



REVIEW PAPER

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Fatty acid binding proteins (FABPs) – a new laboratory biomarker for kidney diseases

Łukasz Dobrek

Department of Pharmacology, Faculty of Medicine and Health Sciences, Andrzej Frycz Modrzewski Krakow University, Poland

ABSTRACT

Fatty acid binding proteins (FABPs) are a family of intracellular proteins involved in metabolism of lipids. By regulating the intracellular level of free fatty acids, those proteins indirectly influence intracellular signaling pathways. FABPs also play a role in regulation of cell growth and differentiation, and exert a significant antioxidant effect. Some reports suggest that FABPs are released by various organs (heart, liver, intestines, kidneys) in response to tissue damage. The article briefly summarizes the structure, classification and function of FABPs and discusses the applicability of liver- (L-FABP) and heart-type (H-FABP) FABPs in laboratory diagnosis of selected clinical entities, particularly kidney diseases.

Keywords: fatty acid binding protein (FABP), biomarker, kidney diseases.

Introduction. Classification, structure and function of fatty acid binding proteins

Fatty Acids (FAs) are compounds possessing various important biological functions. First of all, along with phospholipids and cholesterol they build biological membranes. They also form triglycerides (TGs) – esters of glycerol, the main energetic material. Some FAs are also source of eicosanoids – compounds that modulate many physiological functions in auto- and paracrine mechanisms [1, 2]. Fatty acids as exogenous compounds are delivered with a diet mainly in form of TGs. In the gastrointestinal tract, in the presence of bile, triglycerides are emulsified to micelles and subjected to enzymatic degradation by lipase. That results in TGs breakdown into free FAs and glycerol absorbed by enterocytes. In enterocytes those compounds are reassembled into TGs and, when combined with the corresponding apoproteins, released into the lymphatic fluid as one of lipoproteins – chylomicrons.

Finally, chylomicrons reach the systemic circulation and they are subjected to the action of lipoprotein lipase present in the endothelium of blood vessels, muscles, and in the adipose tissue. The action of that enzyme results in release of FAs, that are then absorbed by adipocytes, muscle cells and the liver and stored in those tissues again assembled into TGs. In turn, the TGs lipolysis process, or *de novo* synthesis of new FAs from glucose, provides endogenous FAs that are transported in blood as VLDL lipoproteins, that undergo catabolic changes similar to those of chylomicrons, releasing FAs necessary for various cells functions [1, 3].

In the abovementioned briefly described FAs metabolism, an important role is also played by fatty acid binding proteins (Fatty Acid Binding Proteins; FABPs), described in 1972 by Mishkin et al. [4], as a low molecular weight cytoplasmic agent isolated from the liver of laboratory rats, binding long chain fatty acids (LCFAs). In the same year Ockner et al. [5] also described the protein demonstrating the same properties and confirmed its presence in other tissues.

FAs intracellular influx from plasma takes place by both passive diffusion and an active transport with transmembrane protein carriers. One of the proteins that carry FAs through the cell membrane are FABP associated with plasma membrane – FABP_{PM}. Those proteins are low molecular weight translocases, found in different cells characterized by high lipid-turnover: hepatocytes, adipocytes, enterocytes and cardiomyocytes [2].

After entering the cell, FAs are linked to cytosolic FABPs. Those proteins are also low molecular weight (14–15 kDa), widely distributed compounds. They form a family of proteins, classified according to their localizations and are products of specific genes. Moreover, the FABPs family belongs to a super-family of other proteins that also bind fatty acids (e.g. FABP_{PM} mentioned above, fetuin, heat shock protein, S-transferase). The superfamily also includes some less characterized compounds that appear to be structurally related to cytosolic FABPs: cellular retinoid binding proteins (CRBPs), cellular retinoid acid binding proteins (CRABPs), mammary-derived growth inhibitor (MDGI), fibroblast growth regulator (FGR) and gastrotropin binding bile salts and bilirubin in the ileal mucosa. The currently distinguished FABPs and FABPs-related compounds are listed in the **Table 1** [1, 6–8].

