices.

Table 3. The Effect of fat distribution indexes on carotid and coronary atherosclerosis

	Carotid atherosclerosis OR (CI 95%)	Coronary atherosclerosis OR (CI 95%)
Visceral fat(gr)		
• First model (Crude)	1.038 (0.999-1.079)	1.009 (0.998-1.021)
• Second model (Adjusted)	1.034 (0.980-1.090)	1.004 (0.992-1.016)
Subcutaneous fat(cm)		
• First model (Crude)	1.772 (0.612-5.130)	0.894 (0.548-1.458)
• Second Model (Adjusted)	1.975 (0.371–10.504)	0.717 (0.387-1.327)
Heart/Height(kg/cm)		
• First model (Crude)	8.558 (0.620-118.132)	11.185 (1.398-89.468)
• Second model (Adjusted)	4.498 (0.481-50.948)	7.831 (0.365-168.054)
Waist(cm)		
• First model (Crude)	1.050 (0.977-1.129)	1.029 (0.987-1.072)
• Second model (Adjusted)	1.062 (0.907-1.244)	1.002 (0.952-1.055)

First Model: Only fat distribution index was included as a variable in the model.
Second Model: The model was adjusted based on age, smoking, LDL, HDL-C, HBA1c and history of CVD

Some found abdominal fat (AF) to be an independent factor for atherosclerosis. For instance, in 2005, Kawamoto et al. studied the association between SAF and common carotid artery intima-media thickness in 297 non-obese male individuals aging 16 to 79. Their findings revealed a direct and independent link between-SAF and common carotid atherosclerosis,[30] identical to the one they had previously discovered among women.[31]] Another cross-sectional experiment on 955 subjects with normal weight confirmed the relation between VAF and atherosclerosis risk factors, comprising hyperlipidemia and blood sugar. It also suggested VAF as more important than BMI in predicting the incidence of CVD risk factors.[32]

However, some publications showed no connection between carotid atherosclerosis, VAF, and SAF. In a study performed on 849 Japanese subjects, Takami et al. found a relation between VAF, SAF and carotid artery intima-media thickness before adjustments for other obesity indices such as BMI and WHR, which did not remain significant after adjustment. Takami et al. did not suggest AF as an independent factor for carotid atherosclerosis.[33] Another study investigating the relationship between VAF, SAF and coronary artery calcification in 410 individuals aging 55 to 88 did not indicate any link between body fat distribution and plaque formation.[34]

The correlation between PF and atherosclerosis, especially in coronary arteries, has been emphasized in many papers including Framingham longitudinal study that employed CT scan to measure VAF and SAF in 1267 persons. Its results, suggesting only PF was related with myocardial infarction after regression analysis and adjustment of other factors, supported the hypothesis of PF being an independent risk factor for atherosclerosis.[35]

In a cohort study, Ding et al. examined PF as a CHD incidence predictor in 998 Multi-Ethnic Study of Atherosclerosis (MESA) participants during 2000-2005. They found an independent correlation between PF and CHD incidence after adjustment of all other risk factors. They introduced PF as a useful predictive factor that can be more reliable than general fat distribution indices such as BMI and waist circumference.[36] Another study on the correlation between calcified coronary plaque and PF in 159 MESA participants with no CHD symptoms confirmed PF as an independent factor for calcified coronary plaque.[20]

A review article by Vela et al. on atherosclerosis risk factors indicated periadventitial fat of coronary arteries and therefore PF to be a crucial factor for coronary atherosclerosis.[37] Despite VAF and SAF being vaster than PF, the link between PF and coronary artery atherosclerosis found in many studies is thought-provoking. Research revealed inflammatory factors and free fatty acids to be more abundant in PF than in any other body fat.[38-40] They also proved PF and inflammatory factors accumulated in PF to have a local effect on coronary artery atherosclerosis.[41,42] In a review article, Sacks and Fain reported the existence of cytokines and macrophages in PF and a direct link between PF and coronary arteries, which is the result of no fibrosis fascial layers impeding the diffusion of fatty acids and adipokines between PF and the underlying vessel wall as well as myocardium.[43] As a study by Zamani et al. on gene mutation in the development of atherosclerosis in Iranian cases, showed that the

relation between different factors and plaque formation is a field for further research.[44]

Among VAF, SAF, PF and waist circumference, our study only demonstrated a significant link between PF and coronary artery atherosclerosis, which supports the hypothesis of PF being more effective. Since no significant association was observed between carotid atherosclerosis and PF, it can be concluded that PF has a local effect on artery atherosclerosis. In addition, the Iranian race and genetic condition can be a resistant factor for occurrence of atherosclerosis in association with VAF, SAF.

However, a drawback to the study was that cadavers were not weighed and therefore BMI could not be calculated and BMI-adjusted models could not be made.

Although, sample size in the present study was not large enough, it might be concluded that PF measurement through different methods can be an important atherosclerosis predictive factor. In order to confirm this theory, conducting further cross-sectional and longitudinal studies using practical methods, applicable to living subjects, such as CT scan, MRI and echocardiography to investigate the relation between PF and CVD incidences and also atherosclerosis is suggested.

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