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Review

Heart-type fatty acid-binding protein in cardiovascular disease: A systemic review

Yoichiro Otaki, Tetsu Watanabe*, Isao Kubota

Department of Cardiology, Pulmonology, and Nephrology, Yamagata University School of Medicine, Yamagata, Japan

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ABSTRACT

Fatty acid-binding proteins, whose clinical applications have been studied, are a family of proteins that reflect tissue injury. Heart-type fatty acid-binding protein (H-FABP) is a marker of ongoing myocardial damage and useful for early diagnosis of acute myocardial infarction (AMI). In the past decade, compared to other cardiac enzymes, H-FABP has shown more promise as an early detection marker for AMI. However, the role of H-FABP is being re-examined due to recent refinement in the search for newer biomarkers, and greater understanding of the role of high-sensitivity troponin. We discuss the current role of H-FABP as an early marker for AMI in the era of high sensitive troponin.

H-FABP is highlighted as a prognostic marker for a broad spectrum of fatal diseases, viz., AMI, heart failure, arrhythmia, and pulmonary embolism that could be associated with poor clinical outcomes. Because the cut-off value of what constitutes an abnormal H-FABP potentially differs for each cardiovascular event and depends on the clinical setting, an optimal cut-off value has not been clearly established. Of note, several factors such as age, gender, and cardiovascular risk factors, which affect H-FABP levels need to be considered in this context. In this review, we discuss the clinical applications of H-FABP as a prognostic marker in various clinical settings.

1. Introduction

1.1. Discovery of the FABP family

Mammalian fatty acid-binding proteins (FABPs) were discovered in the early 1970s [1,2]. These 14–15 kDa low-weight proteins abundantly present in cytosol are involved with binding and transport of long-chain fatty acids. To date, 12 and 10 isoforms have been identified in vertebrates and human beings, respectively [3]. Detailed properties of FABPs such as their tertiary structure, distribution, ligand-binding affinities and specificities, and molecular mechanism of action in intracellular lipid metabolism have been elucidated [4]. In keeping Conforming to their vital role in lipid metabolism, several FABPs were discovered in organs such as the heart, liver, and intestine, which are actively involved with lipid metabolism [5]. FABPs were also purified after extraction from tissues not associated with active lipid metabolism. Notably, cytoplasmic FABPs are universally expressed in all human tissues. Awareness regarding the rapid release of FABPs by injured tissues has elicited growing interest in the clinical application of FABPs as a marker of tissue injury [6]. Table 1 illustrates a growing body of evidence to demonstrate that FABPs play a pivotal role in the development of cardiovascular disease. For example, FABP 1–6 are related to diabetes mellitus. FABPs present in adipose tissue and macrophages such as FABP 4 and 5 are closely associated with cardiovascular disease through development/acceleration of atherosclerosis and worsening cardiac function [7–10]. In this review, we focus on the heart-type fatty acid-binding protein (H-FABP), a major isoform found in the heart.

1.2. Character of H-FABP

H-FABP, also called FABP3, is a dominant isoform present in the heart and skeletal muscles. H-FABP is also expressed to a lesser extent in brown adipose tissue, the distal nephron, nervous system, lactating mammary gland, and the placenta [11–16]. That H-FABP is released by the injured myocardium was first discovered in 1988 [17]. Nowadays, H-FABP is clinically used for early diagnosis of acute myocardial infarction (AMI). The *H-FABP* gene is reportedly located on chromosome 1 in the human genome or on chromosome 5 in the mouse genome, which is a quantitative trait locus linked to hypertension, whose activation is controlled by the sympathetic nervous system [18].

H-FABP reportedly plays a key role in mitochondrial β oxidation through partitioning of long-chain fatty acids toward the mitochondria [19]. H-FABP knockout mice show a dramatic decrease in long-chain

* Corresponding author at: Department of Cardiology, Pulmonology, and Nephrology, Yamagata University School of Medicine, 2-2-2 Iida-Nishi, Yamagata 990-9585, Japan.
E-mail address: tewatana@med.id.yamagata-u.ac.jp (T. Watanabe).

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Table 1
Chromosome and tissue location of each fatty acid-binding protein family member.

FABP	Name	Chr	Major location	Potential clinical application
1	Liver type	2	Liver, kidney, intestine, lung	AKI, CKD, DM
2	Intestine type	4	Intestine	Obesity, IR, DM, HL
3	Heart type	1	Heart, skeletal muscle, mammary	AMI, obesity, IR, HT, DM, Mets, CVD, HF
4	Adipocyte type	8	Adipose tissue, macrophages	Obesity, IR, DM, HT, Mets, CVD, HF
5	Epidermal type	8	Heart, lung, brain, tongue, stomach, intestine, testis, mammary, retina, adipose tissue, macrophage	IR, atherosclerosis, HL, mets, CVD, COPD
6	Ileal type	5	Ileum, ovary	DM
7	Brain type	6	Brain, olfactory bulb	Alzheimer disease, schizophrenia
8	Peripheral myelin protein 2	8	Peripheral nervous system	Charcot-Marie-tooth disease
9	Testis type	8	Testis	
10	Basic liver type	(−)	Liver	Absence in mammals
11		(−)		Absence in mammals
12		8	Retina, testis	

AKI, acute kidney injury; AMI, acute myocardial infarction; CKD, chronic kidney disease; Chr, chromosome; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; FABP, fatty acid-binding protein.

