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Review Article

Exercise in the Metabolic Syndrome

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The metabolic syndrome is a clustering of obesity, diabetes, hyperlipidemia, and hypertension that is occurring in increasing frequency across the global population. Although there is some controversy about its diagnostic criteria, oxidative stress, which is defined as imbalance between the production and inactivation of reactive oxygen species, has a major pathophysiological role in all the components of this disease. Oxidative stress and consequent inflammation induce insulin resistance, which likely links the various components of this disease. We briefly review the role of oxidative stress as a major component of the metabolic syndrome and then discuss the impact of exercise on these pathophysiological pathways. Included in this paper is the effect of exercise in reducing fat-induced inflammation, blood pressure, and improving muscular metabolism.

1. Introduction

The metabolic syndrome (MS) describes a constellation of hypertension, diabetes, and dyslipidemia that is caused by abdominal obesity [1, 2] and has also been variously termed X syndrome, insulin resistance syndrome, and the deadly quartet [3]. The diagnostic criteria for MS have been set out by different organizations with slight variations in these criteria as shown in Table 1. The global increase in prevalence of the MS that is rampant in both industrialized and developing countries is associated with an increase in obesity. For example, in a study of 12363 US men and women using the National Cholesterol Education Program's Adult Treatment Panel III guidelines, the MS was diagnosed in 22.8% and 22.6% of the men and women, respectively [4]. This syndrome was present in 4.6%, 22.4%, and 59% of normal weight, overweight, and obese men, respectively, and a similar distribution was observed in women. Higher body mass index (BMI), current smoking, low household income, high carbohydrate intake, and physical inactivity were associated with increased odds.

The MS can be present in different forms, according to the combination of the different components of the syndrome, and it is well established that it increases the risk for the development of cardiovascular disease, type II diabetes, and cancer [5–7]. It is not yet known how the MS is triggered or how the different components are causally linked, but insulin resistance is strongly suspected as a common pathophysiologic link [8, 9], since it is clear that there is a positive correlation between body weight and insulin resistance and the risk of developing all the metabolic abnormalities associated with insulin resistance [9]. However, recent data suggests that MS and obesity do not always occur in concordance as there is some evidence for conditions of benign obesity [10–14]. For example, some studies suggest that frank obesity does not necessarily translate into insulin resistance and increased risk for metabolic comorbidities. In a cross sectional study of 5440 participants of the National Health and Nutrition Examination Surveys 1999–2004, 31.7% of obese adults (BMI $\geq$ 30) were metabolically healthy [12]. In general, healthy obesity describes the lack of any metabolic disorder including type II diabetes, dyslipidemia, and hypertension in an obese individual. To date, there is no prospective study of the healthy obese phenotype and there are a myriad of questions that can be addressed by studying this subtype of obesity. Amongst these are the following questions : do healthy obese subjects represent a delayed onset of obesity related insulin resistance, or is it a permanent condition? What are the causal factor(s) that lead the transition between healthy and unhealthy obese phenotypes? What

Table 1: Comparison of definitions of the metabolic syndrome.

WHO	EGIR	NCEP	IDF
Presence of one of the following:	Insulin resistance AND two or more of the following:	Presence of three of the following (2001):	Central obesity[13] AND any two of the following:
(i) DM	(i) Central obesity[4]	(i) Central obesity[6]	(i) Raised TG[14]
(ii) IGT	(ii) Dyslipidemia[5]	(ii) Dislipidemia[7]	(ii) ↓ HDL[15]
(iii) IFG	(iii) BP ≥ 140/90	(iii) BP ≥ 130/85	(iii) ↑ BP[16]
(iv) Insulin resistance	(iv) FBG ≥ 6.1 mmol/L (110 mg/dL)	(iv) FPG ≥ 6.1 mmol/L (110 mg/dL)	(iv) ↑ FBG[17]
AND two of the following:		Update (2004):	
(i) BP ≥ 140/90		(i) Elevated waist circumferences[8]	
(ii) Dyslipidemia[1]		(ii) Elevated TG[9]	
(iii) Central obesity[2]		(iii) Reduced HDL[10]	
(iv) Microalbuminuria[3]		(iv) Elevated BP[11]	
		(v) Elevated fasting glucose[12]	

