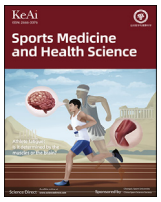
Sports Medicine and Health Science 4 (2022) 18–28

Contents lists available at ScienceDirect

Sports Medicine and Health Science

journal homepage: www.keaipublishing.com/en/journals/sports-medicine-and-health-science/



Review

Exercise training modulates adipokine dysregulations in metabolic syndrome

Parvin Babaei [a,b,c,*], Rastegar Hoseini [d]

[a] Cellular & Molecular Research Center, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran
[b] Neuroscience Research Center, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran
[c] Department of Physiology, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran
[d] Department of Sports Physiology, Faculty of Sport Sciences, Razi University, Kermanshah, Iran

ARTICLE INFO

Keywords:
Adipokines
Insulin resistance
Aerobic training
Resistance training
Metabolic syndrome

ABSTRACT

Metabolic syndrome (MetS) is a cluster of risk factors for various metabolic diseases, and it is characterized by central obesity, dyslipidemia, hypertension, and insulin resistance. The core component for MetS is adipose tissue, which releases adipokines and influences physical health. Adipokines consist of pro and anti-inflammatory cytokines and contribute to various physiological functions. Generally, a sedentary lifestyle promotes fat accumulation and secretion of pro-inflammatory adipokines. However, regular exercise has been known to exert various beneficial effects on metabolic and cognitive disorders. Although the mechanisms underlying exercise beneficial effects in MetS are not fully understood, changes in energy expenditure, fat accumulation, circulatory level of myokines, and adipokines might be involved. This review article focuses on some of the selected adipokines in MetS, and their responses to exercise training considering possible mechanisms.

Introduction

Metabolic syndrome

Metabolic syndrome (MetS) is a clustering of symptoms or conditions including; central obesity, high blood pressure, hyperglycemia, insulin resistance, and dyslipidemia.[1] Among them, central obesity, has been viewed as a serious problem of the 21st-century,[2] and is associated with various metabolic disorders.[3] Excess visceral fat, causes the secretion of bioactive peptides; known as adipokines, and thus, links with other parts of the body. Adipokines comprise classical cytokines and chemokines and contribute to different physiological functions such as regulation of appetite, energy expenditure, and metabolism.[4,5] Currently their numbers supersede 800, because of heterogeneity of the adipose tissue. To simplify, they are categorized into two distinct classes of pro-inflammatory and anti-inflammatory adipokines.[6,7] These peptides fuel the crosstalk feedback loops with other organs[8,9] particularly with skeletal muscles and mediate metabolic regulations. Since the production and secretion of adipokines, play a central role in chronic inflammation,[10] understanding the scenario behind physiological mechanisms, may provide appropriate strategies for controlling insulin resistance and further related disorders.

Insulin and its signaling cascade normally control cell growth, metabolism, and survival through activation of Mitogen-Activated Protein Kinases (MAPKs) and Phosphoinositide-3-Kinase (PI3K), of which activation of PI-3K-associated with Insulin Receptor Substrate (IRS)-1/2, Protein Kinase B (Akt), Forkhead Box O1 (FOXO1). Inactivation of Akt and activation of FOXO1, through suppression of IRS1 and IRS-2 in different organs following hyperinsulinemia and metabolic inflammation, may provide the underlying mechanisms for MetS in humans.[11] Insulin regulates fat metabolism in peripheral tissues by activating complex signaling pathways including PI3K/AKT, and MAPK, by binding to FOXO and proliferator-activated receptor γ (PPARγ) transcription factors. Insulin resistance disrupts these pathways and causes hyperglycemia and dyslipidemia. Dyslipidemia, or fatty disorders, is the result of the accumulation of free fatty acids in the liver along with insulin-enhanced lipogenesis, which increases triglyceride production and secretion. This condition, along with increased hepatic absorption and renal clearance of High-Density Lipoprotein (HDL) cholesterol, causes a disturbance of the fat profile, i.e., decreasing HDL cholesterol and increasing triglycerides (TG), both of which are seen in the MetS.[11]

MetS prevention and treatment require appropriate behavioral interventions including both dietary and exercise. Considering the important roles of adipokines in MetS, and the molecular link between exercise and other tissues, here we review the effects of aerobic and resistance

* Corresponding author. Cellular & Molecular Research Center, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran.
E-mail addresses: p_babaei@gums.ac.ir (P. Babaei), r.hoseini@razi.ac.ir (R. Hoseini).

https://doi.org/10.1016/j.smhs.2022.01.001
Received 22 September 2021; Received in revised form 1 January 2022; Accepted 7 January 2022
Available online 20 January 2022

Abbreviations

AMPK	5′ Adenosine Monophosphate-Activated Protein Kinase
AT	Aerobic Training
BAIBA	β-amino-isobutyric Acid
ERK	Extracellular Signal-Regulated Protein Kinase
FOXO	Forkhead Box O
GLUT4	Glucose Transporter Type 4
JNK	c-Jun N-terminal kinases
HDL	High-Density Lipoprotein
IKK	Inhibitory-κB Kinase
IL	Interleukin
IRS-1/2	Insulin receptor substrate 1/2
LDL	Low-Density Lipoprotein
MAPK	Mitogen-Activated Protein Kinase
MetS	Metabolic Syndrome
NF-κB	Nuclear Factor Kappa-Light-Chain-Enhancer Of Activated B Cells
PGC-1α	PPARγ Co-Activator 1α
PKB	Protein kinase B
PPAR	Peroxisome Proliferator-Activated Receptor
PI3K	Phosphoinositide 3-kinase
RT	Resistance Training
SFRP5	Secreted Frizzled Related Protein 5
SREBP-1c	Sterol Regulatory Element-Binding Protein 1c
TG	Triglyceride
TNFR	Tumor Necrosis Factor receptor
TNF-α	Tumor Necrosis Factor- Alpha
eNOS	Nitric Oxide Synthase
ROS	Reactive Oxygen Species
TLR4	Toll-Like Receptors 4
Wnt5a	Wnt Family Member 5A
p38–MAPK	p38 Mitogen-Activated Protein Kinase
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
mTOR	Mammalian Target of Rapamycin
TNFR1	Tumor Necrosis Factor Receptor Type 1
HR_{max}	Maximum Heart Rate

Table 1
Summary of the selected adipokines alteration in response to MetS, RT, and AT.

Adipokines	MetS	AT	Possible Mechanisms	RT	Possible Mechanisms
Irisin	Decrease	Increase	Decreased body fat percentage and insulin resistance	Increase	Improved body composition and insulin function
Visfatin	Increase	Decrease	Body fat mass reduction	Decrease	Improved body composition
Resistin	Increase	Decrease	Improved insulin resistance, inflammatory markers, and glycosylated hemoglobin	Decrease	Decreased body fat percentage and insulin resistance
Chemerin	Increase	Decrease	Decreased body fat percentage and improved lipid profile	Decrease	Decreased body fat percentage and insulin resistance
Retinol Binding Protein 4 (RBP4)	Increase	Decrease	Decreased body fat percentage	Decrease	Decreased glucose and improved insulin sensitivity
Interleukin 8 (IL-8)	Increase	Decrease	Decreased body fat mass and inflammatory markers	Decrease	Decreased body fat mass and increased proinflammatory cytokines
Interleukin 10 (IL-10)	Increase	Decrease	Weight loss and body fat percentage reduction	Decrease	Body fat mass reduction
Interferon gamma (IFN-γ)	Increase	Decrease	Decreased inflammatory markers	Decrease	Improved body composition and insulin sensitivity
C1q/TNF-related protein (CTRP4)	Increase	Decrease	Decreased insulin and increased fat oxidation	Decrease	Decreased body fat percentage and insulin resistance

training (AT and RT) on the selected adipokines in MetS models. Some of the other classical adipokines have been summarized in Table 1 briefly.

It is worth mentioning that information provided in the manuscript is the most current knowledge on signaling pathways and these pathways are not fully elucidated.

Effects of exercise on MetS

A sedentary lifestyle results in hypertension, dyslipidemia, high blood glucose, and obesity, while regular physical activity successfully prevents the progression of metabolic diseases.[12] Exercise is an important non-pharmacological tool, which exerts remarkable beneficial effects on various functional systems of the human body.[12] Although the exact mechanism of the beneficial effect of regular exercise on organs function has not been understood yet, several biological mechanisms may be responsible including reduced visceral adiposity, TG, Low-Density Lipoproteins (LDL),[13] blood pressure,[14] and systemic inflammation,[15] increased HDL[16,17] and improved insulin sensitivity.[18] Regular exercise, importantly, performed at low/moderate intensities, exerts anti-inflammatory effects[19,20] and modulate metabolic homeostasis,[21] partly by increasing anti-inflammatory adipokines.[22,23]

It has been known that skeletal muscles and adipose tissues are among the first target organs for exercise training. They are characterized as an endocrine organ due to the various cytokines production (those are produced by adipose tissues are named adipokines, and those by skeletal muscles are named myokines).[24] These molecules demonstrate autocrine, paracrine, and endocrine effects, and have metabolic consequents.[25] Exercise alters adipokines levels by modulating genes expression and also activating/inactivating proteins involved in their signaling pathways.[26] For example, the lipolytic action of exercise needs phosphorylation of 5′ Adenosine Monophosphate-Activated Protein Kinase (AMPK) to reduce the Sterol Regulatory Element-Binding Protein 1c (SREBP-1c).[27,28] AMPK inhibits hepatic TG synthesis suppressing acetyl-CoA carboxylase,[29] and promotes fatty acid oxidation and reduction in fat mass.[30,31] Other beneficial effects of exercise are related to increased peripheral glucose uptake[32] which takes place via activating PI3K, and translocating the Glucose Transporter Type 4 (GLUT4) into the skeletal muscles cell membranes,[33] and also increasing AMPK activity, which increases insulin sensitivity.[34] Some of these signaling pathways are likely regulated by adipokines secreted by adipose tissues during exercise which provide health benefits. Bellow, we review some of the important adipokines alteration, first in response to MetS and then exercise training.

Adiponectin in MetS

Human adiponectin is a peptide, comprised of 244 amino acids produced by adipose tissues, skeletal muscles, and cardiac cells.[35,36] It has been known that low adiponectin level is associated with MetS prevalence,[35,36] insulin resistance,[37,38] coronary heart disease,[39] and

inflammation-related diseases.[40,41] Adiponectin exerts a multitude of physiological actions against inflammation, insulin resistance, MetS, obesity, cardiac fibrosis,[42] fat accumulation in the liver,[37,38] and atherosclerosis.[43] The increased adiponectin induces insulin sensitivity in skeletal muscles by binding with adiponectin receptor type 1 and 2, leading to the activation of various signaling pathways such as IRS-1/2, AMPK, and p38 Mitogen-Activated Protein Kinase (p38–MAPK).[44] Also adiponectin alters nitric oxide level and leads to vasoprotective effects via activating AMPK[45] and cyclooxygenase II.[46] Moreover, adiponectin alleviates the inflammatory responses by inhibiting Tumor Necrosis Factor-Alpha (TNF-α), Interleukin-6 (IL-6), Interleukin-10 (IL-10), and Interleukin-1 (IL-1),[42] via Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells (NF-κB), and Protein Kinase A (PKA).[47] In consistency, deficiency in adiponectin receptors or AMPK, leads to significantly reduced glucose intolerance, increased hepatic triglyceride, inflammation, and oxidative stress.[48]

Effect of AT and RT on adiponectin levels

AT has been shown to cause weight loss and increase lipolysis,[49] partly via elevating adiponectin secretion in both human and animal models.[50,51] Subsequently, adiponectin modifies HDL and LDL concentration and stimulates glucose uptake in peripheral tissues.[52,53] It is assumed that lactate accumulation, elevated adrenalin, glycogen depletion, and acidosis, have stimulatory effects on adiponectin secretion in both ovariectomized rats model of MetS[54] and obese humans.[55,56] To date, the exact effect of Resistance Training (RT) on adiponectin is not apparent. Ward et al.[57] showed a significantly decreased plasma adiponectin in postmenopausal women and elevation after 15 weeks of RT engagement. Also, de Mello et al.[58] showed a significant increased in adiponectin level, following both protocols of AT singly, and combined with RT, however, combination of AT and RT showed superiority to AT in obese adolescents with MetS.

Mechanistically, RT has been shown to increase muscle mass, decrease body fat percentage by increasing resting energy consumption in MetS patients,[59] increasing blood flow, and shifting adiponectin to plasma.[60] Moreover, a combination of AT with RT, has been shown to increase adiponectin levels in obese Type 2 diabetes (T2D) patients and reduce insulin resistance and central adiposity.[61] Although other mechanisms such as releasing myokines, or various hormones such as adrenalin and glucocorticoids are warranted.[62]

Finally, exercise-increased adiponectin level demonstrates an excellent potential strategy for developing novel therapeutic approaches for MetS.

