

# Obesity, Oxidative Stress, Adipose Tissue Dysfunction, and the Associated Health Risks: Causes and Therapeutic Strategies

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## Abstract

Obesity is gaining acceptance as a serious primary health burden that impairs the quality of life because of its associated complications, including diabetes, cardiovascular diseases, cancer, asthma, sleep disorders, hepatic dysfunction, renal dysfunction, and infertility. It is a complex metabolic disorder with a multifactorial origin. Growing evidence suggests that oxidative stress plays a role as the critical factor linking obesity with its associated complications. Obesity *per se* can induce systemic oxidative stress through various biochemical mechanisms, such as superoxide generation from NADPH oxidases, oxidative phosphorylation, glyceraldehyde auto-oxidation, protein kinase C activation, and polyol and hexosamine pathways. Other factors that also contribute to oxidative stress in obesity include hyperleptinemia, low antioxidant defense, chronic inflammation, and postprandial reactive oxygen species generation. In addition, recent studies suggest that adipose tissue plays a critical role in regulating the pathophysiological mechanisms of obesity and its related co-morbidities. To establish an adequate platform for the prevention of obesity and its associated health risks, understanding the factors that contribute to the cause of obesity is necessary. The most current list of obesity determinants includes genetic factors, dietary intake, physical activity, environmental and socioeconomic factors, eating disorders, and societal influences. On the basis of the currently identified predominant determinants of obesity, a broad range of strategies have been recommended to reduce the prevalence of obesity, such as regular physical activity, *ad libitum* food intake limiting to certain micronutrients, increased dietary intake of fruits and vegetables, and meal replacements. This review aims to highlight recent findings regarding the role of oxidative stress in the pathogenesis of obesity and its associated risk factors, the role of dysfunctional adipose tissue in development of these risk factors, and potential strategies to regulate body weight loss/gain for better health benefits.

## Introduction

**O**BESITY, THE PRIMARY HEALTH burden of the 21st century, is a chronic disease that affects the quality of individual life physiologically, economically, and psychologically, irrespective of cultural, financial, or ethnic background.<sup>1</sup> An excess amount of body fat not only reduces the quality of life but also increases both healthcare-associated costs and the risk of death.<sup>2</sup> Obesity is associated with the development of a large number of health disorders, including diabetes, cardiovascular complications, cancer, asthma, sleep disorders, hepatic dysfunction, renal dysfunction, and infertility.<sup>3,4</sup>

The World Health Organization (WHO) defines overweight as a body mass index (BMI) of 25.0 to 29.9 kg/m<sup>2</sup> and obesity as a BMI of  $\geq 30$  kg/m<sup>2</sup>.<sup>5</sup> However, as a defining

parameter, BMI has certain limitations as it does not distinguish the difference between lean mass and fat nor does it identify fat distribution. Recent studies have shown that obesity-associated risk factors depend not on excess body weight *per se*, but rather on the regional distribution of the excess body fat.<sup>6</sup> In light of this, it is now well recognized that abdominal fat is a significant risk factor for obesity-associated diseases; in fact, visceral fat accumulation stimulates pro-oxidant and proinflammatory states.<sup>7</sup>

Epidemiological, clinical, and animal studies have reported the role of oxidative stress in the pathogenesis of obesity and its associated risk factors.<sup>8</sup> Oxidative stress could trigger obesity by stimulating the deposition of white adipose tissue (WAT) and altering food intake; both cell culture and animal studies have demonstrated that oxidative stress can cause an increase in preadipocyte proliferation,

adipocyte differentiation, and the size of mature adipocytes.<sup>9–11</sup> Reactive oxygen species (ROS) have been found to be involved in the control of body weight by exerting different effects on hypothalamic neurons, which control satiety and hunger behavior.<sup>12</sup> Obesity *per se* can also induce systemic oxidative stress through multiple biochemical mechanisms, such as superoxide generation from NADPH oxidases (NOX), oxidative phosphorylation, glyceraldehyde auto-oxidation, protein kinase C (PKC) activation, and polyol and hexosamine pathways.<sup>8,13</sup> Other factors that also contribute oxidative stress to obesity include hyperleptinemia,<sup>14</sup> tissue dysfunction,<sup>13</sup> low antioxidant defense,<sup>15</sup> chronic inflammation,<sup>7</sup> and postprandial ROS generation.<sup>16</sup>

A broad range of strategies are recommended to reduce the increasing prevalence of obesity, including regular physical activity, *ad libitum* food intake, meal replacements, micro-nutrient supplementation, and dietary intake of fruits and vegetables. It is well documented that weight reduction decreases oxidation markers, increases antioxidant defenses, and reduces obesity-associated pathological risk factors.<sup>17</sup> Dietary consumption of foods rich in monounsaturated fatty acids,  $\omega$ -3 polyunsaturated fatty acids, antioxidants, micronutrients, phytochemicals, and probiotics has been found to be helpful in maintaining body weight and reducing the incidence of metabolic diseases.<sup>18,19</sup> Data from observational and human interventional studies suggest that consumption of multiple nutrients rather than a single dietary component is beneficial in reducing obesity and its associated pathologies.<sup>20,21</sup>

This review gives information about the recent findings regarding the role of oxidative stress in the pathogenesis of obesity and its associated risk factors, the role of dysfunctional adipose tissue in the development of obesity-associated risk factors, the etiology of obesity, and potential strategies that could regulate body weight loss/gain for better health benefits.

