

Retraction

Retracted: A Comprehensive Review on Metabolic Syndrome

Cardiology Research and Practice

Received 14 November 2018; Accepted 14 November 2018; Published 6 March 2019

Copyright © 2019 Cardiology Research and Practice. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Cardiology Research and Practice has retracted the article titled “A Comprehensive Review on Metabolic Syndrome” [1]. The article was found to contain a substantial amount of material from previously published articles (85% of the text), mostly without citation, including the following sources:

- (i) M.-A. Cornier, Dabelea D., Hernandez T. L. et al., “The metabolic syndrome,” *Endocrine Reviews*, vol. 29, no. 7, pp. 777–822, 2008, <https://doi.org/10.1210/er.2008-0024> (not cited) [2], mainly in section 5, Pathophysiology, and section 6, Treatment.
- (ii) C. Peters, “Metabolic syndrome-a literature review,” Master of Nursing Thesis, University of Arizona, 2007. <http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.503.728&rep=rep1&type=pdf> (not cited) [3], mainly in section 5, Pathophysiology, and section 6, Treatment.
- (iii) S. M. Grundy, Cleeman J. I., Daniels S. R. et al., “Diagnosis and management of the metabolic syndrome: an american heart association/national heart, lung, and blood institute scientific statement,” *Circulation*, vol. 112, pp. 2735–2752, 2005, <https://doi.org/10.1161/circulationaha.105.169404>, <http://circ.ahajournals.org/content/112/17/2735.full> (cited as reference 20) [4], mainly in section 5, Pathophysiology, and section 6, Treatment.
- (iv) P. C. Deedwania, R. Gupta, “Management issues in the metabolic syndrome,” *Journal of the Association of Physicians of India*, vol. 54, 2006, <http://www.japi.org/october2006/R-797.pdf> (not cited) [5], mainly in section 6, Treatment.
- (v) P. L. Huang, “A comprehensive definition for metabolic syndrome,” *Disease Models & Mechanisms*, vol. 2, no. 5-6, pp. 231–237, 2009, doi: <https://doi.org/10.1242/dmm.001180>, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2675814/> (not cited) [6], mainly in section 5, Pathophysiology.

nih.gov/pmc/articles/PMC2675814/ (not cited) [6], mainly in section 5, Pathophysiology.

This was raised to our attention by the publisher of Cornier et al. Hindawi regrets that this was not identified before publication. The authors said that their aim was to write a comprehensive review extracted from previously published studies on metabolic syndrome and their components, and they apologize for unintentionally not citing most of the sources, but disagree with retraction.

References

- [1] J. Kaur, “A comprehensive review on metabolic syndrome,” *Cardiology Research and Practice*, vol. 2014, Article ID 943162, 21 pages, 2014.
- [2] M.-A. Cornier, D. Dabelea, T. L. Hernandez et al., “The metabolic syndrome,” *Endocrine Reviews*, vol. 29, no. 7, pp. 777–822, 2008.
- [3] C. Peters, “Metabolic syndrome-a literature review,” Master of Nursing Thesis, University of Arizona, Tucson, AZ, USA, 2007, <http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.503.728&rep=rep1&type=pdf>.
- [4] S. M. Grundy, J. I. Cleeman, S. R. Daniels et al., “Diagnosis and management of the metabolic syndrome,” *Circulation*, vol. 112, no. 17, pp. 2735–2752, 2005, <http://circ.ahajournals.org/content/112/17/2735.full>.
- [5] P. C. Deedwania and R. Gupta, “Management issues in the metabolic syndrome,” *Journal of the Association of Physicians of India*, vol. 54, pp. 797–810, 2006, <http://www.japi.org/october2006/R-797.pdf>.
- [6] P. L. Huang, “A comprehensive definition for metabolic syndrome,” *Disease Models & Mechanisms*, vol. 2, no. 5-6, pp. 231–237, 2009, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2675814/>.

Review Article

A Comprehensive Review on Metabolic Syndrome

Jaspinder Kaur

Ex-Servicemen Contributory Health Scheme (ECHS) Polyclinic, Sultanpur Lodhi, Kapurthala District 144626, India

Correspondence should be addressed to Jaspinder Kaur; mailtojaspinder@yahoo.in

Received 20 November 2013; Accepted 19 January 2014; Published 11 March 2014

Academic Editor: Paul Holvoet

Copyright © 2014 Jaspinder Kaur. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Metabolic syndrome is defined by a constellation of interconnected physiological, biochemical, clinical, and metabolic factors that directly increases the risk of cardiovascular disease, type 2 diabetes mellitus, and all cause mortality. Insulin resistance, visceral adiposity, atherogenic dyslipidemia, endothelial dysfunction, genetic susceptibility, elevated blood pressure, hypercoagulable state, and chronic stress are the several factors which constitute the syndrome. Chronic inflammation is known to be associated with visceral obesity and insulin resistance which is characterized by production of abnormal adipocytokines such as tumor necrosis factor α , interleukin-1 (IL-1), IL-6, leptin, and adiponectin. The interaction between components of the clinical phenotype of the syndrome with its biological phenotype (insulin resistance, dyslipidemia, etc.) contributes to the development of a proinflammatory state and further a chronic, subclinical vascular inflammation which modulates and results in atherosclerotic processes. Lifestyle modification remains the initial intervention of choice for such population. Modern lifestyle modification therapy combines specific recommendations on diet and exercise with behavioural strategies. Pharmacological treatment should be considered for those whose risk factors are not adequately reduced with lifestyle changes. This review provides summary of literature related to the syndrome's definition, epidemiology, underlying pathogenesis, and treatment approaches of each of the risk factors comprising metabolic syndrome.

1. Introduction

The metabolic syndrome (MetS) is a major and escalating public-health and clinical challenge worldwide in the wake of urbanization, surplus energy intake, increasing obesity, and sedentary life habits. MetS confers a 5-fold increase in the risk of type 2 diabetes mellitus (T2DM) and 2-fold the risk of developing cardiovascular disease (CVD) over the next 5 to 10 years [1]. Further, patients with the MetS are at 2- to 4-fold increased risk of stroke, a 3- to 4-fold increased risk of myocardial infarction (MI), and 2-fold the risk of dying from such an event compared with those without the syndrome [2] regardless of a previous history of cardiovascular events [3]. A version of MetS has a WHO International Classification of Disease (ICD-9) code (277.7) which permits healthcare reimbursement. This shows that the term "metabolic syndrome" is institutionalized and a part of the medical vocabulary. MetS is considered as a first order risk factor for atherothrombotic complications. Its presence or absence should therefore be considered an indicator of long-term risk. On the other hand, the short-term (5–10

years) risk is better calculated using the classical algorithms (Framingham, REGICOR {Registre Gironí del COR}), as they include age, sex, total cholesterol or LDL, and smoking [4].

2. Background

MetS started as a concept rather than a diagnosis [11]. The metabolic syndrome has its origins in 1920 when Kylin, a Swedish physician, demonstrated the association of high blood pressure (hypertension), high blood glucose (hyperglycemia), and gout [12]. Later in 1947, Vague described that the visceral obesity was commonly associated with the metabolic abnormalities found in CVD and T2DM [13]. Following this, in 1965, an abstract was presented at the European Association for the Study of Diabetes annual meeting by Avogaro and Crepaldi [14] which again described a syndrome which comprised hypertension, hyperglycemia, and obesity. The field moved forward significantly following the 1988 Banting Lecture given by Reaven [15]. He described "a cluster of risk factors for diabetes and cardiovascular

TABLE 1: Diagnostic criteria proposed for the clinical diagnosis of the MetS.

Clinical measures	WHO (1998) [5]	EGIR (1999) [6]	ATPIII (2001) [7]	AACE (2003) [8]	IDF (2005) [9]
Insulin resistance	IGT, IFG, T2DM, or lowered insulin Sensitivity ^a plus any 2 of the following	Plasma insulin >75th percentile plus any 2 of the following	None, but any 3 of the following 5 features	IGT or IFG plus any of the following based on the clinical judgment	None
Body weight	Men: waist-to-hip ratio >0.90; women: waist-to-hip ratio >0.85 and/or BMI > 30 kg/m ²	WC ≥94 cm in men or ≥80 cm in women	WC ≥102 cm in men or ≥88 cm in women	BMI ≥ 25 kg/m ²	Increased WC (population specific) plus any 2 of the following
Lipids	TGs ≥150 mg/dL and/or HDL-C <35 mg/dL in men or <39 mg/dL in women	TGs ≥150 mg/dL and/or HDL-C <39 mg/dL in men or women	TGs ≥150 mg/dL HDL-C <40 mg/dL in men or <50 mg/dL in women	TGs ≥150 mg/dL and HDL-C <40 mg/dL in men or <50 mg/dL in women	TGs ≥150 mg/dL or on TGs Rx. HDL-C <40 mg/dL in men or <50 mg/dL in women or on HDL-C Rx
Blood pressure	≥140/90 mm Hg	≥140/90 mm Hg or on hypertension Rx	≥130/85 mm Hg	≥130/85 mm Hg	≥130 mm Hg systolic or ≥85 mm Hg diastolic or on hypertension Rx
Glucose	IGT, IFG, or T2DM	IGT or IFG (but not diabetes)	>110 mg/dL (includes diabetes)	IGT or IFG (but not diabetes)	≥100 mg/dL (includes diabetes) ^b
Other	Microalbuminuria: Urinary excretion rate of >20 mg/min or albumin: creatinine ratio of >30 mg/g.			Other features of insulin resistance ^c	

^aInsulin sensitivity measured under hyperinsulinemic euglycemic conditions, glucose uptake below lowest quartile for background population under investigation.

^bIn 2003, the American Diabetes Association (ADA) changed the criteria for IFG tolerance from >110 mg/dl to >100 mg/dl [10].

^cIncludes family history of type 2 diabetes mellitus, polycystic ovary syndrome, sedentary lifestyle, advancing age, and ethnic groups susceptible to type 2 diabetes mellitus.

BMI: body mass index; HDL-C: high density lipoprotein cholesterol; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; Rx: receiving treatment; TGs: triglycerides; T2DM: type 2 diabetes mellitus; WC: waist circumference.

disease” and named it “Syndrome X”. His main contribution was an introduction of the concept of the insulin resistance. However, he surprisingly missed obesity or visceral obesity from the definition which was later added as a crucial abnormality. In 1989, Kaplan [16] renamed the syndrome “The Deadly Quartet” for the combination of upper body obesity, glucose intolerance, hypertriglyceridemia, and hypertension and however, in 1992, it was again renamed “The Insulin Resistance Syndrome” [17]. Several groups have attempted to develop diagnostic criteria for the diagnosis of the MetS [18]. The first attempt was made by a World Health Organization (WHO) diabetes group in 1998 to provide a definition of the MetS [5]. In response, the European Group for the study of Insulin Resistance (EGIR) countered with a modification of the WHO definition in 1999 [6]. In 2001, the National Cholesterol Education Program Adult Treatment Panel (NCEP/ATP) released its definition [7]. Subsequently, the American Association of Clinical Endocrinologists (AACE) in 2003 offered its views regarding the definition of the syndrome [8]. The proliferation of definitions suggested that a single unifying definition was desirable [19]. In the hope of accomplishing this, the International Diabetes Federation

(IDF) proposed a new definition of the MetS in April 2005 [9].

3. Definition

MetS is defined by a constellation of an interconnected physiological, biochemical, clinical, and metabolic factors that directly increases the risk of atherosclerotic cardiovascular disease (ASCVD), T2DM, and all cause mortality [20, 21]. This collection of unhealthy body measurements and abnormal laboratory test results include atherogenic dyslipidemia, hypertension, glucose intolerance, proinflammatory state, and a prothrombotic state. There have been several definitions of MetS, but the most commonly used criteria for definition at present are from the World Health Organization (WHO) [5], the European Group for the study of Insulin Resistance (EGIR) [6], the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) [7], American Association of Clinical Endocrinologists (AACE) [8], and the International Diabetes Federation (IDF) [9] (Table 1).

TABLE 2: Gender and age-specific waist circumference cut-offs [1].

Country/ethnic group	Waist circumference cut-off	
	Male (cm)	Female (cm)
Europeans In USA, the ATP III values (102 cm males; 88 cm females) are likely to continue to be used for clinical purposes.	≥94	≥80
South Asians Based on a Chinese, Malay, and Asian-Indian population.	≥90	≥80
Chinese	≥90	≥80
Japanese	≥90	≥80
Ethnic South and Central Americans	Use South Asians recommendations until more specific data are available.	
Sub-Saharan Africans	Use European data until more specific data are available.	
Eastern Mediterranean and Middle East (Arabs) population	Use European data until more specific data are available.	

Although each definition possesses common features, there are several parameters that differ which results in difficulty in terms of applicability, uniformity, and positive predictive value with all these definitions. The AACE, WHO, and EGIR definitions are all largely focused on insulin resistance, which is determined by an oral glucose tolerance test and hyperinsulinemic-euglycemic clamp. However, this labour intensive method is primarily used in a research environment [22]. In contrast, the ATP III definitions were developed which use measurements and laboratory results that are readily available to physicians, facilitating their clinical and epidemiological application and therefore have remained a backbone for subsequent classifications such as the IDF diagnostic criterion [22]. However, a major problem with the WHO and NCEP ATP III definitions has been their applicability to the different ethnic groups, especially when trying to define obesity cut-offs. This is particularly evident for the risk of T2DM, which is apparent at much lower levels of obesity in Asians compared to Europeans. The IDF, having recognized the difficulties in identifying unified criteria for MetS that were applicable across all the ethnicities, has proposed a new set of criteria with ethnic/racial specific cut-offs [1] (Table 2). This accounts for the fact that the different populations, ethnicities, and nationalities have the different distributions of norms for body weight and waist circumference. It also recognizes that the relationship between these values and the risk of T2DM or CVD differs in different populations.

4. Epidemiology

Worldwide prevalence of MetS ranges from <10% to as much as 84%, depending on the region, urban or rural environment, composition (sex, age, race, and ethnicity) of the population studied, and the definition of the syndrome used [23, 24]. In general, the IDF estimates that one-quarter of the world's adult population has the MetS [9]. Higher socioeconomic status, sedentary lifestyle, and high body mass index (BMI) were significantly associated with MetS. Cameron et al. have concluded that the differences in genetic background, diet, levels of physical activity, smoking, family history of diabetes, and education all influence the prevalence

of the MetS and its components [25]. The observed prevalence of the MetS in National Health and Nutrition Examination Survey (NHANES) was 5% among the subjects of normal weight, 22% among the overweight, and 60% among the obese [26]. It further increases with age (10% in individuals aged 20–29, 20% in individuals aged 40–49, and 45% in individuals aged 60–69) [27]. The prevalence of MetS (based on NCEP-ATP III criteria, 2001) varied from 8% to 43% in men and from 7% to 56% in women around the world [25]. Park et al. [26] noticed that there is an increase in the prevalence of MetS from 20 years old through the sixth and seventh decade of life for males and females, respectively. Ponzolzer et al. reported that there is high prevalence of MetS among postmenopausal women, which varies from 32.6% to 41.5% [28]. A Framingham Heart Study report indicated that a weight increase of ≥2.25 kg over a period of 16 yr was associated with an up to 45% increased risk of developing the MetS [29], and it has been shown by Palaniappan et al. that each 11 cm increase in waist circumference (WC) is associated with an adjusted 80% increased risk of developing the syndrome within 5 years [30]. The metabolic alterations occur simultaneously more frequently than would be expected by chance and the concurrence of several factors increases cardiovascular risk over and above the risk associated with the individual factors alone [31]. The risk increases with the number of MetS components present [32].

