Japanese Journal of Gastroenterology and Hepatology

Review Article

Fatty Acid Binding Proteins asa Biomarker for Diagnosing Celiac Disease

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Received: 01 Oct 2019
Accepted: 02 Nov 2019
Published: 07 Nov 2019

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1. Abstract

Celiac disease is a chronic autoimmune gastrointestinal disorder that is caused in genetically predisposed people using gluten protein. Various methods, including histopathologic, genetic, and autoantibody titration are used for diagnosis and follow up of celiac disease patients.Severe changes in the intestinal mucosa of untreated celiac patients have been associated with altered levels and expression patterns of different genes.This disorder is cause of the damage to the enterocyte which causes malabsorption.According to the current literature,serum intestinal fatty acid binding protein (I-FABP) is a sensitive marker for the assessment of enterocyte damage.In the clinical management of celiac disease, a new, noninvasive approach to assessing intestinal injury is essential for the follow-up and diagnosis of people under a gluten free diet.Therefore, I-FABPis recently proposed as noninvasive marker for this purpose.FABP is a small cytosolic protein of 15 kDa that binds and transports long chain fatty acids and also has important biological roles in the signaling pathway. The role of this molecule has been studied in different diseases, including celiac disease, heart disease, prostate cancer, diabetes, and etc. In this paper, we reviewed the importance of this molecule in patients with celiac disease, as well as its role as a diagnostic test and screening the disease activity in patients under gluten free diet.

2. Keywords: IFABP; Celiac disease; Serum level; Histopathology

3. Introduction

As a chronic complication, celiac disease (CD) is known to be highly associated with the immune system and geneticfactors.Intestinal villous atrophy, intestinal crypt hyperplasia, absorption imbalance, malnutritionand growth impairment during childhood are the most important findings in patients who are affected by CD. To diagnosis and screen celiacpatients, the duodenoscopy with biopsies of the intestine and serologic tests such as the known (anti-gliadinAb), EMA (endomysialAb), anti-DGP (anti-deamidatedgliadin peptide) and anti-tTG (anti-Tissue transglutaminase) areusually performed[1].In patients who are under gluten free diet, endoscopy and duodenal biopsy is invasive and expensive procedures, and by taking into account that serological tests and auto-antibody titration are time consuming and need high level of the gluten for the accurate reading, it can be argued that these diagnostic tests do not give reliableinformation on changes in the intestinal epithelial cells during the course of treatment

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and patients' recovery. Recent studies have shown that in many cases,antibodieslevelsdo not correlate properly with histopathological findings and clinical symptoms of GFD- patients[2].In order to properly manage the clinical condition of celiac disease, we need new non-invasive methods to investigate intestinal epithelial damage for diagnosis and track the efficiency of the GFD diet. The aim of this review was to evaluate the importance of fatty acid binding proteins (FABP)molecule as a biomarker for diagnosing celiac disease.

4. Fatty Acid Binding Proteins Structure

Fatty acidscontain high level of energy storage in the form of triglycerides that are produced in the liver and muscle tissues. Fatty acids are also utilizedto synthesize complex lipids, such as phospholipids and cholesterol, moreover they are essential parts of the structure of multiple hormones and signaling factors[3].Fatty acid-binding proteins (FABP) isa member of the lipid binding proteins (LBP) super-family.Thisintracellular protein family has a molecular weight of 14-15 kDa, and was first discovered in the early 1970s[4,5].The FABPs family has a highly conservedtertiarystructure that consists of two antiparallel beta-sheet, each have five strands. In this beta structure, there is a positively-charged amino acid that binds to the constructionof fatty acids with a negative charge [6]. The Helix turn helix (HTH) motif isconsisted of the A and B joined beta strands, and plays an important role in the transfer of ligands[3,7]. Despite the similarity of the third structural in this protein family (FABP), 20 to 70 amino acids have homology[8].The regulation of lipid metabolism leads to moderation in energy production, which requires complementary systems in the body to co-ordinate. A group of transcriptionfactors that collaborate with theFABPsis a family of PPARs -PPAR-α, PPAR–δ and PPAR–γ (peroxisome proliferator-activated receptor) that acts as a nuclear receptor to regulate the transcription of many genes involved in the metabolism of lipids [9].

