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STUDY OF HEART TYPE FATTY ACID BINDING PROTEIN IN DIABETIC PATIENTS
(Article Review)

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Abstract
The majority of the cytoplasmic molecule the heart contains a protein called heart-type fatty acid-binding protein (H-FABP). After a myocardial infarction, it can be seen as early as 30 to 90 minutes in the blood. After peaking at 4 to 6 hours, it takes about 24 hours to recover to baseline levels. Because H-FABP is so sensitive early on in an acute MI episode, it has been recommended for usage in milder forms of subclinical myocyte injury as well as in the initial diagnosis of MI. Type 2 diabetes mellitus increases the risk of heart failure (T2D), based on an increasing amount of studies. Conclusion: H-FABP is a crucial predicator of HF in DM. Higher threat of perioperative cardiac death in diabetic patients associated with H-FABP. H-FABP intensities are higher in patients with HF who have a lower ejection fraction. An elevated plasma H-FABP may take a part in the etiology of chronic kidney diseases in diabetic patients. The review that is being given summarizes research on diabetes mellitus and H-FABP that was conducted in Iraq and a few other nations.

Keywords: H-FABP, Diabetes mellitus, heart failure, MI.

Introduction
A growing body of research indicates that the risk of heart failure (HF) is higher in those with type 2 diabetic mellitus (T2D) (1). Indeed, one of the most common cardiovascular (CV) symptoms found in T2D patients is HF (2, 3). In spite of this, the prognosis for those with T2D and HF remains uncertain. In this sense, recognized risk variables are unable to adequately account for the increased mortality risk in these people (4-8). Consequently, categorization of the mortality risk associated with HF continues to be difficult for these individuals, and more HF biomarkers among T2D people ought to be taken into account.

Postoperative myocardial ischemia is rarely accompanied by chest discomfort or changes in the electrocardiogram ST segment. Therefore, the primary cause of postoperative MI diagnosis is variations in biochemical markers, particularly cardiac troponin (cTn). Heart-type fatty acid-binding protein (H-FABP) is primarily composed of cytoplasmic components that are found within the heart. As early as 30 to 90 minutes following a myocardial infarction, it can be detected in the blood. After peaking at 4 to 6 hours, it takes about 24 hours to recover to baseline levels. H-FABP has been proposed for use in the identification of both milder forms of subclinical myocyte injury and the initial MI because of its high sensitivity in the early stages of acute MI (9).

Metabolic problems, even in the absence of coronary artery disease, have been linked to an increased risk of heart failure, including altered glucose and fatty acid metabolism (10).

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Apoptosis of cardiomyocytes, impaired mitochondrial activity, and elevated oxidative stress are some of the primary molecular causes behind cardiac dysfunction (11). An increasing amount of research suggests that serum circulating molecules may play a role. These molecules may serve as sensors of changes in metabolism and may make those with type 2 diabetes more susceptible to cardiac failure. As a result, a number of metabolic disorders associated with cardiac problems have been connected to members of the Fatty Acid Binding Protein (FABP) family (12). This family of molecules consists of intracellular lipid transporters that regulate intracellular lipid trafficking and the subsequent responses. Specifically, the modulation of cardiac insulin resistance has been linked to the heart-specific fatty acid binding protein (FABP3) (13), and the absorption of fat acids (14). Adipose-tissue-specific FABP (FABP4) is a different type of FABP that has direct effects on insulin signaling in cardiac cells. Additionally, it has cardiodepressant properties and aids in the trans-endothelial transfer of nutrients to the cardiomyocyte (12, 15, 16). It has been reported that FABP3 and FABP4 are circulating biomarkers of a number of cardiac and metabolic disorders. Following an acute myocardial damage, FABP3 is quickly released into the bloodstream (17-19). Elevations of FABP3 have also been linked to other cardiac diseases, such as heart failure (HF), acute coronary syndrome (ACS), and multiple cardiomyopathies (20), was recommended as a silent biomarker for individuals with insulin resistance to track the development of cardiac damage (21). However, HF and CV disease have also been linked to FABP4. Serum concentrations of FABP4 and the N-terminal pro-B-type natriuretic peptide (NT-proBNP), an HF biomarker specifically correlate favorably; this connection is significantly tougher in individuals with diabetes and HF. FABP4 has been linked in recent studies to ectopic fat deposition in the heart, which is one of the primary indicators of diabetic myocardial dysfunction (22).

