Review

Healthy versus Unhealthy Adipose Tissue Expansion: the Role of Exercise

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Although the hallmark of obesity is the expansion of adipose tissue, not all adipose tissue expansion is the same. Expansion of healthy adipose tissue is accompanied by adequate capillary angiogenesis and mitochondria-centered metabolic integrity, whereas expansion of unhealthy adipose tissue is associated with capillary and mitochondrial derangement, resulting in deposition of immune cells (M1-stage macrophages) and excess production of pro-inflammatory cytokines. Accumulation of these dysfunctional adipose tissues has been linked to the development of obesity comorbidities, such as type 2 diabetes, hypertension, dyslipidemia, and cardiovascular disease, which are leading causes of human mortality and morbidity in modern society. Mechanistically, vascular rarefaction and mitochondrial incompetency (for example, low mitochondrial content, fragmented mitochondria, defective mitochondrial respiratory function, and excess production of mitochondrial reactive oxygen species) are frequently observed in adipose tissue of obese patients. Recent studies have demonstrated that exercise is a potent behavioral intervention for preventing and reducing obesity and other metabolic diseases. However, our understanding of potential cellular mechanisms of exercise, which promote healthy adipose tissue expansion, is at the beginning stage. In this review, we hypothesize that exercise can induce unique physiological stimuli that can alter angiogenesis and mitochondrial remodeling in adipose tissues and ultimately promote the development and progression of healthy adipogenesis. We summarize recent reports on how regular exercise can impose differential processes that lead to the formation of either healthy or unhealthy adipose tissue and discuss key knowledge gaps that warrant future research.

Key words: Exercise, Adipose tissue, Angiogenesis, Mitochondrion

INTRODUCTION

Obesity is a major risk factor for cardio-metabolic diseases such as dyslipidemia, type 2 diabetes, hypertension, coronary heart disease, stroke, gall bladder disease, respiratory problems, sleep apnea, osteoarthritis, and some cancers. However, in some diseases, obese but otherwise metabolically healthy patients present with well-preserved adipose tissue function that is often associated with fewer comorbidities and lower mortality rates compared with lean patients.[1-3] In order to address this long-lasting paradox, extensive research has been conducted to identify the differences in adipose tissue phenotype between patients showing these contradictory outcomes. As a result, the current understanding of adipose tissue biology predicts that expansion of adipose tissue is possible without accompanying adipose tissue dysfunction.[4-6]

Adipose tissue is highly vascularized and contains a remarkable microvascular network. Formation of both white and brown adipose tissue (WAT and BAT, respectively), as well as recently identified beige adipose tissue, rely heavily on concomitant capillary angiogenesis during adipogenesis to maintain their metabolic activi-

ties. Contrarily, adipose tissue dysfunction can arise through chronic hypoxia, inflammation, and mitochondrial dysfunction. Progression of adipose tissue dysfunction in unhealthy metabolic obesity proceeds without a well-coordinated response, which leads to insulin resistance, hypertension, and atherosclerosis.[7,8] Angiogenesis, the growth of new blood vessels, and mitochondrial biogenesis, the growth of new functional mitochondria, are tightly and distinctively coupled with the formation of healthy and unhealthy adipose tissue.

In the present review, we summarize existing knowledge of the molecular mechanisms and underlying effects of exercise on angiogenesis as well as mitochondrial remodeling in the context of the expansion of adipose tissue.

FACTORS AFFECTING HEALTHY VS. UNHEALTHY ADIPOSE TISSUE EXPANSION

As a primary energy-storing organ, adipose tissue changes in size and shape throughout an individual's life. Type of adipose tissue growth (hypertrophy or hyperplasia), adipose tissue anatomical location, adipose tissue inflammation, ectopic fat accumulation, genetics, and lifestyles factors (i.e., diet and physical activity) collectively contribute to the development of either metabolically healthy or unhealthy adipose tissue.[9]

Angiogenesis and mitochondrial biogenesis are key factors influencing healthy and unhealthy adipose tissue expansion.[10,11] As preadipocytes differentiate into mature adipocytes, mitochondrial biogenesis and oxygen consumption increase 20- to 30-fold.[11] An increase in metabolic activity requires angiogenesis because blood vessels enable adipose tissue metabolism by delivering oxygen and nutrients and removing metabolic waste. Similarly, promoting mitochondrial biogenesis is essential to preserving adipose tissue function during the early stages of obesity and preventing the development of unhealthy metabolic adipose tissue. In this section, we briefly discuss the critical roles of each angiogenic and mitochondrial factor affecting the expansion of adipose tissue.

