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Exploring the role of fatty acid binding protein 4 in insulin resistance and obesity

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Abstract

Background: Fatty Acid Binding Protein 4, also known as FABP4, is a protein found in the cytoplasm of cells, which is abundantly expressed in adipocytes and macrophages, typically expelled by these cells. Once outside the cell, it binds to a receptor and functions as a transportation protein for fatty acids. Consequently, FABP4 governs and enhances the rate at which fat is broken down for energy usage, a process called lipolysis. Higher levels than normal were proposed to be associated with some metabolic disorders, most importantly insulin resistance and obesity.

Materials and Methods: Keywords, such as FABP4, obesity, insulin resistance, Type 2 diabetes and T2DM were looked for in many search engines to review the possible role of Fatty Acid Binding Protein 4 in development of insulin resistance and obesity for providing deep insight into understanding the significance of this protein in evolving such debilitating metabolic disorders.

Results: Many studies have shown that elevated levels of Fatty Acid Binding Protein 4 in the blood is positively correlated with pathogenesis of obesity and type 2 diabetes, other studies have shown that it has a role in disrupting lipolysis and fatty acid metabolism in adipocytes.

Conclusion: Several of the reviewed studies indicated that elevated levels of Fatty Acid Binding Protein 4 are associated with cases of obesity, insulin resistance, type 2 diabetes mellitus. Being familiar with these findings is crucial to understand the missing parts in disrupted metabolic pathways in insulin resistance, obesity as well as finding effective treatment in targeting or modulating such protein.

Keywords: Protein, fatty acid, FABP4

Introduction

Fatty Acid Binding Protein 4, also known as FABP4, is not a widely recognized protein or process within the group of fatty acid oxidation. It is a protein found in the cytoplasm of cells, typically expelled by these cells. Once outside the cell, it binds to a receptor and functions as a transportation protein for fatty acids. Consequently, FABP4 governs and enhances the rate at which fat is broken down for energy usage, a process called lipolysis. While the kidneys primarily carry out this process within the body, research has indicated that FABP4 also enhances fat oxidation in monocytes and macrophages. Moreover, FABP4 is involved in the synthesis of triglycerides in the liver, and recent scientific investigations have suggested a potential association between disruptions in FABP4 and obesity (Moreno-Vedia *et al.*, 2022; Osorio-Conles *et al.*, 2023) ^[30, 37].

Diabetes is a complicated metabolic disease linked to a higher risk of neurological and cardiovascular problems. Between 1980 and 2014, the prevalence of diabetes worldwide rose quickly from 4.7% to 8.7%. (Zhou *et al.*, 2016) ^[64].

The International Diabetes Federation projects that by 2045, there will be 673 million diabetics globally, up from 451 million in 2017 (Cho *et al.*, 2018) ^[6]. 85-90% of diabetic patients have type II diabetes mellitus (T2D), formerly known as non-insulin-dependent diabetes. T2D is characterized by elevated blood glucose, decreased beta-cell activity, and reduced insulin sensitivity (Pei *et al.*, 2022) ^[40]. Obesity, a medical condition more common in developed countries, is associated with a lot of medical issues as well as terminal illnesses such as heart disease and cancer. In the UK, almost 30% of adults are obese and it is estimated that more than 5% of deaths can be linked to obesity.

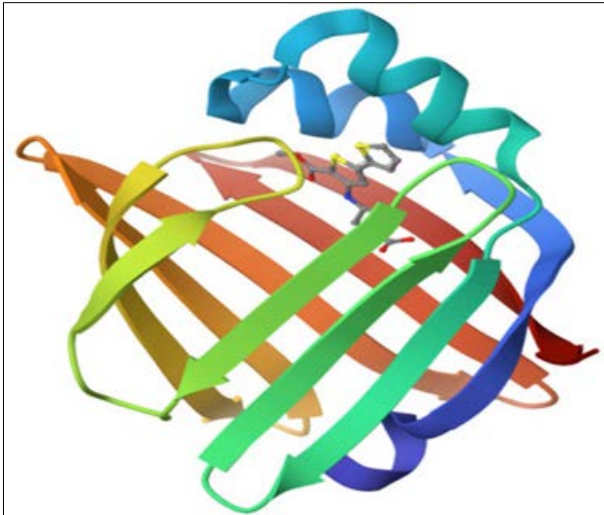


Fig 1: Crystal structure of mouse adipocyte fatty acid binding protein bound by inhibitor (Hertzel *et al.*, 2009) [23].

As a serious medical condition, fat loss is essential; especially as the NHS spent around £6.1 billion on diabetes alone in 2014 (Powell-Wiley *et al.*, 2021; Aparecida *et al.*, 2020; Bendor *et al.*, 2020) [42, 1, 4].

This Review aims to provide an overview about the FABP4 and its relation with insulin and obesity. Role of FABP4 in adipocyte function and Role of FABP4 in adipocyte function will also be discussed.

Review of Literature

Fatty Acid-Binding Proteins

Fatty Acid-Binding Proteins (FABP4), which are a relatively new adipokine that are a member of the calycin protein superfamily, are also known as adipocyte fatty acid-binding protein (AFABP) in the literature (Zhang *et al.*, 2018) [62]. This protein is also known as adipocyte P2 (aP2) due to its significant sequence similarity (67%) with the myelin P2 protein (M-FABP/FABP8) (Ning *et al.*, 2016) [34]. FABP4 molecules make up around 1% of all the proteins that are water-soluble in adipose tissue, which are abundantly expressed in adipocytes (Ning *et al.*, 2016) [34]. Hydrophobic ligands, including eicosanoids, other lipids, and both unsaturated and saturated long-chain fatty acids, may be reversibly bound by FABP4. As such, it participates in the control of lipid transport and cellular reactions (Furuhashi *et al.*, 2011; Tanaka *et al.*, 2015; Rodríguez-Calvo *et al.*, 2017; Kucharski and Kaczor, 2017) [17, 52, 45, 26].

