Hormones (2018) 17:299–313
https://doi.org/10.1007/s42000-018-0051-3

REVIEW ARTICLE

Metabolic syndrome: an update on diagnostic criteria, pathogenesis, and genetic links

Uzma Zafar[1,2] · Saba Khaliq[1] · Hafiz Usman Ahmad[1] · Sobia Manzoor[3] · Khalid P. Lone[1]

Received: 15 February 2018 / Accepted: 19 June 2018 / Published online: 31 August 2018

Abstract

Metabolic syndrome (MetS), today a major global public health problem, is a cluster of clinical, metabolic, and biochemical abnormalities, such as central adiposity, hypertension, insulin resistance, and dyslipidemias. These MetS-related traits significantly increase the risk of type 2 diabetes mellitus, adverse cardiac events, stroke, and hepatic steatosis. The pathogenesis of MetS is multifactorial, with the interplay of environmental, nutritional, and genetic factors. Chronic low-grade inflammation together with visceral adipose tissue, adipocyte dysfunction, and insulin resistance plays a major role in the progression of the syndrome by impairing lipid and glucose homeostasis in insulin-sensitive tissues, such as the liver, muscle, and adipocytes. Adipose-derived inflammatory cytokines and non-esterified fatty acids establish the link between central obesity IR, inflammation, and atherogenesis. Various studies have reported an association between MetS and related traits with single-nucleotide polymorphisms of different susceptibility genes. Modulation of cytokine levels, pro-oxidants, and disturbed energy homeostasis, in relation to the genetic variations, is described in this review of the recent literature, which also provides updated data regarding the epidemiology, diagnostic criteria, and pathogenesis of MetS.

Keywords Metabolic syndrome · Insulin resistance · Central obesity · Cytokines · Single-nucleotide polymorphisms

Introduction

Metabolic syndrome (MetS) is the commonly used term for a cluster of clinical and metabolic factors that increase the risk for type 2 diabetes mellitus (T2DM), coronary artery disease (CAD), and stroke. The interrelated risk factors include central obesity, dyslipidemias, hypertension, hypercoagulable state, and insulin resistance [1]. In persons with MetS, the risk of developing T2DM is five times greater and the risk of stroke and myocardial infarction is three times higher as compared to normal/healthy subjects [2]. During the last decade, MetS has also been associated with other clinical conditions, such as hepatic steatosis and non-alcoholic fatty liver disease (NAFLD), hypogonadism, polycystic ovary syndrome (PCOS), obstructive sleep apnea, vascular dementia, Alzheimer's disease, and carcinomas, especially pancreatic and colorectal cancers [3, 4].

The term MetS has the International Classification of Disease (ICD-9) code 277.7, which implies healthcare services and reimbursement. The metabolic syndrome was first described in 1923 by Kylin et al. as an association of gout with hypertension and hyperglycemia [5]. In 1947, Vague demonstrated the link between abdominal obesity and metabolic derangements in T2DM and cardiovascular diseases (CVD) [6]. The importance of insulin resistance (IR) in type 2 diabetes was established by Reaven in 1988, while he named the cluster of risk factors for CVD and DM syndrome X [7]. Some

✉ Uzma Zafar
Uzma.zargham@gmail.com

✉ Khalid P. Lone
khalid.lone@gmail.com

Saba Khaliq
sabakhaliq@uhs.edu.pk; sabahat711@yahoo.com

Hafiz Usman Ahmad
Hafizusmanahmad786@yahoo.com

Sobia Manzoor
lcianunique@yahoo.com

[1] Department of Physiology & Cell Biology, University of Health Sciences, Lahore, Pakistan

[2] Department of Physiology, Lahore Medical and Dental College, Lahore, Pakistan

[3] Department of Healthcare Biotechnology, Atta-ur-Rahman School of Applied Biosciences, NUST, Islamabad, Pakistan

years later, in 1992, central obesity was added as a core component in the definition and the entity and was renamed insulin resistance syndrome (IRS) [8]. Today, MetS has become a global health issue of great concern. According to the International Diabetes Federation (IDF) criteria, the prevalence of MetS in the United States is 33–39%, with a significant number being female, while Europe is marked by considerable diversity, the prevalence ranging from 18 to 30% [9, 10]. The prevalence also varies in various regions of the world, this being due both to different definitions of MetS using different diagnostic criteria and to other factors, including genotype, ethnicity, lifestyle, diet, and physical activity. The prevalence of MetS also differs by gender and age, since below the age of 50 it is slightly higher in men, reversing after that age to show a female preponderance [11]. According to the National Health and Nutrition Examination Survey (NHANES) 2003–2006, the burden of this condition is higher in males than in females before the age of 60, with a frequency of 41 and 34%, respectively; however, sex difference diminishes with advancing age due to the fact that cardiometabolic protection decreases in women after menopause, while the role of sex hormones in females diminishes regarding distribution of body fat [12]. The overall prevalence of MetS in India is 18%, with about 10% affected males in the total population, while in China 18% of females and 9.8% of males have MetS [13]. The prevalence of the disease in Pakistan was found to be very high, ranging from 45 to 60% [14], though the reported higher prevalence of MetS in India, Pakistan, Bangladesh, Sri Lanka, Nepal, and Afghanistan, in general, is likely to be due to low cut-off values for waist circumference (WC) [15]. A study conducted at outdoor clinics of Agha Khan Hospital, Karachi, estimated 60% prevalence, in accordance with the IDF definition and based on a strong association of MetS with male sex, family history of diabetes, and higher body mass index [16]. MetS is more prevalent in the older than the younger age group, but variants of MetS are associated with higher mortality in younger persons than in elders [17].

Methods

The terms “metabolic syndrome,” “T2DM,” “insulin resistance,” “polymorphisms,” and “genetic variants” were used to search electronic databases including PubMed, MEDLINE, Google Scholar, and Google. Studies from 2000 to 2017 were searched. Research articles included were case control studies, cohort studies, meta-analyses, and literature reviews published in official peer-reviewed journals. It took about 6 to 8 months to streamline the data of the present literature review.

Diagnostic criteria for MetS

MetS is a polymorphic entity characterized by a cluster of medical conditions. Over the years, there have been several attempts by various groups to establish the diagnostic criteria for MetS [18]. The World Health Organization (WHO) created the first internationally recognized definition of MetS in 1998, which was modified by the European Group for the Study of Insulin Resistance (EGSIR) in 1999. In 2001, the National Cholesterol Education Program Adult Treatment Panel (NCEP/ATP111) updated the guidelines for MetS, and in 2003, the American Association of Clinical Endocrinologists (AACE) proposed their definition [19]. The AACE, WHO, and EGSIR definitions mainly focus on IR measured by the oral glucose tolerance test and the euglycemic hyperinsulinemic clamp, the latter, however, being time- and labor-intensive and also expensive [20, 21]. Another limitation to the above definitions is that because obesity cut-off values specific for different populations are not defined for more than three definitions, they are not applicable in different ethnic groups. In April 2005, the IDF provided the Consensus Worldwide definition of MetS [22]. This definition includes waist circumference as a prerequisite for the identification of MetS while also comprising a number of the common features of the AACE, WHO, and EGSIR definitions, namely, measurement of triglycerides (TG) and of high-density lipoprotein (HDL)-cholesterol and evaluation of fasting glucose and blood pressure (Table 1) [15, 18–22]. The cut-off limits of WC are specific to the gender and ethnic groups in the IDF criteria (Table 2) [18, 22]. This is because populations of different ethnicities and races have different genetic backgrounds which are predictive of their susceptibility to CVD and T2DM; hence, the distribution of their norms for anthropometric measurements is also specific. Genetic background thus accounts for the fact that prevalence of MetS varies in different populations. In sum, although the exact cause of the various traits of MetS is still not understood, intra-abdominal fat deposition leading to central adiposity is considered to be the essential component as per the IDF guidelines [18, 22].

Pathophysiology of MetS

The pathogenesis of MetS is complex, being the interplay of multiple interacting pathways, genetic variations, and environmental factors, the latter including intake of a high-calorie diet and lack of exercise [8]. The exact etiology of MetS has not as yet been completely elucidated, but several studies have reported a strong association of MetS with insulin resistance, oxidative stress, inflammation, obesity, endothelial dysfunction, and cardiovascular diseases [18, 23].

Table 1 Diagnostic criteria for metabolic syndrome

WHO, 1998	EGIR, 1999	NCEP:ATPIII, 2001	AACE, 2003	IDF, 2006
IGT or IFG or diabetes and/ or IR (estimated with the euglycemic hyperinsulinemic clamp method) plus two or more of the following:	IR (defined as hyperinsulinemia measured by top 25% of the fasting insulin values among non-diabetic individuals) and two or more of the following:	Three or more of the following:	IGT and two or more of the following:	Central obesity as defined by ethnic/racial, specific WC, but can be assumed if BMI ≥ 30 kg/m^2 and two or more of the following:
	FPG ≥ 110 mg/dl	FPG ≥ 100 mg/dl* or on treatment for DM		FPG ≥ 100 mg/dl or on treatment for DM
BP ≥ 140/90 mmHg	BP ≥ 140/90 mmHg or on anti-hypertensives	BP ≥ 130/85 mmHg	BP ≥ 130/85 mmHg	BP ≥ 130/85 mmHg or on anti-hypertensives
Abdominal obesity: WHR > 0.9 for men and > 0.85 for women and/or BMI > 30 kg/m^2	WC: ≥ 94 cm for men, ≥ 80 cm for women	WC: ≥ 102 cm for men, ≥ 88 cm for women	BMI: ≥ 25 kg/m^2	
Triglycerides ≥ 150 mg/dl or on treatment	Triglycerides ≥ 178 mg/dl or on treatment	Triglycerides ≥ 150 mg/dl or on treatment	Triglycerides ≥ 150 mg/dl	Triglycerides ≥ 150 mg/dl or on lipid lowering agent
HDL-C: < 35 mg/dl for men and <39 mg/dl for women	HDL-C: < 39 mg/dl or on treatment	HDL-C: < 40 mg/dl for men, < 50 mg/dl for women	HDL-C: < 40 mg/dl for men, < 50 mg/dl for women	HDL-C: < 40 mg/dl for men, < 50 mg/dl for women or on treatment for dyslipidemia
Urine albumin excretion rate ≥ 20 μg/min or urine albumin to creatinine ratio ≥ 30 mg/g				