BP: blood pressure, DM: diabetes mellitus, EGIR: European Group for the Study of Insulin Resistance, FBG: fasting blood glucose, HDL: high density lipoproteins, IDF: International Diabetes Federation, IFG: impaired fasting glucose, IGT: impaired glucose tolerance, NCEP: US National Cholesterol Education Program, TG: triglycerides, WHO: World Health Organization.
[1] TG ≥ 1.695 mmol/L and HDL ≤ 0.9 mmol/L (male), ≤1.0 mmol/L (female).
[2] Waist/hip ratio > 0.90 (male) >0.85 (female), or body mass index > 30 kg/m^2.
[3] Urinary albumin excretion ratio ≥ 20 μg/min or albumin/creatinine ratio ≥ 30 mg/g.
[4] Waist circumference ≥ 94 cm (male), ≥80 cm (female).
[5] TG ≥ 2.0 mmol/L and/or HDL < 1.0 mmol/L or treated for dyslipidemia.
[6] Waist circumference ≥ 102 cm or 40 inches (male), ≥88 cm or 36 inches (female).
[7] TG ≥ 1.7 mmol/L (150 mg/dL) and HDL < 40 mg/dL (male), <50 mg/dL (female).
[8] Men, greater than 40 inches (102 cm) and women, greater than 35 inches (88 cm).
[9] Equal to or greater than 150 mg/dL (1.7 mmol/L).
[10] Men, Less than 40 mg/dL (1.03 mmol/L) and women, Less than 50 mg/dL (1.29 mmol/L).
[11] Equal to or greater than 130/85 mm Hg or use of medication for hypertension.
[12] Equal to or greater than 100 mg/dL (5.6 mmol/L) or use of medication for hyperglycemia.
[13] Defined as waist circumference with ethnicity specific values (If BMI is >30 kg/m^2, central obesity can be assumed and waist circumference does not need to be measured).
[14] TG > 150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality.
[15] HDL < 40 mg/dL (1.03 mmol/L) in males, <50 mg/dL (1.29 mmol/L) in females, or specific treatment for this lipid abnormality.
[16] systolic BP > 130 or diastolic BP > 85 mm Hg, or treatment of previously diagnosed hypertension.
[17] FPG > 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes.

is known with some clarity is that android fat distribution, visceral and ectopic fat accumulation, and insulin resistance are critical factors and potential causative parameters for the development of unhealthy obesity [15–17].

The association between the MS and inflammation is well documented [18]. In an attempt to clarify the relationship between adiposity and inflammation, Welsh et al. [19] used a bidirectional Mendelian randomization approach and deduced that adiposity leads to higher C-reactive protein (CRP) levels, with no evidence for any reversal of this pathway. Accumulating evidence demonstrates a close link among the metabolic syndrome, a state of chronic inflammation, and oxidative stress [20]. In fact, the oxidative stress-inflammation pathway has important roles in all the individual components of MS including vascular alterations [20–24].

2. Oxidative Stress and Ectopic Fat

Ectopic fat refers to the accumulation of triglycerides within cells of nonadipose tissue; these tissues normally contain only small amounts of fat. Visceral areas, liver, heart, and/or muscle are common sites for deposition of ectopic fat [25]. The amount of ectopic fat is directly related to insulin resistance [26], triglyceride level, blood pressure [26, 27], and in general with the metabolic syndrome [27]. The role of adipose tissue in secreting metabolically active substances has been known for some time and it is now believed that a balance between antiatherosclerotic adipokines (such as leptin and adiponectin) and proatherosclerotic cytokines (such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and monocyte chemotactic protein-1 (MCP-1)) adjusts metabolic and cardiovascular homeostasis at both local and remote sites. Mazurek et al. showed inflammatory properties of cardiac fat, as an example of ectopic fat, by a paired sampling of epicardial and subcutaneous adipose tissues before the initiation of cardiopulmonary surgery [28]. Higher levels of IL-1β, IL-6, MCP-1, and TNF-α mRNA and protein occurred in epicardial adipose stores irrespective of clinical variables such as diabetes, BMI, and drug use. Expression levels of the TNF gene were higher in abdominal adipose tissue compared to subcutaneous fat, and importantly, greater TNF gene expression occurs in the adipose tissues of obese animals [29] and humans [30]. At the cellular level,

TNF-dependent activation of stress-related kinases inhibits insulin signaling, causing cellular insulin resistance. Some of these stress-related kinases also promote further production of TNF, perpetuating a positive feedback mechanism for sustained TNF activity and chronic insulin resistance [31]. Targeted disruptions of the genes that encode TNF [32] or TNF receptors [33] markedly improve insulin sensitivity in obese mice. On the other hand, visceral fat obesity is associated with decreased concentrations of insulin-sensitizing and anti-inflammatory adipokines [25]. During lipolytic activity, more fatty acids are released from visceral adipose tissue compared to subcutaneous adipose tissue [34, 35]. Increased TNF levels induce hepatic uptake of these fatty acids that is accompanied by reduced fatty acid oxidation and triglyceride export. These events cause accumulation of fat within hepatocytes (hepatic steatosis). Indeed, nonalcoholic fatty liver disease emerges as a companion of the metabolic syndrome. It is generally believed that the chain of reactions leading to hepatocyte fatty degeneration begins with increased levels of TNF and insulin resistance, which precede fat accumulation [36]. During hepatic insulin resistance, hepatic glucose production is no longer down regulated by insulin, resulting in increased hepatic glucose production and stimulation of increased insulin secretion. Chronic hyperinsulinemia desensitizes peripheral tissues to insulin and causes systemic insulin resistance. Insulin resistance increases adipocyte lipolysis, which results in the release of large amounts of fatty acids into the blood and exacerbation of hepatic steatosis and insulin resistance [37].

