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ENDOTHELIAL DYSFUNCTION IN NONALCOHOLIC FATTY LIVER DISEASE

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Keywords: *endothelial dysfunction, nonalcoholic fatty liver disease, nitric oxide.*

Introduction. *The prevalence of nonalcoholic fatty liver disease (NAFLD) in western countries is increasing rapidly and is considered as component of metabolic syndrome. Endothelial dysfunction is a pathophysiological problem of cardiovascular disease. NAFLD, as a component of metabolic syndrome, is associated with endothelial dysfunction.*

Material and methods. *PubMed database was used in order to review and select articles according to the keywords. A total of 216 articles matching search criteria were found between 2000-2021.*

Results. *The present study has been underlined the role of pathophysiological mechanisms of endothelial dysfunction in nonalcoholic fatty liver disease, that involves oxidative stress, inflammation and insulin resistance. The main factor that influences the occurrence of endothelial dysfunction is related with nitric oxide (NO) biosynthesis. The markers which associated with regulation of nitric oxide biosynthesis, such as asymmetric dimethylarginine, free fatty acid, lectin-like oxidized low density lipoprotein (LDL) receptor-1 and pentraxin-3, are potential targets in assessment of endothelial dysfunction.*

Conclusions. *Insulin resistance, inflammation and oxidative stress have involved in reduction of NO biosynthesis that influence occurrence of endothelial dysfunction. Markers, such as lectin-like oxidized LDL receptor-1 and pentraxin-3, have considered as potential targets in assessment of endothelial dysfunctions in NAFLD.*

Cuvinte cheie: *disfuncție endotelială, boala ficatului gras non-alcoolic, oxid nitric.*

DISFUNCȚIA ENDOTELIALĂ ÎN BOALA FICATULUI GRAS NON-ALCOOLIC

Introducere. *Prevalența bolii ficatului gras non-alcoolic (BFGNA) în țările occidentale este în creștere rapidă și este considerată ca o componentă a sindromului metabolic. Disfuncția endotelială este o problemă fiziopatologică a bolilor cardiovasculare. BFGNA ca o componenta a sindromului metabolic este asociată cu disfuncția endotelială.*

Material și metode. *Baza de date PubMed a fost utilizată pentru a revizui și selecta articole în funcție de cuvintele cheie. Pentru perioada 2000-2021 au fost găsite 216 articole care au corespuns criteriilor de căutare.*

Rezultate. *Prezentul studiu a subliniat rolul mecanismelor fiziopatologice ale disfuncției endoteliale în boala ficatului gras non-alcoolic, care implică stresul oxidativ, inflamația și rezistența la insulină. Factorul principal care influențează apariția disfuncției endoteliale este legat de biosinteza oxidului nitric (ON). Markerii care sunt asociați cu reglarea biosintezei oxidului nitric, cum ar fi dimetilarginina asimetrică, acizii grași liberi, lectin-like oxidized low density lipoprotein (LDL) receptor-1 și pentraxin-3, sunt potențialele ținte pentru evaluarea disfuncției endoteliale.*

Concluzii. *Rezistența la insulină, inflamația și stesul oxidativ sunt implicați în reducerea biosintezei a ON, ce stă la baza apariției disfuncției endoteliale. Markerii, precum lectin-like oxidized LDL receptor-1 și pentraxin-3, sunt considerați ca ținte potențiale pentru evaluarea disfuncției endoteliale în BFGNA.*