Oxidative stress has been connected to both FABP3 and FABP4. For example, circulating FABP3 has been positively connected with oxidative stress indicators including malondialdehyde (MDA) and asymmetric dimethylarginine (ADMA) and negatively correlated with total antioxidant capacity (TAC) in patients with carbon monoxide-induced cardiotoxicity (23). On the other hand, research using animals lacking the enzyme FABP4 demonstrated a decrease in oxidative stress when diabetes-related heart failure and myocardial ischemia/reperfusion (MI/R) injury were present. This was proven by simultaneously generating fewer superoxide anion and activating the eNOS/NO pathway (24). Thus, by controlling oxidative stress, FABP3 and FABP4 may both have a direct effect on the development of the disease.

The idea that serum concentrations of FABP4 and FABP3 can predict CV and all-cause mortality is becoming more and more supported by data; Nevertheless, research has not yet been done on the potential use of these FABPs as predictive biomarkers for the risk of death in individuals with T2D and progressive heart failure (CHF). Finding the prognostic significance of these two FABPs (FABP3 and FABP4) for CV and all-cause mortality in outpatient CHF patients with T2D was the aim of this investigation (22). This article review summarizes the importance of H-FABP in diabetic patients.

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2.Heart-type fatty acid-binding protein:

Without a doubt, the heart-type FABP (H-FABP), sometimes referred to as the mammary-derived growth inhibitor, is the most well-known member of the FABP family. H-FABP is encoded by the FABP3 gene, which is located on chromosome 1's 1p33–p32 region (25). However, studies conducted on animals have shown that different PPARs bind to transcriptional factors at locations called RXRa, KLF15, CREB, and Sp1.

(26). It is expressed in blastocysts as well as tissues with great fatty acid requests, including the tissues of the adrenal gland, brain, kidney, heart, skeletal muscle, and mammary glands (27). Additionally, it was found that FABP3 is expressed in the male mouse anterior cingulate cortex (MAC), proposing that it is vital for maintaining cerebral PUFA homeostasis. These are inhibitory interneurons that are GABA-ergic (28).

The striated muscle cells' cytoplasm contains a large amount of H-FABP, which is produced quickly in response to cardiac damage (29). The heart's ventricles (0.46 mg/g wet weight) and atria (0.25 mg/g wet weight) express H-FABP more often than the skeletal muscles or other organs, which make up less than 10% of the heart's H-FABP content (30). In healthy individuals, serum H-FABP levels are in the single digit ng/ml range (31).

The microRNA miR-1 controls the expression of H-FABP and may be involved in the onset of HF (32). After myocardial damage, H-FABP is quickly discharged from myocytes into the bloodstream because of its small size and free cytoplasmic location. Furthermore, it's likely that H-FABP enters the bloodstream due to transient increases in sarcolemmal membrane permeability (33, 34). Even after brief ventricular stress, this so-called "wounding" of myocytes was seen, and it could be significant for a variety of auto- and paracrine pathways in the etiology of HF (33). Patients with normal renal function have a shorter diagnostic window because H-FABP is eliminated by the kidney. For instance, Kleine *et al*. found that in individuals H-FABP plasma levels with acute myocardial infarction reverted to baseline within 20 hours of the beginning of symptoms (35).

2.1. Acute myocardial infarction and H-FABP:

Geraldine McMahon examined if individuals giving to the ED with chest distress of cardiac origin might be diagnosed with AMI using H-FABP, cTnI, myoglobin, and CK-MB (36) A number of blood samples were obtained upon admission, then every two hours for the next twelve hours, and then every 24 and 48 hours after that. The cardiac array from Randox Laboratories was used to measure biomarkers. The diagnostic cut-offs (99%, CV<10%) were as follows: CKH-FABP: 5.24 µg/L, cTnI: 0.37 µg/L, MYO: 95.57 µg/L, and -MB: 7.18 µg/L. At the earliest time points, H-FABP exhibited the highest sensitivity. 64.3% of the biomarkers checked were discovered up to three hours, while 85.3% were discovered between three and six hours. The greatest NPV (93%–98%) was shown by H-FABP between 0 and 12 hours after the start of chest pain. Furthermore, this study looked more closely at each marker's diagnostic efficacy on the cardiac array at each time point. The results of the ROC curves indicated that, of the four markers, H-FABP had the best diagnosis accuracy between 0 and 12 hours following the start of pain.

