

ORIGINAL ARTICLE

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Is visceral adipose tissue or subcutaneous adipose tissue a risk factor for atherosclerotic heart disease in familial mediterranean fever?

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Abstract

Familial Mediterranean fever (FMF) is an autoimmune chronic systemic inflammatory disease. Adipose tissue (AT) is an endocrine organ that causes systemic inflammation. Systemic inflammation is an important risk factor for the development of atherosclerosis. AT beneath the skin is called subcutaneous adipose tissue (SAT) and the AT surrounding internal organs is called visceral adipose tissue (VAT). This study aimed to evaluate whether VAT and SAT areas differed in FMF patients compared to healthy controls and to evaluate the correlations among VAT and SAT areas with cardiovascular risk factors in FMF patients. This study was planned retrospectively. 46 patients in FMF group and 54 patients in control group were included the study. Laboratory data and demographic characteristics were detected from the hospital file system and recorded. The L3 vertebra reference point was selected to standardize the measurement location in all patients. VAT and SAT areas were separately determined as cm². VAT area was significantly higher in FMF group ($p<0.001$). In FMF group, we found significantly positive correlation between insulin resistance ($r=0.61$, $p<0.001$), systolic blood pressure ($r=0.38$, $p<0.05$), low density lipoprotein cholesterol (LDL-C) ($r=0.62$, $p<0.001$), triglyceride (TG) ($r=0.49$, $p<0.001$) and VAT. Negative correlation was found between high-density lipoprotein cholesterol (HDL-C) and VAT ($r=-0.71$, $p<0.001$). VAT area was increased as the duration of diagnosis increased ($r=0.80$, $p<0.001$). In conclusion, this study revealed that in FMF patients, VAT area was higher than control and associated with cardiovascular risk factors. Increased awareness of this risk can lead to some measures to be taken to prevent possible diseases.

Keywords: Familial mediterranean fever, visceral adipose tissue, subcutaneous adipose tissue, atherosclerotic heart disease

Introduction

Familial Mediterranean Fever (FMF) is an inherited and autoimmune chronic inflammatory disease characterized by serosal inflammation and recurrent attacks of fever [1]. FMF disease is caused by mutations in the Mediterranean fever (MEFV) gene and is inherited autosomal recessively. FMF is diagnosed especially among Turks, Arabs, Jews and Armenians [2]. FMF characterized by episodes of attack and attack-free periods. Systemic inflammation has an important role in both the formation and progression of atherosclerosis [3]. It is thought that sub-clinical inflammation continues in FMF even between attacks. Subclinical inflammation can lead to coronary artery disease by causing endothelial dysfunction [1,4].

Adipose tissue (AT) is an endocrine organ secretes adipokines, chemokines and cytokines [5]. Especially in obese, AT cause systemic inflammation [6]. While the AT under the skin is called subcutaneous adipose tissue (SAT), AT surrounding the internal organs is called visceral adipose tissue (VAT) [7]. In previous studies found that VAT and SAT are closely related to cardiovascular risk factors (CRF) [8-10].

However, we did not find a study about VAT and SAT areas of FMF patients in literature search. We aimed to determine whether VAT and SAT areas differ in patients with FMF compared to healthy controls and show the correlation among VAT, SAT areas and CRF in this study.

Materials and Methods

Patients who were admitted to our hospital from May 1, 2017 to January 1, 2020 and diagnosed with FMF according to Tel-Hashomer clinical criteria [11] were retrospectively detected from hospital file system. FMF patients between 18-70 ages and who underwent abdominal computer tomography (CT)

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separated. Patients who had an FMF attack up to two weeks before admission to the hospital or who did not use colchicine regularly were excluded from the study. Patients who had no disease and underwent abdominal CT scan at the time of admission but did not have any pathognomonic radiological findings were included as controls. Patients with a history of diabetes mellitus, hypertension, dyslipidemia, concomitant inflammatory diseases, malignancy, peritonitis, body mass indexes above 35, patients using cigarette and lipid-lowering drugs were excluded. 46 patients in FMF group and 54 patients in control group were included the study.

Age, weight, height, gender, total cholesterol, triglyceride (TG), body mass index (BMI) (calculated as $\text{weight}/(\text{height})^2$), high-density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), insulin resistance, systolic and diastolic blood pressure of the groups were detected from the hospital file system and recorded.

