Eur J Gen Med 2015; 12(2): 131-135

Original Article

DOI : 10.15197/sabad.1.12.27

Epicardial Fat Thickness and its Association with Cardiovascular Risk in Patients with Type 2 Diabetes Mellitus

Ömer Akyürek[1], Duran Efe[2], Zeynettin Kaya[3]

ABSTRACT

Previous studies have clearly shown that epicardial adipose tissue (EAT) mass is associated with increased incidence of coronary artery disease. In the present study, the relationship between the EAT volume measured by cardiac multislice computerized tomography (MSCT) and cardiovascular risk was investigated in patients with type 2 diabetes mellitus. Ninety type 2 diabetic patients and 62 healthy controls were included in the study. We examined metabolic and anthropometric parameters including body mass index (BMI), fasting glucose and serum lipids and EAT volume of patients in comparison to those of control subjects. EAT volume was higher in Type 2 diabetic patients compared to control group (172.75 ± 64.85 cm3 and 68.94 ± 37.74 cm3, respectively) (p<0.001). Type 2 diabetic patients had significantly higher levels of fasting glucose (p=0.014), total cholesterol (p<0.001), triglycerides (p=0,017) and LDL-cholesterol (p=0,022) versus control group. EAT volume was correlated with BMI, glucose, HbA1c, LDL-cholesterol, total cholesterol. In a stepwise regression analysis, Hba1c emerged as a significant predictor of EAT volume (ß= 0.610, p¤0.001), accounting for 18% of its variability. These results provide additional evidence for the presence of subclinical cardiovascular disease (CVD) in type 2 diabetic patients. It is also important to note that our findings reveal significant relationships between HBA1c and cardiovascular changes and underline the importance of glucose control in predicting CVD.

Key words: *Type 2 diabetes mellitus, epicardial adipose tissue, cardiovascular risk*

Epikardiyal Yağ Kalımlığı ve Tip 2 Diyabet Mellituslu Hastalarda Kardiyovasküler Risk ile İlişkisi

ÖZET

Epikardiyal yağ dokusu miktarının koroner arter hastalığı sıklığında, yaygınlığında ve ciddiyetinde artış ile ilişkili olduğu önceki çalışmalarda açık şekilde gösterilmiştir. Çalışmamızda çok kesitli tomografi (ÇKBT) ile ölçülen epikardiyal yağ hacmi Tip 2 Diabetes mellitus hastalarında kardiyovasküler risk yönünden değerlendirilmiştir. Doksan Tip 2 diabet hastası ve 62 sağlıklı gönüllü çalışmaya dahil edildi. Vücut kitle endeksi, açlık kan şekeri, serum lipid değerleri gibi metabolik ve antropometrik parametreler ile epikardiyal yağ hacmi karşılaştırıldı. Çalışmaya dahil edilen DM hastaların epikardiyal yağ hacmi 172,75 ± 64,85 cm3 iken kontrol grubunun epikardiyal yağ hacmi 68,94 ± 37,74 cm3 olarak ölçüldü (p<0.001). DM grubundaki hastaların AKŞ (p<0.001), kolesterol (p<0.001), trigliserid (p=0,017) ve LDL (p=0,022) değerleri kontrol grubundan anlamlı olarak yüksek saptandı. Epikardiyal yağ hacmi ile HbA1c, kilo, AKŞ, kolesterol, LDL ve VKI arasında kuvvetli pozitif korelasyon mevcuttu. Aşamalı regresyon analizinde, HbA1c epikardiyal yağ hacmi için önemli bir predictör olduğu (ß= 0,610, p<0,001) ve % 18 oranında öngörü sağlayabileceği sonucuna varıldı. Bu sonuçlar, tip 2 diyabetik hastalarda subklinik kardiyovasküler hastalık (CVD) varlığı için ek kanıt sağlar. Ayrıca HbA1c ile kardiyovasküler değişiklikler arasında anlamlı ilişkileri gösterir ve glikoz kontrolünün CVD için önemini bir kez daha ortaya koyar.