The intracellular lipid chaperones known as FABPs are responsible for moving fatty acids to certain organelles inside the cell, such as the endoplasmic reticulum, peroxisomes, mitochondria, and nucleus (Okazaki *et al.*, 2014; Rodríguez-Calvo *et al.*, 2017) [36, 45]. Thus, FABPs are important for signaling, trafficking, membrane formation, lipid oxidation, and lipid-mediated transcriptional control. Furthermore, FABPs control the enzymatic activity and cytoplasmic storage of lipid droplets (Trojnar *et al.*, 2019) [53], as well as the process of converting fatty acids into eicosanoids and stabilizing leukotrienes (Zimmer *et al.*, 2004) [66].

FABP4 in humans is composed of 132 amino acids. A molecular mass of 14.6 kDa has been determined for it. The expression of FABP4 rises significantly during the development of adipocytes (Rodríguez-Calvo *et al.*, 2017) [45].

The previously described finding has resulted in the suggestion of this molecule as a marker for adipocyte differentiation. (Smith *et al.*, 1988). Furthermore, during the transformation of monocytes into macrophages, the expression of FABP4 is elevated. Various proinflammatory stimuli have the ability to modulate or regulate the expression of FABP4 inside various cellular entities (Makowski *et al.*, 2005) [29]. FABP4 induces the generation of foam cells in macrophages. Modified low density lipoproteins (LDLs) are thought to facilitate the development of foam cells, which are commonly seen in the presence of elevated levels of insulin and glucose. The observed elevation in levels serves as an indication of insulin resistance, a condition that is specifically associated with obesity, diabetes, and the metabolic syndrome (Shashkin *et al.*, 2006) [49].

A rise in insulin sensitivity may then encourage the PPAR γ gene's expression in adipose tissue, which will help to speed up the differentiation of adipocytes. PPAR γ and C/EBP regulate FABP4 expression at the transcriptional level (Rodríguez-Calvo *et al.*, 2017) [45].

Insulin sensitivity may be influenced by FABP4, an adipokine. Conversely, FABP4 expression is transcriptionally regulated by PPAR γ agonists, fatty acids, dexamethasone, and insulin, and is significantly elevated during adipocyte development. Only FABP4 that is mediated by microvesicles and released by them is downregulated by insulin. However, only a tiny portion of FABP4 is released by adipocyte-derived microvesicles, and this activity is minimal (Furuhashi, 2019) [15].

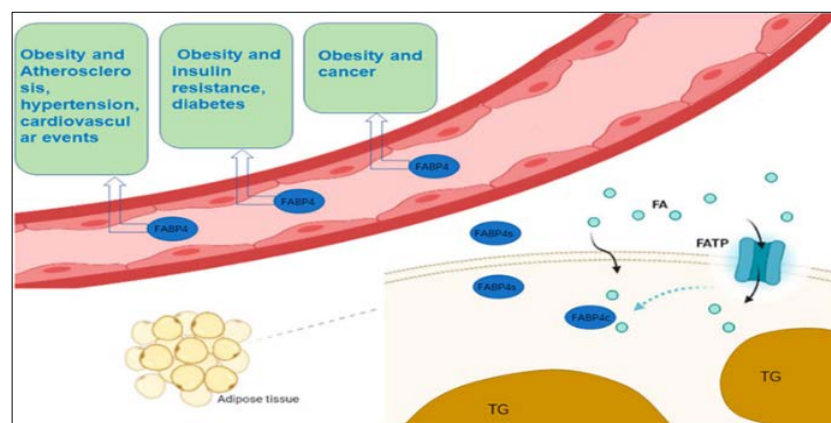


Fig 2: FABP4's function in blood and cells. FABP4 binds to FAs in adipocytes to help in their transport once they penetrate the cell membrane. Fat cells produce FABP4 concurrently and release some of it into the bloodstream (Liu *et al.*, 2022) [28].

Fatty acid-binding protein 4 role in adipocyte function

Adipocyte fatty acid-binding protein (A-FABP), often referred to as fatty acid-binding protein 4 (FABP4), is mostly expressed in macrophages and adipocytes (Moreno-Vedia *et al.*, 2022; Xiao *et al.*, 2021; Frances *et al.*, 2021) [30, 56, 40].

It has been discovered that it is essential to the development of metabolic syndrome and insulin resistance. Studies have shown that this protein is released by adipocytes and functions as a signaling molecule to induce insulin resistance in the body, hence adipocytes are essential for the expression of this protein.

Adipocytes, which are found in white adipose tissue and also known as white adipocytes, are cells that primarily serve to store fat. These types of cells are mainly associated with obesity and a disrupted FABP4 synthesis. When FABP4 is missing in adipocytes, studies have shown that the size of the fat cells is reduced and therefore, the development of metabolic syndrome decreases.

Metabolic syndrome is a term that describes a condition of obesity-associated, a pro-inflammatory state characterized by the presence of abdominal obesity, insulin resistance, hypertension, altered lipid metabolism, and a pro-thrombotic diathesis. It is a severe condition that can lead to type 2 diabetes and cardiovascular disease (Prentice *et al.*, 2021) [43].

Fatty acid binding protein 4 is involved in the development of insulin resistance, diabetes mellitus, and atherosclerosis. It functions at the intersection of metabolic and inflammatory pathways in adipocytes and macrophages. One potential treatment approach for metabolic and cardiovascular disorders is chemical suppression of FABP4. One of the particular FABP4 inhibitors, BMS309403, is an orally active small molecule that inhibits the binding of endogenous fatty acid (FA) by interacting with the fatty acid-binding pocket inside the interior of FABP4. FABP4 binds to intracellular FA (PDB code: 2hnx). Ligand-bound FABP4 (Furuhashi *et al.*, 2015) [18].