FPG ≥ 100 mg/dl* modified in 2004 according to the IDF definition of impaired fasting glucose. The 2001 definition of NCEP-ATPIII identified FPG ≥ 110 mg/dl as elevated

American Association of Clinical Endocrinologists (AACE), body mass index (BMI), European Group for the study of insulin resistance (EGSIR), fasting plasma glucose (FPG), impaired fasting glucose (IFG), impaired glucose tolerance (IGT), insulin resistance (IR), International Diabetes Federation (IDF), National Cholesterol Education Program Adult Treatment Panel (NCEP/ATP111), waist circumference (WC), waist to hip (W/H) ratio, World Health Organization (WHO)

Insulin resistance

The core component of MetS is insulin resistance (IR), hence the alternate name "insulin resistance syndrome." IR is the decreased ability of the target organs, such as the liver, skeletal muscles, and adipose tissues, to respond to normal levels of insulin [24]. Insulin regulates a variety of biological processes by acting on its cell surface receptors at the insulin-sensitive sites, while insulin-receptor binding initiates a series of events that lead to phosphorylation of the insulin receptor, followed by insulin receptor substrate (IRS) proteins and activation of two important post-receptor transduction pathways, PI3K (phosphatidylinositide 3 kinase) Akt (protein kinase B) mTOR (molecular target for rapamycin) and Ras-MAPK (mitogen-activated protein kinase) signaling cascade [25]. PI3K is a heterodimer of a catalytic and regulatory subunit. Activation of PI3 kinase depends upon binding of its SH2 domains in the regulatory subunit with phosphorylated IRS-1. This in turn activates its catalytic subunit, which immediately phosphorylates phosphatidyl inositol biphosphate (PIP2) to phosphatidyl inositol triphosphate (PIP3), which is a second messenger [26]. PIP3 recruits protein kinase B (Akt) to the plasma membrane, the activation of which further requires phosphorylation by PDK-1 (phosphoinositide-dependent protein kinase). Activated Akt is responsible for translocation of GLUT4 transporters, uptake of glucose by the cells, and inactivation of enzyme glycogen synthase kinase, a potent inhibitor of glycogen synthase, thus promoting glycogen synthesis in the cells [27]. The PIP2/PIP3/Akt pathway is mainly responsible for mediating various actions of insulin on metabolism by regulating the activity and expression of transcription factors, enzymes, and proteins responsible for proliferation and apoptosis of cells [28]. The activation of the Ras-MAPK signaling pathway is responsible for the effects of insulin on cell growth, proliferation, and mitogenesis [29]. In vascular endothelial cells, insulin-mediated activation of the PIP2/PIP3 pathway promotes the production of nitric oxide that inhibits vascular smooth muscle proliferation and induces vasodilation [30]. By contrast, activation of the MAPK pathway results in vasoconstriction and proliferation of vascular smooth muscles [31].

Table 2 Gender and ethnic specific limits for waist circumference

Ethnic group	Waist circumference	
	Male (cm)	Female (cm)
Europids	≥ 94	≥ 80
South Asians	≥ 90	≥ 80
Chinese	≥ 90	≥ 80
Japanese	≥ 90	≥ 80

In IR, the PI3K-Akt pathway regulating cellular metabolic activities in tissues is mainly affected, while the MAPK signaling pathway is spared [32]. Chronic hyperglycemia, systemic inflammation, and IR are all capable of activating the p38MAPK signaling cascade. In the endothelium, selective impairment of PI3K-mediated nitric oxide production and activation of the MAPK pathway lead to endothelial dysfunction, atherogenesis, and cardiovascular complications [30–32]. A number of defects in post-receptor events have been identified as being responsible for impairment of PI3K signaling in IR and T2DM. Several studies have consistently reported reduced insulin signal transduction via the IRS-1/PI3K pathway, decreased glucose phosphorylation, and impaired glycogen synthase activity [33, 34]. Moreover, mitochondrial dysfunction in IR results in activation of different serine kinases responsible for serine phosphorylation of IRS-1 [35]. Another distinct mechanism is activation of p85α, which displaces p110 from IRS-1 and, in combination with the activation of serine kinases, worsens IR through early degradation of IRS-1. This cascade of events leads to impaired hepatic insulin action, altered transcriptional activity of Forkhead box O1 nuclear factors, increase in hepatic glucose output, and synthesis of proinflammatory cytokines and triglycerides [36]. Adipose tissue IR results in impaired suppression of lipolysis in the presence of high insulin levels with increased release of free fatty acids (FFA) in the blood, which favors hepatic gluconeogenesis, glucose intolerance, and increased delivery of FFA to the muscles [37, 38].

Skeletal muscle IR is considered to be the primary or initiating defect preceding hepatic IR, pancreatic beta-cell failure, and T2DM [39]. In skeletal muscles, the key defect in IR is present at the level of interaction of the IRS regulatory subunit with PIK3 not involving the MAP kinase signaling pathway. This expression of selective IR globally affects glucose metabolism, which results in impaired translocation of GLUT4 transporters, decreased glycogen synthesis, overt hyperglycemia, and worsening of IR. A number of studies have also focused attention on accumulation of lipid intermediates, such as diacylglycerol, fatty acyl Co A, and ceramides in muscles, resulting in serine phosphorylation of IRS-1 responsible for altered insulin signaling and IR [39, 40]. Excessive delivery of free fatty acids to the mitochondria results in production of increased amounts of NADH and FADH2. These entities alter the membrane potential of the mitochondria, leading to increased levels of ROS and further worsening of IR [41, 42]. However, the molecular and cellular mechanisms linking ROS with IR are still not known. Insulin resistance, which is the driving factor that leads to T2DM, is present several years before the onset of T2DM. Furthermore, first-degree relatives of type 2 diabetics often have IR even when they have normal glucose tolerance and are non-obese, this pointing to a strong genetic component in the development of IR [43, 44].

Role of central obesity and adipokines in MetS

Central obesity, disturbances in lipid metabolism, and altered energy homeostasis are also linked to IR and MetS traits [45]. According to the IDF criteria, central obesity is a mandatory component of MetS, with deposition of fat in the waist and perivisceral areas resulting in a proinflammatory state that leads to adverse cardiometabolic outcomes [18, 22]. In patients with IR, the process of lipolysis within adipose tissue is accelerated, resulting in increased FFA release into the portal circulation. Moreover, macrophage infiltration of adipose tissue, altered immune response, and imbalance in the synthesis of pro- and anti-inflammatory cytokines affect the activity of insulin in the liver and muscle [46, 47]. Macrophages constitute about 40% of the total cells of obese adipose tissue, compared to 10% in lean adipose tissue. They can generally be categorized as classically activated macrophages (M1) and alternatively activated macrophages (M2). The M1 phenotype is characterized by increased expression of inflammatory proteins, such as TNF-α, IL-6, and IL-12 as well as inducible nitric oxide synthase, and M2 by increased expression of anti-inflammatory proteins like arginase. There is an increased ratio of M1 to M2 in obese adipose tissue, while M1 also correlates with inflammation and insulin resistance [48]. Adipose tissue is the most abundant metabolically active endocrine organ in the body and a source of such hormones as adiponectin, IL-6, and TNF-α. Among these, adiponectin, encoded by the *ADIPOQ* gene, exerts a potent insulin-sensitizing effect, while the proinflammatory cytokines, interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α), contribute to the development of inflammation in obese subjects [49, 50]. As MetS is associated with central obesity and adipose dysfunction, adipokines are strong candidates to predict the future development of IR, T2DM, and MetS.

Adiponectin, the insulin-sensitizing and anti-inflammatory adipokine

Adiponectin, the peptide most abundantly secreted by the adipocytes, has insulin-sensitizing and anti-inflammatory actions [51]. It is involved in glucose metabolism, hepatic gluconeogenesis, fatty acid oxidation, and nitric oxide synthesis. Adiponectin, acting through *ADIPOQ* receptor 1 (R1), enhances AMP activation and translocation of GLUT 4 transporters while favoring enhanced glucose uptake by the skeletal muscles, while *ADIPOQ* receptor 2 (R2), mainly expressed in the liver, on stimulation, activates peroxisome proliferator-activated receptor gamma (PPAR-γ) [52, 53]. Adiponectin also inhibits hepatic gluconeogenesis by hampering phosphoenolpyruvate carboxykinase activity. The actions of adiponectin on vascular smooth muscle and endothelial cells are protective and are mediated through T-cadherin, a membrane-associated adiponectin-binding molecule. It decreases the expression of vascular cell adhesion molecules (VCAM-1) and E selectins on the endothelial cell surface, inhibiting adhesion of monocytes and transformation of macrophages to foam cells. Adiponectin also promotes vascular repair by upgrading the function and number of endothelial progenitor cells [54–57].

Adiponectin secretion is reduced in MetS due to IR, oxidative stress, excessive adiposity, and inflammation [58]. Molecular mechanisms establishing the link between ROS and *ADIPOQ* gene regulation are still under investigation; however, it has been reported that elevated levels of ROS in mitochondria increase the production of uncoupling protein-2, resulting in suppression of the C/EBP binding region in the promoter area of the *ADIPOQ* gene, which is responsible for decreased *ADIPOQ* mRNA expression [59, 60]. The reciprocal relationship between adiponectin and inflammation is supported by data demonstrating that IL-6, CRP, and TNF-α reduce *ADIPOQ* gene expression and mRNA by interfering with the PIK3 insulin signaling pathway. Not only is *ADIPOQ* production reduced, but there is also reduced expression of *ADIPOQR1* and *ADIPOQR2*, contributing to metabolic dysregulation, *ADIPOQ* resistance, and IR (Fig. 1) [58–61].