Leptin in MetS

Leptin is a 167 amino acid peptide, which is transcribed from the *LEP* gene, located on chromosome 7 in adipocytes. It acts on a specific cytokine family receptor in the arcuate and ventromedial nucleus of the hypothalamus,[63] and regulates energy balance by suppressing appetite and increasing energy expenditure.[64,65] Also leptin acts peripherally, regulating lipid and glucose metabolism, through other hormones such as insulin, glucagon, insulin-like growth factor, growth hormone, and glucocorticoids.[64,65] An animal study reported that both leptin muted mice of ob/ob and db/db are markedly hyperglycemic and glucose intolerant, independently of their body weight and that, the hyperglycemia of ob/ob mice can be readily normalized by leptin infusion into the brain.[66] Circulating leptin levels are correlated with body fat stores, so that, the decreased leptin levels set off a series of biological reactions to reduce energy expenditure and prevent weight loss.[67] The binding of leptin to its receptors leads to activation of Janus Kinase 2 (JAK2)/Signal Transducer And Activator Of Transcription 3 (STAT3), IRS-1, PI3K, and AMPK signaling pathways.[68–70] In particular, the activation of JAK2/STAT3 signaling was found to be critically involved in the modulatory effects of leptin on energy homeostasis.[70] When the cytosolic domain of the leptin receptor becomes phosphorylated by JAK proteins, it activates the MAPK/Extracellular Signal-Regulated Protein Kinase (ERK) 1/2 pathway. Pharmacological inhibition of this domain and ERK1/2 in the hypothalamus blocks the anorectic effects of leptin and results in mild obesity.[71] While, leptin activates AMPK in hepatocytes and muscle tissue,[72] it inhibits AMPK in the hypothalamus, hence reducing food intake and body weight.[73,74]

Although leptin reduces appetite as a circulating signal, obese individuals exhibit a higher circulating leptin concentration than normal-weight, suggesting a leptin resistance condition in obese individuals.[75]

Effect of AT and RT on leptin levels

Studies showed that lower physical activity levels, induce leptin resistance and hyperleptinemia,[76] but higher levels, decrease circulating leptin by targeting a negative energy balance in obese individuals.[77] It has been suggested that AT (in Wistar rats)[78,79] and RT (in elderly postmenopausal women),[80] exert beneficial effects on leptin sensitivity with or without weight loss. AT has been shown to reverse leptin resistance and reduce serum leptin levels in obese mice by down-regulating the suppressor of cytokines-3 in the JAK/STAT pathway.[81] Moreover, leptin is very sensitive to energy-deficient status, so that, two or three days of fasting, lowers plasma leptin levels even before any loss in body fat mass.[64,65] There is evidence showing that AT might regulate leptin secretion by increasing energy expenditure, sympathetic activity, and exercise stress metabolites.[77]

However, some studies suggested relatively unchanged or reduced serum leptin following RT in overweight individuals,[82,83] and some studies reported an increased fat-free mass together with decreased leptin concentrations in MetS following RT.[67,84] For an instant, Fedewa et al.[85] reported that chronic exercise training (≥2 weeks; both AT or RT) leads to reduced leptin levels in elderly postmenopausal women, regardless of age and sex, but dependent on body fat percentage. Besides reducing fat mass, other mechanisms involved during a moderate to severe RT on leptin levels include peripheral glucose uptake, in the presence of lactate and acidosis, sympathetic stimulation of the adrenal gland, and glycogen depletion in elderly postmenopausal women.[86]

The mechanisms by which exercise training increases leptin levels have not been elucidated yet. It seems that PI3K/AKT, and Mammalian Target of Rapamycin (mTOR),[87,88] PPARγ pathways, might be involved.[89,90] Exercise training also affects the secretion of leptin, indirectly by altering glucocorticoids, serotonin, and estrogen levels in obese children.[91] Insulin and glucocorticoid are known to function synergistically as long-term regulators of leptin expression by transcriptional or post-transcriptional mechanisms.[92]

In conclusion, long-term AT and RT with moderate to high intensities, modulate leptin serum concentration and thus regulate energy balance, appetite, and lipid/glucose metabolism in MetS.[89,90]

Omentin in MetS

Omentin is a 313 amino acids adipokine, with two isoforms of omentin-1 and omentin-2. Omentin-1 mRNA is expressed in visceral adipose tissue and stands as a predominant form of plasma.[93,94] Clinical studies showed that circulating omentin-1 concentration is decreased in MetS and obesity.[95,96] In contrast, an increased level of omentin might reflect the physiological compensatory mechanism in regulating insulin sensitivity[97] and glucose homeostasis.[95] Omentin-1 stimulates IRS and increases high-density lipoprotein, and finally, stimulates lipolysis.[98,99] Also, administration of exogenous omentin-1, significantly decreases blood pressure in normotensive rats probably via enhancing the synthesis of NO and inhibiting Interleukin 6 (IL-6),[100] besides energy expenditure regulation in skeletal muscles.[101,102] In addition, omentin exerts extensive protective effects via various cell signaling pathways including AMPK.[101,102] Then omentin-induced AMPK phosphorylation reduces the Ras/ERK signaling cascade,[103] and suppresses TNF-α in macrophages.[104]

In addition, omentin-1 enhances glucose uptake via activating PKB[105,106] and synergistically potentiates the adiponectin functions and alleviates insulin resistance.[107]

Effect of AT and RT on omentin levels

Studies showed that both AT and RT protocols increase omentin levels, and omentin exerts anti-inflammatory and insulin-sensitizing effects by inserting GLUT4 into the target cells membranes.[95,96] Animal studies showed an increase in serum omentin level parallel with alleviating MetS components in ovariectomized obese rats following AT and RT intervention.[108] For example, Madsen et al.[109] demonstrated increased serum omentin level following strenuous and moderate AT in ovariectomized rats. In contrast, Urbanová et al.[110] and Faramarzi et al.[111] showed no change in omentin following long-term low intensity AT intervention, despite a significant reduction in body weight, fasting insulin, and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR). Interestingly, Huang L, reported a reduction in serum omentin levels in obese rats following AT (75% $\dot{V}O_2$max).[112] Collectively, AT is capable to modulate the production of omentin, as a cross-talk cytokine linking muscle and adipose tissues in T2D Mellitus rat models.[99] Finally, increased omentin level by AT and RT improves insulin sensitivity and glucose metabolism[113] via stimulating phosphorylation of PKB and AMPK.[102,114] Conversely, a negative correlation between omentin-1 and insulin, glucose, and IL-6 [99,115] but a positive with adiponectin levels[114] have been found. Thus, exercise-induced omentin elevation might regulate glucose homeostasis and stimulate lipolysis. Taken all together, high and moderate-intensity AT induce more favorable effects on the increased omentin production and secretion. RT is also capable to increase omentin serum levels, however, the evidence on different intensities is rare.

Apelin in MetS

Apelin is a 36 amino-acid peptide that contributes to glucose metabolism, lipolysis, blood pressure, cardiovascular functions, fluid homeostasis, food intake, and vasodilation.[116] A positive association has been reported between high circulating apelin levels and insulin resistance,[117,118] hypertension, heart failure, central obesity,[118] high blood glucose, and dyslipidemia,[119] although elevated apelin might be a physiological compensatory response to MetS.[120] Apelin is expressed by adipose tissue and promotes glucose uptake through GLUT4, and alleviates insulin resistance by activating PI3K/AKT.[121] In agreement with these findings, administration of recombinant apelin, increases glucose utilization[122] and reduces blood glucose.[123–125] Apelin receptor is a G protein-coupled receptor, which is expressed in vascular smooth muscle and myocardial cells.[126] Clinical and experimental studies support a role for apelin in cardiovascular and metabolic disorders[127] via AMPK, Endothelial Nitric Oxide Synthase (eNOS), PKB,[124] and ERK1/2,[128] pathways. Apelin improves glucose tolerance and insulin sensitivity, mainly by improving the skeletal muscles' metabolic functions[125] and stimulating glucose transport in an AMPK-dependent manner.[124] The ability of apelin to decrease blood glucose together with vasodilation and also reduction in blood pressure may open new therapeutic avenues for MetS.

Effect of AT and RT on apelin levels

The literature regarding exercise effects on apelin concentration in MetS status is inconsistent. For example, Besse-Patin et al.[129] reported a twofold increase in apelin mRNA level in muscle, but not in adipose tissue following an 8-week AT program indicating upregulated muscle apelin expression in obese men. Another study in overweight subjects reported a considerable upregulation in apelin following 12 weeks of AT even with no significant weight loss in patients with T2D.[130] Jang et al.[131] and Nikseresht et al.[132] suggested a significant elevation in apelin only following AT, but not RT in obese individuals. However a recent study reported an elevated apelin by RT.[133] Considering the mechanisms underlying the effects of exercise on apelin, rodent studies have shown that the AT mediates GLUT-4 translocation to the cell membranes, and then might decrease apelin gene expression.[129,132] On the other hand, RT-induced fatty acid oxidation might reduce apelin levels by increasing lipoprotein lipase activity in muscles and decreasing insulin resistance.[133]

Taken all together, long-term AT and RT, are efficient in reducing apelin levels in favor of AT.

Future studies are needed to clarify the effect of exercise intensity on apelin level in MetS.

Vaspin in MetS

Vaspin is formed of 412–415 amino acids released by adipose tissue that is associated with insulin resistance, obesity, and glucose intolerance in many diseases.[134,135] Kloting et al.[136] stated in their study that insulin sensitivity is the critical determinant of vaspin gene expression in adipose tissue. Surprisingly, administration of insulin, significantly upregulated vaspin mRNA in subcutaneous adipose tissue but reduced visceral fat.[137,138] Conversely, administration of recombinant human vaspin in diabetic mice, significantly improved insulin sensitivity and glucose tolerance, increased GLUT4 and adiponectin in adipose tissues, whereas, suppressed leptin, resistin, and TNF-α.[137,138] Overall, vaspin serves as an insulin sensitizer and anti-inflammatory adipokine.[139]

It has been reported that the effects of vaspin on glycemic control are mediated by inhibiting kallikrein 7; an in vitro protease degradation of human insulin.[140] Also, vaspin might protect blood vessels by preventing free fatty acid-induced apoptosis in human vascular endothelial cells via PI3K/AKT/eNOS signaling pathway upregulation.[141,142] In addition, vaspin inhibits NF-κB/Protein Kinase C (PKC) in vascular smooth muscle cells,[143,144] and suppresses the JAK2/STAT3 signaling pathway activity.[145]

Effect of AT and RT on vaspin levels

Studies suggested that vaspin levels could be suppressed following different exercise protocols.[146,147] It is known that vaspin concentration is lower in well-trained individuals compared to those with low physical fitness.[148] Chang et al. and Shahdadi et al.[135,149] showed a reduction in serum vaspin levels after AT in obese subjects. In contrast, a higher vaspin level has been found following 4-week AT in obese and T2D subjects.[148] Also, Kadoglou et al. and Youn et al.[130,148] reported an increase in serum vaspin levels in T2D patients and suggested that vaspin improves insulin sensitivity. Similar to AT, vaspin serum level is changed differently in response to RT. For example, two studies reported a significant reduction in serum vaspin level following RT in obese individuals,[135,149] in contrast with Mahdirejei et al.[150] who reported no significant alteration. RT might induce decreased vaspin mRNA expression secondary to muscle hypertrophy, increased basal metabolic rate, fat oxidation, and ultimately weight loss.[151] It seems that vaspin serum concentration might be differentially regulated in an enzyme (nicotinamide phosphoribosyl transferase enzyme)-dependent manner.[135,149] The exact signaling pathways by which AT and RT suppress vaspin production needs more investigation.

TNF-α and IL-6 in MetS

MetS is accompanied by an increase in pro-inflammatory cytokines,[152] particularly TNF-α and IL-6.[153,154] TNF-*α* is secreted by abdominal adipose tissue and immune system, and plays significant roles in inflammation and insulin resistance.[155] For instance, TNF-*α* and its receptor genetic deletion, significantly improved insulin signaling in muscle and adipose tissue.[156] Although the baseline expression of TNF-*α*

in adipose tissues is relatively low, it is positively correlated with obesity and negatively with weight loss.[157] TNF-α elevation has been repo reported to associate with morbidity and mortality in MetS.[158,159] A parallel increase in both TNF-α and insulin resistance, together with visceral fat accumulation has been also found in rats model of MetS.[160,161] It has been known that TNF-α induces insulin resistance in the skeletal muscles by promoting fatty acids incorporation into triacylglycerol via increasing several kinases.[162] Some of these stress-related kinases, perpetuate a positive feedback mechanism for more TNF-α production, and promote chronic insulin resistance.[163] In addition, increased TNF-α level induces hepatic fatty acids uptake, reduces fatty acid oxidation and TG export, together with elevation in mitochondrial Reactive Oxygen Species (ROS).[164] Besides, higher level of TNF-α causes elevation in IL-6 as the secondary defense response. IL-6 secreted from adipose tissues has both pro-and anti-inflammatory effects and causes a wide range of different effects on lipid and glucose metabolism.[165,166] Thus, TNF-α likely stands as a pro-inflammatory adipokine, and representative marker in the MetS pathogenesis and cardiovascular burden. TNF-α neutralization by antibodies or antagonists might be a future candidate therapy in MetS.