5. Pathophysiology

MetS is a state of chronic low grade inflammation as a consequence of complex interplay between genetic and environmental factors. Insulin resistance, visceral adiposity, atherogenic dyslipidemia, endothelial dysfunction, genetic susceptibility, elevated blood pressure, hypercoagulable state, and chronic stress are the several factors which constitute the syndrome (Figure 1).

5.1. Abdominal Obesity. The “obesity epidemic” is principally driven by an increased consumption of cheap, calorie-dense food and reduced physical activity. Adipose tissue is a heterogeneous mix of adipocytes, stromal preadipocytes, immune cells, and endothelium, and it can respond rapidly

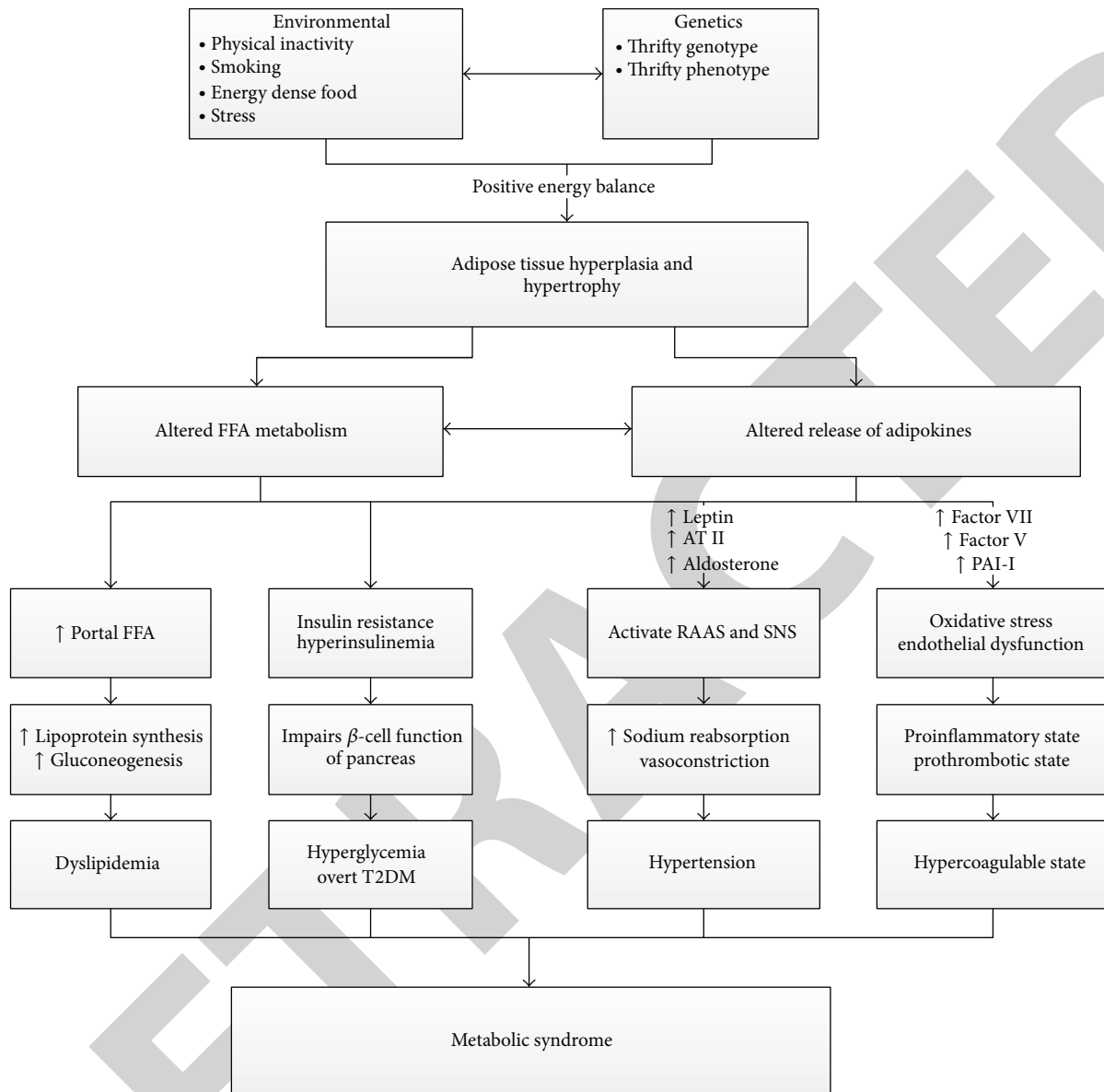


FIGURE 1: Schematic presentation of MetS. (FFA: free fatty acid, ATII: angiotensin II, PAI-1: plasminogen activator inhibitor-1, RAAS: renin angiotensin aldosterone system, SNS: sympathetic nervous system.)

and dynamically to alterations in nutrient excess through adipocytes hypertrophy and hyperplasia [33]. With obesity and progressive adipocytes enlargement, the blood supply to adipocytes may be reduced with consequent hypoxia [34]. Hypoxia has been proposed to be an inciting etiology of necrosis and macrophage infiltration into adipose tissue that leads to an overproduction of biologically active metabolites known as adipocytokines which includes glycerol, free fatty acids (FFA), proinflammatory mediators (tumor necrosis factor alpha (TNF α) and interleukin-6 (IL-6)), plasminogen activator inhibitor-1 (PAI-1), and C-reactive protein (CRP) [35]. This results in a localized inflammation in adipose tissue that propagates an overall systemic inflammation associated with the development of obesity related comorbidities [36]. Adipocytokines integrate the endocrine, autocrine,

and paracrine signals to mediate the multiple processes including insulin sensitivity [37], oxidant stress [38], energy metabolism, blood coagulation, and inflammatory responses [39] which are thought to accelerate atherosclerosis, plaque rupture, and atherothrombosis. This shows that the adipose tissue is not only specialized in the storage and mobilization of lipids but it is also a remarkable endocrine organ releasing the numerous cytokines.

5.1.1. FFA. Upper body subcutaneous adipocytes generate a majority of circulating FFA while an intra-abdominal fat content has been positively correlated with the splanchnic FFA levels which may contribute to the liver fat accumulation commonly found in abdominal obesity [40]. Further, an acute

exposure of skeletal muscle to the elevated levels of FFA induces insulin resistance by inhibiting the insulin-mediated glucose uptake, while, a chronic exposure of the pancreas to the elevated FFA impairs a pancreatic β -cell function [41]. FFAs increase fibrinogen and PAI-1 production [42].

5.1.2. *TNF α* . It is a paracrine mediator in adipocytes and appears to act locally to reduce the insulin sensitivity of adipocytes [35]. Evidence suggests that TNF- α induces adipocytes apoptosis [43] and promotes insulin resistance by the inhibition of the insulin receptor substrate 1 signalling pathway [44]. The paracrine action would further tend to exacerbate the FFA release, inducing an atherogenic dyslipidemia [45]. Plasma TNF α is positively associated with the body weight, WC, and triglycerides (TGs), while, a negative association exists between the plasma TNF α and High density lipoprotein-cholesterol (HDL-C) [43].

5.1.3. *CRP*. Elevated levels of CRP are associated with an increased WC [46], insulin resistance [47], BMI [48], and hyperglycemia [46] and are increased with the number of the MetS components. It is more likely to be elevated in obese insulin-resistant, but, not in obese insulin-sensitive subjects [49]. In addition, it has been demonstrated that regardless of the presence or degree of the MetS in an individual, CRP levels independently predicted the occurrence of future CVD events [50]. Because the MetS has been linked with a greater chance of future CVD events [51], CRP levels may be an important independent predictor of unfavourable outcomes in the MetS.

5.1.4. *IL-6*. It is released by both adipose tissue and skeletal muscle in humans [52]. It has both an inflammatory and an anti-inflammatory action. IL-6 receptor is also expressed in the several regions of the brain, such as the hypothalamus, in which it controls an appetite and energy intake [53]. It is a systemic adipokine, which not only impairs insulin sensitivity but is also a major determinant of the hepatic production of CRP [54]. IL-6 is capable of suppressing lipoprotein lipase activity. It has been shown to be positively associated with BMI, fasting insulin, and the development of T2DM [55] and negatively associated HDL-C [56].

5.1.5. *PAI-1*. A serine protease inhibitor is secreted from intra-abdominal adipocytes, platelets, and the vascular endothelium [35]. It exerts its effects by inhibiting the tissue plasminogen activator (tPA) [57] and thus is considered as a marker of an impaired fibrinolysis and atherothrombosis. Plasma PAI-1 levels are increased in abdominally obese subjects [58] and inflammatory states [59], thus, increasing the risk of an intravascular thrombus and adverse cardiovascular outcomes [60].

5.1.6. *Adiponectin*. It regulates the lipid and glucose metabolism, increases insulin sensitivity, regulates food intake and body weight, and protects against a chronic inflammation [61]. It inhibits hepatic gluconeogenic enzymes and the rate of an endogenous glucose production in the liver.

It increases glucose transport in muscles and enhances fatty acid oxidation [18]. It has a multifactorial antiatherogenic action which includes an inhibition of endothelial activation, a reduced conversion of macrophages to foam cells, and inhibition of the smooth muscle proliferation and arterial remodelling that characterizes the development of the mature atherosclerotic plaque [62]. Adiponectin is inversely associated with CVD risk factors such as blood pressure, low density lipoprotein cholesterol (LDL-C), and TGs [63]. Moreover, Pischon et al. have shown adiponectin to be a strong inverse independent risk factor for CVD [64]. Further, Fumeron et al. concluded that hypo adiponectinemia is associated with insulin resistance, hyperinsulinemia, and the possibility of developing T2DM, independent of fat mass [65]. The anti-inflammatory molecule, adiponectin, is negatively associated with the body weight, WC, TGs, fasting insulin, insulin resistance (HOMA-Homeostasis Model Assessment) [43], BMI, and blood pressure, whereas a positive association exists between adiponectin and HDL-C [43, 66]. Its expressions and secretions are reduced by TNF α [67], possibly through a stimulated production of IL-6, which also inhibits adiponectin secretion [68]. Adiponectin is seen to be “protective,” not only in its inverse relationship with the features of MetS [69] but also through its antagonism of TNF α action [70].

5.1.7. *Leptin*. It is an adipokine involved in the regulation of satiety and energy intake [35]. Levels of leptin in the plasma increase during the development of obesity and decline during the weight loss. Leptin receptors are located mostly in the hypothalamus and the brain stem and signals through these receptors controls satiety, energy expenditure, and neuroendocrine function. Most overweight and obese individuals have an elevated level of leptin that do not suppress appetite, or in other words, leptin resistance. Leptin resistance is thought to be a fundamental pathology in obesity [71]. Besides its effect on appetite and metabolism, leptin acts in the hypothalamus to increase the blood pressure through activation of the sympathetic nervous system (SNS) [72]. High circulating levels of leptin are reported to explain much of the increase in the renal sympathetic tone observed in obese human subjects [73]. Leptin-induced increase in renal sympathetic activity and blood pressure is mediated by the ventromedial and dorsomedial hypothalamus [74]. Leptin is an nitric oxide (NO) dependent vasodilator but also increases the peripheral vascular resistance and the sympathetic nerve activity [75]. The concentration of plasma leptin is correlated with adiposity, and hyperleptinemia is indeed considered an independent cardiovascular disease risk factor [76].

5.2. *Insulin Resistance*. Characteristics of the insulin-sensitive phenotype include a normal body weight [77] without abdominal or visceral obesity [78], being moderately active [79], and consuming a diet low in saturated fats [80]. Alternatively, insulin-resistant individuals demonstrate an impaired glucose metabolism or tolerance by an abnormal response to a glucose challenge, an elevated fasting glucose levels and/or overt hyperglycemia, or a

reduction in insulin action after intravenous administration of insulin (euglycemic clamp technique) with decreased insulin-mediated glucose clearance and/or reductions in the suppression of endogenous glucose production. It is defined as a pathophysiological condition in which a normal insulin concentration does not adequately produce a normal insulin response in the peripheral target tissues such as adipose, muscle, and liver. Under this condition, pancreatic beta cell secretes more insulin (i.e., hyperinsulinemia) to overcome the hyperglycemia among insulin-resistant individuals. Although hyperinsulinemia may compensate for insulin resistance to some biological actions of insulin, that is, maintenance of normoglycemia, however, it may cause an overexpression of insulin activity in some normally sensitive tissues. This accentuation of some insulin actions coupled with a resistance to other actions of insulin results in the clinical manifestations of MetS [81]. An inability of the pancreatic beta cells over time to produce a sufficient insulin to correct the worsening tissue insulin resistance leads to hyperglycemia and overt T2DM [82]. Physiological insulin signalling occurs following the binding of insulin to the insulin receptor, a ligand-activated tyrosine kinase. Binding of insulin results in a tyrosine phosphorylation of downstream substrates and activation of two parallel pathways: the phosphoinositide 3-kinase (PI3K) pathway and the mitogen activated protein (MAP) kinase pathway. The PI3K-Akt pathway is affected, while, the MAP kinase pathway functions normally in insulin resistance. This leads to a change in the balance between these two parallel pathways. Inhibition of the PI3K-Akt pathway leads to a reduction in endothelial NO production, resulting in an endothelial dysfunction, and a reduction in GLUT4 translocation, leading to a decreased skeletal muscle and fat glucose uptake. By contrast, the MAP kinase pathway is unaffected, so there is a continued endothelin-1 (ET-1) production, an expression of vascular cell adhesion molecules, and a mitogenic stimulus to vascular smooth muscle cells. In these ways, an insulin resistance leads to the vascular abnormalities that predispose to atherosclerosis. Although insulin-resistant individuals need not be clinically obese, they nevertheless commonly have an abnormal fat distribution that is characterized by a predominant upper body fat. Regardless of the relative contributions of visceral fat and abdominal subcutaneous fat to insulin resistance, a pattern of abdominal (or upper body) obesity correlates more strongly with the insulin resistance and the MetS than does lower body obesity [83].

5.3. Dyslipidemia. This dyslipidemia is characterised by a spectrum of qualitative lipid abnormalities reflecting perturbations in the structure, metabolism, and biological activities of both atherogenic lipoproteins and antiatherogenic HDL-C which includes an elevation of lipoproteins containing apolipoprotein B (apoB), elevated TGs, increased levels of small particles of LDL, and low levels of HDL-C. Insulin resistance leads to an atherogenic dyslipidemia in several ways. First, insulin normally suppresses lipolysis in adipocytes, so an impaired insulin signalling increases

lipolysis, resulting in increased FFA levels. In the liver, FFAs serve as a substrate for the synthesis of TGs. FFAs also stabilize the production of apoB, the major lipoprotein of very low density lipoprotein (VLDL) particles, resulting in a more VLDL production. Second, insulin normally degrades apoB through PI3K-dependent pathways, so an insulin resistance directly increases VLDL production. Third, insulin regulates the activity of lipoprotein lipase, the rate-limiting and major mediator of VLDL clearance. Thus, hypertriglyceridemia in insulin resistance is the result of both an increase in VLDL production and a decrease in VLDL clearance. VLDL is metabolized to remnant lipoproteins and small dense LDL, both of which can promote an atheroma formation. The TGs in VLDL are transferred to HDL by the cholesterol ester transport protein (CETP) in exchange for cholesteryl esters, resulting in the TG-enriched HDL and cholesteryl ester-enriched VLDL particles. Further, the TG-enriched HDL is a better substrate for hepatic lipase, so it is cleared rapidly from the circulation, leaving a fewer HDL particles to participate in a reverse cholesterol transport from the vasculature. Thus, in the liver of insulin-resistant patients, FFA flux is high, TGs synthesis and storage are increased, and excess TG is secreted as VLDL [84]. For the most part, it is believed that the dyslipidemia associated with insulin resistance is a direct consequence of increased VLDL secretion by the liver [85]. These anomalies are closely associated with an increased oxidative stress and an endothelial dysfunction, thereby reinforcing the proinflammatory nature of macrovascular atherosclerotic disease.