## Oxidative Stress, Obesity, and Its Associated Health Risks

Oxidative stress plays an important role in the development of co-morbidities in obesity. Over the last few years, evidence of obesity-induced oxidative stress in humans has been reported in the literature.<sup>22</sup> The possible contributors to oxidative stress in obesity include hyperglycemia,<sup>23</sup> elevated tissue lipid levels,<sup>24</sup> vitamin and mineral deficiencies,<sup>25,26</sup> chronic inflammation,<sup>7</sup> hyperleptinemia,<sup>27</sup> increased muscle activity to carry excessive weight,<sup>28</sup> endothelial dysfunction,<sup>29</sup> impaired mitochondrial function,<sup>30</sup> and type of diet.<sup>31</sup> Malondialdehyde (MDA), F-2 isoprostanes (F2-IsoP), 8-iso Prostaglandin F<sub>2</sub> $\alpha$  (8-isoPGF<sub>2 $\alpha$</sub> ), and protein carbonylation are well-known plasma, serum, or urine oxidative stress biomarkers. A significant positive correlation has been observed between BMI and oxidative stress biomarkers.<sup>22</sup> Activities of the antioxidant enzymes, Cu-Zn superoxide dismutase (SOD) and glutathione peroxidase (GPx), were found to be lower in the erythrocytes of obese subjects compared to those of nonobese controls.<sup>32,33</sup> Ferric reducing antioxidant power (FRAP) and total antioxidant status (TAS) have been used as comprehensive measures of radical quenching capacity by antioxidants in plasma. Several studies have reported lower plasma levels of FRAP and TAS in obese subjects compared to those seen in nonobese controls.<sup>22,34,35</sup> Obesity-induced oxidative stress causes the development of



**FIG. 1.** Conditions generating oxidative stress in the pathogenesis of obesity and the role of oxidative stress in the development of obesity associated health risks.

various pathological events, including insulin resistance and diabetes, cardiovascular complications, sleep disorders, asthma, oncological problems, reproduction, rheumatological problems, and liver failure.<sup>3,4</sup> In this study, we will discuss in detail about the role of various contributing factors in developing oxidative stress in obesity. In addition, we will also discuss the role of oxidative stress underlying the development of different health risks associated with obesity (Fig. 1).

### Conditions generating oxidative stress in obesity

**Hyperglycemia and oxidative stress in obesity.** Obesity is directly associated with insulin resistance and hyperglycemia. Intracellular glucose overload increases the glycolytic pathway and the tricarboxylic acid cycle, leading to the overproduction of NADH and FADH<sub>2</sub>; the resulting increase in proton gradient across the mitochondrial inner membrane causes electron leakage at complex III, leading to superoxide production. The free radical thus inhibits glyceraldehyde-3-phosphate dehydrogenase and thereby re-directs upstream metabolites into four alternative pathways<sup>36</sup>: (1) glucose is shifted to the polyol pathway; (2) fructose-6-phosphate is shifted to the hexosamine pathway; (3) triose phosphates produce methylglyoxal, the main precursor of advanced glycation end products (AGE); and (4) dihydroxyacetone phosphate is converted to diacylglycerol, which activates the PKC pathway. Activation of these alternative pathways induces oxidative/nitrosative stress either by enhancing free radical production or by impairing antioxidant defenses. Activation of the polyol pathway causes NADPH depletion and increases the conversion of glucose to sorbitol, which activates several stress genes and causes oxidative stress, as evidenced in several animal studies.<sup>37</sup> Formation of glucosamine-6-phosphate in the hexosamine pathway inhibits thioredoxin activity and induces oxidative and endoplasmic reticulum (ER) stress; AGE and PKC stimulate the production of ROS/RNS by activating NOX and NF- $\kappa$ B.<sup>38,39</sup> Activation of NOX enzymes increases the production of superoxide radicals (O<sub>2</sub><sup>-</sup>) by catalyzing the

reduction of oxygen using NADPH as an internal electron donor.<sup>40</sup> Glucose auto-oxidation also produces reactive oxidants similar to hydroxyl and superoxide radicals.<sup>23</sup> AGE binds to specific cell surface receptors causing the modification of postreceptor signaling and promotes further generation of ROS.<sup>41</sup> Activation of NF- $\kappa$ B drives transcription of adhesion molecules (E-selectin, intercellular adhesion molecule-1, and endothelin-1), proinflammatory cytokines [tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin (IL)-6], iNOS, and microRNAs involved in adipogenesis, inflammation, and oxidative stress.<sup>42</sup>