Two TNF-α receptors have been identified: Tumor Necrosis Factor Receptor Type 1 (TNFR1) and 2 (TNFR2). It is believed that TNFR1 is responsible for inflammatory actions, and mediates insulin resistance[167] via down-regulating the insulin receptor expression, insulin-related substrate-1, stress-related kinases, and GLUT4.[168] In other words, increased TNF-α directly inhibits IRS-1 tyrosine phosphorylation, and also activates protein-tyrosine phosphatases,[169] and indirectly acts via increasing IL-6, to reduce insulin-dependent glucose uptake.[170] IL-6 enhances lipolysis and fat oxidation via activation of AMPK[171] and increases the activity of the insulin-degrading enzyme, and thus inhibits downstream signaling of insulin.[172] Generally, TNF-α and IL-6 synergistically impair insulin signaling and induce chronic MetS.[173]

Effect of AT and RT on TNF-α and IL-6 levels

Exercise training has been known as the best non-invasive intervention without serious side effects, which alleviates inflammation and immune function in patients with MetS and diabetes.[174,175] Since adipose tissue releases inflammatory markers, long-term weight loss is a useful strategy to reduce the risk of high TNF-α and IL-6 levels in overweight and obese individuals.[176] However, existing literature regarding the TNF-α alteration following exercise seems to be dual. For instant, acute, intensive, and unaccustomed exercise training sessions increase the TNF-α and IL-6, while adaptation to long-term exercise protocols might reduce TNF- α and IL-6.[177,178] Allen et al.[179] reported no change in serum TNF- α following 9-week high-intensity AT in sedentary adults. While Abd El-Kader et al.[180] showed significantly decreased TNF-α and IL-6 following 3 months of AT in obese T2D patients (both men and women; aged 40–55 years). They also reported that moderate AT (65%–75% of maximum heart rate [HR_{max}]) was more effective in reducing TNF-α and IL-6 than mild AT (55%–65% of HR_{max}). Gerosa-Neto et al.[181] investigated the impact of 16-week high-intensity interval (90% HR_{max}) and moderate-intensity AT (70% HR_{max}) on subclinical inflammation in overweight or obese adults. They demonstrated that 16 weeks of training decreased blood levels of IL-6, but increased TNF-α in the high-intensity group. Interestingly TNF-α was decreased in the moderate-intensity group, suggesting efficacy for both high and moderate-intensity AT promoting changes in inflammatory profile in overweight or obesity subjects, in favor of moderate-intensity in case of TNF-α responses.

It seems that besides the contracting skeletal muscle cells, the local connective tissue produces more IL-6 as well, in response to a single-bout prolonged exercise in women with MetS.[182] It should be noticed that a single exercise session induces an acute robust inflammatory response, while chronic AT induces long-lasting adaptation that might be different from the primary response regardless of fat loss.[152,183] Studies showed that AT and RT (to a fewer extent) could be effective in the prevention and delay of chronic inflammatory diseases onset via reducing pro-inflammatory cytokines, particularly TNF-α in patients with MetS.[62,184,185]

Anti-inflammatory effects of exercise are related not only to adipose tissue but also to the skeletal muscle and peripheral blood mononuclear cells.[186] One of the possible exercise-induced mechanisms (in favor of AT) might be the reduced Toll-Like Receptors 4 (TLR4) expression in monocytes,[187,188] which are capable to induce TNF-α and IL-6 expression by activating NF-κB.[189] Increase in Inhibitory-κB Kinase (IKK) β phosphorylation, but inhibition in nicotinamide adenine dinucleotide phosphate oxidase, are the mechanisms by which RT might lead to reduced TNF-α and IL-6 mRNA expression and secretion in men with MetS.[174,190] Furthermore, in an animal study, 15-week moderate AT has been shown to confront metabolic disorders by suppressing TNF-α signaling responses and also promoting muscle energy-sensing network proteins, including AMPK, Sirtuin-1, PPARγ Co-Activator 1α (PGC-1α).[191]

Overall, regarding anti-inflammatory effects, long-term moderate AT and RT protocols, especially those inducing fat loss and muscle hypertrophy might be a good candidate therapy in MetS.

Wnt5a and SFRP-5 in MetS

Extensive investigations have reported the significance of the Wnt Family Member 5A (WNT5a) pathways in regulating body mass, glucose metabolism, lipogenesis, LDL clearance, vascular smooth muscle plasticity, liver fat, and liver inflammation.[192,193] WNT5a is an adipokine contributing to obesity-associated inflammation.[194,195] The WNT5a activity is regulated by Secreted Frizzled-Related Protein 5 (SFRP-5), an extracellular Wnt signaling antagonist. SFRP5 is an anti-inflammatory adipokine, secreted by adipocytes acts as a decoy receptor by binding WNT5a and preventing its association with frizzled proteins. Lower SFRP-5 levels are correlated with obesity, impaired glucose tolerance, insulin resistance, and T2D[196,197] which results in the activation of WNT5A canonical/non-canonical signaling pathways.[198,199] WNT5a exerts both inflammatory and anti-inflammatory effects, in part by modulating the NF-κB pathway.[200] Moreover, TNF-α has been known to induce WNT5a secretion from adipocytes and causes an imbalance in WNT5a/SFRP5 signaling.[194,201]

The Wnt signaling pathway is a ubiquitous signaling cascade that regulates a wide range of physiologic processes. There are three signaling pathways; the canonical pathway (β-catenin dependent), the non-canonical, and the Wnt/calcium signaling pathway.[193,202] In the canonical pathway, Wnt ligands bind to the frizzled receptor and low-density lipoprotein receptor-related protein (LRP) 5 or 6, resulting in the internuclear β-catenin accumulation and leading to transcriptional regulation.[193] In the non-canonical pathway, the Wnt ligands bind to the frizzled receptor and the receptor-like tyrosine kinase/RTK-like orphan co-receptors and activate the Rho/Rac signaling cascades. However, the non-canonical pathway promotes pro-inflammatory cytokines expression.[203] It should be also noticed that Wnt and SFRP-5 proteins undergo several post-translational modifications, including N-glycosylation and acylation, both of which are required for signaling activity rather than secretion.[204] Also, lipid modification, which is identified as palmitoleoylation, is essential for Wnt protein secretion.[204] In the Wnt/calcium signaling pathway, Wnt ligands bind to the frizzled receptor and activate phospholipase C, and then increase intracellular calcium level.[205] Some studies suggested non-canonical Wnt signaling as a metabolic dysregulation biomarker in both rats and humans with MetS.[195,206] Inversely, a higher SFRP5 level inhibits the non-canonical WNT5A pathway to improve insulin sensitivity.[207] Non-canonical Wnt signaling shifts the lipids storage from adipose tissue to liver and muscle, promoting metabolic complications of obesity such as insulin resistance[208,209] via activating c-Jun N-terminal Kinases (JNK) cascade, and IRS-1 serine phosphorylation.[210] Therefore, crosstalk of these signaling pathways promotes the pro-inflammatory state and MetS progression.[194,211] On the other hand, SFRP5 neutralizes non-canonical JNK activation by WNT5a in macrophages and adipocytes.[192] The JNK signaling pathway in

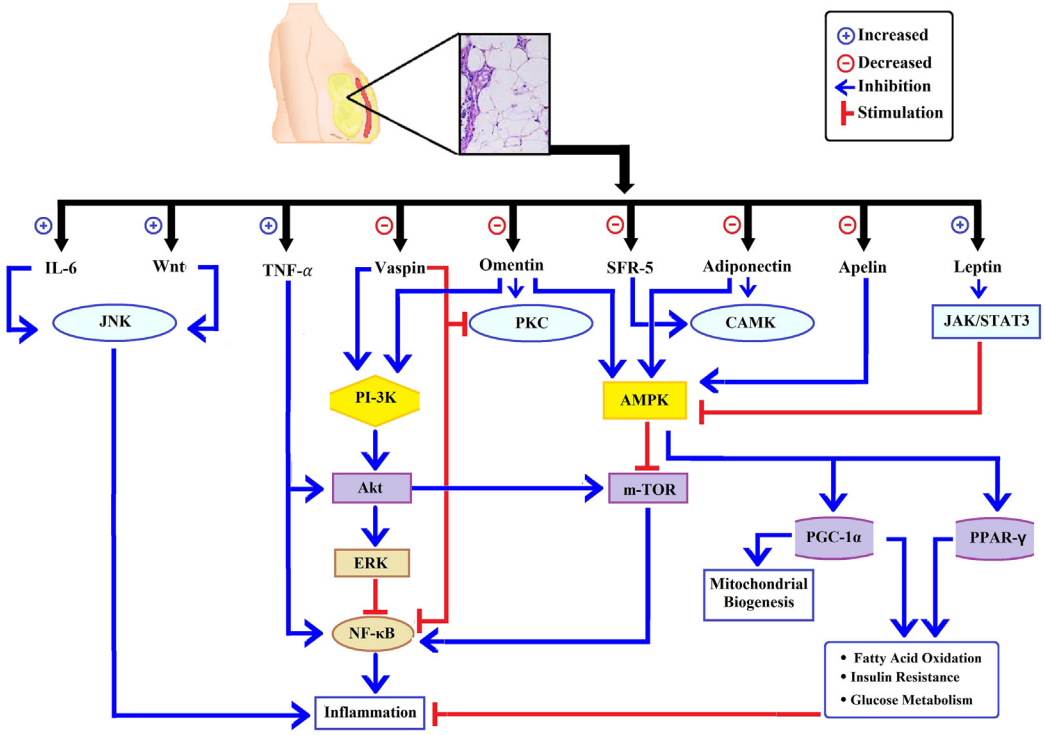


Fig. 1. Role of adipokines and AMPK/PPARɣ, mTOR and NF-Kβ, pathways in the development or progression of insulin resistance. in metabolic syndrome.

adipocytes and macrophages has emerged as an essential mediator of adipose tissue inflammation that affects systemic metabolism.[192,212] Thus, the SFRP5/JNK regulatory axis in fat represents a potential target for controlling obesity-linked abnormalities in glucose homeostasis by blocking the WNT5a.[213] Generally, impaired canonical Wnt signaling and the activation of non-canonical Wnt signaling constitute the underlying mechanisms for cardio-metabolic abnormalities.

Effect of AT and RT on Wnt and SFRP-5

It has been reported that an increase in non-canonical Wnt signaling in human visceral adipose tissue is positively associated with cardiovascular risk factors and insulin resistance, which can be alleviated by high-intensity AT.[160,195] Few studies considered the effect of RT on WNT5A/SFRP5. For example, Leal et al.[214] stated that eight-week RT triggers more significant responses in the Wnt pathway, and potently elevates the expression of Wnt pathway genes and β-catenin.[215,216] However, Mir et al.[217] showed an improvement of T2D as a result of increased SFRP5 serum level and decreased WNT5a serum level after 12 weeks of combined exercise (high intensity AT and RT) possibly due to the reduction in fat mass. They also reported a significant negative relationship between SFRP5 and WNT5A.

It seems that dysregulated Wnt signaling pathway, which underlies the pleiotropy of MetS might be alleviated by both AT and RT protocols. RT might potentiate the Wnt function by influencing various post-translational mediators of this pathway.[218] Then, Wnt binds to the cell surface transmembrane receptors which involve direct binding to several intracellular proteins including glycogen synthase kinase-3β, and disheveled.[204,219,220]

Therefore, combined AT and RT might elevate SFRP5 and reduce Wnt more significantly than a single protocol of either AT or RT.

Conclusion

Considering diverse and complex adipokines functions in MetS, summarizing their role and selecting one core link to the MetS, seems to be an oversimplification. Thus, a panel of adipokines rather than an individual biomarker would be a useful and relatively reliable marker for identifying those who are at risk for developing MetS and related diseases.

Our search strategy for this review focused on those adipokines that have been studied on MetS in various laboratories including ours. Data for this review were identified by searches of science direct advance search, PubMed, and WOS to get any related articles available using the terms" adipokine, adiponectin, omentin, apelin, leptin, Wnt5a, Sfrp5, IL-6, and MetS, AT and RT. We tried to include articles on the English language with preference to publications from the past 15 years.

