Review

Fatty acid-binding proteins as plasma markers of tissue injury

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Abstract

Background: One of the novel and promising plasma markers for detection of tissue injury is the family of 15 kDa cytoplasmic fatty acid-binding proteins of which various tissue-specific types occur.

Aims and Objectives: The present status of heart-type fatty acid-binding protein (H-FABP) as a diagnostic and prognostic marker for acute and chronic cardiac injury, as well as the preliminary diagnostic use of other types of FABP for detecting injury in other organs, is reviewed.

Methods: This review is based on an overview of the literature on clinical diagnostics of various forms of organ injury, and uses additional literature on physiological aspects relevant for the interpretation of plasma marker concentrations.

Results: H-FABP not only proves to be an excellent early marker for cardiac injury in acute coronary syndromes, but also allows detection of minor myocardial injury in heart failure and unstable angina. Preliminary results indicate that sensitivity, rule-out power and prognostic value of H-FABP in cardiac injury surpass the performance of the standard early marker myoglobin. The liver only contains liver-type FABP (L-FABP), but co-expression of H-FABP and L-FABP occurs in the kidney. Similarly, intestinal-type FABP (I-FABP) and L-FABP are found in intestines, and brain-type FABP (B-FABP) and H-FABP occur in the brain. Preliminary but promising applications of these proteins have been demonstrated for liver rejection, viability selection of kidneys from non-heart-beating donors (NHBD), inflammatory and ischemic bowel disease, traumatic brain injury and in the prevention of muscle injury in trained athletes.

Conclusions: Further study of the diagnostic and prognostic use of various FABP types is warranted, but their clinical application will require further commercialization of automated and rapid assays.

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Keywords: FABP; Tissue injury; ELISA; Myocardial infarction; Point-of-care testing
1. Introduction

The appearance in plasma of cellular proteins released after tissue injury, or produced by malignant cells, commonly referred to as biochemical markers, is gaining more and more interest as being important in the management of patients with tissue injury due to acute ischemia/reperfusion, neurological disorders, cancer, organ rejection or trauma.

One of the promising new biomarker proteins is the fatty acid-binding protein (FABP). This relatively small (15 kDa) cytoplasmic protein is abundantly expressed in tissues with an active fatty acid metabolism like heart and liver [1,2]. Presently, nine distinct types have been identified, with each type showing a characteristic pattern of tissue distribution and a stable intracellular half-life of 2–3 days [1]. These FABP types are named after the tissue in which they were first identified and belong to a multigene family of intracellular lipid-binding proteins [1,3,4]. Their tertiary structure resembles a clam shell in which the ligand is bound between the two halves of the clam by interaction with specific amino acid residues within the binding pocket, the so-called β-barrel [3,5]. The primary function of FABP is the facilitation of intracellular long-chain fatty acid transport [6], while other functions include regulation of gene expression by mediating fatty acid signal translocation to peroxisome proliferator activated receptors (PPARs) [7] and putative protection of cardiac myocytes against the detergent-like effects of locally high concentrations of long-chain fatty acids, especially during ischemia [1,8]. The cellular expression of FABPs is regulated primarily at the transcriptional level and is responsive to changes in lipid metabolism as induced by (patho)physiological and pharmacological stimuli like ischemia [9], endurance training [10], diabetes [11,12], hypertrophy [13,14] and hypolipidemic drugs [15].

When evaluating FABP as clinical tissue injury marker, we have to take into account that after cell damage small proteins diffuse more rapidly than large proteins through the interstitial space via endothelial clefts into vascular space. The size of these endothelial clefts is variable, from large clefts in the liver to smaller pores in the heart, the skeletal muscle and finally to almost complete impermeability in the brain (blood–brain barrier). As a result, the diffusion rate of the released proteins into the circulation also differs. Therefore, the time of appearance of these marker proteins in plasma is not only dependent on the time course of the disease, but also on the molecular size...
and distribution over extravascular compartments [16].

Heart-type FABP (H-FABP) was first shown to be released from injured myocardium in 1988 [17], after which several studies have investigated its application as a biochemical marker of myocardial injury. Following the finding that H-FABP is an early and sensitive marker for injured myocardium [18,19], additional studies were set up to evaluate the application of this and other FABP types for the monitoring of tissue injury. In this paper we review the current status of FABP assays, and the clinical application of plasma FABP determination for monitoring cardiac, skeletal muscle, kidney, liver, intestinal and brain injury, in comparison with currently used markers of tissue injury.

2. Tissue content and distribution of FABP types

Cytoplasmic FABPs have been detected in virtually all rodent and human tissues. These proteins of the intracellular lipid-binding family contain 126–137 amino acid residues and show an amino acid sequence homology of 20–70%. Due to single amino acid mutations, different isoforms are reported, mainly differing in isoelectric point [1]. Initially, FABPs from human kidney [20] and mammary gland [21], as well as rat skeletal muscle [22] each were regarded as distinct FABP types, but later were identified as already existing types [1]. H-FABP and L-FABP are the main types showing a multi-tissue expression. H-FABP is abundantly expressed in cardiomyocytes, but to a lesser extent also in skeletal muscle [21,23–25], distal tubular cells of the kidney [26], specific parts of the brain [27–29], lactating mammary glands and placenta [21]. However, cross-reactivity of used polyclonal antibodies with other FABP types might have identified a false positive presence of H-FABP in different tissues. Newly developed monoclonal antibodies with no cross-reactivity to other FABP types need to clarify this issue [30]. L-FABP is mainly expressed in hepatocytes [31], but also in jejunal and ileal enterocytes [32–34], colonocytes and proximal tubular cells of the kidney [20,26,35]. Due to this multi-tissue expression, several tissues contain more than one type of FABP either because of various cell species in one tissue or of co-expression of different FABP types in a single cell [33,34]. Interestingly, in human and rodent brain and the intestinal tract, the tissue-specific types B-FABP and I-FABP are expressed to a lower extent than the co-expressed H-FABP and L-FABP, respectively. An overview of tissue protein contents of the different FABP types is presented in Table 1.