Measurement of visceral and subcutaneous tissue thickness

The images were acquired without contrast on Toshiba Aquilion Prime (80 x 2) multi-slice CT device (Toshiba Medical Systems, Japan). Contrast-enhance images were obtained at the portal venous phase with a start delay of 70 second after each patient received a total of 90–100 mL of nonionic contrast agent and a 30 mL of saline injection at a flow rate of 2–3 mL/s. The CT protocol was as follows: peak kilo voltage 120 kVp, tube current, 150–165 mAs; maximum collimation, 2.5 mm; slice thickness, 2 mm; and rotation time, 0.75 second. In all patients, fat tissue was assessed from the cross-section of the L3 vertebra using a 3-dimensional workstation (Aquarius 3D Workstation, Tera Recon Inc., San Mateo, CA, USA). The L3 vertebra reference point was selected to standardize the measurement location in all patients. VAT and SAT areas were separately determined (cm^2). In addition, abdominal circumference (cm) at the same level was calculated. Measurements were repeated twice and averaged. With this software, VAT and SAT areas measurements are performed automatically.

Approval was obtained from the ethics committee of Afyonkarahisar Health Sciences University Clinical Research Ethics Committee (Date: 07/02/2020, Decision no: 2020/88). This study was performed in line with the principles of the 1964 Helsinki Declaration and Good Clinical Practice.

Statistical analysis

SPSS (Statistical Package for Social Sciences) 20.0 program was used for the statistical analysis of the data. Whether the data showed normal distribution was determined by Kolmogorov – Smirnov test. The t test was used to analyze the data with normal distribution. Data that did not show normal distribution were compared using the Mann-Whitney U test. The relationship between variables was evaluated using Pearson-Spearman's correlation analysis. P value<0.05 was considered statistically significant. Data were expressed as mean±standard deviation (Mean±SD).

Results

The study included 46 patients with FMF and 54 healthy controls. In FMF group, 24 were male (52.2%), 22 were female (47.8%). In the control group, 28 were male (51.9%), 26 were female (48.1%). In FMF group, the mean BMI was $30.1 \pm 4.77 \text{ kg/m}^2$. In the control group, the mean BMI was $31.8 \pm 4.53 \text{ kg/m}^2$. There were no significant differences between the groups in terms of gender, age, or BMI. In FMF group, the mean abdominal circumference was $85.97 \pm 5.74 \text{ cm}$, VAT area was $96.84 \pm 90.52 \text{ cm}^2$ and SAT area was $143.2 \pm 106.5 \text{ cm}^2$. In control group, the mean abdominal circumference was $90.18 \pm 11.48 \text{ cm}$, VAT area was $85.2 \pm 76.1 \text{ cm}^2$ and SAT area was $146.61 \pm 112.90 \text{ cm}^2$ (Figure 1). Sociodemographic characteristics, laboratory parameters and adipose tissue thickness of the participants were summarized in Table 1. VAT area was significantly higher in FMF group. There was no difference between groups in terms of SAT area measurements. While systolic blood pressure, insulin resistance, LDL-C, TG levels were significantly higher, HDL-C was significantly lower in FMF group (Table 1).

Table 1. Sociodemographic characteristics, laboratory parameters and adipose tissue thickness of the participants

Parameter	FMF (n=46) (mean±sd)	Control (n=54) (mean±sd)	P value
Age (year)	25.34±4.99	24.64±5.02	>0.05
Gender (male)	Male (n=24)	Male (n=28)	>0.05
Gender (female)	Female (n=22)	Female (n=26)	>0.05
Height (cm)	170±7	173±6	>0.05
Weight (kg)	78.70±9.6	82.40±6.4	>0.05
BMI (kg/m^2)	30.1±4.77	31.8±4.53	>0.05
Insulin Resistance	6.48±4.35	3.15±2.77	<0.001
Abdominal Circumference (cm)	85.97±5.74	90.18 ±11.48	>0.05
Systolic Blood Pressure(mmHg)	135±20.50	120±15	<0.05
Diastolic Blood Pressure(mmHg)	80±15	75±10	>0.05
TG (mg/dl)	146.79±35.43	132.79±24.60	<0.001
HDL-C (mg/dl)	36.57±10.90	41.10±11.20	<0.05
Total cholesterol (mg/dl)	190.20±28.2	182.95±30.10	>0.05
LDL-C (mg/dl)	132.75±21.50	123.50±26.50	<0.001
VAT (cm^2)	96.84±90.52	85.2±76.1	<0.001
SAT (cm^2)	143.2±106.5	146.61±112.90	>0.05

We evaluated the relationship of both VAT and SAT areas with CRF. In FMF group, we found significantly positive correlation between insulin resistance ($r=0.61$, $p<0.001$), systolic blood pressure ($r=0.38$, $p<0.05$), LDL-C ($r=0.62$, $p<0.001$), TG ($r=0.49$, $p<0.001$) and VAT area. Negative correlation was found between HDL-C and VAT area ($r=-0.71$, $p<0.001$). VAT area was increased as the

duration of diagnosis increased ($r=0.80$, $p<0.001$). Abdominal circumference ($r=0.39$, $p<0.001$), BMI ($r=0.28$, $p<0.05$), insulin resistance ($r=0.21$, $p<0.05$), and TG levels ($r=0.61$, $p<0.001$) were associated with SAT. However, no correlations were found between SAT area and duration of diagnosis (Table 2).