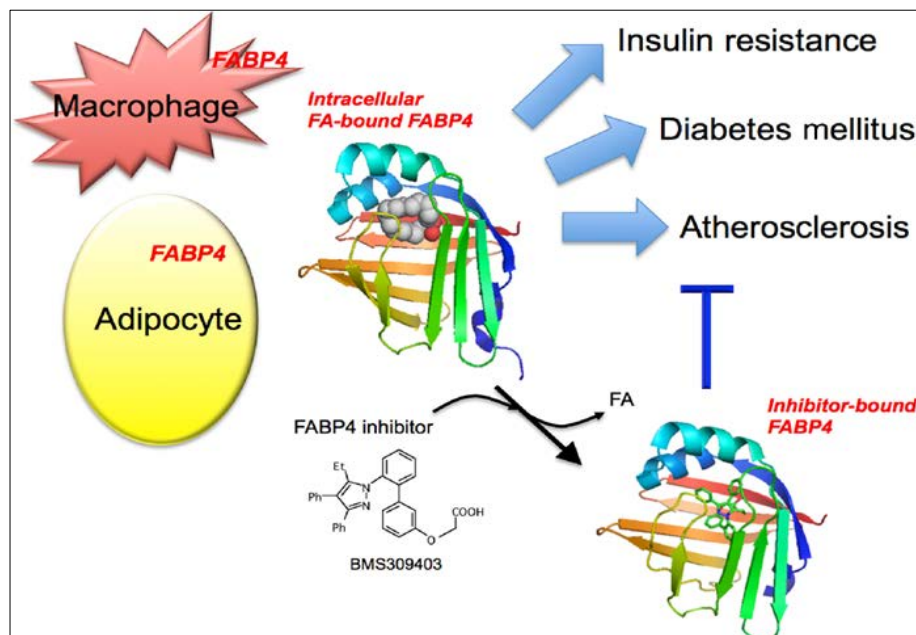


Fig 3: FABP4 in macrophages and adipocytes is associated with metabolic and cardiovascular disorders (Furuhashi *et al.*, 2015) [18].

Obesity

Globally, obesity is becoming more and more common. The incidence of obesity and overweight in people worldwide has risen steadily over the last several decades by more than 27% (Avgerinos *et al.*, 2019) [2]. More than 25% of children and more than 35% of adults were overweight or obese in 2013; these percentages are continually rising (Quail and Dannenberg, 2019) [44]. Body mass index (BMI) values of ≥ 25 kg/m² and < 30 kg/m² were considered overweight, whereas BMI values of ≥ 30 kg/m² were considered obese (Avgerinos *et al.*, 2019; Piche *et al.*, 2020) [2, 41].

As per Stolarczyk (2017) [51], The association between obesity and a persistent systemic inflammatory response in humans has been widely recognized, resulting in a range of health complications. Several instances of chronic health conditions include hypertension, cardiovascular disease, dyslipidemia, metabolic syndrome, type 2 diabetes mellitus, Alzheimer's disease, non-alcoholic fatty liver disease, oncology, and numerous more. Numerous studies have provided substantial evidence indicating that alterations in the microenvironment of adipose tissue resulting from

obesity significantly contribute to the initiation and advancement of various cancers (Zhou *et al.*, 2016) [64].

The connection between fatty acid-binding protein 4 and obesity

Those who are obese produce an excess of unhealthy adipocytes, which may result in insulin resistance and other negative outcomes. The results of the study indicate that FABP4 plays a critical role in the development of diseases associated with obesity (Liu *et al.*, 2022; Yang *et al.*, 2023; Chung *et al.*, 2021; Dou *et al.*, 2020) [28, 59, 7, 12].

The initial evidence suggesting that FABP4 may be implicated in obesity-induced insulin resistance stems from experiments conducted on mice. These mice's adipocytes had an excess of FABP4 after they were fed a high-fat diet designed to make them obese (Zhou *et al.*, 2020; Schwärzler *et al.*, 2022) [65, 47].

Conversely, the mice lacking the FABP4 gene did not develop insulin resistance, thereby granting further insight into the potential implications for human beings. This research bears great significance as it seeks to unveil the

cellular factors contributing to obesity and its associated diseases, thereby providing a foundation to ascertain whether FABP4 could serve as a valuable molecular target for treating insulin resistance. Ongoing studies continue to investigate this possibility. Additionally, it was discovered that obesity-induced insulin resistance was accompanied by the release of specific proteins unique to adipocytes (Schwartzler *et al.*, 2022; Prentice *et al.*, 2021; Yao *et al.*, 2020; Nguyen-Tu *et al.*, 2021) [47, 43, 60, 33].

These proteins contribute to the development of type 2 diabetes mellitus, a metabolic condition associated with

obesity. FABP4 helps to enhance the release of these proteins even though they are secreted (Moreno-Vedia *et al.*, 2022; Liu *et al.*, 2022; Xiao *et al.*, 2021) [30, 28, 56].

The precise mechanisms by which FABP4 facilitates the secretion of these proteins remain unknown; however, the revelation of the relationship between these proteins and FABP4 is a significant advancement in obesity-related research. The potential use of these proteins to assess the development of type 2 diabetes has not been substantiated (Liu *et al.*, 2022; Chung *et al.*, 2021; Gormez *et al.*, 2020; Moreno-Vedia *et al.*, 2022) [28, 7, 21, 30].