<table>
<thead>
<tr>
<th>Tissue (reference)</th>
<th>Part</th>
<th>H-FABP (μg/g ww)</th>
<th>L-FABP (μg/g ww)</th>
<th>I-FABP (μg/g ww)</th>
<th>B-FABP (μg/g ww)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart [13]</td>
<td>Epicardial</td>
<td>540</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Midcardial</td>
<td>600</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Endocardial</td>
<td>550</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Skeletal muscle [24]</td>
<td></td>
<td>173</td>
<td>2700</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Liver [32]</td>
<td>Duodenum</td>
<td>3.5</td>
<td>124</td>
<td>2.22</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Jejunum</td>
<td>4.9</td>
<td>198</td>
<td>4.79</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Ileum</td>
<td>3.2</td>
<td>58</td>
<td>1.04</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Colon</td>
<td>2.7</td>
<td>26</td>
<td>0.27</td>
<td>–</td>
</tr>
<tr>
<td>Brain [27]</td>
<td>Frontal lobe</td>
<td>26.3</td>
<td>–</td>
<td>–</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>Temporal lobe</td>
<td>31.9</td>
<td>–</td>
<td>–</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>Occipital lobe</td>
<td>21.2</td>
<td>–</td>
<td>–</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Striatum</td>
<td>30.6</td>
<td>–</td>
<td>–</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>Pons</td>
<td>39.5</td>
<td>–</td>
<td>–</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>Cerebellum</td>
<td>16.2</td>
<td>–</td>
<td>–</td>
<td>2.8</td>
</tr>
</tbody>
</table>

(–) Not present or not detectable.
3. Assays for FABPs

Mono- and polyclonal antibodies were raised against different types of FABP and both immunohistochemical and immunological assays were developed to measure tissue contents and serum/plasma and urine concentrations of specific FABP types [30,36–46].

For H-FABP, polyclonal antibodies were first used in ELISAs to study the role of FABP in fatty acid metabolism in the rat [22,44,47], pig [23], cattle [41, 48], birds [49,50], antarctic icefish [51] and locust [52], or the application of FABP as clinical plasma biomarker in human studies [53–56]. Subsequently, anti-human H-FABP mAbs were applied in sandwich-type ELISAs [36–40] such as a one-step ELISA with a total performance time of 45 min [38]. Two assays are now commercially available and are used in clinical research (see Table 2).

Lately, more rapid detection systems than the manual sandwich ELISAs have been developed for H-FABP in order to improve the diagnostic power because there is a need for rapid detection of cardiac markers by point-of-care (POC) testing as evaluated by Azzazy et al. [56]. These rapid assays include an EIA by Fiebig et al. [57], an automated sandwich immunoassay by Ghani et al. [58,59] and a micro-particle enhanced immunoassay described by Robers et al. [60]. This latter, fully automated latex-agglutination assay (performed by using a COBAS® MIRA Plus analyzer (Hoffmann-La Roche) uses carboxylated latex particles on which three monoclonal anti-human H-FABP antibodies are coated, each recognizing a different epitope [30]. Unfortunately, these assays are not yet commercially available.

Qualitative lateral-flow assays are also being applied for POC testing of H-FABP, as described by Chan et al. [61,62] and Watanabe et al. [63], and are presently commercially available. These whole blood tests with a 15 min duration of analysis, detect either normal or elevated H-FABP above a cut-off value set at 6 µg/L. However, inter-observer differences in interpretation of colour development, and the inability

<table>
<thead>
<tr>
<th>FABP type</th>
<th>Year (reference)</th>
<th>Assay type</th>
<th>Assay time (min)</th>
<th>Sample type</th>
<th>Calibration range (µg/L)</th>
<th>Detection limit (µg/L)</th>
<th>URL (µg/L)</th>
<th>No cross reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>1991 [55]</td>
<td>C-EIA</td>
<td>9600</td>
<td>serum urine</td>
<td>0–1000</td>
<td>1</td>
<td>0.6^a</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>1992 [53]</td>
<td>ELISA (pAb)</td>
<td>245</td>
<td>serum plasma</td>
<td>0–5</td>
<td>0.5</td>
<td>19</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>1995 [36]</td>
<td>ELISA</td>
<td>90</td>
<td>plasma</td>
<td>0–250</td>
<td>1.25</td>
<td>9.1</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>1996 [46]</td>
<td>ELISA</td>
<td>–</td>
<td>serum</td>
<td>0–250</td>
<td>2</td>
<td>10</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>1997 [38]</td>
<td>ELISA</td>
<td>45</td>
<td>serum plasma</td>
<td>0–60</td>
<td>0.3</td>
<td>6</td>
<td>L-, L-FABP</td>
</tr>
<tr>
<td></td>
<td>1997 [37]</td>
<td>EIA</td>
<td>50</td>
<td>serum plasma</td>
<td>0–300</td>
<td>0.1</td>
<td>6</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>1997 [56]</td>
<td>Immunosensor</td>
<td>20</td>
<td>plasma</td>
<td>0–350</td>
<td>5</td>
<td>10</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>1998 [60]</td>
<td>Latex</td>
<td>10</td>
<td>serum</td>
<td>0–150</td>
<td>1.1</td>
<td>14</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>1998 [58]</td>
<td>IFMA</td>
<td>23</td>
<td>serum plasma</td>
<td>0–1000</td>
<td>1</td>
<td>6</td>
<td>not specified</td>
</tr>
<tr>
<td></td>
<td>2001 [63]</td>
<td>Lateral flow</td>
<td>15</td>
<td>whole blood</td>
<td>–</td>
<td>6.2</td>
<td>6.2</td>
<td>L-, I-FABP</td>
</tr>
<tr>
<td></td>
<td>2002 [67]</td>
<td>Immunosensor</td>
<td>50</td>
<td>whole blood</td>
<td>0–250</td>
<td>4</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>2003 [61]</td>
<td>Lateral flow</td>
<td>15</td>
<td>whole blood</td>
<td>0–125</td>
<td>2.8</td>
<td>7</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>2004 [68]</td>
<td>PEIA</td>
<td>10</td>
<td>plasma</td>
<td>0–100</td>
<td>0.3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Liver</td>
<td>1999 [70]</td>
<td>ELISA (mAb)</td>
<td>–</td>
<td>serum plasma</td>
<td>0–4</td>
<td>0.1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>2002 [31]</td>
<td>ELISA (mAb)</td>
<td>240</td>
<td>serum plasma</td>
<td>0–4</td>
<td>0.1</td>
<td>17</td>
<td>I-, H-FABP</td>
</tr>
<tr>
<td>Intestinal</td>
<td>1997 [72]</td>
<td>RIA (pAb)</td>
<td>240</td>
<td>urinun urine</td>
<td>0–4</td>
<td>0.1</td>
<td>18.7</td>
<td>H-FABP</td>
</tr>
<tr>
<td></td>
<td>2002 [73]</td>
<td>ELISA (pAb)</td>
<td>180</td>
<td>serum plasma</td>
<td>0–4</td>
<td>0.1</td>
<td>1</td>
<td>L-FABP</td>
</tr>
<tr>
<td></td>
<td>2003 [32]</td>
<td>ELISA (pAb)</td>
<td>240</td>
<td>serum plasma</td>
<td>0–5</td>
<td>0.1</td>
<td>0.1</td>
<td>L-, H-FABP</td>
</tr>
<tr>
<td>Brain</td>
<td>2003 [27]</td>
<td>ELISA (pAb)</td>
<td>180</td>
<td>serum plasma</td>
<td>0–1000</td>
<td>5</td>
<td>5</td>
<td>I,H,I,E</td>
</tr>
</tbody>
</table>