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common form of chronic liver disease with high prevalence in western world (1). The prevalence of NAFLD is higher than 25% (2). NAFLD is considered to be component of metabolic syndrome that is defined as combination of abnormalities that includes obesity, hypertension, dyslipidemia and hyperglycemia (3). NAFLD is a group of conditions occurring in patients without alcohol consumption, it has broad spectrum of manifestation ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), more severe form of NAFLD, which eventually progresses to cirrhosis and hepatocellular carcinoma (HCC) (4). Insulin resistance is a characteristic feature of NAFLD (5). Study shows that insulin resistance plays major role in imbalance of the nitric oxide (NO) dependent vasodilator and endothelin-1 (ET-1), which lead to endothelial dysfunction (ED) (6). The incidence of cardiovascular disease has increased significantly in patient with NAFLD (7). The relation between endothelial dysfunction and NAFLD among patient with absence of any risk factors for cardiac disease is established (8). This explains that NAFLD isn't related to comorbidity, but it might be involved in cardiovascular disease (CVD) pathogenesis. Liver releases some mediators such as C-reactive protein (CRP), fibrinogen and plasminogen which is considered pro-atherogenic, and can be related to the pathogenesis of CVD and endothelial dysfunction (9). Endothelial dysfunction is a predictable factor that increases risk of development of atherosclerosis (10). Assessment flow mediated dilatation (FMD) of brachial artery most common noninvasive technique for diagnosis of endothelial dysfunction (11). NAFLD is associated with endothelial dysfunction and arterial stiffness (12).

The aim of this article is to analyze the role of endothelial dysfunction in development of nonalcoholic fatty liver disease and to examine the methods of assessment of endothelial dysfunction.

MATERIAL AND METHODS

We performed a systematic review to analyze the pathophysiology, markers and emerging therapy of endothelial dysfunction in NAFLD. We searched for articles on *PubMed* database by applying the following keywords: endothelial dysfunction, nonalcoholic fatty liver disease, nitric oxide. We selected 47 articles that we deemed relevant to the proposed research topic out of a total of 216 articles matching the search criteria found between 2000-2021.

RESULTS

Pathophysiology of endothelial dysfunction in NAFLD

The term "endothelial dysfunction" typically is characterized by abnormalities in the production or bioavailability of endothelial-derived nitric oxide (NO), increase oxidative stress in endothelium, and eventually leads to abnormal prothrombotic, pro-inflammatory conditions, vasoconstriction and resultant changes in vascular reactivity (13). The endothelium is composed of monolayer cells, called endothelial cells that play major role in normal vascular wall function (14). Distribution of this layer is characterized by circulating endothelial progenitor cell (EPC) which plays the major role in regeneration of the endothelial lining of blood vessels. Level of endothelial progenitor cell in patient with NAFLD were decreased and their function were attenuated, which have correlated with endothelial dysfunction. The maintenance of endothelium wall is important in protecting against atherosclerosis (15). Endothelial dysfunction leads to imbalance in generating vasodilator substance (NO, endothelium-derived hyper-polarizing factor (EDHF) and prostacyclin) and vasoconstrictor substance (angiotensin ll, secretory ET-1, norepinephrine, leukotriene and thromboxane A) essential substance for vascular homeostasis (16). When the irregularly production of vasoactive vasodilator substances occurs, this provokes the vasculature towards pro-thrombotic and pro-atherogenic effects (leukocyte adhesion, platelet activation, pro-oxidation, impaired coagulations, vascular inflammation, atherosclerosis and thrombosis) (17).

Insulin resistance

The liver contain fat that seems to be the best predictor of insulin resistance in adipose tissue, skeletal muscle and liver. Insulin resistance at the level of endothelium can be detected before progression to inflammation, cirrhosis or any other sign of advanced NAFLD (18). Endothelial dysfunction has been related to insulin resistance that is an early common finding in patients with metabolic syndrome (19) and the main pathophysiological hallmark of NAFLD (20). The main factor in development NAFLD is the insulin resis-

tance which cause metabolic abnormalities that include glucotoxicity, lipotoxicity, and inflammation which also lead to endothelial dysfunction. In the presence of insulin resistance, insulin signaling system is disrupted, pathway-specific phosphoinositide 3-kinase dependent signaling is impaired and induce reduction in production of NO, leading to endothelial dysfunction (21). Insulin resistance increase the possibility of patient with ED to develop cardiovascular complications (atherosclerosis, diabetes, dyslipidemia, hypertension and coronary heart disease).