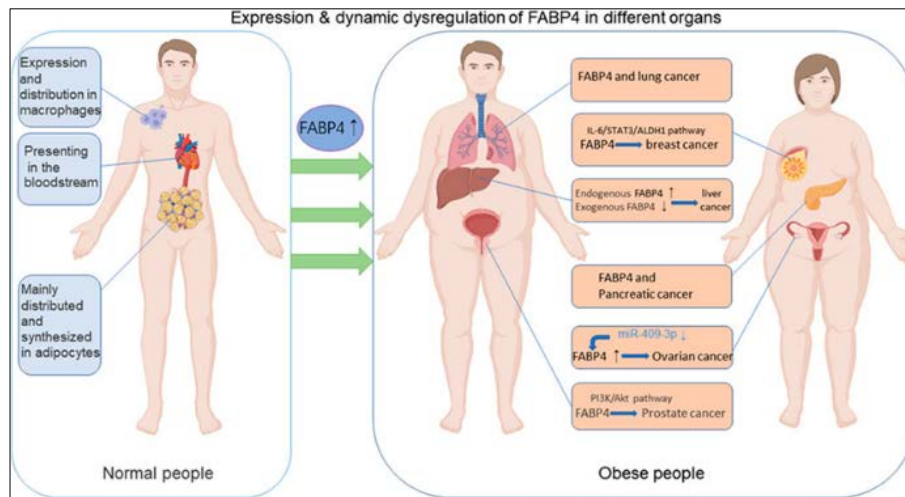


Fig 4: FABP 4 functions in healthy and obese individuals. FABP4 may be released into the bloodstream and is primarily produced and distributed in macrophages and adipocytes. When compared to normal persons, obese people have higher FABP4 levels (Liu *et al.*, 2022) [28].

Insulin Resistance

Insulin resistance refers to the physiological occurrence in which affected tissues exhibit reduced physiological responsiveness to the stimulation of insulin. Insulin resistance can manifest in several tissues possessing insulin receptors, with adipose tissue, skeletal muscle, and the liver being the most prevalent sites of occurrence. Insulin resistance hinders the digestion of glucose, resulting in elevated levels of insulin and an augmentation in the synthesis of insulin by beta cells as a compensatory measure. Insulin resistance is associated with several metabolic consequences, including hyperglycemia, hypertension, dyslipidemia, hyperuricemia, elevated inflammatory markers, endothelial dysfunction, and a prothrombotic state. An elevation in insulin resistance can lead to the development of type 2 diabetes, metabolic syndrome, and nonalcoholic fatty liver disease (NAFLD) (Seong *et al.*, 2019; Brown *et al.*, 2019; Nolan and Prentki, 2019; Deacon, 2019) [48, 5, 35, 10].

Relationship between Fatty acid-binding protein 4 and Insulin Resistance

It is evident that the cytoplasmic fatty acid chaperone fatty acid-binding protein 4 plays a role in the development of insulin resistance (Garin *et al.*, 2014) [19]. FABP4 may be crucial for maintaining glucose homeostasis, according to research done in animal models (Tu *et al.*, 2017) [54]. Mice that had the FABP4 gene deleted were shielded against insulin resistance and hyperinsulinemia, which are linked to hereditary and diet-induced obesity (Tu *et al.*, 2017; Nakamura *et al.*, 2017; Kralisch *et al.*, 2015; Furuhashi *et al.*, 2007; Zhang *et al.*, 2016; Xie *et al.*, 2016) [54, 31, 25, 16, 61].

[57]. Insulin resistance and the development of type 2 diabetes are mostly caused by irregularities in the release of adipokines by adipocytes and a diminished capacity of adipocytes to take up and retain free fatty acids, which results in ectopic lipid buildup (Xie *et al.*, 2016) [57].

FABP4 possesses the capability to initiate complex mechanisms that undermine the effectiveness of insulin communication in specific cellular objectives. Clearly, Fabp4 assumes a vital role in the advancement of insulin resistance, exerting its impact on the obesity-related expression of insulin resistance by carefully adjusting the receptiveness of hormones involved in the release of fatty tissue, while simultaneously producing the direct inhibition of insulin pathways through the initiation of cellular stress reactions. The multifaceted consequences of Fabp4 make it an extremely encouraging therapeutic aim in the continuous battle against obesity (Chung *et al.*, 2021; Dou *et al.*, 2020) [27, 12].

Discussion

Fatty Acid Binding Protein 4 (FABP 4) and Insulin Resistance

Fatty acid-binding protein 4 (FABP 4) and the glucose-disposal rate (GDR) have been shown to be adversely associated (Hsu *et al.*, 2011) [24]. Insulin sensitivity was shown by a negative connection between non-DM individuals' serum FABP concentrations and the mean rate of glucose infusion during the last half-hour of the clamp test. Nakamura *et al.* (Garin-Shkolnik *et al.*, 2014) [19]. Further shown a negative correlation between circulating FABP4 concentrations and GDR, a measure of insulin resistance in skeletal muscle in people with type 2 diabetes.

Conversely, among individuals who were not diabetic, FABP4 concentration was positively correlated with the insulinogenic index. According to Wu *et al.*, (2014) [55], in healthy controls, there was a correlation between circulating FABP4 concentrations and glucose-stimulated insulin secretion.

Garin-Shkolnik *et al.*, (2014) [19] have put out the idea that FABP4's insulinotropic potential is similar to GLP-1's effects. FABP4 may change insulin secretion and activate β cells to preserve glucose homeostasis. Furthermore, FABP4 showed an early positive correlation with insulin secretion in the non-diabetic group, which may be because T2DM causes very early impairment to insulin secretion.

Nakamura *et al.* (Garin-Shkolnik *et al.*, 2014) [16] found the strongest negative correlation between FABP4 and GDR when compared to other markers of insulin resistance and body composition in type 2 diabetes. According to Greco *et al.* (2014), FABP4 has been shown to negatively correlate with GDR in Asian American controls, type 1 diabetes mellitus, and type 2 diabetes. One significant molecule addressing insulin resistance in type 2 diabetes is FABP4.

FABP4 and connections with clinical variables we looked at the connections between lnFABP4 and metabolic variables using Pearson's bivariate correlation analysis (Table1) (Wang *et al.*, 2021) [58].

Table 1: Relationships between HC and Type 2 Diabetes patients' blood lnFABP4 and key metabolic variables (Wang *et al.*, 2021) [58].

