Adipocyte Fatty Acid-Binding Protein, Cardiovascular Diseases and Mortality

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It has been increasingly recognized that inflammation plays an important role in the pathogenesis of cardiovascular disease (CVD). In obesity, adipose tissue inflammation, especially in the visceral fat depots, contributes to systemic inflammation and promotes the development of atherosclerosis. Adipocyte fatty acid-binding protein (AFABP), a lipid chaperone abundantly secreted from the adipocytes and macrophages, is one of the key players mediating this adipose-vascular cross-talk, in part *via* its interaction with c-Jun NH2-terminal kinase (JNK) and activator protein-1 (AP-1) to form a positive feedback loop, and perpetuate inflammatory responses. In mice, selective JNK inactivation in the adipose tissue significantly reduced the expression of AFABP in their adipose tissue, as well as circulating AFABP levels. Importantly, fat transplant experiments showed that adipose-specific JNK inactivation in the visceral fat was sufficient to protect mice with apoE deficiency from atherosclerosis, with the beneficial effects attenuated by the continuous infusion of recombinant AFABP, supporting the role of AFABP as the link between visceral fat inflammation and atherosclerosis. In humans, raised circulating AFABP levels are associated with incident metabolic syndrome, type 2 diabetes and CVD, as well as non-alcoholic steatohepatitis, diabetic nephropathy and adverse renal outcomes, all being conditions closely related to inflammation and enhanced CV mortality. Collectively, these clinical data have provided support to AFABP as an important adipokine linking obesity, inflammation and CVD. This review will discuss recent findings on the role of AFABP in CVD and mortality, the possible underlying mechanisms, and pharmacological inhibition of AFABP as a potential strategy to combat CVD.

Keywords: cardiovascular disease, adipocyte fatty acid-binding protein, mortality, inflammation, adipokine

INTRODUCTION

Obesity is a global health problem. Based on the data from the World Health Organization (WHO), in 2016, more than 1.9 billion adults aged 18 years or above were overweight, and among them, 650 million were obese (1). In a pooled analysis of 19.2 million participants, the age-standardized prevalence of obesity has tripled in men and doubled in women over the last four decades. If these trends continue, around 1 in 5 of the global population will become obese by year 2025 (2).

Obesity leads to increased risks of type 2 diabetes (3, 4), non-alcoholic fatty liver disease (NAFLD) (5), cardiovascular disease (CVD) (6), cancer (7), and mortality. Indeed, high body mass index (BMI) has become one of the top five leading causes of all-cause mortality and disability-adjusted life-years (8). In 2015, high BMI contributed to 7.1% of global deaths. Strikingly, CVD accounted for two-thirds of these deaths and more than half of disability-adjusted life-years related to high BMI (9). Recently, in a Mendelian randomization (MR) study involving more than 360,000 participants from the UK Biobank, each genetically instrumented increase in BMI of 1 kg/m^2 was associated with a significantly higher risk of most cardiovascular outcomes including hypertension, atrial fibrillation, coronary heart disease (CHD), heart failure and peripheral vascular disease (PVD) (10). Genetically predicted fat mass index was associated with an even broader list of cardiovascular outcomes including ischemic stroke. These findings corroborated with another large MR study which demonstrated the causal effects of adiposity on CVD (11). Taken together, both observational and MR studies provided strong epidemiological evidence that obesity, in particular central adiposity, is closely linked with CVD and cardiovascular mortality.

Inflammation, on the other hand, is an established important risk factor of CVD and cardiovascular mortality (12). Previous observational studies had demonstrated that markers of inflammation such as C-reactive protein (CRP) and tumor necrosis factor alpha (TNF-α) receptor 1 were independent prognostic markers of adverse cardiovascular outcomes among individuals with and without prevalent CVD (13, 14). Recently, the use of Canakinumab, an anti-inflammatory monoclonal antibody targeting interleukin-1, was also shown in a randomized controlled trial to significantly reduce the incidence of non-fatal myocardial infarction, non-fatal stroke and cardiovascular death, confirming that inflammation plays a crucial role in the pathogenesis of CVD (15). Obesity is a state of chronic low-grade systemic inflammation, which is induced by a cascade of cellular events that occur in the dysfunctional adipose tissue, and perpetuated by dysregulated secretion of adipokines through their local and systemic actions (16). This review will focus on adipocyte fatty acid-binding protein (AFABP) and present the recent data on its role as an important adipokine linking obesity, inflammation and CVD.

