

Possible Role of Fatty Acid Binding Protein in Type 2 Diabetes and Peripheral Artery Disease: Review Article

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ABSTRACT

Background: As many as 200 million people around the world are affected with peripheral artery disease (PAD), a long-term atherosclerotic problem. The majority of individuals with PAD are asymptomatic, but those who do experience symptoms, such as limb claudication or complete tissue loss, should seek medical attention right away. PAD and its consequences are widespread because of the worldwide growth in the frequency of Type 2 Diabetes Mellitus (T2DM) and the ageing of the general population. Peripheral artery disease can be caused by a combination of vessel wall stiffness and T2DM. Fatty acid binding proteins (FABPs) have been related to the onset of insulin resistance and other manifestations of the metabolic syndrome, and it has been shown that FABPs play an important role in metabolic control. FABP has been linked to fatty acid absorption and chylomicron release in the gastrointestinal tract, according to studies.

Objective: The present review aims to assess of possible role of FABPs in T2DM and PAD.

Method: FABPs, T2DM and PAD were all looked for in PubMed, Google scholar, and Science direct. References from relevant literature were also evaluated by the authors, but only the most recent or complete study from January 2000 to May 2021 was included. Due to the lack of sources for translation, documents in languages other than English have been ruled out. Papers that did not fall under the purview of major scientific investigations, such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations, were omitted.

Conclusion: High levels of some of FABPs in the blood have been linked to both the existence and severity of PAD.

Keywords: Fatty Acid Binding Protein, Type 2 Diabetes, Peripheral Artery Disease, Atherosclerosis, Review.

INTRODUCTION

As a public health issue, type 2 diabetes mellitus (T2DM) has a significant influence on human life and healthcare costs. Many countries throughout the world have seen an increase in the prevalence of diabetes as a result of rapid economic development in urban areas ⁽¹⁾.

In order to prevent T2DM, you need to change your diet, exercise, and control your weight. The containment of this burgeoning epidemic is still dependent on the public's understanding of the disease. There is still no cure for the disease, despite new knowledge about the disease's pathogenesis being gained ⁽²⁾. With a 17.9 percent prevalence rate in 2014, Egypt was ranked third among the Middle East and North Africa region for diabetes, according to the World Health Organization (WHO). Egypt came in second place in the Middle East and North Africa in 2019. The most recent update ⁽³⁾, diabetes affects 18.4% of Egyptian adults, with a total of 10,000,000 cases.

Diabetic complications and co-morbidities, such as peripheral arterial disease (PAD), are all too prevalent. As many as half the people who suffer from diabetic foot ulcers are also suffering from PAD ⁽⁴⁾. Diabetes-related PAD is a major health problem. An atherosclerotic constriction of the peripheral arteries of the legs, stomach, arms, and head, most typically affecting the arteries of the lower limbs, is known as PAD ⁽⁵⁾.

The lower limbs systemic atherosclerotic process, which includes coronary artery disease (CAD), frequently, coexists with the onset of PAD. Detecting PAD in CAD patients can enable cardiac rehab programmes tailor their activity plans to better accommodate individuals with both conditions and, if

necessary, begin treatment or intervention sooner rather than later ⁽⁶⁾.

The objective of the present review is to assess of possible role of Fatty Acid Binding Proteins (FABPs) in T2DM and PAD.

METHOD

FABPs, T2DM and PAD were all looked for in PubMed, Google scholar, and Science direct. References from relevant literature were also evaluated by the authors, but only the most recent or complete study from January 2000 to May 2021 was included. Due to the lack of sources for translation, documents in languages other than English have been ruled out. Papers that did not fall under the purview of major scientific investigations, such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations, were omitted.

Fatty Acid Binding Proteins (FABPs):

They are a family of transporters for fatty acids and other lipophilic substances such as eicosanoid and retinal transporters. These proteins are thought to aid in the transfer of fatty acids ⁽⁷⁾.

Fettle proteins help to transport and store fats by attaching to their respective fatty acid chains. In addition to oxidation and signalling, these lipid chaperones also regulate gene transcription and storage. There are a variety of FABP isoforms that can be found in a variety of tissues, although some are active in several organs. In both number and quality, pathological disorders are connected to variations in FABPs. Among other things, FABPs are biomarkers for obesity, insulin resistance, heart disease, and cancer. A genetic alteration or a

posttranslational modification can cause FABP expression or malfunction, both of which can be detrimental ⁽⁸⁾.

Antioxidant properties are another essential aspect of FABPs. FABPs may shield cell membranes from the harmful effects of excessive concentrations of FAs and other lipid derivatives, according to this theory. During chronic ischemia, the myocardium accumulates an unwanted amount of LCFAs and acyl-CoAs, and this abnormal oxidation process generates free oxygen radicals that damage membrane macromolecules. FABPs operate as scavengers of free radicals by binding LCFAs and reducing oxidative stress ⁽⁹⁾.

Heart-Type FABP; FABP-3 (HFABP):

An estimated 17.9 million people died in 2015 as a result of cardiovascular disease, making it the leading cause of death from noncommunicable diseases ⁽¹⁰⁾.

Diabetes is a risk factor for heart failure on its own. Diabetic cardiomyopathy may be facilitated by increased fatty acids (FAs) absorption and disordered utilization, which results in decreased cardiac efficiency and the accumulation of cardiotoxic lipids. Diabetes has been demonstrated to cause abnormal FAs usage in the heart ⁽¹¹⁾. As of now, FABPs have been split into multiple subtypes, each of which is located in a different organ system at a different level of concentration. It has been widely discussed, particularly because of the association of HFABP as an independent risk factor for all-cause mortality and cardiovascular (CV) fatalities in the elderly ⁽¹²⁾. FABP3 is a 15 kDa soluble non-enzyme protein that can be found in the bloodstream. In the heart and skeletal muscle, 132 amino acids are expressed ⁽¹³⁾.