5. Types of FABPs

FABPs can be divides into two main groups that are associated with plasma membrane (FABPPM) and intracellular or cytoplasmic proteins (FABPCs). The intracellular or cytoplasmic proteins have now been classified into9 classes based ontissuesthat constructliver (L-), intestinal (I-), heart (H-), adipocyte (A-), epidermal (E-), ileal (Il-), brain (B-), myelin (M-) and testis (T-) FABPs[3,10].Intestinal FABP is expressed in the epithelium of the small intestine and is known as FABP2. In the small intestine there are three classes of FABP calledL-FABP, I-FABP and Il-FABP that eachof them take different positions in the intestinal tissue. Most of the time L-FABP presented in the proximal section, in contrast of Il-FABP and I-FABP that are expressed in distal part and throughout the small intestine (jejunum) respectively. The polymorphism(G>A) in the I-FABP gene in codon 54, which is caused by the transfer of alanine to threonine, has been shown to be insulin resistance and reduces fatty acid oxidation in the Indian population[11,12].I-FABP has aoneligand binding site among the FABP family. IFABPhas a very high affinityto bind to saturated and unsaturated fatty acids, but shows a lower tendency toward binding to unsaturated fatty acids than its liver counterpart[13].Unlike the hepatic type of this protein,I-FABP, similar to other members of the family, transfers fatty acids to the membrane through a collisional mechanism[14].Generally, FABP serum concentrations act as a biomarker to detect damage, for example, B-FABP is a marker to track damage in the brain and I-FABP is used for tracking damage to the intestine[15]. When the enterocytes were damaged, I-FABP released from these epithelial cells that is indicated by the elevated plasma level of I-FABP, but the authorsreported that a plasma level of I-FABP did not have avalid correlation withdysbiosis and intestinal dysfunction in obesity[16]. Other study indicated thatmRNA and protein expression of FABP typesweredifferent between carcinoma cell lines such as prostate, bladder and kidney, for example in the renal carcinoma cell line the level of B- and IL-FABP were increased, due to this high level of IL-FABP, Fatty acids were transported that induces antioxidant production in the cells that can lead to good prognosis and reduction of tumor metastasis[17].H-FABP in serum of CT-scanpositive patients for an mTBI (Mild Traumatic Brain Injury) showing high level in comparison to CT scan-negative patients with both 6h and 24h after trauma onset[18].

Citation: Nejad MR, Fatty Acid Binding Proteins asa Biomarker for Diagnosing Celiac Disease. Japanese Journal of Gastroenterology and Hepatology. 2019; v2(5):1-8.

6. Functions of FABPs

Several roles have been proposed for FABP.FABP allows the transport of fatty acids from one cell to another for various purposes, such as storage, signaling, membrane synthesis, oxidation, regulation of enzyme activity and gene expression.The amount of FABP in each cell is depending on the rate of fatty acid metabolism in that cell[19]. This protein contributesto the conversion of fatty acids to eicosanoid and also to the stabilization ofleukotrienes[20,21]. Furthermore,FABP also has the ability to enter the nucleus and interact with the nuclear hormone receptorsdirectly[22].L-FABP and I-FABP have several roles in intestinal fat metabolism[23]. The roles of L-FABP and I-FABP in the transfer and delivery of fatty acids into enterocytes wereinvestigated. Studies show that L-FABP, regardless of entrysites (apical or basolateral), binds to more fatty acids thanIFABP plays an important role in the transfer of dietary fatty acids into the blood-stream.Both FABPs are located in the apical portion of the enterocytein the fasted state and are seen in the cytoplasm in the fed state[24].One of the important roles of FABP proteins in enterocyte is the regulation of intracellular free fatty acid concentration,since increasing the concentration of free fatty acid in enterocytes is toxic[25].FABP, with the storage of fatty acids as a source, regulates the synthesis of triglycerides, phospholipids, chylomicrons and cell signaling.In support of the role of FABP, the expression of this protein in enterocyte upregulatesduring satiation, which canbe due to the increase in the amount of fatty acid that enters the enterocyte.