Anahtar kelimeler: *Tip 2 Diabetes mellitus, epikardiyal yağ hacmi, kardiyovaküler risk*

Mevlana University, Medical Faculty, Departments of Internal Medicine[1], Radiology[2] and Cardiology[3], Konya, Turkey

Received: 21.01.2014, Accepted: 03.07.2014

Correspondence: *Ömer Akyürek,*
Department of Internal Medicine, Mevlana University, Konya, Turkey
Tel: +90 332285 35 38 Fax: + 90 332 285 35 16
E-mail: dromerakyurek@gmail.com

INTRODUCTION

Cardiovascular diseases (CVD) are a major cause of mortality worldwide (1). Atherosclerotic cardiovascular complications are responsible for increased mortality and morbidity particularly among diabetic patients (2-4). CVD including coronary artery disease (CAD) and stroke account for 80% of all deaths in diabetic patients (5). There is evidence that abnormal lipid profile of excessive visceral fat tissue is linked with increased systemic inflammation, diabetes mellitus (DM) and CVD (6-8). Epicardial adipose tissue (EAT) is one of the visceral fat depots found in the body (9,10). It shares a common embryogenetic origin with intraabdominal fat and both epicardial and intra-abdominal fat evolve from brown adipose tissue during embryogenesis (11). EAT is located between myocardium and visceral layer of pericardium and shares the same microcirculation with myocardium (10). It is the source of several pro-inflammatory and proatherogenic cytokines as well as anti-inflammatory and antiatherogenic adipokines such as adiponectin and adrenomedulin (12). Studies have shown that EAT mass clearly reflects abdominal visceral fat accumulation as measured by MRI (13,14). EAT may be quantified using MRI, CT and echocardiography, with each method having its advantages and disadvantages (15).

A number of studies demonstrated the relation of visceral adipose tissue and specifically EAT with the risk for metabolic syndrome, CVD and CAD (15-19). EAT thickness has been associated with the extent and severity of CAD in CVD patients (19,20). Since the association between EAT volume and CAD was clearly shown by previous studies, in the present study we retrospectively examined EAT volume and its relation with cardiovascular risk in DM patients who had undergone multislice computed tomography scans (MSCT) for various reasons.

MATERIAL AND METHOD

In this retrospective cohort study, data were reviewed for a total of 90 Type 2 DM patients and control group of 62 patients who had admitted to Mevlana University outpatient clinics and undergone (MSCT) scans for any reason between March 2011 and April 2013. Patients with missing and/or unavailable laboratory data, patients who had undergone percutaneous or surgical revascularization for management of CAD, patients with peripheral artery disease, atrial fibrillation, active chronic obstructive pulmonary disease, heart failure or chronic renal failure and morbidly obese patients were excluded from the study. Control group patients were healthy individuals who did not have chronic renal failure, CAD, vasculitic lesions, DM, hypertension, hepatic parenchymal disease or any current acute infections.Clinical conditions recorded on admission and laboratory results simultaneously obtained during MSCT scans were reviewed for all patients. Body mass index (BMI) was estimated by dividing the body weight (in kilogramme) by height squared (meter) for patients whose height and weight recordings were available. Study procedures were approved by the local ethics committee.

MSCT scans were conducted for all patients (Somatom Sensation 64, Siemens, Forchheim, Germany). A CT attenuation threshold between -≤200 and -≤ 50 HU was used to define the adipose tissue density. EAT volumes were measured using cardiac workstation volume analysis software tool (Siemens, Leonardo) and manual ROI (Region of interest) drawings in cm3.

Statistical Analysis

For statistical analysis, the SPSS (version 16.0) software package was used. Categorical parameters were presented as percentage. Continuous variables (age, body mass index, body weight, height, lipid panel, blood glucose, EAT) were presented with mean ± standard deviation. Kolmogorov–Smirnov test was applied to ascertain the normality of the variables. Differences between data were studied using the Student's t-test. Statistical correlation was assessed using Pearson's test (r). A multiple linear regression analysis was performed first using the standard method and then forward stepwise selection to identify independent factors affecting EAT, Hba1c, and to estimate the final predictors of their variability. Statistical significance was set at $p < 0.05$.

