World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(RESEARCH ARTICLE)

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Monocyte to HDL cholesterol ratio and smoking are predictors of epicardial fat tissue thickness

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World Journal of Biology Pharmacy and Health Sciences, 2024, 18(01), 012–020

Publication history: Received on 19 February 2024; revised on 01 April 2024; accepted on 04 April 2024

Article DOI: https://doi.org/10.30574/wjbphs.2024.18.1.0160

Abstract

Objective: Smoking stimulates lipid accumulation and causes non-alcoholic fatty liver disease. Epicardial Fat Tissue (EFT) resides between the visceral pericardium and myocardium. The aim of this study was to determine whether if smoking may accumulate Epicardial Fat Tissue thickness (EFTt).

Material and methods: 266 smoking and 500 non-smoking subjects were included in the study. The subjects were chosen to be healthy individuals, without any cardiovascular/systemicdisorders or risk factors for atherosclerosis (except hyperlipidemia). Transthoracic echocardiography (TTE) was applied to all subjects, and EFTt was measured in both diastole and systole (EFTtd and EFTts respectively).

Results: EFTtd, EFTts, low-density lipoprotein cholesterol, triglyceride, and monocyte to the HDL cholesterol ratio (MHR) values were found to be significantly increased in the smoking group when compared to the non-smoking group. Pearson's correlation analyses revealed that EFTtd and EFTts were related to pack.year, low-density lipoprotein cholesterol, triglyceride, MHR, BMI, and age. Linear regression analysis results showed that smoking, pack.year, BMI, age, and MHR were independent predictors of EFTtd, EFTts.

Conclusions: The study results showed that smoking increases the EFTtd and EFTts. Smoking and MHR were independent predictors of EFTt. Evaluating blood parameters together with EFTt may guide primary prevention in smokers.

Keywords: Epicardial fat tissue thickness; Smoking; Monocyte to the HDL cholesterol ratio

1. Introduction

The World Health Organization defines smoking as the world's fastest-spreading and longest-lasting epidemic (1). Smoking is one of the most important causes of cardiovascular system diseases. (2). Smoking which can increase the risk of coronary heart disease by 2-4 times, plays a role as a risk-increasing factor in more than 70% of deaths caused by this disease and in sudden deaths (3).

Epicardial fat tissue (EFT) is a visceral fatty tissue located around the heart and coronary arteries and has paracrine, vasocrine and inflammatory effects (4-6). There is no fascia separating epicardial fat tissue and myocardium, so these two tissues share the same microcirculation (7). Although epicardial fat tissue is important for the protective regulation of vascular functions and the provision of energy needs in healthy situations, the increase in epicardial fat tissue turns it into a lipolytic, prothrombotic and pro-inflammatory organ (8).

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Smoking has been shown to stimulate lipid accumulation in mouse hepatocytes and adenosine monophosphate-activated cultured cells (9). Some recent studies have shown smoking to be an independent risk factor for non-alcoholic fatty liver disease (10,11). In this study, we wanted to investigate whether there is a connection between EFT thickness (EFTt) and smoking.

2. Material and method

2.1. Population of the study

A total of 766 subjects who applied to Elazığ Fethi Sekin City Hospital Cardiology outpatient clinics between December 1 2018- July 1 2021 were recruited retrospectively. The ages of the subjects differed from 17 to 75 and they had neither any cardiovascular/systemic disorder nor risk factor for atherosclerosis (Except from hyperlipidemia) , which were detected by anamnesis, transthoracic echocardiography (TTE), and exercise stress test. The study was carried out in conformity with Helsinki principles and ethics approval was taken from the Presidency of T.C. Firat University Ethics Committee.

In addition to subjects who do not have sufficient data in their files or hematological, biochemical or serological abnormalities, subjectsts with routine alcohol intake, marijuana, and use other tobacco products, and ex-smokers, professional athletes, subjects with BMI> 35 and pregnant women were excluded from the study.

Participants who smoked one or more cigarettes per day were accepted as smokers. Smoking characteristics such as the number of cigarettes smoked daily and the number of pack years of smoking, which represents a combined measure of dose and duration of smoking, were also evaluated. Pack.years was calculated as number of cigarettes smoked per day number of years smoked/20.