Lipid accumulation and insulin resistance activate a variety of hepatic reactive oxygen species (ROS) producing pathways such as (a) cytochrome P450 2E1 and 4A, which produce ROS during the metabolism of endogenous ketones [38], (b) mitochondrial NADPHs (nicotinamide adenine dinucleotide phosphate), which generate ROS continuously, and (c) peroxisomes, which produce hydrogen peroxide and are activated when mitochondrial β-oxidation is saturated or impaired [39]. TNF is a potent inducer of mitochondrial ROS [40] and increases ROS production in fatty hepatocytes. In order to mitigate or reverse this chronic oxidative stress, adaptive mechanisms such as uncoupling proteins are activated or upregulated. Mitochondrial respiration can be uncoupled by the controlled transfer of protons across the inner mitochondrial membrane, thereby dissipating the proton gradient and reduce the harmful effects of ROS. The family of inner mitochondrial membrane uncoupling proteins plays important roles in the thermogenesis of brown adipose tissue and in regulating the disposal of mitochondrial ROS in other tissues [41]. Decreases in the mitochondrial membrane potential reduce ATP synthesis and make cells susceptible to necrotic cell death [42]. These events lead to local inflammatory reactions by attracting inflammatory cells, leading to the histopathology of nonalcoholic steatohepatitis [43].

Confrontation with various stressors (oxidative stress, inflammatory cytokines, and elevated concentrations of fatty acids) activates stress kinases, including mitogen-activated protein kinases (MAPKs), c-Jun N-terminal kinase (JNK), extracellular signal regulated kinase, inhibitor of nuclear factor kappa B (NFκB)-kinase (IKK), and conventional and atypical protein kinases C (PKC) [44]. The action of these kinases induces insulin resistance through phosphorylation of insulin receptor substrate (IRS). IRS-1 serine phosphorylation disrupts insulin receptor signaling through several distinct mechanisms and blocks insulin action. These kinases also exert powerful effects on gene expression, including promoting further inflammatory gene expression through activation of activator protein-1 (AP-1) complexes and NFκB [45]. NFκB, in turn, interacts with other transcription factors such as peroxisome proliferator activated receptor (PPAR)γ, which is necessary for adipocyte differentiation. Reduction of PPARγ activity prevents normal induction of some adipocyte genes such as TNF antagonist and adiponectin, which have direct effects on intermediary metabolism [46]. Adiponectin helps in the removal of free fatty acids from the circulation and deposition in fat depots [47]. In hepatocytes, it reduces hepatic glucose production and fatty acid uptake. Adiponectin also increases fatty acid oxidation in liver and skeletal muscle, resulting in a global increase in insulin sensitivity [48–50].

Decreased antioxidant capacity accompanied with increased lipid peroxidation has been reported in patients with fatty liver, visceral obesity, and metabolic syndrome. There is a correlation between the amount of visceral fat and systemic oxidative markers, indicating that visceral fat is an independent regulator of oxidative changes [51]. In nondiabetic human subjects, lipid peroxidation (represented by plasma thiobarbituric acid reactive substance and urinary 8-epi-prostaglandin-$F_2\alpha$) was positively correlated with body mass index and waist circumference [52]. The role of the liver both as an affected organ and a contributory source for impaired redox balance in patients with the MS and visceral adiposity has been strongly implicated [53]. The increased prevalence of fatty liver with hypertension and metabolic syndrome in nonobese patients provides additional support for role of liver in this condition [54].