Nitric oxide and endothelial dysfunction in NAFLD

NO is an important protective molecule and main biochemical mediator of endothelium-dependent vasodilation in blood vessels (22). NO is produced by endothelial nitric oxide synthase (eNOS) in response to oxidative stress and vasoconstriction stimuli and has vasodilatory function in regulation of blood flow and blood pressure. Activation of eNOS suggest an increase of intracellular calcium (Ca^{2+}) and binding of Ca^{2+}/calmodulin to the enzyme. This pathway can be stimulated by oxidative stress and insulin resistance and lead to decrease in NO production and provoke endothelial dysfunction (23). Inflammation and oxidative stress are important factors that influence appearance of endothelial dysfunction and NO bioavailability reduction, which is important in vascular homeostasis. Reduced NO bioavailability (due to decrease NO production or NO breakdown induce by the chemical reaction with oxidant radicles) can same lead to endothelial dysfunction (fig. 1).

Oxidative stress and endothelial dysfunction in NAFLD

Oxidative stress is provoked by overproduction of reactive oxygen species (ROS) in the cells and tissue. Overproduction of ROS can cause tissue imbalance, cell injury (24) and lead to ED. Inflammation plays major role in determination of endothelial dysfunction caused by ROS overproduction (25). The overproduction of ROS occurs with the reduction of NO and nitric oxide synthase (NOS) level. NO react with superoxide anion O_2 to produce most powerful oxidant peroxynitrite (ONOO), which generates vasoconstriction, decreases the bioavailability of NO and influences the vasodilator response. Together, the reduction in NO synthesis and the uncoupling of eNOS lead to the loss of vascular tone regulation, especially the NO-dependent vasodilatation producing ED. The vascular hypertension is favored by ED, leading to worsening of the portal hypertension prognosis and contributes to the development of new vascular events, such as atherosclerosis (26, 27). ED in early stage of NAFLD is related to a decrease in NO bioavailability combined with elevated end product of cyclooxygenase and oxidative stress. Both pathways are involved in pathophysiology and may help to develop the treatment goals to stop disease evolution (28).

Inflammation and endothelial dysfunction in NAFLD

Oxidative stress cause release of inflammatory cytokines that play major role in development of endothelial dysfunction (29). Liver release C-reactive protein, fibrinogen and plasminogen which is considered pro-atherogenic. There is a strong association between insulin resistance that plays a major role in endothelial dysfunction, and C-reactivate protein. The fibrinogen and plasminogen-1 activation inhibitor (PAI-1) also are released from liver and activate the coagulation system. *Targher et al.*, confirm that patient with NAFLD had higher levels of high sensitivity CRP, fibrinogen, and PAI-1 (9). The renin-angiotensin system (RAS) has an important role in regulating vascular function. Angiotensin-2 is the main component of RAS. The effect of angiotensin-2 on endothelial dysfunction is regulated by interaction with the plasma receptor membrane angiotensin-2 type 1 and leads to NO reduction by inducing eNOS and promoting NOS uncoupling (30). Nuclear factor kappa-B (NF-Kb) is a transcription factor that plays a major role in intrahepatic inflammation and oxidative stress. Increasing level of NF-Kb lead to hepatic production of inflammatory cytokines interleukin-6, interleukin-1b and tumor necrosis factor alfa (29).

Markers of endothelial dysfunction in NAFLD

ED assessment is one of the most recent research areas in the field of NAFLD, and its evaluation may be essential to define patients with a higher risk of developing of cardiovascular diseases. A possible joining link between NAFLD and cardiovascular diseases has therefore been identified in ED. For this reason, in order to predict the cardiovascular risk of NAFLD patients, it is necessary to develop new diagnostic methods that can measure ED.

Therefore, for ED evaluation it is possible to use invasive methods (intravascular injection of acetylcholine and the measurement of vasodilation