RESULTS

One hundred and fifty two patients between 18 to 75 years of age were included in the study. They were divided into two groups: 90 patients in Type 2 DM group and 62 in control groups. Of Type 2 DM patients, 73.2% were male 26.8% were female and 26% were current smokers. 64.4% of the control patients were male, 35.6% were female and 31.8% were current smokers. There was no difference between the two groups in age, gender or smoking status.

Table 1. *Baseline Charecteristics in the study groups*

	DM	Control	p value
Age, years	*57.69 ± 11.43*	*55.59 ± 10.71*	*0.142*
Glucose, mg/dL	*158.10 ± 59.28*	*92.41 ± 7.21*	*<0.001*
EAT, cm³	*172.75 ± 64.85*	*68.94 ± 37.74*	*<0.001*
BUN, mg/dL	*32.09 ± 12.97*	*27.87 ± 9.63*	*0.389*
Creatinine, mg/dL	*0.96 ± 0.16*	*0.72 ± 0.19*	*0.448*
AST, U/L	*25.76 ± 11.45*	*23.31 ± 7.11*	*0.673*
ALT U/L	*31.55 ± 24.14*	*28.44 ± 9.51*	*0.166*
Total cholesterol, mg/dl	*210.20 ± 51.49*	*168.18 ± 37.75*	*<0.001*
TG, mg/dl	*183.30 ± 106.36*	*133.02 ± 61.92*	*0.017*
HDL, mg/dl	*39.00 ± 15.49*	*44.44 ± 10.92*	*0.299*
LDL, mg/dl	*129.37 ± 52.27*	*106.10 ± 20.87*	*0.022*
BMI, kg/m²	*28.90 ± 4.42*	*26.49 ± 2.93*	*0.115*

hemoglobin A1c (HbA1c) (%), high density lipoprotein cholesterol (HDL-C; mg/dL)-cholesterol, low density lipoprotein-cholesterol (LDL-C; mg/dL), aspartate aminotransferase (AST; mg/dL), alanine aminotransferase (ALT; mg/dL), blood urea nitrogen (BUN; mg/dL) triglyceridetrigl (TG) epicardial adipose tissue (EAT) body mass index (BMI)

The HbA1c was 7.69 ± 2.44 % for Type 2 DM patients. EAT volume was 172.75 ± 64.85 cm3 for Type 2 DM patients and 68.94 ± 37.74 cm3 for control group and the difference was statistically significant (p<0.001). Patients in DM group had significantly higher values of FBG (p<0.001), total cholesterol (p<0.001), triglycerides (p=0,017) and LDL-cholesterol (p=0.022) compared to control group. Anthropometric measurements and laboratory data of all participants are shown in Table 1. A gender-based analysis of DM patients divided in two subgroups as females and males showed that there was no significant difference in laboratory values and EAT volume (p=0.264 for EAT volume). Of DM group patients, 63.4% had hypertension and when patients were divided into two groups as normotensives and hypertensives, there was still no significant difference among them with respect to laboratory values or EAT volume (p=0.246 for EAT volume). Similarly, there was no significant difference between smokers and non-smokers in EAT volume (p=0.412).

Pearson's correlation analysis was used for assessment of the relation of EAT volume with other clinical parameters in DM patients. A strong and positive correlation was found between EAT volume and HbA1c, weight, FBG, total cholesterol, LDL cholesterol and BMI. (Table 2). In a stepwise regression analysis, Hba1c emerged as a significant predictor of epicardial fat volume (ß= 0.610, p¤0.001), accounting for 18% of its variability.