*Elevated lipid levels and oxidative stress in obesity.* Obesity is associated with an increase in plasma free fatty acids (FFA) as well as excessive fat storage in WAT. Elevated plasma FFA promote the generation of O<sub>2</sub><sup>•-</sup> in the mitochondrial electron transport chain by inhibiting the translocation of adenine nucleotides.<sup>43</sup> FFA stimulate the production of reactive intermediates through PKC-dependent activation of NOX in cultured vascular cells.<sup>44</sup> Conjugated fatty acids are susceptible to oxidation, stimulate the formation of radicals, and enhance the accumulation of oxidative by-products.<sup>9</sup> The susceptibility of lipids to oxidative modification is shown by the higher concentrations of 4-hydroxynonenal (4-HNE) per unit of intramuscular triglycerides in obese patients.<sup>45</sup> Higher concentrations of lipid molecules in the obese may also present an enlarged target for oxidative modification by ROS.<sup>46</sup> In a study with several animal models of obesity, Furukawa et al. found that accumulation of excessive fat in WAT caused an increase in lipid peroxidation in the WAT itself.<sup>9</sup> In the animal studies, it was observed that obesity increased the NOX activity and decreased the mRNA expression and the activities of antioxidant enzymes such as SOD, catalase (CAT), and GPx in WAT.<sup>9</sup> Dietary intake of specific lipids also induces systematic oxidative stress. Consumption of conjugated linolenic acid increased the urinary concentration of 8-epi PGF<sub>2 $\alpha$</sub>  in middle-aged men with abdominal obesity.<sup>47</sup>

*Vitamin and mineral deficiencies and oxidative stress in obesity.* Adequate intracellular antioxidant defenses are necessary to maintain the antioxidant-pro-oxidant balance in tissues. Deficiencies in vitamins and minerals can also contribute to the development of an impaired antioxidant defense in the pathogenesis of obesity.<sup>25,26</sup> Plasma levels of  $\alpha$ -tocopherol or  $\beta$ -carotene expressed per unit of plasma low-density lipoprotein (LDL) are well-known biomarkers for estimating the antioxidant protection within circulating lipids. An increase in BMI has been found to be related to low levels of carotenoids, vitamin C, and vitamin E.<sup>48-50</sup> The Coronary Artery Risk Development in Young Adults (CARDIA) study reported an inverse relationship between BMI and the concentration of total serum carotenoids ( $\alpha$ -carotene,  $\beta$ -carotene,  $\alpha$ -cryptoxanthin, and zeaxanthin/lutein).<sup>51</sup> In the National Health and Examination survey, obese children showed levels of serum  $\beta$ -carotene lower than those seen in normal control subjects.<sup>25</sup> For instance, in one study, it was observed that obese girls had lower plasma levels of  $\alpha$ -tocopherol/LDL and  $\beta$ -carotene/LDL than those seen in nonobese girls.<sup>52</sup> Aasheim and Bohmer reported that most obese patients have profound reductions in vitamin levels, especially vitamins A, B<sub>6</sub>, C, D, and E.<sup>53</sup> The multicenter prospective population study in Europe (EPIC) showed that the plasma vitamin C level was inversely related to central fat distribution.<sup>54</sup> Obese adults (BMI >50) also had lower plasma levels of vitamin E/triglycerides compared to nonobese adults

(BMI <30).<sup>55</sup> Lower selenium and zinc levels have been observed in obese children, especially in children with central obesity.<sup>25,56</sup> In addition, morbidly obese patients also show magnesium, selenium, iron, and zinc deficiencies.<sup>57</sup> These results suggest that in the obese population, inadequate concentrations of vitamins and minerals cause the observed impaired antioxidant defense.