3. Oxidative Stress and Hyperglycemia

Hyperglycemia can induce oxidative stress by several different mechanisms including nonenzymatic, enzymatic, and mitochondrial pathways, and so accelerate the four important molecular mechanisms involved in hyperglycemia-induced oxidative tissue damage [55, 56]. Nonenzymatic sources of oxidative stress originate from the oxidative biochemistry of glucose. Hyperglycemia directly increases ROS generation since glucose undergoes autoxidation to generate $^{\bullet}$OH radicals [57]. In addition, glucose reacts with proteins in a nonenzymatic manner leading to the development of Amadori products followed by formation of advanced glycation end products (AGEs). Enzymatic sources of augmented generation of ROS in diabetes include nitric oxide synthase (NOS), NAD(P)H oxidase, and xanthine oxidase [58–60]. All isoforms of NOS require five cofactors/prosthetic groups such as flavin adenine dinucleotide (FAD), flavin mononucleotide (FMN), heme, tetrahydrobiopterin (BH4), and Ca^{2+}-calmodulin. NOS becomes "uncoupled" when the

enzyme lacks its substrate L-arginine or one of its cofactors, and when uncoupled, NOS produces $O_2^{\bullet-}$ instead of $^{\bullet}NO$ [58–61]. A major source of $O_2^{\bullet-}$ production is NAD(P)H oxidase, a membrane associated enzyme that consists of five subunits [58, 59, 62, 63]. Guzik et al. investigated $O_2^{\bullet-}$ levels in vascular specimens from diabetic patients and probed sources of $O_2^{\bullet-}$ using inhibitors of NOS, NAD(P)H oxidase, xanthine oxidase, and the mitochondrial electron transport chain and reported that the enhanced production of $O_2^{\bullet-}$ in diabetic patients is predominantly formed by NAD(P)H oxidase [59].

The mitochondrial respiratory chain is a nonenzymatic source of reactive species. During oxidative phosphorylation, electrons are transferred from the electron carriers NADH and FADH2, through four complexes in the inner mitochondrial membrane, to oxygen, and generating ATP in the process [64]. Under normal conditions, $O_2^{\bullet-}$ is immediately eliminated by natural defense mechanisms. Hyperglycemia-induced generation of $O_2^{\bullet-}$ at the mitochondrial level is thought to be the major driver of the vicious cycle of oxidative stress in diabetes [65, 66]. There is an increased generation of ROS (especially $O_2^{\bullet-}$) when endothelial cells are exposed to clinically relevant hyperglycemic conditions. The augmented generation of pyruvate via accelerated glycolysis under hyperglycemic conditions is thought to flood the mitochondria and thus generates $O_2^{\bullet-}$ formation at the level of complex II in the respiratory chain [65].

Superoxide anions can activate several pathways in diabetes including accelerated formation of AGE's, polyol pathway, hexosamine pathway, and protein kinase C (PKC), all of which have been proven to be involved in micro- and macrovascular diabetic complications. Both $O_2^{\bullet-}$ and H_2O_2 stimulate stress-related signaling mechanisms such as NF-κB, p38-MAPK, and signal transducers and activators of transcription-Janus kinases (STAT-JAK), resulting in vascular smooth muscle cell migration and proliferation. In endothelial cells, H_2O_2 mediates apoptosis and pathological angiogenesis [67]. Furthermore, $O_2^{\bullet-}$ immediately reacts with $^{\bullet}NO$ to generate cytotoxic peroxynitrite ($ONOO^-$) and this reaction itself has several consequences. First, $ONOO^-$ alters the function of biomolecules by protein nitration as well as by causing lipid peroxidation [57]. For example, potassium channels, which regulate vasorelaxation, are inhibited by nitration [68, 69]. As reviewed by Turko et al., increased levels of nitrotyrosine are associated with apoptosis of myocytes, endothelial cells, and fibroblasts in diabetes [57]. Second, $ONOO^-$ causes single-strand DNA breakage, which in turn activates nuclear enzyme poly(ADP-ribose) polymerase (PARP) (a nuclear DNA-repair enzyme that is able to cause a depletion of NAD^+) [70]. Third, it decreases $^{\bullet}NO$ bioavailability causing impaired relaxation and inhibition of the antiproliferative effects of $^{\bullet}NO$ [64]. Furthermore, $ONOO^-$ oxidizes BH_4, an important cofactor for NOS, and causes uncoupling of NOS to produce $O_2^{\bullet-}$ instead of $^{\bullet}NO$ [61]. ROS-induced peroxidation of membrane lipids alters the structure and the fluidity of biological membranes, which will have global effects that alter vascular function [61, 67–71].