Table 2. *Correlation analysis for EAT volume*

	p value	r
Age, years	*0.39*	*0.217*
HbA1c	*¤0.001*	*0.610*
Weight, kg	*¤0.001*	*0.421*
Glucose, mg/dL	*¤0.001*	*0.344*
Total cholesterol, mg/dl	*0.009*	*0.259*
TG, mg/dl	*0.340*	*0.100*
LDL, mg/dl	*0.013*	*0.258*
HDL mg/dl	*0.144*	*0.153*
BMI, kg/m2	*0.001*	*0.339*
Height, cm	*0.525*	*0.067*
BUN, mg/dL	*0.675*	*-0.044*
AST, U/L	*0.580*	*-0.058*
ALT U/L	*0.865*	*0.018*
Creatinine, mg/dL	*0.800*	*-0.027*

high density lipoprotein cholesterol (HDL-C; mg/dL)-cholesterol, low density lipoprotein-cholesterol (LDL-C; mg/dL), aspartate aminotransferase (AST; mg/dL), alanine aminotransferase (ALT; mg/dL), blood urea nitrogen (BUN; mg/dL) triglyceridetrigl (TG) epicardial adipose tissue (EAT) body mass index (BMI)

DISCUSSION

The results of the current study showed that Type 2 DM patients had a greater EAT volume compared to control group and there was a strong and positive correlation between EAT volume and HbA1c, weight, FBG, total cholesterol, LDL cholesterol and BMI. Several studies showed the link between EAT volume and metabolic syndrome, CVD and CAD suggested that EAT volume might be an important marker for predicting CVD risk (15-19). Consistently, in the present study, we found that EAT volume was significantly greater in DM patients compared to control group and HbA1c was a strong predictor of EAT volume.

CVD is the major cause of DM-related mortality and morbitidy, and hypertension, dyslipidemia, obesity and smoking are all factors associated with increased CVD risk among DM patients (3-5). Mansour et al. show that, the prevalence of symptomatic CVD and concomitant hypertension was 44.3%, respectively. 25.0% were current smokers and 70.5% were obese or overweight (21).

In another study, 43.8% of diabetic patients were obese, 35.0% were smokers and 53.2% had hypertension (22). The North Catalonia Diabetes Study demonstrated that 77.7% of DM patients had dyslipidemia (23). In the present study, 26% of patients were smoking and 63.4% were hypertensive, with a mean BMI of 28.90 ± 4.42 and consistent with previous studies, 74. 1% were dyslipidemic. These established factors represent separate individual risk factors for morbidity and mortality in DM patients.

It is well known that visceral fat mass is a prominent cardiac risk factors and a good predictor of metabolic syndrome (17,24). In one study, EAT thickness, measured by echocardiography exhibited an apparent association with diastolic blood pressure and insulin resistance (25). Having been identified as a parameter correlated with visceral fat mass and quantifiable with many methods, EAT mass is related with the development, presence, frequency and severity of CAD, as shown by various studies. EAT was suggested to have a mediating role in the development of atherosclerosis by causing ischemia, oxidative stress and inflammation (15,26). In their study with 202 patients, Jeong JW et al. found a high-level correlation between EAT and the severity of CAD suggested that EAT might be used for risk stratification in CAD patients (27). Ahn et al. measured EAT thickness using echocardiography in 527 patients who had undergone their first coronary angiography procedure and reported an association between EAT thickness and clinical and laboratory activation and extent of CAD. The same study also demonstrated the relation of EAT thickness with insulin resistance and inflammation (19). In a study by Hyun Min Kim et al., increased EAT volume was significantly associated with coronary artery stenosis among asymptomatic Type 2 DM patients (28). Wang et al. conducted a study with 49 Type 2 DM patients and established the relation of MDCT-detected excessive EAT volume with metabolic syndrome and coronary atherosclerosis (29). In a study by Cetin et al., it was emphasized that increased EAT volume and carotid intima-media thickness might be a useful marker for identification of atherosclerosis in Type 2 DM patients (30). A study by Wang CP et al. showed the association of increased EAT volume with coronary artery disease and metabolic syndrome parameters in Type 2 DM patients (31). Consistent with previous studies, in the present study Type 2 DM patients were found to have a significantly greater EAT volume compared to control group. There was no significant difference between females and males in DM group. EAT volume did not significantly differ among hypertensive patients versus normotensives and among smokers versus non-smokers. A strong and positive correlation was found between EAT volume and HbA1c, weight, FBG, total cholesterol, LDL cholesterol and BMI. The regression analysis showed that HbA1c was a strong predictor of EAT. This finding lends further support for the prominence of HbA1c value with respect to CVD risk in DM patients.

