Lipids in Health and Disease

REVIEW

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Interplay of fatty acids, insulin and exercise in vascular health

Kara C. Anderson[1†], Jia Liu[1†] and Zhenqi Liu[1*]

Abstract

Fatty acid metabolism, exercise, and insulin action play critical roles in maintaining vascular health, especially relevant in metabolic disorders such as obesity, type 2 diabetes, and cardiovascular disease. Insulin, a vasoactive hormone, induces arterial vasodilation throughout the arterial tree, increasing arterial compliance and enhancing tissue perfusion. These effects, however, are impaired in individuals with obesity and type 2 diabetes, and evidence suggests that vascular insulin resistance contributes to the pathogenesis of type 2 diabetes and its cardiovascular complications. Elevated plasma levels of free fatty acids in people with insulin resistance engender vascular inflammation, endothelial dysfunction, and vascular insulin resistance. Importantly, these effects are both functionally and structurally dependent, with saturated fatty acids as the primary culprits, while polyunsaturated fatty acids may support insulin sensitivity and endothelial function. Exercise enhances fatty acid oxidation, reduces circulating free fatty acids, and improves insulin sensitivity, thereby mitigating lipotoxicity and promoting endothelial function. Additionally, exercise induces beneficial vascular adaptations. This review examines the complex interplay among fatty acid metabolism, exercise training-induced vascular adaptations, and insulin-mediated vascular changes, highlighting their collective impact on vascular health and underlying mechanisms in both healthy and insulin-resistant states. It also explores the therapeutic potential of targeted exercise prescriptions and fatty acid-focused dietary strategies for enhancing vascular health, emphasizing tailored interventions to maximize metabolic benefits. Future research should investigate the pathways linking fatty acid metabolism to vascular insulin resistance, with a focus on how exercise and dietary modifications can be personalized to enhance vascular insulin sensitivity, optimize vascular health, and reduce the risks of type 2 diabetes and associated cardiovascular complications.

Keywords Endothelial function, Exercise, Fatty acid metabolism, Insulin resistance, Lipotoxicity, Nitric oxide, Tissue perfusion, Type 2 diabetes, Vascular inflammation

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Introduction

e global rise in the prevalence of type 2 diabetes (T2D) and the associated cardiovascular disease (CVD) morbidity and mortality has made the study of metabolic health and vascular function increasingly critical. Most people with T2D have increased adiposity, elevated plasma free fatty acids (FFAs) and hypertension in addition to dysglycemia [1–3], and eventually succumb to the vascular (both microvascular and macrovascular) complications [4]. Insulin is an anabolic hormone that regulates carbohydrate, protein, and lipid metabolism. Importantly, insulin is also a potent vasoactive hormone and actively modulates vascular tone and tissue perfusion, and vascular insulin resistance has been linked to the pathogenesis of T2D and the associated cardiovascular complications [5–8]. FFAs are essential for normal cellular function and play a pivotal role in the regulation of metabolic homeostasis, not only by serving as key energy sources and cellular structural components, but also critically modulating metabolic signaling pathways, including insulin secretion and action. However, excess availability of fatty acids, especially the saturated fatty acids (SFAs), can disrupt insulin signaling and glucose metabolism and lead to insulin resistance and higher risk of developing T2D and the associated CVD complications [9–11]. e impact of FFAs on insulin action and substrate metabolism is structure and concentration dependent, where polyunsaturated fatty acids (PUFAs) have been shown to enhance insulin sensitivity and attenuate glucose intolerance, and SFAs are linked to insulin resistance and metabolic dysfunction [12]. Exercise plays a foundational role in human health, signi cantly in uencing insulin sensitivity, fatty acid metabolism, and vascular function, and remains one of the most e ective non-pharmacological interventions for T2D prevention and management [13–16]. is review explores the intricate relationship among insulin action, fatty acid metabolism, and exercise in metabolic homeostasis and vascular function, with a hope of not only to ll the literature gap but also provide guidance on future studies.

Insulin action and resistance in the vasculature – implications for metabolic abnormalities and CVD

Insulin is an anabolic as well as a vasoactive hormone. It actively modulates vascular tone to regulate tissue perfusion and insulin's vascular actions closely couple with its metabolic actions [17]. Vascular endothelium expresses abundant insulin receptors as well as the insulin-like growth factor I (IGF-1) receptors and the hybrid insulin/IGF-1 receptors [18–22]. At physiological concentrations, insulin binds and activates the insulin receptors exclusively, but at supra-physiological or pharmacological concentrations, insulin also stimulates the IGF-1 receptors and the hybrid insulin/IGF-1 receptors [18]. In the vasculature, insulin signals mainly through the phosphatidylinositol 3-kinase (PI3K) / Protein kinase B (Akt) / endothelial nitric oxide (NO) synthase (eNOS) pathway to produce NO, which is a potent vasodilator [18, 19, 23, 24], and the mitogen-activated protein kinase (MAPK) / extracellular signal regulated kinase (ERK) pathway to mediate endothelial cell proliferation and the expression and secretion of a vasoconstrictor endothelin-1 (ET-1). ET-1 acts on the G protein-coupled endothelin receptors, mainly the ET_A and ET_B subtypes, to engender vasoconstriction, oxidative stress, and vascular smooth muscle cell growth and mitogenesis [25–29]. Insulin exerts actions on all segments of the arterial system, including the conduit arteries, the resistance arterioles, and the microvasculature [30–32]. As each segment of the arterial tree has di erent structure and function, the results of insulin's actions on the vasculature vary depending on the arterial size and location (Fig. 1) [2, 8, 13, 33].