*Chronic low-grade inflammation and oxidative stress in obesity.* Obesity is described as a state of chronic low-grade inflammation, which is another important source of oxidative stress in obesity.<sup>58</sup> Elevated levels of plasma and urinary F2-IsoPs, a biomarker of oxidative stress, have been found in a number of inflammatory diseases, such as Crohn's disease<sup>59</sup> and rheumatic diseases.<sup>60</sup> TNF- $\alpha$ , IL-6, and IL-1 are the most well-known mediators of the early inflammatory response. Other cytokines that are frequently seen in inflammation include IL-8, IFN- $\gamma$ , IL-18, and IL-1ra (IL-1 receptor antagonist).<sup>61</sup> Both TNF- $\alpha$  and IL-6 increase the activities of NOX and the production of superoxide anion.<sup>62,63</sup>

*Hyperleptinemia and oxidative stress in obesity.* Plasma leptin concentrations are associated with the amount of adipose tissue.<sup>64</sup> Obesity is associated with elevated plasma leptin levels.<sup>65</sup> Leptin plays an important role in obesity-induced oxidative stress.<sup>66</sup> The hormone leptin activates NOX and induces the production of reactive intermediates such as H<sub>2</sub>O<sub>2</sub> and hydroxyl radical.<sup>67</sup> In a rodent model, leptin injection caused higher levels of plasma and urinary lipid hydroperoxide, MDA, isoprostane, and protein carbonyl content compared to levels seen in nontreated controls.<sup>68</sup> In addition, leptin also stimulates the proliferation of monocytes and macrophages and thus promotes the production of proinflammatory cytokines.<sup>68,69</sup> Exposure of monocyte-derived macrophages to leptin induces the PKC activity and macrophage lipoprotein lipase activity.<sup>70</sup> Leptin also reduces the activity of the cellular antioxidant paroxase-1 (PON-1); this reduction is related to increased levels of plasma and urinary 8-isoPGF<sub>2 $\alpha$</sub>  and plasma levels of MDA and hydroperoxides.<sup>68</sup>

*Increased muscle activity and oxidative stress in obesity.* In obesity, increased muscle activity can generate excessive free radicals through the activation of metabolic pathways, including increased electron transport chain activity and conversion of hypoxanthine to urate.<sup>71</sup> In addition, rapid electron transfer during increased respiration may cause some electrons to leak from the electron transport chain.<sup>72</sup> For this reason, among obese individuals, the rate of cellular respiration and oxygen consumption may be exacerbated in muscle tissue during physical activities.<sup>34</sup> It has been observed that, during the same amount of load-bearing walking activity, obese persons have a 38% higher oxygen consumption than do nonobese individuals and these values were found to be correlated with postexercise lipid hydroperoxide values.<sup>34</sup> Obese individuals are also mechanically less efficient during exercise and this insufficiency contributes to the increased energy expenditure for a given exercise load.<sup>22</sup> An increase in mitochondrial respiration for energy production is associated with higher levels of lipid hydroperoxide in obese people.<sup>73</sup> During exercise, increased concentrations of hypoxanthine have been reported in obese people; the conversion of hypoxanthine to urate is associated with the formation of superoxide anion.<sup>71</sup>

*Endothelial dysfunction and oxidative stress in obesity.* The vascular endothelium is an important site for several enzymatic

sources of oxidant generation, including NOX, xanthine oxidase, and NO synthase.<sup>74</sup> Activation of NOX is a major player in the production of endothelial  $O_2^{\cdot-}$ .<sup>75</sup> Xanthine oxidase also reacts with  $O_2$  to form  $O_2^{\cdot-}$  and  $H_2O_2$ .<sup>76</sup> Production of excessive  $O_2^{\cdot-}$  leads to rapid reaction with NO to form ONOO<sup>•</sup> and thus reduces NO bioavailability and causes nitrosylation of proteins.<sup>29</sup> The enzyme NO synthase also stimulates the formation of excessive  $O_2^{\cdot-}$  and ONOO<sup>•</sup> by catalyzing the electron transport from NADPH to another heme group.<sup>77</sup> The activities of these oxidant producing enzymes can be modified by other cytokines and hormones such as those present in the renin-angiotensin system. It has been observed that in angiotensin II-induced hypertension, the production of endothelial  $O_2^{\cdot-}$  is significantly elevated as a consequence of increased NADPH-oxidase activity.<sup>78</sup> Obesity is associated with higher concentrations of the hormones in the renin-angiotensin system.<sup>79</sup> Increased concentrations of angiotensin II may promote oxidative stress in vasculature through several mechanisms, including activation of NOX, formation of  $O_2^{\cdot-}$ , and production of  $H_2O_2$ .<sup>80,81</sup> Elevated intraluminal pressure from the hypertension associated with obesity may also stimulate the formation of  $O_2^{\cdot-}$  and ONOO<sup>•</sup>.<sup>82</sup>