5.4. Hypertension. Essential hypertension is frequently associated with the several metabolic abnormalities, of which obesity, glucose intolerance, and dyslipidemia are the most common [86]. Studies suggest that both hyperglycemia and hyperinsulinemia activate the Renin-angiotensin system (RAS) by increasing the expression of angiotensinogen, Angiotensin II (AT II), and the AT1 receptor, which, in concert, may contribute to the development of hypertension in patients with insulin resistance [87]. There is also evidence that insulin resistance and hyperinsulinemia lead to SNS activation, and, as a result, the kidneys increase sodium reabsorption, the heart increases cardiac output, and arteries respond with vasoconstriction resulting in hypertension [88]. It has been recently discovered that adipocytes also produce aldosterone in response to ATII [89]. In this regard, the adipocyte may be considered a miniature renin-angiotensin-aldosterone system.

5.5. Genetics. The great variations in the susceptibility and age of onset in individuals with a very similar risk profile suggest a major interaction between genetic and environmental factors [90]. It is recognized that some people who are not obese by traditional measures nevertheless are insulin-resistant and have abnormal levels of metabolic risk factors. Examples are seen in individuals with 2 diabetic parents or 1 parent and a first- or second-degree relative [91]; the same is true for many individuals of South Asian ethnicity [92]. Considerable individuals and ethnic variations also exist in

the clinical pattern of metabolic risk factors in obese/insulin-resistant subjects [93]. It is likely that the expression of each metabolic risk factor falls partially under its own genetic control, which influences the response to different environmental exposures. For example, a variety of polymorphisms in genes affecting lipoprotein metabolism are associated with the worsening of dyslipidemia among obese people [94]. Similarly, a genetic predisposition to the defective insulin secretion when combined with insulin resistance can raise the plasma glucose to abnormal levels [95]. According to the *thrifty genotype hypothesis* proposed by Neel in 1962 [96], individuals living in a harsh environment with an unstable food supply would maximize their probability of survival if they could maximize a storage of surplus energy. Genetic selection would thus favour the energy-conserving genotypes in such environments. However, the selected genetic variations that were favoured during malnutrition would become unfavourable when nutrition improved. This hypothesis assumes that the common genetic variants of thrifty genes predispose to MetS. Another *thrifty phenotype hypothesis* was introduced by Hales and Barker in 1992 [97]. According to this hypothesis, babies who experienced an intrauterine malnutrition may have adapted to a poor nutrition by reducing energy expenditure and becoming “thrifty.” These metabolic adaptations are beneficial when individuals are poorly nourished during childhood and adult life; however, with an increased food intake, these adaptations are no longer beneficial and would lead to an increased risk of MetS in a later life. Support for this hypothesis comes from the observed associations of low birth weight with later development of insulin resistance and T2DM in several populations [98].

5.6. Endothelial Function. It is characterized by an impaired endothelium-dependent vasodilatation, a reduced arterial compliance, and an accelerated process of atherosclerosis [107]. Various factors like oxidative stress, hyperglycemia, advanced glycation products, FFAs, inflammatory cytokines, or adipokines cause an inability of endothelium to serve its normal physiological and protective mechanisms. Hansson has shown that immune cells play an important role in all the stages of the atherosclerotic process [108]; in addition, a reduction in NO, a key regulator of endothelial homeostasis, and an increase in reactive oxygen species result in an endothelial dysfunction and a proatherogenic vascular bed [109].

5.7. Hypercoagulable State. A proinflammatory state is characterized by elevated circulating cytokines and acute-phase reactants (e.g., CRP). Further, a prothrombotic state signifies anomalies in the procoagulant factors, that is, an increase in fibrinogen, factor VII and factor VIII as well as the antifibrinolytic factor (PAI-1), platelet abrasions, and endothelial dysfunctions. Grundy [110] has shown that a fibrinogen, an acute-phase reactant protein like CRP, rises in response to a high-cytokine state. This shows that the prothrombotic and proinflammatory states may be metabolically interconnected.

5.8. Diet. A study by Aljada et al. has shown that a high dietary fat intake is associated with an oxidative stress and an activation of the proinflammatory transcription factor, that is, nuclear factor kappa-beta (NF κ B) [111]. In contrast, a diet rich in fruits and fibres has no inflammation-inducing capacity compared with a high-fat diet even if it has the same calories content [112].

5.9. Chronic Stress and Glucocorticoid (GC) Action. Chronic hypersecretion of stress mediators, such as cortisol, in individuals with a genetic predisposition exposed to a permissive environment, may lead to the visceral fat accumulation as a result of chronic hypercortisolism, low growth hormone secretion, and hypogonadism [113]. GCs increase the activities of enzymes involved in fatty acid synthesis and promote the secretion of lipoproteins [114]; induce the hepatic gluconeogenic pathway [115]; promote the differentiation of preadipocytes to adipocytes, which could lead to an increased body fat mass [116]; inhibit an insulin-stimulated amino acid uptake by adipocytes [117]; and increase lipolysis or lipid oxidation which leads to the peripheral insulin resistance [118]. A good correlation was observed between plasma cortisol levels, total urinary GC metabolites, and the number of features of the MetS among these patients. Both the secretion rate and the peripheral clearance of cortisol in these patients were positively correlated with the systolic blood pressure, and fasting glucose and insulin [119]. These hormonal alterations may lead to a reactive insulin hypersecretion, an increasing visceral obesity, and sarcopenia, resulting in dyslipidemia, hypertension, and T2DM [120].

6. Treatment

MetS is a state of chronic low grade inflammation with the profound systemic effects (Table 3). Clinical identification and management of patients with the MetS are important to begin efforts to adequately implement the treatments to reduce their risk of subsequent diseases [121]. Effective preventive approaches include lifestyle changes, primarily weight loss, diet, and exercise, and the treatment comprises the appropriate use of pharmacological agents to reduce the specific risk factors. Pharmacological treatment should be considered for those whose risk factors are not adequately reduced with the preventive measures and lifestyle changes [122]. The clinical management of MetS is difficult because there is no recognized method to prevent or improve the whole syndrome, the background of which is essentially insulin resistance [15]. Thus, most physicians treat each component of MetS separately, laying a particular emphasis on those components that are easily amenable to the drug treatment. In fact, it is easier to prescribe a drug to lower blood pressure, blood glucose, or triglycerides rather than initiating a long-term strategy to change people's lifestyle (exercise more and eat better) in the hope that they will ultimately lose weight and tend to have a lower blood pressure, blood glucose, and triglycerides. For the treatment of risk factors of MetS, the physician should follow the current treatment guidelines of the National Cholesterol Education

TABLE 3: Systemic effects of MetS.

Renal	Microalbuminuria, hypofiltration, hyperfiltration, glomerulomegaly, focal segmental glomerulosclerosis, and chronic kidney disease [99].
Hepatic	Increased serum transaminase, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), hepatic fibrosis, and cirrhosis [100].
Skin	Acanthosis nigricans, lichen planus, systemic lupus erythematosus, burn-induced insulin resistance, psoriasis, androgenetic alopecia, skin tags, skin cancer, and acne inversa [101].
Ocular	Nondiabetic retinopathy, age related cataract-nuclear, cortical, posterior subcapsular; central retinal artery occlusion, primary open angle glaucoma, oculomotor nerve palsy, and lower lid entropion [102].
Sleep	Obstructive sleep apnea (OSA) [103].
Reproductive system	Hypogonadism, polycystic ovarian syndrome (PCOS), and erectile dysfunction [104].
Cardiovascular system	Coronary heart disease (CHD), myocardial infarction (MI), and stroke [105].
Cancers	Breast, pancreas, and prostate [106].

Programme (NCEP) [123], the seventh Joint National Commission (JNC-VII) for blood pressure treatment [124], the American Diabetes Association (ADA) [125], the American Heart Association (AHA) [20], and the National Institute of Health Obesity Initiative [126].

6.1. Risk Assessment. The goals of therapy are to reduce both a short-term and lifetime risk. The presence of the MetS *per se* indicates a higher lifetime risk. A practical approach to estimate absolute, short-term CHD/CVD risk in patients with the MetS without ASCVD or diabetes is to use the standard Framingham algorithm to estimate a 10-year risk of the coronary heart disease (CHD) [123]. The standard Framingham risk equations, which include cigarette smoking, blood pressure, total cholesterol, HDL-C, and age, capture most of the risk of CVD in patients with the syndrome. This equation triages patients into 3 risk categories based on a 10-year risk of CHD: *high risk* (10-year risk $\geq 20\%$), *moderately high risk* (10-year risk 10% to 20%), or *lower to moderate risk* (10-year risk $\leq 10\%$), while affected patients with ASCVD or diabetes are already in a high-risk category without the need for Framingham risk scoring.

6.2. Lifestyle Modification. Lifestyle modification treatment should be delivered by a multidisciplinary approach (Table 4) and a team composed of physicians and nonphysician health professionals, such as dietitians or professionals with a master degree in exercise physiology, behavioural psychology, or health education [127]. Although lifestyle therapy may not modify any given risk factor as much as will a particular drug, its benefit lies in the fact that it produces a moderate reduction in all the metabolic risk factors [128].

6.3. Weight Reduction. Four therapies can be used for weight reduction: calorie restriction (e.g., 500 kcal/d deficit), increased physical activity, behavioural modification, and, in appropriate patients, FDA-approved weight-reducing drugs [128]. Several authors [20] recommend a weight loss goal of 10% reduction in body weight in the first six months to a year and continued weight loss thereafter until BMI is less than 25. While many patients find weight loss difficult to achieve, exercise and dietary changes that can lower blood

pressure and improve lipid levels will further improve insulin resistance, even in the absence of weight loss [129]. A weight loss of as small as 5–10% of body weight can significantly reduce TGs and increase HDL-C [130]. Furthermore, both hypertensive individuals and individuals at risk of developing hypertension can see a significant reduction in the blood pressure with a modest weight loss [131]. Fasting blood glucose, insulin, and haemoglobin A1c can also be decreased with a modest weight loss [132]. During weight maintenance (i.e., energy balance), a regular exercise appears to play an important role in abdominal fat loss [133] and the prevention of weight regain in those who have successfully lost weight [134]. Persons who combine calorie restriction and exercise with behavioural modifications should expect to lose 5–10% of preintervention weight over a period of four to six months. This weight loss appears small to the patient but results in an improvement of many obesity related conditions including various abnormal components of the MetS and development of diabetes [135]. Both the Finnish Diabetes Prevention Study [136] and the US Diabetes Prevention Program (DPP) [137] showed that diet and exercise had a significant effect on reducing the progression from IGT to T2DM.

6.4. Diet. The effective and healthful methods for the long-term weight loss are reduced-energy diets, consisting of a modest 500 to 1000 calories/day reduction. Sustained dietary changes may require a referral to a registered dietician to help implement the suggestions and ensure an adequate micronutrient intake (e.g., calcium, iron, and folate) while reducing calories. In the SUN (Seguimiento University of Navarra) prospective cohort study [138], a Mediterranean-style diet was inversely associated with the cumulative incidence of MetS. Adherence to the Mediterranean diet improves the physical and mental domains of health related quality of life (physical function, vitality, general physical health, emotional role, and self-perception of health) [139] and lowers the odds of LDL-C, postchallenge glucose values [140], TGs, and low HDL-C levels [141]. In the PREMIER study [142], the Dietary Approaches to Stop Hypertension (DASH) diet plus lifestyle interventions improved the metabolic parameters, particularly blood pressure. ATP III [123] recommended that the diet should contain 25% to 35% of calories as total fat for

TABLE 4: Multidisciplinary approach to the MetS.

A: assessment	Calculate Framingham risk score: <i>high risk</i> (10-year risk $\geq 20\%$), <i>moderately high risk</i> (10-year risk 10% to 20%), or <i>lower to moderate risk</i> (10-year risk $\leq 10\%$). Make diagnosis of MetS using the diagnostic criteria.
A: aspirin	High risk: aspirin definitely beneficial. High-intermediate risk (10–20%): aspirin likely to be beneficial. Low-intermediate risk (6–10%): “individual clinical judgment”, depending on sex and risk of bleeding. Low risk (<6%): Risk of haemorrhage outweighs the benefits.
B: BP control	Initiate treatment: categorical hypertension (BP $\geq 140/\geq 90$ mm Hg). Patients with established diabetes ($\geq 130/\geq 80$ mm Hg). ACEIs/ARBs first line agent may reduce incident diabetes mellitus. Beta-blockers and thiazides may have an adverse effect on impaired glucose tolerance but outweighed by the benefits of reaching BP goal and lowering the risk of CVD events.
C: cholesterol First target: LDL Second target: non-HDL Third target: HDL Fourth target: CRP	Statin to achieve LDL-C <100 mg/dL in high-risk, <130 mg/dL in intermediate-risk, and <160 mg/dL in low risk patients. Statin intensification, consider niacin and/or fibrates once statin maximized. Consider fibrates, especially for those with combined hypertriglyceridemia/low HDL-C. Consider further reduction in LDL-C with statin therapy to mitigate a risk of low HDL-C, consider niacin. Statin therapy for those with high sensitivity CRP (hsCRP) ≥ 3 mg/dL.
D: diabetes prevention/diet	Intensive lifestyle modification is the most important therapy. Weight reduction of 5–10% of preintervention weight over a period of four to six months. Sodium intake of <65–100 mmol/day with a goal of 90–120 mmol of potassium per day. Mediterranean diet: high consumption of fruits, vegetables, legumes, and grains, moderate alcohol intake, a moderate-to-low consumption of dairy products and meats/meat products, and a high monounsaturated- to-saturated fat ratio. DASH diet: rich in fruits, vegetables, and low-fat dairy products, and low in saturated and total fat intake. Consider low glycemic index food, complex unrefined carbohydrates, viscous soluble fibres, protein intake of 10–35% of total calorie intake and 25% to 35% of calories as total fat. Metformin is second line in delaying the onset of T2DM. Thiazolidinediones (Pioglitazones) and alpha-glucosidase inhibitors (Acarbose) have shown benefit in smaller studies and are therefore third line.
E: exercise	Daily moderate intensity activity of minimum 30 minutes for most days of the week. Recommend use of pedometer with goal >10,000 steps/day.

the individuals entering cholesterol management. If the fat content exceeds 35%, it is difficult to sustain the low intakes of saturated fat required to maintain a low LDL-C. On the other hand, if the fat content falls below 25%, TGs can rise and decline in HDL-C levels can be seen [143]; thus, a very low-fat diet may exacerbate an atherogenic dyslipidemia. A protein intake of 10–35% of total calorie intake is recommended by the Institute Of Medicine (IOM) for the general population with an exception of individuals with chronic kidney disease (CKD) who have markedly reduced glomerular filtration rate, where, an excess protein enhances phosphorus load, which can cause acidosis and worsen the insulin resistance [144]. Adherence may be enhanced by increasing the diet structure and limiting food choices, thereby reducing a temptation and the potential mistakes on calculating an energy intake [145]. A strategy to increase the diet structure is to provide patients with the meal plans, grocery lists, menus, and recipes. Support for this strategy is derived from a study showing that the provision of both low-calorie foods (free of charge or subsidized) and structured meal plans resulted in significantly greater weight loss than a diet with no additional structure [146]. Another effective strategy to increase dietary adherence is the meal replacements [147] which help to overcome some problems that occur while consuming the conventional food

diets (i.e., underestimation of calorie intake, difficulties in estimating portion sizes, macronutrient composition, calorie content, and in recalling the consumed food). A clear positive association has been shown between sodium intake and blood pressure, with excessive sodium intake associated with hypertension [148]. Furthermore, a sodium restriction has also been associated with reduced CVD events [149] and congestive heart failure [150]. Guidelines therefore recommend that a daily sodium intake should be restricted to no more than 65–100 mmol [151]. In addition to sodium restriction, an increased potassium intake has also been shown to improve blood pressure, especially in the setting of high sodium intake [152]. Guidelines have recommended the intake of foods enriched with potassium, such as fruits and vegetables, with a goal of 90–120 mmol of potassium per day [151]. Incorporation of monounsaturated fatty acid (fat from plant source like olive oil, soybean oil, canola oil, safflower oil, peanut oil, peanuts, peanut butter, almond, and cashew nut) may be beneficial as it improves the atherogenic dyslipidemia. Similarly, n-3 polyunsaturated fatty acids (mainly from fish) have cardioprotective effect and it should constitute approximately 10% of total energy intake. Viscous (soluble) fibres (mainly in oat products, psyllium, and pectin) intake of 10–25 g/day also improves an atherogenic dyslipidemia [153].