The physical examinations and laboratory analysis were conducted to record fasting blood glucose and lipid levels, the blood pressure, and the BMI parameters. Patients who take antihypertensive drugs were not included in the analysis. Also the blood pressure measurements were taken to discriminate the hypertensive patients that, according to the blood pressure records, the subjects who have a diastolic blood pressure ≥90 mmHg and a systolic blood pressure higher than ≥140 mmHg were not accepted to be subjects of the study.

To approve a subject was diabetic, usage of antidiabetic medications or a measurement of fasting blood glucose level ≥126 mg/dL was required and these subjects were not included in analysis.

BMI was evaluated according the formula that is presented in the following:

$$BMI: \frac{Weight(kg)}{Height2(m2)}$$

2.2. Echocardiography

In order to perform the transthoracic echocardiography, the Vivid 5 instrument with a 2.5-MHz transducer (GE Medical Systems, Milwaukee, WI, USA) was applied. American Society of Echocardiography suggestions was followed (12). The measurements of EFTt were carried out by a procedure which was suggested by Iacobellis G, et al (13). In accordance with the aforementioned procedure, the measurements were taken on the outer wall of the right ventricle from the parasternal long axis view. The EFT was discriminated by determining the echo-free space which resides in-between the pericardium visceral lamina and external wall of the myocardium (Figure 1).

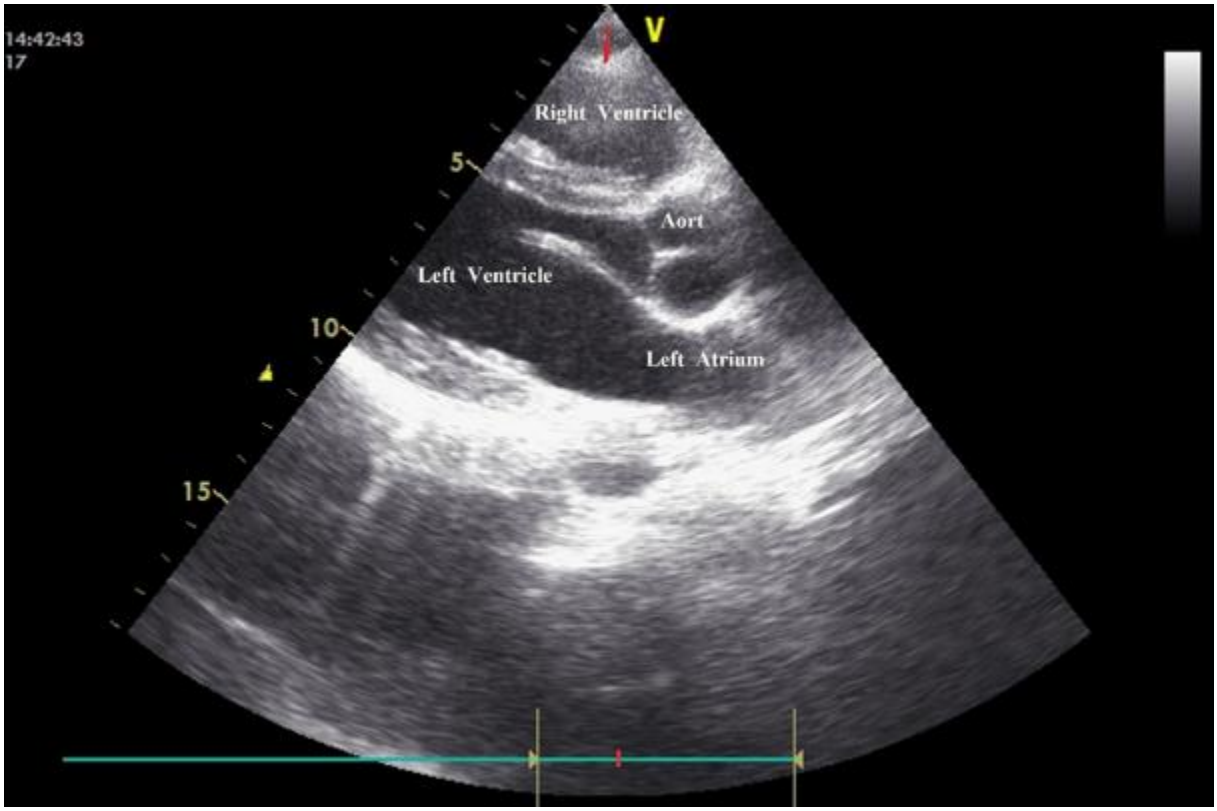

Figure 1 Measurement of epicardial fat tissue thickness (EFTt) by two-dimensional transthoracic echocardiography

Evaluations on M-mode strips were gathered from longitudinal cursor beam orientation in 3 cardiac cycles at the end-systole and end- diastole. The maximum values were measured and the derived values were averaged.