*Impaired mitochondrial function and oxidative stress in obesity.* Mitochondrial dysfunction has been implicated in the pathogenesis of a variety of diseases, including obesity and its associated risk factors.<sup>83</sup> During the adipocyte differentiation process, mitochondrial biogenesis and activity increase rapidly, suggesting a critical role for mitochondria in this organelle.<sup>84</sup> Mitochondria play a central role in ATP production, energy expenditure, and disposal of ROS.<sup>83</sup> The process of oxidative phosphorylation in mitochondria is very efficient; however, a small excess of electrons cause a reduction of oxygen resulting in the formation of potentially toxic-free radicals.<sup>7</sup> In addition to this, under certain conditions, protons can be reintroduced into the mitochondrial matrix through different uncoupling proteins, leading to an alteration in the regulation of free radical production in mitochondria.<sup>30</sup> Excessive energy substrate causes mitochondrial dysfunction, which has been linked to the dysregulated secretion of adipokines,<sup>85</sup> defects in fatty acid oxidation,<sup>86</sup> increased production of ROS,<sup>86</sup> and alteration of glucose homeostasis.<sup>87</sup>

*Role of diet type in inducing oxidative stress in obesity.* Diet is another possible contributing factor in the generation of ROS during the pathogenesis of obesity and its associated risk factors. Consumption of a high-fat diet may alter oxygen metabolism. It has been observed that consumption of a diet high in fat and carbohydrates induces significant oxidative stress and inflammation in persons with obesity.<sup>16</sup> Lower dietary intake of protective phytochemicals rich in antioxidants ( $\beta$ -carotene, vitamin E and C, etc.) may cause an inadequate antioxidant defense.<sup>88</sup> Dietary intake of antioxidant phytochemicals is inversely associated with degree of adiposity,<sup>89</sup> BMI, and lipid peroxidation.<sup>88</sup> Serum levels of dietary antioxidants and levels of trace minerals (zinc, selenium, etc.), which are cofactors for antioxidant enzymes, were found to be lower in obese people compared to those seen in nonobese individuals.<sup>49,89,90</sup>

### *Role of oxidative stress in obesity-associated health risks*

*Obesity, oxidative stress, and type 2 diabetes.* In vivo studies. Both obesity and diabetes are major public health

problems throughout the world and are associated with significant, potentially life-threatening co-morbidities. Results from metabolic and epidemiological studies provide strong evidence that the increasing prevalence of obesity is closely associated with the increase in type 2 diabetes.<sup>91,92</sup> Some experts call this dual epidemic diabetes.<sup>93</sup> However, while it has been observed that not all subjects with type 2 diabetes are obese and that, conversely, many obese subjects do not have diabetes, most subjects with type 2 diabetes are overweight or obese. According to the guidelines of the American Diabetes Association, the diagnosis criteria of diabetes mellitus include the following: (1)  $A_{1C} \geq 6.5\%$  or fasting plasma glucose after an 8-hr fast  $\geq 126$  mg/dL, or 2-hr postload glucose  $\geq 200$  mg/dL during an OGTT, or symptoms of diabetes mellitus and a random plasma glucose concentration  $\geq 200$  mg/dL. Several studies in the literature reported a linear association between BMI and type 2 diabetes<sup>94,95</sup> and it has been observed that the risk of type 2 diabetes increases as BMI increases above 23.<sup>96</sup> Very recently, in a systematic review of 18 weight-related diseases, the investigators found that diabetes is at the top of the risk list: men with BMI  $\geq 30$  had a 7-fold and women with BMI  $\geq 30$  had a 12-fold higher risk of developing type 2 diabetes compared with men and women in the normal weight ranges (BMI  $\leq 25$ ).<sup>97</sup> In addition to total body fat, distribution of fat and the relative proportions of lipids in various insulin-sensitive tissues (liver, skeletal muscle, and adipose) also play an important role in this pathophysiology.<sup>98</sup> Abdominal obesity is one the most important, and most dangerous, forms of obesity. Accumulation of intra-abdominal or visceral fat is major feature of metabolic syndrome and is associated with a higher incidence of diabetes and cardiovascular disease (CVD) risk factors.<sup>99,100</sup> Waist circumference (WC) as a measure of abdominal obesity has been considered as a better predictor of the risk of developing type 2 diabetes.<sup>101</sup> Insulin resistance coupled with pancreatic  $\beta$ -cell dysfunction is a critical factor for the development of type 2 diabetes.