Conduit arteries are large arteries containing collagen and elastin laments in the tunica media and expand in response to cardiac ejection to maintain a relatively constant pressure in the arteries [34]. Insulin infusion in healthy humans enhances the responsiveness of the femoral artery to methacholine-induced vasodilation [35] and decreases augmentation index (AI) (i.e., increased distensibility / compliance) [30, 36, 37]. e resistance arterioles, which range from 400 μm to 100 μm, are the major determinant of vascular resistance and total tissue blood ow [38]. Insulin infusion dilates resistance arterioles, and results in decreased vascular resistance and increased total tissue blood ow in humans [35, 39–43].

e microvasculature, including small arterioles, capillaries, and small venules, plays a pivotal role in maintaining tissue health by delivering adequate supply of oxygen, nutrients, and hormones to the tissues and removing metabolic waste and by-products away from the tissues. Over the past two decades, the actions of insulin on the microvasculature have garnered high attention as numerous studies have con rmed that muscle microvasculature is an insulin target, insulin is an important physiological modulator of muscle microvascular perfusion, and there is a close coupling between insulin-mediated microvascular perfusion and insulin-stimulated glucose disposal in the skeletal muscle [5, 17]. Insulin-mediated muscle microvascular recruitment occurs within 5–10 min and this precedes insulin-stimulated glucose disposal in muscle which occurs in ~20–30 min, and inhibition of NO synthesis during insulin infusion via eNOS inhibition abolishes insulin-induced microvascular recruitment in muscle and reduces insulin-stimulated muscle glucose disposal by up to 40% [44, 45].

Insulin's actions on di erent arterial segments are interconnected either directly or indirectly. We have

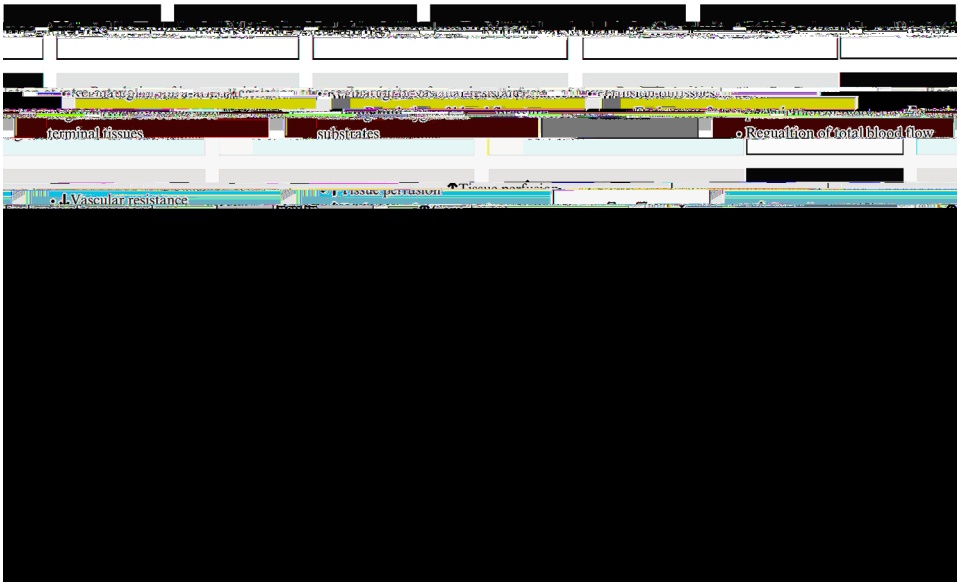

Fig. 1 Vascular function and the impact of insulin and exercise. Vascular function varies depending on vessel size and location. Insulin and exercise lead to bene□cial e□ects throughout the vasculature, while insulin resistance and endothelial dysfunction impair vascular function. (Abbreviations: FMD, □ow mediated dilation; PWV, pulse wave velocity; AI, augmentation index)

previously shown that insulin-enhanced ow-mediated dilation (FMD) is independently associated with insulin-mediated microvascular perfusion in muscle [2]. is is important as FMD re ects endothelial function mainly in the conduit artery (with some component of resistance arterioles) and microvascular perfusion is mostly controlled by resistance and microvascular arterioles. is is also not surprising as both FMD and insulin-mediated microvascular perfusion are predominately NO-dependent [46–48]. In healthy humans and adults with metabolic syndrome, there is a clear correlation between FMD and insulin-mediated glucose disposal during the insulin clamp [31] while insulin-stimulated glucose disposal and insulin-mediated changes in microvascular perfusion are mutually predictive in a cohort including healthy, obese, and type 1 diabetes populations [49].