Table 2. Correlation between VAT and cardiovascular risk factors in FMF and control groups

Parameters	VAT (FMF)		VAT (Controls)	
	r	P value	r	P value
Age (year)	0.33	0.524	0.14	0.120
BMI (kg/m ²)	0.19	0.610	0.28	<0.05
Abdominal Circumference (cm)	0.25	0.592	0.39	<0.001
Systolic Blood Press (mm/Hg)	0.38	<0.05	0.17	0.098
Diastolic Blood Press (mm/Hg)	0.25	0.687	0.32	0.897
Insulin Resistance	0.61	<0.001	0.21	<0.05
Total cholesterol (mg/dl)	0.11	0.537	0.19	0.225
LDL-C (mg/dl)	0.62	<0.001	0.56	0.063
HDL-C (mg/dl)	-0.71	<0.001	0.44	0.078
TG (mg/dl)	0.49	<0.001	0.61	<0.001
Duration of diagnosis	0.80	<0.001	0.23	0.440

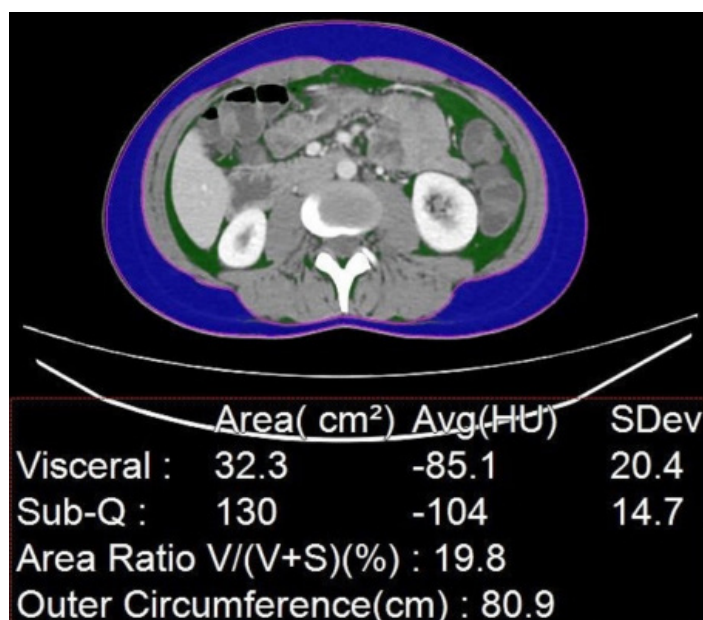


Figure 1. CT image at the L3 vertebral level shows segmentation of VAT (green) and SAT (blue) by the automated tool

Discussion

In literature, there are no studies investigating the relationship of FMF with VAT and SAT areas, and the relationship among VAT area, SAT area and CRF in FMF patients. In this study, we found that VAT area was significantly higher in FMF patients. VAT area was associated with CRF such as LDL-C, TG, systolic blood pressure and insulin resistance. Also, VAT area was associated with duration of diagnosis. As the diagnosis time of the patients was delayed, VAT area was increased.

Systemic inflammation is a risk factor for development and progression of atherosclerosis. [12]. FMF is an Interleukin 1

beta (IL-1 β) dependent autoinflammatory disease that cytokine levels such as Interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF- α) are high during both attack and non-attack periods [13,14]. It has been stated that the inflammation seen in FMF increased the susceptibility to atherosclerosis [15-17]. Visceral fat is an endocrine organ closely related to obesity and systemic inflammation [18]. In previous studies, acute phase proteins, pro-inflammatory cytokines such as IL-6, TNF- α and pro-inflammatory proteins such as adipokines, neuropeptides (eg, substance P) were found to be higher in obese patients. All of these proinflammatories are secreted by adipocytes, macrophages and lymphocytes found in mesenteric adipose tissue. In other words, systemic inflammation can be triggered by proinflammatory factors secreted from mesenteric adipose tissue [19-23]. According to Kabir et al, VAT area has an important role in both production of inflammatory cytokines and transfer of free fatty acids to the liver [24]. Shulman et al. indicated that the VAT area causes CRF like insulin resistance and low-grade systemic inflammation [25]. In the study conducted by Ohman et al., they transplanted fat pad to mice, they indicate that visceral adipose-related inflammation accelerated atherosclerosis [26]. Mahabadi et al. stated that pericardial adipose tissue and VAT area are associated with cardiovascular diseases independent of conventional obesity measures [27].