Low glycemic index foods (i.e., those that are minimally processed) have been shown to improve the components of the MetS including hyperlipidemia and hyperglycemia [154], whereas, a higher glycemic index has been shown to be positively associated with the insulin resistance and MetS prevalence [155]. Therefore, a diet high in complex, unrefined carbohydrates with an emphasis on fibres (14 g/1000 calories consumed daily) and low in added sugars ($\leq 25\%$ of calorie intake) is recommended for individuals with or at risk of the MetS.

6.5. Physical Activity. Current physical activity guidelines [156] recommend practical, regular, and moderate regimens for exercise. The standard exercise recommendation is a daily minimum of 30 minutes of moderate-intensity physical activity. However, a preference is given to 60 minutes of moderate-intensity brisk walking to be supplemented by other activities [157]. The latter includes multiple short (10 to 15 minutes) bouts of activity (walking breaks at work, gardening, or household work), using simple exercise equipment (e.g., treadmills), jogging, swimming, biking, golfing, team sports, and engaging in resistance training [158]; avoiding common sedentary activities in a leisure time (television watching and computer games) is also advised. Current AHA guidelines [156] call for a clinical assessment of the risk of the future ASCVD events before initiating a new exercise regimen. For high-risk patients (e.g., those with recent acute coronary syndromes or recent revascularization), physical activity should be carried out under the medical supervision. Clinicians should evaluate which type of activity is feasible for the patient, considering the barriers (e.g., arthritis and time constraints) that can prevent a successful increase in the physical activity. Accordingly, they should assist patients in developing a physical activity plan based on the initial assessment. However, any type of physical activity should be encouraged. Lifestyle activity should be increased slowly in intensity and duration (by 5 min/session/week), starting from a low-intensity exercise (< 3 metabolic equivalent) in sedentary subjects, to avoid excessive fatigue, muscle pain, strains, or injuries [159]. Patients should be encouraged to register their baseline physical activity or to check their baseline number of steps by a pedometer. Whenever the brisk walking is chosen as the preferred activity, they should be instructed to add 500 steps at 3-day intervals to a target value of 10,000–12,000 steps/day [126]. Prescribing multiple short bouts (10 min each) rather than one long session may help the patients to accumulate more minutes of exercise. This 30 minutes of physical activity achieved in three 10-minute sessions is equivalent to the energy expenditure of 1500 kcal a week. The impact of exercise on insulin sensitivity is evident for 24 to 48 hours and disappears within three to five days. Thus, an individual would need to follow the AHA and American College of Sports Medicine recommendation to exercise at least 30 min/d most days of the week [160] for a continued benefit of exercise on insulin action. Physical training has been shown to reduce the skeletal muscle lipid levels and insulin resistance, regardless of BMI [161]. A combination of resistance and aerobic exercise is the best, but

any activity is better than none, and patients who have been sedentary need to start with walking and gradually increase duration and intensity [162]. According to the Centre for Disease Control and Prevention (CDC) and the American College of Sports Medicine, physically inactive or sedentary subjects were defined as those who did not engage in at least 150 minutes of physical activities per week [163]. The odds of having the MetS were almost doubled in adults reporting no moderate or vigorous physical activity compared with those who engage in at least 150 min/wk [164]. Furthermore, Koplan and Dietz have shown that a regular exercise improves insulin sensitivity, decreases plasma TGs levels, and reduces cardiovascular morbidity and mortality [165].

6.6. Behaviour Therapy. It has been designed to provide the patients with a set of principles and techniques to modify their eating and activity habits [145]. The emphasis in behavioural change should include the benefit of social support, stress management, the value of a regular exercise regimen, and an improvement in eating habits (e.g., setting goals, planning meals, reading labels, eating regular meals, reducing portion sizes, self-monitoring, and avoiding eating binges). Originally, the treatment was exclusively based on the learning theory (behaviourism). The theory postulates that the behaviours causing obesity (excess eating and low exercising) are largely learnt and therefore could be modified or relearned. The theory further postulated that the positive changes in eating and exercising can be achieved by modifying the environmental cues (antecedents) and the reinforcements of these behaviours [166]. The intervention was later integrated with the cognitive strategies (e.g., problem solving and cognitive restructuring) and with the specific recommendations on diet and exercise [167]. Exercise promotion to decrease the chronic disease risk is also important in adults and the middle-aged since it can slow down the functional decline associated with ageing [168].

6.7. Pharmacological Approach. The National Institutes of Health guidelines for the treatment of obesity recommend a consideration of pharmaceutical therapy for weight loss for the individuals with a BMI of at least 30 kg/m^2 or for those with a BMI of at least 27 kg/m^2 and comorbidities associated with their excess weight. Pharmacological approaches to weight loss include two main classes: appetite suppressants and inhibitors of nutrient absorption. A single agent is generally recommended and an average weight loss ranges greatly from 5% to 10% of initial weight [169]. Appetite suppressants include phentermine derivatives and sibutramine. These agents are usually taken in the late morning and reduce appetite in the late afternoon and evening. Krejs reported that sibutramine-induced weight loss and weight maintenance lead to clinically relevant reductions in the risk factors associated with the syndrome [170]. Treatment with the drug decreases visceral fat, improves lipid levels, and decreases glycosylated haemoglobin and uric acid concentrations. Orlistat (an inhibitor of gastrointestinal lipase) is the only nutrient absorption inhibitor currently available. It prevents absorption of up to 30% of the fat consumed and

must be taken at the time of consumption. Undesirable side effects such as flatulence and oil leakage in the stool often occur early in the course of treatment with this medication. In randomized clinical trials, orlistat in obese persons with T2DM at baseline led to an improved glycemic control and a weight reduction of 6% over 1 year versus 4% weight loss with placebo [171]. A recently published meta-analysis concerning the efficacy of pharmacological agents for obesity reported that an average weight loss was approximately four kilograms more than for placebo users and that no drug or class of drugs was clearly superior [172]. However, the major problem with these currently available antiobesity drugs is a relatively high rate of adverse side effects leading to a poor tolerance and compliance for the long-term use.

6.8. Bariatric Surgery. Surgery is recommended for the individuals who do not respond to weight loss diet or medications, are extremely obese ($BMI > 40 \text{ kg/m}^2$), or if they have a $BMI > 35$ to 40 kg/m^2 and one or more comorbid conditions [169]. Improvements in the metabolic profile have been documented presumably due to the redistribution of adiposity [174]. Bariatric surgery techniques using laparoscopic adjustable banding of stomach along with Roux-en-Y and other forms of gastric bypass are now favoured for the severe and morbid obesity [18]. It results in a weight loss of 25–30% and rapid normalization of glucose handling and blood pressure in patients with diabetes and hypertension [175] with 95% of patients being free of the syndrome one year after a surgery [18]. It has been found to be associated with the improvement and resolution of multiple comorbidities associated with obesity, including hypertension, T2DM, NAFLD, OSA, cardiopulmonary failure, CVD, arthritis, PCOS, dyslipidemia (exclusive of hypercholesterolemia), hyperuricemia, and infertility [175]. However, the long-term results are not available and recent reports of substantial mortality and morbidity of this procedure, especially in the elderly, have raised important safety issues for this procedure [176].

6.9. Dyslipidemia. The guidelines recommend that the LDL-C goals (Table 5) should be set at less than 130 mg/dL with the option of targeting less than 100 mg/dL in the moderately high-risk individuals. Target goals should be set at an LDL-C less than 100 mg/dL in the high-risk patients with the option of aiming for less than 70 mg/dL in the “very high-risk” patient [173]. The goal for the non-HDL-C is 30 mg/dL greater than LDL-C. In patients with an atherogenic dyslipidemia in whom the serum TGs levels are $\geq 200 \text{ mg/dL}$, non-HDL-C becomes the next target of treatment after the LDL-C goal is reached. If the TGs level is higher than 500 mg per dL, then lowering the TGs level to 500 mg per dL or less takes primacy over LDL-C lowering to prevent the development of acute pancreatitis. After LDL-C and non-HDL-C goals are achieved, a tertiary target is raising the HDL-C level. No goals for raising HDL-C levels are specified but HDL-C should be raised to the possible extent after attaining the goals for LDL-C and non-HDL-C [123].

Statins are considered to be the most effective class of drugs for reducing the LDL-C concentrations due to their minimal drug-drug interactions and side effects [123]. Depending on the dose and the specific type of statin used, LDL-C reductions of 15 to 60 mg/dL are observed [177]. Statins increase HDL-C by 5–10%, with greater increases seen in individuals with lower HDL-C and elevated TGs, and reduce TGs concentrations by 7–30% primarily with moderate to high doses [178] and further decrease very low density lipoprotein (VLDL) levels by 39% [157]. Non-lipid-lowering or pleiotropic effects of statins have also been implicated in their beneficial effects on inflammation, endothelial function, and CVD events [179] and may therefore be beneficial for individuals with the MetS [180]. Statins also lower the incidence of MI or stroke by more than 33% in patients with coronary artery disease. Statins can also be safely combined with a fibrate, especially fenofibrate, and niacin to achieve the target levels of non-HDL-C, TGs, and HDL-C [7]. All statins had favourable effects on atherogenic dyslipidemia, with rosuvastatin generally having the greatest effect [181].

Niacin has favourable effects on essentially all of the abnormalities of the metabolic dyslipidemia. It is considered the most effective agent for raising HDL-C (15 to 35%) and increasing HDL particle size [182]. Niacin significantly lowers TGs (20 to 50%) and LDL-C (5–25%) [123]. Niacin also causes beneficial changes in the lipoprotein subclasses because it has been shown to reduce the proportion of small, dense LDL-C particles while increasing large, more buoyant LDL-C particles and larger HDL-C particles [183]. Combination therapy of a niacin and statin produces greater effects on the lipid levels than does an either agent given alone [184]. The primary limitations for the use of niacin include flushing (most often associated with immediate-release niacin) and hyperglycemia [185]. Therefore, if nicotinic acid is used in patients with impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or diabetes, its dose should be kept relatively low (e.g., 1 to 2 g per day) and deserves careful monitoring for the worsening of hyperglycemia [186]. Niacin has the greatest effect on increasing HDL-C levels (15%–35%), with fibrates (6%–15%) and statins (3%–15%) having a more moderate effect [123].

The two fibrates currently used clinically are gemfibrozil and fenofibrate, both of which can lower TGs by 25% to 30% with the greater reductions in individuals that are hypertriglyceridemic. Fibrates further increases HDL-C by 5–15% and reduces LDL-C by 0–30% [187]. Although fibrates reduce the plasma TGs and increase the HDL-C extent when used in patients with diabetes mellitus, there have been no studies specifically examining the effect of fibrates treatment in patients with the MetS [188]. The advantage of gemfibrozil is that it is lower in cost, but fenofibrate has a fewer drug interactions, especially when prescribed along with a statin. Several studies have reported an isolated severe myopathy occurring from the combination of a statin with gemfibrozil due to pharmacological interaction of statin glucuronidation and increase in the level of statins when used in conjunction [157]. ATP III has recommended the combination of fenofibrate and statin due to a very low risk of associated myopathy [7]. Although the treatment with statin/fibrate and

TABLE 5: Goals for lowering LDL-C [173].

Risk category	LDL-C goals	Recommendations
Lower risk 0-1 major risk factor 10-yr risk <10%	<160 mg/dL	Lifestyle modifications Consider pharmacotherapy if LDL-C \geq 190 mg/dL after lifestyle modifications
Moderate risk \geq 2 major risk factors 10-yr risk <10%	<130 mg/dL	Lifestyle modifications Consider pharmacotherapy if LDL-C \geq 160 mg/dL after lifestyle modifications
Moderately high risk \geq 2 major risk factors 10-yr risk 10–20%	<130 mg/dL Optional <100 mg/dL	Lifestyle modifications Consider pharmacotherapy if LDL-C \geq 130 mg/dL or optionally \geq 100 mg/dL after lifestyle modifications
High risk CHD or CHD risk equivalents	<100 mg/dL Optional <70 mg/dL	Lifestyle modifications Consider pharmacotherapy if LDL-C \geq 100 mg/dL or optionally \geq 70 mg/dL after lifestyle modifications

statin/niacin has been reported to increase the risk of drug induced myopathy and rhabdomyolysis, such combination therapies are considered safe [189]. Low or intermediate doses of statins (10–40 mg/day) with fenofibrate (200 mg/day) or bezafibrate (400 mg/day) are considered effective and safe for the treatment of an atherogenic dyslipidemia [190]. Risk factors that predispose patients to myopathy caused by the above combinations include increased age, female sex, renal or liver disease, diabetes, hypothyroidism, debilitated status, surgery, trauma, excessive alcohol intake, heavy exercise, uncontrolled dose of niacin or fibrate, and use of additional medications (cyclosporine, protease inhibitors, or drugs metabolised through cytochrome P450) [191].

Bile acid sequestrants (BAS) and cholesterol absorption inhibitors (CAI) lower the LDL-C by decreasing the absorption of intestinal bile acids and cholesterol, respectively. BAS results in 15 to 30% reductions in LDL-C [192]. The only clinically available CAI, ezetimibe, has been shown to result in 15–25% reductions in LDL-C [193]. Although BAS and CAI are both effective as monotherapy, the greater benefits are obtained when used in combination with statins, an effect that may be due to their complementary mechanism of actions [194]. The study trial has shown that BAS and ezetimibe reduce the potential risk of major coronary events in patients with the MetS [195].