AFABP EXPRESSION AND SECRETION

AFABP is a major cytosolic protein of the mature adipocytes (17). As a fatty acid binding protein, it acts as a lipid chaperone that facilitates the trafficking of non-esterified fatty acids throughout cellular compartments such as peroxisome, endoplasmic reticulum (ER), mitochondria and nucleus (18). AFABP also regulates lipid storage and oxidation, and is involved in lipolysis though its interaction with the hormone-sensitive lipase (HSL) and a co-activator of adipose triglyceride lipase (ATGL) (19, 20). The expression of AFABP in adipocytes is induced during adipocyte differentiation, and is transcriptionally activated by fatty acids, glucocorticoids, cyclic adenosine monophosphate (cAMP), and peroxisome proliferator-activated receptor gamma (PPARγ) agonists (21–23).

Studies in recent years have shown that AFABP is secreted from the adipocytes, and circulates in the blood stream in both mice and humans (24) (25). However, since it lacks a signal peptide sequence for classical secretory pathway (25), it has recently been reported that AFABP is secreted unconventionally *via* endosomes and secretory lysosomes in response to lipolytic and fasting related signals, such as adrenergic signaling, beta agonists, branched-chain amino acids and glycerol (25, 26), and the involvement of sirtuin-1 activation has been implicated (27). While it is also expressed in the macrophages (28) and endothelial cells (29), *in vivo* data suggest that the adipocyte is the predominant contributor to circulating AFABP levels (25).

AFABP IN RELATION TO ADIPOSE TISSUE INFLAMMATION AND INSULIN RESISTANCE IN OBESITY

AFABP secretion is dysregulated in obesity, with raised circulating AFABP concentrations being found in obese individuals (24). With chronic nutrient excess, pathological expansion of the adipose tissue causes several maladaptive changes especially in the visceral fat depots. Hypertrophic adipocytes undergo high rates of spontaneous lipolysis (30), which increases free fatty acid (FFA) efflux and stimulates AFABP release. Lipo-toxicity ensues as lipid intermediates such as ceramides and diacylglycerols accumulate. Moreover, adipocyte hypoxia and cell death develop as a consequence of its continuous expansion despite relative under-perfusion and increased mechanical stress (31), and hypoxia is another known stimulus for AFABP release from adipocytes (32). On the other hand, AFABP (33), as a lipid chaperone, has been implicated in ER stress in response to lipotoxic signals, leading to activation of stress kinases such as nuclear factor kappa B (NFκB) and c-Jun NH2-terminal kinase (JNK) (34), enhancing adipocyte insulin resistance that potentiates lipolysis and lipotoxicity. Adipocyte insulin resistance also augments the secretion of pro-inflammatory cytokines including the chemokine monocyte chemoattractant protein 1 (MCP1) (35), which stimulates the recruitment of macrophages into the adipose tissue (36). Furthermore, it induces a phenotypic switch in the macrophages from the anti-inflammatory M2 polarized state to the pro-inflammatory phenotype typical of M1 classical inflammation in metabolically-activated macrophages (MMe) (37, 38).

Both innate and adaptive immunity are activated in obesity. In addition to macrophage infiltration, adaptive immune cells including CD4+ T helper (Th1) cells, CD8+ T cells and B cells also accumulate in the visceral adipose tissue (39). Transient enhancement of AFABP expression has been reported in murine splenic lymphocytes after dexamethasone administration (40). However, among the major human leucocyte subsets, the