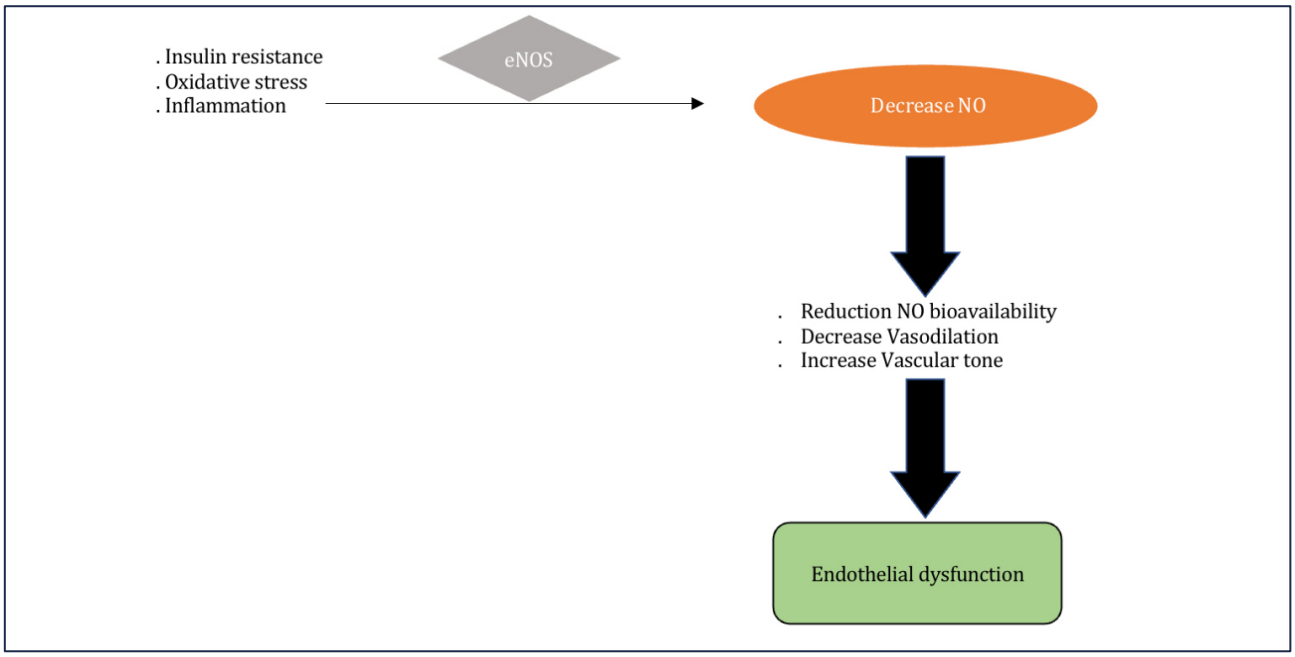

Figure 1. Pathophysiology of endothelial dysfunction in nonalcoholic fatty liver disease.

caused by this neurotransmitter). Economically unfavorable non-invasive methods for screening ED dysfunction (flow mediated dilatation FMD), up to dosage of ED serum markers. However, we focus on non-invasive, inexpensive, and useful biomarkers in clinical practice. Hence, there is a need to study the role of circulating biomarkers in relation to endothelial dysfunction and the severity of the underlying liver disease.

Asymmetric dimethylarginine

The methylated arginine is a natural occurring product of metabolism regulated by a hepatic enzyme called dimethylarginine diaminohydrolase (DDAH). There is two isoforms of DDAH exist in human, DDHA-1 it's isoform that participate in regulation of hepatic and systemic asymmetric dimethylarginine (ADMA) and exists in the expressing neuronal nitric oxide synthase (nNOS). The second form is DDAH-2 that has important function in regulating NO activity, and present in tissue that expressing eNOS. Therefore, increased intracellular DDAH has an important role in regulating ADMA. Dysfunction of DDAH activity can lead to increasing of intracellular ADMA concentration and reduction in NO signaling, which induce endothelial dysfunction (31). The overexpression of DDAH-1 in human endothelial cells shows a moderate increase in NO concentration by 3 times (32). DDAH1 is one of the target genes of farnesoid X receptor (FXR). Treatment of cirrhotic rats with FXR agonists can restore NO levels (33). *Colak Y. et al.* (34) suggested that the plasma levels of ADMA were higher in patients with NASH, and there was no significant difference between any NAFLD patients' group and control group. Therefore, it can be suggested that possible treatments for diseases or endothelial dysfunction may effectively reduce the cardiovascular risk of NAFLD patients.

