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Original Article

Meta-Analysis of Non-Alcoholic Fatty Liver Disease and Electromechanical Reconstruction of Myocardium

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Abstract

In developed countries, non-alcoholic fatty liver disease (NAFLD), which results from obesity, has become endemic and kills many adults annually. Health research centers in most countries are looking to examine the relationship between metabolic syndrome (MetS) and metabolic biomarkers. A bleeding-prone standard liver biopsy or costly magnetic resonance imaging scan is used to diagnose NAFLD. The present study aimed to analyze medical databases using various scientific articles; moreover, this experiment analyzed medical databases using published scientific articles related to NAFLD, endovascular treatment, cardiac arrhythmias and conduction disorders, changes in the geometry of atria and ventricles, changes in myocardial mass volume as well as diastolic flow left and right ventricular systolic functions, coronary blood flow, analysis of the dependence of epicardial fat tissue (EFT) thickness, and the presence of chronic heart failure (CHF). It is demonstrated that the index of EFT in NAFLD positively correlated with the criteria of cardiovascular health, values of the carotid intima-media thickness, and calcification of the coronary arteries on the coronary artery calcium scale (P<0.0001). The index of per EFT significantly correlated with the factor of the age of the NAFLD patients (P=0.04), hemoglobin A1C level (P<0.001), systemic inflammatory index (P=0.02), the index of impaired glucose tolerance (P=0.03), and especially, the patient's diabetes factor (P<0.001). In addition, adiponectin levels were significantly lower in individuals with NAFLD (P=0.001) and patients with MetS (P=0.02). NAFLD in association with an increase in epicardial adipose tissue (EAT) is an independent risk factor for atherosclerosis, coronary heart disease, CHF, as well as structural and electrophysiological myocardial remodeling. The study of pathogenetic mechanisms in the context of the role of EAT and clinical monitoring of its condition are urgent problems of modern medicine.

Keywords: Epicardial adipose tissue, Electrophysiological, Myocardial remodeling, Non-alcoholic fatty liver

1. Introduction

Fatty liver disease is a disease of human liver cells, and its importance is due to the destruction of liver cells (1). Non-alcoholic fatty liver disease (NAFLD) is a condition in which triglycerides accumulate in the liver cells of people who have no history of alcohol consumption (2). This disease is caused by the accumulation of fat in the liver of more than 5% by weight of the liver. Hypertension, hyperlipidemia, obesity, and diabetes (components of metabolic syndrome [MetS]) have been associated with fatty liver disease (3). Etiologically, NAFLD is a multidimensional disease in which several factors, including genetics, lifestyle, diet, and physical activity, are involved (4). For this reason, the treatment of this disease mainly focuses on behavioral and lifestyle

change interventions, including diet, increased physical activity, and weight loss.

Fatty liver disease is one of the most common liver diseases globally, and its prevalence varies from 2.8% to 24% in different communities (5). The prevalence of NAFLD is 20%-30% and 15% in Western countries and Asian nations, respectively (6). Due to differences in methods and sensitivity in imaging methods, statistics may be somewhat different, and the detection rate of fatty liver disease that varies according to the sensitivity of the imaging was 12%-24% (7). As a result, the prevalence of this disease will be different in various studies based on the imaging methods. In some studies, the prevalence of fatty liver based on liver ultrasound findings was 68%; however, when magnetic resonance imaging was used to diagnose the disease, the prevalence in the same population reached approximately 40% (8). Moreover, the prevalence of fatty liver in society is related to the prevalence of obesity (9), and according to available information, the prevalence of the disease is higher in men, compared to women (10).

This nosology, being a link in the pathological metabolic continuum, including an increase in visceral fat, metabolic syndrome (MetS), insulin resistance, dyslipidemia, and arterial hypertension, is associated with structural and functional changes in the myocardium of the atria and ventricles (11). However, new explanations have recently appeared for the formation of electromechanical remodeling of the heart in the presence of NAFLD, where the factor of epicardial adipose tissue (EAT) acts as a pathological determinant independently associated with hepatic dysfunction (12). Epicardial fat tissue (EFT) is anatomically and functionally closely related to the myocardium, modulating its electrophysiological and structural properties and acquiring an independent pathogenetic role in the situation of NAFLD. The present study aimed to analyze such a relationship.