expression of AFABP is largely restricted to the macrophages and myeloid dendritic cells (DC) (41). Specifically, owing to its high expression in the macrophages (28), AFABP is more closely linked with the innate immune cells. It has been shown that AFABP perpetuates lipopolysaccharide (LPS)-induced inflammatory responses in macrophages through its interaction with JNK and activator protein-1 (AP-1) forming a positive feedback loop. Upon stimulation by LPS *via* toll like receptor 4 (TLR4), JNK is activated, leading to the induction of c-Jun phosphorylation and its recruitment to a highly conserved AP-1 consensus binding motif located within the AFABP gene promoter. As a result, AFABP gene transcription is upregulated, which further potentiates LPS-induced JNK phosphorylation, activation of AP-1 complex and amplification of pro-inflammatory responses in the macrophages (42). Nonetheless, AFABP can also affect adaptive immunity through the modulation of DC responses. NFκB activation is impaired in AFABP deficient DCs, which exhibit reduced DC function in T cell priming and cytokine production (41). Recently, AFABP was also found to be upregulated in a subpopulation of tissue-resident memory CD8+ T cells which have high requirement for fatty acid metabolism. Importantly, the lack of AFABP in these cells could negatively impact their survival and hence attenuate their function in protective immunity (43). In a viral infection model, mice with genetic deficiency of AFABP had decreased interferon gamma production and increased viral load (41). However, in a rodent model of sepsis, pharmacological inhibition of AFABP in fact was demonstrated to be beneficial, with attenuation of sepsis-triggered inflammatory responses, reduced hepatic and pulmonary tissue injury, as well as improved survival (44).

Taken together, these studies highlight the close and complex relationship between AFABP and cellular immunity.

In the adipose tissue, infiltration of these immune cells drives further release of pro-inflammatory adipokines including TNF-α, interleukin-6 (IL-6) and AFABP, and reduces the secretion of the anti-inflammatory adipokine adiponectin. Increased AFABP secretion induces further lipolysis and inflammation in the adipocytes *via* the p38/mitogen-activated protein kinase (MAPK) pathway (45), and contributes to this vicious cycle of adipose tissue insulin resistance and inflammation (46) (**Figure 1**). Whole-body insulin sensitivity was ultimately impaired, accompanied by a chronic state of subclinical systemic inflammation, and the development of an array of obesity-related complications including CVD and cardiovascular mortality (**Table 1**).

AFABP AND CARDIOVASCULAR RISK FACTORS

The detrimental role of AFABP on the development of CVD begins with its effects on traditional cardiovascular risk factors in addition to excess adiposity. AFABP-deficient mice displayed improved glycemia, insulin sensitivity and lipid metabolism in both dietary and genetically induced obesity (47, 48), secondary to a reduced FFA efflux and increased glucose utilization in muscles (49). Moreover, AFABP increases the hepatic expression of gluconeogenic enzymes phosphoenolpyruvate carboxylase 1 (*Pck1*) and glucose-6-phosphatase (*G6pc*), leading to enhanced hepatic glucose production and impaired glucose metabolism (25).
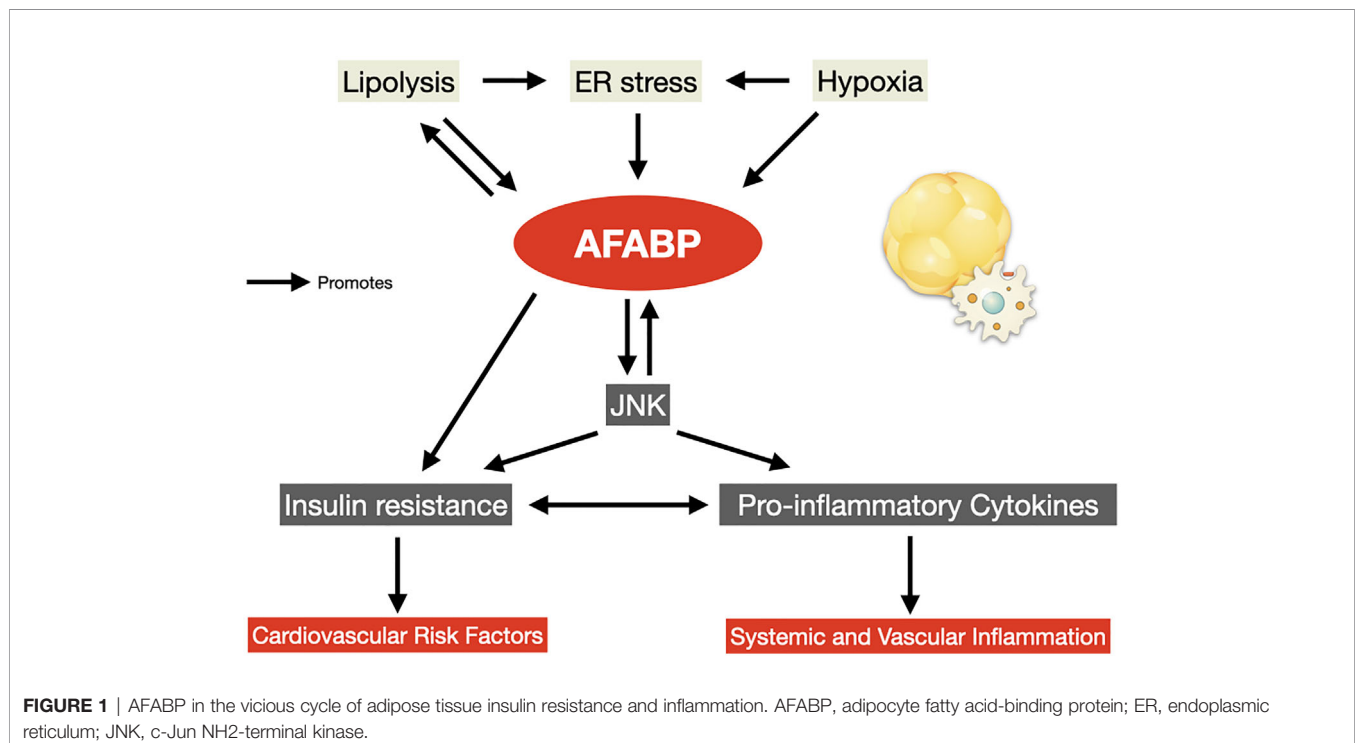