Proinflammatory cytokines: tumor necrosis factor alpha and interleukin

TNF-α and IL-6 are cytokines having endocrine, autocrine, and paracrine activities and whose gene expression is increased in adipocytes, macrophages, and lymphocytes of obese subjects [62]. TNF-α, a membrane-bound protein, is cleaved by the metalloprotease TNF-α-converting enzyme (TACE). The soluble trimeric forms of TNF-α interact with their receptors TNFR1 and R2. Soluble TNF-α acts as an endocrine hormone and, on binding with TNFR1, results in apoptotic death, induced by a cascade of caspase activation in cancer cells or virally infected cells. In primary human cells, TNF/TNFR interaction results in activation of NFκB and additional pathways, like mitogen-activated protein kinase (MAPK) and c-Jun-terminal kinase (JNK) [63]. NFκB activation results in increased production and acceleration of TNF and TNF/TNFR interaction. Activation of the JNK pathway leads to synthesis and release of cytokines, such as IL-2 and IL-6, further worsening inflammation [64]. TNF-α acts locally on the adipocytes and reduces insulin sensitivity by different mechanisms, including (a) inhibition of insulin receptor substrate-1 activation, (b) downregulation of PPAR-γ in adipocytes, and (c) decreased affinity of these receptors for a class of drugs named thiazolidinediones [64, 65]. TNF-α decreases nitric oxide-mediated vasodilation and is involved in

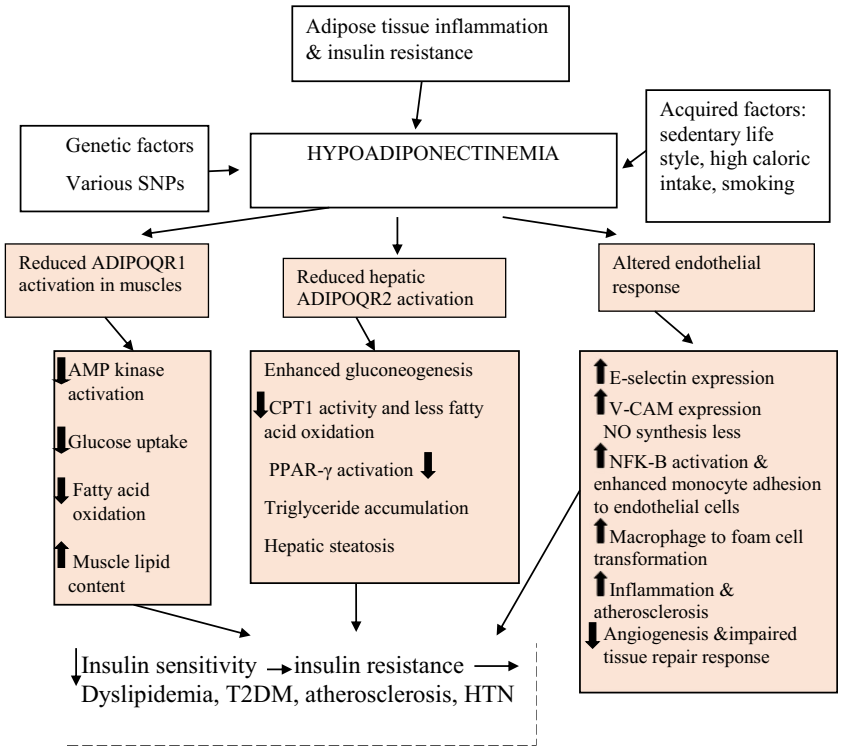

Fig. 1 Schematic illustration linking hypoadiponectinemia with insulin resistance and adverse clinical outcomes. *ADIPOQR*, adiponectin receptor; *AMP*, adenosine monophosphate; *CPT1*, carnitine-palmitoyltransferase; *NFK-B*, nuclear factor kappa B; *NO*, nitric oxide; *PPAR-Ɣ*, peroxisome proliferator-activated receptor gamma; *SNP*, single-nucleotide polymorphism; *V-CAM*, vascular cell adhesion molecule

the vascular pathology of MetS, atherosclerosis, and coronary artery disease [66, 67].

IL-6, which is a glycosylated protein made up of four alpha helices having three receptor binding domains, is also called beta cell stimulating factor. It acts via two mechanisms, i.e. a classical pathway and a trans-signaling pathway [68]. In the classical pathway, IL-6 binds with the membrane-bound receptor which, on activation, associates with another protein, gp130, resulting in signal transduction by the JNK/MAPK pathway [69]. Certain cells do not express the IL-6 receptor, but instead express gp130 proteins. These are activated by circulating IL-6 receptors (when they are activated by IL-6 in blood) via the trans-signaling pathway. Signal transduction through the trans-signaling pathway is mediated by JAK-STAT and MAPK activation. It creates IR in the liver by compromising insulin actions through STAT3-SOCs pathways while also increasing hepatic synthesis of acute phase proteins, such as C-reactive proteins and fibrinogen [70]. Various epidemiological studies link C-reactive proteins with metabolic risk, atherosclerotic lesions, and cardiac events [23, 69, 70]. Moreover, IL-6 also targets vascular smooth muscle cells and endothelium, resulting in increased expression of cell adhesion molecules and activation of the local renin-angiotensin pathway, which induces vessel wall inflammation and damage [1]. Given that proinflammatory actions of IL-6 are mediated through the trans-signaling pathway, blockade of this pathway is a potential therapeutic target. Meanwhile, both macrophages and adipocytes within fat tissue secrete numerous cytokines and peptides that contribute to local and systemic inflammation and IR [71, 72]. Further studies are required to gather information that can shed light on the link between metabolism and inflammation so as to target the cytokine pathways as a therapeutic option.

Risk of cardiovascular diseases in MetS

The role of MetS in the development of CVD has been explored extensively, various studies revealing that MetS is associated with significantly higher risk of such cardiovascular complications as coronary and peripheral arterial diseases, arrhythmias, congestive cardiac failure, and stroke [73–75]. In addition, fat accumulation, in particular visceral fat, is strongly associated with both MetS during childhood and the onset of CVD later in life [76, 77]. Dyslipidemia, characterized by increased triglyceride levels and decreased HDL, is an important criterion for the diagnosis of MetS in adults, adolescents, and children. Elevated triglycerides with low HDL has been shown to be a disease marker and an added risk for CVD in obese children with MetS [78–80]. A triglyceride/HDL-cholesterol ratio of three or greater is also associated with a significantly higher concentration of small LDLs than a ratio of less than three [80, 81].

The molecular mechanisms underlying CVD, IR, and MetS are complex and not to date fully characterized. In IR, the effect of insulin on endothelial cells is minimized with reduced synthesis of endothelial nitric oxide synthase and nitric oxide, making endothelial cells more susceptible to oxidized lipid-induced injury and atherosclerosis. Hyperinsulinemia resulting from IR enhances prenylation of

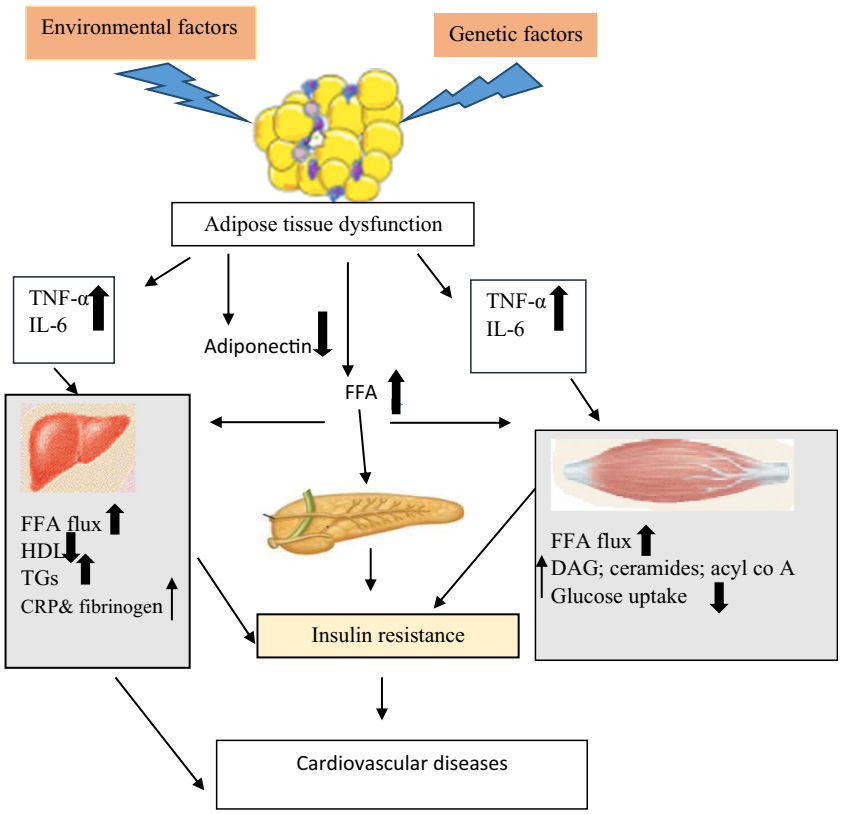

Fig. 2 Inflammatory cytokines and free fatty acids (FFA) establish a link between adipose tissue, insulin resistance, and associated morbidity. Adipose dysfunction favors accelerated release of FFA and inflammatory adipokines into the circulation. Uninhibited FFA release deranges glucose and fat homeostasis in the liver, pancreas, and skeletal muscles, resulting in lipotoxicity and insulin resistance. TNF-α and IL-6 from inflamed adipose tissue also worsen insulin resistance in the liver and skeletal muscles. IL-6 increases acute phase protein synthesis in the liver and TNF-α through the NFκB pathway, causing serine/threonine phosphorylation of insulin receptor and IRS-1 and impairing the PIK3 insulin signaling pathway. *DAG*, diacylglycerol; *FFA*, free fatty acids; *HDL*, high-density lipoproteins; *IL-6*, interleukin 6; *TG*, triglyceride; *TNF-α*, tumor necrosis factor alpha

Ras and Rho proteins in endothelial cells, augmenting the response of these cells to mitogenic and growth promoting effects of platelet-derived growth factor, epidermal growth factor, and angiotensin II [30, 31].

Several studies have identified important molecular pathways linking obesity to cardiac dysfunction, particularly alterations in myocardial calcium via changes in the functional expression of SERCA2a (sarco/endoplasmic reticulum Ca) and ryanodine receptors (RyR2), inducing myocellular and beta cell dysfunction [82, 83]. The above-mentioned pathways also affect several subcellular structures in addition to the abnormalities in intracellular calcium [84, 85]. Further work is needed to fully elucidate the underlying mechanisms responsible for dysfunctional regulation of SERCA2a and altered calcium signaling in myocardium and beta cells in obesity/MetS.