The strength of this review is summarizing the selected adipokines alteration in MetS and response to AT and RT. However, there are some limitations such as not including myokines and other adipokines due to complexities and varieties.

Reviewing literature revealed that adipokines are categorized into two groups of pro and anti-inflammatory molecules. Pro-inflammatory is related to insulin resistance and inflammation, in contrast to anti-inflammatory which exerts insulin sensitivity and lipid homeostasis. Furthermore, both moderate AT and RT, successfully modulate the adipokines profile toward the health-promoting adipokines. Also, it could be concluded that the constant, long-lasting alterations in adipokines level are more prominent following long-term exercise protocols, in contrast with acute and high-intensity exercise which stimulates pro-inflammatory adipokines.

Although the exact mechanisms underlying the beneficial effects of AT and RT in MetS have not been understood well, modulation of adipokines secreted from adipose tissues, together with weight loss consequences, might be the most important factor linking the molecular signaling pathways with improved glucose homeostasis, and better metabolic state.

Moderate-intensity AT and RT are associated with improved insulin sensitivity, improved circulation, mitochondrial biogenesis, and the release of numerous adipokines. Currently, among various mechanisms, adiponectin/AMPK signaling seems to be the main mediator of metabotropic effects of exercise. These molecular signalings anticipate a better

understanding of mechanisms that will enable the development of pharmaceuticals, particularly for sedentary individuals who are at higher risk of developing Mets (Fig. 1, Graphical abstract).

For future studies, several important points should be considered:

- To clarify the source of circulating adipokines in response to MetS, AT, and RT
- To elucidate both up and down streams of adipokines together in response to a specified protocol of exercise to distinguish between cause and effect, compensatory or operative functions.
- To administrate recombinant adipokines, and also monoclonal antibodies in a rodent model to evaluate their effects on MetS.

Authors' contributions

Parvin Babaei drafted the MetS part based on the studies carried out in her lab and coordinated the contents of the manuscript. Rastegar Hoseini wrote the theoretical parts of the exercise. Both authors have read and approved the final version of the manuscript and agreed with the order of presentation of the authors.

Funding

No external source of funding was used in the preparation of this article.

Submission statement

Hereby we attest that the submitted manuscript has not been published previously, and it is not under consideration for publication elsewhere. We also agree that if accepted, it will not be published elsewhere including electronically in the same form, in English or in any other language.

Conflict of interest

The authors report no biomedical financial interests or potential conflicts of interest.

References

1. Alonso-Gómez AM, Tojal Sierra L, Fortuny Frau E, et al. Diastolic dysfunction and exercise capacity in patients with metabolic syndrome and overweight/obesity. *Int J Cardiol Heart Vasc*. 2018;22:67–72. https://doi.org/10.1016/j.ijcha.2018.12.010.
2. Dibaise JK, Foxx-Orenstein AE. Role of the gastroenterologist in managing obesity. *Expet Rev Gastroenterol Hepatol*. 2013;7(5):439–451. https://doi.org/10.1586/17474124.2013.811061.
3. Abdelaal M, le Roux CW, Docherty NG. Morbidity and mortality associated with obesity. *Ann Transl Med*. 2017;5(7):161. https://doi.org/10.21037/atm.2017.03.107.
4. Funcke J-B, Scherer PE. Beyond adiponectin and leptin: adipose tissue-derived mediators of inter-organ communication. *J Lipid Res*. 2019;60(10):1648–1684. https://doi.org/10.1194/jlr.r094060.
5. Santilli F, D'Ardes D, Teresa Guagnano M, Davi G. Metabolic syndrome: sex-related cardiovascular risk and therapeutic approach. *Curr Med Chem*. 2017;24(24):2602–2627. https://doi.org/10.2174/0929867324666170710121145.
6. Chung HS, Choi KM. Adipokines and myokines: a pivotal role in metabolic and cardiovascular disorders. *Curr Med Chem*. 2018;25(20):2401–2415. https://doi.org/10.2174/0929867325666171205144627.
7. Peterson JM, Clark WA, Marrs J-A, Alamian A. Serum adipokines and metabolic syndrome risk factors in hispanic children. *Faseb J*. 2017;31(S1):1037. https://doi.org/10.1096/fasebj.31.1_supplement.1037.5.
8. Hu X, Guo F. Amino acid sensing in metabolic homeostasis and health. *Endocr Rev*. 2021;42(1):56–76. https://doi.org/10.1210/endrev/bnaa026.
9. Sinha RA, Singh BK, Yen PM. Reciprocal crosstalk between autophagic and endocrine signaling in metabolic homeostasis. *Endocr Rev*. 2017;38(1):69–102. https://doi.org/10.1210/er.2016-1103.
10. You T, Nicklas BJ, Ding J, et al. The metabolic syndrome is associated with circulating adipokines in older adults across a wide range of adiposity. *J Gerontol A Biol Sci Med Sci*. 2008;63(4):414–419. https://doi.org/10.1093/gerona/63.4.414.
11. Guo S. Insulin signaling, resistance, and the metabolic syndrome: insights from mouse models to disease mechanisms. *J Endocrinol*. 2014;220(2):T1–T23. https://doi.org/10.1530/joe-13-0327.
12. Nieman DC, Wentz LM. The compelling link between physical activity and the body's defense system. *J Sport Health Sci*. 2019;8(3):201–217. https://doi.org/10.1016/j.jshs.2018.09.009.
13. Smith GI, Mittendorfer B, Klein S. Metabolically healthy obesity: facts and fantasies. *J Clin Invest*. 2019;129(10):3978–3989. https://doi.org/10.1172/jci129186.
14. Imazu AA, Goessler KF, Casonatto J, Polito MD. The influence of physical training status on postexercise hypotension in patients with hypertension: a cross-sectional study. *Blood Pres Monit*. 2017;22(4):196–201. https://doi.org/10.1097/mbp.0000000000000255.
15. Batista Jr M, Rosa J, Lopes R, et al. Exercise training changes IL-10/TNF-α ratio in the skeletal muscle of post-MI rats. *Cytokine*. 2010;49(1):102–110. https://doi.org/10.1016/j.cyto.2009.10.007.
16. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. *CMAJ (Can Med Assoc J)*. 2006;174(6):801–809. https://doi.org/10.1503/cmaj.051351.
17. Mitsui R, Fukushima M, Taniguchi A, et al. Insulin secretory capacity and insulin sensitivity in impaired fasting glucose in Japanese. *J Diabetes Investig*. 2012;3(4):377–383. https://doi.org/10.1111/j.2040-1124.2012.00201.x.
18. Tan X, Chapman CD, Cedernaes J, Benedict C. Association between long sleep duration and increased risk of obesity and type 2 diabetes: a review of possible mechanisms. *Sleep Med Rev*. 2018;40:127–134. https://doi.org/10.1016/j.smrv.2017.11.001.
19. Lira FS, Rosa JC, Zanchi NE, et al. Regulation of inflammation in the adipose tissue in cancer cachexia: effect of exercise. *Cell Biochem Funct*. 2009;27(2):71–75. https://doi.org/10.1002/cbf.1540.
20. Batista Júnior ML, Lopes RD, Seelaender MCL, Lopes AC. Anti-inflammatory effect of physical training in heart failure: role of TNF-α and IL-10. *Arq Bras Cardiol* [in Portuguese]. 2009;93(6):692–700. https://doi.org/10.1590/s0066-782x2009001200021.
21. Kruk J, Kotarska K, Aboul-Enein BH. Physical exercise and catecholamines response: benefits and health risk: possible mechanisms. *Free Radic Res*. 2020;54(2-3):105–125. https://doi.org/10.1080/10715762.2020.1726343.
22. Bruunsgaard H. Physical activity and modulation of systemic low-level inflammation. *J Leukoc Biol*. 2005;78(4):819–835. https://doi.org/10.1189/jlb.0505247.
23. Neves M, Retameiro ACB, Tavares ALF, et al. Physical exercise and low-level laser therapy on the nociception and leukocyte migration of Wistar rats submitted to a model of rheumatoid arthritis. *Laser Med Sci*. 2020;35(6):1277–1287. https://doi.org/10.1007/s10103-019-02905-2.
24. Trayhurn P, Drevon CA, Eckel J. Secreted proteins from adipose tissue and skeletal muscle–adipokines, myokines and adipose/muscle cross-talk. *Arch Physiol Biochem*. 2011;117(2):47–56. https://doi.org/10.3109/13813455.2010.535835.
25. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. *J Clin Endocrinol Metab*. 2004;89(6):2548–2556. https://doi.org/10.1210/jc.2004-0395.
26. Sjøberg KA, Frøsig C, Kjøbsted R, et al. Exercise increases human skeletal muscle insulin sensitivity via coordinated increases in microvascular perfusion and molecular signaling. *Diabetes*. 2017;66(6):1501–1510. https://doi.org/10.2337/db16-1327.
27. Yoon KJ, Zhang D, Kim SJ, Lee MC, Moon HY. Exercise-induced AMPK activation is involved in delay of skeletal muscle senescence. *Biochem Biophys Res Commun*. 2019;512(3):604–610. https://doi.org/10.1016/j.bbrc.2019.03.086.
28. Huang J, Wang X, Zhu Y, et al. Exercise activates lysosomal function in the brain through AMPK-SIRT1-TFEB pathway. *CNS Neurosci Ther*. 2019;25(6):796–807. https://doi.org/10.1111/cns.13114.
29. Marwarha G, Claycombe-Larson K, Lund J, Ghribi O. Palmitate-Induced SREBP1 expression and activation underlies the increased BACE 1 activity and amyloid beta genesis. *Mol Neurobiol*. 2019;56(7):5256–5269. https://doi.org/10.1007/s12035-018-1451-8.
30. Olivier S, Foretz M, Viollet B. Promise and challenges for direct small molecule AMPK activators. *Biochem Pharmacol*. 2018;153:147–158. https://doi.org/10.1016/j.bcp.2018.01.049.
31. Islam H, Hood DA, Gurd BJ. Looking beyond PGC-1α: emerging regulators of exercise-induced skeletal muscle mitochondrial biogenesis and their activation by dietary compounds. *Appl Physiol Nutr Metabol*. 2020;45(1):11–23. https://doi.org/10.1139/apnm-2019-0069.
32. Ramachandran V, Saravanan R. Glucose uptake through translocation and activation of GLUT4 in PI3K/Akt signaling pathway by asiatic acid in diabetic rats. *Hum Exp Toxicol*. 2015;34(9):884–893. https://doi.org/10.1177/0960327114561663.
33. Vega RB, Konhilas JP, Kelly DP, Leinwand LA. Molecular mechanisms underlying cardiac adaptation to exercise. *Cell Metabol*. 2017;25(5):1012–1026. https://doi.org/10.1016/j.cmet.2017.04.025.
34. Zhang X, Xu A, Chung SK, et al. Selective inactivation of c-Jun NH2-terminal kinase in adipose tissue protects against diet-induced obesity and improves insulin sensitivity in both liver and skeletal muscle in mice. *Diabetes*. 2011;60(2):486–495. https://doi.org/10.2337/db10-0650.
35. Banu N, Elango K. Adiponectin level in type 2 diabetes and its complication–A review. *J Pharmaceut Sci Res*. 2019;11(4):1172–1174.
36. Zohmangaihi D, Sharma S, Madhu S. Adiponectin, IL-6 and hsCRP: interplay of inflammation with obesity and type 2 diabetes in Indian population. *J Diabetes Metabol*. 2019;10(3):1–7. https://doi.org/10.35248/2155-6156.19.10.822.
37. Adiyaman SC, Ozer M, Saydam BO, Akinci B. The role of adiponectin in maintaining metabolic homeostasis. *Curr Diabetes Rev*. 2020;16(2):95–103. https://doi.org/10.2174/1573399815666190702155733.