7. FABPs in Immunity and Inflammation

Since lipids play a crucial role in the immune cell signaling, FABP4 protein affects cellular immunity. PPARγ is the main adipocyte differentiator that is produced in atherosclerotic lesions in response to oxidized LDL[28]. Rapamycin, an immunosuppressive agent, also causes hyperlipidemia and FABP4 expression in macrophages[29]. PPARs trigger the expression of FABP4, and FABP4 acts as a mediator for the delivery of ligands to PPARs[30]. The metabolic effects of FABP (lipolytic activation and inhibition of lipogenesis) are in contrast to the activity of PPARγ. In fact, PPARγ activity increases in FABP4 and FABP5 defects in macrophages[31]. FABP4 and FABP5 stabilize leukotriene and the shortage of these proteins, results in defects in the activation, expression and production of prostaglandin-E[32].Therefore, FABP determinesthe balance of macrophage eicosanoids that are inflammatory mediators in adipose tissue in obese individuals[33]. The lack of FABP in the macrophage reduces stimulation of theinflammatory cytokines expression such as MCP-1 and TNF and also the activity of IKK–β / NF–κB and the synthesis of nitric oxide[34].In macrophages, the deficiency of FABP provides a strong protection against fatty acid potential toxicity, moreover unsaturated fatty acids induce expression of UCP2 that codes for mitochondrial uncoupling protein 2. Alsoincreasing the expression of UCP2 in macrophages causes the cell to shift to the M2 phenotype, reducing endoplasmic stress and oxidative stress[35]. In addition, FABP4 interacts directly with the JAK2 tyrosine kinase protein and may reduce the signaling of cytokines such as IL-6 and IL-10 in macrophages[36].In addition to macrophages, FABP4 is also expressed in the dendritic cells of the myeloid and is amplified during differentiation. Importantly dendritic cells that lack FABP4, produce lower levels of pro-inflammatorycytokines, including IL-12 and TNF, and reduce the activation of T cells[37]. Studies have shown that defect or deficiency of FABP in mice protects against autoimmune encephalomyelitis[38]therefore in addition to its immunological role, FABP4 may have broad effects on autoimmunityand sensitivity to infections.

8. FABP as a Diagnostic Marker in Celiac Disease

Factors affecting the integrity of the intestinal epithelialare: intestinal permeability, the displacement of bacteria and their products, transmural injury, splanchnic perfusion, functional enterocyte mass, tight junctions and condition of enterocytes[39].To evaluate the integrity of epithelial barrier, measuring the FAPs in both blood and urine by ELISA, plasma level of Glutathione S-transferases and detection of tight junction statussuchasurineclaudin-3levelsarerecommended[40]. There are three types of FABP in the intestine; intestinal FABP (I-FABP), liver FABP (L-FABP) and ileal bile acid binding protein (I-BABP).FABP distribution in the intestine was first investigated by Plesser et al and Dickens et al and reported that I-FABP in jejunum and (I-BABP) are mainly expressed in ileum and both in the intestine, while L-FABP is in the liver and kidneys[1,15].