(–) Not given.


^a Reported URL is below the detection limit of the assay.
to discriminate between moderate and high H-FABP elevations could be major drawbacks of these tests. Quantitative plasma or whole blood tests, using electrochemical immunosensors [64–67] or precipitation ellipsometry [68], have been developed only in a prototype form.

Recently, a prototype of an immunodisplacement sensor has been developed for continuous monitoring of H-FABP [69]. This assay enables the sampling of blood constituents via a microdialysis probe or via continuous ultrafiltration of venous blood (at a rate of 0.1–1 μL/min), and is expected to be useful for the online monitoring of patients during open heart surgery or with unstable angina, having the advantage of a rapid determination of changes in plasma FABP concentration, independent of its reference concentration, and therefore a more early diagnosis or exclusion of AMI.

To determine liver-type FABP (L-FABP) in human tissue and plasma, two groups have developed a sandwich ELISA, using recombinant L-FABP [31, 70]. For intestinal-type FABP (I-FABP), ELISAs specific for either rat- or human I-FABP have been developed [32,71–73]. Finally, a sandwich-type ELISA for brain-type FABP (B-FABP) was developed using affinity purified polyclonal antibodies raised against recombinant human B-FABP [27]. An overview of the developed assays and their main characteristics is given in Table 2.

The specificity of the reported immunochemical assays for FABP generally is very high, because essentially no cross-reactivity of the used poly- or monoclonal antibodies (pAbs and mAbs, respectively) with other FABP types was observed [27,30,32,36,71, 74]. For clinical application, it is noteworthy to mention that, generally, no differences were observed in performance of the FABP immunoassay among serum, and EDTA, heparin and citrated plasma [38,75]. In general, samples need to be diluted at least two- to fivefold to prevent matrix effects. Recombinant H-FABP reacts immunochemically equivalent to the tissue-derived protein and is therefore commonly applied as standard in immunoassays [30,74]. H-FABP appears as a very stable protein as both plasma samples and recombinant protein solutions can be subjected to repeated freezing/thawing at least eight times without loss of immunoreactivity [38]. Samples could also be stored (at least) for 2 years at −80°C [76]. No data have been reported about possible endogenous and exogenous interfering substances.

4. Reference limits

Proper interpretation of plasma concentrations of biochemical markers for clinical diagnosis is dependent on the establishment of reference limits. As already stated by Jaffe [77], the minimal detection limit and reproducibility of the assay, as well as biological variation and upper reference limit (URL) of the marker must be stated correctly to enable efficient comparison of clinical data. Many clinical investigators have used apparently healthy individuals to obtain reference values for FABPs. In general, the 97.5% confidence interval (mean values±2S.D.) is used to express the reference interval, although the tendency nowadays is to use the 99% confidence interval (mean±3S.D.). As FABP is rapidly cleared from the circulation by the kidney, relatively low concentrations are maintained in plasma. Several studies reported H-FABP reference limits. An upper reference limit of 6 μg/L has been proposed independently by Pelsers et al. [43], Kathrukha et al. [78] and Pagani et al. [79].

Importantly, age, sex and circadian rhythm significantly influence H-FABP normal values [43]. A higher plasma H-FABP concentration was found in men compared to women, which may reflect larger muscle mass. The increase of plasma H-FABP concentration during aging, from 20 to 70 years and especially after 50 years, is most likely explained by the fact that H-FABP is eliminated from the circulation predominantly by renal clearance [53,55] and renal function decreases with age. In addition, release of H-FABP from skeletal muscle may increase with age or exercise as has been described for myoglobin [80,81]. Renal function also accounts for the significant higher plasma H-FABP concentration in the night as result of decreased nocturnal glomerular filtration [43]. No influence of age or sex was observed for L-FABP in plasma [31]. However, L-FABP plasma concentrations were also higher during the night. B-FABP could not be detected in plasma of healthy individuals [27], while four studies reported undetectable I-FABP concentrations in plasma of healthy
individuals [32,73,82,83]. One study reported a relatively high I-FABP plasma concentration of up to 65 µg/L [84], but no assay characteristics were reported.