2.3. Exercise stress test

In order to conduct the stress test, Cardiosis TEPA Exercise Stress Test device (TEPA Medical and Electronic Products Industry and Trade Company, Ankara, Turkey) is utilized. Specifically the tests were done according to the Bruce or modified Bruce treadmill protocols. Such protocols are known to be non-invasive for functional capacity and exercise tolerance for patients who are doubted to have cardiovascular disorders (14).

2.4. Statistical analysis:

SPSS 27 package program will be used for statistical evaluation. Kolmogorov-Smirnov test was applied to determine whether the continous variables showed normal distribution or not. Since no continuous variable showed normal distribution, the Mann-Whitney U test was used to analyze these parameters. The Chi-square test was used to analysis of categorical variables. Data were presented as median with 25th–75th percentiles for continuous variables and categorical variables were expressed as numbers and percentages. Degrees of association between continuous variables were analyzed by Pearson' correlation analysis. Linear regression analysis was performed to determine which clinical variables independently affected EFTt existence. $p<0.05$ was required for statistical significance.

3. Results

266 smoking and 500 non-smoking subjects with neither any cardiovascular/systemic disorder nor risk factor for atherosclerosis were included in the study. Echocardiographic measurements, baseline clinical characteristics of the study participants, and findings were summarized in below (Table I).

Table 1 Inter-group comparison of demographic and laboratory data

	The Smokers (266)	**The Non-Smokers (500)**	***p* Value**
Gender (Male/Female)	147/119	216/284	0.001
Age (year)	44.5(31.0-55.0)	45.0(30.0-56.0)	0.51
Hyperlipidemia n (%)	56(21.1)	89(17.8)	0.27
Low-density lipoprotein cholesterol (mg/dL)	104.0(75.75-125.25)	91.40(75.0-116.72)	0.002
Triglycerides (mg/dL)	134.0(98.75-150)	110.0(75.0-145.0)	<0.001
High-density lipoprotein (HDL) cholesterol (mg/dL)	42.0(37.0-46.0)	50.0(45.0-55.0)	<0.001
Monocyte to the HDL cholesterol ratio (MHR)	14.51(11.79-17.50)	11.95(9.38-15.0)	<0.001
BMI (body mass index)	25.96(23.93-27.55)	27.01(24.97-26.61)	<0.001
White blood cell ($10^3/mm^3$)	7.80(6.65-9.19)	7.21(6.02-9.00)	0.02
Hematocrit (%)	44.0(41.0-46.81)	42.0(40.0-45.0)	<0.001
Fasting plasma glucose (mg/dl)	90.0(79.95-102.0)	90.0(79.0-99.0)	0.24
EFTtd (mm)	2.60(1.97-3.50)	2.50(1.2-3.0)	0.002
EFTts (mm)	5.0(4.0-6.0)	5.0(3.2-5.5)	<0.001
EFTtd: (Epicardial fat tissue thickness measured in diastole) EFTts: (Epicardial fat tissue thickness measured in systole)			

EFTtd (Epicardial fat tissue thickness measured in diastole), EFTts (Epicardial fat tissue thickness measured in systole), low-density lipoprotein cholesterol, triglyceride, monocyte to the HDL cholesterol ratio (MHR), white blood cell, hematocrit values were found to be significantly increased in the smoking group when compared to the non-smoking group (Table I, Figure 2).