Adipose tissue dysfunction and lipotoxicity

Lipotoxicity is defined as an accumulation of lipid intermediates in non-adipose tissues, including the kidney, liver, heart, and skeletal muscles, resulting in deleterious effects and organ damage [86]. Due to IR, insulin-stimulated uptake of glucose and fatty acids is reduced by the adipocytes and there is impaired suppression of postprandial FFA release in the blood. This increases the net movement of fatty acids towards the skeletal muscles, liver, and pancreas, leading to lipoapoptosis and organ failure [87] (Fig. 2). Lipotoxicity initiates metabolic perturbations through a variety of cellular mechanisms, worsening insulin resistance, ROS-induced mitochondrial, endoplasmic reticulum, and lysosomal stress, alteration of the tissue renin-angiotensin pathways, and increased expression of adrenergic receptors on vascular smooth muscles [86–88]. In hepatocytes, endoplasmic reticulum stress and JNK pathways are mainly responsible for lipoapoptosis. Saturated and free fatty acids also stimulate the production of toll-like receptor 4 (TLR4), which increases the synthesis of TNF-α by the hepatocytes [89]. This cytokine enhances the expression of proapoptotic proteins in the liver BH-3 and PUMA (p53-upregulated modulator of apoptosis). PUMA interacts with other proapoptotic BCL-2 family proteins (B cell lymphoma-2), inducing mitochondrial damage and a cascade of events leading to cell death by cytochrome C release, caspase activation, and DNA fragmentation [90, 91]. There are several pathways linking dysfunctional adipocytes in IR with lipotoxic liver disease and non-alcoholic steatohepatitis (NASH) [92].

Ferritin, hepcidin, and uric acid: mediators of inflammation in MetS

A number of studies have revealed a link between serum uric acid, hepcidin, ferritin, and inflammatory cytokines [93].

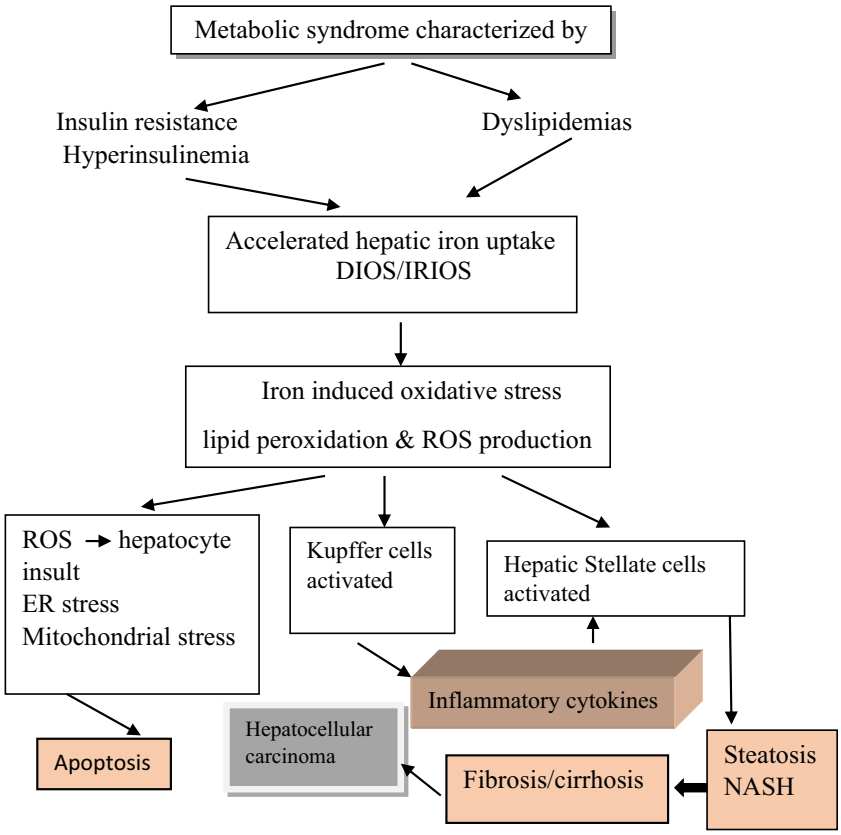

Fig. 3 A postulated pathway illustrating the mechanism of iron induced oxidative stress, responsible for the development of liver fibrosis and carcinogenesis. Insulin resistance induces hepatic steatosis and dysmetabolic iron overload syndrome (DIOS) or insulin resistance iron overload syndrome (IRIOS). DIO causes oxidative stress in hepatocytes with the activation of liver macrophages, "Kupffer cells," and hepatic "Stellate cells" that are responsible for liver fibrosis following hepatic insult due to iron-induced oxidative stress

Hyperferritinemia is common in patients with MetS, raised serum ferritin levels predicting liver iron overload, non-alcoholic fatty liver disease (NAFLD), and hepatic fibrosis, also called dysmetabolic iron overload syndrome (DIOS) or insulin resistance iron overload syndrome (Fig. 3) [94, 95]. The relation between IR and body iron status is bidirectional. In IR, there is hyperinsulinemia, and insulin, being an anabolic hormone, promotes the entry of iron into the tissues. Iron, which is closely associated with oxidative stress, produces superoxide and peroxide radicals, this resulting in lipid peroxidation of membranes and increasing the levels of fatty acids in the blood [96–98]. The master regulatory protein of iron homeostasis is hepcidin, a 25 amino acid peptide. It acts through its receptor, ferroportin, expressed in cells involved in iron transport or export, i.e., enterocyte, hepatocytes, and macrophages [99], its production being increased by the liver in states of iron overload. Raised serum ferritin levels are also associated with raised serum hepcidin levels [100]. Increased levels of hepcidin downregulate ferroportin and inhibit transport of iron from enterocytes while also decreasing intestinal absorption of iron. Serum hepcidin levels increase linearly with any increase in MetS components in the patient. Hepcidin binds to ferroportin, acting through the JAK/STAT pathway, and increases intracellular levels of suppressors of cytokine signaling 3 (SOCS3) [99, 100]. Studies in mouse models have revealed that SOCS3 have a central role in the pathology of hepatic steatosis [101]. Hepcidin also has a role in destabilizing atherosclerotic plaques through its action on macrophage function. Levels of hepcidin are also upregulated by various inflammatory cytokines, including TNF-α and IL-6 [102].

Uric acid, an end product of purine metabolism, is produced when hypoxanthine is converted to xanthine, which is later converted to uric acid by the catalytic actions of enzyme xanthine oxidase [103]. Previous studies have reported a tight relationship between serum uric acid levels and MetS or its individual components [104, 105]. Plasma uric acid is a marker of oxidant stress and injury in a variety of conditions, including hepatic steatosis, atherosclerosis, diabetes, and dyslipidemias [106]. The bridge between uric acid and MetS is IR. Hyperinsulinemia due to IR increases the reabsorption of uric acid from the proximal tubules of the kidneys and decreases urinary excretion of uric acid [105, 106]. Uric acid has both pro- and anti-inflammatory actions. Inside the cells, it acts as a pro-oxidant by promoting oxidation of lipids, increases the levels of reactive oxygen species (ROS), and decreases the availability of nitric oxide in endothelial cells, thus hampering insulin action and generating IR [107]. The pro-oxidant effects of uric acid are mediated through the NADPH oxidase-dependent pathway. Uric acid-induced oxidative stress in adipocytes leads to decreased adiponectin synthesis and damages the islets of Langerhans in the pancreas. It also

activates the renin-angiotensin pathway, which increases salt reabsorption from the kidneys. Serum levels of uric acid are associated with atherosclerosis, diabetes, hyperlipidemia, and hypertension [108, 109].

Genetic links determine susceptibility to MetS

Central obesity leads to chronic low-grade inflammation and, in genetically predisposed individuals, results in MetS and an array of associated comorbidities, including atherosclerosis, ischemic heart disease, and stroke [110, 111]. Left unchecked, the imbalances of MetS can become self-perpetuating leading to increased susceptibility to various complications. Response to therapy also depends upon the patient's genetic background and family history [12]. First-degree relatives of type 2 diabetics are prone to have insulin resistance and related traits [112, 113]. A number of genome-wide association studies (GWAS) have identified 90 loci associated with hypertension and more than 100 associated with obesity, lipoprotein, and lipid levels [114, 115].

Adipokine genetic variations in relation to MetS

Genetic variations in *ADIPOQ*, the adiponectin gene, are reported to be associated with T2DM and obesity. Polymorphisms of *ADIPOQ* result in decreased secretion and altered structure, with impaired multimerization of the adiponectin molecule, resulting in unstable trimer formation [116]. According to the data published by the prospective study DESIR (Data from an Epidemiological Study on the Insulin Resistance syndrome), *ADIPOQ* is a candidate gene for diabetes mellitus and IR [117]. Various single-nucleotide polymorphisms of this gene, such as +45T>G in exon 2, 276 T>G in intron 2, -11377C>G, and -11391G>A, have been studied in heterogeneous and multiethnic populations, although the results are conflicting. Nevertheless, it was concluded that genetic variations in adiponectin were associated with MetS and related disorders [117–121].

IL-6 increases the synthesis of acute-phase proteins by the liver and also regulates immune reactions in the body. A genetic variant of IL-6, -174 C>G, is involved in the regulation of the transcriptional activity of IL-6 [122]. This polymorphism has been linked to high levels of IL-6 in the blood, whereas the presence of the C allele is associated with lower production of IL-6 than the G allele. Various other studies have shown increased levels of mRNA of IL-6 in G/G homozygotes in different diseases [123]. An association has also been found between the IL-6 promoter polymorphism and ischemic heart disease and T2DM in Pakistani families [124, 125].

The G allele of TNF-α at -308 G>A (rs1800629) is a wild type which is replaced by the A allele in a certain percentage of the population. This allele is associated with high levels of TNF-α in the blood due to increased expression of its mRNA [126]. The A allele of TNF-α is associated with various disorders, including asthma, allograft rejection, and chronic obstructive lung disorders [127, 128]. A study on Egyptian children revealed a strong association between the AA homozygous genotype and rheumatic heart disease, showing an odds ratio of 5.7 and a p value of 0.001 [129, 130]. Presence of the A allele is also associated with increased risk of acute coronary syndrome in the South Indian population [131].