Angiogenesis and adipogenesis

Adipose tissue differs from other tissues because it can expand during times of overnutrition to store extra calories. As adipose tissue expands, the demand for both nutrients and oxygen increases, leading to local hypoxic conditions surrounding newly formed adipose tissue. Insufficient blood flow into growing adipose tissue can result in the formation of metabolically unhealthy adipose tissue. Angiogenesis needs to be properly activated in new tissue to meet the metabolic demand of the expanded adipose tissue.

The main mechanism of angiogenesis appears to be mediated by hypoxia inducible factor-1α (HIF-1α) and vascular endothelial growth factor (VEGF). Under normoxic conditions, HIF-1α is hydroxylated by prolyl hydroxylase domains (PHDs), leading to proteome degradation of HIF-1α through the von Hippel-Lindau tumor-suppressor protein.[12] In contrast, hypoxic conditions inhibit PHDs activity, stabilize HIF-1α, and enable binding to hypoxic-response elements of target genes such as *VEGF* to create new blood vessels that grow toward hypoxic tissues.[12] When this mechanism is successful, hypoxic response can serve as a regulator of angiogenesis to ensure that blood vessels grow at the same rate as the tissues they perfuse because blood vessels expand toward hypoxic areas that do not receive adequate blood flow. Periods of growth of new adipose tissue, such as those involving high caloric intake or experimental high-fat diet (HFD), seem to protect metabolic functions of the new adipose tissue.

Conversely, when these pathways are disrupted, adipose tissue can become dysfunctional, which can lead to various metabolic diseases. For example, VEGF ablation in mice increased adipose tissue hypoxia and inflammation, resulting in dyslipidemia and insulin insensitivity, when the mice were fed an HFD,[13] whereas VEGF-overexpressing mice exhibited improved adipose tissue metabolic function and insulin sensitivity.[14] If the angiogenic response is insufficient to provide oxygen, chronic hypoxia initiates low-grade inflammation in adipose tissue.[15] An increase in pro-inflammatory gene expression leads to adipose tissue fibrosis,[16] impairment of endothelial angiogenic potentials,[17] and, in more severe cases, necrosis. Angiogenesis serves as an important immediate response mechanism against hypoxic conditions in expanding adipose tissue.

Mitochondrial function and adipogenesis

Mitochondrial content in growing adipose tissue is a hallmark of healthy adipogenesis. In adipose tissue, mitochondria play an important role in maintaining energy homeostasis by regulating lipid

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turnover, adipogenesis, adipokine secretion, and metabolic substrate utilization. Early obesity studies discovered links between obesity and mitochondrial oxidative stress.[18] Mitochondrial reactive oxygen species (mtROS) can serve as second messengers that are integral to fundamental cellular[19] and biological responses.[20] Adequate production of mtROS is beneficial for insulin sensitivity,[21] adipocyte differentiation,[22] adipogenesis, and WAT function.[23] Specifically, inhibition of oxidative phosphorylation (complex I and III) prevents adipogenesis induction,[22] suggesting that mtROS play a causal role in adipogenesis induction. However, adipocytes exposed to excess mtROS can activate various stress pathways,[24] leading to increased production of pro-inflammatory adipokines, interleukin 6, and tumor necrosis factor alpha (TNF-α).[25] In addition, mtROS and oxidative damage have been shown to be elevated in the WAT of obese humans[26] and animals.[27] Chemical induction of mtROS can decrease adiponectin release and glucose uptake in adipocytes.[28] Overall, the current consensus is that mtROS are both necessary for (at appropriate levels) and detrimental to (at abnormal levels) adipose function in various pathologies.

Mitochondria possess their own DNA (mtDNA), which encode for 13 proteins critical to oxidative phosphorylation.[29] Mitochondria can increase or decrease mitochondrial mass through activation of peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α), which activates genes such as nuclear respiratory factors 1 and 2 (NRF-1 and NRF-2) and mitochondrial transcription factor A (TFAM), which modulates mtDNA transcription and replication. A reduced copy number of mtDNA was reported in obese WAT.[30,31] Reduced activities of complexes I–IV were observed in isolated adipose tissue mitochondria obtained from obese patients.[32] An HFD also disrupted mitochondrial biogenesis and mtDNA content in adipose mitochondria.[33,34] Knock-down of other mitochondrial biogenesis genes, such as TFAM and NRF-1, in adipocytes decreased mtDNA, resulting in insulin resistance.[28,35] Overexpression of NRF-1 in WAT restored the release of adiponectin from adipose tissue.[28] Collectively, mitochondrial biogenesis, content, and function are closely related to adipogenesis, adipose tissue function, and insulin sensitivity.