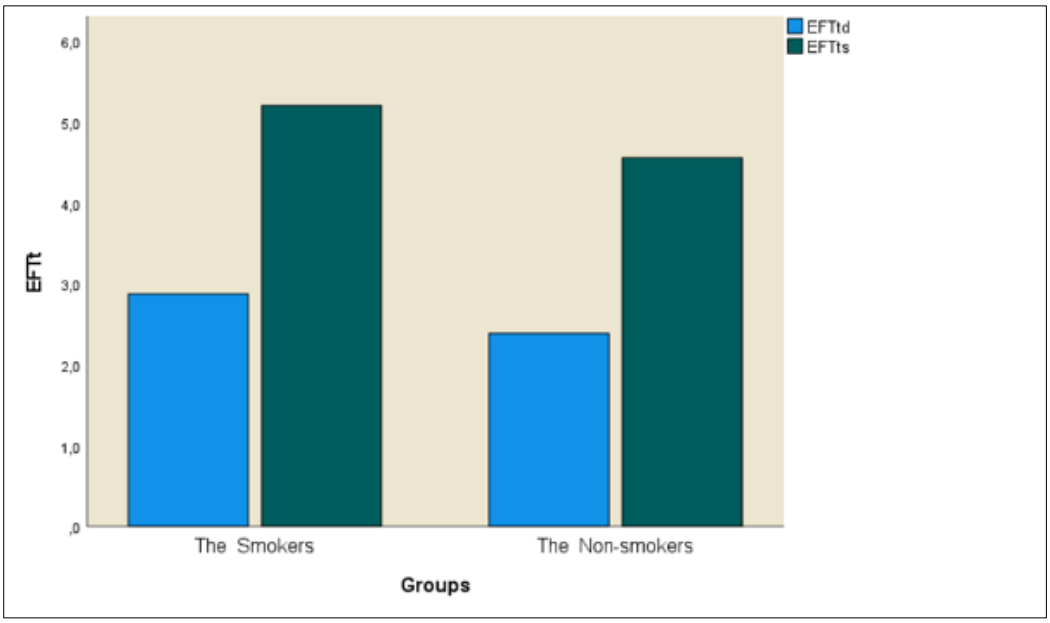

Figure 2 Comparison of EFTt between the smokers and the non-smokers both diastole and systole

High-density lipoprotein (HDL) cholesterol and BMI (body mass index) was significantly lower in the smoker group than the non-smoker group. On the other hand other laboratory and age parameters did not reach a statistically significant difference between the two groups (Table I).

Pearson's correlation analyses exposed that EFTtd and EFTts were meaningfully related to:

- age of the subjects,
- MHR,
- Pack.year
- HDL,
- LDL,
- Triglyceride,
- BMI (Table II, Figure 3).

Table 2 Pearson correlation analysis between EFTt and baseline characteristics, echocardiography and some laboratory measurements

	EFTtd		**EFTts**	
	r	**p**	**r**	**p**
Age	0.504	<0.001	0.494	<0.001
Fasting plasma glucose (mg/dL)	0.121	0.04	0.144	0.019
LDL (mg/dL)	0.185	0.002	0.146	0.017
Triglyceride(mg/dL)	0.247	<0.001	0.210	<0.001
HDL (mg/dL)	-0.148	0.016	-0.167	0.006
MHR	0.347	<0.001	0.345	<0.001
Pack.year	0.539	<0.001	0.539	<0.001
BMI (kg/ m^2)	0.119	0.03	0.137	0.025
LDL ; low-density lipoprotein cholesterol, HDL;High-density lipoprotein cholesterol, BMI; Body mass index, BSA; Body surface area, LV mass ; Left ventricle mass, MHR: Monocyte to the HDL cholesterol ratio				