Role of HIF-1α and its genetic variant in MetS-related traits

Hypoxia has a major role in the pathogenesis of complications of diabetes, including diabetic nephropathy, coronary artery disease, and foot ulcers. Oxygen homeostasis in the cells is maintained through the transcription factor hypoxia-inducible factor (HIF), a heterodimer composed of HIF-1α and HIF-1β [132]. The activity of this factor is regulated by and dependent on the HIF-1α component. In hypoxic states, it is activated, moves to the nucleus, binds to the hypoxia-response element of DNA, and upregulates the genes involved in (a) erythropoiesis, (b) angiogenesis, (c) glucose transport, and (d) iron and energy homeostasis. It controls the expression of more than 100 genes involved in oxygen homeostasis [132, 133]. In normoxic states, HIF-1α is hydroxylated at proline residues and undergoes proteasomal degradation [132–134]. A non-synonymous polymorphism, g.C45035T (rs11549465), which results in Pro582Ser substitution of the HIF-1α protein, is associated with decreased risk of T2DM. Previous studies by Yamada et al. and Nagi et al. reported that the T allele was more frequent in controls than in cases with T2DM, while the minor T allele of HIF-1α was associated with higher transcriptional activity as compared to the wild type in hypoxic states [135, 136]. This genetic variant was also found to have a protective role against diabetic nephropathy [137]. Increasing the levels of hypoxia-inducible factors might be considered as a potential therapeutic target for the treatment of T2DM and associated renal complications [133].

Altered lipid homeostasis in MetS and genetic links

Dyslipidemias, especially those marked by elevated levels of triglycerides and VLDL and low levels of HDL, are considered important risk factors for coronary artery disease and

stroke in subjects with MetS [113]. Variants of the genes related to lipid homeostasis, such as liver X receptor (LXR), retinoid X receptor (RXR), peroxisome proliferator-activated receptor gamma (PPPAR-γ), and apolipoprotein (APO) A5, may lead to dyslipidemias as well as to prothrombotic and atherosclerotic states [138, 139].

Liver X receptor alpha is a member of the nuclear receptor family and is involved in regulating cellular cholesterol levels, lipoprotein synthesis, and fat metabolism. It promotes uptake of cholesterol by increasing expression of ABCA1, ABCG1, ABCG5, ABCG4, and ABCG8 [140]. It activates human macrophage Niemann Pick C1 and C2 signaling proteins to transport cholesterol from the endosomal chambers to the plasma membrane [140, 141]. The *LXR-α* gene also suppresses chemokines and cytokines involved in the process of inflammation [141–143]. It has been shown by Wang et al. that the LXR-α polymorphism rsl2221497 (G>A) is associated with increased risk of ischemic heart disease and stroke [144]. Retinoid X receptors (RXR) are heterodimeric transcription factors with three isoforms, RXR-α, β, and γ. The *RXR-γ* gene is expressed in adipose tissue, skeletal muscles, the central nervous system, skin, and intestines. This gene suppresses lipoprotein lipase (LPL) promoter gene activity by various mechanisms. A serine variant of *RXR-α*, rather than the wild type glycine, is a more potent suppressor of the LPL promoter area, which leads to dyslipidemias and atherosclerosis. There is an association between the glycine 14 serine variant of RXR and familial hyperlipidemias and coronary artery disease [145]. However, limited data are available regarding the association of this genetic variant with other MetS-related traits in different ethnic groups.

Apolipoprotein A5 (APOA5) is a strong determinant of plasma triglyceride levels, increased concentrations being a risk factor for coronary disease and MetS [146]. APOA5 is present in very small concentrations in plasma, ranging from 24 to 406 μg/L, while it is also present in association with HDL, VLDL, and chylomicrons [147]. Various studies have revealed that APOA5 levels in plasma are inversely related to triglycerides and VLDL and that there is a positive association of APOA5 with HDL [148]. APOA5 decreases plasma triglycerides by enhancing the activity of lipoprotein lipase. It is also postulated that APOA5 interferes with storage of triglycerides in adipose tissue and the synthesis of VLDL by the liver [148, 149]. Genomic studies have revealed that the T-1131>C polymorphism in the regulatory area of the *APOA5* gene is associated with decreased levels of ApoA5 mRNA and increased levels of triglycerides in the blood [150–152].

The ADRB3 polymorphism and disturbed energy homeostasis in MetS

Adrenergic receptor β3 (ADRβ3), expressed in adipose tissue, is involved in thermogenesis and energy expenditure. It is a transmembrane G-protein coupled receptor and, on activation, it increases the levels of intracellular c-AMP and promotes lipolysis [153]. Hence, the expression of this receptor is important for delivering increased amounts of fatty acids to the portal vein. The tryptophan 64 arginine polymorphism of ADRβ3 is found to be associated with low basal metabolism, IR, and related traits like BMI and WC [154]. It is a missense mutation located in the first transmembrane domain of ADRβ3. This change in amino acid sequence is associated with altered affinity of the receptor for norepinephrine, as a result of which intracellular fat and energy homeostasis is deranged [155, 156].

Clinical applications

Although susceptibility to environmental factors is determined by genes, the current global epidemic of MetS is to a large extent due to our modern-day lifestyle characterized by the consumption of lipogenic food coupled with a lack of physical exercise. Metabolic derangements in MetS should thus be addressed at multiple levels through a variety of strategies. Studies and pharmacological trials strongly support the important the role of lifestyle interventions involving weight reduction and the adoption of a healthy diet, accompanied when necessary by antiobesity drugs and other pharmacotherapies to decrease or delay the progression of MetS and its complications. Increased physical activity is the single most important lifestyle intervention that can substantially improve insulin sensitivity, glycemic control, and cardiovascular remodeling [157], and, in this effort, the role of health educators, physical therapists, and exercise specialists is critical to explain the goal, purpose, intensity, and frequency of the exercise program. Meanwhile, the main role of the physician is to screen for complications of MetS, such as diabetes mellitus, with associated retinopathy, neuropathy, or subclinical CAD, while also setting personalized guidelines for the prescription of exercise programs. A number of studies have reported that the lowering of IR through exercise or else with insulin sensitizers is a much better approach than the use of insulin secretagogues or insulin. In this connection, multiple classes of drugs are available that address different pathophysiological mechanisms of IR, such as insulin sensitizers acting on liver (metformin) or peripheral tissue insulin sensitizers (thiazolidinediones) [158]. Attempts can also be made to minimize lipotoxicity by decreasing the transport of fatty acids to non-adipose tissue with the use of peroxisome proliferator-activated receptor gamma agonists [159].

Clinical studies and experimental trials support the role of xanthine oxidase inhibitors for the control of a variety of disorders, such as NASH and atherosclerosis, by reducing uric acid levels and inflammation [160]. Several pharmacological trials have reported the therapeutic potential of

blocking paracrine or autocrine signaling via the NFκB pathway in adipocytes. Antihypertensive and lipid-lowering agents also reduce inflammation by decreasing the levels of IL-6, CRP, and TNF-α [161]. Bariatric surgery is also reported to be associated with decreased IL-6 serum levels and improved insulin sensitivity [162, 163]. However, lifestyle modification remains the cornerstone of any successful diabetes and cardiovascular prevention program [164].

Conclusions

MetS is characterized by IR, central obesity, and adipose dysfunction. It has been observed that different patients with the same duration and degree of dyslipidemias or hyperglycemia differ significantly in their susceptibility to the cardiovascular and microvascular complications of MetS. Such observations support the role of genetic factors controlling various pathways of IR and inflammation. IR is triggered by cellular disturbances, such as inflammation, lipotoxicity, mitochondrial dysfunction, and endoplasmic stress, which may lead to impaired insulin signal transduction, dysregulation of genes, and modifications of regulatory proteins. The current review suggests that additional studies are required to better understand the role of inflammation and lipotoxicity and treatment options for the increasing numbers of patients with MetS, both to improve their quality of life and to promote healthy aging. Finally, emphasis needs to be placed on the early diagnosis and treatment of the individual components of MetS.

Acknowledgements Our acknowledgments go to HEC for providing help with the literature survey through the digital library.

Author contribution UZ and SK contributed to the literature survey and manuscript write-up. HU helped in the literature survey. KPL conceived the idea and proofread the manuscript.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical statement This article does not contain studies with patients or animals performed by the authors.

Consent for publication All authors read and approved the manuscript for publication.