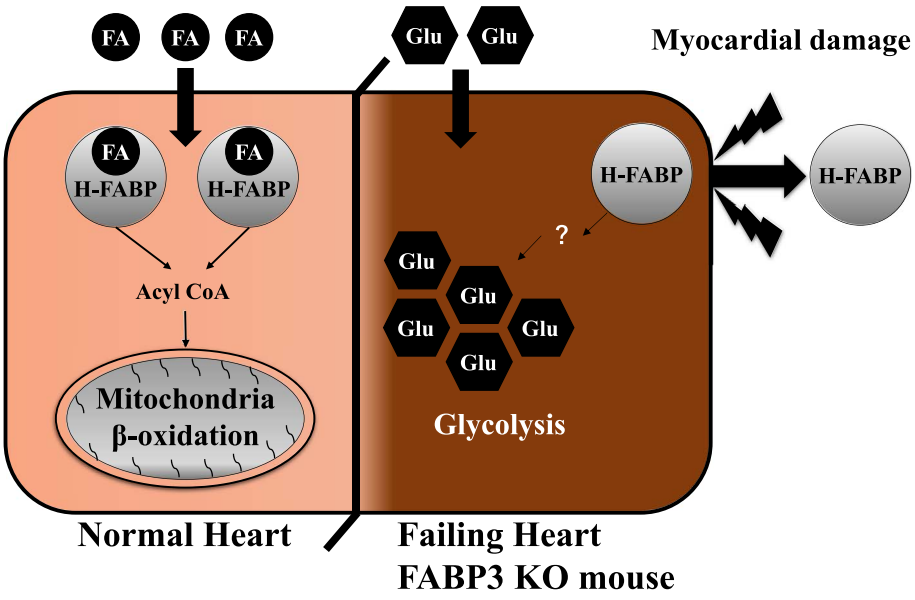

Fig. 1. Schematics depicting the proposed role of H-FABP in the heart. Similar to FABP3 knockout mice, the H-FABP level is decreased in the failing heart. FA: fatty acid. Glu: glucose. H-FABP: heart type fatty acid-binding protein.

fatty acid uptake and an increase in glucose uptake in the heart. The major energy source of the myocardium shifts from lipids to carbohydrates in H-FABP knockout mice, indicating the key role of H-FABP in lipid metabolism in the normal heart [20] (Fig. 1).

Cardiovascular disease is a major cause of death globally and its prevention and risk stratification remains an unmet medical need. Recent clinical studies have focused on the prognostic capacity of H-FABP in several clinical settings, viz., AMI, heart failure (HF), arrhythmia, acute pulmonary thrombosis, chronic thromboembolic pulmonary hypertension, peripheral artery disease (PAD), and in the general population. In this review, we discuss the current role of H-FABP in early diagnosis of AMI and provide new insights into the prognostic capacity of H-FABP in a broad spectrum of fatal diseases.

1.3. H-FABP assay

The assay methods of H-FABP mainly reviewed in this paper were shown in Tables 2 and 3. H-FABP levels were determined by enzyme-linked immunosorbent assay (ELISA), immunochromatographic lateral-flow test, and immunoturbidimetric method. Recent study reviewed in this paper used FABPulous BV as point of care test, which enable us to detect H-FABP within 5 min.

2. Role of H-FABP in patients with acute coronary syndrome

2.1. Diagnostic role in detection of acute coronary syndrome

Acute coronary syndrome (ACS) is a major cause of death worldwide, and early and accurate diagnosis of ACS is critical for initiation of timely and effective treatment and management. American College of Cardiology/American Heart Association (ACC/AHA) guidelines specify an electrocardiogram and cardiac troponins as key elements in the diagnosis of ACS [21]. Cardiac troponins, which constitute the structural proteins of the contractile apparatus of the myocardium, show a high specificity as preferred markers to detect ACS. Despite technological refinements in cardiac troponin assays, diagnosing ACS in patients presenting with non-ST elevation myocardial infarction (NSTEMI) immediately after symptom onset continues to be challenging.

Clinical application of H-FABP for early diagnosis of ACS has been extensively studied. Basic and clinical research has demonstrated that by a mechanism different from that exhibited by cardiac troponins, H-FABP leakage occurs through the porous membranes of damaged myocardial cells without cardiomyocyte necrosis. Because H-FABP is abundantly expressed and normally confined to the cytoplasm of cardiomyocytes. Thus, an elevated serum H-FABP concentration would indicate myocardial damage [22–25]. Generally, serum concentration of H-FABP is increased 1–2 h after symptom onset, and a peak