38. Bouassida A, Chamari K, Zaouali M, Feki Y, Zbidi A, Tabka Z. Review on leptin and adiponectin responses and adaptations to acute and chronic exercise. *Br J Sports Med*. 2010;44(9):620–630. https://doi.org/10.1136/bjsm.2008.046151.
39. Lindberg S, Jensen JS, Bjerre M, et al. Low adiponectin levels at baseline and decreasing adiponectin levels over 10 years of follow-up predict risk of the metabolic syndrome. *Diabetes Metab*. 2017;43(2):134–139. https://doi.org/10.1016/j.diabet.2016.07.027.
40. Muppala S, Konduru SK, Merchant N, et al. Adiponectin: its role in obesity-associated colon and prostate cancers. *Crit Rev Oncol Hematol*. 2017;116:125–133. https://doi.org/10.1016/j.critrevonc.2017.06.003.
41. Wang X, Chen Q, Pu H, et al. Adiponectin improves NF-κB-mediated inflammation and abates atherosclerosis progression in apolipoprotein E-deficient mice. *Lipids Health Dis*. 2016;15:33. https://doi.org/10.1186/s12944-016-0202-y.
42. Tore F, Tonchev A, Fiore M, et al. From adipose tissue protein secretion to adipopharmacology of disease. *Immunol Endocr Metab Agents Med Chem*. 2007;7(2):149–155. https://doi.org/10.2174/187152207780363712.
43. Okamoto Y, Kihara S, Ouchi N, et al. Adiponectin reduces atherosclerosis in apolipoprotein E-deficient mice. *Circulation*. 2002;106(22):2767–2770. https://doi.org/10.1161/01.cir.0000042707.50032.19.
44. Roy B, Palaniyandi SS. Tissue-specific role and associated downstream signaling pathways of adiponectin. *Cell Biosci*. 2021;11(1):77. https://doi.org/10.1186/s13578-021-00587-4.
45. Miyamoto L, Yamane M, Tomida Y, et al. Nitrite activates 5′ AMP-activated protein kinase-endothelial nitric oxide synthase pathway in human glomerular endothelial cells. *Biol Pharm Bull*. 2017;40(11):1866–1872. https://doi.org/10.1248/bpb.b17-00316.
46. Wang Y, Ma XL, Lau WB. Cardiovascular adiponectin resistance: the critical role of adiponectin receptor modification. *Trends Endocrinol Metabol*. 2017;28(7):519–530. https://doi.org/10.1016/j.tem.2017.03.004.
47. Chen Y, Zheng Y, Liu L, et al. Adiponectin inhibits TNF-α-activated PAI-1 expression via the cAMP-PKA-AMPK-NF-κB axis in human umbilical vein endothelial cells. *Cell Physiol Biochem*. 2017;42(6):2342–2352. https://doi.org/10.1159/000480006.
48. Yamauchi T, Nio Y, Maki T, et al. Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. *Nat Med*. 2007;13(3):332–339. https://doi.org/10.1038/nm1557.
49. Yamada H, Suzuki D, Kakei M, Kusaka I, Ishikawa S. Close association of hypoadiponectinemia and increased insulin resistance in non-obese Japanese type 2 diabetes with visceral adiposity. *J Metab Syndrome*. 2016;5(4):215. https://doi.org/10.4172/2167-0943.1000215.
50. Zeng Q, Isobe K, Fu L, et al. Effects of exercise on adiponectin and adiponectin receptor levels in rats. *Life Sci*. 2007;80(5):454–459. https://doi.org/10.1016/j.lfs.2006.09.031.
51. Sun L, Lv Y, Tian J, et al. Regular swimming exercise attenuated neuroma pain in rats: involvement of leptin and adiponectin. *J Pain*. 2019;20(9):1112–1124. https://doi.org/10.1016/j.jpain.2019.02.097.
52. Jürimäe J, Purge P, Jürimäe T. Adiponectin and stress hormone responses to maximal sculling after volume-extended training season in elite rowers. *Metabolism*. 2006;55(1):13–19. https://doi.org/10.1016/j.metabol.2005.06.020.
53. Magherini F, Fiaschi T, Marzocchini R, et al. Oxidative stress in exercise training: the involvement of inflammation and peripheral signals. *Free Radic Res*. 2019;53(11-12):1155–1165. https://doi.org/10.1080/10715762.2019.1697438.
54. Damirchi A, Mehdizade R, Ansar M, Soltani B, Babaei P. Effects of aerobic exercise training on visceral fat and serum adiponectin concentration in ovariectomized rats. *Climacteric*. 2010;13(2):171–178. https://doi.org/10.3109/13697130903360234.
55. Lee JA, Kim JW, Kim DY. Effects of yoga exercise on serum adiponectin and metabolic syndrome factors in obese postmenopausal women. published correction appears in Menopause. 2012 Apr;19(4):486 *Menopause*. 2012;19(3):296–301. https://doi.org/10.1097/gme.0b013e31822d59a2.
56. ADv Frankenberg, Reis AF, Gerchman F. Relationships between adiponectin levels, the metabolic syndrome, and type 2 diabetes: a literature review. *Arch Endocrinol Metab*. 2017;61(6):614–622. https://doi.org/10.1590/2359-3997000000316.
57. Ward LJ, Nilsson S, Hammar M, et al. Resistance training decreases plasma levels of adipokines in postmenopausal women. *Sci Rep*. 2020;10(1):19837. https://doi.org/10.1038/s41598-020-76901-w.
58. de Mello MT, de Piano A, Carnier J, et al. Long-term effects of aerobic plus resistance training on the metabolic syndrome and adiponectinemia in obese adolescents. *J Clin Hypertens*. 2011;13(5):343–350. https://doi.org/10.1111/j.1751-7176.2010.00388.x.
59. Strasser B, Siebert U, Schobersberger W. Resistance training in the treatment of the metabolic syndrome : a systematic review and meta-analysis of the effect of resistance training on metabolic clustering in patients with abnormal glucose metabolism. *Sports Med*. 2010;40(5):397–415. https://doi.org/10.2165/11531380-000000000-00000.
60. Gastebois C, Villars C, Drai J, et al. Effects of training and detraining on adiponectin plasma concentration and muscle sensitivity in lean and overweight men. *Eur J Appl Physiol*. 2016;116(11-12):2135–2144. https://doi.org/10.1007/s00421-016-3466-z.
61. Lucotti P, Monti LD, Setola E, et al. Aerobic and resistance training effects compared to aerobic training alone in obese type 2 diabetic patients on diet treatment. *Diabetes Res Clin Pract*. 2011;94(3):395–403. https://doi.org/10.1016/j.diabres.2011.08.002.
62. Ostman C, Smart N, Morcos D, Duller A, Ridley W, Jewiss D. The effect of exercise training on clinical outcomes in patients with the metabolic syndrome: a systematic review and meta-analysis. *Cardiovasc Diabetol*. 2017;16(1):110. https://doi.org/10.1186/s12933-017-0590-y.
63. Choi JR, Kim JY, Huh JH, Kim SH, Koh SB. Contribution of obesity as an effect regulator to an association between serum leptin and incident metabolic syndrome. *Clin Chim Acta*. 2018;487:275–280. https://doi.org/10.1016/j.cca.2018.09.038.
64. Ahsan F, Sharif MK, Butt MS, Shehzad A, Khan MI. Pathophysiological role of leptin for human health: a review. *Pakistan J Food Sci*. 2017;27(1):46–52.
65. Perry RJ, Wang Y, Cline GW, et al. Leptin mediates a glucose-fatty acid cycle to maintain glucose homeostasis in starvation. *Cell*. 2018;172(1-2):234–248. https://doi.org/10.1016/j.cell.2017.12.001.
66. Considine RV, Sinha MK, Heiman ML, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N Engl J Med*. 1996;334(5):292–295. https://doi.org/10.1056/nejm199602013340503.
67. Ghadge AA, Khaire AA. Leptin as a predictive marker for metabolic syndrome. *Cytokine*. 2019;121:154735. https://doi.org/10.1016/j.cyto.2019.154735.
68. Barnes TM, Shah K, Allison MB, et al. Identification of the leptin receptor sequences crucial for the STAT3-Independent control of metabolism. *Mol Metabol*. 2020;32:168–175. https://doi.org/10.1016/j.molmet.2019.12.013.
69. Ghasemi A, Saeidi J, Azimi-Nejad M, Hashemy SI. Leptin-induced signaling pathways in cancer cell migration and invasion. *Cell Oncol*. 2019;42(3):243–260. https://doi.org/10.1007/s13402-019-00428-0.
70. Barrios-Correa AA, Estrada JA, Contreras I. Leptin signaling in the control of metabolism and appetite: lessons from animal models. *Mol Neurosci*. 2018;66(3):390–402. https://doi.org/10.1007/s12031-018-1185-0.
71. Zhang EE, Chapeau E, Hagihara K, Feng G-S. Neuronal Shp2 tyrosine phosphatase controls energy balance and metabolism. *Proc Natl Acad Sci U S A*. 2004;101(45):16064–16069. https://doi.org/10.1073/pnas.0405041101.
72. Uotani S, Abe T, Yamaguchi Y. Leptin activates AMP-activated protein kinase in hepatic cells via a JAK2-dependent pathway. *Biophys Res Commun*. 2006;351(1):171–175. https://doi.org/10.1016/j.bbrc.2006.10.015.
73. Minokoshi Y, Alquier T, Furukawa N, et al. AMP-kinase regulates food intake by responding to hormonal and nutrient signals in the hypothalamus. *Nature*. 2004;428(6982):569–574. https://doi.org/10.1038/nature02440.
74. Claret M, Smith MA, Batterham RL, et al. AMPK is essential for energy homeostasis regulation and glucose sensing by POMC and AgRP neurons. *J Clin Invest*. 2007;117(8):2325–2336. https://doi.org/10.1172/jci31516.
75. Zimmermann GS, Bastos MF, Dias Gonçalves TE, Chambrone L, Duarte PM. Local and circulating levels of adipocytokines in obese and normal weight individuals with chronic periodontitis. *J Periodontol*. 2013;84(5):624–633. https://doi.org/10.1902/jop.2012.120254.
76. De Git K, Adan R. Leptin resistance in diet-induced obesity: the role of hypothalamic inflammation. *Obes Rev*. 2015;16(3):207–224. https://doi.org/10.1111/obr.12243.
77. Gar C, Rottenkolber M, Grallert H, et al. Physical fitness and plasma leptin in women with recent gestational diabetes. *PLoS One*. 2017;12(6), e0179128. https://doi.org/10.1371/journal.pone.0179128.
78. Garcia NF, Silva CP, Ferreira Jr M, Oharomari LK, Rocha T, Moraes Cd. 7-week aerobic exercise training reduces adipocyte area and improves insulin sensitivity in Wistar rats fed a highly palatable diet. *Motriz: Revista de Educação Física*. 2016;22(1):12–17. https://doi.org/10.1590/s1980-65742016000100002.
79. Zhao J, Tian Y, Xu J, Liu D, Wang X, Zhao B. Endurance exercise is a leptin signaling mimetic in hypothalamus of Wistar rats. *Lipids Health Dis*. 2011;10:225. https://doi.org/10.1186/1476-511X-10-225.
80. Botero JP, Shiguemoto GE, Prestes J, et al. Effects of long-term periodized resistance training on body composition, leptin, resistin and muscle strength in elderly post-menopausal women. *J Sports Med Phys Fit*. 2013;53(3):289–294.
81. Ramos-Lobo AM, Donato Jr J. The role of leptin in health and disease. *Temperature (Austin)*. 2017;4(3):258–291. https://doi.org/10.1080/23328940.2017.1327003.
82. Lau PW, Kong Z, Choi C-r, et al. Effects of short-term resistance training on serum leptin levels in obese adolescents. *J Exerc Sci Fit* 2010;8(1):54–60. https://doi.org/10.1016/s1728-869x(10)60008-1.
83. Ahmadizad S, Ghorbani S, Ghasemikaram M, Bahmanzadeh M. Effects of short-term nonperiodized, linear periodized and daily undulating periodized resistance training on plasma adiponectin, leptin and insulin resistance. *Clin Biochem*. 2014;47(6):417–422. https://doi.org/10.1016/j.clinbiochem.2013.12.019.
84. Nappo A, Gonzalez-Gil E, Ahrens W, et al. Analysis of the association of leptin and adiponectin concentrations with metabolic syndrome in children: results from the IDEFICS study. *Nutr Metabol Cardiovasc Dis*. 2017;27(6):543–551. https://doi.org/10.1016/j.numecd.2017.04.003.
85. Fedewa MV, Hathaway ED, Ward-Ritacco CL, Williams TD, Dobbs WC. The effect of chronic exercise training on leptin: a systematic review and meta-analysis of randomized controlled trials. *Sports Med*. 2018;48(6):1437–1450. https://doi.org/10.1007/s40279-018-0897-1.
86. Prestes J, da Cunha Nascimento D, de Sousa Neto IV, et al. The effects of muscle strength responsiveness to periodized resistance training on resistin, leptin, and cytokine in elderly postmenopausal women. *J Strength Condit Res*. 2018;32(1):113–120. https://doi.org/10.1519/jsc.0000000000001718.
87. Marques-Oliveira GH, Silva TM, Lima WG, Valadares HMS, Chaves VE. Insulin as a hormone regulator of the synthesis and release of leptin by white adipose tissue. *Peptides*. 2018;106:49–58. https://doi.org/10.1016/j.peptides.2018.06.007.
88. Dantas WS, Roschel H, Murai IH, et al. Exercise-induced increases in insulin sensitivity after bariatric surgery are mediated by muscle extracellular matrix remodeling. *Diabetes*. 2020;69(8):1675–1691. https://doi.org/10.2337/db19-1180.
89. Petridou A, Tsalouhidou S, Tsalis G, Schulz T, Michna H, Mougios V. Long-term exercise increases the DNA binding activity of peroxisome proliferator–activated receptor γ in rat adipose tissue. *Metabolism*. 2007;56(8):1029–1036. https://doi.org/10.1016/j.metabol.2007.03.011.