Variables	HC		T2D	
	r	P value	r	P value
FPG (mmol/L)	- 0.056	0.604	0.299	0.002
TG (mmol/L)	0.096	0.373	0.066	0.494
TC (mmol/L)	0.010	0.923	- 0.097	0.312
HDLC (mmol/L)	0.023	0.834	- 0.050	0.608
LDLC (mmol/L)	0.247	0.020	- 0.152	0.120
UA (umol/L)	0.022	0.840	0.248	0.011
eGFR (ml/min/1.73 m ²)	0.067	0.232	- 0.127	0.196

Similar observations have been made regarding ailments in which insulin resistance pervades the body, such as non-alcoholic fatty liver disease. This particular condition entails the buildup of fat within the liver due to metabolic complications. It is closely linked to obesity and may culminate in liver impairment and the onset of metabolic syndrome. Through the inhibition of Fabp4, which hinders the accumulation of fat and curbs localized inflammation in the liver, not only does insulin sensitivity witness enhancement, but liver damage is also mitigated (Yang *et al.*, 2021; Yao *et al.*, 2020) [58, 60].

This implies that the potential impact of Fabp4 inhibitors in averting obesity-related ailments among individuals at risk is substantial. Ultimately, the activation of diverse stress pathways can induce insulin resistance. Recent studies propose that Fabp4 can function as a "bridge molecule" that connects biochemical stress signaling with the hindrance of regular insulin activity (Nguyen *et al.*, 2020; Ruszala *et al.*, 2021; Dagpo *et al.*, 2020) [32, 46, 9].

Through the generation of harmful lipid compounds and the promotion of oxidative pressure, Fabp4 possesses the capability to initiate complex mechanisms that undermine the effectiveness of insulin communication in specific cellular objectives. Clearly, Fabp4 assumes a vital role in the advancement of insulin resistance, exerting its impact on the obesity-related expression of insulin resistance by carefully adjusting the receptiveness of hormones involved in the release of fatty tissue, while simultaneously producing the direct inhibition of insulin pathways through the initiation of cellular stress reactions. The multifaceted consequences of Fabp4 make it an extremely encouraging therapeutic aim in the continuous battle against obesity (Chung *et al.*, 2021; Dou *et al.*, 2020) [7, 12].

Fatty Acid Binding Protein 4 and obesity

Numerous studies have observed statistically significant increases in serum FABP4 levels among individuals who are obese (Yang *et al.*, 2023) [59]. For instance, a study conducted in 2012 discovered that fasting serum FABP4

levels were markedly higher in morbidly obese women during the final trimester of pregnancy, in comparison to levels observed in pregnant women who are lean. An interesting finding from this study was that there was a link between FABP4 levels and the number of adipocytes found in fat samples from obese people (Parrettini *et al.*, 2020; Frances *et al.*, 2021) [39, 14].

Similarly, a study published in the International Journal of Endocrinology in 2013 found that serum FABP4 levels were significantly elevated in a cohort of overweight and obese individuals when compared to lean controls. Furthermore, these levels were also significantly associated with other markers of metabolic syndrome and obesity, such as insulin resistance and BMI (Osorio-Conles *et al.*, 2023; Yang *et al.*, 2023) [37, 59].

These observations hold significant value, as they provide further substantiation for a connection between FABP4 and obesity, while also suggesting that FABP4 may serve as a useful biomarker for complications related to obesity. Additionally, some studies have delved into investigating the effects of inhibiting FABP4 in animal models of obesity. For instance, a study featured in the journal Obesity in 2015 explored the impact of a small molecule inhibitor of FABP4 in a murine model of obesity and insulin resistance. The primary findings from this study indicated that inhibiting FABP4 led to a noteworthy decrease in both body weight and fat mass. Furthermore, it also resulted in significant improvements in insulin sensitivity and glucose metabolism. These findings suggest that FABP4 could be a good target for treatments aimed at reducing obesity, since blocking its activity has been linked to better effects for obesity-related outcomes (Balci *et al.*, 2021; Chung *et al.*, 2021; Liu *et al.*, 2022) [3, 7, 28].

Studies investigating Fatty acid-binding protein 4 levels in obese individuals

A 2013 paper by Guaita-Esteruelas *et al.* used a different study population-group of 42 Caucasian subjects, and included in the study, 15 patients were with type 2 diabetes.

The authors have used methods to measure FABP4 levels in the blood, as well as gene expression and protein levels of FABP4 in fat tissue biopsies. The main findings of the paper were that both FABP4 levels in the blood and the gene expressions and proteins of FABP4 in the fat tissues were significantly higher in obese subjects. Additionally, the amount of FABP4 in the blood was linked to how bad insulin tolerance and type 2 diabetes were. It seems that FABP4 from fat tissue is linked to obesity and may also play a role in the development of metabolic diseases by making insulin resistance worse (Gormez *et al.*, 2020) [21] (Osorio- Conles *et al.*, 2023) [37]. Such results may provide new opportunities for therapeutic options for type 2 diabetes and obesity by targeting FABP4.

A 2014 paper by Xu *et al.* studied FABP4 levels and obesity in children. The authors measured the FABP4 levels in the blood of 75 obese children and 25 non-obese children. The children were all aged around 10 years old and all obese children were Chinese in the Shandong province. The authors reported that FABP4 levels were significantly higher in the obese children compared to the non-obese children. Also, FABP4 levels were shown to be strongly correlated with Body Mass Index (BMI) of the children. This may suggest that FABP4 levels in the blood could be a good marker for obesity and more specifically, for the degree of obesity, and further supports the idea that fat tissue-derived FABP4 could be linked to obesity development (Liu *et al.*, 2022) [28].

Conclusion

Large amounts of the intracellular lipid chaperone fatty acid-binding protein 4 (FABP4) are found in adipocytes and macrophages. It has been found that changes in FABP4 levels are linked to cholesterol, oxidative stress, and fat. FABP4 plays a big part in inflammation, insulin resistance, and how fats and starches are broken down.

Several studies have shown that high levels of FABP4 in the blood are linked to obesity and type 2 diabetes (T2DM). The amount of FABP4 in the blood is linked to health effects like body mass index, insulin resistance, and cholesterol. Being aware of this makes it very interesting to try to find effective ways to treat metabolic and circulatory diseases, since the plasma-circulating FABP4 may change the way different types of cells work.