6.10. Hypertension. Categorical hypertension (BP \geq 140/ \geq 90 mm Hg) should be treated according to the USA JNC VII guidelines on the prevention, detection, evaluation, and treatment of the high blood pressure recommendations [124]. Antihypertensive drugs should be introduced at even lower blood pressures (\geq 130/ \geq 80 mm Hg) in the patients with established diabetes. Mild elevations of blood pressure often can be effectively controlled with the lifestyle therapies. A simple 5% weight reduction in obese women lowered the systolic blood pressure by 7 mmHg and was associated with the decreased levels of angiotensinogen (–27%), renin (–43%), angiotensin-converting enzyme (–12%), aldosterone (–31%), and angiotensinogen expression in adipocytes (–20%) [196]. It is estimated that 5 mmHg reduction of systolic blood pressure across the general population would result in overall reductions of 14% in stroke mortality, 9% in CHD mortality,

and 7% in all cause mortality [197]. However, if hypertension cannot be adequately controlled by lifestyle therapies, antihypertensive drugs usually are necessary to prevent the long-term adverse effects, for example, MI, stroke, and CKD [124]. It has been proposed that angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) should be the first-line classes of agents in the MetS, especially in the setting of diabetes or CKD [198]. ARBs may be used in those who cannot tolerate ACE inhibitors or as an alternative to ACE inhibitors in people who have a left ventricular dysfunction [199]. Certainly these classes of agents have been shown to be effective in reducing the incidence of albuminuria or progression of nephropathy in patients with diabetes [200]. Although a number of trials have shown that ACE inhibitors and ARBs may reduce the risk of diabetes [201], a more recent study designed to examine this issue directly found that the ACE inhibitor ramipril did not prevent the progression of diabetes in persons with IFG or IGT [202]. In general, treatment with these classes of drugs reduces the rate of new-onset diabetes as compared with the use of diuretic and/or β -blockers [203] but the long-term safety and efficacy of β -blockers and diuretics has been effectively demonstrated in many clinical trials, including the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) that included >40,000 patients [204]. The ALLHAT showed that the treatment with a thiazide-type diuretic in patients with the MetS results in superior CVD outcomes compared to the treatment with calcium channel blockers, β -blockers, or ACE inhibitors despite the less favourable metabolic profile associated with the thiazide diuretics [205]. The ALLHAT and the United Kingdom Prospective Diabetes Study (UKPDS) have shown that agents such as thiazide diuretics and β -blockers lower the risk of CVD events even in the patients with diabetes [206]. These agents, however, have also been associated with an increased risk for diabetes [205, 206]. Certainly the majority of patients who need an antihypertensive therapy will likely need more than one agent for the proper blood pressure control [207].

6.11. Insulin Resistance and Hyperglycemia. In MetS, patients with IFG (or IGT if assessed), weight reduction, increased physical activity, or both will delay (or prevent) the onset

of T2DM [137]. In addition, metformin [137], thiazolidinediones [208], and acarbose [209] will lower the risk of T2DM in people with IFG or IGT. Metformin, which has a primary mechanism of action of reducing hepatic glucose production, has been shown to reduce the progression of diabetes from IGT by approximately 31% in the DPP, of which 53% had the MetS [137]. Incidence of the MetS was also reduced by 17% in the metformin-treated group of the DPP, which was driven primarily by improvements in WC and fasting glucose, whereas, intensive therapeutic lifestyle changes reduced this risk by 58% compared to placebo [210]. Other cardiac risk factors, however, did not improve with metformin to the same degree as with the intensive lifestyle intervention [211]. The study trial has suggested that metformin is in fact treating IGT and not necessarily “preventing” progression to T2DM in the long-term follow-up [212]. In the Study to Prevent Non-Insulin Dependent Diabetes Mellitus (STOP-NIDDM) trial, acarbose, a drug that affects carbohydrate absorption and is approved for the treatment of T2DM, was also shown to reduce the progression to T2DM in individuals with IGT [209]. This trial also showed that acarbose treatment was in fact associated with reduced CVD and hypertension [213]. The main limitation of the use of this agent is its poor patient tolerability. Pioglitazone has been shown to reduce the multiple components of MetS such as high blood pressure, high blood glucose, and TGs in addition to a decrease in urinary albumin/creatinine ratio [214]. It was concluded that pioglitazone may be useful in the prevention of cardiovascular events in high risk patients with T2DM although the usefulness of this approach in MetS or IGT subjects is not clear. However, no clinical trial evidence is yet available to document that the oral hypoglycemic agents will lessen the risk for cardiovascular events in MetS, IGT, or IFG except for a preliminary trial with acarbose [213].

6.12. Hypercoagulable State. Measurement of CRP is the most practical way to assess the presence of an inflammatory state. An elevated CRP (≥ 3 mg/L) is an emerging risk factor for CVD [123]. The AHA and CDC [215] recently issued guidelines for the measurement of CRP in the clinical practice. They suggested that such measurements can be made at the physician's discretion, but testing should be limited to the individuals assessed to be at an intermediate risk by Framingham scoring, that is, those whose 10-year risk for CHD is in the range of 10% to 20%. Several drugs used to treat the other metabolic risk factors have been reported to reduce the CRP levels (e.g., statins, nicotinic acid, fibrates, ACE inhibitors, and thiazolidinediones) [216]. However, these drugs cannot be recommended specifically to reduce a proinflammatory state independent of their indications for the other risk factors. Furthermore, The Justification for the Use of statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial [217] has emphasized an added benefit of statin in targeting the individuals with high CRP levels even in the presence of normal LDL. Low-dose aspirin is frequently recommended to the patients with MetS [218]; however, the use of aspirin in the primary prevention of CVD should remain as an “individual clinical judgment”

[219]. Further, there is no evidence to indicate that the use of aspirin in low-risk groups (<6%) is beneficial, and the risk of haemorrhage outweighs the benefit in this category. Patients in the low intermediate risk group (6–10%) will need an individualized decision-making, whereas most patients in the conventional intermediate risk category (10–20%) should receive aspirin. Blaha et al. have advised that all older patients (≥ 65 years old) and patients at high Framingham risk with MetS should receive a low-dose aspirin in the absence of contraindications [220]. A recently published meta-analysis shows that aspirin significantly reduces the risk of first MI by a third, stroke by approximately one-third, and CVD by approximately one sixth [221].

7. Conclusion

MetS is defined by a constellation of interconnected physiological, biochemical, clinical, and metabolic factors that directly increases the risk of atherosclerotic cardiovascular disease, type 2 diabetes mellitus, and all cause mortality. Insulin resistance, visceral adiposity, atherogenic dyslipidemia, endothelial dysfunction, genetic susceptibility, elevated blood pressure, hypercoagulable state, and chronic stress are the several factors which constitute the metabolic syndrome. Lifestyle modification remains the initial intervention of choice for this population. Modern lifestyle modification therapy combines specific recommendations on diet and exercise with behavioural strategies. Pharmacological treatment should be considered for those whose risk factors are not adequately reduced with lifestyle changes.

A realistic goal for overweight/obese persons is to reduce the body weight by >7% to 10% over a period of 6 to 12 months. Weight reduction should be combined with a daily minimum of 30 minutes of moderate-intensity physical activity. Nutritional therapy calls for a low intake of saturated and total fat intake; reduced consumption of simple sugars and high glycemic index foods; and increased intakes of fruits, vegetables, legumes, and whole grains. Statins can be combined with fibrates and niacin to achieve the target levels of LDL-C, triglycerides, and HDL-C. Further, the majority of patients who need an antihypertensive therapy will likely need more than one agent for the proper blood pressure control with ACEI/ARBs and beta blockers/Thiazides/CCBs as the first and second line agents, respectively. Metformin, thiazolidinediones, and acarbose will lower the risk for type 2 diabetes mellitus in people with IFG or IGT.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

Acknowledgment

The author is grateful to all his patients who realized and encouraged him to write a review on metabolic syndrome.

References

- [1] K. G. M. M. Alberti, R. H. Eckel, S. M. Grundy et al., "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*, vol. 120, no. 16, pp. 1640–1645, 2009.
- [2] K. G. M. M. Alberti and P. Zimmet, "The metabolic syndrome—a new worldwide definition," *The Lancet*, vol. 366, no. 9491, pp. 1059–1062, 2005.
- [3] J. K. Olijhoek, Y. Van Der Graaf, J.-D. Banga, A. Algra, T. J. Rabelink, and F. L. J. Visseren, "The Metabolic Syndrome is associated with advanced vascular damage in patients with coronary heart disease, stroke, peripheral arterial disease or abdominal aortic aneurysm," *European Heart Journal*, vol. 25, no. 4, pp. 342–348, 2004.
- [4] S. M. Grundy, "Metabolic syndrome: connecting and reconciling cardiovascular and diabetes worlds," *Journal of the American College of Cardiology*, vol. 47, no. 6, pp. 1093–1100, 2006.
- [5] K. G. Alberti and P. Z. Zimmet, "Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation," *Diabetic Medicine*, vol. 15, no. 7, pp. 539–553, 1998.
- [6] B. Balkau and M. A. Charles, "Comment on the provisional report from the WHO consultation: European Group for the Study of Insulin Resistance (EGIR)," *Diabetic Medicine*, vol. 16, no. 5, pp. 442–443, 1999.
- [7] J. I. Cleeman, "Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III)," *Journal of the American Medical Association*, vol. 285, no. 19, pp. 2486–2497, 2001.
- [8] D. Einhorn, G. M. Reaven, R. H. Cobin et al., "American College of Endocrinology position statement on the insulin resistance syndrome," *Endocrine Practice*, vol. 9, no. 3, pp. 237–252, 2003.
- [9] International Diabetes Federation: The IDF consensus worldwide definition of the metabolic syndrome, <http://www.idf.org/metabolic-syndrome>.
- [10] J. E. Shaw and K. G. M. M. Alberti, "Point: impaired fasting glucose: the case for the new American Diabetes Association criterion," *Diabetes Care*, vol. 29, no. 5, pp. 1170–1172, 2006.
- [11] J. E. Shaw and D. J. Chisholm, "Epidemiology and prevention of type 2 diabetes and the metabolic syndrome," *Medical Journal of Australia*, vol. 179, no. 7, pp. 379–383, 2003.
- [12] E. Kylin, "Studien ueber das Hypertonie-Hyperglyca "mie-Hyperurika" miesyndrom," *Zentralblatt fuer Innere Medizin*, vol. 44, pp. 105–127, 1923.
- [13] J. Vague, "Sexual differentiation. A factor affecting the forms of obesity," *Presse Medicale*, vol. 30, pp. S39–S40, 1947.
- [14] P. Avogaro and G. Crepaldi, "Essential hyperlipidemia, obesity and diabetes," *Diabetologia*, vol. 1, p. 137, 1965.
- [15] G. M. Reaven, "Role of insulin resistance in human disease," *Diabetes*, vol. 37, no. 12, pp. 1595–1607, 1988.
- [16] N. M. Kaplan, "The deadly quartet. Upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension," *Archives of Internal Medicine*, vol. 149, no. 7, pp. 1514–1520, 1989.
- [17] S. M. Haffner, R. A. Valdez, H. P. Hazuda, B. D. Mitchell, P. A. Morales, and M. P. Stern, "Prospective analysis of the insulin-resistance syndrome (Syndrome X)," *Diabetes*, vol. 41, no. 6, pp. 715–722, 1992.
- [18] R. H. Eckel, S. M. Grundy, and P. Z. Zimmet, "The metabolic syndrome," *The Lancet*, vol. 365, no. 9468, pp. 1415–1428, 2005.
- [19] E. S. Ford, "Prevalence of the metabolic syndrome in US populations," *Endocrinology and Metabolism Clinics of North America*, vol. 33, no. 2, pp. 333–350, 2004.
- [20] S. M. Grundy, J. I. Cleeman, S. R. Daniels et al., "Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement," *Circulation*, vol. 112, no. 17, pp. 2735–2752, 2005.
- [21] P. W. F. Wilson, R. B. D'Agostino, H. Parise, L. Sullivan, and J. B. Meigs, "Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus," *Circulation*, vol. 112, no. 20, pp. 3066–3072, 2005.
- [22] S. A. Ritchie and J. M. C. Connell, "The link between abdominal obesity, metabolic syndrome and cardiovascular disease," *Nutrition, Metabolism and Cardiovascular Diseases*, vol. 17, no. 4, pp. 319–326, 2007.
- [23] S. Desroches and B. Lamarche, "The evolving definitions and increasing prevalence of the metabolic syndrome," *Applied Physiology, Nutrition and Metabolism*, vol. 32, no. 1, pp. 23–32, 2007.
- [24] G. D. Kolovou, K. K. Anagnostopoulou, K. D. Salpea, and D. P. Mikhailidis, "The prevalence of metabolic syndrome in various populations," *The American Journal of the Medical Sciences*, vol. 333, no. 6, pp. 362–371, 2007.
- [25] A. J. Cameron, J. E. Shaw, and P. Z. Zimmet, "The metabolic syndrome: prevalence in worldwide populations," *Endocrinology and Metabolism Clinics of North America*, vol. 33, no. 2, pp. 351–375, 2004.
- [26] Y.-W. Park, S. Zhu, L. Palaniappan, S. Heshka, M. R. Carnethon, and S. B. Heymsfield, "The metabolic syndrome: prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988–1994," *Archives of Internal Medicine*, vol. 163, no. 4, pp. 427–436, 2003.
- [27] E. S. Ford, W. H. Giles, and W. H. Dietz, "Prevalence of the metabolic syndrome among US adults: findings from the Third National Health and Nutrition Examination Survey," *Journal of the American Medical Association*, vol. 287, no. 3, pp. 356–359, 2002.
- [28] A. Ponholzer, C. Temml, M. Rauchenwald, M. Marszalek, and S. Madersbacher, "Is the metabolic syndrome a risk factor for female sexual dysfunction in sexually active women?" *International Journal of Impotence Research*, vol. 20, no. 1, pp. 100–104, 2008.
- [29] P. W. F. Wilson, W. B. Kannel, H. Silbershatz, and R. B. D'Agostino, "Clustering of metabolic factors and coronary heart disease," *Archives of Internal Medicine*, vol. 159, no. 10, pp. 1104–1109, 1999.
- [30] L. Palaniappan, M. R. Carnethon, Y. Wang et al., "Predictors of the incident metabolic syndrome in adults: The Insulin Resistance Atherosclerosis Study," *Diabetes Care*, vol. 27, no. 3, pp. 788–793, 2004.
- [31] M. P. Reilly and D. J. Rader, "The metabolic syndrome: more than the sum of its parts?" *Circulation*, vol. 108, no. 13, pp. 1546–1551, 2003.
- [32] E. A. Andreadis, G. I. Tsourous, C. K. Tzavara et al., "Metabolic syndrome and incident cardiovascular morbidity and mortality