Table 1. Effects of aerobic exercise training on angiogenesis and blood perfusion in adipose tissue

Author (year)	Subject	Treatment	Result
Human study			
Moro et al. (2005)[36]	10 Untrained overweight men	45–60-minute at 50%–85% VO₂peak EXTR 5–7 day/wk for 4 months (cycling or running)	↑ ATBF measured by ethanol outflow/inflow ratio, ↑ fat-free mass, ↑ VO₂max, ↓ plasma insulin, ↓ glucose, ↓ NEFA, ↓ LDL-C, and ↓ RER at rest; ↑ lipid-mobilizing effect of ANP, isoproterenol
Walton et al. (2015)[37]	12 Insulin-sensitive; 14 IR adults	12-Week cycling EXTR	↑ Angiogenesis in SAT of insulin-sensitive individuals but not SAT of IR individuals; exercise training did not increase insulin sensitivity in IR subjects.
Animal study			
Lee (2018)[38]	16 C57BL/6J mice	6-Week VW	↓ Vegfa, Flk1 mRNA expression and ↑ Ang2, Pdgfrb mRNA expression in eWAT; ↑ Vegfa mRNA expression and ↓Ang1 in iWAT; no change in BAT gene expression
Loustau et al. (2020)[39]	85 C57BL/6J mice fed HFD	7-Week VW	↑ Capillary density in WAT, ↓ adipocytes hypertrophy, ↓ adipose inflammation, ↑ adipose insulin sensitivity, ↑ browning process of SAT, ↓ ectopic fat deposition
Disanzo and You (2014)[40]	30 Lean, obese Zucker rats	Treadmill exercise 5 day/wk for 8 weeks	↑ Vegfa in eWAT, ↓ lactate in iWAT
Min et al. (2019)[41]	C57BL/6J mice fed HFD (n=5–7 per group)	30-Minute treadmill EXTR at ~70% VO₂max 5 day/wk for 7 weeks	ET: ↑ capillary sprouting; ↑ Ucp1 mRNA; ↑ vessel density in VAT and SAT HFD: ↓ glucose handling attenuated by ET, ↓ Vegfa, ↓ Nos3 in WAT attenuated by ET
Kolahdouzi et al. (2019)[42]	48 Male Wistar rats	Continuous and interval aerobic EXTR	Exercise training prevents HFD-induced adipose tissue remodeling by increased capillary density.

EXTR, exercise training; ↑, increased; ↓, decreased; ATBF, adipose tissue blood flow; NEFA, non-esterified fatty acids; LDL-C, low-density lipoprotein cholesterol; RER, respiratory exchange ratio; ANP, natriuretic peptide A; IR, insulin-resistant; SAT, subcutaneous adipose tissue; VW, voluntary wheel running; Vegfa, vascular endothelial growth factor A; Flk1, fetal liver kinase-1 (or vascular endothelial growth factor receptor 2); Ang2, angiopoietin 2; Pdgfrb, platelet derived growth factor receptor beta; eWAT, epididymal white adipose tissue; iWAT, inguinal white adipose tissue; BAT, brown adipose tissue; HFD, high-fat diet; ET, exercise training; Ucp1, uncoupling protein 1; VAT, visceral adipose tissue; Nos3, endothelial nitric oxide synthase.

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EXERCISE AND ADIPOSE TISSUE ANGIOGENESIS

Angiogenic potential

The effects of exercise on angiogenesis and blood perfusion in adipose tissue are summarized in Table 1. Exercise is believed to increase the angiogenic potential for blood vessel growth throughout the body in a dose-dependent manner.[43] Acute endurance exercise induces VEGF mRNA in subcutaneous adipose tissue (SAT) in animal[44] and human[45] models and can be stimulated through hypoxia[12] and local shear stress.[46] VEGF is believed to be the primary, albeit not the only, growth factor implicated.[38] Increased VEGF expression in SAT of exercise-trained animals reportedly corresponds with an increase in vessel density, reduced inflammation, improved glucose tolerance,[41] and decreased lactate in SAT.[40] Similar increases of VEGF in blood have been linked to improved weight loss[47] in obese humans following 12 weeks of exercise training. However, this study found no effect of exercise training on VEGF in abdominal SAT.[47] Collectively, these studies suggest a differential effect of exercise on angiogenesis in certain fat depots.[38,47] It is likely that angiogenesis improves in adipose tissue near active muscles in a manner similar to adipose tissue blood flow (ATBF).

