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 is the result of obesity, has become endemic and kills a large number of adults annually. Health research centers in most countries are looking to examine the relationship between metabolic syndrome and metabolic biomarkers. A standard liver biopsy or magnetic resonance imaging (MRI) scan is used to diagnose NAFLD, the first of which is bleeding-prone and the second is costly. The purpose of this study was to analyze medical databases using various scientific articles. This experiment was analyzed medical databases using published scientific articles related to NAFLD, EVT, cardiac arrhythmias and conduction disorders, changes in the geometry of atria and ventricles, changes in myocardial mass volume and diastolic flow left and right ventricular systolic functions, coronary blood flow; Analysis of EFT thickness dependence, presence of chronic heart failure (CHF). It is demonstrated that the index of epicardial fat thickness 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 CAC scale (p<0.0001). The index of per epicardial fat thickness significantly correlated with the factor of the patient's age with NAFLD (p = 0.04), HbA1c level (p <0.001), systemic inflammatory index (p = 0.02), the index of impaired glucose tolerance (p = 0.03) and, especially, with 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 metabolic syndrome (p = 0.02). Non-alcoholic fatty liver disease in association with an increase in epicardial adipose tissue is an independent risk factor for atherosclerosis, coronary heart disease, chronic heart failure, structural and electrophysiological
myocardial remodeling; the study of pathogenetic mechanisms in the context of the role of epicardial adipose tissue and clinical monitoring of its condition are urgent problems of modern medicine.

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

### 1. Introduction

Fatty liver disease is a disease of human liver cells and is important because of 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). Non-alcoholic fatty liver is caused by the accumulation of fat in the liver of more than 5% by weight of the liver. Hypertension, hyperlipidemia, obesity, and diabetes (all of which are components of metabolic syndrome) have been associated with fatty liver disease (3). Etiologically, non-alcoholic fatty liver disease is a multidimensional disease in which a number of factors, including genetics and lifestyle, including 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 in the world and its prevalence varies from 2.8% to 24% in different communities (5). The prevalence of non-alcoholic fatty liver disease in Western countries is 20-30% and in Asian countries is 15% (6). Due to differences in methods and sensitivity in imaging methods, statistics may be somewhat different. The detection rate of the fatty liver disease 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%, but when MRI was used to diagnose the disease, the prevalence in the same population reached about 40% (8). 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 than women (10).

This nosology, being a link in the pathological metabolic continuum, including an increase in visceral fat, metabolic syndrome, insulin resistance, dyslipidemia and arterial hypertension, is associated with structural and functional changes in the myocardium of the atria and ventricles (11). However, recently, new explanations have appeared for the formation of electromechanical remodeling of the heart in the presence of NAFLD, where the factor of epicardial adipose tissue (EFT) acts as a pathological determinant independently associated with hepatic dysfunction (12). 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 purpose of this work is to analyze such a relationship.

Metabolic syndrome affects approximately 30% of the American adult population (13). Researchers have reported several cases of MetS-associated visceral fat accumulation with nonalcoholic fatty liver disease (NAFLD) and epicardial adipose tissue (EAT) as clinical markers of heart risk (14). In one study, the theoretical and experimental basis of electrical impedance tomography (EIT) was applied to measure liver fat in a model of atherosclerosis in New Zealand white rabbit fatty liver disease. Each body tissue has its electrical conductor, and the penetration of fat 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 boundary voltages obtained by the electrodes were obtained. Muscle and blood are more conductive to AC than adipose tissue, bone, or lung because of the different ion content (15). The purpose of this study was to analyze medical databases using various scientific articles.

2. Materials and Methods

In this research, meta-analysis method was used and after reviewing a large number of articles and researches, 50 studies were selected using databases such as Elsevier, Wiley, BMJ, Proquest, PubMed, Springer, and DOJA, which were published from 2000 to 2020 in reputable medical databases were reviewed and meta-analyzed. Study traits were included NAFLD EVT, cardiac arrhythmias and 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 Left and right ventricular systole, coronary blood flow, analysis of the dependence of EFT thickness on severity and clinical types of NAFLD, presence of chronic heart failure (CHF) with impaired or intact discharge fraction (HfpEF).

To analyze the data, data analysis, fixed and random models, heterogeneity analysis, one-way analysis of variance using CMA (Comprehensive Meta Analysis) and SPSS software were used. The results related to the size of the combined effect were favorable for the stochastic effects model.