All FABPs demonstrate a similar tertiary structure associated with a twisted-barrel hydrophobic core. They are composed of 10 anti-parallel β -strands organized into two β -sheets forming an elliptical β -barrel. Inside the barrel there is a water-filled cavity (the bound ligand place) with polar and hydrophobic amino acids and different amino acids probably determine the volume of the cavity and the binding specificity of various

types of FABPs [1, 2, 6]. All FABPs mainly bind both long chain, saturated and unsaturated FAs with no specificity for a particular fatty acid and the binding affinities of FABPs correlate with FAs hydrophobicity. Derivatives of LCFAs – acyl-CoA units are also ligands for FABPs. Moreover, L-FABP and I-FABP bind other hydrophobic agents such as lysophospholipids, phosphatidylserine, prostaglandins E1 and other eicosanoids (lipoxigenase metabolites), bile acids and some drugs [1, 6, 9].

FABPs intracellular concentration is variable and depends on environmental (e.g dietary), physiological and pharmacological conditions. The H-FABP level is higher in women compared to men, increases during pregnancy and lactation and decreases with age. The gender dependency of the FABPs amount is a result of influence of sex hormones – some experimental studies indicated that testosterone decreases, whereas estrogen increases FABPs levels in rats. High fat and high carbohydrate diets increase FABPs in the liver and intestine. A similar effect was observed during chronic alcohol intake, even at low dose [1, 10].

FABPs have several functions, mostly related to transport and metabolism of FAs. As mentioned above, the intracellular uptake of FAs is a protein-mediated phenomenon, based on membrane FABP_{PM}, and the process is parallel to a simple transmembrane diffusion. The finding that incubation of hepatocytes with an anti-FABP_{PM} antibody decreased the saturable oleate uptake by 70% provided an evidence for the FABP_{PM} role in FAs uptake, and a similar observation was made for cardiomyocytes, enterocytes and adipocytes [1]. After entering cells, FAs are bound to cytosolic FABPs that mediate the transport to or from various intracel-

Table 1. Cytosolic fatty acid binding proteins (FABPs) and FABPs-related proteins

| Name and abbreviation | Previous / alternative names | Gene name | Tissue localization |
|---|--|-----------|--|
| Liver FABP; L-FABP | Z-protein, heme-binding protein | FABP1 | liver, small intestine, kidney, stomach |
| Intestinal FABP; I-FABP | gut FABP | FABP2 | small intestine (proximal), stomach |
| Heart FABP; H-FABP | Muscle FABP | FABP3 | heart, aorta, vascular endothelium, skeletal muscle, brain, mammary gland, kidney, ovaries, testis |
| Adipocyte FABP; A-FABP | aP2 | FABP4 | adipose, monocytes |
| Epidermal FABP; E-FABP | psoriasis-associated FABP (PAFABP), KFABP, skin FABP | FABP5 | epidermis, adipose, mammary tissue, testis, lens, retina |
| Ileal FABP; II-FABP | gastrotropin | FABP6 | small intestine (distal) |
| Brain FABP; B-FABP | | FABP7 | central nervous system |
| Myelin FABP; M-FABP | myelin P2, MP2 | FABP8 | peripheral nervous system |
| Testis FABP; T-FABP | | FABP9 | |
| Cellular retinol binding protein I; CRBP I | | | liver, kidney, testis, lung |
| Cellular retinol binding protein II; CRBP II | | | small intestine |
| Cellular retinoic acid binding protein; CRABP | | | brain, skin, testis, epidermis, adrenal |

Note: the indication of the given FABP in the listed tissue is not equivalent to the presence of the protein in all cells of the listed tissue – FABP may be present only in selected cells or in selected developmental periods of the mentioned tissue

ular organelles (e.g. mitochondria, peroxisomes), thus enabling their translocation to enzymes involved in lipid metabolism. FABPs also stimulate activities of those enzymes, that catalyze both synthesis, oxidation and esterification of FAs [1, 6].

In addition to the influence on transport and metabolism of FAs, FABPs also perform other functions associated with modulation of intracellular FAs as important regulators of many cellular metabolic processes. FAs and other lipid derivatives (such as eicosanoids) regulate some processes by affecting membrane ion channels, cellular receptors or genes. Unsaturated FAs are considered to be secondary messengers responsible for signal transduction inside the cell. Experimental studies indicated that FAs inhibit growth factor-induced diacylglycerol kinase α activation in vascular smooth muscle cells and may contribute to chronic protein kinase C activation observed in diabetes. Moreover, FAs are ligands of nuclear peroxisome proliferator-activated receptors – PPAR- α (expressed in the liver and adipose tissue, mediating FAs catabolism) and of PPAR- γ (present in adipocytes, regulating adipose differentiation and adipogenesis) [1, 6].