4. Oxidative Stress and Hypertension

There is a growing body of evidence supporting an important central role of the renin angiotensin aldosterone system (RAAS) in the coexistence of obesity, insulin resistance, dyslipidemia, and hypertension [72–74]. Indeed, aldosterone has a firm role in the pathogenesis and progression of the MS. Adipose tissue produces a lipid soluble factor that stimulates aldosterone secretion [75], which is then (along with other glucocorticoids) able to enhance adipogenesis and increase macrophage infiltration into fat depots [75, 76]. Elevated plasma aldosterone level induces insulin resistance in fat, skeletal muscle, liver, and cardiovascular tissue, independent of other RAAS components such as angiotensin II [74, 77]. Aldosterone induces proinflammatory adipokine expression and oxidative stress, resulting in diminished insulin receptor expression and impaired insulin induced glucose uptake [78]. Studies in animal models show that mineralocorticoid receptor blockade reduces expression of proinflammatory and prothrombotic factors in adipose tissue and increases the expression of adiponectin in heart and adipose tissue [79]. In humans, there is evidence to suggest that oxidative stress drives the production of aldosterone-stimulating oxidized fatty acids. Compounds such as 12,13-epoxy-9-keto-10(trans)-octadecenoic acid, derived from linoleic acid, can affect adrenal steroid production and mediate some of the harmful effects of obesity and oxidative stress [80]. Reduction of blood pressure, plasma renin activity, and aldosterone levels in both obese hypertensive and normotensive subjects who underwent weight reduction provides further evidence for the association of excess aldosterone and fat tissue [81, 82]. The deleterious effects of aldosterone on blood vessels and skeletal muscle tissue are partly mediated by stimulation of NAD(P)H oxidase, which induces excessive amount of ROS and oxidative stress. Exogenous aldosterone induces aortic expression of NAD(P)H oxidase (NOX2) (through mineralocorticoid receptor-dependent mechanisms) and of p47 phox (subunit of NADPH oxidase) mRNA (through both angiotensin receptor (AT1) and mineralocorticoid receptor-dependent mechanisms) [83]. Mineralocorticoid receptor activation contributes to angiotensin II mediated activation of NAD(P)H oxidase in the heart and aorta [84–86]. This in turn leads to induction of redox sensitive stress kinases (PKC, MAPK, JNK, etc.), phosphorylation of IRS-1 docking protein, and finally impaired glucose utilization [87, 88]. Aldosterone induces activation of NF-κB in the heart, an effect that is prevented in NOX-2 deficient mice [85]. Activation of NF-κB by aldosterone induces further production of adhesion molecules, chemokines such as monocyte chemoattractant protein (MCP-1), and inflammatory cytokines. In a rat model of aldosterone/salt hypertension, aldosterone induced severe hypertension, increased the expression of proinflammatory molecules in the heart, and cause inflammatory arterial lesions with infiltration of perivascular macrophages [89]. Several studies show that mineralocorticoid receptor blockade improves systemic insulin sensitivity and skeletal muscle glucose uptake that is associated with reduced NADPH oxidase activity and the attenuation of ROS [72, 74]. Mineralocorticoid receptor

antagonism in hypertensive rats decreases aortic inflammation, fibrosis, and hypertrophy [90–92] while it also decreases oxidative stress and inflammation in apolipoprotein E-deficient mice fed a high-cholesterol diet, a model of atherosclerosis [93]. Other proposed mechanisms for aldosterone induced metabolic effects include the effects of hypokalemia on pancreatic β-cell function, induction of hepatic gluconeogenesis, interfering with sodium-glucose transport, and fibrosis-induced malfunction in insulin secreting or insulin sensitive tissues [87, 94, 95]. Mosso et al. investigated insulin sensitivity and insulin secretion in patients with idiopathic primary aldosteronism and showed an association between aldosterone and lower pancreatic β-cell mass [94]. There is a negative correlation between C-peptide and serum aldosterone levels that are independent of serum potassium. Other data suggests that the harmful effects of aldosterone on β-cell function are mediated through induction of islet cell inflammation and oxidative stress [95].

5. Exercise and Metabolic Syndrome

Reduced daily physical activity in healthy young adults is associated with negative metabolic consequences such as decreased insulin sensitivity and increased abdominal fat [96, 97]. Therefore, increased physical activity is likely to be the evolutionary favored pathway to prevent the development of insulin resistance during metabolic derangements. According to Nunn et al. [98], chronic subclinical inflammation associated with the metabolic syndrome could be one reason for the continued physical inactivity and the induction of a vicious cycle. In the presence of inflammation, physical activity becomes less desirable, both physically and psychologically. The "inflammatory-induced sickness behavior" in animal studies is in support of this theory [99, 100]. Injection of lipopolysaccharide (which induces cytokine release) or direct injection of cytokines results in fatigue reduced movement and depressive symptoms. In contrast, hormetic stimuli, including exercise, calorie restriction, or polyphenols, can induce anti-inflammatory effects and enhance exercise capability, leading to better biological fitness. Low/moderate amounts of ROS produced during regular skeletal muscle work, are part of hormesis, which describes the generally favorable biological responses to low exposures to toxins and other stressors. A pollutant or toxin showing hormesis has opposite effects in small versus large doses. Hormesis is characterized by stimulation at low doses and inhibition at higher doses, resulting in an inverted U-shaped dose-response effect [101]. For example, exercise-induced increased production of ROS can be beneficial by evoking specific adaptations, such as increased antioxidant/oxidative damage repairing enzyme activity, increased resistance to oxidative stress, and lower levels of oxidative damage. On the other hand, excessive production of ROS is usually associated with detrimental effects.