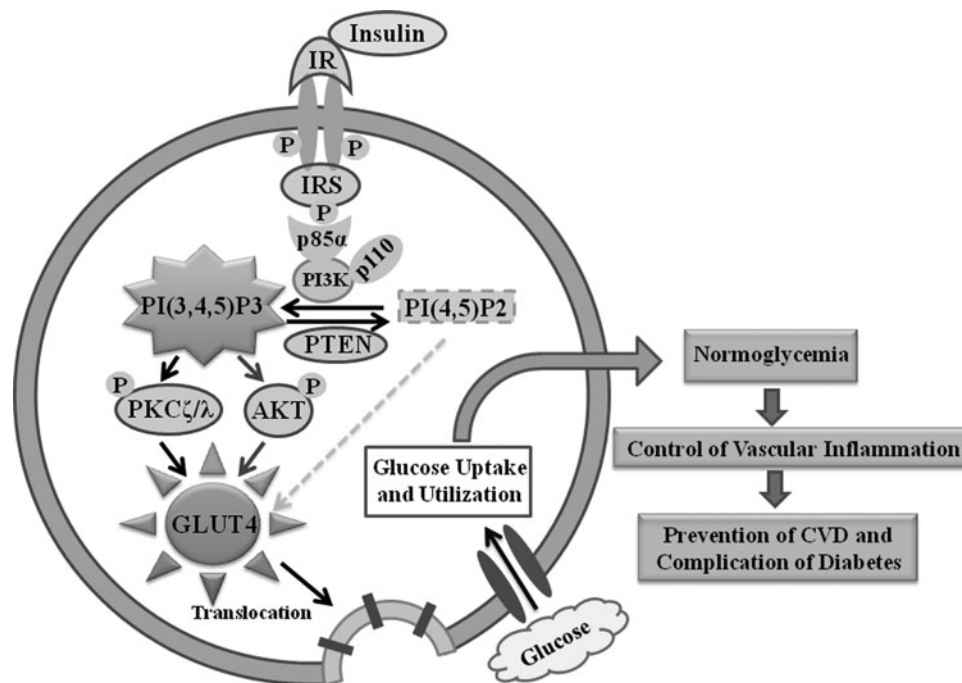
*Mechanistic studies—Oxidative stress and  $\beta$ -cell dysfunction.* Glucotoxicity and lipotoxicity have been recognized as the major contributors to  $\beta$ -cell dysfunction in the pathogenesis of type 2 diabetes.<sup>102</sup> Pancreatic  $\beta$ -cells have a relatively low expression of many antioxidant enzymes, including catalase and GPx, which makes them susceptible to ROS-induced damage.<sup>103</sup> In addition, overexpression of catalase or GPx can reverse these effects and protect  $\beta$ -cells.<sup>104,105</sup> Hou et al. demonstrated that chronic exposure to high glucose and/or circulating FFA increases ROS production and decreases insulin content and glucose-stimulated insulin secretion of  $\beta$ -cells.<sup>106</sup> ROS has been shown to reduce insulin gene expression and insulin secretion, probably through post-translational repression of two key transcriptional factors, musculoaponeurotic fibrosarcoma protein A (MafA) and pancreatic duodenal homeobox-1 (PDX-1), which bind to the promoter region of the insulin gene.<sup>107,108</sup> Superoxide-induced activation of uncoupling protein 2 (UCP2) lowers ATP levels and negatively regulates glucose-stimulated insulin secretion.<sup>109–111</sup> UCP2 knockout mice do not experience hyperglycemia- and obesity-induced loss of glucose responsiveness.<sup>111</sup>

*Mechanistic studies—Oxidative stress and insulin resistance.* The insulin signaling cascade is initiated by the binding of insulin with its receptor (IR), which undergoes

receptor autophosphorylation and enhanced tyrosine kinase activity. Subsequent phosphorylation of insulin receptor substrate (IRS) on tyrosine residues stimulates the downstream signaling cascade of glucose metabolism<sup>112</sup> (Fig. 2). In contrast, serine/threonine phosphorylation of the IR and IRS provides a negative regulatory mechanism by opposing their tyrosine phosphorylation.<sup>113</sup> Elevated ROS production has been shown to activate the stress-sensitive serine/threonine kinase, *c-jun*-N-terminal kinase (JNK), which in turn causes phosphorylation of IRS at serine residues and thus attenuates insulin signaling.<sup>114</sup> Although the precise mechanism by which ROS activates JNK remains uncertain, it has been shown that H<sub>2</sub>O<sub>2</sub> can inhibit thioredoxin by modification of its cysteine residues and cause full activation of apoptosis signal-regulating kinase 1 (ASK1), which in turn activates JNK.<sup>115,116</sup> H<sub>2</sub>O<sub>2</sub> has also been shown to activate JNK through inhibition of mitogen-activated protein kinase (MAPK) phosphatase by oxidation of the cysteine.<sup>106</sup> Intake of a high-fat diet has been shown to increase mitochondrial ROS production and direct the cellular redox environment to a more oxidized state in skeletal muscle of rodents or humans.<sup>9,117,118</sup> Reduction in mitochondrial ROS production by antioxidant treatment or overexpression of catalase or MnSOD has been found to prevent high-fat diet-induced insulin resistance in mice.<sup>117</sup> These findings suggest that elevated mitochondrial ROS production by excessive metabolic flux promotes insulin resistance. Transgenic mice [overexpressing peroxisome proliferator-activated receptor- $\alpha$  (PPAR $\alpha$ )] engineered to increase fatty acid  $\beta$ -oxidation develop severe insulin resistance and glucose intolerance despite being protected from