Therefore, by regulating the FAs intracellular level, FABPs indirectly control the mentioned above processes influenced by FAs.

Furthermore, FABPs are thought to be factors implicated in regulation of growth and differentiation of other cells besides adipocytes. In experimental studies, bovine mammary-derived growth inhibitor (MDGI) that was later identified as a mixture of both H-FABP and A-FABP, caused inhibition of growth and proliferation of bovine, murine and human mammary epithelial cells. Those findings led to the conclusion that H-FABP should be considered a tumor suppressor.

Another important feature of FABPs is their antioxidant properties. It is hypothesized that FABPs provide protection against toxic effect on cell membranes induced by high concentration of FAs and other lipid derivatives. An undesired accumulation of LCFAs and acyl-CoA is noted in the myocardium during prolonged ischemia, and the disturbed oxidation of those compounds leads to the generation of free oxygen radicals that oxidize membranous macromolecules. By binding LCFAs, FABPs reduce oxidative stress and they also act as direct scavengers of free radicals [1, 6].

To sum up, in addition to their primary role in transport and metabolism of FAs, FABPs have also some important functions as regulatory compounds of cell growth and differentiation, and exert a significant antioxidant effect reducing the ischemic cell damage.

FABPs as diagnostic marker for tissue damage

Taking into account some features of FABPs (small size, solubility in water and body fluids, tissue specificity), those compounds seem to be attractive candidates for laboratory biomarkers for tissue damage. There are premises to consider H-FABP as a diagnostic tool of a heart failure. Some reports suggest that plasma H-FABP may be considered a marker for the estimation of infarction size because the protein is released into circulation by dying cardiomyocytes in prolonged ischemic conditions [11–13]. H-FABP also seemed to be a more sensitive parameter of myocardial injury compared to myoglobin. In patients undergoing a thrombolytic therapy, plasma peak of H-FABP was observed in about 4 hours after the first symptoms and returns to normal ranges within 24 hours after an infarction. When no thrombolytic treatment was applied, the plasma H-FABP peak was observed after 8 hours and reached normal values in 36 hours after the infarction [14]. On the other hand, however, some studies brought contradictory results, indicating that H-FABP cannot be used as a laboratory marker due to its unsatisfactory specificity and sensitivity compared to currently used parameters [15]. A transient, elevated plasma level of H-FABP was also reported in about half of patients with unstable angina. Some studies suggest that H-FABP is a promising laboratory marker of progressive deterioration of the heart function and of inferior prognosis in patients with congestive heart failure. Due to the fact that H-FABP is also (to a lesser extent) expressed in skeletal muscles, interpretation of recognized heart/muscle damage must be based on the myoglobin to H-FABP ratio assessment to avoid the risk of false positive results (the myoglobin/H-FABP ratio of 2–10 suggests a heart injury, whereas the result of 20–70 suggests injury of skeletal muscles) [14].

Similarly, increased I-FABP plasma level was found in early period of acute phase of intestinal ischemia [14, 16, 17]. However, some studies brought different results [18, 19]. In turn, there are preliminary studies revealing that L-FABP is released into plasma from the liver in diseases of that organ, which makes the protein a candidate for a novel, biochemical marker of diseases of the liver [14, 20]. The most recent attempt of application of FABPs as diagnostic parameters is the estimation of B-FABP and H-FABP as markers of brain injury. In healthy people, B-FABP is not found in the plasma. In mild traumatic brain injury, an increase in serum B-FABP and H-FABP was observed in 68% and 70% of

patients, respectively. The electroconvulsive therapy led to elevated plasma B-FABP levels in 6% while H-FABP in 17% of the patients. Hence, it seems that B-FABP and H-FABP may be used for laboratory evaluation of brain trauma and it is expected that those proteins will widen the laboratory diagnostic capabilities, currently based primarily on the S100B protein, neuron-specific enolase (NSE) or the myelin basic protein [14].

FABPs as another "troponin-like" biomarker of kidney diseases

Plasma and/or urinary H-FABP and L-FABP estimation is also considered in the context of diagnostics of kidney diseases. In the early 1990's Maatman et al. [21] demonstrated presence of two types of FABPs in the kidneys, primarily labelled as A and B, that at further stages of experiments were identified as L-FABPs and H-FABPs, respectively. Moreover, the same researchers confirmed the presence of both FABPs isoforms in their rat kidney experimental studies [22]. There is some specificity regarding the location of individual FABPs isoforms in the kidney – H-FABPs are expressed mostly in distal tubular cells whereas L-FABP is found in proximal ones [21, 22].