6. Exercise and Adipose Tissue

Several studies show a strong association between obesity and physical inactivity [102, 103]. There is an inverse relationship between physical activity, body mass index (BMI), hip-waist ratio, and waist circumference [102–104]. These studies demonstrate that maintaining an active lifestyle can prevent the development of the MS. Weight reduction, via exercise, results in less loss of muscle (compared to fat) than weight loss through diet [105]. Maintaining lean body mass is essential for better glucose transport and fat metabolism. Reduction in fat mass is helpful in increasing adiponectin levels and improving cytokine profiles; changes in adipokines and cytokines are associated with the MS [106]. Controlling the release and activity of at least two cytokines, TNF-α and IL-6, could contribute to the natural protective effects of physical activity. Interleukine-6 (IL-6) is the first cytokine to be released into the circulation during exercise, and its levels increase in an exponential fashion in response to exercise [107]. IL-6 mRNA is upregulated in contracting skeletal muscle [108] and the transcriptional rate of the IL-6 gene is also markedly enhanced by exercise [109]. IL-6 acts as both a proinflammatory and anti-inflammatory cytokine. When secreted by T cells and macrophages, IL-6 stimulates the immune response and boosts inflammatory reactions, while muscle-produced IL-6 exerts anti-inflammatory effects through its inhibitory effects on TNF-α, IL-1β, and activation of interleukin-1 receptor antagonist (IL-1ra) and IL-10 [110]. Exercise-induced increases in plasma IL-6 correlate with the muscle mass involved in exercise activity and also with the mode, duration, and, especially, the intensity of exercise [111]. Exercise also confers protection against TNF-induced insulin resistance [112]. In addition, Starkie et al. reported that infusion of recombinant human IL-6 (rhIL-6) into human subjects simulated the exercise induced IL-6 response in the prevention of endotoxin-induced increase in plasma TNF-α [113]. Exercise can also suppress TNF-α production by an IL-6-independent pathway, as demonstrated by Keller et al. who reported only modest decreases in plasma TNF-α after exercise in IL-6 knockout mice [114]. Exercise induced increases in epinephrine levels can also blunt the TNF-α response [115]. In addition, Petersen et al. showed that IL-6 enhances lipid turnover and stimulates lipolysis as well as fat oxidation via activation of AMP-activated protein kinase [116]. Consistent with this, Wallenius et al. demonstrated that IL-6 deficient mice (IL6$-/-$) develop mature onset obesity and have disturbed carbohydrate and lipid metabolism that is partly reversed by IL-6 replacement. Other data indicate that centrally acting IL-6 exerts an antiobesity effect in rodents [117]. The lipolytic effect of IL-6 on fat metabolism was confirmed in two clinical studies of healthy and diabetic subjects [116, 118]. Visceral fat is potentially a cause of low-grade systemic inflammation, which in turn leads to insulin resistance, type II diabetes, and atherosclerosis [119]. During exercise, IL-6 also increases hepatic glucose production. Glucose ingestion during exercise reduces IL-6 production by muscles, suggesting that IL-6 is released due to the reduction in glycogen levels during endurance exercise and the consequent adrenergic

stimulation of IL-6 gene transcription via protein kinase A activation [120].