Adipocytes also interact with endothelial cells during angiogenesis. Secreted adipokines and angiogenic molecules, such as leptin, hepatocyte growth factor, and VEGF, activate angiogenesis via a VEGF receptor-dependent mechanism.[10] It is important to note that the effects of leptin and adiponectin on endothelial cells are largely opposite, with leptin promoting and adiponectin inhibiting angiogenesis.[48] Interestingly, most exercise studies report improved insulin sensitivity,[49,50] increased angiogenesis,[41] and reduced leptin[51] and inflammation in adipose tissue,[51-53] with no change or a slight increase in adiponectin[54-56] reported in obese animals. Similar increases in angiogenesis and decreases in leptin and inflammation have been observed, with no change in adiponectin, in humans following 12 weeks of aerobic exercise.[37,55] Although a 12-week program of aerobic exercise was sufficient to increase the number of vessels per adipocyte in insulin-sensitive humans, blood vessel numbers in insulin-resistant humans did not change.[37] Generally, regular exercise reduces inflammatory adipokine release (TNF-α, leptin, etc.) and central adiposity and improves whole-body insulin sensitivity.[57]

Fat perfusion

ATBF is an important determinant of adipose tissue function and a measure of vessels' ability to deliver nutrients and oxygen while mobilizing and distributing adipokines and metabolites into circulation. Early studies demonstrated that ATBF is impaired by obesity and diabetic conditions.[58,59] Exercise increases heart rate and cardiac output, which could also prevent adipose tissue hypoxia if blood flow to adipose tissue increases. ATBF increases during exercise in dogs[60] and humans.[61-63] During exercise, blood flow to working muscles increases. This phenomenon is mirrored in adipose tissue because acute exercise increases ATBF in specific fat deposits that are close to working muscle.[64,65] Cycling exercises did not increase blood flow to abdominal adipose tissue in humans,[63,66] suggesting that blood flow during exercise is depot-specific. However, increase in ATBF near active muscle occurs in obese subjects independent of insulin sensitivity,[67] suggesting that an exercise-induced increase in ATBF can improve tissue function in obese patients.

This exercise-induced increase in ATBF might be a mechanism to mobilize fatty acids for use as a substrate in the metabolism of working muscles. The results of acute-exercise studies that also measured increased lipolysis, fatty-acid mobilization, and esterification in animals[60] and humans[62] support this hypothesis. Chronic aerobic training increased resting ATBF after training in animals[68] and healthy humans[36] without altering resting ATBF or lipolysis in obese humans.[67] For example, in older women, no alterations to ATBF were observed acutely during exercise[66,69] or chronically following exercise training.[66] Future research should attempt to confirm these results in more diverse subject populations and age groups.

Adipose tissue capillaries can be visualized microscopically, and a common view is that at least one capillary is in close contact with each adipocyte. Perfusion of SAT is easier to measure, but less is known about visceral adipose tissue (VAT) blood flow. The only accepted method of measuring visceral ATBF is positron emission tomography. Measurement of ATBF during exercise is a challenge due to current limitations in dynamic techniques to measure ATBF. How much does blood flow to VAT change during exercise? Future advancements in technology and further study in this area might be of clinical interest because VAT releases more pro-inflammatory adipokines, contributing to atherosclerosis progression.[70]

EXERCISE AND MITOCHONDRIAL REMODELING

Mitochondria in adipocytes

The effect of exercise on mitochondrial remodeling in adipose tissue is summarized in Table 2. Exercise is a non-pharmacological treatment that improves insulin sensitivity in muscle and adipose tissues. A common theory is that exercise increases systemic insulin sensitivity by improving mitochondrial biogenesis, respiration, and content in the skeletal muscles of individuals with diabetes.[84] These adaptations are believed to be a result of increased expression by genes for 5′ AMP-activated protein kinase (AMPK) and PGC-1α, which is elevated following exercise training in skeletal muscle.[85] Studies of similar mitochondrial adaptations in adipose tissue to exercise training suggest a role for adipose tissue mitochondria in the exercise-induced improvement of insulin sensitivity.