It has been well-documented that insulin resistance can occur in all segments of the arterial tree, and vascular insulin resistance typically co-exists with endothelial dysfunction and metabolic insulin resistance. Insulin's vasodilatory action in the conduit arteries and resistance arterioles is clearly impaired in insulin resistant conditions [31, 35, 50] and people with T2D frequently have both impaired endothelium-dependent FMD [51] and reduced insulin-mediated NO-dependent vasodilation [41, 52]. In humans with obesity or metabolic syndrome, there is a marked resistance of the ability of insulin to decrease arterial sti ness [50, 53]. is is very important as reduced compliance of the conduit arteries independently predicts atherosclerotic coronary and cerebral artery diseases [53–56]. Mounting evidence con rms that insulin-mediated microvascular perfusion in cardiac and skeletal muscle is lost in insulin resistant conditions like obesity and metabolic syndrome [31, 57, 58]. Vascular insulin resistance is also present in the microvasculature in insulin resistant states, and there is clear evidence of generalized microvascular dysfunction in people with prediabetes or T2D [59]. Impaired insulin-mediated microvascular perfusion has been seen in obese and diabetic animals [60, 61], humans with T2D [62], and humans with obesity [58, 63]. Insulin resistance at the microvasculature level appears to be more closely coupled with metabolic insulin resistance as the microvasculature plays a pivotal role in regulating insulin delivery from the circulation to the tissue interstitium [17]. It is important to note that microvascular insulin resistance contributes to the development of systemic insulin resistance and occurs early in the disease course [64]. In mice on a HFD, vascular insulin resistance occurs within one week, while it takes 4–8 weeks to develop in muscle and liver and 14 weeks in adipose tissue [65]. In rats on a HFD, microvascular insulin resistance was observed 3 days after the initiation of the HFD, while impaired insulin-mediated glucose disposal and muscle Akt phosphorylation were not observed until one week after [64]. As such, early intervention that targets microvascular insulin resistance might a ord an opportunity to delay the development of systemic insulin resistance and the onset of T2D.

e fundamental pathophysiology of endothelial insulin resistance resides in the PI3K/Akt/eNOS signalling pathway, while the MAPK signalling pathway is spared or even enhanced due to the compensatory insulin secretion [29, 66, 67]. is selective insulin resistance results in a

reduced NO production and ampli es the MAPK-mediated cell proliferation and ET-1 production [68], leading to a decreased vasodilation and increased vascular tone in arterioles with subsequently less tissue perfusion [26, 27] and predisposing a ected people to atherosclerosis, hypertension, and/or microvascular complications.

Fatty acids, metabolic regulation and insulin action

In addition to regulating carbohydrate and protein metabolism, vascular tone, and tissue perfusion, insulin also actively regulates lipid metabolism, with an overall e ect of increasing fat storage [69–71]. It activates capillary endothelium lipoprotein lipase to hydrolyze circulating lipoprotein triglycerides and generate free fatty acids (FFAs) that are either oxidized by tissue or stored by fat cells. It also facilitates the re-esteri cation of FFAs into triglycerides within fat cells and inhibits hormone-sensitive lipase, a rate-limiting enzyme in the lipolytic pathway, both of which lead to decreased plasma levels of FFAs.

Fatty acids are a key energy source for cells, particularly during periods of fasting or prolonged physical activity when carbohydrate stores are depleted. In times of increased energy demand, lipolysis occurs to generate FFAs which are transported into cells, and β-oxidized in the mitochondria to generate adenosine triphosphate (ATP) [69, 71]. e balance among fatty acid intake (either from food sources or lipolysis), storage locations (i.e., adipose tissue vs. ectopic storage in muscle and liver), and rate of oxidation is critical for metabolic homeostasis. Chronic elevation of plasma FFA levels, and excess accumulation of fatty acids in tissues other than adipose tissue are associated with insulin resistance, in ammation, and tissue dysfunction [2, 72, 73]. FFAs are perhaps the most important physiological factors that regulate glucose metabolism and insulin action in vivo. FFAs are classi ed based on the number of double bonds in their hydrocarbon chains. Monounsaturated fatty acids (MUFAs) contain one double bond, and polyunsaturated fatty acids (PUFAs) contain two or more double bonds, while SFAs lack double bonds. Each class of fatty acids has distinct e ects on glucose metabolism and insulin secretion and action. Short-term exposure of β-cells to FFAs potentiates glucose-stimulated insulin secretion through GPR40-mediated process [74], and the potency increases with chain length and degree of saturation [75–77]. On the other hand, prolonged exposures of β-cells to fatty acids increases basal insulin release but inhibits glucose-stimulated insulin secretion in vitro [78, 79] as well as in vivo [80, 81]. e prolonged exposure ndings are more clinically relevant as plasma FFAs are elevated in people with obesity and insulin resistance / T2D [82], and there is clear evidence of glucolipotoxicity causing β-cell dysfunction [83].