3. Results
The autopsy results of initially healthy people who did not have any cardiovascular diseases and diabetes mellitus during their lifetime showed that the share of EFT is about 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 correlates with the state of the electrophysiological properties of the myocardium. On the example of a representative sample of patients (n = 2238), it is demonstrated that the index of epicardial fat thickness 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 (CIMT) and calcification of the coronary arteries on the CAC scale (CAC score), p<0.0001 (17). However, the index of peri-epicardial fat thickness significantly correlated with the factor of the patient's age with NAFLD (p = 0.04), HbA1c level (p <0.001), with systemic inflammatory index (in terms of interleukin 6, IL-6, p = 0.02), the index of impaired glucose tolerance (p = 0.03) and, especially, with 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 metabolic syndrome (p = 0.02).

Excess EFT can determine a change in the geometry of the atria and ventricles, thus becoming a condition for the appearance of electromechanical prerequisites for atrial fibrillation (AFib) (18). Thus, in patients with visceral obesity, atrial dilatation and diastolic dysfunction are significantly more likely to form, which is associated with an increased risk of Afib and atrial flutter (AF).

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). EFT, 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. IL-8 secreted by these adipocytes generates a local vascular inflammatory response. In addition, the thermogenic factor (mitochondrial protein that uncouples oxidation and phosphorylation) Ucp1 of epicardial adipocytes also changes folding processes, lowers the level of adhesion factors of endothelial cells of coronary vessels, alters local homeostasis (20). In contrast, resection or removal of the EFT inhibits atherogenesis. Thus, 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 ultrasound intravascular scanning and a change in the level of T-cadherin, scavenger receptor-a and adiponectin in the intramural plot (21).
It should be additionally noted that under physiological conditions, epi-/pericardial (but not paracardial fat) exerts cardioprotection, which is explained by its antiatherogenic and anti-inflammatory effects, high release and absorption of free fatty acids, and 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). In turn, non-alcoholic steatosis and steatohepatitis act as independent risk factors for cardiovascular pathology. A number of population studies have found that the severity of NAFLD is associated with an indicator of epicardial fat thickness (12, 27, 28) and the formation and prognostic unfavorableness of cardiovascular disease.

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

In a study by Psychari, Rekleiti (12), when assessing 105 participants with hepatic dysfunction who had signs of hepatosis, 54.3% (57 people) were diagnosed with NAFLD; subsequent analysis of echocardiographic data, including indicators of epicardial and pericardial fat thickness, left ventricular ejection fraction (LVEF), left ventricular posterior wall thickness (LVPW) and interventricular septum (IVS), left ventricular diastolic function, did not establish a significant relationship between them (respectively p1 = 0.27; p2 = 0.61; p3 = 0.70; p4 > 0.05) (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. Thus, the electromechanical properties of the myocardium modulate pro-inflammatory factors of epicardial adipocytes: resistin, tumor necrosis factor (TNF)-α, IL-6, IL-8, monocytic chemotactic protein (MCP)-1, fatty acid binding proteins (FABPs). The latter form diastolic dysfunction and determine the development of heart failure with impaired or intact ejection fraction (29, 30). In turn, the long-term course of NAFLD and latent heart failure does not have a decrease in the ejection fraction, and the presence of atrial fibrillation 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 by Blumensatt, Fahlbusch (20), it was proved that EFT can cause an energy deficit of cardiomyocytes: the experimental model demonstrates the effects of secretory factors of epicardial adipocytes, which impair the contractile function of cardiomyocytes and β-oxidation of fatty acids as
a result of activation of the cardiospecific RAS system (suppressed in this example by an angiotensin II type 1 receptor antagonist, losartan) and induction of miR-208a.

EFT in ischemic heart disease realizes its pro-inflammatory activity not only due to endocrine and paracrine mechanisms. It has been proven that there is an excessive presence in this tissue of people (a group of 45 people) suffering from ischemic disease of CD3 + cells and macrophages (CD68 + cells); in parallel, the concentration of scavenger receptors increases according to the criterion of overexpression of the corresponding mRNA in macrophages (31). Additionally, epicardial adipocytes themselves are capable of expressing the scavenger receptor group. In addition, in atherosclerosis, a significant inflammatory transformation in EFT was recorded due to changes in antigen-resining cells and the growth of CD11c proinflammatory macrophages and a decrease in CD206 anti-inflammatory macrophages (32). Such pro-inflammatory activity is capable of forming 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, in addition, 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.

It should be additionally noted that under physiological conditions, epicardial (but not paracardial fat) exerts cardioprotection, which is explained by its antiatherogenic and anti-inflammatory effects, high release and absorption of free fatty acids, and low glucose requirements (22, 23). Non-alcoholic fatty liver disease in association with an increase in epicardial adipose tissue is an independent risk factor for atherosclerosis, coronary heart disease, chronic heart failure, structural and electrophysiological myocardial remodeling; the study of pathogenetic mechanisms in the context of the role of epicardial adipose tissue and clinical monitoring of its condition are urgent problems of modern medicine.

Conflict of interest isn’t declared.

References