References

1. Weiss R, Bremer AA, Lustig RH (2013) What is metabolic syndrome, and why are children getting it? Ann N Y Acad Sci 1281: 123–140
2. Alberti KG, Zimmet P, Shaw J (2005) IDF epidemiology task force consensus group. The metabolic syndrome—a new worldwide definition. Lancet 366:1059–1062
3. Grundy SM (2008) Metabolic syndrome pandemic. Arterioscler Thromb Vasc Biol 28:629–663
4. Uzunlulu M, Telci Caklili O, Oguz A (2016) Association between metabolic syndrome and cancer. Ann Nutr Metab 68:173–179
5. Kylin E (1923) Studien ueber das Hypertonie-Hyperglyca "mie-Hyperurika" miesyndrom. Zentralblatt fuer Innere Medizin 44: 105–127
6. Vague J (1947) Sexual differentiation. A factor affecting the forms of obesity. Presse Med 30:S39–S40
7. Reaven GM (1988) Role of insulin resistance in human disease. Diabetes 37:1595–1607
8. Kaur J (2014) A comprehensive review on metabolic syndrome. Cardiol Res Pract 2014:943162
9. Aguilar M, Bhuket T, Torres S, Liu B, Wong RJ (2015) Prevalence of the metabolic syndrome in the United States, 2003–2012. JAMA 313:1973–1974
10. O'Neill S, O'Driscol L (2015) Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies. Obes Rev 16:1–12
11. Pucci G, Alcidi R, Tap L, Battista F, Mattace-Raso F, Schillaci Pucci G (2017) Sex and gender related prevalence, cardiovascular risk and therapeutic approach in metabolic syndrome: a review of the literature. Pharmacol Res 120:34–42
12. Kuk JL, Ardern CI (2010) Age and sex differences in the clustering of metabolic syndrome factors: association with mortality risk. Diabetes Care 33:2457–2461
13. Beltrán-Sánchez H, Harhay MO (2013) Prevalence and trends of metabolic syndrome in the adult US population, 1999–2010. J Am Coll Cardiol 62:697–703
14. Ali NS, Khuwaja AK, Adnan-ur-Rehman, Nauji K (2012) Retrospective analysis of metabolic syndrome: prevalence and distribution in executive population in urban Pakistan. Int J Family Med 2012:649383
15. Alberti KG, Zimmet P, Shaw J (2006) Metabolic syndrome-a new world-wide definition. A consensus statement from the International Diabetes Federation. Diabet Med 23:469–480
16. Basit A, Shera AS (2008) Prevalence of metabolic syndrome in Pakistan. Metab Syndr Relat Disord 6:15–17
17. Hydrie MZ, Shera AS, Fawwad A, Basit A, Hussain A (2009) Prevalence of metabolic syndrome in urban Pakistan (Karachi): comparison of newly proposed International Diabetes Federation and modified Adult Treatment Panel III criteria. Metab Syndr Relat Disord 7:119–124
18. Wen J, Yang J, Shi Y (2015) Comparisons of different metabolic syndrome definitions and associations with coronary heart disease, stroke, and peripheral arterial disease in a rural Chinese population. PLoS One 10:e0126832
19. Alberti KG, Eckel RH, Grundy SM et al (2009) Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on epidemiology and prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 120:1640–1645
20. Kassi E, Pervanidou P, Kaltsas G, Chrousos G (2011) Metabolic syndrome: definitions and controversies. BMC Med 9:48
21. Ahmed A, Khan T, Yasmeen T, Awan S, Islam N (2012) Metabolic syndrome in type 2 diabetes: comparison of WHO, modified ATPIII & IDF criteria. J Pak Med Assoc 62:569–574
22. Ford ES (2005) Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the U.S. Diabetes Care 28:2745–2749

23. Wisse BE (2004) The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. J Am Soc Nephrol 15:2792–2800
24. Buse JB, Polonsky KS, Burant CF (2003) Type 2 diabetes mellitus. In: Laren PR, Kronenberg HM, Melmed S, Polonsky KS (eds) Williams text book of endocrinology. Saunders, Philadelphia, pp 1427–1442
25. Boucher J, Kleinridders A, Kahn CR (2014) Insulin receptor signaling in normal and insulin-resistant states. Cold Spring Harb Perspect Biol 6:a009191. https://doi.org/10.1101/cshperspect.a009191
26. Fröjdö S, Vidal H, Pirola L (2009) Alterations of insulin signaling in type 2 diabetes: a review of the current evidence from humans. Biochim Biophys Acta 1792:83–92
27. Ijuin T, Takenawa T (2012) Regulation of insulin signaling by the phosphatidylinositol 3, 4, 5-triphosphate phosphatase SKIP through the scaffolding function of Pak1. J Mol Cell Biol 32: 3570–3584
28. Jason S, Cui W (2016) Proliferation, survival and metabolism: the role of PI3K/AKT/mTOR signaling in pluripotency and cell fate determination. Development 143:3050–3060
29. Draznin B (2010) Mitogenic action of insulin: friend foe or "frenemy"? Diabetologia 53:229–233
30. Schulman IH, Zhou MS (2009) Vascular insulin resistance: a potential link between cardiovascular and metabolic diseases. Curr Hypertens Rep 11:48–55
31. Zhou M-S, Wang A, Yu H (2014) Link between insulin resistance and hypertension: what is the evidence from evolutionary biology? Diabetol Metab Syndr 6:12
32. Brown MS, Goldstein JL (2008) Selective versus total insulin resistance: a pathogenic paradox. Cell Metab 7:95–96
33. Wilcox G (2005) Insulin and insulin resistance. Clin Biochem Rev 26:19
34. Shah A, Mehta N, Reilly MP (2008) Adipose inflammation, insulin resistance, and cardiovascular disease. J Parenter Enter Nutr 32:638–644
35. Montgomery MK, Turner N (2015) Mitochondrial dysfunction and insulin resistance: an update. Endocr Connect 4:R1–R15
36. Naimi M, Gautier N, Chaussade C, Valverde AM, Accili D, Van Obberghen E (2007) Nuclear forkhead box O1 controls and integrates key signaling pathways in hepatocytes. Endocrinology 148: 2424–2434
37. Ginsberg HN, Zhang YL, Hernandez-Ono A (2005) Regulation of plasma triglycerides in insulin resistance and diabetes. Arch Med Res 36:232–240
38. Gastaldelli A, Gaggini M, DeFronzo RA (2017) Role of adipose tissue insulin resistance in the natural history of type 2 diabetes: results from the San Antonio metabolism study. Diabetes 66:815–822
39. Consitt LA, Bell JA, Houmard JA (2009) Intramuscular lipid metabolism, insulin action, and obesity. IUBMB Life 61:47–55
40. Martins AR, Nachbar RT, Gorjao R (2012) Mechanisms underlying skeletal muscle insulin resistance induced by fatty acids: importance of the mitochondrial function. Lipids Health Dis 11:30
41. DeFronzo RA, Tripathy D (2009) Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. Diabetes Care 32: S157–S163
42. Petersen KF, Dufour S, Savage DB et al (2007) The role of skeletal muscle insulin resistance in the pathogenesis of the metabolic syndrome. Proc Natl Acad Sci U S A 104:12587–12594
43. Kumar A, Tewari P, Sahoo SS, Srivastava AK (2005) Prevalence of insulin resistance in first degree relatives of type-2 diabetes mellitus patients: a prospective study in North Indian population. Indian J Clin Biochem 20:10–17
44. Buchanan TA (2007) Perspectives in diabetes. How can we prevent type 2 diabetes? Diabetes 56:1502–1507
45. Cornier M-A, Dabelea D, Hernandez TL (2008) The metabolic syndrome. Endocr Rev 29:777–822
46. Gustafson B, Hammarstedt A, Andersson CX, Smith U (2007) Inflamed adipose tissue: a culprit underlying the metabolic syndrome and atherosclerosis. Arterioscler Thromb Vasc Biol 27: 2276–2283
47. Heilbronn LK, Campbell LV (2008) Adipose tissue macrophages, low grade inflammation and insulin resistance in human obesity. Curr Pharm Des 14:1225–1230
48. Castouldi A, de Souza CN, Camara NOS, Moraes-Vieira VM (2015) The macrophage switch in obesity development. Front Immunol 6:637
49. Usman S, Jafri SA (2014) Insulin resistance study in diabetes mellitus type II and its correlation with obesity. Am J Life Sci 2: 96–102
50. Abu-Farha M, Behbehani MK, Elkum N (2014) Comprehensive analysis of circulating adipokines and hsCRP association with cardiovascular disease risk factors and metabolic syndrome in Arabs. Cardiovasc Diabetol 13:76
51. Gnacinska M, Małgorzewicz S, Stojek M, Lysiak-Szydłowska W, Sworczak K (2009) Role of adipokines in complications related to obesity: a review. Adv Med Sci 54:150–157
52. Yamauchi T, Nio Y, Maki T, Kobayashi M, Takazawa T, Iwabu M (2007) Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. Nat Med 13:332–339
53. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K (2006) Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest 116: 1784–1792
54. Yoon MJ, Lee GY, Chung JJ, Ahn YH, Hong SH, Kim JB (2006) Adiponectin increases fatty acid oxidation in skeletal muscle cells by sequential activation of AMP-activated protein kinase, p38 mitogen-activated protein kinase, and peroxisome proliferator activated receptor alpha. Diabetes 55:2562–2570
55. Chandran M, Phillips SA, Ciaraldi T, Henry RR (2003) Adiponectin: more than just another fat cell hormone? Diabetes Care 26:2442–2450
56. Okamoto Y, Arita Y, Nishida M et al (2000) An adipocyte-derived plasma protein, adiponectin, adheres to injured vascular walls. Horm Metab Res 32:47–50
57. Valsamakis G, Chetty R, McTernan PG, Al-Daghri NM, Barnett AH, Kumar S (2003) Fasting serum adiponectin concentration is reduced in Indo-Asian subjects and is related to HDL cholesterol. Diabetes Obes Metab 5:131–135
58. Fisman EZ, Tenenbaum A (2014) Adiponectin: a manifold therapeutic target for metabolic syndrome, diabetes, and coronary disease? Cardiovasc Diabetol 13:103
59. Swarbrick MM, Havel PJ (2008) Physiological, pharmacological, and nutritional regulation of circulating adiponectin concentrations in humans. Metab Syndr Relat Disord 6:87–102
60. Matsuzawa Y, Funahashi T, Kihara S, Shimomura I (2004) Adiponectin and metabolic syndrome. Arterioscler Thromb Vasc Biol 24:29–33
61. Kim JY, Ahn SV, Yoon JH et al (2013) Prospective study of serum adiponectin and incident metabolic syndrome. Diabetes Care 36: 1547–1553
62. Mohammadi M, Gozashti MH, Aghadavood M, Mehdizadeh MR, Hayatbakhsh MM (2017) Clinical significance of serum IL-6 and TNF-α levels in patients with metabolic syndrome. Rep Biochem Mol Biol 6:74–79
63. Sedger LM, McDermott MF (2014) TNF and TNF-receptors: from mediators of cell death and inflammation to therapeutic giants—past, present and future. Cytokine Growth Factor Rev 25: 453–472