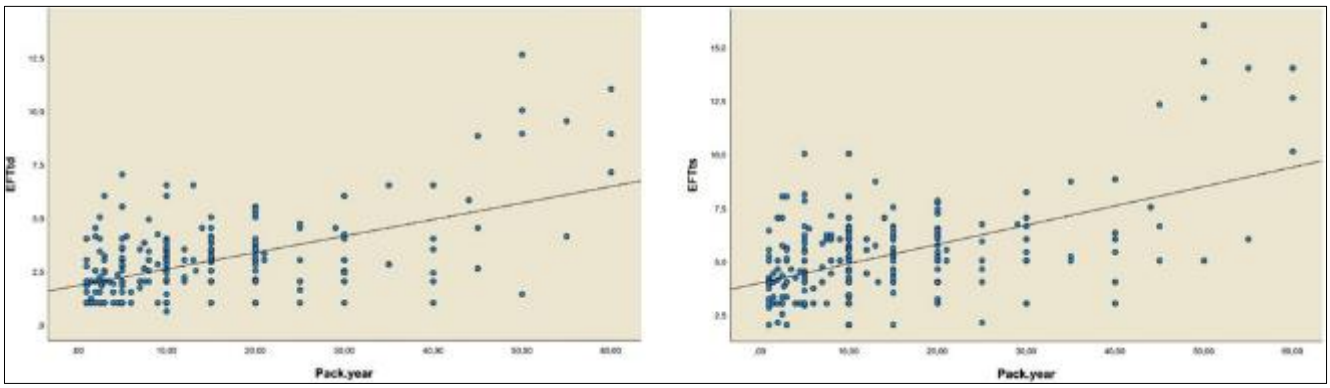

Figure 3 The correlations between Pack.year and EFTt both diastole and systole

Linear regression analysis results showed that smoking, pack.year, BMI, age, and MHR were independent predictors of EFTtd and EFTts (Table III, IV).

Table 3 Model-1. Linear Regression for Variables (Dependent Variable: EFTtd)

	Unstandardized Coefficients		**Standardized Coefficients**	**t**	***P***
	B	**Std. Error**	**Beta**		
(Constant)	-2.651	1.601		-1.656	0.10
Smoking	-0.488	0.106	-0.164	-4.588	<0.001
Pack.year	0.053	0.009	0.368	6.098	<0.001
Age	0.038	0.007	0.317	5.764	<0.001
Hyperlipidemia	-0.284	0.258	-0.065	-1.100	0.27
High-density lipoprotein (HDL) cholesterol	0.028	0.015	0.128	1.938	0.60
Monocyte to the HDL cholesterol ratio (MHR)	0.079	0.020	0.257	3.995	<0.001
Low-density lipoprotein cholesterol (mg/dL)	0.001	0.002	0.035	0.721	0.48
Triglyceride	0.002	0.001	0.084	1.466	0.14
Model p<0.001; Nagelke R^2 = 0.498					

Table 4 Model-2. Linear Regression for Variables (Dependent Variable: EFTts)

	Unstandardized Coefficients		**Standardized Coefficients**	**t**	***P***
	B	**Std. Error**	**Beta**		
(Constant)	-2.160	1.552		-1.392	0.16
Smoking	-0.644	0.127	-0.180	-5.059	<0.001
Pack.year	0.067	0.009	0.399	7.837	<0.001
Age	0.044	0.007	0.314	5.842	<0.001
Hyperlipidemia	-0.017	0.307	-0.003	-0.055	0.75
High-density lipoprotein (HDL) cholesterol	0.041	0.017	0.161	2.506	0.03
Monocyte to the HDL cholesterol ratio (MHR)	0.087	0.024	0.243	3.675	<0.001
Low-density lipoprotein cholesterol (mg/dL)	0.001	0.002	0.017	0.348	0.62
Triglyceride	0.003	0.002	0.105	1.815	0.10
Model p<0.001; Nagelke R^2 = 0.445					

When model-1 is examined, it was seen that the linear regression model established was significant and the explanatory value of the variables in the model was 49.8%. (Nagelke R2 = 0,498; P < 0,001) According to this model, it was determined that a 1-unit increase in the pack.year score increased the EFTtd value by 0.053 mm (Table III). When model-2 is examined, it was seen that the linear regression model established was significant and the explanatory value of the variables in the model was 44.5%. (Nagelke R2 = 0,445; P < 0,001) According to this model, it was determined that a 1-unit increase in the pack.year score increased the EFTts value by 0.067 mm (Table IV).

4. Discussion

The findings showed that smoking habit elevates transthoracic echocardiographic EFTt both diastole and systole (Table I, Figure 2). It was also observed that EFTt had a significant association with the pack.year, age, BMI, triglyceride, LDL,

HDL, and MHR (Table II, Figure 3). Last, the study demonstrated smoking, pack.year, BMI, age, and MHR were independent predictors of EFTtd and EFTts (Table III, IV).

Epicardial fat is a kind of visceral fat that deposits in the heart. EFT is situated between the visceral segment of pericardium and the myocardium. It is known to be highly active with a fatty acid metabolism and bears highly expressed thermogenic genes (15). The functional complexity of human epicardial fat is not fully elucidated. However, the role of epicardial fat in the heart can generally be identified as mechanical, metabolic, thermogenic and endocrine / paracrine(16) .

The EFT is very close to the myocardium, which imposes it to have a vital role. Anatomically, there is no border between the myocardium and the EFT and because of this anatomical phenomenon; the myocardium is effected vasocrinely and paracrinely by some factors which are released from the EFT. Specifically, some of the factors can be named as the adipokines and cytokines (17,18). Recent studies suggest that the cytokines which are released from the EFT has a significant effect on some cardiovascular disease development (19-22).