Numerous studies have con rmed a causative e ect of FFAs on insulin resistance through mechanisms involving intracellular accumulation of diacylglycerol and ceramide, activation of protein kinase C (PKC), activation of the nuclear factor kappa B (NF-κB) pathway, decreased *PPAR* coactivator-1 / activation, recruitment of immune cells like macrophages, neutrophils, and bone marrow-derived dendritic cells to adipose tissue and muscle, and decreased tyrosine phosphorylation of insulin receptor substrate 1/2 [84–89]. However, it is important to note that di erent FFAs appear to have distinctly di erent impacts on glucose metabolism. It is well known that SFAs, such as palmitic acid, potently trigger insulin resistance [89–92] while MUFAs, such as oleic acid found in olive oil, have neutral or even bene cial e ects on glucose metabolism [89, 93]. A good example is the Mediterranean diet, which is rich in MUFAs. In clinical trials, the Mediterranean-type diet was found to improve glycemia in those with T2D [94], and the risk of T2D was 83% lower among those who closely adhered to the diet [95]. Even among those at high CVD risks and without calorie restriction, the Mediterranean diet seems to be e ective in preventing T2D [96]. Whether these bene cial actions are the direct results of unsaturated fatty acids remain to be determined, as in vivo and in vitro evidence has suggested that unsaturated fatty acids also cause insulin resistance [97] despite the experimental evidence of unsaturated fatty acids reducing in ammation and improving insulin sensitivity.

Fatty acids, endothelial function, and vascular insulin action

While the endothelial cells derive their energy primarily through glycolysis [98–100], fatty acid oxidation in endothelial cells critically regulates endothelial function [101]. Equally important is the uptake and transport of fatty acids by endothelial cells to meet the needs of surrounding cells for a variety of cellular processes, including membrane synthesis, intracellular signal transduction, ATP generation, protein posttranslational modi cations, and metabolic gene transcriptional regulation [102, 103]. However, abnormalities in lipid and fatty acid metabolism are detrimental to endothelial biology and function [104]. People with T2D frequently manifest lipid abnormalities such as hypertriglyceridemia and elevated levels of plasma FFAs [105], where both are well-established risk factors of CVD.

Endothelial cells take up and metabolize fatty acids through the tricarboxylic acid cycle in the mitochondria to produce ATP and store excess fatty acids as cytosolic lipid droplets, protecting cells from endoplasmic reticulum stress from excess FFAs [106]. When the levels of FFAs surpass the cellular protective capacity, endothelial dysfunction ensues. Multiple mechanisms contribute to

FFA-induced endothelial dysfunction, including oxidative stress, in ammation, cellular apoptosis, impaired insulin signaling, and reduced NO bioavailability [6, 104, 107]. Studies have con rmed a causative role of FFAs in endothelial dysfunction and endothelial insulin resistance, which are closely coupled, mutually perpetuate, and contribute together to accelerate cardiovascular diseases [42, 43, 104, 108, 109]. ey are present throughout the arterial tree, and the outcomes di er based on the structure and location of the arteries a ected [2]. us, endothelial dysfunction and insulin resistance in the conduit arteries accelerate atherosclerosis, in the resistance arterioles elevate blood pressure, and in the microvasculature perturbs glycemia [5, 110–112], all pathophysiological manifestations seen frequently in the setting of T2D (Fig. 1**&** Fig. 2). Elevated circulating FFA levels (similar to those in the post-absorptive state in T2D [82] or metabolic syndrome [31]) interfere with shear stress-induced NO production and reduce insulin-mediated vasodilation of the conduit and resistance arteries [42], blunt insulin-induced increases in FMD and reduction in AI [2], as well as induce microvascular insulin resistance in both cardiac and skeletal muscle [2, 108, 109]. Findings of lipid-inducing microvascular insulin resistance were similarly reported in a rodent study [113]. In a multivariate regression analysis, insulin-mediated muscle microvascular perfusion was independently associated with insulin-mediated FMD and pulse wave velocity [2].

us, clinically relevant elevation of plasma FFA concentrations induces pan-arterial insulin resistance and the outcomes of insulin resistance in various arterial segment are interconnected.

e raising plasma levels of FFAs reduces NO ux, impairs shear-stress-induced NO production, depresses