diet-induced obesity.<sup>119</sup> However, genetically engineered mice (AIF, apoptosis inducing factor knockout) with reduced mitochondrial oxidative phosphorylation are protected from obesity and diabetes.<sup>120</sup> These observations suggest that reduction in mitochondrial oxidative phosphorylation prevents insulin resistance. In addition to post-translational modification of the insulin signaling pathway, oxidative stress also influences glucose metabolism through the regulation of transcriptional factors. The FoxO family of Forkhead transcription factor regulates gluconeogenesis, adipocyte differentiation, and  $\beta$ -cell proliferation.<sup>121–123</sup> FoxO1 is a negative regulator of insulin sensitivity. Oxidative stress can activate FoxO through the formation of the cysteine thiol disulfide-dependent complex with p300/CBP acetyl transferase and subsequent acetylation of FoxO.<sup>124</sup> FoxO also regulates various biological functions, such as cell cycle arrest, antioxidant response, DNA repair, and apoptosis.<sup>125</sup> Deletion of FoxO1 in diabetic mice reverses the diabetic phenotype.<sup>123</sup>

*Obesity, oxidative stress, and CVD.* In vivo studies: Obesity is a major contributor to the development of fatal and nonfatal CVD such as coronary artery disease, stroke, peripheral artery disease, cardiomyopathy, and congestive heart failure.<sup>126,127</sup> Excessive body weight is directly associated with a number of cardiovascular risk factors, including hypertension, dyslipidemia, and hemostatic and rheological factors.<sup>128</sup> Numerous studies in the literature have reported a clear association between the risk of coronary heart disease (CHD) and a modest increase in BMI.<sup>129,130</sup> In a 16-year follow-up study among middle-aged US women (35 to 55 years), it was demonstrated that a small increase in BMI (>23 but <25) was associated with



**FIG. 2.** Insulin stimulated signaling cascade of glucose metabolism. Binding of insulin with its receptor (IR) undergoes receptor autophosphorylation and enhances its kinase activity. Subsequent binding of IRS (insulin receptor substrate) with the p85 regulatory subunit of PI3K (phosphoinositide 3-kinase) upregulates the synthesis of PtdIns(3,4,5)P<sub>3</sub> utilizing PtdIns(4,5)P<sub>2</sub> as a substrate. The phosphatase, PTEN (phosphatase and tensin homolog deleted on chromosome 10) dephosphorylates PtdIns(3,4,5)P<sub>3</sub> at the 3'-position. Formation of PtdIns(3,4,5)P<sub>3</sub> activates downstream effector protein molecules, Akt (serine/threonine protein kinase) and PKC $\zeta$ / $\lambda$  (protein kinase C zeta/lambda). This causes the translocation of GLUT (glucose transporter) from intracellular site to the plasma membrane followed by glucose uptake and utilization by the cells leading to normoglycemia, control of vascular inflammation, and prevention of CVD (cardiovascular diseases) and the complications of diabetes.

a 50% increase in risk for nonfatal or fatal CHD.<sup>130</sup> Among the male US population, those aged 40–65 years with a BMI >23 but <29 had a 72% increased risk of CHD after adjusting for other coronary risk factors.<sup>129</sup>

**Mechanistic studies.** Oxidative stress plays an important role in the development of CVD risk factors among the obese population. Low levels of circulating high-density lipoprotein (HDL), increased clearance of HDL particles, higher levels of postprandial triglycerides, and elevated levels of LDL induce ROS generation in the endothelium.<sup>131</sup> Elevated ROS can directly cause damage to lipids, proteins, or DNA molecules and thereby modulate intracellular signaling cascades, such as MAPK and redox-sensitive transcription factors.<sup>131</sup> ROS-mediated changes in lipid expression, formation of oxidized lipid products, such as oxidized LDL (Ox-LDL) particles, and activation of macrophages induce the formation of atherosclerotic lesions. Paraoxonase-1 (PON-1) is a HDL-attached extracellular esterase that contributes to the antiatherogenic, antioxidant, and anti-inflammatory properties of HDL.<sup>132</sup> A decrease in PON-1 is a risk factor for CVD and has recently been found to be associated with obesity.<sup>133</sup> Activation of the NOX system and renin-angiotensin system and stimulation of proinflammatory cytokine release also induce ROS production and the progression of vascular disease. Elevated ROS in the blood stream causes migration of monocytes/macrophages and apoptosis of endothelial cells, which promotes vascular inflammation and injury. Endothelium NO causes vascular relaxation, and a decrease in endothelium NO release reduces vasodilation, which can favor the development of hypertension.<sup>134</sup> Various studies have reported the role for oxidative stress in the development of hypertension.<sup>134</sup> Elevated ROS as well as lower NO levels and high levels of F2-isoprostanes induce vasoconstriction and platelet hyperactivity.<sup>135</sup> Ox-LDL induces adipocyte proliferation either directly or indirectly by increasing the accumulation of fatty acids in adipocytes,<sup>136</sup> by inducing the expression of lipoprotein lipase,<sup>136</sup> or by increasing the infiltration of monocytes/macrophages.<sup>137</sup> Ox-LDL-induced alteration in adipokine secretion can also induce CVD complications.<sup>138</sup> Higher Ox-LDL in obese subjects may be due to lower serum activity of antioxidant enzymes<sup>139</sup> or reduced PON-1 levels.<sup>132</sup>