Some of the known pathophysiological factors responsible for kidney damage are external toxic factors, ischemia and endogenous noxious factors. Among endogenous toxic factors, proteins (such as the complement system, LDL lipoproteins or FAs that are transported with blood in association with lipoproteins and albumin), filtered in the glomerulus, should be mentioned. FAs are then re-absorbed into proximal tubules and subjected to FABP-mediated pathways [23]. When FAs are overloaded in the glomerulus and tubules, those compounds initiate both cellular inflammatory reactions and inflammatory mediators overproduction contributing to tubulointestinal damage. The developing inflammatory response also leads to up-regulation of FABPs in kidney tubules and their final damage with release of those proteins into urine and circulating blood [24–27]. FABPs found in kidneys play the same roles as those already mentioned in the general description of FABPs. Taking the pathophysiology of kidney damage into account, oxidative stress plays an important role in initiation and maintenance of the inflammation. FAs, especially unsaturated LCFAs, are also a direct source of reactive oxygen species. FABPs are antioxidant compounds, so they are overproduced in the renal tubules as part of a compensatory anti-inflammatory response, and that explains their increased

levels observed during kidney damage. Moreover, FABPs are also responsible for the maintenance of low FAs inside tubular cells by carrying them into the mitochondria and peroxisomes for accelerated metabolic breakdown. Therefore, FABPs play a strong cytoprotective role in the development of kidney injury [23].

One of the most important clinical entities that may be diagnosed based on the analysis of plasma or urinary concentration of FABPs is acute kidney injury (AKI).

AKI is defined as a rapid deterioration of kidney function resulting in retention of nitrogenous waste (compounds that would normally be excreted with urine, such as urea and creatinine) [28]. The disorder is characterized by a wide spectrum of symptoms – from transient elevation of biochemical indicators of kidney damage (e.g. creatinine) with moderately intensified symptoms usually resulting from oliguria, to total anuria, severe overhydration and electrolyte and metabolic disturbances taking the form of acute renal failure requiring the renal replacement therapy.

The detailed diagnostic criteria for AKI are based on the Acute Dialysis Quality Initiative Guidelines (ADQI) Group (2004) [29], Acute Kidney Injury Network (2007) [30], and recently published Kidney Disease Improving Global Guidelines (KDIGO) Clinical Practice Guidelines for Acute Kidney Injury (2012) [31]. These guidelines are based on the assessment of elevated plasma creatinine level, diminished diuresis per hour and the estimated decrease in glomerular filtration rate (eGFR).

Pathophysiologically, AKI is a consequence of impairment of kidneys function due to noxious, toxic agents affecting the kidney, or develops as a result of some co-existing pre- or post-renal disturbances. Pre-renal etiological AKI factors, such as hypovolemia, generalized vasodilatation with hypotension, or rapid reduction in cardiac output, finally lead to reduction of renal blood flow and consequently to decrease of the effective glomerular filtration pressure. Similarly, post-renal factors cause an increase in hydrostatic pressure in the urinary tract that exceeds the glomerular pressure. The mechanism also contributes to decrease of the effective filtering pressure and to development of oliguria/anuria. The final pathophysiological consequence, independently of the nature of the etiologic AKI factor, is the development of Acute Tubular Necrosis (ATN). The condition is defined as an irreversible, morphological destruction of renal tubules manifesting in kidney failure [28].

As mentioned above, progressive damage of kidney tubules is responsible for the excessive FABPs

release, as well as for an excessive synthesis and disturbed renal excretion of the other proteins that may be considered as laboratory markers of kidney damage. According to current reports [32–35], cystatin C, kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin-1 (NGAL-1), interleukine-18, N-acetyl- β -glucosaminidase (NAG) and FABPs should be mostly listed among the novel AKI biomarkers ("renal troponins"), for they are characterized by a better sensitivity and specificity in the early diagnosis of AKI during its asymptomatic period, compared to the currently used ones (e.g. creatinine, urea, electrolytes). The clinical entities associated with AKI development, in which the FABPs increase was observed are listed in the **Table 2**.