Table 2. Effects of aerobic exercise training on mitochondrial remodeling in adipose tissue

Author (year)	Subject	Treatment	Result
Human study			
De Carvalho et al. (2021)[71]	24 Obese women	8-Week aerobic and resistance EXTR (3 day/wk for 55 min)	↑ WAT mitochondrial respiratory capacity; ↑ genes related to fat oxidation (ACO2 and ACOX1)
Mendham et al. (2020)[72]	Obese, black South African women (n=45)	12-Week aerobic and resistance EXTR	↑ Mitochondrial respiration, ↑ respiratory coupling in abdominal SAT, ↑ insulin sensitivity in SAT and SKM, ↓ gynoid fat mass, ↓ mtDNA in gluteal SAT
Pino et al. (2016)[73]	16 Lean/overweight human participants	30–60-Minute cycling exercise at 75%–85% VO₂ 6 day/wk for 3 weeks	1.5 to 2-fold ↑ PGC-1α expression in WAT, ↑ mitochondrial content in WAT
Hoffmann et al. (2020)[74]	25 Obese subjects	8-Week EXTR 1 hour at 80% VO₂ (3 day/wk)	↑ Mitochondrial protein content in SKM not WAT, ↑ insulin sensitivity, WAT respiration showed a preference for β-oxidation and complex II substrates
Dohlmann et al. (2018)[75]	12 Overweight subjects (M, 5; F, 7)	HIIT 3 day/wk for 6 weeks supervised EXTR	↑ Mitochondrial respiration in SKM not WAT, ↓ mtDNA in WAT
Larsen et al. (2015)[76]	10 Overweight subjects (F, 2; M, 8)	HIIT 3 day/wk for 6 weeks EXTR	↑ Mitochondrial content and mitochondrial OXPHOS capacity in SKM not WAT; ↑ mtDNA in WAT
Brandao et al. (2019)[77]	14 Obese women	8-Week aerobic and resistance EXTR	↑ Mitochondrial enzymes in WAT, ↑ mitochondrial enzyme activity, ↓ coupling in WAT, ↑ RMR, ↓ Ucp1 mRNA expression in WAT, ↑ lipid oxidation
Animal study			
Trevellin et al. (2014)[78]	36 C57BL/6J mice	7-Week swim EXTR	↑ Mitochondrial biogenesis gene expression (Ppargc1, Tfam, Nrf1), ↑ mtDNA content, ↑ glucose uptake in SAT of WT but not Nos3 KO mice
Laye et al. (2009)[79]	Obese OLETF rat (n=6–8 per group)	13-, 20-, and 40-week VW	↓ Mitochondrial protein content in WAT, ↓ insulin sensitivity in WAT at 13 weeks, ↑ type 2 diabetes at 40 weeks restored cytochrome c and COXIV-subunit I protein content to match healthy controls, ↑insulin sensitivity at 13 weeks, ↓ type 2 diabetes incidence at 40 weeks
Brenmoehl et al. (2020)[80]	16 Mice (↑ running capacity vs. WT)	5-Week VW	↓ Reduced mtDNA, ↓ Nrf1, ↓ fission- (Dnm1), ↓ fusion-transcripts (Mfn1 and 2) in response to voluntary physical activity
Peppler et al. (2017)[81]	40 C57BL/6J mice	10-Week VW	↑ Ppargc1 mRNA and protein content in WAT, ↑ glucose tolerance in WAT, ↓ Tnf and IL-6 mRNA in WAT
Monaco et al. (2018)[82]	32 Obese Zucker rats	45-Minute treadmill 5 day/wk for 4 weeks	↑ Mitochondrial respiration, ↓ mtDNA in WAT, no change OXPHOS protein in WAT, ↑ whole-body glucose homeostasis
Xu et al. (2011)[83]	8 C57BL/6 mice per group	Sedentary vs. 40-minute treadmill EXTR 5 day/wk for 8 weeks; normal chow vs. HFD	↑ Ucp1, ↑ WAT mitochondria number, ↑ PGC-1α in WAT of HFD mice, ↓ abdominal fat, ↓ inflammation, ↑ glucose tolerance, ↑ vascular constriction and relaxation responses; ↑ preadipocytes differentiation into brown adipocytes

EXTR, exercise training; ↑, increased; ↓, decreased; WAT, white adipose tissue; SAT, subcutaneous adipose tissue; SKM, skeletal muscle; mtDNA, mitochondrial DNA; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1α; HIIT, high-intensity interval training; OXPHOS, oxidative phosphorylation; RMR, resting metabolic rate; Ucp1, uncoupling protein 1; Ppargc1, peroxisome proliferator-activated receptor gamma coactivator 1α; Tfam, mitochondrial transcription factor A; Nrf1, nuclear respiratory factors 1; WT, wild-type; Nos3, endothelial nitric oxide synthase; KO, knock-out; OLETF, Otsuka Long-Evans Tokushima Fatty; VW, voluntary wheel running; COXIV, cytochrome c oxidase subunit 4; Tnf, tumor necrosis factor; IL-6, interleukin-6; HFD, high-fat diet.