- in a Mediterranean hypertensive population," *The American Journal of Hypertension*, vol. 20, no. 5, pp. 558–564, 2007.
- [33] N. Halberg, I. Wernstedt-Asterholm, and P. E. Scherer, "The adipocyte as an endocrine cell," *Endocrinology and Metabolism Clinics of North America*, vol. 37, no. 3, pp. 753–768, 2008.
- [34] S. Cinti, G. Mitchell, G. Barbatelli et al., "Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans," *Journal of Lipid Research*, vol. 46, no. 11, pp. 2347–2355, 2005.
- [35] D. C. W. Lau, B. Dhillon, H. Yan, P. E. Szmitko, and S. Verma, "Adipokines: molecular links between obesity and atherosclerosis," *The American Journal of Physiology—Heart and Circulatory Physiology*, vol. 288, no. 5, pp. H2031–H2041, 2005.
- [36] P. Trayhurn and I. S. Wood, "Adipokines: inflammation and the pleiotropic role of white adipose tissue," *British Journal of Nutrition*, vol. 92, no. 3, pp. 347–355, 2004.
- [37] U. Saleem, M. Khaleghi, N. G. Morgenthaler et al., "Plasma carboxy-terminal provasopressin (copeptin): a novel marker of insulin resistance and metabolic syndrome," *Journal of Clinical Endocrinology and Metabolism*, vol. 94, no. 7, pp. 2558–2564, 2009.
- [38] S. Tsimikas, J. Willeit, M. Knoflach et al., "Lipoprotein-associated phospholipase A2 activity, ferritin levels, metabolic syndrome, and 10-year cardiovascular and non-cardiovascular mortality: results from the Bruneck study," *European Heart Journal*, vol. 30, no. 1, pp. 107–115, 2009.
- [39] M. Jacobs, M. M. J. Van Greevenbroek, C. J. H. Van Der Kallen et al., "Low-grade inflammation can partly explain the association between the metabolic syndrome and either coronary artery disease or severity of peripheral arterial disease: the CODAM study," *European Journal of Clinical Investigation*, vol. 39, no. 6, pp. 437–444, 2009.
- [40] J. M. Miles and M. D. Jensen, "Counterpoint: visceral adiposity is not causally related to insulin resistance," *Diabetes Care*, vol. 28, no. 9, pp. 2326–2328, 2005.
- [41] G. Boden, B. Lebed, M. Schatz, C. Homko, and S. Lemieux, "Effects of acute changes of plasma free fatty acids on intramyocellular fat content and insulin resistance in healthy subjects," *Diabetes*, vol. 50, no. 7, pp. 1612–1617, 2001.
- [42] S. E. Kahn, R. L. Prigeon, R. S. Schwartz et al., "Obesity, body fat distribution, insulin sensitivity and islet β -cell function as explanations for metabolic diversity," *Journal of Nutrition*, vol. 131, no. 2, pp. 354S–360S, 2001.
- [43] A. M. Xydakis, C. C. Case, P. H. Jones et al., "Adiponectin, inflammation, and the expression of the metabolic syndrome in obese individuals: the impact of rapid weight loss through caloric restriction," *Journal of Clinical Endocrinology and Metabolism*, vol. 89, no. 6, pp. 2697–2703, 2004.
- [44] G. S. Hotamisligil, P. Peraldi, A. Budavari, R. Ellis, M. F. White, and B. M. Spiegelman, "IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF- α and obesity-induced insulin resistance," *Science*, vol. 271, no. 5249, pp. 665–668, 1996.
- [45] R. M. Krauss, "Lipids and lipoproteins in patients with type 2 diabetes," *Diabetes Care*, vol. 27, no. 6, pp. 1496–1504, 2004.
- [46] A. Soto González, D. Bellido Guerrero, M. Buño Soto, S. Pértiga Díaz, M. Martínez-Olmos, and O. Vidal, "Metabolic syndrome, insulin resistance and the inflammation markers C-reactive protein and ferritin," *European Journal of Clinical Nutrition*, vol. 60, no. 6, pp. 802–809, 2006.
- [47] R. Deepa, K. Velmurugan, K. Arvind et al., "Serum levels of interleukin 6, C-reactive protein, vascular cell adhesion molecule 1, and monocyte chemoattractant protein 1 in relation to insulin resistance and glucose intolerance—the Chennai Urban Rural Epidemiology Study (CURES)," *Metabolism*, vol. 55, no. 9, pp. 1232–1238, 2006.
- [48] S. Guldiken, M. Demir, E. Arikan et al., "The levels of circulating markers of atherosclerosis and inflammation in subjects with different degrees of body mass index: soluble CD40 ligand and high-sensitivity C-reactive protein," *Thrombosis Research*, vol. 119, no. 1, pp. 79–84, 2007.
- [49] T. McLaughlin, F. Abbasi, C. Lamendola et al., "Differentiation between obesity and insulin resistance in the association with C-reactive protein," *Circulation*, vol. 106, no. 23, pp. 2908–2912, 2002.
- [50] P. M. Ridker, J. E. Buring, N. R. Cook, and N. Rifai, "C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women," *Circulation*, vol. 107, no. 3, pp. 391–397, 2003.
- [51] M. B. Clearfield, "C-reactive protein: a new risk assessment tool for cardiovascular disease," *Journal of the American Osteopathic Association*, vol. 105, no. 9, pp. 409–416, 2005.
- [52] B. K. Pedersen, A. Steensberg, C. Fischer et al., "Searching for the exercise factor: is IL-6 a candidate?" *Journal of Muscle Research and Cell Motility*, vol. 24, no. 2–3, pp. 113–119, 2003.
- [53] K. Stenlöf, I. Wernstedt, T. Fjällman, V. Wallenius, K. Wallenius, and J.-O. Jansson, "Interleukin-6 levels in the central nervous system are negatively correlated with fat mass in overweight/obese subjects," *Journal of Clinical Endocrinology and Metabolism*, vol. 88, no. 9, pp. 4379–4383, 2003.
- [54] M. Diamant, H. J. Lamb, M. A. Van De Ree et al., "The association between abdominal visceral fat and carotid stiffness is mediated by circulating inflammatory markers in uncomplicated type 2 diabetes," *Journal of Clinical Endocrinology and Metabolism*, vol. 90, no. 3, pp. 1495–1501, 2005.
- [55] A. D. Pradhan, J. E. Manson, N. Rifai, J. E. Buring, and P. M. Ridker, "C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus," *Journal of the American Medical Association*, vol. 286, no. 3, pp. 327–334, 2001.
- [56] G. Zuliani, S. Volpato, A. Blè et al., "High interleukin-6 plasma levels are associated with low HDL-C levels in community-dwelling older adults: the InChianti study," *Atherosclerosis*, vol. 192, no. 2, pp. 384–390, 2007.
- [57] M.-C. Alessi and I. Juhan-Vague, "PAI-1 and the metabolic syndrome: links, causes, and consequences," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 26, no. 10, pp. 2200–2207, 2006.
- [58] M. Cigolini, G. Targher, I. A. B. Andreis, M. Tonoli, G. Agostino, and G. De Sandre, "Visceral fat accumulation and its relation to plasma hemostatic factors in healthy men," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 16, no. 3, pp. 368–374, 1996.
- [59] M. C. Alessi and I. Juhan-Vague, "Contribution of PAI-1 in cardiovascular pathology," *Archives des Maladies du Cœur et des Vaisseaux*, vol. 97, no. 6, pp. 673–678, 2004.
- [60] H. P. Kohler and P. J. Grant, "Plasminogen-activator inhibitor type 1 and coronary artery disease," *The New England Journal of Medicine*, vol. 342, no. 24, pp. 1792–1801, 2000.
- [61] M. Liu and F. Liu, "Transcriptional and post-translational regulation of adiponectin," *Biochemical Journal*, vol. 425, no. 1, pp. 41–52, 2010.
- [62] Y. Matsuzawa, T. Funahashi, S. Kihara, and I. Shimomura, "Adiponectin and metabolic syndrome," *Arteriosclerosis*,

- Thrombosis, and Vascular Biology*, vol. 24, no. 1, pp. 29–33, 2004.
- [63] T. Kazumi, A. Kawaguchi, K. Sakai, T. Hirano, and G. Yoshino, “Young men with high-normal blood pressure have lower serum adiponectin, smaller LDL size, and higher elevated heart rate than those with optimal blood pressure,” *Diabetes Care*, vol. 25, no. 6, pp. 971–976, 2002.
- [64] T. Pischon, C. J. Girman, G. S. Hotamisligil, N. Rifai, F. B. Hu, and E. B. Rimm, “Plasma adiponectin levels and risk of myocardial infarction in men,” *Journal of the American Medical Association*, vol. 291, no. 14, pp. 1730–1737, 2004.
- [65] F. Fumeron, R. Aubert, A. Siddiq et al., “Adiponectin gene polymorphisms and adiponectin levels are independently associated with the development of hyperglycemia during a 3-year period: the epidemiologic data on the insulin resistance syndrome prospective study,” *Diabetes*, vol. 53, no. 4, pp. 1150–1157, 2004.
- [66] H.-S. Lee, M. Lee, and H. Joung, “Adiponectin represents an independent risk factor for hypertension in middle aged Korean women,” *Asia Pacific Journal of Clinical Nutrition*, vol. 16, no. 1, pp. 10–15, 2007.
- [67] N. Maeda, M. Takahashi, T. Funahashi et al., “PPAR γ ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein,” *Diabetes*, vol. 50, no. 9, pp. 2094–2099, 2001.
- [68] M. Fasshauer, S. Kralisch, M. Klier et al., “Adiponectin gene expression and secretion is inhibited by interleukin-6 in 3T3-L1 adipocytes,” *Biochemical and Biophysical Research Communications*, vol. 301, no. 4, pp. 1045–1050, 2003.
- [69] S. Engeli, M. Feldpausch, K. Gorzelnik et al., “Association between adiponectin and mediators of inflammation in obese women,” *Diabetes*, vol. 52, no. 4, pp. 942–947, 2003.
- [70] N. Ouchi, S. Kihara, Y. Arita et al., “Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF- κ B signaling through a cAMP-dependent pathway,” *Circulation*, vol. 102, no. 11, pp. 1296–1301, 2000.
- [71] L. Hutley and J. B. Prins, “Fat as an endocrine organ: relationship to the metabolic syndrome,” *The American Journal of the Medical Sciences*, vol. 330, no. 6, pp. 280–289, 2005.
- [72] M. Carlyle, O. B. Jones, J. J. Kuo, and J. E. Hall, “Chronic cardiovascular and renal actions of leptin: role of adrenergic activity,” *Hypertension*, vol. 39, no. 2, pp. 496–501, 2002.
- [73] N. Eikelis, M. Schlaich, A. Aggarwal, D. Kaye, and M. Esler, “Interactions between leptin and the human sympathetic nervous system,” *Hypertension*, vol. 41, no. 5, pp. 1072–1079, 2003.
- [74] A. J. Marsh, M. A. P. Fontes, S. Killinger, D. B. Pawlak, J. W. Polson, and R. A. L. Dampney, “Cardiovascular responses evoked by leptin acting on neurons in the ventromedial and dorsomedial hypothalamus,” *Hypertension*, vol. 42, no. 4, pp. 488–493, 2003.
- [75] T. Shirasaka, M. Takasaki, and H. Kannan, “Cardiovascular effects of leptin and orexins,” *The American Journal of Physiology—Regulatory Integrative and Comparative Physiology*, vol. 284, no. 3, pp. R639–R651, 2003.
- [76] R. V. Considine, M. K. Sinha, M. L. Heiman et al., “Serum immunoreactive-leptin concentrations in normal-weight and obese humans,” *The New England Journal of Medicine*, vol. 334, no. 5, pp. 292–295, 1996.
- [77] D. M. Bravata, C. K. Wells, J. Concato, W. N. Kernan, L. M. Brass, and B. I. Gulanski, “Two measures of insulin sensitivity provided similar information in a U.S. population,” *Journal of Clinical Epidemiology*, vol. 57, no. 11, pp. 1214–1217, 2004.
- [78] D. G. Carey, A. B. Jenkins, L. V. Campbell, J. Freund, and D. J. Chisholm, “Abdominal fat and insulin resistance in normal and overweight women: direct measurements reveal a strong relationship in subjects at both low and high risk of NIDDM,” *Diabetes*, vol. 45, no. 5, pp. 633–638, 1996.
- [79] E. J. Mayer-Davis, R. D’Agostino Jr., A. J. Karter et al., “Intensity and amount of physical activity in relation to insulin sensitivity the Insulin Resistance Atherosclerosis Study,” *Journal of the American Medical Association*, vol. 279, no. 9, pp. 669–674, 1998.
- [80] B. Vessby, M. Uusitupa, K. Hermansen et al., “Substituting dietary saturated for monounsaturated fat impairs insulin sensitivity in healthy men and women: the KANWU study,” *Diabetologia*, vol. 44, no. 3, pp. 312–319, 2001.
- [81] H. Gill, M. Mugo, A. Whaley-Connell, C. Stump, and J. R. Sowers, “The key role of insulin resistance in the cardiometabolic syndrome,” *The American Journal of the Medical Sciences*, vol. 330, no. 6, pp. 290–294, 2005.
- [82] K. F. Petersen and G. I. Shulman, “Etiology of insulin resistance,” *The American Journal of Medicine*, vol. 119, no. 5, pp. S10–S16, 2006.
- [83] M. D. Jensen, M. W. Haymond, R. A. Rizza, P. E. Cryer, and J. M. Miles, “Influence of body fat distribution on free fatty acid metabolism in obesity,” *Journal of Clinical Investigation*, vol. 83, no. 4, pp. 1168–1173, 1989.
- [84] G. F. Lewis and G. Steiner, “Acute effects of insulin in the control of VLDL production in humans: implications for the insulin-resistant state,” *Diabetes Care*, vol. 19, no. 4, pp. 390–393, 1996.
- [85] H. N. Ginsberg, Y.-L. Zhang, and A. Hernandez-Ono, “Regulation of plasma triglycerides in insulin resistance and diabetes,” *Archives of Medical Research*, vol. 36, no. 3, pp. 232–240, 2005.
- [86] E. Ferrannini and A. Natali, “Essential hypertension, metabolic disorders, and insulin resistance,” *The American Heart Journal*, vol. 121, no. 4, pp. 1274–1282, 1991.
- [87] A. Malhotra, B. P. S. Kang, S. Cheung, D. Opawumi, and L. G. Meggs, “Angiotensin II promotes glucose-induced activation of cardiac protein kinase C isozymes and phosphorylation of troponin I,” *Diabetes*, vol. 50, no. 8, pp. 1918–1926, 2001.
- [88] S. A. Morse, R. Zhang, V. Thakur, and E. Reisin, “Hypertension and the metabolic syndrome,” *The American Journal of the Medical Sciences*, vol. 330, no. 6, pp. 303–310, 2005.
- [89] A. M. Briones, A. N. D. Cat, G. E. Callera et al., “Adipocytes produce aldosterone through calcineurin-dependent signaling pathways: implications in diabetes mellitus-associated obesity and vascular dysfunction,” *Hypertension*, vol. 59, no. 5, pp. 1069–1078, 2012.
- [90] J. M. Ordovas, “Genetic links between diabetes mellitus and coronary atherosclerosis,” *Current Atherosclerosis Reports*, vol. 9, no. 3, pp. 204–210, 2007.
- [91] G. Perseghin, S. Ghosh, K. Gerow, and G. I. Shulman, “Metabolic defects in lean nondiabetic offspring of NIDDM parents: a cross-sectional study,” *Diabetes*, vol. 46, no. 6, pp. 1001–1009, 1997.
- [92] N. Abate, M. Chandalia, P. G. Snell, and S. M. Grundy, “Adipose tissue metabolites and insulin resistance in nondiabetic Asian Indian men,” *Journal of Clinical Endocrinology and Metabolism*, vol. 89, no. 6, pp. 2750–2755, 2004.
- [93] L. J. Martin, K. E. North, T. Dyer, J. Blangero, A. G. Comuzzie, and J. Williams, “Phenotypic, genetic, and genome-wide structure in the metabolic syndrome,” *BMC Genetics*, vol. 4, supplement 1, article S95, 2003.