Fig. 2 FFAs impair endothelial function and vascular health. FFAs are released from adipose tissue and enter the bloodstream. Elevated plasma FFAs induce endothelial in□ammation through upregulation of in□ammatory genes and increased ROS production to promote a selective insulin resistance in the vascular endothelium, resulting in reduced NO bioavailability, increased arterial sti□ness and vascular resistance, less tissue perfusion, and reduced capillary substrate supply and exchange. (Abbreviations: FFAs, free fatty acids; ROS, reactive oxygen species; JNK, c-jun N-terminal kinase; IKKβ, inhibitor of nuclear factor kappa-B kinase subunit beta; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PPARs, peroxisome proliferator-activated receptors; IRS, insulin receptor substrate; PI3-K, Phosphatidylinositol 3-kinase; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; MEK, mitogen-activated protein kinase kinase; MAPK, mitogen-activated protein kinase; P, phosphorylation.)

methacholine-induced vasodilation which is endothelium-dependent but not nitroprusside-induced vasodilation which is endothelium-independent suggest that NO bioavailability is crucial in FFA-induced endothelial insulin resistance and endothelial dysfunction [42, 43]. While multiple mechanisms could have contributed to FFA-induced reduction in NO bioavailability, the most likely culprit is FFA-induced oxidative stress and vascular in ammation (Fig. 2) [6, 114, 115]. FFAs are important inciters of a chronic, low-grade systemic in ammation state seen in insulin resistant conditions such as obesity, metabolic syndrome and T2D [42, 43, 87, 108, 109, 116, 117]. Multiple signaling pathways and factors seem to have been implicated in this process, including the endoplasmic reticulum stress pathway, PKC pathway, c-Jun NH2-terminal kinase (JNK), toll like receptor 4 (TLR4) pathway, and inhibitor of nuclear factor kappa B (IκB) kinase β (IKKβ) [89, 92, 118–121]. Activation of these pathways increases the production of reactive oxygen species (ROS) which reduces NO bioavailability. Additionally, reduced NO production also contributes to low NO bioavailability, as raising plasma FFA concentrations not only decreases shear stress-induced NO production but also blunt insulin-mediated eNOS activation and NO production [2, 104, 122].

FFA-induced oxidative stress and in ammation are crucial in the pathogenesis of endothelial insulin resistance, speci cally in the PI3K/eNOS/NO pathway [64, 104, 123], and it appears that the endothelium is more sensitive to FFA insult than other tissues. Feeding mice a HFD for one week decreases insulin signaling in the aorta, while taking 8 weeks to do so in the skeletal muscle [65]. Our data suggest that insulin resistance in the microvasculature occurs even earlier than that in the aorta, as feeding rats a HFD blocks insulin-mediated muscle microvascular recruitment in as early as 3 days [64]. e in ammation-induced microvascular insulin resistance is clearly an early event in diet-induced obesity, as inhibition of the NFκB pathway attenuates microvascular as well as metabolic insulin resistance during HFD feeding [64].

FFAs also contribute to capillary rarefaction, a phenomenon well recognized in the insulin resistant tissues, particularly in the muscle [124–126]. e degree of reduction in muscle capillary density correlates with the severity of insulin resistance [125, 127, 128], possibly through the expression and action of the vascular endothelial growth factor (VEGF) family of proteins [129], which recruit and di erentiate endothelial progenitor cells and induce endothelial cell proliferation and migration, leading to new vessel formation [129]. In the insulin resistant state, VEGF action on muscle vasculature is impaired, which triggers muscle capillary regression [124, 130]. We have shown previously that feeding rats a HFD for 4 weeks reduced muscle VEGF expression as well as muscle capillary density [131]. In vitro cell culture studies have clearly demonstrated that FFAs directly lead to endothelial cell apoptosis. Incubation of endothelial cells with palmitate showed that palmitate dose- and time-dependently induced apoptosis, likely through a p38 MAPK-mediated mechanism [107]. However, it is important to note that not all FFAs trigger endothelial apoptosis. Stearic acid (a SFA), but not oleic acid (a MUFA), time and concentration dependently increases endothelial apoptosis [132].

Together, FFAs-induced endothelial dysfunction, endothelial insulin resistance, and endothelial cell apoptosis contribute to the pathogenesis of metabolic insulin resistance and the associated cardiovascular complications, thus making the vascular endothelium a viable therapeutic target for T2D prevention and management [112]. As currently available evidence, both preclinical and clinical, link excess saturated but not unsaturated fatty acids with the risk of CVD, more studies are needed to optimize dietary fatty acid intake for maintaining a good vascular health.