MetS affects approximately 30% of the American adult population (13). Researchers have reported several cases of MetS-associated visceral fat accumulation with NAFLD and EAT as clinical markers of heart risk (14). In a study, the theoretical and experimental basis of electrical impedance tomography (EIT) was applied to measure liver fat in a model of atherosclerosis in fatty liver disease in New Zealand white rabbits. Each body tissue has its electrical conductor, and the fat penetration into the liver was determined by frequency-dependent electrical impedance (Z) in response to applied alternating current (AC) (11). At low frequencies, cell membranes block current flow and lead to high conductivity, while at high frequencies, they act as defective capacitors, resulting in tissue-fluid impedance. Chang, Huang (15) applied a multi-electrode array to measure EIT voltage by directing electrical currents (at 2-4 mA and 50-250 kHz) to the upper abdomen. They revealed that currents penetrated the body at different depths and the obtained boundary voltages were gained by the electrodes. Moreover, muscle and blood are more conductive to AC than the adipose tissue, bone, or lung because of the different ion content (15). This study aimed to analyze medical databases using various scientific articles.

2. Materials and Methods

This meta-analysis reviewed a large number of articles, and 50 studies that were reviewed, meta-analyzed, and published from 2000 to 2020 in reputable medical databases were selected using some databases, such as Elsevier, Wiley, BMJ, Proquest, PubMed, Springer, and DOJA. Study traits included NAFLD, endovascular treatment, cardiac arrhythmias, conduction disorders (atrial and flutter fibrillation, extraventricular and supraventricular, supraventricular and intraventricular blocks), changes in atrial and ventricular geometry, changes in ventricular myocardial mass and diastolic flow, functional status of left and right ventricular systole, coronary blood flow, analysis of the dependence of EFT thickness on the severity and clinical types of NAFLD, and the presence of chronic heart failure (CHF) with impaired or intact discharge fraction (HfpEF).

The fixed and random models, data analysis, heterogeneity analysis, one-way analysis of variance using comprehensive meta-analysis software, and SPSS software were used to analyze the data. The results related to the size of the combined effect were favorable for the stochastic effects model.

3. Results

The autopsy results of the initially healthy people who did not have any cardiovascular diseases and diabetes mellitus during their lifetime revealed that the share of EFT was approximately 20% of the total mass of the ventricles of the human heart while occupying about 80% of its area (16). Due to this, the severity and quality of the functioning of the EFT positively correlate with the state of the electrophysiological properties of the myocardium. As an example of a representative sample of patients (n=2,238), it is demonstrated that the index of EFT in NAFLD positively correlated with the criteria of cardiovascular health (P<0.0001 [CVH metrics]), values of the carotid intima-media thickness (P<0.0001; carotid intima-media thickness test), and calcification of the coronary arteries on the coronary artery calcium (CAC) scale (CAC score) (P<0.0001) (17). However, the index of peri/epicardial fat thickness significantly correlated with the age factor of the patient with NAFLD (P=0.04), hemoglobin A1C level (P<0.001), systemic inflammatory index (in terms of interleukin 6, [IL-6], P=0.02), the index of impaired glucose tolerance (P=0.03), and especially, the patient's diabetes factor (P<0.001). In addition, adiponectin levels were significantly lower in individuals with NAFLD (P=0.001) and patients with MetS (P=0.02).

Excessive EFT can determine a change in the geometry of the atria and ventricles, thereby becoming a condition for the appearance of electromechanical prerequisites for atrial fibrillation (AFib) (18). Therefore, in patients with visceral obesity, atrial dilatation and diastolic dysfunction are significantly more likely to form and associated with an increased risk of Afib and atrial flutter. The expansion of the ventricular cavities can determine the formation of electrical heterogeneity of the myocardium with prolongation of the QT interval, causing life-threatening ventricular arrhythmias, especially in patients with reduced systolic function (19). Epicardial fat tissue, acting as a depot of fatty acids, is a necessary source of energy for the myocardium during the period of increased demand. In addition, epicardial adipocytes regulate their level in the coronary arteries at a high concentration of lipoproteins; in addition, epicardial fat changes the concentration of toxic lipids. These metabolic effects of EFT are associated with the processes of coronary atherosclerosis. It has long been known that the localization of an atherosclerotic plaque often coincides with the geography of the distribution of epicardial fat. The IL-8 secreted by these adipocytes generates a local vascular inflammatory response. In addition, the thermogenic factor of epicardial adipocytes, namely uncoupling protein 1 (a mitochondrial protein that uncouples oxidation and phosphorylation), changes folding processes, lowers the level of adhesion factors of endothelial cells of coronary vessels, and alters local homeostasis (20). In contrast, resection or removal of the EFT inhibits atherogenesis; therefore, in the model of the development of experimental atherosclerosis by feeding animals with an atherogenic mixture, subsequent excision of epicardial fat in the area of the left anterior descending artery locally reduced the formation of plaque, as evidenced by intravascular ultrasound scanning and a change in the level of T-cadherin, scavenger receptor-a, and adiponectin in the intramural plot (21).