There is a strong link between the FABP4 gene and obesity, as shown by many studies. This result is very important and has been confirmed by many separate studies. It suggests that blocking FABP4 could be a new and effective way to treat many health problems linked to fat. Also, blocking FABP4 seems to improve performance and speed up the process of turning white fat into a more biologically active state.

References

1. Aparecida Silveira E, Vaseghi G, De Carvalho Santos AS, Kliemann N, Masoudkabar F, Noll M, *et al.* Visceral obesity and its shared role in cancer and cardiovascular disease: A scoping review of the pathophysiology and pharmacological treatments. *Int J Mol Sci.* 2020;21(23):9042. Available from: link
2. Avgerinos KI, Spyrou N, Mantzoros CS, Dalamaga M. Obesity and cancer risk: Emerging biological mechanisms and perspectives. *Metabolism.* 2019;92:121-135. Available from: Google Scholar
3. Balci T, Kocabas R, Cuce G, Akoz M. Inhibition of fatty acid binding protein 4 in obese male mice adversely affects reproductive parameters. *J Reprod Infertil.* 2021;22(1):16. Available from: link
4. Bendor CD, Bardugo A, Pinhas-Hamiel O, Afek A, Twig G. Cardiovascular morbidity, diabetes and cancer risk among children and adolescents with severe obesity. *Cardiovasc Diabetol.* 2020;19(1):1-14. Available from: link
5. Brown JC, Harhay MO, Harhay MN. The Value of Anthropometric Measures in Nutrition and Metabolism: Comment on Anthropometrically Predicted Visceral Adipose Tissue and Blood-Based Biomarkers: A Cross-Sectional Analysis. *Nutr Metab Insights.* 2019;12:1178638819831712. Available from: PubMed
6. Cho NH, Shaw JE, Karuranga S, *et al.* IDF diabetes atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract.* 2018;138:271-281. Available from: PubMed
7. Chung JY, Hong J, Kim HJ, *et al.* White adipocyte-targeted dual gene silencing of FABP4/5 for anti-obesity, anti-inflammation and reversal of insulin resistance: Efficacy and comparison of administration routes. *Biomaterials.* 2021;279:121209. Available from: link
8. Chung JY, Hong J, Kim HJ, *et al.* White adipocyte-targeted dual gene silencing of FABP4/5 for anti-obesity, anti-inflammation and reversal of insulin resistance: Efficacy and comparison of administration routes. *Biomaterials.* 2021;279:121209. Available from: link
9. Dago TD, Nolan CJ, Delghingaro-Augusto V. Exploring therapeutic targets to reverse or prevent the transition from metabolically healthy to unhealthy obesity. *Cells.* 2020. Available from: link
10. Deacon CF. Physiology and Pharmacology of DPP-4 in Glucose Homeostasis and the Treatment of Type 2 Diabetes. *Front Endocrinol (Lausanne).* 2019;10:80. Available from: PubMed
11. Dickinson Zimmer JS, Dyckes DF, Bernlohr DA, Murphy RC. Fatty acid binding proteins stabilize leukotriene A4. *J Lipid Res.* 2004;45(11):2138-2144. PubMed
12. Dou HX, Wang T, Su HX, Gao DD, Xu YC, Li YX, *et al.* 2020.
13. Duan B, Li Y, Dong K, Sun Y, Ma A, Yang X. Regulative effect of maternal serum fatty acid-binding protein 4 on insulin resistance and the development of gestational diabetes mellitus. *Prostaglandins Leukot Essent Fatty Acids.* 2020;163:102213. HTML
14. Frances L, Tavernier G, Viguerie N. Adipose-derived lipid-binding proteins: the good, the bad and the metabolic diseases. *Int. J Mol Sci.* 2021;22(19):10460. MDPI
15. Furuhashi M. Fatty Acid-Binding Protein 4 in Cardiovascular and Metabolic Diseases. *J Atheroscler Thromb.* PubMed; c2019.
16. Furuhashi M, Tuncman G, Görgün CZ, Makowski L, Atsumi G, Vaillancourt E, *et al.* Treatment of diabetes and atherosclerosis by inhibiting fatty-acid-binding protein aP2. *Nature.* 2007;447:959-965. Google Scholar
17. Furuhashi M, Ishimura S, Ota H, Miura T. Lipid chaperones and metabolic inflammation. *Int. J Inflamm.* PubMed; c2011. P.1-12.