FABPs are also considered in the context of their suitability for the laboratory diagnosis of chronic kidney disease (CKD) – a clinical entity ultimately leading to chronic renal failure (CRF). CKD may be a consequence of all diseases that primarily affect kidneys (e.g. chronic glomerulonephritis), as well as of currently commonly occurring civilization diseases: diabetes and hypertension. Moreover, in some cases, CKD develops as a result of AKI [36]. According to current guidelines, chronic kidney disease is a multi-symptomatic syndrome resulting from permanent and progressive damage of the kidney structure and abnormalities of all of the kidney functions (excretory, endocrine, metabolic), and conditioned by a variety of pathological processes in the glomeruli and tubulointerstitial compartment [36]. The general CKD definition was established by a team of experts in the *Kidney Disease Outcome Quality Initiative (KDOQI)* in 2002 [37], and then confirmed by the *Kidney Disease Improving Global Outcome (KDIGO)* [38]. CKD is defined as a kidney disease that lasts for at least 3 months and associated with

signs of kidney damage (such as albuminuria at least 30 mg/24h, electrolyte disturbances, pathological findings in kidney histological assessment, abnormalities revealed in imaging studies), or a GFR decrease to < 60 ml/min/1.73 m², with or without the abovementioned disturbances, and with a negative effect on health. Depending on the eGFR value, the degree of progression of CKD is gradated (grades G1-G5), with uremia as a CKD descent recognized in G5 grade [39].

Current data demonstrate that about 4 million people in Poland suffer from CKD, but it appears that the disease is much more common than previously thought, being unrecognized for long periods of time due to its extensive latent course in grades G1 and G2 [36]. Hence, the thorough and accurate diagnosis of renal dysfunction plays an important role, because only a careful monitoring of the patient allows efficient diagnosis of early, clinically asymptomatic CKD. However, despite the fact that measurement of serum creatinine concentration remains at present the simplest and most commonly used method for the assessment of renal function, there is an ongoing search for new biomarkers of CKD, just as it is in case of AKI. Those parameters should be characterized by superior laboratory features (sensitivity, specificity, dynamic change already at an early stage of the estimated disorder) compared to creatinine used currently.

Cystatin C, markers of fibrosis and Klotho-FGF23 axis are most likely reported to be novel biomarkers for CKD. [40–43]. Noticeably, some biomarkers (NGAL, KIM-1, NAG and FABPs) may be used for both diagnosis and monitoring of AKI and CKD [44, 45]. Therefore it can be concluded that FABPs may be useful in recognition of various kidney diseases, including both acute and chronic kidney damage. The detailed information is provided in the **Table 2**. The table also lists other

Table 2. The clinical entities associated with increased plasma / urinary FABPs levels as a potential diagnostic value

| Kidney or urinary tract disease | A closer description of the disease | Reference number |
|---------------------------------|---|------------------|
| Acute kidney injury (AKI) | kidney transplantation | 46 |
| | cardiac surgery | 47, 48 |
| | contrast induced | 49, 50 |
| | cis-platin induced | 51 |
| | sepsis | 52 |
| | AKI of various etiology | 53 |
| Chronic kidney disease (CKD) | non-diabetic CKD | 54, 55 |
| | diabetic nephropathy | 56, 57 |
| Glomerulonephritis | newly diagnosed, biopsy-proven primary chronic glomerulonephritis | 58 |
| Unilateral ureteral obstruction | unilateral ureteral obstruction experimental model in mice | 59 |
| Vesicoureteral reflux | children with primary vesicoureteral reflux confirmed by voiding cystourethrography | 60 |
| Renal toxicology | cyclooxygenase-inhibitor-induced renal injury | 61 |

nephrological and urological disorders associated with increased FABPs levels, therefore it is considered as a marker of those clinical entities.

Conclusions

To sum up, FABPs appear to be proteins that meet the requirements for biomarkers of kidney damage in the course of various diseases of the organ. It is expected that the new panel of proteins, including L-FABP and H-FABP (currently the most commonly used from FABPs family), NGAL-1, KIM-1 or interleukin-18 will be soon introduced to common practice in the laboratory diagnosis of kidney diseases.

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Conflict of interest statement

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Correspondence address:

Department of Pharmacology
Faculty of Medicine and Health Sciences
Andrzej Frycz Modrzewski Krakow University
1 Gustawa Herlinga-Grudzińskiego Street
30-705 Krakow, Poland
phone: +48 122524505
fax: +48 122524502
email: xlukasz@onet.eu