In addition, it is noteworthy that epi/pericardial (not paracardial) fat exerts cardioprotection under physiological conditions, which is explained by its antiatherogenic and anti-inflammatory effects, high release and absorption of free fatty acids, as well as low glucose requirements (22, 23).

4. Discussion

The prevalence of NAFLD ranges from 6.3% to 33% in the global population, while the incidence of non-alcoholic steatohepatitis ranges from 1-2% to 7-9% (15, 24). In Russia, NAFLD reached 37.1% by 2010, surpassing the USA (34% of the country's adult population or over 60 million people) and Japan (29% of the adult population) (25, 26). Alternatively, non-alcoholic steatosis and steatohepatitis act as independent risk factors for cardiovascular pathology. Some population studies have found that the severity of NAFLD is associated with an indicator of EFT (12, 27, 28) as well as the formation and prognostic unfavorableness of the cardiovascular disease.

The process of lipolysis and synthesis of fatty acids in EFT are carried out faster in the rest of the visceral fat, which is achieved by a particular morphology of epicardial adipocytes and their special biochemical organization.

In a study conducted by Psychari, Rekleiti (12), when assessing 105 participants with hepatic dysfunction who had the signs of hepatosis, 54.3% (n=57) of the cases were diagnosed with NAFLD. Subsequent analysis of echocardiographic data, including the indicators of epicardial and pericardial fat thickness, left ventricular ejection fraction, left ventricular posterior wall thickness and interventricular septum, as well as left ventricular diastolic function, did not establish a significant relationship among them (P_1=0.27, P_2=0.61, P_3=0.70, and P_4>0.05, respectively) (12).

In the EFT, there is a synthesis, paracrine, and systemic delivery of a number of hormones and cytokines (adipokines) to the myocytes of the ventricles and atria. Therefore, the electromechanical properties of the myocardium modulate pro-inflammatory factors of epicardial adipocytes include resistin, tumor necrosis factor-α, IL-6, IL-8, monocytic chemotactic protein-1, and fatty acid-binding proteins. The latter forms diastolic dysfunction and determines the development of heart failure with impaired or intact ejection fraction (29, 30). In addition, the long-term course of NAFLD and latent heart failure does not experience a decrease in the ejection fraction, and the presence of AFib and HfpEF in such patients contributes to the development of further liver dysfunction, being a condition for adverse clinical outcomes associated with the progression of NAFLD.

In a study carried out by Blumensatt, Fahlbusch (20), it was proved that EFT could cause an energy deficit of cardiomyocytes. The experimental model demonstrated the effects of secretory factors of epicardial adipocytes, which impaired the contractile function of cardiomyocytes and β-oxidation of fatty acids as a result of activation of the cardiac-specific renin-angiotensin system (suppressed in this example by an angiotensin II type 1 receptor antagonist, losartan) and induction of miR-208a.

Epicardial fat tissue in ischemic heart disease realizes its pro-inflammatory activity due to endocrine and paracrine mechanisms. Moreover, it has been proven that there was an excessive presence of this tissue in people (a group of 45 people) suffering from an ischemic disease of CD3+cells and macrophages (CD68+cells). In parallel, the concentration of scavenger receptors was increased according to the criterion of overexpression of the corresponding mRNA in macrophages (31). Furthermore, epicardial adipocytes are capable of expressing the scavenger receptor group. In addition, in atherosclerosis, a significant inflammatory transformation in EFT, was recorded due to some changes in antigen-resining cells, the growth of CD11c pro-inflammatory macrophages, and a reduction in CD206 anti-inflammatory macrophages (32). Such pro-inflammatory activity can form chronic oxidative stress of myocytes, especially in the posterior part of the left atrium. The EAT thickness index in this zone is associated with persistent AFib. Moreover, a higher frequency of this arrhythmia is recorded as paroxysmal (OR=1.11, 95% Di: 1.01-1.23, *P*=0.04) and persistent (OR=1.18, 95% Di: 1.05-1.33, *P*=0.004), regardless of other risk factors.