Mi-Gil Moon performed point-of-care testing (POCT) and laboratory analyses for H-FABP, CK-MB, and cTnI for patients who were sent to the ED for suspected ACS and who were

brought in within 24 hours of reporting dyspnea or chest discomfort (37) The ED first collected a venous blood sample in order to do POCT and laboratory analysis. Further samples were collected in order to perform successive laboratory analyses on cardiac indicators. A laboratory technique called latex turbidimetric immunoassay (LTIA) was employed to analyze H-FABP. For the POCT of cardiac markers, rapid kits utilizing the immune chromatography (ICA) approach were utilized. The following are the observed AUC values for each patient: H-FABP -0.771 (95% CI, 0.674–0.868), TnI -0.759 (95% CI, 0.664–0.854), and CK-MB -0.690 (95% CI, 0.580–0.801). The study found that there was no statistically significant difference between H-FABP and TnI (P=0.81), despite the fact that H-FABP had the greatest AUC value.

3.Cardiovascular disease:

A illness of the circulatory system, cardiovascular disease (CVD) affects blood vessels and vascularized systems, such as the heart, brain, and limbs. CVDs are categorizable according to the presence or absence of an ischemic condition, which occurs when the affected blood arteries thicken luminally, reducing blood flow and resulting in ischemia in the organs downstream. Ischemic CVDs, which are more prevalent, include peripheral vascular diseases (PAD), ischemic heart disease (IHD), and cerebrovascular illnesses. These phrases describe obstacles in the arteries providing the brain, the heart, and the lower limbs, in that order. These illnesses result in serious clinical symptoms such as limb ischemia, angina (chest discomfort), hypertension, stroke, and acute myocardial infarction (AMI) (38, 39).

3.1. Cardiovascular Disease's Burden:

Globally and in the US, Every year, the leading cause of death is cardiovascular disease. According to estimates from the World Economic Forum, non-communicable diseases cause 50% of deaths globally, with 37% of those deaths occurring in those under the age of 70. According to the World Health Organization, 17 million individuals decease from CVD each year, with over 70% of those deaths taking place in low- to middle-income nations. This number increased throughout the years 2016 and 2017. The frequency of CVD is higher in men than in women, although it also rises in elder age sets for both sexes, particularly those above 35 (40). Additionally, the population with lower socioeconomic status has a higher prevalence (41). The global age-adjusted death rate, incidence, and prevalence of cardiovascular disease (CVD) were around 233 per 100,000 people, 6000 cases per 100,000 people, and 485 million cases overall in 2017, according to a 2020 American Heart Association study. It is anticipated that these figures will rise. It's interesting to note that while disease-related mortality rates were highest in Eastern Europe and Central Asia, there were notable rates of CVD prevalence in the US, Central Europe, North Africa, and the Middle East. The United States was expected to spend $351 billion on CVD in total in 2014. Of that amount, $213 billion may be attributable to direct costs such prescription drugs and healthcare services like hospitals and doctor's offices. The remaining $138 billion was spent on indirect costs related to premature death, disability, and lost income, productivity, and employment. By 2035, it's predicted that the entire cost of CVD would be $1.1 trillion. About 48% of adult Americans were diagnosed with cardiovascular diseases (CVDs) in 2016, and over 1000 people died from CVDs per day. About 220 fatalities per 100,000 people were caused by CVD in 2017, which was a higher death toll than the total

deaths from cancer and chronic lung illnesses. If CVD continues to be the world's top reason of death, it is predicted to reason for more than 20 million fatalities by 2030 (42, 43).