18. Furuhashi M, Saitoh S, Shimamoto K, Miura T. Fatty Acid-Binding Protein 4 (FABP4): Pathophysiological Insights and Potent Clinical Biomarker of Metabolic and Cardiovascular Diseases. *Clin Med Insights Cardiol.* Pubmed.com. 2015;8(Suppl 3):23-33.
19. Garin-Shkolnik T, Rudich A, Hotamisligil GS, Rubinstein M. FABP4 attenuates PPAR γ and adipogenesis and is inversely correlated with PPAR γ in adipose tissues. *Diabetes.* 2014;63:900-911. PubMed
20. Garin-Shkolnik T, Rudich A, Hotamisligil GS, Rubinstein M. FABP4 attenuates PPAR γ and adipogenesis and is inversely correlated with PPAR γ in adipose tissues. *Diabetes.* 2014;63:900-911. Google Scholar
21. Gormez S, Erdim R, Akan G, Caynak B, Duran C, Gunay D, *et al.* Relationships between visceral/subcutaneous adipose tissue FABP4 expression and coronary atherosclerosis in patients with metabolic syndrome. *Cardiovasc Pathol.* 2020;46:107192.
22. Greco EA, Francomano D, Fornari R, Marocco C, Lubrano C, Papa V, *et al.* Negative association between trunk fat, insulin resistance and skeleton in obese women. *World J Diabetes.* 2013;4:31-39. Google Scholar
23. Hertzog AV, Hellberg K, Reynolds JM, Kruse AC, Juhlmann BE, Smith AJ, *et al.* Identification and characterization of a small molecule inhibitor of Fatty Acid binding proteins. *J Med Chem.* 2009;52(19):6024-31.
24. Hsu WC, Okeke E, Cheung S, Keenan H, Tsui T, Cheng K, *et al.* A cross-sectional characterization of insulin resistance by phenotype and insulin clamp in East Asian Americans with type 1 and type 2 diabetes. *PLoS ONE.* 2011;6:e28311. Google Scholar
25. Kralisch S, Klötting N, Ebert T, Kern M, Hoffmann A, Krause K, *et al.* Circulating adipocyte fatty acid-binding protein induces insulin resistance in mice *in vivo*. *Obesity (Silver Spring).* 2015;23:1007-1013. PubMed
26. Kucharski M, Kaczor U. Fatty Acid Binding Protein 4 (FABP4) and the Body Lipid Balance. *Folia Biologica.* 2017;65(4):181-186. Google Scholar
27. Liu B, Du Y, Wu Y, Snetselaar LG, Wallace RB, Bao W. Trends in obesity and adiposity measures by race or ethnicity among adults in the United States 2011-18: population based study. *BMJ;* c2021.
28. Liu S, Wu D, Fan Z, Yang J, Li Y, Meng Y, *et al.* FABP4 in obesity-associated carcinogenesis: Novel insights into mechanisms and therapeutic implications. *Front Mol Biosci.* 2022;9:973955.
29. Makowski L, Brittingham KC, Reynolds JM, Suttles J, Hotamisligil GS. The fatty acid-binding protein, aP2, coordinates macrophage cholesterol trafficking and inflammatory activity. Macrophage expression of aP2 impacts peroxisome proliferator-activated receptor gamma and IkappaB kinase activities. *J Biol Chem.* Google Scholar. 2005;280:12888-12895.
30. Moreno-Vedia J, Girona J, Ibarretxe D, Masana L, Rodríguez-Calvo R. Unveiling the role of the fatty acid binding protein 4 in the metabolic-associated fatty liver disease. *Biomedicines.* MDPI. 2022;10(1):197.
31. Nakamura R, Okura T, Fujioka Y, Sumi K, Matsuzawa K, Izawa S, *et al.* Serum fatty acid-binding protein 4 (FABP4) concentration is associated with insulin resistance in peripheral tissues, A clinical study. *PLoS ONE.* 2017;12:e0179737. PubMed
32. Nguyen HC, Qadura M, Singh KK. Role of the fatty acid binding proteins in cardiovascular diseases: a systematic review. *J Clin Med;* c2020.
33. Nguyen-Tu MS, Martinez-Sanchez A, Leclerc I, Rutter GA, Da Silva Xavier G. Adipocyte-specific deletion of Tcf7l2 induces dysregulated lipid metabolism and impairs glucose tolerance in mice. *Diabetologia.* 2021;64:129-141. Springer.com
34. Ning H, Tao H, Weng Z, Zhao X. Plasma fatty acid-binding protein 4 (FABP4) as a novel biomarker to predict gestational diabetes mellitus. *Acta Diabetol.* 2016;53(6):891-8. Available from: Google Scholar
35. Nolan CJ, Prentki M. Insulin resistance and insulin hypersecretion in the metabolic syndrome and type 2 diabetes: Time for a conceptual framework shift. *Diab Vasc Dis Res.* 2019;16(2):118-127. Available from: PubMed
36. Okazaki Y, Furuhashi M, Tanaka M, Mita T, Fuseya T, Ishimura S, *et al.* Urinary excretion of fatty acid-binding protein 4 is associated with albuminuria and renal dysfunction. *PLOS ONE.* 2014;9(12):e115429. Available from: PubMed
37. Osorio-Conles Ó, Ibarzabal A, Balibrea JM, Vidal J, Ortega E, de Hollanda A. FABP4 expression in subcutaneous adipose tissue is independently associated with circulating triglycerides in obesity. *J Clin Med.* 2023;12(3):1013. Available from: mdpi.com
38. Ota H, Furuhashi M, Ishimura S, Koyama M, Okazaki Y, Mita T, *et al.* Elevation of fatty acid-binding protein 4 is predisposed by family history of hypertension and contributes to blood pressure elevation. *Am J Hypertens.* 2012;25:1124-30. Available from: Google Scholar
39. Parrettini S, Caroli A, Torlone E. Nutrition and metabolic adaptations in physiological and complicated pregnancy: focus on obesity and gestational diabetes. *Front Endocrinol.* 2020. Available from: frontiersin.org
40. Pei J, Wang B, Wang D. Current studies on molecular mechanisms of insulin resistance. *J Diabetes Res.* 2022;2022:1863429. Available from: NIH
41. Piche ME, Tchernof A, Despres JP. Obesity phenotypes, diabetes, and cardiovascular diseases. *Circ Res.* 2020;126:1477-500. Available from: Google Scholar
42. Powell-Wiley TM, Poirier P, Burke LE, Després JP, Gordon-Larsen P, Lavie CJ, *et al.* Obesity and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation.* 2021;143(21):e984-e1010. Available from: ahajournals.org
43. Prentice KJ, Saksi J, Robertson LT, Lee GY, Inouye KE, Eguchi K, *et al.* A hormone complex of FABP4 and nucleoside kinases regulates islet function. *Nature.* 2021;600(7890):720-726. Available from: NIH
44. Quail DF, Dannenberg AJ. The obese adipose tissue microenvironment in cancer development and progression. *Nat Rev Endocrinol.* 2019;15:139-54. Available from: Google Scholar
45. Rodríguez-Calvo R, Girona J, Alegret JM, Bosquet A, Ibarretxe D, Masana L. Role of the fatty acid-binding protein 4 in heart failure and cardiovascular disease. *J*