5. Clinical utility of FABP in comparison with other tissue injury markers

5.1. Detection of myocardial injury and re-infarction

The potential of H-FABP as sensitive and early marker for myocardial injury has been reported by several groups [18,19,39,53,55,79,85–94]. The characteristics of the release of H-FABP from injured myocardium closely resemble those of myoglobin. However, because the cardiac tissue content of H-FABP is much higher than that of myoglobin and the normal plasma value of H-FABP is much lower than that of myoglobin, H-FABP is a more sensitive marker of myocardial injury compared to myoglobin (see Section 5.1.1). As an example, Fig. 1 shows mean plasma release curves of H-FABP, myoglobin, and for comparison, cardiac Troponin T (cTnT), for 15 AMI patients, treated with reperfusion therapy, from whom blood samples were obtained frequently during the first 24 h of hospitalization [19]. The rise in plasma concentrations relative to the URL, is highest for H-FABP (Fig. 1, middle graph). In patients treated with standard thrombolytic therapy after AMI, peak plasma concentrations of H-FABP and myoglobin are reached at about 4 h after first symptoms (Fig. 1, left graph), whereas for creatine kinase (CK or CK-MB), this takes about 12 h, and for lactate dehydrogenase (LDH) about 20 h [76]. Furthermore, plasma H-FABP and myoglobin return to their respective reference ranges already within 24 h after AMI, enhancing the usefulness of both markers for the assessment of a recurrent infarction within 10 h after first AMI [24], which might be missed by CK-MB, cTnT and cTnI as these markers return much slower to their normal plasma value [95,96]. If no thrombolytic therapy is administered, the H-FABP plasma level peaks at 8 h and returns to normal only after 36 h, comparable to myoglobin [96]. However, these differences in release kinetics do not cause any changes on the recovery of the amount of cardiac proteins in plasma [24,76,96]. Because cardiac troponin T and I are the most specific markers of myocardial injury but appear later in plasma, H-FABP and cTnT appear the ideal combination to cover the diagnostic window.

5.1.1. Myocardial infarction

The recent redefinition of myocardial infarction stresses the use of biochemical markers in the initial evaluation of ACS, especially in the patient group without ST-segment elevation (NSTEMIACS), with cardiac troponin T or I as the preferred marker for the diagnosis of AMI [97–101]. For patients present-
ing within 6 h after onset of symptoms, myoglobin is suggested as additional marker to troponin because the combined use of both markers may be useful for the early exclusion of AMI. However, myoglobin is limited in specificity due to its high concentration in skeletal muscle. Table 3 lists the studies reported to date that compared the diagnostic performance of H-FABP with that of the established early marker myoglobin in patients admitted to hospital with chest pain suggestive of AMI. It is shown that in each study, the area under the receiver operating characteristic (ROC) curve (AUC), using the admission blood samples from all patients, was significantly larger for H-FABP than for myoglobin, indicating a excellent performance of H-FABP within 6 h after onset of symptoms. For earlier admitted patients, subgroup analysis showed even better performance of H-FABP compared with myoglobin [18,102,103]. For instance in the EUROCARDI multi-center study [102], the subgroup of patients admitted 0-3 h after onset of symptoms showed an AUC of 0.845 for H-FABP and 0.717 for myoglobin, while the subgroup of patients admitted 3-6 h after onset of symptoms showed 0.945 for H-FABP and 0.892 for myoglobin (Fig. 2). Both AUCs are significant different ($P<0.001$). These observations extend similar previous results [58,85–87]. Specificity, sensitivity and AUC were not reported in all studies, but in general, H-FABP performs better or similar to myoglobin. Ghani et al. [59] reported a low sensitivity and specificity, but this study used time delays after admission, instead of after onset of symptoms.

To further improve the diagnostic value of the marker (i.e., rule out power), the concept of more frequent or continuous measurement of H-FABP in plasma has been applied. By using two plasma samples, one at admission and the other 1–2 h after admission, sequential FABP monitoring may permit diagnosing patients suspected of AMI already 1–2 h after admission. Chan et al. [104] reported a 100% exclusion of non-AMI patients using this method. Haastrup et al. [88] used the same approach of serial measurements and reported an increased probability of detecting an AMI. In both studies, patients were