- [94] M. Laakso, "Gene variants, insulin resistance, and dyslipidaemia," *Current Opinion in Lipidology*, vol. 15, no. 2, pp. 115–120, 2004.
- [95] P. Poulsen, K. Levin, I. Petersen, K. Christensen, H. Beck-Nielsen, and A. Vaag, "Heritability of insulin secretion, peripheral and hepatic insulin action, and intracellular glucose partitioning in young and old Danish twins," *Diabetes*, vol. 54, no. 1, pp. 275–283, 2005.
- [96] J. V. Neel, "Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"?" *The American Journal of Human Genetics*, vol. 14, pp. 353–362, 1962.
- [97] C. N. Hales and D. J. P. Barker, "Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis," *Diabetologia*, vol. 35, no. 7, pp. 595–601, 1992.
- [98] C. N. Hales, M. Desai, and S. E. Ozanne, "The thrifty phenotype hypothesis: how does it look after 5 years?" *Diabetic Medicine*, vol. 14, no. 3, pp. 189–195, 1997.
- [99] F. Locatelli, P. Pozzoni, and L. Del Vecchio, "Renal manifestations in the metabolic syndrome," *Journal of the American Society of Nephrology*, vol. 17, no. 4, supplement 2, pp. S81–S85, 2006.
- [100] K. D. Bruce and C. D. Byrne, "The metabolic syndrome: common origins of a multifactorial disorder," *Postgraduate Medical Journal*, vol. 85, no. 1009, pp. 614–621, 2009.
- [101] T. Padhi and Garima, "Metabolic syndrome and skin: psoriasis and beyond," *Indian Journal of Dermatology*, vol. 58, no. 3, pp. 299–305, 2013.
- [102] R. Chopra, A. Chander, and J. J. Jacob, "Ocular associations of metabolic syndrome," *Indian Journal of Endocrinology and Metabolism*, vol. 16, supplement 1, pp. S6–S11, 2012.
- [103] J. C. M. Lam and S. M. I. Mary, "Sleep & the metabolic syndrome," *Indian Journal of Medical Research*, vol. 131, no. 2, pp. 206–216, 2010.
- [104] A. Dokras, M. Bochner, E. Hollinrake, S. Markham, B. Van Voorhis, and D. H. Jagasia, "Screening women with polycystic ovary syndrome for metabolic syndrome," *Obstetrics and Gynecology*, vol. 106, no. 1, pp. 131–137, 2005.
- [105] E. Standl, "Aetiology and consequences of the metabolic syndrome," *European Heart Journal, Supplement*, vol. 7, supplement D, pp. D10–D13, 2005.
- [106] Y. Handelsman, "Metabolic syndrome pathophysiology and clinical presentation," *Toxicologic Pathology*, vol. 37, no. 1, pp. 18–20, 2009.
- [107] L. G. Kraemer-Aguiar, C. M. Laflor, and E. Bouskela, "Skin microcirculatory dysfunction is already present in normoglycemic subjects with metabolic syndrome," *Metabolism*, vol. 57, no. 12, pp. 1740–1746, 2008.
- [108] G. K. Hansson, "Mechanisms of disease: inflammation, atherosclerosis, and coronary artery disease," *The New England Journal of Medicine*, vol. 352, no. 16, pp. 1685–1695, 2005.
- [109] D. G. Harrison, "Cellular and molecular mechanisms of endothelial cell dysfunction," *Journal of Clinical Investigation*, vol. 100, no. 9, pp. 2153–2157, 1997.
- [110] S. M. Grundy, "Obesity, metabolic syndrome, and cardiovascular disease," *Journal of Clinical Endocrinology and Metabolism*, vol. 89, no. 6, pp. 2595–2600, 2004.
- [111] A. Aljada, P. Mohanty, H. Ghanim et al., "Increase in intranuclear nuclear factor κ B and decrease in inhibitor κ B in mononuclear cells after a mixed meal: evidence for a proinflammatory effect," *The American Journal of Clinical Nutrition*, vol. 79, no. 4, pp. 682–690, 2004.
- [112] P. Dandona, A. Aljada, A. Chaudhuri, P. Mohanty, and R. Garg, "Metabolic syndrome: a comprehensive perspective based on interactions between obesity, diabetes, and inflammation," *Circulation*, vol. 111, no. 11, pp. 1448–1454, 2005.
- [113] E. Charmandari, C. Tsigos, and G. Chrousos, "Endocrinology of the stress response," *Annual Review of Physiology*, vol. 67, pp. 259–284, 2005.
- [114] C.-N. Wang, R. S. McLeod, Z. Yao, and D. N. Brindley, "Effects of dexamethasone on the synthesis, degradation, and secretion of apolipoprotein B in cultured rat hepatocytes," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 15, no. 9, pp. 1481–1491, 1995.
- [115] D. Argaud, Q. Zhang, W. Pan, S. Maitra, S. J. Pilkis, and A. J. Lange, "Regulation of rat liver glucose-6-phosphatase gene expression in different nutritional and hormonal states: gene structure and 5'-flanking sequence," *Diabetes*, vol. 45, no. 11, pp. 1563–1571, 1996.
- [116] H. Hauner, G. Entenmann, M. Wabitsch et al., "Promoting effect of glucocorticoids on the differentiation of human adipocyte precursor cells cultured in a chemically defined medium," *Journal of Clinical Investigation*, vol. 84, no. 5, pp. 1663–1670, 1989.
- [117] C. Grunfeld and D. S. Jones, "Glucocorticoid-induced insulin resistance in vitro: inhibition of insulin-stimulated methylaminoisobutyric acid uptake," *Hormone and Metabolic Research*, vol. 18, no. 3, pp. 149–152, 1986.
- [118] C. Guillaume-Gentil, F. Assimacopoulos-Jeannet, and B. Jeanrenaud, "Involvement of non-esterified fatty acid oxidation in glucocorticoid-induced peripheral insulin resistance *in vivo* in rats," *Diabetologia*, vol. 36, no. 10, pp. 899–906, 1993.
- [119] R. Andrew, C. R. Gale, B. R. Walker, J. R. Seckl, and C. N. Martyn, "Glucocorticoid metabolism and the metabolic syndrome: associations in an elderly cohort," *Experimental and Clinical Endocrinology and Diabetes*, vol. 110, no. 6, pp. 284–290, 2002.
- [120] G. P. Chrousos, "Stress and disorders of the stress system," *Nature Reviews Endocrinology*, vol. 5, no. 7, pp. 374–381, 2009.
- [121] N. D. Wong, "Intensified screening and treatment of the metabolic syndrome for cardiovascular risk reduction," *Preventive Cardiology*, vol. 8, no. 1, pp. 47–54, 2005.
- [122] D. Deen, "Metabolic syndrome: time for action," *The American Family Physician*, vol. 69, no. 12, pp. 2875–2887, 2004.
- [123] "National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult treatment panel III) final report," *Circulation*, vol. 106, no. 25, pp. 3143–3421, 2002.
- [124] A. V. Chobanian, G. L. Bakris, H. R. Black et al., "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 Report," *Journal of the American Medical Association*, vol. 289, no. 19, pp. 2560–2572, 2003.
- [125] "American Diabetes Association. Clinical practice recommendations 2005," *Diabetes Care*, vol. 28, supplement 1, pp. S1–S9, 2005.
- [126] "Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. The Evidence Report. National Institutes of Health," *Obesity Research*, vol. 6, supplement 2, pp. 51S–209S, 1998.

- [127] S. Bellentani, R. D. Grave, A. Suppini et al., "Behavior therapy for nonalcoholic fatty liver disease: the need for a multidisciplinary approach," *Hepatology*, vol. 47, no. 2, pp. 746–754, 2008.
- [128] K. A. Donato, "Executive summary of the clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults," *Archives of Internal Medicine*, vol. 158, no. 17, pp. 1855–1867, 1998.
- [129] G. E. Duncan, M. G. Perri, D. W. Theriaque, A. D. Hutson, R. H. Eckel, and P. W. Stacpoole, "Exercise training, without weight loss, increases insulin sensitivity and postheparin plasma lipase activity in previously sedentary adults," *Diabetes Care*, vol. 26, no. 3, pp. 557–562, 2003.
- [130] L. F. Van Gaal, M. A. Wauters, and I. H. De Leeuw, "The beneficial effects of modest weight loss on cardiovascular risk factors," *International Journal of Obesity*, vol. 21, supplement 1, pp. S5–S9, 1997.
- [131] P. K. Whelton, L. J. Appel, M. A. Espeland et al., "Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). TONE Collaborative Research Group," *Journal of the American Medical Association*, vol. 279, no. 11, pp. 839–846, 1998.
- [132] R. R. Wing, R. Koeske, L. H. Epstein, M. P. Nowalk, W. Gooding, and D. Becker, "Long-term effects of modest weight loss in type II diabetic patients," *Archives of Internal Medicine*, vol. 147, no. 10, pp. 1749–1753, 1987.
- [133] R. Ross, I. Janssen, J. Dawson et al., "Exercise-induced reduction in obesity and insulin resistance in women: a randomized controlled trial," *Obesity Research*, vol. 12, no. 5, pp. 789–798, 2004.
- [134] J. O. Hill and H. R. Wyatt, "Role of physical activity in preventing and treating obesity," *Journal of Applied Physiology*, vol. 99, no. 2, pp. 765–770, 2005.
- [135] D. W. Haslam and W. P. T. James, "Obesity," *The Lancet*, vol. 366, no. 9492, pp. 1197–1209, 2005.
- [136] J. Toumilheto, J. Lindstrom, J. G. Eriksson et al., "Prevention of type 2 diabetes mellitus with lifestyle intervention or metformin," *The New England Journal of Medicine*, vol. 344, no. 18, pp. 1343–1350, 2001.
- [137] W. C. Knowler, E. Barrett-Connor, S. E. Fowler et al., "Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin," *The New England Journal of Medicine*, vol. 346, no. 6, pp. 393–403, 2002.
- [138] A. Tortosa, M. Bes-Rastrollo, A. Sanchez-Villegas, F. J. Basterra-Gortari, J. M. Nñez-Cordoba, and M. A. Martinez-Gonzalez, "Mediterranean diet inversely associated with the incidence of metabolic syndrome: the SUN prospective cohort," *Diabetes Care*, vol. 30, no. 11, pp. 2957–2959, 2007.
- [139] L. Landaeta-Diaz, J. M. Fernandez, M. Da Silva-Grigoletto et al., "Mediterranean diet, moderate-to-high intensity training, and health-related quality of life in adults with metabolic syndrome," *European Journal of Preventive Cardiology*, vol. 20, no. 4, pp. 555–564, 2013.
- [140] K. Paletas, E. Athanasiadou, M. Sarigianni et al., "The protective role of the mediterranean diet on the prevalence of metabolic syndrome in a population of greek obese subjects," *Journal of the American College of Nutrition*, vol. 29, no. 1, pp. 41–45, 2010.
- [141] N. Babio, M. Bulló, J. Basora et al., "Adherence to the Mediterranean diet and risk of metabolic syndrome and its components," *Nutrition, Metabolism and Cardiovascular Diseases*, vol. 19, no. 8, pp. 563–570, 2009.
- [142] L. F. Lien, A. J. Brown, J. D. Ard et al., "Effects of PREMIER lifestyle modifications on participants with and without the metabolic syndrome," *Hypertension*, vol. 50, no. 4, pp. 609–616, 2007.
- [143] A. Garg, J. P. Bantle, R. R. Henry et al., "Effects of varying carbohydrate content of diet in patients with non-insulin-dependent diabetes mellitus," *Journal of the American Medical Association*, vol. 271, no. 18, pp. 1421–1428, 1994.
- [144] W. E. Mitch, "Beneficial responses to modified diets in treating patients with chronic kidney disease," *Kidney International, Supplement*, vol. 67, no. 94, pp. S133–S135, 2005.
- [145] A. N. Fabricatore, "Behavior therapy and cognitive-behavioral therapy of obesity: is there a difference?" *Journal of the American Dietetic Association*, vol. 107, no. 1, pp. 92–99, 2007.
- [146] R. R. Wing, R. W. Jeffery, L. R. Burton, C. Thorson, K. S. Nissinoff, and J. E. Baxter, "Food provision vs structured meal plans in the behavioral treatment of obesity," *International Journal of Obesity*, vol. 20, no. 1, pp. 56–62, 1996.
- [147] T. A. Wadden, M. L. Butryn, and K. J. Byrne, "Efficacy of lifestyle modification for long-term weight control," *Obesity Research*, vol. 12, no. S12, pp. 151S–162S, 2004.
- [148] A. G. Johnson, T. V. Nguyen, and D. Davis, "Blood pressure is linked to salt intake and modulated by the angiotensinogen gene in normotensive and hypertensive elderly subjects," *Journal of Hypertension*, vol. 19, no. 6, pp. 1053–1060, 2001.
- [149] J. He, L. G. Ogden, S. Vupputuri, L. A. Bazzano, C. Loria, and P. K. Whelton, "Dietary sodium intake and subsequent risk of cardiovascular disease in overweight adults," *Journal of the American Medical Association*, vol. 282, no. 21, pp. 2027–2034, 1999.
- [150] J. He, L. G. Ogden, L. A. Bazzano, S. Vupputuri, C. Loria, and P. K. Whelton, "Dietary sodium intake and incidence of congestive heart failure in overweight US men and women: first national health and nutrition examination survey epidemiologic follow-up study," *Archives of Internal Medicine*, vol. 162, no. 14, pp. 1619–1624, 2002.
- [151] L. J. Appel, M. W. Brands, S. R. Daniels, N. Karanja, P. J. Elmer, and F. M. Sacks, "Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association," *Hypertension*, vol. 47, no. 2, pp. 296–308, 2006.
- [152] P. K. Whelton, J. He, J. A. Cutler et al., "Effects of oral potassium on blood pressure: meta-analysis of randomized controlled clinical trials," *Journal of the American Medical Association*, vol. 277, no. 20, pp. 1624–1632, 1997.
- [153] American Diabetes Association, "Evidence based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications," *Diabetes Care*, vol. 25, no. 1, pp. 202–212, 2002.
- [154] D. J. A. Jenkins, C. W. C. Kendall, L. S. A. Augustin et al., "Glycemic index: overview of implications in health and disease," *The American Journal of Clinical Nutrition*, vol. 76, no. 1, pp. 266S–273S, 2002.
- [155] N. M. McKeown, J. B. Meigs, S. Liu, E. Saltzman, P. W. F. Wilson, and P. F. Jacques, "Carbohydrate nutrition, insulin resistance, and the prevalence of the metabolic syndrome in the Framingham Offspring Cohort," *Diabetes Care*, vol. 27, no. 2, pp. 538–546, 2004.
- [156] P. D. Thompson, D. Buchner, I. L. Piña et al., "Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the council on clinical cardiology (subcommittee on exercise, rehabilitation, and