- Endocrinol. 2017;233(3):R173-R184. Available from: Google Scholar
46. Ruszała M, Niebrzydowska M, Pilszyk A, Kimber-Trojnar Ź, Trojnar M, Leszczyńska-Gorzela B. Novel biomolecules in the pathogenesis of gestational diabetes mellitus. 2021.
 47. Schwärzler J, Mayr L, Radlinger B, Grabherr F, Philipp M, Texler B, *et al.* Adipocyte GPX4 protects against inflammation, hepatic insulin resistance and metabolic dysregulation. *Int J Obes.* 2022;46(5):951-959. Available from: HTML
 48. Seong J, Kang JY, Sun JS, Kim KW. Hypothalamic inflammation and obesity: a mechanistic review. *Arch Pharm Res.* 2019 May;42(5):383-392. [PubMed]
 49. Shashkin PN, Jain N, Miller YI, Rissing BA, Huo Y, Keller SR, *et al.* Insulin and glucose play a role in foam cell formation and function. *Cardiovasc Diabetol.* 2006;5:13. [PubMed]
 50. Smith PJ, Wise LS, Berkowitz R, Wan C, Rubin CS. Insulin-like growth factor-I is an essential regulator of the differentiation of 3T3-L1 adipocytes. *J Biol Chem.* 1988;263:9402-9408. [Google Scholar]
 51. Stolarczyk E. Adipose tissue inflammation in obesity: A metabolic or immune response? *Curr Opin Pharmacol.* 2017;37:35-40. [Google Scholar]
 52. Tanaka M, Furuhashi M, Okazaki Y, Mita T, Fuseya T, Ohno K, *et al.* Ectopic expression of fatty acid-binding protein 4 in the glomerulus is associated with proteinuria and renal dysfunction. *Nephron.* 2015;128(3-4):345-351. [Google Scholar]
 53. Trojnar M, Patro-Małyśza J, Kimber-Trojnar Ź, Leszczyńska-Gorzela B, Mosiewicz J. Associations between Fatty Acid-Binding Protein 4-A Proinflammatory Adipokine and Insulin Resistance, Gestational and Type 2 Diabetes Mellitus. *Cells.* 2019;8(3):227. [NIH]
 54. Tu WJ, Guo M, Shi XD, Cai Y, Liu Q, Fu CW. First-Trimester Serum Fatty Acid-Binding Protein 4 and Subsequent Gestational Diabetes Mellitus. *Obstet Gynecol.* 2017;130:1011-1016. [Google Scholar]
 55. Wu LE, Samocha-Bonet D, Whitworth PT, Fazakerley DJ, Turner N, Biden TJ, *et al.* Identification of fatty acid binding protein 4 as an adipokine that regulates insulin secretion during obesity. *Mol Metab.* 2014;3:465-473. [Google Scholar]
 56. Xiao Y, Shu L, Wu X, Liu Y, Cheong LY, Liao B, *et al.* Fatty acid binding protein 4 promotes autoimmune diabetes by recruitment and activation of pancreatic islet macrophages. *JCI insight.* 2021;6(7). [PubMed]
 57. Xie X, Yi Z, Sinha S, Madan M, Bowen BP, Langlais P, *et al.* Proteomics analyses of subcutaneous adipocytes reveal novel abnormalities in human insulin resistance. *Obesity (Silver Spring).* 2016;24:1506-1514. [Google Scholar]
 58. Yang H, Deng Q, Ni T, Lu L, Dai H, Wang H, *et al.* Targeted inhibition of LPL/FABP4/CPT1 fatty acid metabolic axis can effectively prevent the progression of nonalcoholic steatohepatitis to liver cancer. *Int J Biol Sci.* 2021;17(15):4207. [NIH]
 59. Yang J, Liu S, Li Y, Fan Z, Meng Y, Zhou B, *et al.* FABP4 in macrophages facilitates obesity-associated pancreatic cancer progression via the NLRP3/IL-1 β axis. *Cancer Lett.* 2023;575:216403. [HTML]
 60. Yao F, Jiang DD, Guo WH, Guo LS, Gao MM, Bai Y, *et al.* FABP4 inhibitor attenuates inflammation and endoplasmic reticulum stress of islet in leptin receptor knockout rats. *Eur Rev Med Pharmacol Sci.* 2020;24(24). [European Review]
 61. Zhang Y, Zhang HH, Lu JH, Zheng SY, Long T, Li YT, *et al.* Changes in serum adipocyte fatty acid-binding protein in women with gestational diabetes mellitus and normal pregnant women during mid- and late pregnancy. *J Diabetes Investig.* 2016;7:797-804. [Google Scholar]
 62. Zhang X, Tu WJ, Wang H, Zhao Q, Liu Q, Sun L, *et al.* Circulating serum fatty acid-binding protein 4 levels predict the development of diabetic retinopathy in type 2 diabetic patients. *Am J Ophthalmol.* 2018;187:71-79. [Google Scholar]
 63. Zhao W, Rasheed A, Tikkanen E, Lee JJ, Butterworth AS, Howson JMM, *et al.* Identification of new susceptibility loci for type 2 diabetes and shared etiological pathways with coronary heart disease. *Nat Genet.* 2017;49:1450-1457. [Google Scholar]
 64. Zhou B, Lu Y, Hajifathalian K, *et al.* Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4*4 million participants. *Lancet.* 2016;387(10027):1513-1530. [Google Scholar]
 65. Zhou H, Zhang Z, Qian G, Zhou J. Omentin-1 attenuates adipose tissue inflammation via restoration of TXNIP/NLRP3 signaling in high-fat diet-induced obese mice. *Fundam Clin Pharmacol.* 2020;34(6):721-735. [HTML]
 66. Zimmer JS, Dyckes DF, Bernlohr DA, Murphy RC. Fatty acid binding proteins stabilize leukotriene A4: Competition with arachidonic acid but not other lipoygenase products. *J Lipid Res.* 2004;45:2138-21.