64. Dalziel B, Gosby AK, Richman RM, Bryson JM, Caterson ID (2002) Association of the TNF -308 G/A promoter polymorphism with insulin resistance in obesity. Obes Res 10:401–407
65. Navarro-González JF, Mora-Fernández C (2008) The role of inflammatory cytokines in diabetic nephropathy. J Am Soc Nephrol 19:433–442
66. Vikram NK, Bhatt SP, Bhushan B (2011) Associations of -308G/A polymorphism of tumor necrosis factor (TNF)-α gene and serum TNF-α levels with measures of obesity, intra-abdominal and subcutaneous abdominal fat, subclinical inflammation and insulin resistance in Asian Indians in North India. Dis Markers 31:39–46
67. Picchi A, Gao X, Belmadani S, Potter BJ, Focardi M, Chilian WM (2006) Tumor necrosis factor alpha induces endothelial dysfunction in the prediabetic metabolic syndrome. Circ Res 99:69–77
68. Kim JH, Bachmann RA, Chen J (2009) Interleukin-6 and insulin resistance. Vitam Horm 80:613–633
69. Bastard J-P, Maachi M, Lagathu C et al (2006) Recent advances in the relationship between obesity, inflammation, and insulin resistance. Eur Cytokine Netw 17:4–12
70. Senn JJ, Klover PJ, Nowak IA, Mooney RA (2005) Interleukin-6 induces cellular insulin resistance in hepatocytes. Diabetes 51: 3391–3399
71. Antuna-Puente B, Feve B, Fellahi S, Bastard J-P (2008) Adipokines: the missing link between insulin resistance and obesity. Diabete Metab 34:2–11
72. Kern PA, Ranganathan S, Li C, Wood L, Ranganathan G (2001) Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. Am J Physiol Endocrinol Metab 280:E745–E751
73. Garg PK, Biggs ML, Carnethon M et al (2014) Metabolic syndrome and risk of incident peripheral artery disease: the cardiovascular health study. Hypertension 63:413–419
74. Mottillo S, Filion KB, Genest J et al (2010) The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. J Am Coll Cardiol 56:1113–1132
75. Kahn RBJ, Ferrannini E, Stern M et al (2005) American Diabetes Association; European Association for the study of diabetes. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European association for the study of diabetes. Diabetes Care 28:2289–2304
76. Jurimae J, Gruodyte R, Saar M et al (2011) Plasma visfatin and adiponectin concentrations in physically active adolescent girls: relationships with insulin sensitivity and body composition variables. J Pediatr Endocrinol Metab 24:419–425
77. Rhie YJ, Choi BM, Eun SH et al (2011) Association of serum retinol binding protein 4 with adiposity and pubertal development in Korean children and adolescents. J Korean Med Sci 26:797–802
78. Janssen I, Katzmarzyk PT, Srinivasan SR et al (2005) Combined influence of body mass index and waist circumference on coronary artery disease risk factors among children and adolescents. Pediatrics 115:1623–1630
79. Urbina EM, Khoury PR, McCoy CE et al (2013) Triglyceride to HDL-c ratio and increased arterial stiffness in children, adolescents, and young adults. Pediatrics 131:e1082–e1090
80. Burns SF, Lee SJ, Arslanian SA (2012) Surrogate lipid markers for small dense low-density lipoprotein particles in overweight youth. J Pediatr 161:991–996
81. Sassoon DJ, Goodwill AG, Noblet JN et al (2016) Obesity alters molecular and functional cardiac responses to ischemia/reperfusion and glucagon-like peptide-1 receptor agonism. Basic Res Cardiol 111:43
82. Dincer UD (2012) Cardiac ryanodine receptor in metabolic syndrome: is JTV519 (K201) future therapy? Diabetes Metab Syndr Obes 5:89–99
83. Okatan EN, Durak AT, Turan B (2016) Electrophysiological basis of metabolic-syndrome-induced cardiac dysfunction. Can J Physiol Pharmacol 94:1064–1073
84. Santulli G, Pagano G, Sardu C et al (2015) Calcium release channel RyR2 regulates insulin release and glucose homeostasis. J Clin Invest 125:1968–1978
85. Lavorato M, Huang TQ, Iyer VR et al (2015) Dyad content is reduced in cardiac myocytes of mice with impaired calmodulin regulation of RyR2. J Muscle Res Cell Motil 36:205–214
86. Engin AB (2017) What is lipotoxicity? Adv Exp Med Biol 960: 197–220
87. Kahn SE, Prigeon RL, Schwartz RS et al (2001) Obesity, body fat distribution, insulin sensitivity and islet beta-cell function as explanations for metabolic diversity. J Nutr 131:354S–360S
88. Berg AH, Scherer PE (2005) Adipose tissue inflammation and cardiovascular disease. Circ Res 90:939–949
89. Lelliot C, Vidal Puig AJ (2004) Lipotoxicity, an imbalance between lipogenesis de novo and fatty acid oxidation. Int J Obes Relat Metab Disord 28:S22–S28
90. Schaffer JE (2016) Lipotoxicity: many roads to cell dysfunction and cell death: introduction to a thematic review series. J Lipid Res 57:1327–1328
91. Estadella D, da Penha Oller do Nascimento CM, Oyama LM, Ribeiro EB, Damaso AR, de Piano A (2013) Lipotoxicity: effects of dietary saturated and trans fatty acids. Mediat Inflamm 2013:13. https://doi.org/10.1155/2013/13757
92. Jaeschke H (2011) Reactive oxygen and mechanisms of inflammatory liver injury: present concepts. J Gastroenterol Hepatol 26: 173–179
93. Lyngdoh T, Marques-Vidal P, Paccaud F (2011) Elevated serum uric acid is associated with high circulating inflammatory cytokines in the population-based colaus study. PLoS One 2011:6
94. Kowdley KV, Belt P, Wilson LA, Yeh MM, Neuschwander-Tetri BA (2012) Serum ferritin is an independent predictor of histologic severity and advanced fibrosis in patients with nonalcoholic fatty liver disease. Hepatology 55:77–85
95. Kohgo Y, Ikuta K, Ohtake T, Torimoto Y, Kato J (2007) Iron overload and cofactors with special reference to alcohol, hepatitis C virus infection and steatosis/insulin resistance. World J Gastroenterol 13:4699–4706
96. Zafar U, Qureshi HJ, Imran M (2015) Comparison of iron status and insulin resistance between non-diabetic offspring of type 2 diabetics and non-diabetic offspring of non-diabetics. J Ayub Med Coll 27:307–311
97. Zafar U, Qureshi HJ, Karim S (2011) Insulin resistance and serum parameters of iron status in type 2 diabetics. Pak J Physiol 7:28–31
98. Fernandez-Real JM, Bermejo AL, Ricart W (2002) Cross-talk between iron metabolism and diabetes. Diabetes 51:2348–2354
99. Rishi G, Wallace DF, Subramaniam VN (2015) 2015 Hepcidin: regulation of the master iron regulator. Biosci Rep 35:e00192
100. Ganz T (2011) Hepcidin and iron regulation, 10 years later. Blood 117:4425–4433
101. Ueki K, Kondo T, Tseng YH, Kahn CR (2004) Central role of suppressors of cytokine signaling proteins in hepatic steatosis, insulin resistance, and the metabolic syndrome in the mouse. Proc Natl Acad Sci U S A 101:10422–10427
102. Martinelli N, Traglia M, Campostrini N, Biino G, Corbella M (2013) Increased serum hepcidin levels in subjects with the metabolic syndrome: a population study. PLoS One 8:10.1371
103. Billiet L, Doaty S, Katz JD, Velasquez MT (2014) Review of hyperuricemia as new marker for metabolic syndrome. JSRN Rheumatol 2014:852954
104. Liu M, He Y, Jiang B (2014) Association between serum uric acid level and metabolic syndrome and its sex difference in a Chinese community elderly population. Int J Endocrinol 2014:754678