90. Tsai M, Asakawa A, Amitani H, Inui A. Stimulation of leptin secretion by insulin. *Indian J Endocrinol Metab*. 2012;16(Suppl 3):S543–S548. https://doi.org/10.4103/2230-8210.105570.
91. Sirico F, Bianco A, D'Alicandro G, et al. Effects of physical exercise on adiponectin, leptin, and inflammatory markers in childhood obesity: systematic review and meta-analysis. *Child Obes*. 2018;14(4):207–217. https://doi.org/10.1089/chi.2017.0269.
92. McGee SL, Hargreaves M. Exercise adaptations: molecular mechanisms and potential targets for therapeutic benefit. *Nat Rev Endocrinol*. 2020;16(9):495–505. https://doi.org/10.1038/s41574-020-0377-1.
93. Shibata R, Ouchi N, Ohashi K, Murohara T. The role of adipokines in cardiovascular disease. *J Cardiol*. 2017;70(4):329–334. https://doi.org/10.1016/j.jjcc.2017.02.006.
94. Yang R-Z, Lee M-J, Hu H, et al. Identification of omentin as a novel depot-specific adipokine in human adipose tissue: possible role in modulating insulin action. *Am J Physiol Endocrinol Metab*. 2006;290(6):E1253–E1261. https://doi.org/10.1152/ajpendo.00572.2004.
95. Buyukinan M, Atar M, Can U, Pirgon O, Guzelant A, Deniz I. The association between serum vaspin and omentin-1 levels in obese children with metabolic syndrome. *Metab Syndr Relat Disord*. 2018;16(2):76–81. https://doi.org/10.1089/met.2017.0133.
96. Zhang M, Tan X, Yin C, Wang L, Tie Y, Xiao Y. Serum levels of omentin-1 are increased after weight loss and are particularly associated with increases in obese children with metabolic syndrome. *Acta Paediatr*. 2017;106(11):1851–1856. https://doi.org/10.1111/apa.14026.
97. Sitticharoon C, Nway NC, Chatree S, Churintaraphan M, Boonpuan P, Maikaew P. Interactions between adiponectin, visfatin, and omentin in subcutaneous and visceral adipose tissues and serum, and correlations with clinical and peripheral metabolic factors. *Peptides*. 2014;62:164–175. https://doi.org/10.1016/j.peptides.2014.10.006.
98. Pan X, Kaminga AC, Wen SW, Acheampong K, Liu A. Omentin-1 in diabetes mellitus: a systematic review and meta-analysis. *PLoS One*. 2019;14(12), e0226292. https://doi.org/10.1371/journal.pone.0226292.
99. Castro CAd, Silva KAd, Rocha MC, et al. Exercise and omentin: their role in the crosstalk between muscle and adipose tissues in type 2 diabetes mellitus rat models. *Front Physiol*. 2019;9:1881. https://doi.org/10.3389/fphys.2018.01881.
100. Brunetti L, Leone S, Orlando G, et al. Hypotensive effects of omentin-1 related to increased adiponectin and decreased interleukin-6 in intra-thoracic pericardial adipose tissue. *Pharmacol Rep*. 2014;66(6):991–995. https://doi.org/10.1016/j.pharep.2014.06.014.
101. Stejskal D, Vaclavik J, Smekal A, Svobodova G, Richterova R, Svestak M. Omentin-1 levels in patients with premature coronary artery disease, metabolic syndrome and healthy controls. Short communication. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2016;160(2):219–221. https://doi.org/10.5507/bp.2016.019.
102. Liu F, Fang S, Liu X, et al. Omentin-1 protects against high glucose-induced endothelial dysfunction via the AMPK/PPARδ signaling pathway. *Biochem Pharmacol*. 2020;174, 113830. https://doi.org/10.1016/j.bcp.2020.113830.
103. Watanabe K, Watanabe R, Konii H, et al. Counteractive effects of omentin-1 against atherogenesis. *Cardiovasc Res*. 2016;110(1):118–128. https://doi.org/10.1093/cvr/cvw016.
104. Hiramatsu-Ito M, Shibata R, Ohashi K, et al. Omentin attenuates atherosclerotic lesion formation in apolipoprotein E-deficient mice. *Cardiovasc Res*. 2016;110(1):107–117. https://doi.org/10.1093/cvr/cvv282.
105. Zhou Y, Hao C, Li C, et al. Omentin-1 protects against bleomycin-induced acute lung injury. *Mol Immunol*. 2018;103:96–105. https://doi.org/10.1016/j.molimm.2018.09.007.
106. Jiang R, Lönnerdal B. Cloning and characterization of the human lactoferrin receptor gene promoter. *Biometals*. 2018;31(3):357–368. https://doi.org/10.1007/s10534-018-0080-z.
107. Rashid R, Maqbool M, Jan A, Geer MI. Role of adipokines and free fatty acids in insulin resistance-a review. *Int J Adv Res Sci Eng*. 2018;7(4):2115–2123.
108. Babaei P, Pourrahim Ghouroghchi A, Damirchi A, Soltani Tehrani B. The interactive effect of aerobic-resistance training and estrogen therapy on metabolic syndrome indices and omentin-1. *Physiol Pharmacol*. 2015;19(3):200–207.
109. Madsen SM, Thorup AC, Bjerre M, Jeppesen PB. Does 8 weeks of strenuous bicycle exercise improve diabetes-related inflammatory cytokines and free fatty acids in type 2 diabetes patients and individuals at high-risk of metabolic syndrome? *Arch Physiol Biochem*. 2015;121(4):129–138. https://doi.org/10.3109/13813455.2015.1082600.
110. Urbanová M, Dostálová I, Trachta P, et al. Serum concentrations and subcutaneous adipose tissue mRNA expression of omentin in morbid obesity and type 2 diabetes mellitus: the effect of very-low-calorie diet, physical activity and laparoscopic sleeve gastrectomy. *Physiol Res*. 2014;63(2):207–218. https://doi.org/10.33549/physiolres.932530.
111. Faramarzi M, Banitalebi E, Nori S, Farzin S, Taghavian Z. Effects of rhythmic aerobic exercise plus core stability training on serum omentin, chemerin and vaspin levels and insulin resistance of overweight women. *J Sports Med Phys Fit*. 2016;56(4):476–482.
112. Ge H, Huang L, Pourbahrami T, Li C. Generation of soluble leptin receptor by ectodomain shedding of membrane-spanning receptors in vitro and in vivo. *J Biol Chem*. 2002;277(48):45898–45903. https://doi.org/10.1074/jbc.m205825200.
113. Yan P, Liu D, Long M, Ren Y, Pang J, Li R. Changes of serum omentin levels and relationship between omentin and adiponectin concentrations in type 2 diabetes mellitus. *Exp Clin Endocrinol Diabetes*. 2011;119(4):257–263. https://doi.org/10.1055/s-0030-1269912.
114. Kataoka Y, Shibata R, Ohashi K, et al. Omentin prevents myocardial ischemic injury through AMP-activated protein kinase-and Akt-dependent mechanisms. *J Am Coll Cardiol*. 2014;63(24):2722–2733. https://doi.org/10.1016/j.jacc.2014.03.032.
115. de Souza Batista CM, Yang R-Z, Lee M-J, et al. Omentin plasma levels and gene expression are decreased in obesity. *Diabetes*. 2007;56(6):1655–1661. https://doi.org/10.2337/db06-1506.
116. Boucher J, Masri B, Daviaud D, et al. Apelin, a newly identified adipokine up-regulated by insulin and obesity. *Endocrinology*. 2005;146(4):1764–1771. https://doi.org/10.1210/en.2004-1427.
117. Kleinz MJ, Davenport AP. Emerging roles of apelin in biology and medicine. *Pharmacol Ther*. 2005;107(2):198–211. https://doi.org/10.1016/j.pharmthera.2005.04.001.
118. Li L, Yang G, Li Q, et al. Changes and relations of circulating visfatin, apelin, and resistin levels in normal, impaired glucose tolerance, and type 2 diabetic subjects. *Exp Clin Endocrinol Diabetes*. 2006;114(10):544–548. https://doi.org/10.1055/s-2006-948309.
119. Babaei P, Dastras A, Tehrani BS, Pourali Roudbaneh S. The effect of estrogen replacement therapy on visceral fat, serum glucose, lipid profiles and apelin level in ovariectomized rats. *J Menopausal Med*. 2017;23(3):182–189. https://doi.org/10.6118/jmm.2017.23.3.182.
120. Choi YS, Yang HI, Cho S, et al. Serum asymmetric dimethylarginine, apelin, and tumor necrosis factor-α levels in non-obese women with polycystic ovary syndrome. *Steroids*. 2012;77(13):1352–1358. https://doi.org/10.1016/j.steroids.2012.08.005.
121. Zhu S, Sun F, Li W, et al. Apelin stimulates glucose uptake through the PI3K/Akt pathway and improves insulin resistance in 3T3-L1 adipocytes. *Mol Cell Biochem*. 2011;353(1-2):305–313. https://doi.org/10.1007/s11010-011-0799-0.
122. Dray C, Knauf C, Daviaud D, et al. Apelin stimulates glucose utilization in normal and obese insulin-resistant mice. *Cell Metabol*. 2008;8(5):437–445. https://doi.org/10.1016/j.cmet.2008.10.003.
123. Castan-Laurell I, Masri B, Valet P. The apelin/APJ system as a therapeutic target in metabolic diseases. *Expert Opin Ther Targets*. 2019;23(3):215–225. https://doi.org/10.1080/14728222.2019.1561871.
124. Bertrand C, Valet P, Castan-Laurell I. Apelin and energy metabolism. *Front Physiol*. 2015;6:115. https://doi.org/10.3389/fphys.2015.00115.
125. Castan-Laurell I, Dray C, Attané C, Duparc T, Knauf C, Valet P. Apelin, diabetes, and obesity. *Endocrine*. 2011;40(1):1–9. https://doi.org/10.1007/s12020-011-9507-9.
126. Maguire JJ, Kleinz MJ, Pitkin SL, Davenport AP. [Pyr1] apelin-13 identified as the predominant apelin isoform in the human heart: vasoactive mechanisms and inotropic action in disease. *Hypertension*. 2009;54(3):598–604. https://doi.org/10.1161/hypertensionaha.109.134619.
127. Yu X-H, Tang Z-B, Liu L-J, et al. Apelin and its receptor APJ in cardiovascular diseases. *Clin Chim Acta*. 2014;428:1–8. https://doi.org/10.1016/j.cca.2013.09.001.
128. Masri B, Morin N, Pedebernade L, Knibiehler B, Audigier Y. The apelin receptor is coupled to Gi1 or Gi2 protein and is differentially desensitized by apelin fragments. *J Biol Chem*. 2006;281(27):18317–18326. https://doi.org/10.1074/jbc.m600606200.
129. Besse-Patin A, Montastier E, Vinel C, et al. Effect of endurance training on skeletal muscle myokine expression in obese men: identification of apelin as a novel myokine. *Int J Obes*. 2014;38(5):707–713. https://doi.org/10.1038/ijo.2013.158.
130. Kadoglou NP, Vrabas IS, Kapelouzou A, et al. The impact of aerobic exercise training on novel adipokines, apelin and ghrelin, in patients with type 2 diabetes. *Med Sci Mon Int Med J Exp Clin Res*. 2012;18(5):CR290–CR295. https://doi.org/10.12659/msm.882734.
131. Jang S-H, Paik I-Y, Ryu J-H, Lee T-H, Kim D-E. Effects of aerobic and resistance exercises on circulating apelin-12 and apelin-36 concentrations in obese middle-aged women: a randomized controlled trial. *BMC Wom Health*. 2019;19(1):23. https://doi.org/10.1186/s12905-019-0722-5.
132. Nikseresht M, Rajabi H, Nikseresht A. The effects of nonlinear resistance and aerobic interval training on serum levels of apelin and insulin resistance in middle-aged obese men. *Tehran Univ Med J*. 2015;73(5):375–383.
133. Ghanbari-Niaki A, Saeidi A, Gharahcholo L, et al. Influence of resistance training and herbal supplementation on plasma apelin and metabolic syndrome risk factors in postmenopausal women. *Sci Sports*. 2020;35(2):109.e1–109.e5. https://doi.org/10.1016/j.scispo.2019.04.010.
134. Green JS, Lowe RC, Pronk N, Jacobsen D, Rohack JJ, Crouse SF. Low and high intensity endurance exercise training does not significantly alter the apolipoprotein-b/apoliporotienal ratio in hypercholesterolemic men. *Med Sci Sports Exerc*. 2005;37:S470. https://doi.org/10.1097/00005768-200505001-02459.
135. Chang HM, Lee HJ, Park HS, et al. Effects of weight reduction on serum vaspin concentrations in obese subjects: modification by insulin resistance. *Obesity*. 2010;18(11):2105–2110. https://doi.org/10.1038/oby.2010.60.
136. Klöting N, Kovacs P, Kern M, et al. Central vaspin administration acutely reduces food intake and has sustained blood glucose-lowering effects. *Diabetologia*. 2011;54(7):1819–1823. https://doi.org/10.1007/s00125-011-2137-1.
137. Klöting N, Berndt J, Kralisch S, et al. Vaspin gene expression in human adipose tissue: association with obesity and type 2 diabetes. *Biochem Biophys Res Commun*. 2006;339(1):430–436. https://doi.org/10.1016/j.bbrc.2005.11.039.
138. Mansour SW, Tawfiq MS, Khalefa AA, Hadhoud SE, El-Shorbgy EAA. Effect of diet regimen on serum vaspin level in obese diabetic female patients. *Zagazig University Medical Journal*. 2019;25(5):699–707. https://doi.org/10.21608/zumj.2019.10713.11170.
139. El-Lebedy DH, Ibrahim AA, Ashmawy IO. Novel adipokines vaspin and irisin as risk biomarkers for cardiovascular diseases in type 2 diabetes mellitus. *Diabetes Metab Syndr*. 2018;12(5):643–648. https://doi.org/10.1016/j.dsx.2018.04.025.