FIGURE 1 | AFABP in the vicious cycle of adipose tissue insulin resistance and inflammation. AFABP, adipocyte fatty acid-binding protein; ER, endoplasmic reticulum; JNK, c-Jun NH2-terminal kinase.

TABLE 1 | Associations of AFABP with cardiometabolic conditions.

	Circulating AFABP level	Potential mechanistic actions	References
Type 2 diabetes	• Predicts the development of type 2 diabetes	• Increases free fatty acid efflux • Reduces glucose utilization in muscles • Increases hepatic expression of gluconeogenic enzymes	(25, 47–51)
Hypertension	• Correlates positively with blood pressure	• Increases endothelial dysfunction • Worsens insulin sensitivity	(47, 48, 50, 52)
Dyslipidemia	• Correlates positively with low-density lipoprotein cholesterol • Correlates negatively with high-density lipoprotein cholesterol	• Increases free fatty acid efflux • Negative effects on lipid metabolism • Worsens insulin sensitivity	(47, 48, 50)
Coronary heart disease	• Predicts the development of cardiovascular diseases • Associates with coronary calcium score in patients with type 2 diabetes • Associates with the coronary plaque burden in patients with coronary heart disease	• Promotes atherosclerosis development: • Alters lipid metabolism in macrophages and facilitates foam cell formation • Promotes saturated fatty acid-induced ceramide production in macrophages • Mediates toxic lipids-induced endoplasmic reticulum stress in macrophages • Increases adipose tissue and systemic inflammation	(33, 53–60)
Stroke	• Associates with the presence of carotid atherosclerosis • Correlates positively with the vulnerable carotid plaque phenotype • Doubles the risk of incident adverse cardiovascular events including cardiovascular mortality, non-fatal myocardial infarction and non-fatal stroke. • Predicts poor functional outcome and mortality from ischemic stroke	• Promotes atherosclerosis development (as above) • Enhances the production of matrix metalloproteinases-9 which degrade the tight junction proteins in the blood brain barrier, leading to cerebral edema, increased neuro-inflammation and poor neurological outcomes	(61–68)
Heart failure	• Correlates positively with circulating levels of N-terminal fragment of pro-B-type natriuretic peptide • Associates with the presence of left ventricular systolic and/or diastolic dysfunction • Associates with increasing severity of clinical heart failure • Predicts incident heart failure among older individuals	• Negative inotropic effect on cardiomyocytes • Reduces phosphorylation of endothelial nitric oxide synthase in acute myocardial ischemia/reperfusion injury • Increases oxidative stress and cardiac inflammation • Increases cardiac hypertrophy and fibrosis	(52, 69–75)
Cardiovascular mortality	• Associates with both short- and long-term cardiovascular morbidity and mortality in patients with established coronary heart disease • Predicts cardiovascular deaths in patients with type 2 diabetes	• See above	(76–80)