7. Exercise and Glucose Metabolism in Skeletal Muscles

At least two distinct pathways are involved in glucose transport; one is stimulated by insulin or insulin mimetics and the other is activated by contraction or hypoxia [121–123]. Phosphatidylinositol 3 kinase (PI3-kinase) is involved in insulin activated (but not contraction-activated) pathway [124], while 5′AMP-activated protein kinase participates in contraction-activated reactions [125]. Insulin-stimulated tyrosine phosphorylation of IRS-1 and activity of PI3 kinase [126], and insulin-stimulated Akt kinase activity are both diminished in skeletal muscle of obese and diabetic patients. Therefore, exercise can provide an alternative way to bypass the impaired insulin signal transduction in muscles of diabetic patients [127]. Regular physical activity mends insulin function and glucose tolerance in healthy individuals [128], patients with obesity [129], insulin resistance [130], and diabetics [131, 132]. Molecular mechanisms for improved glucose clearance and insulin sensitivity following exercise are related to the increased expression and activity of signaling proteins and enzymes which are involved in skeletal glucose and fat metabolism [133, 134]. Glucose transporter isoform 4 (GLUT4) is a key enzyme in this chain of reactions and its mitochondrial biogenesis is increased due to exercise training [135, 136]. It has been reported that peroxisome proliferator-activated receptor γ coactivator-1 (PGC-1) stimulates GLUT4 expression [137]. PGC-1 is a member of a group of transcription coactivators which play a key role in the regulation of cellular energy metabolism. It increases mitochondrial biogenesis and participates in the regulation of both carbohydrate and lipid metabolism. PGC-1 promotes the remodeling of muscle tissue to a fiber type composition that has greater oxidative capacity and less glycolytic metabolism in nature [138]. A single bout of exercise can increase muscular PCG1-1 content [139]. It should be noted that exercise-induced improvement in insulin signaling is not exclusively restricted to increased GLUT4 protein expression, as its concentration is similar in sedentary diabetics and insulin sensitive control subjects [140, 141]. While exercise increases GLUT4 protein and mRNA in diabetic patients [142], increased post receptor insulin signaling, especially at the distal step of the insulin PI3-kinase cascade (which results in GLUT4 translocation and glucose uptake), is the main mechanism [134, 143, 144]. Atypical protein kinase C (aPKC) and Akt substrate of 160 kDa (AS160) are among newly characterized insulin signaling molecules [145, 146]. AS160 in the basal nonphosphorylated state acts as an inhibitor for GLUT4 translocation. Insulin stimulates AS160 phosphorylation by Akt on five of six phosphor-Akt substrate motifs, leading to increased GLUT4 membrane trafficking events [147]. The exact mechanisms of aPKC in controlling GLUT4 translocation is still not clear, however, reports suggest that parallel to Akt, activation of aPKC is essential in both the process of translocation and docking/fusion of GLUT4 to the plasma membrane [148].

8. Exercise and Lipid Metabolism in Skeletal Muscles

As stated earlier, in addition to hyperglycemia and/or hyperinsulinemia, patients with the MS show a serious dysregulation in lipid metabolism as manifested by increased levels of circulating free fatty acids (FFAs) and triglycerides, accompanied by lipid accumulation in skeletal muscles [149]. Increased intramyocellular lipids will increase cellular oxidative stress with subsequent generation of ROS, stimulating lipid membrane peroxidative injury of mitochondrial membranes. One of the basic effects of exercise training is augmenting oxidative capacity of skeletal muscles, which results in an improvement in the rate of whole body fat oxidation [150]. This increase in fat oxidation capacity is partly due to an increase in fatty acid transport proteins, which leads to increased removal of plasma FFAs [151]. $FABP_{PM}$ and CD36 are among several key proteins that have been identified as fatty acid transporter proteins in human and animal muscles [152]. The effects of exercise training on the mRNA and protein expression of CD36 and $FABP_{PM}$ in muscles have shown different results [153, 154]. It may well be that increases in those proteins is totally protocol dependent, in terms of exercise duration and intensity. Exercise also activates AMP kinase, which stimulates fatty acid oxidation, glucose uptake, and mitochondrial biogenesis.

The AMPK complex is evolutionally a well-conserved serine/threonine kinase that functions as a fuel sensor in the cell and is activated when cellular energy is depleted and the AMP/ADP ratio rises [155]. The result of AMPK activation is the inhibition of energy-consuming biosynthetic pathways and the activation of ATP producing catabolic pathways. AMPK can also affect transcription of specific genes involved in energy metabolism, thereby exerting long-term metabolic control [156]. Cellular stresses that increase the AMP/ATP ratio such as hypoxia, oxidative stress, hypoglycemia, exercise, or nutrient deprivation can affect cellular metabolic conditions partially through this pathway [155]. In vivo and in vitro studies have shown that activation of AMPK leads to reduced glucose output form the liver [157]. Insulin sensitivity is also improved through reduced triglyceride accumulation by skeletal muscles [158]. This occurs as a result of AMPK phosphorylation, and thus inactivation, of acetyl-CoA carboxylase (ACC), resulting in decreases in malonyl-coenzyme A [159, 160]. ACC is an important rate-limiting enzyme for the synthesis of malonyl-CoA, which in turn is a critical precursor of fatty acids biosynthesis and a potent inhibitor of mitochondrial fatty acid oxidation. Decreases in malonyl-CoA content result in the reduction of fatty acid synthesis and increases in fatty acid oxidation. Amplified AMP kinase activity is also associated with increased cytochrome-c content, mitochondrial density, and DNA binding activity of nuclear respiratory factor-1, a transcription factor that acts on a nuclear set of genes required for transcription of respiratory chain proteins

in addition to mitochondrial transcription and replication [161].