Since FABP protein is a small cytosolic protein, it can easily enter the bloodstream after damage to the enterocyte. The half-life of this protein is about 11 minutes[41]. This point emphasizes that FABP is a sensitiveand accurate marker for cell pairing, and the evaluation of its urinary concentration reflects thedamage of enterocyte, because it is rapidly removed by the kidney; especially in infants andchildren.This is a great benefit because blood collection for diagnostic purposes is harmful tochildren and is the main cause of anemia in neonates[42,43]. For this reason, it is easy to measure by ELISA in urine.In early stage of enterocyte damage and inflammation,I-FABP plasma level and also other gut specific FABP such as I-BABP(Ile-al-Bile Acid Binding Protein)in mature enterocytes of the jejunum and ileum are increased. It is proposed that these proteins can be biomarkers to detect intestinal disease[44].Increased blood and urine concentrations of FABP have been reported in patients with intestinal ischemiasystemic, inflammatory response syndrome and necrotizing enterocolitis[45].Furthermore, increased concentrations of FABP have been reportedin patients with intestinal ischemia during surgery and in patients with mesenteric infarction[46]. In the event of acute injury to the intestine, the concentration of FABP in urine and blood is a good marker for evaluating the damage to the intestinal epithelium.In contrast to I-FABP, L-FABP shows a multi tissueexpression. Besides the expression in the intestine, L-FABPis also present in hepatocytes and tubular cells of thekidney. Increased L-FABP levels in serum can thereforebe derived from other organs then the intestine. I-FABP isexclusively expressed in the intestine and the test accuracyof I-FABP is higher than for L-FABP. Therefore I-FABPmeasurement is preferable for diagnosis and follow-up inceliac disease[15].Enterocyte damage assessed by serum I-FABP correlates with the severityof villous atrophy in celiac disease at the time of diagnosis. Although enterocytedamage improves upon treatment, substantial enterocyte damagepersists despite absence of villous atrophy and low IgA-tTG levels in themajority of cases. Elevated I-FABP levels noneresponding to gluten-free dietare indicative of histological abnormalities and warrant further evaluation[47].In 2009,Derikxetalexamined the distribution and microscopic location of FABP in 39 normal individuals with surgery, and then intestinal concentration of I -FABP and L-FABPdeterminedin 26 healthy subjects and 13 patients with celiac disease that had been confirmed by intestinal biopsy.Ten patients were re-evaluated after a year of receiving gluten-free diet.I-FABP and L-FABP are usuallyexistingin the small intestine, especially jejunum. This protein is expressed above the top of the villi, which is the site of the onset of injury in the celiac disease. Serum concentrations of FABP in individuals with celiac disease are significantly increased compared with controlsand after receiving a GFD diet,serum concentrations of FABP are normalized[1].Adriaanseetalin 2013studiedthe severity of injury to enterocytes in treated and untreated CD patients. The association between enterocyte damage, CD auto-antibodies and histological abnormalities during illness were evaluated as well.Serum concentrations of FABP were determined in 96 adult patients with celiac disease that 32 people (40%) have Marsh IIIA, 23 (28.8%) Marsh IIIB and 25 (31.3%) Marsh IIIC, 69 treated patients and 141 healthy subjects as controls. The associations of I-FABP concentration with the degree of villous atrophy (Marsh classifications) and IgA-tTG were investigated.Serum concentrations of FABP wereincreased in untreated celiac disease patients compared tocontroland had significant association withthe Marsh classification.In treated group, the serum concentrations of FABP decreased, but did not reach to normal level whilethe serum IgA-tTG concentration reached its normal range and the histological abnormalities alleviated. People with celiac disease who do not respond to the diet showed sustained histological defects[48].In 2015Bottasso Arias et al.examined the concentration of IFABP as well as the expression of IFABP and LFABP in both levels of protein and mRNA in the intestines of people with severe entropy and healthy normal individuals as a control group.In this study, there wasa significant increase in IFABP serum concentration in untreated celiac disease compared to control group and celiac patient under GFD diet.The expression of FABP in the intestinal mucosa showeda different pattern. The study of the reduction of FABPs' expression in individuals with severe enteropathy compared to control can be resulted from the loss of intestine epithelial due to the severe enteropathy[49].In 2016 Adriaanse et al. studied20adult CD patients in remission who underwent a two-week gluten challengewith 3 or 7.5 g of gluten every