105. Sun HL, Pei D, Lue KH, Chen YL (2015) Uric acid levels can predict metabolic syndrome and hypertension in adolescents: a 10-year longitudinal study. PLoS One. https://doi.org/10.1371/journal.pone.0143786
106. Lin S-D, Tsai D-H, Hsu S-R (2006) Association between serum uric acid level and components of the metabolic syndrome. Chin Med J 69:512–516
107. Kanbay M, Jensen T, Solak Y et al (2016) Uric acid in metabolic syndrome: from an innocent bystander to a central player. Eur J Intern Med 29:3–8
108. Khosla UM, Zharikov S, Finch JL (2005) Hyperuricemia induces endothelial dysfunction. Kidney Int 67:1739–1742
109. Soltani Z, Rasheed K, Kapusta DR, Reisin E (2013) Potential role of uric acid in metabolic syndrome, hypertension, kidney injury, and cardiovascular diseases: is it time for reappraisal? Curr Hypertens Rep 15:175–181
110. Emanuela F, Grazia M, de Marco R, Maria Paola L, Giorgio F, Marco B (2012) Inflammation as a link between obesity and metabolic syndrome. J Nutr Metab 2012:476380
111. Stancakova A, Laakso M (2014) Genetics of metabolic syndrome. Rev Endocr Metab Disord 15:243–252
112. Roomi MA, Lone KP, Madassar A (2014) Vitamin D and cardiometabolic risk factors in adult non-diabetic offspring of type 2 diabetic parents. J Pak Med Assoc 64:1229
113. Shahid A, Lone KP, Saeed S, Arslan M (2008) Male offspring of both diabetic parents have higher insulin resistance and serum leptin levels compared to those with one diabetic parent. Hormones 7:313–319
114. Brunetti A (2014) Recent advances in the molecular genetics of type 2 diabetes mellitus. World J Diabetes 5:128–140
115. van Tilburg J, Van Haeften TW, Pearson P, Wijmenga C (2001) Defining the genetic contribution of type 2 diabetes mellitus. J Med Genet 38:569–578
116. Kottyan LC, Woo JG, Keddache M et al (2012) Novel variations in the adiponectin gene (ADIPOQ) may affect distribution of oligomeric complexes. SpringerPlus 1:66
117. Vaxillaire M, Veslot J, Dina C (2008) Impact of common type 2 diabetes risk polymorphisms in the DESIR prospective study. Diabetes 57:244–254
118. Y-y L, Yang Z-j, C-w Z, Wang X-m, Qian Y (2013) Adiponectin-11377CG gene polymorphism and type 2 diabetes mellitus in the Chinese population: a meta-analysis of 6425 subjects. PLoS One 8:e61153
119. Gupta V, Khadgawat R, Tony Ng HK et al (2012) Association of TCF7L2 and ADIPOQ with body mass index, waist-hip ratio, and systolic blood pressure in an endogamous ethnic group of India. Genet Test Mol Biomarkers 16:948–951
120. Chu H, Wang M, Zhong D, Shi D, Ma L, Tong N (2013) AdipoQ polymorphisms are associated with type 2 diabetes mellitus: a meta-analysis study. Diabetes Metab Res Rev 29:532–545
121. Lu JF, Zhou Y, Huang GH, Jiang HX, Hu BL, Qin SY (2014) Association of ADIPOQ polymorphisms with obesity risk: a meta-analysis. Hum Immunol 75:1062–1068
122. Hulkkonen J, Pertovaara M, Antonen J, Pasternack A, Hurme M (2001) Elevated interleukin-6 plasma levels are regulated by the promoter region polymorphism of the IL6 gene in primary Sjogren's syndrome and correlate with the clinical manifestations of the disease. Rheumatology 40:656–661
123. Cardellini M, Perego L, D'Adamo M et al (2005) C-174G polymorphism in the promoter of the interleukin-6 gene is associated with insulin resistance. Diabetes Care 28:2007–2012
124. Satti HS, Hussain S, Javed Q (2013) Association of Interleukin-6 gene promoter polymorphism with coronary artery disease in Pakistani families. Sci World J 2013:538365
125. Nadeem A, Mumtaz S, Naveed AK et al (2017) Association of IL-6 C-174G (rs 1800795) single nucleotide polymorphism with type 2 diabetes mellitus in Pakistani population. J Pak Med Assoc 67(428):433
126. Pawlik A, Domanski L, Rozanski J et al (2005) IL-2 and TNF-alpha promoter polymorphisms in patients with acute kidney graft rejection. Transpl Immunol 37:49–52
127. Aoki T, Hirota T, Tamari M, Ichikawa K, Takeda K, Arinami T (2006) An association between asthma and TNF-308G/A polymorphism: meta-analysis. J Hum Genet 51:677–685
128. Zhang LG, Lu H, Lu Y et al (2016) Association between the tumor necrosis factor-α-308G/A polymorphism and COPD susceptibility: a meta-analysis update. Int J Chron Obstruct Pulmon Dis 11:1367–1379
129. Nascimento H, Vieira E, Coimbra S et al (2016) Adipokine gene single-nucleotide polymorphisms in Portuguese obese adolescents: associations with plasma concentrations of adiponectin, resistin, IL-6, IL-1β, and TNF-α. Child Obes 12:300–313
130. Settin A, Abdel-Hady H, El-Baz R et al (2007) Gene polymorphisms of TNF-alpha (-308), IL-10(-1082), IL-6(-174), and IL-1Ra(VNTR) related to susceptibility and severity of rheumatic heart disease. Pediatr Cardiol 28:363–371
131. Babu BM, Reddy BP, Priya VH et al (2012) Cytokine gene polymorphisms in the susceptibility to acute coronary syndrome. Genet Test Mol Biomarkers 16:359–365
132. Takiyama Y, Haneda M (2014) Hypoxia in diabetic kidneys. Biomed Res Int 2014:837421
133. Locatelli F, Fishbane S, Block GA, Macdougall IC (2017) Targeting hypoxia-inducible factors for the treatment of anemia in chronic kidney disease patients. Am J Nephrol 45:187–199
134. Semenza GL (2014) Hypoxia-inducible factor 1 and cardiovascular disease. Annu Rev Physiol 76:39–56
135. Yamada N, Horikawa Y, Oda N et al (2005) Genetic variation in the hypoxia-inducible factor-1alpha gene is associated with type 2 diabetes in Japanese. J Clin Endocrinol Metab 90:5841–5847
136. Nagy G, Kovacs-Nagy R, Kereszturi E, Somogyi A, Szekely A, Nemeth N (2009) Association of hypoxia inducible factor-1 alpha gene polymorphism with both type 1 and type 2 diabetes in a Caucasian (Hungarian) sample. BMC Med Genet 10:79
137. Gu HF, Zheng X, Abu Seman N et al (2013) Impact of the hypoxia-inducible factor-1 α (HIF1A) Pro582Ser polymorphism on diabetes nephropathy. Diabetes Care 36:415–421
138. Rankinen T, Sarzynski MA, Ghosh S, Bouchard C (2015) Are there genetic paths common to obesity, cardiovascular disease outcomes, and cardiovascular risk factors? Circ Res 116:909–922
139. Silander K, Scott LJ, Valle TT, Mohlke KL, Stringham HM, Wiles KR (2004) A large set of Finnish affected sibling pair families with type 2 diabetes suggests susceptibility loci on chromosomes 6, 11, and 14. Diabetes 53:821–829
140. Jia Y, Hoang MH, Jun HJ, Lee JH, Lee SJ (2013) Cyanidin, a natural flavonoid, is an agonistic ligand for liver X receptor alpha and beta and reduces cellular lipid accumulation in macrophages and hepatocytes. Bioorg Med Chem Lett 23:4185–4190
141. Watanabe K, Sakurai K, Tsuchiya Y, Yamazoe Y, Yoshinari K (2013) Dual roles of nuclear receptor liver X receptor α (LXRα) in the CYP3A4 expression in human hepatocytes as a positive and negative regulator. Biochem Pharmacol 86:428–436
142. Chen Y, Zhang S, Zhou T, Huang C, McLaughlin A, Chen G (2013) Liver X receptor alpha mediated genistein induction of human dehydroepiandrosterone sulfotransferase (hSULT2A1) in Hep G2 cells. Toxicol Appl Pharmacol 268:106–112
143. Zhao JF, Shyue SK, Lin SJ, Wei J, Lee TS (2014) Excess nitric oxide impairs LXR(α)- ABCA1-dependent cholesterol efflux in macrophage foam cells. J Cell Physiol 229:117–125
144. Wang HX, Zhang K, Zhao L, Tang JW, Gao LY, Wei ZP (2015) Association of liver X receptor α (LXRα) gene polymorphism and ischemic stroke. Genet Mol Res 14:118–122

145. Nohara A, Kawashiri MA, Claudel T, Mizuno M, Tsuchida M, Takata M (2007) High frequency of a retinoid X receptor gamma gene variant in familial combined hyperlipidemia that associates with atherogenic dyslipidemia. Arterioscler Thromb Vasc Biol 27: 923–928
146. Pennacchio LA, Rubin EA (2003) Apolipoprotein A5, a newly identified gene that affects plasma triglyceride levels in human and mice. Arterioscler Thromb Vasc Biol 23:529–534
147. Hubacek JA, Adamkova V, Vrablik M, Kadlecona M, Zicha J, Kunes J (2009) Apolipoprotein A5 in health and diseases. Physiol Res 58:S101–S109
148. O'Brien PJ, Alborn WE, Sloan JH et al (2005) The novel apolipoprotein A5 is present in human serum, is associated with VLDL, HDL, and chylomicrons, and circulates at very low concentrations compared with other apolipoproteins. Clin Chem 51:351–359
149. Weinberg RB, Cook VR, Beckstead JA et al (2003) Structure and interfacial properties of human apolipoprotein A-V. J Biol Chem 278:34438–34444
150. Zhao T, Zhao J (2010) Association of the apolipoprotein A5 gene–1131 T>C polymorphism with fasting plasma lipids: a meta-analysis in 37859 subjects. BMC Med Genet 11:120
151. Song KW, Cha S, Yu S, Yu H, Oh SA, Kang NS (2013) Association of apolipoprotein A5 gene −1131T>C polymorphism with the risk of metabolic syndrome in Korean subjects. Bio Med Res Int 2013:585134 7 pages
152. Grallert H, Sedlmeier EM, Huth C et al (2007) APOA5 variants and metabolic syndrome in Caucasians. J Lipid Res 48:2614–2621
153. Ursino MG, Vasina V, Raschi E, Crema F, De Ponti F (2009) The B3-adrenoceptor as a therapeutic target: current perspectives. Pharmacol Res 59:221–234
154. Saliba LF, Reis RS, Brownson RC et al (2014) Obesity-related gene ADRB2, ADRB3 and GHRL polymorphisms and the response to a weight loss diet intervention in adult women. Genet Mol Biol 37:15–22
155. Mirrakhimov AE, Kerimkulova AS, Lunegova OS, Moldokeeva CB, Zalesskaya YV, Abilova SS (2011) An association between TRP64ARG polymorphism of the B3 adrenoreceptor gene and some metabolic disturbances. Cardiovasc Diabetol 10:89
156. Yang H, Cai D, Zhu Q, Wu D, Wang Q, Wang Z (2017) The mutation of Trp64Arg in β3-adrenoreceptor-encoding gene is significantly associated with increased hypertension risk and elevated blood pressure: a meta-analysis. Oncotarget 8:46480–46490
157. Li J, Siegrist J (2012) Physical activity and risk of cardiovascular disease—a meta-analysis of prospective cohort studies. Int J Environ Res Public Health 9:391–407
158. Chaudhury A, Duvoor C, Reddy Dendi VS et al (2017) Clinical review of antidiabetic drugs: implications for type 2 diabetes mellitus management. Front Endocrinol (Lausanne) 8:6. https://doi.org/10.3389/fendo.2017.00006
159. Nyenwe EA, Jerkins TW, Umpierrez GE et al (2011) Management of type 2 diabetes: evolving strategies for the treatment of patients with type 2 diabetes. Metab Clin Exp 60:1–23
160. Dawson J, Walters M (2006) Uric acid and xanthine oxidase: future therapeutic targets in the prevention of cardiovascular disease? Br J Clin Pharmacol 62:633–644
161. Reilly SM, Chiang SH, Decker SJ (2013) An inhibitor of the protein kinases TBK1 and IKK-ε improves obesity-related metabolic dysfunctions in mice. Nat Med 19:313–321
162. Bruce M, Wolfe, Kvach E et al (2016) Treatment of obesity: weight loss and bariatric surgery. Circ Res 118:1844–1855
163. Evers SS, Sandoval DA, Seeley RJ (2016) The physiology and molecular underpinnings of the effects of bariatric surgery on obesity and diabetes. Annu Rev Physiol 79:313–334
164. Kolovou G, Anagnostopoulou K, Cokkinos D (2005) Pathophysiology of dyslipidaemia in the metabolic syndrome. Postgrad Med J 81:358–366