EFT is located in interventricular and atrioventricular grooves that cover the atria, the main branches of coronary arteries, outer wall of right ventricle and, the apex of the left ventricle (15). The increase in the size of the epicardial fat brings about the coronary arteries and myocardium to be surrounded by fat. It is also a known fact that the fat can get into the connective tissue out-setting the subepicardial connective tissue, which stands in the muscle bundles and muscle fibers (17). Furthermore, when extreme obesity exists, the heart may become completely covered with fat that can be as thick as 20 mm (23).

Today, EFT has attracted many researchers owing to its anatomic and functional characteristics, which mainly stem from its closeness to the myocardium. Many research studies have been conducted to illuminate its role as an endocrine organ. In addition, several researches have been carried out to reveal the role of EFT in the occurrence of pathogenic conditions. Specifically, in some studies, the lipid-storing depot characteristics of the EFT has been investigated, which mainly aimed to explain the secreting of cytokines and chemokines under pathogenic conditions as an inflammotary tissue (17). Strong evidence shows that epicardial fat actively excretes many pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β), interleukin-6 (IL-6), interleukin β (IL-1β), monocyte chemoattractant protein-1 (MCP-1) (a chemokine), and *IL-6 sR* (interleukin 6 soluble receptor) (24).

It is known that there is a connection between smoking and systemic inflammation parameters and lipid profile panel. It has been reported that there is an increase in total cholesterol, triglyceride, LDL, CRP, and MHR levels in smokers compared to non-smokers, while a decrease in HDL levels is observed (3,25,26). Cigarette smoking has been shown to stimulate lipid accumulation in mouse hepatocytes and cultured cells that inactivate adenosine monophosphate-activated kinase and is an independent risk factor for non-alcoholic fatty liver disease (9-11).

The relationship between smoking, systemic inflammatory response, vascular endothelial injury and atherosclerosis has been well defined and MHR also accepted as a marker of systemic inflammation and endothelial dysfunction (27-29).

Our study shows a positive association between smoking, age, BMI, triglyceride, LDL, and EFTt (Table III). EFTtd and EFTts was also found to correlate with MHR which accepted as an inflammatory marker. In light of the findings in this study, it can be thought that there may be a direct relationship between EFTt, smoking and MHR.

5. Conclusion

Since inflammation and smoking are considered major risk factors for atherosclerosis, EFTt, which can be easily detected with TTE, can be considered an important marker for coronary artery disease in the coming years. In addition to traditional risk assessment, evaluating blood parameters together with EFTt may help predict the risk of atherosclerotic events may guide primary prevention in smokers.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

The ethical approval was obtained from the Ethics Committee of T.C. Fırat University ((No: 2021/01–39). 'The present research work does not contain any studies performed on animals/humans subjects by any of the authors'.

Statement of informed consent

Patient consent was waived due to the retrospective nature of this study.

Authors contribution

- Conception of the work: Yılmaz M, Mirzaoğlu Ç.
- Design and writing of the work: Yılmaz M, Mirzaoğlu Ç.
- Acquisition of data: Mirzaoğlu Ç.
- Analysis of data: Yılmaz M.
- Interpretation of data: Yılmaz M, Mirzaoğlu Ç.

References

[1] World Health Organization. World Health Report 2003: Shaping the future. Geneva: World Health Organization 2003;92.

[2] Selim GM, Elia RZ, El Bohey AS, El Meniawy KA. Effect of shisha vs. cigarette smoking on endothelial function by brachialartery duplex ultrasonography: an observationalstudy. Anatol J Cardiol 2013; 13(8):759-765.

[3] Lakier JB. Smoking and cardiovascular disease. Am J Med 1992; 93(1): 8-12.

[4] Iacobellis G, Corradi D, Sharma AM. Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart. Nat Clin Pract Cardiovasc Med 2005; 2: 536-543.

[5] Sacks HS, Fain JN. Human epicardial adipose tissue: a review. Am Heart J 2007; 153:907-917.

[6] Iacobellis G, Bianco AC. Epicardial adipose tissue: emerging physiological, pathophysiological and clinical features. Trends Endocrinol Metab 2011; 22: 450-457.