Cytokines released from VAT area and increased cytokines in FMF disease increase the levels of inflammation in the blood. This suggests that both can individually increase systemic inflammation, thereby increasing atherosclerosis. According to this, detection of higher VAT area in FMF compared to the control group shows us that FMF patients have a much higher risk of atherosclerosis. The reason for this may be that as the VAT area increases, the number of cytokines secreted into the blood increases and this increases the level of systemic inflammation. The reason for the higher VAT area in FMF compared to the control group may be that pro-inflammatory cytokines secreted from VAT cause auto-

inflammation and increase the area of visceral adipose tissue. That may also show that in FMF patients, atherosclerotic risk is closely related to VAT area as well as auto-inflammation.

Paulus and et al indicated that VAT area has a more harmful effect on cardiovascular events than SAT area [28]. Kamimura et al. found that VAT area was a predictor of cardiovascular events in chronic renal failure patients with not receive renal replacement therapy. In addition, they found that cardiovascular events were observed 3 times more in patients with VAT/SAT area ratio greater than 0.55. [29]. Ladeiras et al. found that, irrespective of coronary artery calcification and CRF, VAT/SAT area ratio was an independent predictor of death and coronary artery event [30]. Similar to these studies in our study, VAT area was found to be significantly higher in FMF patients. There was no significant difference in terms of SAT area between FMF patients and control group. Data from recent studies show that visceral fat is associated with hypertension, coronary artery disease, impaired fasting glucose, and metabolic syndrome. Therefore, the distinction between VAT and SAT seems important [31]. Fox et al. evaluated the correlation of visceral and subcutaneous fat with risk factors for metabolic syndrome and coronary artery disease and found that visceral fat had a stronger association with both [8]. Age, LDL-C, HDL-C, presence of diabetes mellitus and smoking, according to Framingham scoring, are used to calculate 10-year cardiovascular survival [32]. Preis et al. conducted a study with non-diabetic patients from the Framingham Heart Study and evaluated the relationship of VAT and SAT areas with insulin resistance that one of the CRF. They found that both VAT and SAT areas were positively correlated with insulin resistance; however, they stated that the relationship between VAT area and insulin resistance was more significant [33]. We investigated whether VAT area or SAT area was associated with CRF in FMF patients. In our study, similar to the above studies, a positive correlation was found among insulin resistance, VAT and SAT areas. Differently, we also found a positive correlation among TG levels, VAT and SAT areas. However, considering the SAT area relationship, the relationship between insulin resistance and VAT area, TG levels and VAT area were more significant in FMF patients. The reason for this may be the negative effects of inflammation/sub inflammation, detected in patients with FMF, on glucose metabolism and lipid profile.

In the present study, systolic blood pressure, insulin resistance, LDL-C and TG levels were found to be positive correlated and HDL-C levels were found to be negative correlated with VAT area in FMF group. Positive correlations were found between abdominal circumference, BMI, insulin resistance, TG levels and SAT area. When considered, VAT area appears to be positively correlated with more CRF.

Also, in the present study, we found that VAT area is positively correlated with the lipid profile. It is considered to be the predictor and main risk factor for cardiovascular diseases [34]. There is a strong correlation between TG, LDL-C and HDL-C levels in the development of atherosclerosis [35]. In our study, the positive correlations among LDL-C, TG and VAT area, which have important roles in the development of atherosclerosis, and a negative correlation between HDL-C levels and VAT area, show us that VAT area can be a predictor parameter for cardiovascular diseases in FMF patients.

In our study, as the duration of diagnosis increased, VAT area increased. We think that the reason for this is that cytokines secreted from VAT increase visceral adipose tissue as a result of autoinflammatory effects. Thus, growing VAT area may secrete more cytokines and increase the level of cardiovascular risk.

The main limitation of the study is the small sample size and cross-sectional evaluation of parameters related to atherosclerosis. Another limitation of the study is that the follow-up measurements of the groups were not taken.

Conclusion

Increasing systemic inflammation due to both FMF and VAT area increases the risk of atherosclerotic heart disease. The positive correlation of VAT area with CRF in FMF patients indicates that FMF patients are at higher atherosclerotic risk than normal healthy control. Increased awareness of this risk can lead to some measures to be taken to prevent possible diseases.

Conflict of interests

The authors declare that they have no competing interests.

Financial Disclosure

All authors declare no financial support.

Ethical approval

Local Ethics Committee of Afyonkarahisar Health Sciences University Clinical Research Ethics Committee (Date: 07/02/2020, Decision no: 2020/88).

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