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Some exercise studies report increased mitochondrial respiration in adipose tissue.[72,86] However, mitochondrial respiration changes in adipose tissue appear to be unrelated to insulin sensitivity because other studies found improved insulin sensitivity without any change in mitochondrial respiration following exercise training.[74,77] Instead, the efficiency of abdominal SAT mitochondria appears to be the difference between healthy and insulin-resistant patients.[87] Mendham et al.[72] showed that 12 weeks of aerobic and resistance exercise training increased mitochondrial respiration and mitochondrial coupling in abdominal SAT. These adaptations in mitochondrial function occurred alongside improvements in insulin sensitivity in both adipose tissue and skeletal muscle. Interestingly, the same study reported decreases in gluteal SAT mitochondrial content and H_2O_2 production. Most studies of adipose tissue mitochondria focus on markers of mitochondrial biogenesis.[73,78,81] Few studies of mitophagy and mitochondrial fission and fusion have involved adipose tissue. Further research is necessary to test whether mitochondrial morphological changes can explain these depot-specific changes in adipose tissue and insulin sensitivity following exercise training.

Increased PGC-1α mRNA and protein expression is observed in both WAT[33,78,81] and BAT[88,89] in animal studies. Similar increases in PGC-1α mRNA have been observed following aerobic exercise training in obese humans.[73] These studies suggest that exercise leads to mitochondrial biogenesis in both skeletal muscle and adipose tissue. Furthermore, the increase in PGC-1α expression in adipose tissue following exercise typically coincides with an increase in mtDNA content,[73,78] but not all studies have observed this increase in mtDNA. For example, one study of obese animals reported that an improvement in insulin sensitivity following exercise training resulted in decreased mtDNA and increased mitochondrial respiration and mtROS.[82] Interestingly, antioxidants reversed the beneficial effects of exercise on insulin sensitivity by reducing mtROS and their downstream signaling.[82] Exercise increases mtDNA and enhances mitochondrial respiratory function, which is quickly followed by an increase in antioxidant and cytoprotective gene expression post-exercise.[86]

Mitochondria in vascular endothelial cells

Recent studies have shown that endothelial mitochondria play multiple roles in maintaining endothelial homeostasis, serving as bioenergetic, biosynthetic, and signaling organelles. As such, mitochondrial dysfunction has been linked to endothelial dysfunction that predisposes individuals to vascular diseases. Accumulating evidence shows that chronic exercise training improves aortic endothelial function and prevents vascular diseases through improved mitochondrial function. Chen et al.[90] demonstrated that 6 weeks of daily treadmill exercise significantly increased aortic mitochondrial content in mouse thoracic aorta as measured by complex I expression and mtDNA copy number, concomitant with elevation of vasodilatory function and endothelial nitric oxide synthase phosphorylation in an AMPKα2-dependent manner. In addition, Gu et al.[91] showed that chronic aerobic exercise attenuated age-related aortic stiffening and endothelial dysfunction in aged rat aorta. These preventive effects of exercise were associated with preserved aortic mitochondrial function as manifested by reduced mtROS production, increased mitochondrial content, elevated complex I and III activities, and elevation of protein expression involved in mitochondrial homeostasis, including uncoupling protein 2, PGC-1α, and manganese superoxide dismutase, in rat aorta.[91] Kim et al.[92] reported that voluntary wheel-running exercise significantly increases mitochondrial biogenesis in the endothelium of mouse abdominal aorta, while mRNA expression of genes involved in mitochondrial biogenesis, including PGC-1α, TFAM, and NRF-1, was increased in abdominal aortas of exercised mice.