In humans, circulating AFABP concentrations also correlate positively with adverse cardiometabolic risk factors including age, obesity indices, hypertension, homeostatic model of insulin resistance (HOMA-IR), low-density lipoprotein cholesterol (LDL-C), and negatively with high-density lipoprotein cholesterol (HDL-C) (50). Moreover, high circulating AFABP concentrations predicted incident metabolic syndrome and type 2 diabetes, both of which are associated with increased risks of CVD and mortality (50, 51).

AFABP AND ATHEROSCLEROSIS

AFABP promotes atherosclerosis, the central event in the pathogenesis of CVD (81). Bone marrow transplant experiments revealed that macrophage-specific AFABP deficiency reduced atherosclerotic lesions in mice with apolipoprotein E (ApoE) deficiency, to a similar extent as those with whole body AFABP deficiency, suggesting that much of the pro-atherogenic effects of AFABP are specific to its actions in macrophages (28). The expression of AFABP in macrophages can be upregulated in response to oxidized LDL (oxLDL) and LPS (82, 83), which are both increased in obesity (84, 85). On the other hand, metformin has been shown to inhibit AFABP expression in macrophages (86). AFABP alters lipid metabolism in macrophages and facilitates the formation of

foam cell enriched with cholesterol and triglyceride (53, 54). AFABP also promotes macrophage cell death through saturated fatty acid-induced ceramide production (55). Moreover, AFABP has been shown as an obligatory mediator of toxic lipids-induced ER stress in macrophages, through inhibiting liver X receptor alpha (LXRα) to reduce macrophage *de novo* fatty acid synthesis which confers resistance to ER stress (33), as well as impairing macrophage autophagy by attenuation of Janus Kinase 2 (JAK2) activity (87). The elevated ER stress potentiates JNK activation and further exacerbates inflammation.

However, there was recent evidence suggesting that the negative impact of AFABP on atherosclerosis was not exclusively due to its action in the macrophages. In mice, selective JNK inactivation in the adipose tissue significantly reduced both the expression of AFABP in their adipose tissue, as well as circulating AFABP levels. Importantly, fat transplant experiments showed that adipose-specific JNK inactivation in the visceral fat was sufficient to protect mice with apolipoprotein E (ApoE) deficiency from atherosclerosis, with the beneficial effects attenuated by the continuous infusion of recombinant AFABP, supporting the participation of adipocyte-derived AFABP as a link between visceral fat inflammation and atherosclerosis (56).

In humans, elevated baseline AFABP concentration predicted incident CVD over a median follow-up of around 10 years in a community-based cohort (57). Moreover, high circulating

AFABP concentration was associated with coronary calcium score in patients with type 2 diabetes (58), as well as the coronary plaque burden in patients with coronary heart disease (59). In keeping with observations from preclinical studies, AFABP was not only expressed in macrophages within atherosclerotic plaques of the coronary arteries in patients with CHD, but also in both macrophages and adipocytes in their epicardial and perivascular fat. *In vitro* studies showed that treatment of human coronary artery smooth muscle and vascular endothelial cells with AFABP augmented palmitic acid-induced inflammation, suggesting that AFABP from epicardial and perivascular fat could also participate in the development of coronary atherosclerosis in a paracrine manner (60). Furthermore, individuals who harbored the single nucleotide polymorphism (SNP) T-87C, which reduced AFABP gene expression in their adipose tissue, was found to have a lower risk of CHD (88).