- prevention) and the council on nutrition, physical activity, and metabolism (subcommittee on physical activity)," *Circulation*, vol. 107, no. 24, pp. 3109–3116, 2003.
- [157] S. M. Grundy, B. Hansen, S. C. Smith Jr., J. I. Cleeman, and R. A. Kahn, "American Heart Association; National Heart, Lung, and Blood Institute; American Diabetes Association. Clinical management of metabolic syndrome: report of the American Heart Association/National Heart, Lung, and Blood Institute/American Diabetes Association conference on scientific issues related to management," *Circulation*, vol. 109, no. 4, pp. 551–556, 2004.
- [158] M. L. Pollock, B. A. Franklin, G. J. Balady et al., "Resistance exercise in individuals with and without cardiovascular disease: benefits, rationale, safety, and prescription: an advisory from the Committee on Exercise, Rehabilitation, and Prevention, Council on Clinical Cardiology, American Heart Association," *Circulation*, vol. 101, no. 7, pp. 828–833, 2000.
- [159] The Diabetes Prevention Program Research Group, "The Diabetes Prevention Program (DPP): description of lifestyle intervention," *Diabetes Care*, vol. 25, no. 12, pp. 2165–2171, 2002.
- [160] W. L. Haskell, I.-M. Lee, R. R. Pate et al., "Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association," *Circulation*, vol. 116, no. 9, pp. 1081–1093, 2007.
- [161] B. H. Goodpaster, J. He, S. Watkins, and D. E. Kelley, "Skeletal muscle lipid content and insulin resistance: evidence for a paradox in endurance-trained athletes," *Journal of Clinical Endocrinology and Metabolism*, vol. 86, no. 12, pp. 5755–5761, 2001.
- [162] C. A. Slentz, B. D. Duscha, J. L. Johnson et al., "Effects of the amount of exercise on body weight, body composition, and measures of central obesity: STRRIDE—a randomized controlled study," *Archives of Internal Medicine*, vol. 164, no. 1, pp. 31–39, 2004.
- [163] R. R. Pate, M. Pratt, S. N. Blair et al., "Physical activity and public health: a recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine," *Journal of the American Medical Association*, vol. 273, no. 5, pp. 402–407, 1995.
- [164] E. S. Ford, H. W. Kohl III, A. H. Mokdad, and U. A. Ajani, "Sedentary behavior, physical activity, and the metabolic syndrome among U.S. adults," *Obesity Research*, vol. 13, no. 3, pp. 608–614, 2005.
- [165] J. P. Koplan and W. H. Dietz, "Caloric imbalance and public health policy," *Journal of the American Medical Association*, vol. 282, no. 16, pp. 1579–1581, 1999.
- [166] R. R. Wing, "Behavioral weight control," in *Handbook of Obesity Treatment*, T. A. Wadden and A. J. Stunkard, Eds., pp. 301–316, Guildford Press, New York, NY, USA, 2002.
- [167] T. A. Wadden, B. G. McGuckin, R. A. Rothman, and S. L. Sargent, "Lifestyle modification in the management of obesity," *Journal of Gastrointestinal Surgery*, vol. 7, no. 4, pp. 452–463, 2003.
- [168] C. K. B. Ferrari, "Functional foods and physical activities in health promotion of aging people," *Maturitas*, vol. 58, no. 4, pp. 327–339, 2007.
- [169] P. W. F. Wilson and S. M. Grundy, "The metabolic syndrome practical guide to origins and treatment: part I," *Circulation*, vol. 108, no. 12, pp. 1422–1424, 2003.
- [170] G. J. Krejcs, "Metabolic benefits associated with sibutramine therapy," *International Journal of Obesity*, vol. 26, supplement 4, pp. S34–S37, 2002.
- [171] J. M. Miles, L. Leiter, P. Hollander et al., "Effect of orlistat in overweight and obese patients with type 2 diabetes treated with metformin," *Diabetes Care*, vol. 25, no. 7, pp. 1123–1128, 2002.
- [172] C. K. Haddock, W. S. C. Poston, P. L. Dill, J. P. Foreyt, and M. Ericsson, "Pharmacotherapy for obesity: a quantitative analysis of four decades of published randomized clinical trials," *International Journal of Obesity*, vol. 26, no. 2, pp. 262–273, 2002.
- [173] S. M. Grundy, J. I. Cleeman, C. N. Bairey Merz et al., "Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines," *Circulation*, vol. 110, no. 2, pp. 227–239, 2004.
- [174] F. Folli, A. E. Pontiroli, and W. H. Schwesinger, "Metabolic aspects of bariatric surgery," *Medical Clinics of North America*, vol. 91, no. 3, pp. 393–414, 2007.
- [175] L. Sjöström, A.-K. Lindroos, M. Peltonen et al., "Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery," *The New England Journal of Medicine*, vol. 351, no. 26, pp. 2683–2693, 2004.
- [176] B. M. Wolfe and J. M. Morton, "Weighing in on bariatric surgery: procedure use, readmission rates, and mortality," *Journal of the American Medical Association*, vol. 294, no. 15, pp. 1960–1963, 2005.
- [177] R. G. Bakker-Arkema, M. H. Davidson, R. J. Goldstein et al., "Efficacy and safety of a new HMG-CoA reductase inhibitor, atorvastatin, in patients with hypertriglyceridemia," *Journal of the American Medical Association*, vol. 275, no. 2, pp. 128–133, 1996.
- [178] J. R. Downs, M. Clearfield, S. Weis et al., "Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study," *Journal of the American Medical Association*, vol. 279, no. 20, pp. 1615–1622, 1998.
- [179] J. Davignon, "Beneficial cardiovascular pleiotropic effects of statins," *Circulation*, vol. 109, no. 23, pp. III39–III43, 2004.
- [180] Z. T. Bloomgarden, "Obesity, hypertension, and insulin resistance," *Diabetes Care*, vol. 25, no. 11, pp. 2088–2097, 2002.
- [181] P. C. Deedwania, D. B. Hunninghake, H. E. Bays, P. H. Jones, V. A. Cain, and J. W. Blasetto, "Effects of rosuvastatin, atorvastatin, simvastatin, and pravastatin on atherogenic dyslipidemia in patients with characteristics of the metabolic syndrome," *The American Journal of Cardiology*, vol. 95, no. 3, pp. 360–366, 2005.
- [182] M. L. Kashyap, M. E. McGovern, K. Berra et al., "Long-term safety and efficacy of a once-daily niacin/lovastatin formulation for patients with dyslipidemia," *The American Journal of Cardiology*, vol. 89, no. 6, pp. 672–678, 2002.
- [183] J. M. Morgan, D. M. Capuzzi, R. I. Baksh et al., "Effects of extended-release Niacin on lipoprotein subclass distribution," *The American Journal of Cardiology*, vol. 91, no. 12, pp. 1432–1436, 2003.
- [184] D. B. Hunninghake, M. E. McGovern, M. Koren et al., "A dose-ranging study of a new, once-daily, dual-component drug product containing niacin extended-release and lovastatin," *Clinical Cardiology*, vol. 26, no. 3, pp. 112–118, 2003.
- [185] E. Mills, J. Prousky, G. Raskin et al., "The safety of over-the-counter niacin. A randomized placebo-controlled trial [ISRCTN18054903]," *BMC Clinical Pharmacology*, vol. 3, article 4, 2003.
- [186] S. M. Grundy, G. L. Vega, M. E. McGovern et al., "Efficacy, safety, and tolerability of once-daily niacin for the treatment

- of dyslipidemia associated with type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of Niaspan trial," *Archives of Internal Medicine*, vol. 162, no. 14, pp. 1568–1576, 2002.
- [187] D. A. Leaf, W. E. Connor, D. R. Illingworth, S. P. Bacon, and G. Sexton, "The hypolipidemic effects of gemfibrozil in type V hyperlipidemia. A double-blind, crossover study," *Journal of the American Medical Association*, vol. 262, no. 22, pp. 3154–3160, 1989.
- [188] G. Steiner, "Fibrates in the metabolic syndrome and in the diabetes," *Endocrinology and Metabolism Clinics of North America*, vol. 33, no. 3, pp. 545–556, 2004.
- [189] D. Streja, "Combination therapy for the treatment of dyslipidemia," *Current Opinion in Investigational Drugs*, vol. 5, no. 3, pp. 306–312, 2004.
- [190] G. L. Vega, P. T. S. Ma, N. B. Cater et al., "Effects of adding fenofibrate (200 mg/day) to simvastatin (10 mg/day) in patients with combined hyperlipidemia and metabolic syndrome," *The American Journal of Cardiology*, vol. 91, no. 8, pp. 956–960, 2003.
- [191] A. S. Wierzbicki, D. P. Mikhailidis, R. Wray et al., "Statin-fibrate combination therapy for hyperlipidaemia: a review," *Current Medical Research and Opinion*, vol. 19, no. 3, pp. 155–168, 2003.
- [192] S. D. Turley and J. M. Dietschy, "The intestinal absorption of biliary and dietary cholesterol as a drug target for lowering the plasma cholesterol level," *Preventive Cardiology*, vol. 6, no. 1, pp. 29–64, 2003.
- [193] C. A. Dujovne, M. P. Ettinger, J. F. McNeer et al., "Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia," *The American Journal of Cardiology*, vol. 90, no. 10, pp. 1092–1097, 2002.
- [194] D. P. Mikhailidis, G. C. Sibbring, C. M. Ballantyne, G. M. Davies, and A. L. Catapano, "Meta-analysis of the cholesterol-lowering effect of ezetimibe added to ongoing statin therapy," *Current Medical Research and Opinion*, vol. 23, no. 8, pp. 2009–2026, 2007.
- [195] "The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering," *Journal of the American Medical Association*, vol. 251, no. 3, pp. 365–374, 1984.
- [196] S. Engeli, J. Böhnke, K. Gorzelnik et al., "Weight loss and the renin-angiotensin-aldosterone system," *Hypertension*, vol. 45, no. 3, pp. 356–362, 2005.
- [197] P. K. Whelton, J. He, L. J. Appel et al., "Primary prevention of hypertension: clinical and public health advisory from the National High Blood Pressure Education Program," *Journal of the American Medical Association*, vol. 288, no. 15, pp. 1882–1888, 2002.
- [198] Z. H. Israïli, B. Lyoussi, R. Hernández-Hernández, and M. Velasco, "Metabolic syndrome: treatment of hypertensive patients," *The American Journal of Therapeutics*, vol. 14, no. 4, pp. 386–402, 2007.
- [199] S. G. Ball and W. B. White, "Debate: angiotensin-converting enzyme inhibitors versus angiotensin II receptor blockers—a gap in evidence-based medicine," *The American Journal of Cardiology*, vol. 91, no. 10, pp. 15G–21G, 2003.
- [200] A. H. Barnett, S. C. Bain, P. Bouter et al., "Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy," *The New England Journal of Medicine*, vol. 351, no. 19, pp. 1952–1961, 2004.
- [201] H. Abuissa, P. G. Jones, S. P. Marso, and J. H. O'Keefe Jr., "Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for prevention of type 2 diabetes: a meta-analysis of randomized clinical trials," *Journal of the American College of Cardiology*, vol. 46, no. 5, pp. 821–826, 2005.
- [202] J. Bosch, S. Yusuf, H. C. Gerstein et al., "Effect of ramipril on the incidence of diabetes," *The New England Journal of Medicine*, vol. 355, no. 15, pp. 1551–1562, 2006.
- [203] G. Mancia, G. Grassi, and A. Zanchetti, "New-onset diabetes and antihypertensive drugs," *Journal of Hypertension*, vol. 24, no. 1, pp. 3–10, 2006.
- [204] R. C. Pasternak, "The ALLHAT lipid lowering trial—less is less," *Journal of the American Medical Association*, vol. 288, no. 23, pp. 3042–3044, 2002.
- [205] H. R. Black, B. Davis, J. Barzilay et al., "Metabolic and clinical outcomes in nondiabetic individuals with the metabolic syndrome assigned to chlorthalidone, amlodipine, or lisinopril as initial treatment for hypertension: a report from the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT)," *Diabetes Care*, vol. 31, no. 2, pp. 353–360, 2008.
- [206] "Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)," *Journal of the American Medical Association*, vol. 288, no. 23, pp. 2981–2997, 2002.
- [207] A. V. Chobanian, G. L. Bakris, H. R. Black et al., "Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure," *Hypertension*, vol. 42, no. 6, pp. 1206–1252, 2003.
- [208] W. C. Knowler, R. F. Hamman, S. L. Edelstein et al., "Prevention of type 2 diabetes with troglitazone in the Diabetes Prevention Program," *Diabetes*, vol. 54, no. 4, pp. 1150–1156, 2005.
- [209] J.-L. Chiasson, R. G. Josse, R. Gomis, M. Hanefeld, A. Karasik, and M. Laakso, "Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial," *The Lancet*, vol. 359, no. 9323, pp. 2072–2077, 2002.
- [210] T. J. Orchard, M. Temprosa, R. Goldberg et al., "The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the diabetes prevention program randomized trial," *Annals of Internal Medicine*, vol. 142, no. 8, pp. 611–619, 2005.
- [211] R. Ratner, R. Goldberg, S. Haffner et al., "Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the diabetes prevention program," *Diabetes Care*, vol. 28, no. 4, pp. 888–894, 2005.
- [212] M. E. Molitch, "Effects of withdrawal from metformin on the development of diabetes in the diabetes prevention program," *Diabetes Care*, vol. 26, no. 4, pp. 977–980, 2003.
- [213] J.-L. Chiasson, R. G. Josse, R. Gomis, M. Hanefeld, A. Karasik, and M. Laakso, "Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial," *Journal of the American Medical Association*, vol. 290, no. 4, pp. 486–494, 2003.
- [214] R. Rajagopalan, S. Iyer, and M. Khan, "Effect of pioglitazone on metabolic syndrome risk factors: results of double-blind, multicenter, randomized clinical trials," *Current Medical Research and Opinion*, vol. 21, no. 1, pp. 163–172, 2005.
- [215] T. A. Pearson, G. A. Mensah, R. W. Alexander et al., "Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the centers for disease control and prevention and the American Heart Association," *Circulation*, vol. 107, no. 3, pp. 499–511, 2003.

- [216] B. Schieffer, C. Bünte, J. Witte et al., "Comparative effects of AT1-antagonism and angiotensin-converting enzyme inhibition on markers of inflammation and platelet aggregation in patients with coronary artery disease," *Journal of the American College of Cardiology*, vol. 44, no. 2, pp. 362–368, 2004.
- [217] P. M. Ridker, E. Danielson, F. A. H. Fonseca et al., "Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein," *The New England Journal of Medicine*, vol. 359, no. 21, pp. 2195–2207, 2008.
- [218] T. M. Shields and C. H. Hennekens, "Management of metabolic syndrome: aspirin," *Endocrinology and Metabolism Clinics of North America*, vol. 33, no. 3, pp. 577–593, 2004.
- [219] C. H. Hennekens, M. L. Dyken, and V. Fuster, "Aspirin as a therapeutic agent in cardiovascular disease: a statement for healthcare professionals from the American heart association," *Circulation*, vol. 96, no. 8, pp. 2751–2753, 1997.
- [220] M. J. Blaha, S. Bansal, R. Rouf, S. H. Golden, R. S. Blumenthal, and A. P. DeFilippis, "A practical "ABCDE" approach to the metabolic syndrome," *Mayo Clinic Proceedings*, vol. 83, no. 8, pp. 932–943, 2008.
- [221] R. S. Eidelman, P. R. Hebert, S. M. Weisman, and C. H. Hennekens, "An update on aspirin in the primary prevention of cardiovascular disease," *Archives of Internal Medicine*, vol. 163, no. 17, pp. 2006–2010, 2003.