Ample evidence has shown that exercise significantly elevates the magnitude of wall shear stress and alters flow patterns in human arteries by increasing laminar blood flow and reducing flow oscillation in atheroprone regions.[93-95] Laminar blood flow and resulting high laminar shear stress (LSS) induce salutary effects on endothelial mitochondrial homeostasis. LSS is also known to facilitate mitochondrial biogenesis via elevation of PGC-1α, NRF-1, and TFAM expression levels in a NAD+-dependent deacetylase sirtuin 1-dependent manner.[92,96,97] In addition, LSS modulates mitochondrial dynamics, leading to an elevation of mitochondrial fusion and an increase in mitochondrial fusion protein expression, including mitofusin-2 (Mfn2) and optic atrophy 1, in cultured endothelial cells.[98] These structural changes are accompanied by functional improvement of mitochondria, showing that LSS leads to intact mitochondrial function by intact oxidative phosphorylation and mito-

chondrial membrane potential.[92,98,99] LSS also maintains endothelial redox homeostasis by increasing mitochondrial antioxidant enzymes, including manganese superoxide dismutase, thioredoxin 2, and peroxiredoxin 3 and 5, which neutralize cellular mtROS level in endothelial cells.[98] Furthermore, LSS enhances mitochondrial quality control mechanisms by maintaining intact mitophagy and autophagy.[100-102]

Increasing evidence has shown that AMPK is a key mediator of mitochondrial homeostasis in endothelial cells.[103] Interestingly, exercise and high LSS activate the AMPK pathway in the abdominal aorta and the endothelial cells, respectively.[17,92,97] This implies that

exercise renders endothelial mitochondria more protective via AMPK activation. Mitochondrial adaptation to exercise in obese subjects has not yet been extensively studied. Preventive effects of exercise on endothelial defects and acceleration of vascular diseases in obese individuals can be explained, at least in part, by improvement of mitochondrial function in endothelial cells.

KEY RESEARCH GAPS AND FUTURE RESEARCH DIRECTIONS

Current understanding suggests that proangiogenic activity dur-
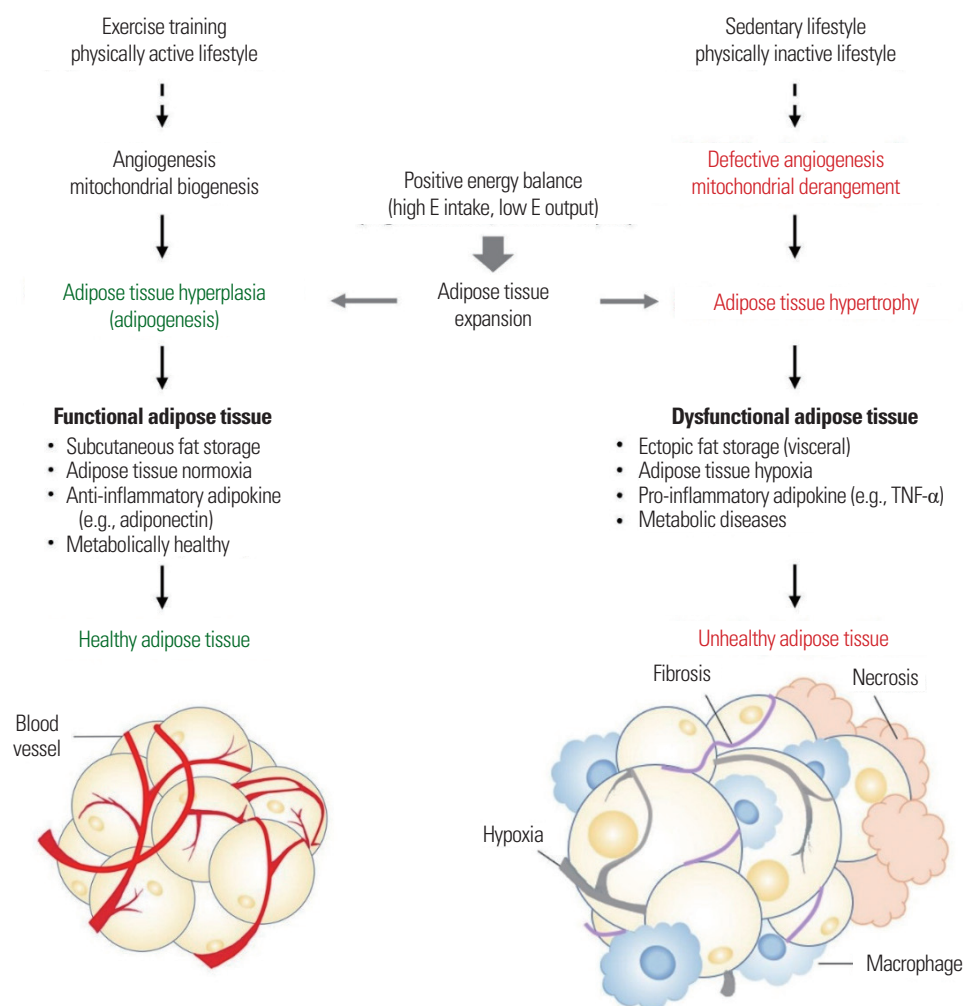
Figure 1. Schematic of the proposed mechanism. Excessive caloric intake and low energy expenditure create a positive energy balance, leading to adipose tissue expansion to store the excess energy. Adipose tissue can grow in size (hypertrophy) or in unit number (hyperplasia). Angiogenesis and mitochondrial remodeling are activated after exercise and act as signals for healthy adipose tissue expansion. Adipogenesis is the primary factor allowing hyperplasia to occur. Hyperplasia appears to preserve metabolic functions of the tissue. Hypertrophied adipose tissue is characterized by hypoxia, inflammation, fibrosis, and insulin insensitivity. When enough adipose tissue is dysfunctional, changes to adipokines, metabolites, and immune cells contribute to metabolic diseases such as diabetes, dyslipidemia, hypertension, and atherosclerosis. TNF-α, tumor necrosis factor alpha.