EAT may be quantified using various techniques (13,24,32). MSCT and three-dimensional MRI were demonstrated to be more sensitive and specific for quantification of epicardial fat mass compared to echocardiography (13). On the other hand, MSCT is a technique that gives the most accurate results for EAT measurement due to its higher resolution (24). It has the advantage to allow for simultaneous assessment of coronary arteries in addition to EAT measurement. However, it has several limitations including exposure to radiation and higher cost. In the present study, EAT volumes were measured for patients previously undergoing MSCT scans due to multiple indications and examined in relation to cardiovascular risk. That way, EAT could be quantified with a high sensitivity and specificity.

In conclusion, EAT which has been previously associated with CVD predicts increased cardiovascular risk in diabetic patients. Our results indicate that patients with diabetes are connoted by higher frequency of dyslipidemia and increased EAT, suggesting an increased cardiovascular risk. Our data underline the importance of glucose monitoring in patients with type 2 diabetes. Measurement of EAT might be considered for early detection and management of potential atherogenic risk factors for complications. In light of these considerations, cardiovascular risk factors should be regularly checked during follow-up of diabetic patients.

Acknowledgments, sources of funding, conflict of interest statements, and all author disclosures: No commercial party having a direct financial support, any conflicts interest in the results of the research supporting this article has or will confer a benefit on the authors or on any organization with which the authors are associated.

REFERENCES

1. *World Health Organization 2011 The top 10 causes of death. Fact Sheet no. 310. http://www.who.int/mediacenter/factsheets/fs310/en/index.html*
2. *Fagan TC, Sowers J. Type 2 diabetes mellitus: Greater cardiovascular risks and greater benefits of therapy. Arch Intern Med 1999; 159:1033-4.*

3. Clarke PM, Gray AM, Briggs A, et al.A model to estimate the lifetime health outcomes of patients with type 2 diabetes: The United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). Diabetologia 2004;47:1747-59.

4. Haffner SM, Lehto S, Rönnemaa T, et al.Mortality from coronary heart disease in subjects with type 2 diabetes and in non diabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229-34.

5. Kannel WB, McGee D, Gordon T. A general cardiovascular risk profile: the Framingham Study. Am J Cardiol 1976; 38:46-51.

6. Yun CH, Lin TY, Wu YJ, et al. Pericardial and thoracic peri-aortic adipose tissues contribute to systemic inflammation and calcified coronary atherosclerosis independent of body fat composition, anthropometric measures and traditional cardiovascular risks. Eur J Radiol 2012; 81:749-56.

7. Mahabadi AA, Massaro JM, Rosito GA, et al. Association of pericardial fat, intrathoracic fat, and visceral abdominal fat with cardiovascular disease burden: the Framingham Heart Study. Eur Heart J 2009;30:850-6.

8. Lehman SJ, Massaro JM, Schlett CL et al. Periaortic fat, cardiovascular disease risk factors, and aortic calcification: the Framingham Heart Study. Atherosclerosis 2010; 210:656-61.

9. Sacks HS, Fain JN. Human epicardial adipose tissue: a review. Am Heart J 2007;153:907-17.

10. Iacobellis G, Corradi D, Sharma AM. Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart. Nat Clin Pract Cardiovasc Med 2005; 2:536-43.

11. Ho E, Shimada Y. Formation of the epicardium studied with the scanning electron microscope. Dev Biol 1978;66: 579-85.