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient number (centers)</th>
<th>AMI (%)</th>
<th>Admission time (h)</th>
<th>URL</th>
<th>AUC FABP</th>
<th>Sens (%) FABP</th>
<th>Spec (%) FABP</th>
<th>URL</th>
<th>AUC Mb</th>
<th>Sens (%) Mb</th>
<th>Spec (%) Mb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abe [87]</td>
<td>123 (1)</td>
<td>100</td>
<td>&lt;8</td>
<td>11</td>
<td>110</td>
<td>–</td>
<td>–</td>
<td>80</td>
<td>69*</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ishii [92]</td>
<td>165 (1)</td>
<td>60</td>
<td>3.5 (3–12)</td>
<td>12</td>
<td>105</td>
<td>0.898***</td>
<td>0.782</td>
<td>82</td>
<td>73</td>
<td>86</td>
<td>76</td>
</tr>
<tr>
<td>Glatz [102]</td>
<td>312 (4)</td>
<td>54</td>
<td>3.3 (2–8)</td>
<td>10</td>
<td>50</td>
<td>0.901****</td>
<td>0.824</td>
<td>63</td>
<td>74</td>
<td>100</td>
<td>88</td>
</tr>
<tr>
<td>Glatz [85]</td>
<td>83 (1)</td>
<td>100</td>
<td>2.8 (1–4)</td>
<td>5</td>
<td>60</td>
<td>–</td>
<td>78**</td>
<td>53</td>
<td>–</td>
<td>–</td>
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</tr>
<tr>
<td>Haastrup [88]</td>
<td>130 (1)</td>
<td>16</td>
<td>&lt;6</td>
<td>8</td>
<td>70</td>
<td>0.890</td>
<td>0.840</td>
<td>90</td>
<td>81</td>
<td>81</td>
<td>89</td>
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<tr>
<td>Okamoto [103]</td>
<td>189 (1)</td>
<td>74</td>
<td>4.0 (0–12)</td>
<td>6.2</td>
<td>50</td>
<td>0.921*</td>
<td>0.843</td>
<td>93</td>
<td>89</td>
<td>67</td>
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<td>Ghani [59]</td>
<td>460 (3)</td>
<td>21</td>
<td>3.0 (3–7)</td>
<td>12</td>
<td>84</td>
<td>0.800</td>
<td>0.730</td>
<td>39</td>
<td>38</td>
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<tr>
<td>Ohkura [93]</td>
<td>88 (1)</td>
<td>65</td>
<td>3.0</td>
<td>6.2</td>
<td>–</td>
<td>–</td>
<td>95</td>
<td>53</td>
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<td>83</td>
</tr>
<tr>
<td>Pagani [79]</td>
<td>41 (1)</td>
<td>83</td>
<td>2.6 (1–4)</td>
<td>6.2</td>
<td>49</td>
<td>0.798</td>
<td>0.771</td>
<td>91**</td>
<td>65</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Nakata [18]</td>
<td>133 (8)</td>
<td>44</td>
<td>6.0 (0–48)</td>
<td>6.2</td>
<td>60</td>
<td>0.936***</td>
<td>0.862</td>
<td>86</td>
<td>77</td>
<td>100</td>
<td>100</td>
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<tr>
<td>Seino [91]</td>
<td>371 (6)</td>
<td>49</td>
<td>2–24</td>
<td>6.2</td>
<td>–</td>
<td>0.790*</td>
<td>0.760</td>
<td>95</td>
<td>62</td>
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<tr>
<td></td>
<td>68*</td>
<td>100</td>
<td>&lt;2</td>
<td>6.2</td>
<td>–</td>
<td>0.720**</td>
<td>0.610</td>
<td>89</td>
<td>22</td>
<td>52</td>
<td>94</td>
</tr>
</tbody>
</table>

The performance of these two early plasma markers is given for measurements made in admission blood samples taken from patients entering the hospital with chest pain suggestive of AMI.

Nakata [18] sen/spec within 6 h with ROC-determined cut-off of 9.5 and 110.

(–) Not given in publication.

AMI=acute myocardial infarction; URL=upper reference limit; AUC=area under the curve; Sens=sensitivity; Spec=specificity; FABP=heart-type fatty acid-binding protein; Mb=myoglobin.

* Subset of patients with admission time within 2 h.

* $P<0.5$.

** $P<0.01$.

*** $P<0.001$. 
admitted to the Coronary Care Unit within 6 h after onset of symptoms, that is, before maximal plasma concentrations were reached.

5.1.2. Unstable angina

In patients with unstable angina (UAP), elevated plasma levels of cTnT or cardiac Troponin I (cTnI) indicate minor myocardial injury due to ischemia [78, 105–107]. In a study by Kathrukha et al. [78], patients (n=31) with UAP showed elevated (>0.2 µg/l) cTnI plasma levels in 13% and elevated H-FABP plasma levels (>6 µg/L) in 54% of the admission samples, whereas at 6 h after admission, cTnI was elevated in 58% and H-FABP in 52% of the samples. Tanaka et al. [18] reported elevated H-FABP plasma concentrations in 13 out of 32 UAP patients. Tambara et al. [107] recently reported elevated levels of H-FABP in pericardial fluid as indication of ischemia in 34 UAP patients. These preliminary data suggest that H-FABP is a sensitive marker for minor myocardial injury in patients with UAP, with similar sensitivity as cTnI, but at an earlier point after admission, again confirming the ability of both markers to cover the diagnostic window.

5.1.3. Prognostic value

The prognostic value of H-FABP for early prediction of adverse clinical outcomes in patients with suspected ACS has only recently been subject of investigation. Although only a small number of studies have been performed, the results are promising as elevated H-FABP plasma concentrations in patients with ACS significantly correlated with increased cardiac event rates and cardiac mortality [18,108–112]. In patients with congestive heart failure (CHF), elevated H-FABP plasma concentrations are correlated with cardiac event rates (see Section 5.1.4) [113]. In the early hours of ACS, selection of patients who are at high risk for cardiac events and could benefit from an aggressive therapeutic strategy, should include the use of H-FABP.

5.1.4. Infarct size, reperfusion and coronary bypass grafting

The cumulative release of H-FABP can be used to estimate myocardial infarct size, taking into account the specific clearance rates from plasma [54,76,114,115]. When evaluating early thrombolytic therapy in patients with AMI, quantification of infarct size can reliably be performed but as the usual enzymatic markers appear relatively late in blood, data become available rather late to have an influence on acute care [116,117]. Because H-FABP and myoglobin are cleared via the kidneys, renal insufficiency could hamper the utility of both proteins. However, to correct for the effect of renal insufficiency, individually estimated clearance rates can successfully be applied for infarct size estimation as suggested by De Groot et al. [76]. As a result, myocardial infarct size can also be measured from plasma H-FABP in patients with renal failure [117].

Detection of successful coronary reperfusion in patients with AMI, using H-FABP, has been reported by three independent groups of investigators [118–120]. Following successful reperfusion both plasma H-FABP and myoglobin were found to rise sharply, whereas in patients with failed reperfusion, these markers rise at a slower rate, but generally relatively low sensitivities and specificities (approximately 70%) were found. Normalization to infarct size improved these to approximately 80%, indicating their suitability in retrospective studies with known infarct size [118,121].
Some studies suggest that H-FABP also can be useful for early detection of postoperative myocardial tissue loss in patients undergoing coronary bypass surgery [93,122–126]. Myocardial injury in such patients may be caused by global ischemia/reperfusion injury and, in addition, by postoperative myocardial infarction. Fransen et al. [122] reported that in patients developing a postoperative myocardial infarction, a second increase in H-FABP was observed already 4 h after reperfusion, while CK and myoglobin increased 8 h after reperfusion, allowing also earlier dismissal of patients without infarction from the intensive care unit. Hasegawa et al. [126] recently also reported significant correlations between serum peak H-FABP concentration and postoperative parameters in pediatric cardiac surgery.