Exercise, fatty acid oxidation, and vascular function

Exercise engenders myriad metabolic and cardiovascular bene ts, and delays the development of T2D [133–136]. Exercise profoundly impacts the vasculature in health and disease by inducing both functional and structural adaptions throughout the arterial tree. For conduit arteries, exercise training improves endothelial dependent dilation, as measured through FMD [137], and this change appears to be magni ed in those with endothelial dysfunction [138]. Exercise training also improves conduit artery wall sti ness, particularly with higher aerobic exercise intensity and in participants with greater arterial sti ness at baseline [139]. Structurally, exercise induces local and systemic arterial wall remodeling, with the localized e ects more evident in the remodeling of arterial size whereas arterial wall thickness is more a ected by systemic factors [140], and the latter appears to be unrelated to exercise type [141]. Exercise-induced improvement in conduit artery endothelial function appear to be mediated through shear stress-induced / Akt-dependent eNOS phosphorylation [142]. However, the exercise-induced changes in shear rate are not obligatory for arterial wall remodeling [143]. Overall, functional adaptations typically precede structural adaptions during exercise training [137]. e results of exercise impact on resistance arteries are inconsistent in healthy individuals, with studies reporting either no change [144, 145] or an improvement [146, 147] in resistance artery endothelial function measured through forearm strain-gauge plethysmography. However, the bene cial e ect of exercise

is clearer in individuals with endothelial dysfunction, with an improvement in function and NO bioavailability reported in a variety of clinical populations, including those with T2D [142, 147–149]. As for the microvasculature, exercise is perhaps the most potent known physiological factor that increases microvascular blood ow in the myocardium and skeletal muscle. In the myocardium, exercise augments coronary blood ow via dilatation of the coronary microvessels to meet the increased oxygen demand as oxygen extraction in the coronary circulation is nearly maximal at rest (70–80%) [150]. Even a simple handgrip exercise potently increases microvascular perfusion in the myocardium [151], as well as the skeletal muscle [152] in healthy humans. Importantly, this exercise- / muscle contraction-induced skeletal muscle microvascular perfusion is preserved in humans [153, 154] as well as in rodents [155–157] with insulin resistance. Exercise also potently stimulates muscle angiogenesis [158], and well-trained endurance athletes may have 3–4 times more capillaries per muscle ber than sedentary individuals [159]. Both shear stress and passive stretch enhance the expression of angiogenic factors and initiation of capillary growth [158, 160, 161]. Among all factors, VEGF is central to exercise-induced muscle capillary growth. In mice with muscle-speci c VEGF de ciency, muscle capillary density is reduced by ~50% and endurance running capacity decreases by 80% [162]. Muscle contraction leads to a redistribution of VEGF-containing vesicles toward the sarcolemma and the release of VEGF to the muscle interstitium, which acts on the capillary endothelial VEGF receptors to stimulate the angiogenic process [158]. Exercise also increases VEGF mRNA expression, which allows for replenishment of VEGF stores lost through secretion during exercise [158]. Together, the functional and structural adaptation to exercise training ensures adequate capacity for oxygen and nutrients delivery to the exercising muscle. However, it is important to note that while exercise augments vascular function in both healthy and insulin resistant states, the e ect of exercise intensity is equivocal due to di erences in exercise protocols and vascular methodology within the existing literature.

Exercise is known to improve insulin sensitivity in both insulin sensitive and resistant states [163]. Even moderate daily exercise can greatly improve insulin sensitivity, and a single bout of exercise increases insulin sensitivity into the next day in humans with obesity [164]. While multiple mechanisms contribute to exercise-mediated insulin sensitization, exercise-induced vascular adaptations, particularly in the microvasculature, play an important role [13]. Increased conduit artery blood ow and reduced resistance in the resistance arterioles result in higher total tissue perfusion, while increased microvascular blood ow leads to more oxygen, nutrients and hormones delivered to the tissue [165–168]. We have recently determined the phenotypic traits that foretell human muscle microvascular insulin responses using a combination of contrast-enhanced ultrasound and hyperinsulinemic euglycemic clamp in adult humans, with insulin sensitivity spanning from normal to resistance. Among all factors associated with metabolic insulin resistance, we found only peak oxygen uptake (VO_2peak) predicted insulin-induced changes in muscle microvascular blood volume [49], suggesting a profound impact of exercise capacity on muscle microvascular insulin responses in humans. How exercise attenuates microvascular insulin resistance remains to be clari ed. In HFD fed rodents, exercise reduces vascular in ammation, endothelial oxidative stress, perivascular macrophage accumulation, and superoxide production in muscle, along with increased endothelial nucleus translocation of Nrf2 and endothelial AMPK phosphorylation [115]. Additionally, exercise induces increased muscle insulin delivery likely via increased microvascular perfusion and expanded microvascular endothelial surface area available for insulin extraction [155, 169]. Indeed, in rats receiving an insulin infusion, muscle contraction markedly increased interstitial insulin concentrations compared with the non-contracting leg [170].