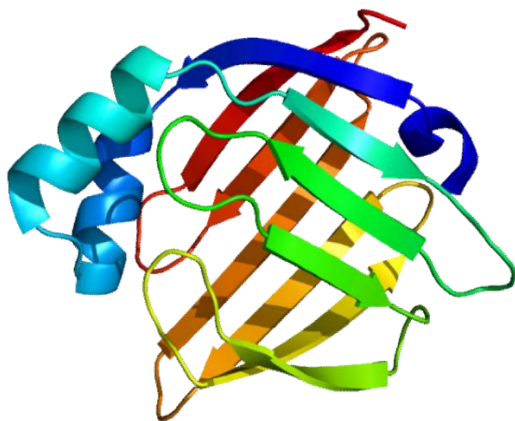


Figure (1): Structure of FABP3 ⁽¹³⁾.

Role of FABPs in T2DM and PAD:

Diabetes is caused by a deficiency or resistance to insulin, which results in a lack of insulin action. In addition to high blood sugar levels, a rise in serum FAs may be a sign of diabetes ⁽¹⁴⁾. Lipolysis is triggered by a loss of insulin activity, which results in the release of FA from white adipose tissue. In cases of hypoglycemia, FA is normally a source of energy for a variety of cells; nevertheless, an excess of FA is likely to be harmful to the body. Serum FA has been linked to inflammation, endothelial dysfunction, and insulin resistance in a

number of recent investigations ⁽¹⁵⁾. Atherosclerosis, the leading cause of cardiovascular disease, is fueled by a number of illnesses, including endothelial dysfunction and hypercholesterolemia. Myocardial infarction and peripheral artery disease are, in fact, clinical problems of the heart and blood vessels ⁽¹⁶⁾.

In addition to fatty acid metabolism, FABPs are involved in a variety of cellular functions, in addition to their role in cellular growth and differentiation, cellular signalling, gene transcription and cytoprotection ⁽⁹⁾.

FABPs have been linked to a variety of disorders, including metabolic syndrome, insulin resistance, and others. An intestinal FABP may regulate chylomicron absorption and synthesis as well as fatty acid absorption ⁽⁹⁾. FABP is necessary for adequate cardiac fatty acid oxidation and controls skeletal muscle fatty acid uptake. Hepatocyte peroxisome proliferator-activated receptors (PPARs) and fatty acid ligand signalling in the nucleus are intimately linked via liver FABP. This FABP (adipocyte FABP) has been implicated in atherosclerosis as a key player in insulin sensitivity and lipid metabolism and lipolysis. Atherogenesis is facilitated by the macrophages' production of Adipocyte FABP, which links insulin resistance, intracellular fatty acid distribution, and foam cell development. Patients with dyslipidemia, insulin resistance, and atherosclerosis could benefit from targeting the fatty acid binding protein ⁽¹⁷⁾.

FABP has been identified as the key player in the regulation of insulin resistance and lipid metabolism in the body. FABPs are proved to play an important function in macrophage biological responses and contribute to the onset of atherosclerosis. ApoE-deficient animals additionally lacking Adipocyte FABP exhibited a protective effect against atherosclerosis in the absence of significant changes in blood lipids or insulin responsiveness. Research with modified lipoproteins led to changes in macrophages' ability to collect cholesterol esters in the presence of adipocyte FABP deficiency ⁽¹⁸⁾.

Glucose dysregulation and the development of T2DM were linked to elevated serum A-FABP ⁽¹⁹⁾. Atherosclerosis development was found to be significantly impacted by AFAP, according to some research, due to changes in macrophage inflammatory responses and cholesterol metabolism ^(17,18). After a cardiac or skeletal injury, FABP3, a tiny intracellular protein, is released into the bloodstream ⁽²⁰⁾. Increased myocyte apoptosis and worsening cardiac dysfunction, with a reduced ejection fraction from the left ventricle, were observed when FABP3 was overexpressed in patients who had undergone an acute myocardial infarction ⁽²¹⁾. FABP3 overexpression in neonatal rat ventricular cardiomyocytes under hypoxia also promoted death and apoptosis. As an added benefit of FABP3 loss, it helped preserve cardiac myocytes from cell death and heart remodelling during myocardial infarction (MI) ⁽²²⁾.

Zamzam et al. ⁽²³⁾ recently discovered for the first time that uFABP3/uCr is raised in patients with T2DM and lower-extremity PAD.

PAD is an atherosclerosis occlusive condition of the lower limbs, which is characterized as PAD. Atherothrombosis in cardiovascular, cerebrovascular and renovascular beds is a sign for PAD, which increases the risk of amputation of the lower extremities. In turn, patients with PAD are more likely to suffer a heart attack, stroke, or death ⁽³⁾. Despite the fact that it is common, many diabetics with PAD go untreated, putting them at an increased risk of lower-extremity amputations and death ^(24,25). T2DM, hypercholesterolemia, hypertension, as well as smoking, represent main risk factors to develop PAD which is clinically significant ⁽²⁶⁾.

Regardless of the presence of additional cardiovascular risk factors, abdomen fat distribution is associated to peripheral artery occlusive disease ⁽²⁷⁾.

There are many factors that contribute to obesity, including lipid metabolism, hormonal axis dysregulation, oxidative stress and systemic inflammation. Ectopic fat distribution also contributes to obesity. Inflammatory mediators and free fatty acids are abundant in adipose tissue (FFAs) ⁽²⁸⁾.

CONCLUSION

FABP levels in the blood have been linked to both the existence and severity of PAD.

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