5.1.5. Congestive heart failure

Preliminary studies of patients with congestive heart failure showed that elevated plasma concentrations of H-FABP and cTnT were associated with progressive deterioration of ventricular function and worse prognosis [127–131]. H-FABP concentrations were higher with more severe heart failure (NYHA classes 3 and 4), and significantly correlated with serum cTnT [130]. In addition, the subgroup of patients with the highest serum H-FABP concentrations showed the highest incidence of subsequent cardiac events [128,130]. Recently, these observations have been confirmed for other patient groups and indicate that H-FABP is a sensitive marker of minor myocardial injury in patients with congestive heart failure [110,132–134]. Increased specificity of H-FABP, compared to cTnT, was indicated by the fact that, when plasma H-FABP was <6 μg/L, the negative predictive value for a recurrent event within 90 days was 81%, while cTnT <0.02 μg/L showed a negative predictive value of 57% [132]. This difference most likely is explained by insufficient sensitivity of the cTnT assay. Although for cTnT a cut-off value of 0.1 μg/L for indication of myocardial injury is commonly used, 0.05 and 0.02 μg/L are being evaluated as proper cut-off now that more sensitive immunoassays are being developed. Also, Arimoto et al. [113] reported a significant correlation between elevated plasma H-FABP levels and cardiac event rate. The significance of the detection of ongoing myocardial injury in CHF by H-FABP and cTnT is still in an early stage and needs to be further evaluated, in combination with the natriuretic peptides BNP and pro-BNP.

5.2. Skeletal muscle injury

H-FABP is mainly expressed in the heart, but to a lesser extent also in skeletal muscle (Table 1). Consequently, monitoring myocardial injury using H-FABP may be hampered when patients suffered skeletal muscle injury either due to cardioversion, multiorgan failure, postoperative states or vigorous exercise. This monitoring problem can be overcome by using the plasma ratio of myoglobin and H-FABP concentrations [24,135]. This ratio in plasma reflects the ratio of the contents of both proteins in the affected tissue, as the latter differs between heart muscle (myoglobin/H-FABP ratio 2–10) and skeletal muscles (myoglobin/H-FABP ratio 20–70, depending on type of muscle [24,94,125]). In patients with AMI, it was found that the plasma myoglobin/H-FABP ratio is approximately 5 during the entire period of elevated plasma levels, while for patients with aortic surgery (causing no-flow ischemia of the lower extremities), the plasma myoglobin/H-FABP ratio was 45 [24,125]. When patients are defibrillated shortly after AMI, intercostal pectoralis muscles are likely to be injured, and an increase in plasma myoglobin/H-FABP was seen rising from 8 to 60 during 24 h after AMI [24]. In cases where a second increase in plasma concentrations of marker proteins occurs, this ratio can be helpful to discriminate a recurrent infarction (ratio remains at 2–10) from additional skeletal muscle injury (ratio rises to 20–70).

In the case of vigorous exercise, skeletal muscle damage occurs which results in a temporary loss of muscle function and coordination [136]. Normally, increased blood levels of CK and myoglobin are used to diagnose exercise induced muscle damage [137, 138], but Sorichter et al. [81] showed that after 20 min of downhill running (eccentric muscle contractions), plasma H-FABP increases after physical exercise by healthy subjects, and that its pattern of release into and clearance from the blood is similar to that of myoglobin. For both H-FABP and myoglobin, a significant increase was reached earlier (30 min) than for CK (2 h), indicating the usefulness of the former for the early detection of muscle injury. cTnI was not detectable in plasma from the investigated athletes,
indicating that the source of muscle protein release after downhill running is damaged skeletal muscle rather than heart muscle, which was confirmed by a plasma myoglobin/H-FABP ratio of 15 [81]. Also in a group of junior rowers, plasma concentrations of H-FABP and of CK were evaluated during 5 weeks of training [139] and showed that acute exercise induced a larger relative increase in plasma H-FABP (70–362%) than in CK (24–156%). Taken together, these data indicate that simultaneous measurement of H-FABP and myoglobin in plasma could be helpful for the early diagnosis of skeletal muscle damage, as the combination of these markers can give trainers and athletes early and specific information about the exercised skeletal muscles in training sessions and after competition. This information will help avoid additional skeletal muscle damage or overtraining and could allow better control of specific training sessions.

5.3. Liver injury

Release of cytoplasmic proteins from damaged hepatocytes into the vascular system can be caused by, e.g., acetaminophen (paracetamol) intoxication, ischemia and reperfusion injury, liver congestion, shock, trauma or rejection after transplantation. The hepatocytes are in close contact with circulation, from which they are separated by a single endothelial layer with large clefts. Biochemical plasma markers of acute hepatocellular injury, including alanine aminotransferase (ALT) and aspartate aminotransferase are commonly used to investigate the presence, and monitor the progress, of liver disease [140]. The currently used markers, with the exception of ALT, lack adequate specificity for liver disease. Although ALT can be measured very quickly and cost-effectively on a routine clinical analyzer, the fact remains that the plasma concentration of this relatively large protein (96 kDa) is rather late to increase above the upper reference limit after cell damage. Thus, more sensitive markers of liver injury in general are needed for patient monitoring [141].

Recently, it was shown that by using the 26 kDa alpha glutathione S-transferase (α-GST), present in the liver, kidney and intestine, for indication of hepatocellular injury due to rejection after liver transplantation, mortality and morbidity decreased due to more effective immunosuppressive therapy [142].