9. Exercise and Increased Blood Pressure

Lifestyle modifications are recommended as the initial treatment strategy for reduction of high blood pressure [162]. Regular exercise training induces a moderate antihypertensive effect, with females and relatively lean participants earning greater benefits [163]. Aerobic exercise also lowers blood pressure and improves blood pressure control among overweight adult subjects [164]. In this regard, a modest weight loss of 3–9% is associated with a significant reduction in systolic and diastolic blood pressure of roughly 3 mm Hg in overweight people [165].

Potential mechanisms for exercise training and weight reduction effects on blood pressure include functional and structural changes in the vasculature, modulation of the renin-angiotensin system, reduction of sympathetic nervous system stimulation, and increased insulin sensitivity. It is been suggested that leptin is the main link between obesity, increased sympathetic nervous system activity, and hypertension [166]. Obesity is associated with resistance to the appetite and weight reduction actions of leptin, although the renal sympathetic activation effects remain intact [167]. Human studies show an interaction between high leptin levels and increased renal sympathetic tone in obese subjects [168]. Chronic hyperleptinemia also has a pressor effect which is mediated by increased sympathetic nervous system activity. Leptin infusion in animal models increases blood pressure, heart rate, and sympathetic nervous in different tissues [169, 170]. Leptin-induced increases in ROS and ET-1 can also contribute to hypertension [171, 172].

Physical activity increases vascular expression of eNOS both in animals and human beings [173–176]. The importance of this phenomenon has been confirmed in patients with stable coronary artery disease and chronic heart failure [177, 178]. There are several reports suggesting that exercise-induced upregulation of vascular eNOS expression is closely related to the changes of frequency and the intensity of physical forces within the vasculature, especially shear stress. Exercise-induced increases in heart rate will augment cardiac output and vascular shear stress, leading to increased expression of eNOS [173]. Increased NO synthesis secondary to amplified shear stress induces extracellular superoxide dismutase (SOD) expression in a positive feedback manner so as to inhibit the degradation of NO by ROS [179]. Another parallel mechanism that participates in this harmony is upregulation of eNOS through exercise-induced ROS production, since exercise-induced increases in shear stress-stimulates vascular production of ROS by an endothelium dependent pathway [180]. Endothelial NAD(P)H oxidase has a critical role in this process [181]. Superoxides are rapidly converted to H_2O_2 by SOD; hydrogen peroxide then diffuses through the vascular wall and increases the expression and activity of eNOS [182, 183]. Thus, increased expression of SOD1 and SOD3 (which facilitate the generation of hydrogen peroxide from superoxide) augments the effect of hydrogen peroxide on exercise-induced eNOS expression. On the other hand, eNOS expression is not increased in catalase overexpressing transgenic mice [174, 184]. Another putative mechanism is exercise-induced increases in arterial compliance which is mediated by reduction of plasma ET-1 concentration as well as the elimination of ET-1-mediated vascular tone. Twelve weeks of aerobic exercise training results in increased arterial compliance, which was accompanied by decreased plasma ET-1 levels. Moreover, the increase in central arterial compliance observed with ET-receptor blockade before the exercise intervention was eliminated after the exercise-training intervention [185]. These results indicate that endogenous ET-1 participates in the mechanisms underlying the beneficial influence of regular aerobic exercise on central arterial compliance.

Exercise training has a significant impact on the morphology of various blood vessels. These structural changes are followed by functional changes and lead to improved blood flow. Exercise induces angiogenesis, which is an expansion of the capillary network by the formation of new blood vessels at the level of capillaries resistance arterioles, and arteriogenesis, which is an enlargement of existing vessels [186].

10. Summary

The metabolic syndrome is an emerging epidemic that affects roughly 20% of the population in Western industrialized countries. It has become evident that inflammation and oxidative stress, which are associated with obesity and overweight, play crucial roles in the pathophysiology of this syndrome. They also greatly impact related pathological outcomes. It seems likely that insulin resistance is at the center of several vicious cycles that exacerbate the disturbances, leading to intensification of oxidative stress. Physical inactivity, a frequent finding in obese patients, escalates these processes. Chronic subclinical inflammation associated with the metabolic syndrome could be one reason for the continued physical inactivity and perpetuation of a vicious cycle. However hormetic stimuli, such as those that result from exercise, can boost antioxidant capacity, induce anti-inflammatory effects, and improve exercise ability. Exercise regulates fat and glucose metabolism and results in an increased action of insulin, while it also lowers blood pressure and improves blood pressure control in overweight adult subjects. In spite of these benefits, the precise duration and intensity of exercise for individual patients remain to be determined.

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