Free fatty acid

The liver plays a key role in lipid homeostasis, regulation of transport and lipid synthesis, abnormal lipid profile it can be associated with development of liver disease. Elevated free fatty acid (FFA) in blood is considered as an important link between insulin resistance, inflammation, obesity, type 2 Diabetes Mellitus (T2DM) and hypertension (HTN). Dyslipidemia, which is frequently associated with NAFLD, increase risk for endothelial dysfunction (35). Insulin resistance, oxidative stress, and inflammatory burden are important causes of FFA-induced ED (36). Free fatty acid-mediated endothelial dysfunction includes many mechanisms that involves impaired of the insulin receptor substrate/phosphatidylinositol 3 kinase pathway of insulin signaling and nitric oxide production. Oxidative stress and inflammation (through activation nuclear factor-kappa B) lead to release pro-inflammatory, pro-atherogenic cy tokines that activate the renin-angiotensin system and apoptosis in the endothelial cells. Moreover, the increase in free fatty acid levels caused

by metabolic syndrome is considered to be an important link in the occurrence of endothelial dysfunction (37). Therefore, previously provided information demonstrates that FFA can be a predictable novel biomarker for ED in NAFLD.

Lectin-like oxidized LDL receptor-1

It has been identified as the key receptor for oxidized low-density lipoprotein in endothelial cells, and regarded as a marker for ED in assessing pathological condition such as atherosclerosis (38). Lectin-like oxidized LDL receptor-1(LOX-1) promote ROS generation, augments endothelial adhesion to monocytes and inhibit NO synthesis (39). Study, represents that serum LOX-1 increased in patients with NAFLD compared to healthy individuals (40) and LOX-1 may be one of the marker for endothelial dysfunction in NAFLD.

Pentraxin-3

Pentraxin-3 (PTX-3) is a prototype protein that belongs to a pentraxin family. Elevated level of PTX-3 is reportedly associated with obesity, metabolic syndrome and cardiovascular disease. PTX3 is involved in endothelial dysfunction by various mechanisms, decreases the synthesis of NO, inhibits cell proliferation and alters its functions. Elevated PTX-3 is highly associated with endothelial dysfunction in NAFLD and may present interest as a marker for ED in NAFLD (41, 42).

Emerging therapy of endothelial dysfunction in NAFLD

Endothelial dysfunction has associated in the pathogenesis of NAFLD. It seems that restoring EDis a very important therapeutic goal in NAFLD management. NAFLD pharmacotherapy hasn't yet been determined. The only treatment that is proved is non-pharmaceutical treatment that includes lifestyle changes, weight loss, physical exercises and proper diet, are the only treatment recommendations that shows proven benefits (43). Novel pharmacotherapy of ED in NAFLD strategy based on underlying disease related factors as the disease progresses (oxidative stress, inflammation, FFA and insulin resistance). Statins which have anti-inflammatory and antioxidant effects, due to cholesterol lowering effect, improve endothelial function reduce hepatic lipid content and serum alanine aminotransferase (44). There is a study demonstrating the association of endothelial dysfunction with angiotensin converting enzyme (ACE) inhibitors, suppresses the degradation of bradykinin and stimulates the bradykinin receptor of the endothelial cell to produce NO and has an important role in preventing the development of endothelial dysfunction (45). The study shows that combination of both statins and ACE inhibitors results in improving function of endothelium and promote amelioration of inflammation (46). It's recommended that patients with ED in NAFLD to undergo medical analysis of liver enzyme before prescribing any medication, instead of detecting an increase in liver enzymes due to the usage of prescribed medication. This process it must be indicated in all type of drugs that has beneficial effects in treatment of endothelial dysfunction (ACE inhibitors, calcium antagonist, beta blockers, statins, insulin resistance improving drugs, renin blockers and antioxidants) (47).

CONCLUSIONS

1. Insulin resistance, inflammation and oxidative stress are involved in reduction of nitric oxide biosynthesis that influences the appearance of endothelial dysfunction. Therefore, markers such as lectin-like oxidized low density lipoprotein receptor-1 and pentraxin-3 are considered as potential target in assessment of ED in NAFLD. Furthermore, NO regulator like dimethylarginine diaminohydrolase could be considered as possible target for therapeutic management. Treating the ED in NAFLD with NO modulators might suppress disease progression. However, further research must be carried out to understand ED markers and the importance of their effect in the assessment of NAFLD.

CONFLICT OF INTERESTS

No conflict of interests.

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