In search of sensitive proteins of liver injury, L-FABP (present in the liver, kidney and intestine) [1, 15,143,144] shows to be a promising new marker. Pelsers et al. [31] investigated L-FABP release following hepatocellular injury due to rejection in a group of liver transplant recipients who had episodes of acute hepatocellular rejection during their post-transplantation stay in the hospital. Such patients are intensely monitored to control their periods of rejection. Acute rejection as final diagnosis is currently based on liver biopsy data [145]. Apart from liver markers, clinical symptoms like fever, malaise and jaundice as well as liver function tests indicate whether a biopsy has to be taken [146]. The aforementioned study showed that L-FABP rises significantly in all rejection periods and can be detected in plasma earlier than α-GST and ALT (Fig. 3) [31]. L-FABP was also earlier when the day of immunosuppressive treatment was taken as reference. Due to the abundant content of L-FABP in liver tissue, the relative elevation of serum values after liver injury is higher than those of α-GST and of ALT, making L-FABP a more sensitive marker [31].

5.4. Kidney injury

The assessment of biomarkers to detect nephrotoxicity has been studied before, but sensitivity and specificity of urinary and serum profiles of these markers still need to be improved [147–149]. Maatman et al. [20,26] discovered already in 1992 the presence of two types of FABP in the kidney, which later turned out to be H-FABP, located in the distal tubular cells, and L-FABP which is located in the proximal tubular cells. Remarkably, however, the application of FABP as marker for kidney injury due to ischemia or toxic heavy metals has only recently been investigated [150–154]. Urinary H-FABP levels were evaluated in a rat model, showing that administration of mercuric chloride, cyclosporin and gentamicin all induced renal damage [155]. Especially in gentamicin-treated rats, urinary H-FABP concentrations increased markedly, indicating distal tubular injury and expressing the sensitivity of H-FABP compared to currently used markers.

For renal transplantation, the use of non-heart-beating donors (NHBD) could increase the pool of transplantable kidneys. However, tissue damage sustained from periods of warm ischemia in these
kidneys is often associated with primary nonfunction and delayed graft function. Continuous hypothermic pulsatile perfusion characteristics (flow, pressure, resistance, temperature, weight gain) together with biochemical marker analysis of kidney effluents are used to assess viability. To evaluate the use of FABP types, Kievit et al. [156] showed that after aortic clamping in rats, H-FABP plasma concentrations were elevated significantly earlier than those of the currently used markers glutathione S-transferase (GST) and lactate dehydrogenase. L-FABP showed no significant changes. Continuing these findings in a human setting, the potential of H-FABP as biochemical marker was compared with alanine aminopeptidase (Ala-AP) [157] and GST, to indicate renal tissue injury in pre-transplantation machine perfusion and to predict long-term renal function [150–153]. GST, Ala-AP and H-FABP plasma concentrations showed similar increases in NHBD kidney perfusates over a 4-h machine perfusion period. The activities of each marker were increased in discarded versus transplanted kidneys, with H-FABP having the tendency to be the most sensitive marker [150–153]. Based on these findings, the conclusion was reached that next to donor age, donor medical history, macroscopic appearance, warm ischemic time and ex vivo perfusion, biomarkers like H-FABP represent useful pre-transplant indicators of the suitability of NHBD kidneys for transplantation [150].

5.5. Intestinal injury

For the early detection of intestinal injury due to small bowel ischemia, inflammation or rejection, no plasma protein is routinely analyzed. Several studies have investigated the use of biochemical markers like hexoaminidase and lactate dehydrogenase [82] or physiological markers like mucosal pH [158], but these were non-conclusive. I-FABP occurs in the enterocytes of small intestine and constitutes 2% of enterocyte protein [159,160]. Interestingly, intestinal cells also express L-FABP. When intestinal ischemia is limited to a period of less than 2 h, only the villi are affected while the crypt cells remain intact, and there is a rapid recovery of function [161]. Because I-FABP and L-FABP are mainly expressed in the villi and not in the crypt [72,159,160], both proteins may be early and sensitive plasma markers of intestinal ischemia. Previous studies described the applicability of I-FABP for the detection of rat intestinal injury after acute ischemic diseases [82], rejection [83,162] and necrotic enterocolitis [71], but in patients, different results were reported [72,163–169]. Lieberman et al. [72,168] showed elevated serum I-FABP concentrations in patients with necrotic enterocolitis, intestinal ischemia and systemic inflammatory response syndrome. During cardiopulmonary bypass surgery, gastrointestinal perfusion was altered and elevated I-FABP urinary concentrations in high risk patients
indicated intestinal ischemia [163]. This was also
shown by Kanda et al. [166,167] in serum of patients
with intestinal ischemia and mesenteric infarction, but
Kaufmann et al. [169] reported lack of utility of I-
FABP in predicting intestinal allograft rejection.

Recently, Guthmann et al. [73] described the use of
both I- and L-FABP as diagnostic markers for necrotic
enterocolitis in preterm infants and concluded that L-
FABP is a promising sensitive marker for stage I, while
I-FABP appears to be a specific parameter for the early
detection of intestinal injury leading to severe stage III.

These data were confirmed by Pelsers et al. [32],
who investigated tissue distribution and contents of
both I-FABP and L-FABP in human intestine along
the duodenal to colonal axis in surgery and autopsy
samples, and the potential of these proteins as plasma
marker for the detection of intestinal injury in patients
with intestinal and/or hepatic disease. The L-FABP
tissue contents in the small intestine were markedly
higher than those of I-FABP (Table 1). For L-FABP,
comparable results were published by Sakai et al.
[170]. Elevated plasma concentrations of both I-FABP
and L-FABP were found in patients suffering from
intestinal diseases, while L-FABP was increased in
cases of hepatocellular injury (Fig. 4) [32].

As a result, besides I-FABP, also L-FABP (appearing
also in liver and kidney) shows to be a useful
plasma marker for the detection of intestinal injury,
especially in patients undergoing intestinal surgery.
However, care has to be taken using L-FABP in

Fig. 4. Plasma concentrations of I-FABP (upper panel) and L-FABP (lower panel) in patients with various intestinal and/or hepatic diseases as measured in the admission blood sample. Dashed lines refer to the upper reference limits of I-FABP (0.1 μg/L) and of L-FABP (17 μg/L) [32].
intestinal diseases as decreased circulation due to intestinal ischemia or transplantation can lead to liver injury and release of relatively large amounts of L-FABP. Although I-FABP and L-FABP show a distinct pattern of tissue distribution, their ratio in plasma after intestinal injury was not significantly different and, therefore, did not allow localization of necrosis. Further studies have to be performed to confirm these preliminary results.