AFABP AND STROKE

The role of AFABP in the development of stroke is multifaceted. First, high circulating AFABP concentration was associated with the presence of carotid atherosclerosis (61, 62), a predisposing condition for cerebral infarction. In patients with carotid atherosclerosis, AFABP concentrations in their carotid plaques correlated positively with the vulnerable plaque phenotype (63, 64), predicted their disease progression (89), and doubled their risk of incident adverse cardiovascular events including cardiovascular mortality, non-fatal myocardial infarction and non-fatal stroke (64). Moreover, circulating AFABP concentration was associated with ischemic stroke in cross-sectional studies, and high AFABP concentration was consistently shown to be predictive of poor functional outcome, as well as short- and long-term mortality in patients who suffered from ischemic stroke (62, 65–67).

Mechanistically, genetic ablation of AFABP in mice was recently found to protect them from severe cerebral ischemic injury induced by surgical occlusion of their middle cerebral artery, which translated to less neurological deficits and improved survival after ischemic stroke. Both circulating and cerebral AFABP concentrations were elevated in response to cerebral ischemia. The increase in AFABP, derived from microglia and infiltrating macrophages, enhanced the production of matrix metalloproteinases-9 (MMP-9) through JNK activity, which degraded the tight junction proteins in the blood brain barrier, leading to cerebral edema, increased neuro-inflammation and poor neurological outcomes (68).

AFABP, HEART FAILURE, AND CARDIOVASCULAR MORTALITY

AFABP plays a critical role in the development of heart failure and predisposes to increased cardiovascular mortality. *In vitro* studies demonstrated that adipocyte-derived AFABP possessed a negative inotropic effect on rat cardiomyocytes and could inhibit their contraction (69). In humans, circulating AFABP concentration positively correlated with circulating levels of N-terminal fragment of pro-B-type natriuretic peptide (NT-proBNP), an established marker of heart failure (70). Moreover, high circulating AFABP concentration was associated with the presence of left ventricular systolic and/or diastolic dysfunction (71–73), as well as increasing severity of clinical heart failure (74). In the Cardiovascular Health Study, circulating AFABP concentration was also shown to be a modest but independent predictor of incident heart failure among older individuals (75).

The negative impact of AFABP on cardiovascular outcomes could also be attributed to their effects on endothelial dysfunction and oxidative stress. Genetic ablation of AFABP protected mice from cardiac dysfunction secondary to diabetes and myocardial ischemia/reperfusion (MI/R) injury. AFABP, whose expression was upregulated in cardiac endothelial cells in response to acute MI/R injury and hyperglycemia, reduced phosphorylation of endothelial nitric oxide synthase (eNOS) in acute MI/R injury, and increased superoxide anions in diabetes. In both situations, endothelial dysfunction ensued, which induced oxidative stress and cardiac inflammation, leading to cardiac hypertrophy, fibrosis and impaired myocardial contractility (52). Indeed, in keeping with findings from studies in mice, high circulating AFABP concentration was associated with both short- and long-term cardiovascular morbidity and mortality in patients with established CHD (76–78),and was an independent predictor of cardiovascular deaths in patients with type 2 diabetes (79, 80).