3.2. Risk factors:

Many CVD risk factors have been recognized and classified as either modifiable or non-modifiable. Among the modifiable risk factors are a healthy diet, regular exercise, quitting smoking, and adopting a healthy lifestyle. Drug treatments can also improve or prevent these hazard causes. Laziness and deprived diets heavy in saturated or trans fats and glucose, which raise blood lipid and cholesterol levels, are the two main modifiable risk factors for CVDs. The most frequent cause of CVD, atherosclerosis, is progressing into these diseases. Smoking can increase the risk of CVDs by harming the endothelium, the liver, and the cells that line every blood vessel. Damage to the endothelium may result in decreased making of high-density lipoprotein and endothelial dysfunction, which may lead to hypercholesterolemia and atherosclerosis (44, 45). Certain people are inherently more susceptible to cardiovascular difficulties than others due to non-modifiable hazard causes. These risk factors include older ages, being male, and genetic variables including an ancestor's history of heart disease. Growing blood cholesterol levels are generally linked to a growth in cardiovascular threat in older adults, particularly those over 55 (46), and deteriorating vascular integrity, including diminished arterial compliance and loss of arterial elasticity (47).

4. Several investigations on H-FABP as a heart failure biomarker:

In a study conducted in Baghdad, Iraq, they found that patients with Beta-Thalassemia Major (β-TM) had higher levels of serum H-FABP, Troponin-I, BNP, and ferritin when compared to healthy control subjects ($P < 0.001$). In the patient group, there was a negative connection seen between serum H-FABP and Troponin-I. In the β-TM Patients, there was a negative connection and an raised amount of H-FABP between blood H-FABP and Troponin I (48). In another study done in Baghdad city, they detected that all of the biomarkers—OPG, NEP, and H-FABP—as well as how they relate to one another were studied because they are critical in the expectation of heart failure. In this patient population, OPG and NEP in particular have demonstrated a strong predictive value for heart failure. These outcomes might contribute to the progression of improved dialysis patient heart failure detection and treatment protocols (49). In Thi-Qar, Iraq, they denoted that sensitive markers such as PCT, Lp-PLA2, H-FABP, and hs-CRP can be utilized to identify and treat stable angina pectoris rapidly (50). In an investigation made by Abdelaaty *et al*, they detected which diastolic dysfunction is a characteristic outcome in T2DM patients. In patients with early diabetic kidney disease, urine albumin-Creatinine ration (UACR) is strongly linked with diastolic dysfunction, but not serum H-FABP. Early DKD is marked by a significantly increased serum H-FABP level, which is strongly linked with albuminuria (51). Gruson *et al*, found that heart failure patients with a decreased ejection fraction have higher H-FABP levels, which are linked to poor CV outcomes and may help doctors manage these patients(52). Lee *et al* stated that, the amount of circulating adipocyte fatty acid-binding protein is connected to incidence heart failure hospitalization in individuals with type 2 diabetes and may be useful in risk assessment to avoid heart failure hospitalization (53). Ramesh *et al*., reported that in pre-diabetics, the new cardiac biomarker H-FAPB may be a useful predictor of

cardiovascular risks (54). YU *et al*., revealed that showed eGFR is correlated with circulating H-FABP in T2DM patients, indicating that elevated plasma H-FABP may play a role in the etiology of CKD(55). In an Egyptian study, they found that peripheral artery disease has been related to both its presence and severity at high blood levels of various FABPs (56). In diabetics, heart-type fatty acid-binding protein was found to be significantly associated with a higher risk of perioperative cardiac death, agreeing to Sari *et al* (9). H-FABP in diabetic patients may be a potential marker for myocardial ischemia, according to a Turkish study (57). While H FABP inhibition may offer a viable treatment strategy for the prevention of lipid metabolism-associated podocyte injury, Gao et al. showed that overexpression of H FABP in diabetic patients enhances fatty acid-induced podocyte injury (58).

5. Review Method and Collection Standards:

Studies that showed a relationship between the incidence of cardiovascular events and H-FABP were deemed appropriate for inclusion in the analysis. Studies that provide information on H-FABP patients with diabetes mellitus and cardiac issues were selected and included

6. Extraction of Data:

Each study's data were taken out and condensed. Publication year, main author, study population, number of cases with cardiac events, and control subjects in diabetic patients were among the data retrieved from all of the studies.

7. Conclusions:

1-H-FABP is a crucial predicator of heart failure in DM patients.
2- Increased risk of perioperative cardiac death in diabetic patients associated with H-FABP.
3- HF patients with a decreased ejection fraction have higher H-FABP levels, which are linked to poor CV outcomes and may help doctors manage these patients.
4- An elevated plasma H-FABP might take a part in the etiology of chronic kidney diseases in diabetic patients.

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