140. Heiker JT, Klöting N, Kovacs P, et al. Vaspin inhibits kallikrein 7 by serpin mechanism. *Cell Mol Life Sci*. 2013;70(14):2569–2583. https://doi.org/10.1007/s00018-013-1258-8.
141. Jung CH, Lee WJ, Hwang JY, et al. Vaspin protects vascular endothelial cells against free fatty acid-induced apoptosis through a phosphatidylinositol 3-kinase/Akt pathway. *Biochem Biophys Res Commun*. 2011;413(2):264–269. https://doi.org/10.1016/j.bbrc.2011.08.083.
142. Zieger K, Weiner J, Krause K, et al. Vaspin suppresses cytokine-induced inflammation in 3T3-L1 adipocytes via inhibition of NFκB pathway. *Mol Cell Endocrinol*. 2018;460:181–188. https://doi.org/10.1016/j.mce.2017.07.022.
143. Phalitakul S, Okada M, Hara Y, Yamawaki H. Vaspin prevents TNF-α-induced intracellular adhesion molecule-1 via inhibiting reactive oxygen species-dependent NF-κB and PKCθ activation in cultured rat vascular smooth muscle cells. *Pharmacol Res*. 2011;64(5):493–500. https://doi.org/10.1016/j.phrs.2011.06.001.
144. Liu S, Dong Y, Wang T, et al. Vaspin inhibited proinflammatory cytokine induced activation of nuclear factor-kappa B and its downstream molecules in human endothelial EA. hy926 cells. *Diabetes Res Clin Pract*. 2014;103(3):482–488. https://doi.org/10.1016/j.diabres.2013.12.002.
145. Tantiwong P, Shanmugasundaram K, Monroy A, et al. NF-κB activity in muscle from obese and type 2 diabetic subjects under basal and exercise-stimulated conditions. *Am J Physiol Endocrinol Metab*. 2010;299(5):E794–E801. https://doi.org/10.1152/ajpendo.00776.2009.
146. Choe SS, Huh JY, Hwang IJ, Kim JI, Kim JB. Adipose tissue remodeling: its role in energy metabolism and metabolic disorders. *Front Endocrinol*. 2016;7:30. https://doi.org/10.3389/fendo.2016.00030.
147. Fabre O, Ingerslev LR, Garde C, Donkin I, Simar D, Barres R. Exercise training alters the genomic response to acute exercise in human adipose tissue. *Epigenomics*. 2018;10(8):1033–1050. https://doi.org/10.2217/epi-2018-0039.
148. Youn B-S, Klöting N, Kratzsch J, et al. Serum vaspin concentrations in human obesity and type 2 diabetes. *Diabetes*. 2008;57(2):372–377. https://doi.org/10.2337/db07-1045.
149. Shahdadi A, Molaei K. The effect of 8 Weeks rhythmic aerobic exercise on vaspin levels and lipid profile in overweight and obese women. *Mediterr J Soc Sci*. 2016;7(4):163–168. https://doi.org/10.5901/mjss.2016.v7n4s2p163.
150. Amouzad Mahdirejei H, Fadaei Reyhan Abadei S, Abbaspour Seidi A, et al. Effects of an eight-week resistance training on plasma vaspin concentrations, metabolic parameters levels and physical fitness in patients with type 2 diabetes. *Cell J*. 2014;16(3):367–374.
151. Oberbach A, Kirsch K, Lehmann S, et al. Serum vaspin concentrations are decreased after exercise-induced oxidative stress. *Obes Facts*. 2010;3(5):328–331. https://doi.org/10.1159/000321637.
152. Briken S, Rosenkranz SC, Keminer O, et al. Effects of exercise on Irisin, BDNF and IL-6 serum levels in patients with progressive multiple sclerosis. *J Neuroimmunol*. 2016;299:53–58. https://doi.org/10.1016/j.jneuroim.2016.08.007.
153. Keller C, Steensberg A, Hansen AK, Fischer CP, Plomgaard P, Pedersen BK. Effect of exercise, training, and glycogen availability on IL-6 receptor expression in human skeletal muscle. *J Appl Physiol (1985)*. 2005;99(6):2075–2079. https://doi.org/10.1152/japplphysiol.00590.2005.
154. Nieman DC, Zwetsloot KA, Lomiwes DD, Meaney MP, Hurst RD. Muscle glycogen depletion following 75-km of cycling is not linked to increased muscle IL-6, IL-8, and MCP-1 mRNA expression and protein content. *Front Physiol*. 2016;7:431. https://doi.org/10.3389/fphys.2016.00431.
155. Samarghandian S, Azimi-Nezhad M, Farkhondeh T. Crocin attenuate Tumor Necrosis Factor-alpha (TNF-α) and interleukin-6 (IL-6) in streptozotocin-induced diabetic rat aorta. *Cytokine*. 2016;88:20–28. https://doi.org/10.1016/j.cyto.2016.08.002.
156. da Costa RM, Neves KB, Mestriner FL, Louzada-Junior P, Bruder-Nascimento T, Tostes RC. TNF-α induces vascular insulin resistance via positive modulation of PTEN and decreased Akt/eNOS/NO signaling in high fat diet-fed mice. *Cardiovasc Diabetol*. 2016;15(1):119. https://doi.org/10.1186/s12933-016-0443-0.
157. Dunmore SJ, Brown J. The role of adipokines in b-cell failure of type 2 diabetes. *J Endocrinol*. 2013;216(1):T37–T45. https://doi.org/10.1530/joe-12-0278.
158. Hagstrom AD, Marshall PW, Lonsdale C, et al. The effect of resistance training on markers of immune function and inflammation in previously sedentary women recovering from breast cancer: a randomized controlled trial. *Breast Cancer Res Treat*. 2016;155(3):471–482. https://doi.org/10.1007/s10549-016-3688-0.
159. Sardeli AV, Tomeleri CM, Cyrino ES, Fernhall B, Cavaglieri CR, Chacon-Mikahil MPT. Effect of resistance training on inflammatory markers of older adults: a meta-analysis. *Exp Gerontol*. 2018;111:188–196. https://doi.org/10.1016/j.exger.2018.07.021.
160. Fayaz E, Damirchi A, Zebardast N, Babaei P. Cinnamon extract combined with high-intensity endurance training alleviates metabolic syndrome via non-canonical WNT signaling. *Nutrition*. 2019;65:173–178. https://doi.org/10.1016/j.nut.2019.03.009.
161. Kouhestani S, Zare S, Babaei P. Flavonoids fraction of mespilus germanica alleviates insulin resistance in metabolic syndrome model of ovariectomized rats via reduction in tumor necrosis factor-α. *J Menopausal Med*. 2018;24(3):169–175. https://doi.org/10.6118/jmm.2018.24.3.169.
162. Wang J, Leung K-S, Chow SK-H, Cheung W-H. Inflammation and age-associated skeletal muscle deterioration (sarcopaenia). *J orthopaedic translat*. 2017;10:94–101. https://doi.org/10.1016/j.jot.2017.05.006.
163. Diehl AM. Tumor necrosis factor and its potential role in insulin resistance and nonalcoholic fatty liver disease. *Clin Liver Dis*. 2004;8(3):619–x. https://doi.org/10.1016/j.cld.2004.04.012.
164. Joshi-Barve S, Barve SS, Butt W, Klein J, McClain CJ. Inhibition of proteasome function leads to NF-κB-independent IL-8 expression in human hepatocytes. *Hepatology*. 2003;38(5):1178–1187. https://doi.org/10.1053/jhep.2003.50470.
165. Vozarova B, Weyer C, Hanson K, Tataranni PA, Bogardus C, Pratley RE. Circulating interleukin-6 in relation to adiposity, insulin action, and insulin secretion. *Obes Res*. 2001;9(7):414–417. https://doi.org/10.1038/oby.2001.54.
166. Oberhauser F, Schulte D, Faust M, et al. Weight loss due to a very low calorie diet differentially affects insulin sensitivity and interleukin-6 serum levels in nondiabetic obese human subjects. *Horm Metab Res*. 2012;44(6):465–470. https://doi.org/10.1055/s-0032-1306341.
167. Akash MSH, Rehman K, Liaqat A. Tumor necrosis factor-alpha: role in development of insulin resistance and pathogenesis of type 2 diabetes mellitus. *J Cell Biochem*. 2018;119(1):105–110. https://doi.org/10.1002/jcb.26174.
168. Zand H, Morshedzadeh N, Naghashian F. Signaling pathways linking inflammation to insulin resistance. *Diabetes Metab Syndr*. 2017;11(Suppl 1):S307–S309. https://doi.org/10.1016/j.dsx.2017.03.006.
169. Bode JG, Schweigart J, Kehrmann J, et al. TNF-α induces tyrosine phosphorylation and recruitment of the Src homology protein-tyrosine phosphatase 2 to the gp130 signal-transducing subunit of the IL-6 receptor complex. *J Immunol*. 2003;171(1):257–266. https://doi.org/10.4049/jimmunol.171.1.257.
170. Rotter V, Nagaev I, Smith U. Interleukin-6 (IL-6) induces insulin resistance in 3T3-L1 adipocytes and is, like IL-8 and tumor necrosis factor-α, overexpressed in human fat cells from insulin-resistant subjects. *J Biol Chem*. 2003;278(46):45777–45784. https://doi.org/10.1074/jbc.m301977200.
171. Grosicki GJ, Barrett B, Englund D, et al. Circulating interleukin-6 is associated with skeletal muscle strength, quality, and functional adaptation with exercise training in mobility-limited older adults. *J Frailty Aging*. 2020;9(1):57–63. https://doi.org/10.14283/jfa.2019.30.
172. Kurauti MA, Costa-Júnior JM, Ferreira SM, et al. Interleukin-6 increases the expression and activity of insulin-degrading enzyme. *Sci Rep*. 2017;7, 46750. https://doi.org/10.1038/srep46750.
173. Alipourfard I, Datukishvili N, Mikeladze D. TNF-α downregulation modifies Insulin Receptor Substrate 1 (IRS-1) in metabolic signaling of diabetic insulin-resistant hepatocytes. *Mediat Inflamm*. 2019, 3560819. https://doi.org/10.1155/2019/3560819.
174. Kränkel N, Bahls M, Van Craenenbroeck EM, et al. Exercise training to reduce cardiovascular risk in patients with metabolic syndrome and type 2 diabetes mellitus: how does it work? *Eur J Prev Cardiol*. 2019;26(7):701–708. https://doi.org/10.1177/2047487318805158.
175. Martínez PYO, López JAH, Diaz DP, Trujillo DAZ, Teixeira AM. Effects of three months of water-based exercise training on metabolic syndrome components in older women. *Retos: nuevas tendencias en educación física, deporte y recreación*. 2019;35:181–184. https://doi.org/10.47197/retos.v0i35.62041.
176. Ho T, Zhao X, Courville A, et al. Effects of a 12-month moderate weight loss intervention on insulin sensitivity and inflammation status in nondiabetic overweight and obese subjects. *Horm Metab Res*. 2015;47(4):289–296. https://doi.org/10.1055/s-0034-1382011.
177. Scott JP, Sale C, Greeves JP, Casey A, Dutton J, Fraser WD. Effect of exercise intensity on the cytokine response to an acute bout of running. *Med Sci Sports Exerc*. 2011;43(12):2297–2306. https://doi.org/10.1249/mss.0b013e31822113a9.
178. Kohut M, McCann D, Russell D, et al. Aerobic exercise, but not flexibility/resistance exercise, reduces serum IL-18, CRP, and IL-6 independent of β-blockers, BMI, and psychosocial factors in older adults. *Brain Behav Immun*. 2006;20(3):201–209. https://doi.org/10.1016/j.bbi.2005.12.002.
179. Allen NG, Higham SM, Mendham AE, Kastelein TE, Larsen PS, Duffield R. The effect of high-intensity aerobic interval training on markers of systemic inflammation in sedentary populations. *Eur J Appl Physiol*. 2017;117(6):1249–1256. https://doi.org/10.1007/s00421-017-3613-1.
180. Abd El-Kader S, Gari A, El-Den AS. Impact of moderate versus mild aerobic exercise training on inflammatory cytokines in obese type 2 diabetic patients: a randomized clinical trial. *Afr Health Sci*. 2013;13(4):857–863. https://doi.org/10.4314/ahs.v13i4.1.
181. Gerosa-Neto J, Antunes BM, Campos EZ, et al. Impact of long-term high-intensity interval and moderate-intensity continuous training on subclinical inflammation in overweight/obese adults. *J Exerc Rehabil*. 2016;12(6):575–580. https://doi.org/10.12965/jer.1632770.385.
182. Farinha JB, Steckling FM, Stefanello ST, et al. Response of oxidative stress and inflammatory biomarkers to a 12-week aerobic exercise training in women with metabolic syndrome. *Sports Med Open*. 2015;1(1):19. https://doi.org/10.1186/s40798-015-0011-2.
183. Beavers KM, Hsu F-C, Isom S, et al. Long-term physical activity and inflammatory biomarkers in older adults. *Med Sci Sports Exerc*. 2010;42(12):2189–2196. https://doi.org/10.1249/mss.0b013e3181e3ac80.
184. Cavalcante PAM, Gregnani MF, Henrique JS, Ornellas FH, Araújo RC. Aerobic but not resistance exercise can induce inflammatory pathways via toll-like 2 and 4: a systematic review. *Sports Med Open*. 2017;3(1):42. https://doi.org/10.1186/s40798-017-0111-2. published correction appears in Sports Med Open. 2018 Jan 31;4(1):7.
185. Monteiro-Junior RS, de Tarso Maciel-Pinheiro P, Portugal EdMM, et al. Effect of exercise on inflammatory profile of older persons: systematic review and meta-analyses. *J Phys Activ Health*. 2018;15(1):64–71. https://doi.org/10.1123/jpah.2016-0735.
186. Kasapis C, Thompson PD. The effects of physical activity on serum C-reactive protein and inflammatory markers: a systematic review. *J Am Coll Cardiol*. 2005;45(10):1563–1569. https://doi.org/10.1016/j.jacc.2004.12.077.
187. Cavalcante PAM, Gregnani MF, Henrique JS, Ornellas FH, Araújo RC. Aerobic but not resistance exercise can induce inflammatory pathways via toll-like 2 and 4: a systematic review. *Sports Med Open*. 2017;3(1):42. https://doi.org/10.1186/