AFABP AND OTHER OBESITY-RELATED CONDITIONS WITH INCREASED CARDIOVASCULAR RISK

AFABP is also implicated in the pathogenesis of several obesity-related complications with increased cardiovascular risk, such as NAFLD, obstructive sleep apnea (OSA) and chronic kidney disease (CKD) (90–92). In NAFLD, for instance, over-expression of AFABP in Kupffer cells of the liver induced non-alcoholic steatohepatitis in mice, while obesity-induced liver injury was alleviated by pharmacological inhibition of AFABP (93). Similar findings had been observed in humans, where circulating AFABP concentration was associated with increasing lobular inflammation, hepatocyte ballooning and higher stages of hepatic fibrosis on liver histology (94). On the other hand, elevated serum AFABP concentration was also found in patients with severe OSA compared with those with milder disease (95, 96), and the use of continuous positive airway pressure was shown to reduce circulating AFABP concentrations in a recent randomized controlled study (97). Moreover, circulating AFABP was associated with adverse renal outcomes including renal deaths in patients with type 2 diabetes (98), which could possibly be a result of macrophage infiltration in the glomerulus and interstitium, ectopic expression of AFABP in the glomerulus, as
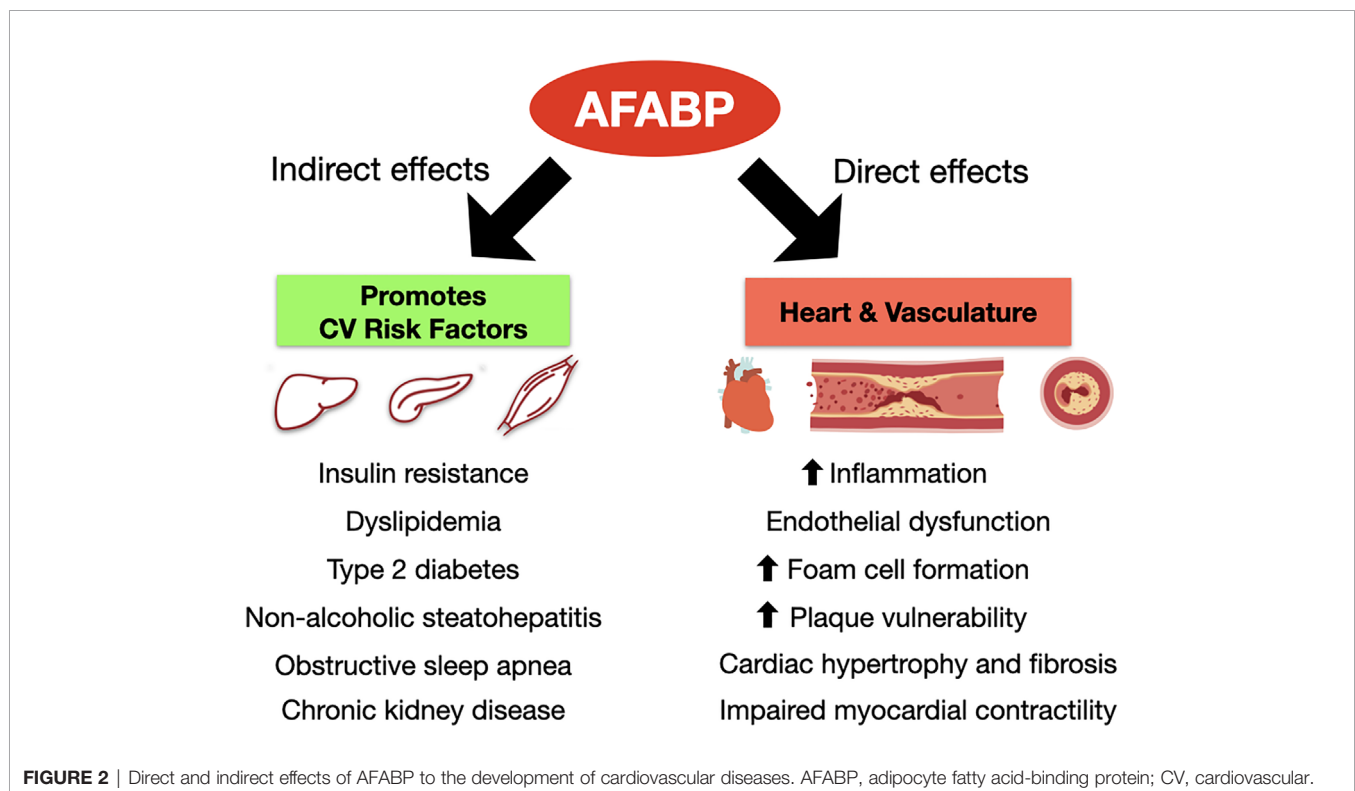
well as AFABP induced increased ER stress in the mesangial cells (99–101). Importantly, high circulating AFABP concentration was also an independent predictor of cardiovascular death in patients with end-stage renal disease (102).