day compared to 43 CD-serology negative individuals. Serum I-FABP was measured at day –14, 0, 3, 7, 14, and 28. The results indicated that the concentration of serum I-FABP increased dramatically during the 2 weeks of gluten challenge). Gluten and the duration of gluten-free diet has no effects on the serum I-FABP concentration during the gluten challenge[50].Vreugdenhil et al.in 2011,examined whether serum I-FABP concentrations could be considered as a reliable test for identifying atrophic villous in children who were positive for celiac antibody testing or not. In addition, the change in serum I-FABP concentrations after a gluten-free diet was evaluated.Concentration of serum I-FABP was investigated using retrospective studies of 49 children with celiac disease and 19 patients with positive celiac antibody and negative biopsy tests. Blood samples were taken prior to biopsy and repeatedly after a gluten-free diet. The results showed that serumI-FABP concentration in celiac patients was significantly higher than control. Also serum I-FABP concentrations wereassociated with the severity of intestinal atrophy.In all patients with celiac disease, I-FABP serum concentrations wererapidly reduced after receiving a gluten-free diet, and in 80% of cases, it returned to normal level ofconcentration after 12 weeks of the GFD[2].Study by Adriaanse and his colleagues have shownthe distinctive features of I-FABP as a marker for enterocyte damage in patientswith positive CD autoantibodies (IgA-tTG) with and without celiac disease (CD). Between 2010 and 2011, children with autoantibody positive for celiac disease were investigated.Plasma concentrations of I-FABP and IgA-tTG were determined at the baseline and after 3, 6, 12 and 26 GFD in 61 children.The results indicated that, plasma concentrations of I-FABP have increased dramatically in the celiac children compared to controls, in association with Marsh classification. Plasma concentrations of I-FABP decreased significantly after receiving GFD, but the mean IgA-tTGtiter did not reached tonormal rangeafter 26 months.Increasing plasma concentrations of I-FABP confirms the diagnosis of celiac disease in 91.7% of patients with positive autoantibody titers and proposed reduced the need for duodenal biopsy in 75% of cases.Plasma concentration of I-FABP was comparable to the control group after 6 to 12 weeksof GFD, which acts faster than IgA-tTG marker[51].The aim ofVreugdenhil et al. study was to evaluate the serum I-FABP concentration in patients with celiac disease and to evaluate the rate of the decreasingof this protein after GFD.Blood samples were collected up to 2 months before biopsy and after starting GFD. The control group included individuals who were suspectedfor celiac disease without tissue abnormalitiesthat were consistent with the patients group.The results showed that the serum I-FABP concentrations in celiac patients have significantly increased compared with the control group. In 81% of patients, serum I-FABP concentrations were higher than the cut-off pointat the time of biopsy. Serum I-FABP concentration was positively correlated with March classification, and in all patients with a MarchIIIc, increased concentration of serum I-FABP was detected. After receiving GFD, I-FABP serum concentrations werereduced.In 81% of those patients, receiving a gluten-free diet for 7 to 12 weeks, led to reduction of serum I-FABP concentrations.These results indicate that plasma I-FABP concentrations are a suitableindicator for evaluating the celiac disease progression and monitoring the response to GFD[52].

9. FABP in Other Diseases

FABP has been studied as a possible marker for the detection and monitoringinvarious diseases. Serum concentration, urinary concentration, expression and polymorphism of this protein have been studied in multiple complicationssuch as prostate, bladder and kidney cancer[17],abdominal pathology[53],neonatal necrotizing enter colitis[54], acute mesenteric ischemia and resultant lung injury[55], coronary heart disease[56], gut injury andpatients with acute pancreatitis[57], acute ischemic stroke[58], intestinal barrier dysfunction[16], prostate cancer and diabetes.

10. Conclusion

For the diagnosis of celiac disease, serologic tests such as anti-gliadinAb, Endomysial auto-antibodies, anti-trans-glutaminaseAband intestinal biopsy (Marsh Classification) are used.One of the non-invasive methods which can be used to diagnose and follow up celiac disease is FABPinvestigation. This protein is considered as a marker for damage to the intestinal epithelium. Previous studies have shown that in patients with celiac disease, its serum and urine concentrations increase and its expression in the intestine decreases due to epithelial

degradation and can be considered as a method fornon-invasive evaluation of intestinal damage in celiac disease. In addition, it can be used to screen GFD-patients.Serum I-FABP levels might be useful in daily monitoring for detecting gluten intake, evaluating new therapeutic method can provide us with a minimal-invasive marker for detection of ongoing mucosal damaged without the use of endoscopy. Some studies indicated that Serum level of I-FABP has a positive correlation with Marsh stage of CD patients.

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