5.6. Brain injury

The most recent development for using FABPs as tissue injury markers is for brain injury. Research in the field of brain-specific proteins as biochemical plasma markers for neurological disorders or brain injury is expanding. Protein S100B, neuron-specific enolase, myelin basic protein and glial fibrillary acidic protein are presently being evaluated as marker proteins in cerebrospinal fluid and/or blood for detection of brain injury in patients with cerebrovascular accidents like traumatic brain injury or stroke and in other diseases [171–174], eventually even to locate the site of injury (neuron, glia or myelin). However, conflicting results on elevated S100B serum concentrations after cardiac injury [175–177] indicate that the specificity of this protein is limited.

B-FABP and H-FABP are new potential markers for the detection of brain injury. B-FABP was first identified in the brain of rodents showing a variable tissue expression during development [28,178–181]. Quantitative data on tissue content in segments of the human brain as well as the potential of both FABPs as plasma marker for the detection of brain injury in patients were recently studied [27]. Frontal, temporal, occipital lobe, striatum, pons and cerebellum showed 10-fold higher tissue contents of H-FABP compared to B-FABP (Table 1). Unlike B-FABP, H-FABP is detected in the neurons of the gray matter (neuronal cell bodies) and constitutes 0.01% of total brain cytosolic protein [28,181].

In healthy individuals, no B-FABP could be detected in plasma or serum [27]. In mild traumatic brain injury, serum concentrations of B-FABP were elevated in 68% and of H-FABP in 70% of the patients, compared to elevated concentrations of S100B found in 45% and of NSE in 51% of the patients. In electroconvulsive therapy, B-FABP in serum was elevated in 6% of all samples (2 out of 14 patients), while H-FABP was above its upper reference limit in 17% of all samples (8 out of 14 patients), and S100B was above its upper reference limit in 0.4% of all samples. These patient studies indicate that B-FABP and H-FABP are more sensitive markers for brain injury than the currently used markers S100B and NSE [27]. Several authors [182–184] recently confirmed these findings by proposing H-FABP and B-FABP as markers for brain injury in Creutzfeld–Jacob and stroke, but unfortunately only qualitative data on H-FABP were presented.

Because the release of cerebrovascular proteins into blood plasma is dependent on the disruption of the blood–brain barrier (reviewed recently by Marchi et al. [185]), release curves and total concentrations of brain markers in plasma have to be evaluated with care to prevent a mixup of changes in blood–brain barrier permeability and real brain tissue injury.

6. Conclusions and perspectives

FABPs are novel biochemical markers with relatively high tissue concentrations and low normal plasma concentrations, which result in sensitive release. Heart-type FABP (H-FABP) has proven not only to be an excellent marker for the early, within 6 h, detection of cardiac injury in acute coronary syndromes, but also showed to be sensitive enough for detecting minor myocardial injury in heart failure and displayed promising prognostic values for cardiac events in ACS and CHF. Importantly, each of the clinical studies (i.e., 12 studies comprising a total of 2130 patients) with patients suspected of having an acute myocardial infarction and evaluating both H-FABP and myoglobin, have revealed a better or similar performance of H-FABP over myoglobin for the early detection of acute myocardial infarction. H-FABP in combination with cTnT would be the preferred combination to cover the complete diagnostic window of patients presenting with ACS in the ED, next to ECG and clinical symptoms. The rule out power of H-FABP in patients with low ACS prevalence is promising but needs further study. Limitations of the use of H-FABP as a diagnostic plasma marker for myocardial injury are the fact that (i) it is not cardiospecific, (ii) the diagnostic window
is relatively small, extending to only 24–30 h after onset of chest pain, and (iii) its elimination from plasma by renal clearance can cause falsely high values in case of kidney malfunction. However, despite these possible drawbacks, H-FABP has been reported still as the most sensitive plasma marker for myocardial injury. In addition, it has the advantage of rapid detection of re-infarction and the ability to be used as a marker for infarct size quantification by using individually estimated renal clearance rates.

Because H-FABP also is expressed in distal tubular cells, it can be used as biomarker for detection of ischemic injury in kidney perfusates of donors. Interestingly, both H-FABP and GST are good markers for renal toxicity induced by heavy metals. Together with B-FABP, H-FABP also appears to be a marker for brain injury as it is expressed in the gray matter of the brain.

L-FABP has only recently been investigated as injury marker, and shows promising results as new marker for rejection induced liver injury. Further study on the clinical application of monitoring immunosuppressive therapy by L-FABP plasma concentrations is needed. The relatively high intestinal content of L-FABP, when compared to I-FABP, makes L-FABP also a more sensitive plasma marker for intestinal injury but care has to be taken in diseases concerning combinations of liver and intestinal injury.

Intestinal injury can more specifically be detected by plasma I-FABP, as this FABP type only occurs in intestinal enterocytes. However, its tissue expression is relatively low, so that more sensitive immunoassays should be developed to fully exploit the potential of this marker, and also to establish a proper reference interval in healthy subjects. This comment also applies to B-FABP. Specific FABP types also occur in adipocytes (A-FABP), ileal enterocytes (ileal lipid binding protein, I-LBP), the peripheral nervous system (myelin lipid binding protein, M-LBP), testis (T-FABP) and epidermal cells (E-FABP) [1]. The use of these proteins as plasma markers for tissue injury has, however, not yet been explored.

Although not all FABPs are tissue specific, this family of small cytoplasmic proteins is gaining more and more interest as early and sensitive plasma markers of tissue injury. Further study on their diagnostic and prognostic use is warranted but will require further commercialization of automated and rapid assays for definitive evaluation and application in clinical practice.

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