In addition, it is noteworthy that epi/pericardial (not paracardial) fat exerts cardioprotection under

physiological conditions, which is explained by its antiatherogenic and anti-inflammatory effects, high release and absorption of free fatty acids, as well as low glucose requirements (22, 23). NAFLD, in association with an increase in EAT, is an independent risk factor for atherosclerosis, coronary heart disease, CHF, as well as structural and electrophysiological myocardial remodeling. Therefore, the study of pathogenetic mechanisms in the context of the role of EAT and clinical monitoring of its condition are urgent problems of modern medicine.

Authors' Contribution

Study concept and design: V. A. T. and A. T.
Acquisition of data: N. I. Z.
Analysis and interpretation of data: N. I. G.
Drafting of the manuscript: O. V. E.
Critical revision of the manuscript for important intellectual content: N. I. Z.
Administrative, technical, and material support: O. S. A. and I. V. G.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Neuman MG. Cytokines—central factors in alcoholic liver disease. Alcohol Res Health. 2003;27(4):307.
2. Kawano Y, Cohen DE. Mechanisms of hepatic triglyceride accumulation in non-alcoholic fatty liver disease. J Gastroenterol. 2013;48(4):434-41.
3. Chen M, Guo W-L, Li Q-Y, Xu J-X, Cao Y-J, Liu B, et al. The protective mechanism of Lactobacillus plantarum FZU3013 against non-alcoholic fatty liver associated with hyperlipidemia in mice fed a high-fat diet. Food Funct. 2020;11(4):3316-31.
4. Fan JG, Cao HX. Role of diet and nutritional management in non-alcoholic fatty liver disease. J Gastroenterol Hepatol. 2013;28:81-7.
5. Neuschwander-Tetri BA, Caldwell SH. Nonalcoholic steatohepatitis: summary of an AASLD Single Topic Conference. J Hepatol. 2003;37(5):1202-19.
6. Sohrabpour AA, Rezvan H, Amini-Kafiabad S, Dayhim M, Merat S, Pourshams A. Prevalence of nonalcoholic steatohepatitis in Iran: a population based study. Middle East J Dig Dis. 2010;2(1):14.
7. Lankarani KB, Ghaffarpasand F, Mahmoodi M, Lotfi M, Zamiri N, Heydari ST, et al. Non alcoholic fatty liver disease in southern Iran: a population based study. Hepat Mon. 2013;13(5).
8. Martín-Domínguez V, González-Casas R, Mendoza-Jiménez-Ridruejo J, García-Buey L, Moreno-Otero R. Pathogenesis, diagnosis and treatment of non-alcoholic fatty liver disease. Rev Esp Enferm Dig. 2013;105(7):409-20.
9. Jamali R, Khonsari M, Merat S, Khoshnia M, Jafari E, Kalhori AB, et al. Persistent alanine aminotransferase elevation among the general Iranian population: prevalence and causes. World J Gastroenterol. 2008;14(18):2867.
10. Le MH, Devaki P, Ha NB, Jun DW, Te HS, Cheung RC, et al. Prevalence of non-alcoholic fatty liver disease and risk factors for advanced fibrosis and mortality in the United States. PloS One. 2017;12(3): 0173499.
11. Cotter TG, Rinella M. Nonalcoholic fatty liver disease 2020: the state of the disease. Gastroenterology. 2020;158(7):1851-64.
12. Psychari SN, Rekleiti N, Papaioannou N, Varhalama E, Drakoulis C, Apostolou TS, et al. Epicardial fat in nonalcoholic fatty liver disease: properties and relationships with metabolic factors, cardiac structure, and cardiac function. Angiology. 2016;67(1):41-8.
13. Moore JX, Chaudhary N, Akinyemiju T. Metabolic Syndrome Prevalence by Race/Ethnicity and Sex in the United States, National Health and Nutrition Examination Survey, 1988-2012. Prev Chronic Dis. 2017;14:24..
14. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, et al. The metabolic syndrome and cardiovascular risk: a systematic review and meta-analysis. J Am Coll Cardiol. 2010;56(14):1113-32.
15. Chang C-C, Huang Z-Y, Shih S-F, Luo Y, Ko A, Cui Q, et al. Electrical impedance tomography for non-invasive identification of fatty liver infiltrate in overweight individuals. Sci Rep. 2021;11(1):19859.
16. Sacks HS, Fain JN. Human epicardial adipose tissue: a review. Am Heart J. 2007;153(6):907-17.
17. Iacobellis G, Pistilli D, Gucciardo M, Leonetti F, Miraldi F, Brancaccio G, et al. Adiponectin expression in human epicardial adipose tissue in vivo is lower in patients