12. Cheng KH, Chu CS, Lee KT, et al. Adipocytokines and proinflammatory mediators from abdominal and epicardial adipose tissue in patients with coronary artery disease. Int J Obes 2008;32:268-74.

13. Iacobellis G, Willens HJ, Barbaro G, et al. Threshold values of high-risk echocardiographic epicardial fat thickness. Obes Silver Spring Md 2008;16:887-92.

14. Iacobellis G, Assael F, Ribaudo MC, et al Epicardial fat from echocardiography: a new method for visceral adipose tissue prediction. Obes Res 2003;11:304-10.

15. Chaldakov GN, Stankulov IS, Aloe L. Subepicardial adipose tissue in human coronary atherosclerosis: another neglected phenomenon. Atherosclerosis 2001;154:237-8.

16. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:937-52.

17. Iacobellis G, Ribaudo MC, Assael F, et al. Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: a new indicator of cardiovascular risk. J Clin Endocrinol Metab 2003; 88:5163-8.

18. Natale F, Tedesco MA, Mocerino R, et al. Visceral adiposity and arterial stiffness: echocardiographic epicardial fat thickness reflects, better than waist circumference, carotid arterial stiffness in a large population of hypertensives. Eur J Echocardiogr J Work Group Echocardiogr Eur Soc Cardiol 2009; 10:549-5.

19. Ahn SG, Lim HS, Joe DY, et al. Relationship of epicardial adipose tissue by echocardiography to coronary artery disease. Heart Br Card Soc 2008; 94-7.

20. Eroglu S, Sade LE, Yildirir A, et al. Epicardial adipose tissue thickness by echocardiography is a marker for the presence and severity of coronary artery disease. Nutr Metab Cardiovasc Dis Nmcd 2009;19:211-7.

21. Mansour AA, Ajeel NA. Atherosclerotic cardiovascular disease among patients with type 2 diabetes in Basrah. World J Diabetes. 2013;4(3):82-7.

22. Taleb N, Salti H, Al-Mokaddam M, et al Prevalence and determinants of albuminuria in a cohort of diabetic patients in Lebanon. Ann Saudi Med 2008;28:420-5.

23. Jurado J, Ybarra J, Solanas P et al. Prevalence of cardiovascular disease and risk factors in a type 2 diabetic population of the North Catalonia diabetes study. J Am Acad Nurse Pract 2009;21:140-8.

24. Greif M, Becker A, von Ziegler F, et al. Pericardial adipose tissue determined by dual source CT is a risk factor for coronary atherosclerosis. Arterioscler Thromb Vasc Biol 2009;29:781-6.

25. Iacobellis G, Leonetti F. Epicardial adipose tissue and insulin resistance in obese subjects. J Clin Endocrinol Metab 2005;90:6300-2.

26. Iacobellis G, Willens HJ. Echocardiographic epicardial fat: a review of research and clinical applications. J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr 2009; 22:1311-9.

27. Jeong J-W, Jeong MH, Yun KH, et al. Echocardiographic epicardial fat thickness and coronary artery disease. Circ J Off J Jpn Circ Soc 2007; 71:536-9.

28. Kim HM, Kim KJ, Lee HJ, et al Epicardial adipose tissue thickness is an indicator for coronary artery stenosis in asymptomatic type 2 diabetic patients: its assessment by cardiac magnetic resonance. Cardiovasc Diabetol 2012 18;11:83.

29. Wang CP, Hsu HL, Hung WC et al. Increased epicardial adipose tissue (EAT) volume in type 2 diabetes mellitus and association with metabolic syndrome and severity of coronary atherosclerosis. Clin Endocrinol (Oxf). 2009;70(6):876-82

30. Cetin M, Cakici M, Polat M, et al. Relation of epicardial fat thickness with carotid intima-media thickness in patients with type 2 diabetes mellitus. Int J Endocrinol 2013;2013:769175.

31. Flüchter S, Haghi D, Dinter D, et al. Volumetric assessment of epicardial adipose tissue with cardiovascular magnetic resonance imaging. Obes Silver Spring Md 2007; 15:870-8.