e exercise induced increase in total tissue blood ow and microvascular perfusion, along with the improvement in microvascular insulin sensitivity in the insulin resistant states, can profoundly a ect fatty acid metabolism. Increased total tissue blood ow leads to more FFAs delivered to the muscle, and expanded microvascular endothelial surface area enables more FFAs extracted from the circulation to the muscle interstitium. At rest, skeletal muscle uses lipid oxidation as the primary fuel source (~60%) but with exercise, both fatty acids and glucose are important energy sources for the exercising muscle [171, 172]. However, lower intensity [≤~50% VO_{2peak}] and prolonged activities rely more on fatty acid utilization while during high intensity exercise lipolysis is inhibited, the availability of FFAs in the blood declines, and the substrate of choice crosses over from fatty acids to carbohydrates [173–175]. is crossover phenomenon is seen in both trained and untrained individuals, with the trained individuals experiencing the shift at a higher intensity level, helping to “spare” carbohydrates and thus delay the depletion of muscle glycogen and development of fatigue during exercise [173, 176]. Studies have shown peak rates of fat oxidation occur at intensities between 59% and 64% VO_{2peak} in trained individuals and between 47% and 52% of VO_{2peak} in untrained individuals [177]. In individuals with insulin resistance, fatty acid oxidation increases in response to training in both healthy and T2D populations [178], and the improvement to lipid metabolism in response to exercise, in healthy individuals as well

as those with insulin resistance, appears to be independent of weight loss [179]. While the exact mechanism remains to be de ned, exercise potently increases the delivery of fatty acids to skeletal muscle and the proteins involved in lipid metabolism, such as transport proteins CD36, FATP4, and FABPpm [179]. Data also suggest that the ability to e ciently oxidize fatty acids is important for glucose homeostasis. One study showed that preprandial fatty acid oxidation is inversely associated with insulin-stimulated glucose disposal rate during a hyperinsulinaemic-euglycaemic clamp in both healthy individuals and individuals with T2D [180]. Another study found that that long-term inhibition of fatty acid oxidation in mice led to hepatic steatosis and whole-body insulin resistance [181]. erefore, exercise can be a powerful tool to improve insulin sensitivity through enhancing fatty acid oxidation.

Interestingly, studies comparing the e ects of high intensity interval training and moderate intensity continuous training have found comparable results regarding fatty acid oxidation [15, 182]. For individuals with insulin resistance, both intensities have been shown to improve fatty acid oxidation and/or markers of oxidative metabolism [183, 184]. From an exercise-induced microvascular perfusion perspective, both low intensity and high intensity muscle contractions are potent in expanding the microvascular blood volume perfusion but higher intensity muscle contraction also increases ow velocity, leading to higher blood ow [152]. Whether this leads to a di erence in fatty acid extraction in the microcirculation is not known.

Unlike skeletal muscle, the heart primarily uses long chain fatty acids as a substrate (~70%). However, in diabetic cardiomyopathy, the reliance on fatty acids increases due to dysfunctional glucose oxidation [185]. is leads to increased oxygen consumption and reduced myocardial e ciency [186]. Exercise training has been shown to induce bene cial cardiac remodeling in both healthy and diabetic hearts, including increases in oxidative enzymes and decreased oxidative stress. Further, after treadmill training in diabetic mice, the overreliance on fatty acids was abolished, due to the restoration of peroxisome proliferator-activated receptor-γ coactivator (PGC-1α) expression, which is involved in glucose oxidation [187]. Collectively, evidence suggests exercise can help restore healthy myocardial function in the insulin resistant states.

Glucagon-like peptide-1 (GLP-1), an incretin hormone, is of increased interest due the growing popularity of GLP-1 receptor agonists (GLP-1RA) o ered as weight loss and glucose control aids. ese drugs profoundly a ect lipid metabolism by promoting fatty acid oxidation and inducing lipolysis [188]. Although data on the e ect of exercise with or without GLP-1RA administration on lipid and glucose metabolism is scarce, one study has shown that the combination of both is superior to exercise alone on β-cell secretory function [189] in T2D. We have recently shown in rodents that combination of exercise with liraglutide is much more e ective in improving muscle insulin sensitivity than either exercise or liraglutide alone in rats fed a HFD [115]. Importantly, GLP-1RA induces signi cant reduction of lean muscle mass in addition to loss of fat mass [190] and supplementing GLP-1RA treatment with exercise may be bene cial for the preservation of muscle mass. Further studies are clearly needed.

Strengths and limitations

is review provides a comprehensive analysis of the intricate relationships among fatty acid metabolism, exercise-induced vascular adaptations, and insulin-mediated vascular changes, emphasizing their collective impact on vascular health and associated mechanisms in both healthy and insulin-resistant states. e review includes evidence from in vitro cell studies, in vivo rodent models, and human studies, enhancing its translational value and clinical relevance.

However, the limitations include a relatively limited focus on in-depth molecular mechanisms, as this is not the primary aim of the review. Additionally, while much of the evidence presented is based on preclinical studies, further research is necessary to corroborate these ndings in human populations. Despite these limitations, the review o ers valuable insights and guidance for future studies exploring the therapeutic potential of targeted exercise interventions and fatty acid-focused dietary strategies to improve vascular health.