with coronary artery disease. Cytokine. 2005;29(6):251-5.
18. Xu L, Yan J, Zhang F, Zhou C, Fan T, Chen X, et al. Use of inflammatory biomarkers and real-time cardiac catheterisation to evaluate the left ventricular diastolic function in patients with diastolic heart failure. Heart Lung Circ. 2021;30(3):396-403.
19. Iacobellis G, Leonetti F, Singh N, Sharma AM. Relationship of epicardial adipose tissue with atrial dimensions and diastolic function in morbidly obese subjects. Int J Cardiol. 2007;115(2):272-3.
20. Blumensatt M, Fahlbusch P, Hilgers R, Bekaert M, De Wiza DH, Akhyari P, et al. Secretory products from epicardial adipose tissue from patients with type 2 diabetes impair mitochondrial β-oxidation in cardiomyocytes via activation of the cardiac renin–angiotensin system and induction of miR-208a. Basic Res. Cardiol. 2017;112(1):1-13.
21. Chechi K, Voisine P, Mathieu P, Laplante M, Bonnet S, Picard F, et al. Functional characterization of the Ucp1-associated oxidative phenotype of human epicardial adipose tissue. Sci Rep. 2017;7(1):1-15.
22. Farias-Itao DS, Pasqualucci CA, Nishizawa A, Silva LFF, Campos FM, Da Silva KCS, et al. Perivascular adipose tissue inflammation and coronary artery disease: an autopsy study protocol. JMIR Res Protoc. 2016;5(4):e211.
23. Noyes AM, Dua K, Devadoss R, Chhabra L. Cardiac adipose tissue and its relationship to diabetes mellitus and cardiovascular disease. World J Diabetes. 2014;5(6):868.
24. Arshad T, Golabi P, Henry L, Younossi ZM. Epidemiology of non-alcoholic fatty liver disease in North America. Curr Pharm Des. 2020;26(10):993-7.
25. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73-84.
26. Younossi ZM, Marchesini G, Pinto-Cortez H, Petta S. Epidemiology of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: implications for liver transplantation. Transplantation. 2019;103(1):22-7.
27. Christensen RH, von Scholten BJ, Lehrskov LL, Rossing P, Jørgensen PG. Epicardial adipose tissue: an emerging biomarker of cardiovascular complications in type 2 diabetes? Ther Adv Endocrinol Metab. 2020;11:2042018820928824.
28. Mitra S, De A, Chowdhury A. Epidemiology of non-alcoholic and alcoholic fatty liver diseases. Transl Gastroenterol Hepatol. 2020;5.
29. Meng X, Wang W, Zhang K, Qi Y, An S, Wang S, et al. Epicardial adipose tissue volume is associated with non-alcoholic fatty liver disease and cardiovascular risk factors in the general population. Ther Clin Risk Manag. 2018;14:1499.
30. Wu M-Z, Lee C-H, Chen Y, Yu S-Y, Yu Y-J, Ren Q-W, et al. Association between adipocyte fatty acid-binding protein with left ventricular remodelling and diastolic function in type 2 diabetes: a prospective echocardiography study. Cardiovasc Diabetol. 2020;19(1):1-11.
31. McKenney ML, Schultz KA, Boyd JH, Byrd JP, Alloosh M, Teague SD, et al. Epicardial adipose excision slows the progression of porcine coronary atherosclerosis. J Cardiothorac Surg. 2014;9(1):1-11.
32. Santiago-Fernández C, Pérez-Belmonte LM, Millán-Gómez M, Moreno-Santos I, Carrasco-Chinchilla F, Ruiz-Salas A, et al. Overexpression of scavenger receptor and infiltration of macrophage in epicardial adipose tissue of patients with ischemic heart disease and diabetes. J Transl Med. 2019;17(1):1-10.