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ing adipose tissue expansion is beneficial and associated with potent protective effects on metabolic integrity of fat cells. As such, promoting angiogenic potential through exercise can be beneficial to prevent future metabolic diseases. However, a paradoxical relationship also exists between angiogenesis and healthy versus unhealthy adipose tissue expansion. Some studies show that anti-angiogenic drug treatment leads to weight loss and improvement in metabolic capacity in pre-existing dysfunctional adipose tissue.[104-107] These data suggest that a proper balance between pro- and anti-angiogenic processes is key to addressing the large public health issues associated with obesity. Investigation of the temporal effect of aerobic exercise training on adipose tissue function throughout the stages of weight gain is imperative.

While there is growing evidence that exercise training increases mitochondrial content and preserves mitochondrial respiratory function in adipose tissues, to the best of our knowledge, the effects of exercise on mitochondrial fusion and fission dynamics and mitochondrial autophagy in adipose tissue have yet to be fully elucidated. Mancini et al.[108] recently reported that expression level of *Mfn2*, a gene promoting mitochondrial fusion and mitochondrion–endoplasmic reticulum interaction, is robustly lower in both animal and human models of obesity. The study further reported that Mfn2 deficiency is associated with adipocyte proliferation, increased lipogenesis, and decreased glucose utilization, suggesting a crucial role for mitochondrial dynamics in adipocytes in triggering systemic metabolic dysregulation. Mitochondrial morphological changes, including mitochondrial biogenesis, mitophagy, fusion, and fission, have been observed in skeletal muscle,[109] but future research is needed to establish whether mitochondrial morphology plays the same role in adipose tissue.

Lifestyle changes, such as nutrition and exercise, that promote endothelial and mitochondrial function also have a place in the prevention of obesity and metabolic syndrome. Exercise mode, duration, and intensity that elicit optimal benefits for adipose tissue function need to be established. Clinically, bariatric surgery seems to preserve a favorable metabolic profile in adipose tissue. Future studies should examine the efficacy of lifestyle modification on preventing redevelopment of obesity after bariatric surgery.

CONCLUSION

In the present review, we summarized existing knowledge of the effects of exercise on angiogenesis and mitochondrial remodeling in the context of healthy and unhealthy adipose tissue expansion, as illustrated in Fig. 1. Future studies are needed to determine the length of time after which adipose tissue is irreparable by stimulating angiogenesis so that physicians can prescribe angiogenesis inhibitors. Furthermore, future research in this area should identify a biomarker that physicians can use to prescribe anti-angiogenic drugs when they are most appropriate. There is a great potential for further research to lead to new treatment options that would be beneficial in the later stages of obesity by promoting mitochondrial fission and inhibit angiogenesis. Overall, identifying genes related to exercise and their related pathways suggest potential novel therapeutic targets for obesity treatments. Exploration in this area will lead to novel mechanisms and applications, along with new treatments for obesity and metabolic syndrome.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

Study concept and design: BMM, JYP; drafting of the manuscript: BMM; acquisition of data: BMM, SGH, and JS (Junchul Shin); critical revision of the manuscript: all authors; analysis and interpretation of data: all authors; obtained funding: JYP; and study supervision: JYP.

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