Conclusions and perspective

In conclusion, the intricate relationships and complex interplay among fatty acid metabolism, exercise training-induced vascular adaptation, and insulin-mediated vascular changes have a signi cant impact on vascular health, particularly in the context of metabolic disorders like obesity, T2D, and CVD (Fig. 3). Fatty acids, as key energy sources and signaling molecules, play essential roles in cellular homeostasis, but an excess or imbalance of certain types - especially SFAs - can disrupt normal metabolic pathways. is disruption can lead to vascular in ammation, endothelial dysfunction, and endothelial insulin resistance, all of which are major contributors to vascular dysfunction and disease. Conversely, PUFAs might o er protective e ects on insulin sensitivity, reduce in ammation, and help preserve endothelial function. erefore, optimizing fatty acid intake and balance through diet may be a critical factor in improving metabolic and vascular health.

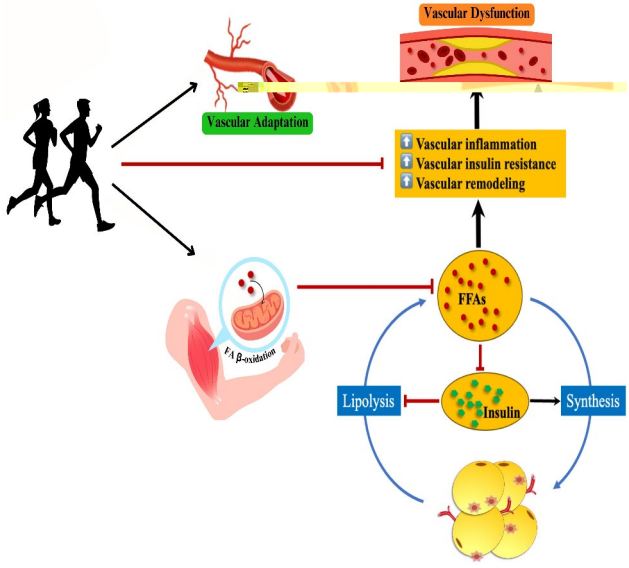

Fig. 3 Interplay of FFAs, insulin and exercise in the vasculature. Plasma FFAs lead to vascular dysfunction through increased vascular in□ammation, insulin resistance, and remodeling. Insulin inhibits lipolysis and enhances synthesis of FFAs, reducing the amount of plasma FFAs. Exercise increases β-oxidation of FFAs and stimulates bene□cial vascular adaptations, thereby combating endothelial dysfunction. (Abbreviations: FA, fatty acid; FFAs, free fatty acids)

Exercise, a well-established intervention for reducing T2D and CVD risk, exerts its bene cial e ects by enhancing fatty acid oxidation, improving insulin sensitivity, and inducing bene cial vascular adaptation. Regular physical activity promotes favorable shifts in fatty acid metabolism, leading to reduced circulating FFAs and decreased ectopic lipid accumulation, thus reducing lipotoxicity, enhancing insulin action and mitigating vascular dysfunction. Exercise further strengthens vascular health through improved endothelial function, increased NO production, and reduced oxidative stress and in ammation. By modulating fatty acid utilization and improving insulin-mediated vasodilation and overall insulin sensitivity, exercise plays a crucial role in sustaining healthy vascular function.

Looking forward, further research is needed to clarify the mechanistic pathways linking speci c fatty acids to vascular insulin resistance, and to understand how exercise may modulate these pathways di erentially in the vasculature. Additionally, personalized exercise programs that consider individual fatty acid metabolic pro les could o er targeted bene ts for patients with metabolic disorders. Investigating the long-term e ects of combining exercise interventions with dietary adjustments to optimize fatty acid composition may further unveil comprehensive approaches to combat vascular diseases. By advancing our understanding of these interconnections, we can better address the dual challenges of metabolic and cardiovascular health, improving outcomes for individuals a ected by T2D and related conditions.

Abbreviations

CVD	Cardiovascular disease
ERK	Extracellular signal regulated kinase
ET-1	Endothelin 1
eNOS	Endothelial nitric oxide synthase
FFA	Free fatty acid
HFD	High fat diet
FMD	Flow-mediated dilation
IGF-1	Insulin like growth factor I
IKKβ	Inhibitor of nuclear factor kappa B kinaseβ
JNK	C-Jun NH2-terminal kinase
MAPK	Mitogen-activated protein kinase
MUFA	Monounsaturated fatty acid
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NO	Nitric oxide
PI3-K	Phosphatidylinositol 3-kinase
PKC	Protein kinase C
PUFA	Polyunsaturated fatty acid
ROS	Reactive oxygen species
SFA	Saturated fatty acid
T2D	Type 2 diabetes
VEGF	Vascular endothelial growth factor
VO_{2peak}	Peak oxygen uptake

Author contributions

KCA and JL prepared Figs. 1, 2 and 3 and contributed to the main manuscript text. ZL wrote the main manuscript text. All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval

N/A.

Competing interests

The authors declare no competing interests.

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