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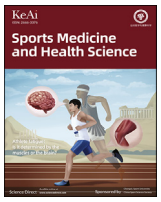

Review

# 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

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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 21$^{st}$-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).

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**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-$\alpha$ 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-$\alpha$ 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-$\alpha$ production, and promote chronic insulin resistance.[163] In addition, increased TNF-$\alpha$ 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-$\alpha$ 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-$\alpha$ likely stands as a pro-inflammatory adipokine, and representative marker in the MetS pathogenesis and cardiovascular burden. TNF-$\alpha$ neutralization by antibodies or antagonists might be a future candidate therapy in MetS.

Two TNF-$\alpha$ 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-$\alpha$ 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-$\alpha$ 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

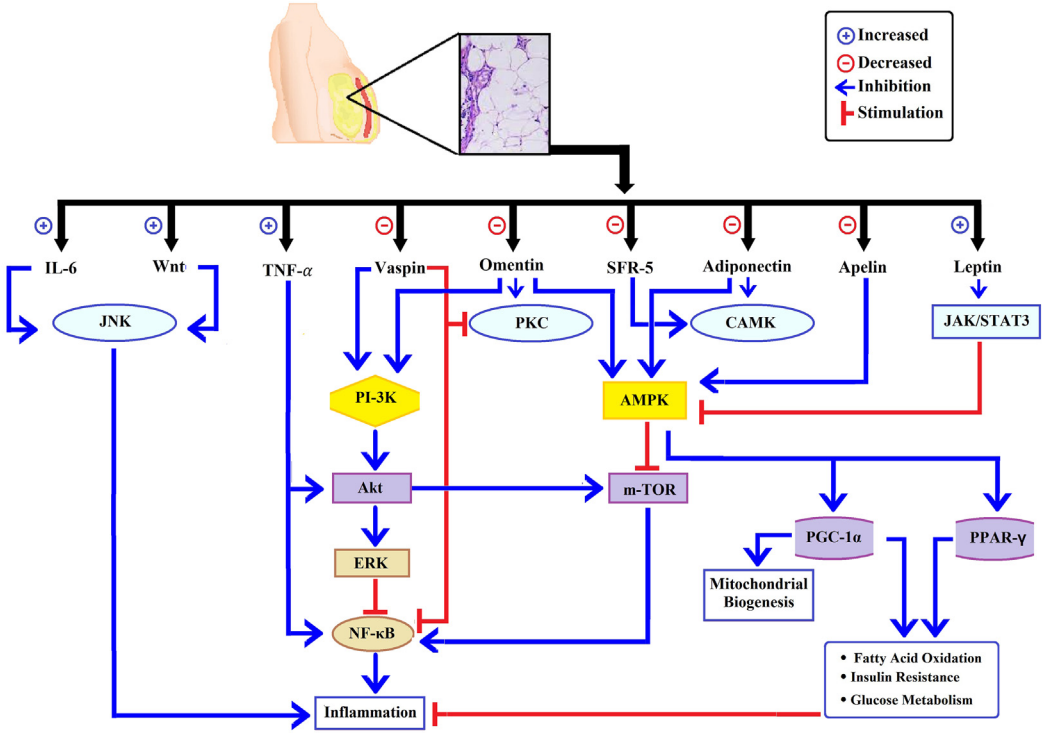


**Fig. 1.** Role of adipokines and AMPK/PPARɣ, mTOR and NF-Kβ, pathways in the development or progression of insulin resistance. in metabolic syndrome.

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.

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## Conflict of interest

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

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