s40798-017-0111-2. published correction appears in Sports Med Open. 2018 Jan 31;4(1):7.
188. Flynn MG, McFarlin BK, Phillips MD, Stewart LK, Timmerman KL. Toll-like receptor 4 and CD14 mRNA expression are lower in resistive exercise-trained elderly women. *J Appl Physiol (1985)*. 2003;95(5):1833–1842. https://doi.org/10.1152/japplphysiol.00359.2003.
189. Kanayama A, Seth RB, Sun L, et al. TAB2 and TAB3 activate the NF-κB pathway through binding to polyubiquitin chains. *Mol Cell*. 2004;15(4):535–548. https://doi.org/10.1016/j.molcel.2004.08.008.
190. Silveira Martins M, Farinha JB, Basso Benetti C, et al. Positive effects OF resistance training ON inflammatory parameters IN men with metabolic syndrome risk factors. *Nutr Hosp*. 2015;32(2):792–798. https://doi.org/10.3305/nh.2015.32.2.8696.
191. Asokan SM, Wang T, Wang M-F, Lin W-T. A novel dipeptide from potato protein hydrolysate augments the effects of exercise training against high-fat diet-induced damages in senescence-accelerated mouse-prone 8 by boosting pAMPK/SIRT1/PGC-1α/pFOXO3 pathway. *Aging (N Y)*. 2020;12(8):7334–7349. https://doi.org/10.18632/aging.103081.
192. Ouchi N, Higuchi A, Ohashi K, et al. Sfrp5 is an anti-inflammatory adipokine that modulates metabolic dysfunction in obesity. *Science*. 2010;329(5990):454–457. https://doi.org/10.1126/science.1188280.
193. Abou Ziki MD, Mani A. The interplay of canonical and noncanonical Wnt signaling in metabolic syndrome. *Nutr Res*. 2019;70:18–25. https://doi.org/10.1016/j.nutres.2018.06.009.
194. Catalán V, Gómez-Ambrosi J, Rodríguez A, et al. Activation of noncanonical Wnt signaling through WNT5A in visceral adipose tissue of obese subjects is related to inflammation. *Clin Endocrinol Metabol*. 2014;99(8):E1407–E1417. https://doi.org/10.1210/jc.2014-1191.
195. Zuriaga MA, Fuster JJ, Farb MG, et al. Activation of non-canonical WNT signaling in human visceral adipose tissue contributes to local and systemic inflammation. *Sci Rep*. 2017;7(1):17326. https://doi.org/10.1038/s41598-017-17509-5.
196. Hu Z, Deng H, Qu H. Plasma SFRP5 levels are decreased in Chinese subjects with obesity and type 2 diabetes and negatively correlated with parameters of insulin resistance. *Diabetes Res Clin Pract*. 2013;99(3):391–395. https://doi.org/10.1016/j.diabres.2012.11.026.
197. Carstensen M, Herder C, Kempf K, et al. Sfrp5 correlates with insulin resistance and oxidative stress. *Eur J Clin Invest*. 2013;43(4):350–357. https://doi.org/10.1111/eci.12052.
198. El Asmar Z, Terrand J, Jenty M, et al. Convergent signaling pathways controlled by LRP1 (receptor-related protein 1) cytoplasmic and extracellular domains limit cellular cholesterol accumulation. *J Biol Chem*. 2016;291(10):5116–5127. https://doi.org/10.1074/jbc.m116.714485.
199. Fujino T, Asaba H, Kang M-J, et al. Low-density lipoprotein receptor-related protein 5 (LRP5) is essential for normal cholesterol metabolism and glucose-induced insulin secretion. *Proc Natl Acad Sci U S A*. 2003;100(1):229–234. https://doi.org/10.1073/pnas.0133792100.
200. Makarov SS. NF-κB as a therapeutic target in chronic inflammation: recent advances. *Mol Med Today*. 2000;6(11):441–448. https://doi.org/10.1016/s1357-4310(00)01814-1.
201. Pessin JE, Kwon H. Adipokines mediate inflammation and insulin resistance. *Front Endocrinol*. 2013;4:71. https://doi.org/10.3389/fendo.2013.00071.
202. De A. Wnt/Ca2+ signaling pathway: a brief overview. *Acta Biochim Biophys Sin*. 2011;43(10):745–756. https://doi.org/10.1093/abbs/gmr079.
203. Komiya Y, Habas R. Wnt signal transduction pathways. *Organogenesis*. 2008;4(2):68–75. https://doi.org/10.4161/org.4.2.5851.
204. Baarsma HA, Königshoff M, Gosens R. The WNT signaling pathway from ligand secretion to gene transcription: molecular mechanisms and pharmacological targets. *Pharmacol Ther*. 2013;138(1):66–83. https://doi.org/10.1016/j.pharmthera.2013.01.002.
205. Kohn AD, Moon RT. Wnt and calcium signaling: β-catenin-independent pathways. *Cell Calcium*. 2005;38(3-4):439–446. https://doi.org/10.1016/j.ceca.2005.06.022.
206. Ackers I, Malgor R. Interrelationship of canonical and non-canonical Wnt signalling pathways in chronic metabolic diseases. *Diabetes Vasc Dis Res*. 2018;15(1):3–13. https://doi.org/10.1177/1479164117738442.
207. Lu YC, Wang CP, Hsu CC, et al. Circulating secreted frizzled-related protein 5 (Sfrp5) and wingless-type MMTV integration site family member 5a (Wnt5a) levels in patients with type 2 diabetes mellitus. *Diabetes Metab Res Rev*. 2013;29(7):551–556. https://doi.org/10.1002/dmrr.2426.
208. Gustafson B, Hammarstedt A, Hedjazifar S, Smith U. Restricted adipogenesis in hypertrophic obesity: the role of WISP2, WNT, and BMP4. *Diabetes*. 2013;62(9):2997–3004. https://doi.org/10.2337/db13-0473.
209. Laudes M. Role of WNT signalling in the determination of human mesenchymal stem cells into preadipocytes. *J Mol Endocrinol*. 2011;46(2):R65–R72. https://doi.org/10.1530/jme-10-0169.
210. Weir GC. Glucolipotoxicity, β-cells, and diabetes: the emperor has no clothes. *Diabetes*. 2020;69(3):273–278. https://doi.org/10.2337/db19-0138.
211. Fuster JJ, Zuriaga MA, Ngo DT-M, et al. Noncanonical Wnt signaling promotes obesity-induced adipose tissue inflammation and metabolic dysfunction independent of adipose tissue expansion. *Diabetes*. 2015;64(4):1235–1248. https://doi.org/10.2337/db14-1164.
212. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. *Nat Rev Immunol*. 2006;6(10):772–783. https://doi.org/10.1038/nri1937.
213. Shi Z, Xu M, Chen X, Wang J, Zhao T, Zha D. The regulatory role of SFRP5/WNT5A axis in allergic rhinitis through inhibiting JNK pathway activation and lowering mucin generation in human nasal epithelial cells. *Exp Mol Pathol*. 2021;118:104591. https://doi.org/10.1016/j.yexmp.2020.104591.
214. Leal ML, Lamas L, Aoki MS, et al. Effect of different resistance-training regimens on the WNT-signaling pathway. *Eur J Appl Physiol*. 2011;111(10):2535–2545. https://doi.org/10.1007/s00421-011-1874-7.
215. Wagenmakers AJ, Pedersen BK. The anti-inflammatory effect of exercise: its role in diabetes and cardiovascular disease control. *Essays Biochem*. 2006;42:105–117. https://doi.org/10.1042/bse0420105.
216. Karki S, Ngo DT, Farb MG, et al. WNT5A regulates adipose tissue angiogenesis via antiangiogenic VEGF-A_{165}b in obese humans. *Am J Physiol Heart Circ Physiol*. 2017;313(1):H200–H206. https://doi.org/10.1152/ajpheart.00776.2016.
217. Mir E, Moazzami M, Bijeh N, Dokht EH, Rahimi N. Changes in SFRP5, WNT5A, HbA1c, BMI, PBF, and insulin resistance in men with type 2 diabetes after 12 weeks of combined exercise (HIIT and resistance). *Int J Diabetes Dev Ctries*. 2020;40(2):248–254. https://doi.org/10.1007/s13410-019-00790-7.
218. Newmire D, Willoughby DS. Wnt and β-catenin signaling and skeletal muscle myogenesis in response to muscle damage and resistance exercise and training. *Int J Kinesiol Sports Sci*. 2015;3(4):40–49. https://doi.org/10.7575/aiac.ijkss.v.3n.4p.40.
219. McCubrey JA, Steelman L, Bertrand FE, et al. Multifaceted roles of GSK-3 and Wnt/β-catenin in hematopoiesis and leukemogenesis: opportunities for therapeutic intervention. *Leukemia*. 2014;28(1):15–33. https://doi.org/10.1038/leu.2013.184.
220. Aschenbach WG, Ho RC, Sakamoto K, et al. Regulation of Dishevelled and β-catenin in rat skeletal muscle: an alternative exercise-induced GSK-3β signaling pathway. *Am J Physiol Endocrinol Metab*. 2006;291(1):E152–E158. https://doi.org/10.1152/ajpendo.00180.2005.