[7] Iacobellis G, Willens HJ, Echocardiographic epicardial fat: A review of research and clinical applications. J Am Soc Echocardiogr 2009; 22(12): 1311-1319.

[8] Iozzo P. Myocardial, perivascular, and epicardial fat. Diabetes Care 2011;34(2):371-379.

[9] Yuan H, Shyy JY, Martins-Green M. Second-hand smoke stimulates lipid accumulation in the liver by modulating AMPK and SREBP-1. J Hepatol 2009; 51(3):535-547.

[10] Ayaka Hamabe, Hirofumi Uto, Yasushi Imamura, et al. Impact of cigarette smoking on onset of nonalcoholic fatty liver disease over a 10-year period. J Gastroenterol 2011; 46(6): 769–778.

[11] Masashi Okamoto, Teruki Miyake, Kohichiro Kitai , et al. Cigarette smoking is a risk factor for the onset of fatty liver disease in nondrinkers: A longitudinal cohort study. PLoS One. 2018 ;13(4): e0195147.

[12] Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification. Eur J Echocardiogr 2006; 7: 79–108.

[13] 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. The Journal of Clinical Endocrinology & Metabolism. 2003; 88:5163-5168.

[14] Bruce R, Blackmon J, Jones J, et al. Exercising testing in adult normal subjects and cardiac patients. Annals of noninvasive electrocardiology. 2004; 9:291-303.

[15] Iacobellis G, Corradi D and Sharma AM. Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart. Nature Reviews Cardiology. 2005; 2:536.

[16] Wu Y, Zhang A, Hamilton DJ, et al. Epicardial Fat in the Maintenance of Cardiovascular Health. Methodist DeBakey cardiovascular journal. 2017; 13:20.

[17] Cherian S, Lopaschuk GD, Carvalho E. Cellular cross-talk between epicardial adipose tissue and myocardium in relation to the pathogenesis of cardiovascular disease. American Journal of Physiology-Endocrinology and Metabolism. 2012; 303:E937-E949.

[18] Patel VB, Mori J, McLean BA, et al. ACE2 deficiency worsens epicardial adipose tissue inflammation and cardiac dysfunction in response to diet-induced obesity. Diabetes. 2016; 65:85-95.

[19] Toczyłowski K, Gruca M and Baranowski M. Epicardial adipose tissue and its role in cardiac physiology and disease. Postepy Hig Med Dosw 2013; 67: 584-593. (Article in Polish)

[20] Çetin M, Erdogan T, Kocaman SA, et al. Increased epicardial adipose tissue in patients with isolated coronary artery ectasia. Internal Medicine. 2012; 51:833-838.

[21] 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. Nutrition, Metabolism and Cardiovascular Diseases. 2009; 19:211-217.

[22] Erdogan T, Canga A, Kocaman SA, et al. Increased epicardial adipose tissue in patients with slow coronary flow phenomenon. Kardiologia Polska (Polish Heart Journal). 2012; 70:903-909.

[23] Sacks HS and Fain JN. Human epicardial adipose tissue: a review. American heart journal. 2007; 153:907-917.

[24] Mazurek T, Zhang L, Zalewski A, et al. Human epicardial adipose tissue is a source of inflammatory mediators. Circulation. 2003; 108:2460-2466.

[25] Yılmaz M, Kayançiçek H. A New Inflammatory Marker: Elevated Monocyte to HDL Cholesterol Ratio Associated with Smoking. J Clin Med 2018; 7(4): 76.

[26] Wang H, Chen H, Fu Y, et al. Effects of Smoking on Inflammatory-Related Cytokine Levels in Human Serum. Molecules 2022; 27(12): 3715.

[27] Li H, Srinivasan SR, Chen W, et al. Vascular abnormalities in asymptomatic, healthy young adult smokers without other major cardiovascular risk factors: The Bogalusa Heart Study. Am. J. Hypertens 2005; 18: 319–324.

[28] Luo HL, Zang WJ, Lu J, et al. The protective effect of captopril on nicotine-induced endothelial dysfunction in rat. Basic Clin Pharmacol Toxicol 2006; 99: 237–245.

[29] Canpolat U, Çetin EH, Cetin S, et al. Association of Monocyte-to-HDL Cholesterol Ratio with Slow Coronary Flow is Linked to Systemic Inflammation. Clin Appl Thromb Hemost 2016 ;22(5):476-82.