AFABP AS A THERAPEUTIC TARGET FOR CVD

Preclinical studies have demonstrated that there is great potential in targeting AFABP as a therapeutic strategy to combat CVD and its risk factors. Several AFABP inhibitors have been developed, including a few biphenyl azole, indole- and carbazole-based compounds. In particular, BMS309403 (BMS) is a selective, high-affinity small molecule oral inhibitor of AFABP which impedes the ligation of fatty acid to its binding cavity on AFABP (103). Pharmacological inhibition of AFABP using BMS alleviated endothelial dysfunction and atherosclerosis in mice with ApoE deficiency. This was accompanied by reduced cholesterol ester accumulation in macrophages, as well as attenuated expression of pro-inflammatory cytokines including MCP1, IL-6 and TNFα (104, 105). Recently, BMS was also shown to improve stroke outcomes by ameliorating neurological deficits and improving the survival in mice with cerebral ischemic injury after surgical occlusion of their middle cerebral artery (68). Moreover, BMS attenuated non-alcoholic steatohepatitis (93), improved glucose tolerance (105) and decreased toxic lipid-induced ER stress associated inflammation in the skeletal muscle of mice with dietary

obesity (106). Another small molecule inhibitor HTS01037, which acts as a competitive antagonist of AFABP mediated protein-protein interactions (107), was shown to alleviate macrophage inflammation and ER stress through upregulating uncoupling protein 2 (UCP2) expression (108). In addition to these oral compounds, alternative approaches of AFABP inhibition have also been investigated. The use of neutralizing antibodies against AFABP was demonstrated to significantly reduce adipose tissue inflammation (34), hepatic glucose production (25), and whole-body insulin resistance in obese mice (109). Likewise, adipocyte targeted silencing of AFABP using short-hairpin RNA treatment resulted in significant weight reduction, improved insulin sensitivity and glycemia in obese mice (110).

Although clinical studies of both BMS and neutralizing antibodies are still not available, several compounds have been found to modulate circulating AFABP concentrations. Treatment with chloroquine in mice diminished AFABP secretion from adipocytes, resulting in a lower circulating concentration (26). In humans, atorvastatin (111), sitagliptin (112), omega-3 fatty acids (113), and angiotensin II receptor blockers (ARBs) including candesartan, olmesartan, telmisartan and valsartan (114) decreased, whereas pioglitazone (115) and canagliflozin increased circulating AFABP concentrations (116). While omega-3 fatty acids and pioglitazone directly affect AFABP expression in adipocytes, it was postulated that ARBs suppressed and canagliflozin promoted catecholamines-induced lipolysis, respectively, causing the changes in the circulating AFABP concentrations despite neutral, if not favorable effects

FIGURE 2 | Direct and indirect effects of AFABP to the development of cardiovascular diseases. AFABP, adipocyte fatty acid-binding protein; CV, cardiovascular.

of ARB and sodium glucose co-transporter 2 inhibitors on adiposity (114, 116).

CONCLUSION

Obesity has reached pandemic levels, and so has CVD. Adipose tissue inflammation with dysregulated adipokine secretion is crucial to the pathogenesis of adverse cardiovascular outcomes in obesity. Recent mechanistic and epidemiological studies have provided further insights to support AFABP as a key player mediating this adipose-vascular cross-talk *via* direct and indirect effects (**Figure 2**). However, from a clinical perspective, further validation studies are certainly required to investigate the potential of employing AFABP as a promising marker of CVD and cardiovascular mortality for clinical application. Moreover, standardization of commercial AFABP ELISA assays is also equally important. On the other hand, while preclinical studies

have clearly demonstrated AFABP as an attractive therapeutic target in battling against CVD, intervention studies to evaluate the efficacy and safety of pharmacological inhibitors of AFABP and/or neutralizing antibodies in humans are eagerly awaited. In summary, although it may still be a long way before its clinical application as a biomarker or therapeutic target, research in recent years have clearly shown that AFABP is another major adipokine linking obesity with inflammation and adverse cardiovascular outcomes.

AUTHOR CONTRIBUTIONS

C-HL researched the data and wrote the manuscript. DL and KL critically reviewed and edited the manuscript. KL initiated and conceptualized this review and is the guarantor of this work. All authors contributed to the article and approved the submitted version.

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