**Obesity, oxidative stress, and carcinogenesis.** *In vivo studies.* Recently, it has been observed that obesity is a major risk factor for cancer.<sup>140</sup> A number of prospective epidemiological studies have demonstrated a direct association between being overweight and developing cancer, although obesity alone does not cause an increase in cancer risk in all tissues by the same extent.<sup>140–142</sup> The International Agency for Research into Cancer (IARC)<sup>143</sup> and the World Cancer Research Fund (WRCF) reports<sup>144</sup> concluded that common cancers in obese people are endometrial, esophageal, adenocarcinoma, colorectal, postmenopausal breast, pancreas, prostate, and renal. There are also some less common malignancies associated with obesity, such as thyroid cancer,<sup>145</sup> leukemia, non-Hodgkin's lymphoma, and multiple myeloma.<sup>146</sup>

**Mechanistic studies.** Oxidative stress is one of the leading causes of DNA damage with the formation of modified bases and mutations of tumor suppressor genes, which is considered to be the most critical factor in carcinogenesis.<sup>147</sup> Obesity-induced inflammation is thought to be a critical link between obesity and cancer. Inflammation-induced increased production of free radicals and subsequent development of oxidative

stress create a microenvironment favorable to tumor development in obese persons.<sup>148</sup> Adiponectin functions as a negative regulator of obesity-related carcinogenesis, and hypoadiponectinemia is a known risk factor for tumorigenesis.<sup>149</sup>

**Obesity, oxidative stress, and asthma.** *In vivo studies:* Both obesity and asthma have a considerable impact on public health.<sup>150–153</sup> Various cross-sectional studies in different countries show an increased prevalence of asthma among obese adults compared to its occurrence in the normal-weight population, suggesting that obesity could increase the risk of asthma.<sup>150</sup> The relationship between obesity and asthma has been observed consistently regardless of the ethnic origin of the studies' population.<sup>150,154–157</sup> In a prospective study with the highest number of subjects and with the longest follow-up (135,000 Norwegians, follow-up for 21 years), the incidence of asthma increased 10% and 7% per unit increase in BMI in men and women, respectively.<sup>158</sup>

**Mechanistic studies.** Oxidative stress plays an important role in the pathogenesis of asthma.<sup>159,160</sup> Children with asthma have higher plasma levels of MDA and 8-isoprostanes compared to those of healthy controls.<sup>161</sup> Asthmatic subjects with more obstructed airways have a higher degree of oxidative stress.<sup>162</sup> Obesity-mediated oxidative stress may affect the lung function of asthmatic subjects by airway inflammation and thus reduce the effectiveness of inhaled corticosteroids.<sup>163</sup> There are several pathways by which obesity may increase airway oxidative stress, such as adipokine imbalance, obstructive sleep apnea (OSA), and reduced antioxidant defense.<sup>163</sup>

**Obesity, oxidative stress, and sleep disorders.** *In vivo studies.* Insomnia, OSA, and sleep-related movement disorders are the three most prevalent types of sleep disorders, as characterized by the International Classification of Sleep Disorders.<sup>164</sup> All of these sleep disorders cause a decrease in sleep duration and quality and this has been associated with an increase in body weight and adiposity.<sup>165,166</sup> People with obesity are significantly more likely to report insomnia or difficulty sleeping.<sup>167</sup> Significant sleep apnea is present among ~40% of obese individuals; ~70% of OSA patients are obese.<sup>168</sup> Several cross-sectional studies have reported an association between an increase in body weight and the risk of OSA.<sup>169</sup> Similarly, weight loss in OSA patients has been found to significantly decrease apnea frequency.<sup>170,171</sup>

**Mechanistic studies.** Oxidative stress in OSA patients has been found to be associated with central obesity rather than intermittent hypoxia or respiratory disturbances.<sup>172</sup> Among obese OSA patients, expression of NF- $\kappa$ B is higher than that observed in obese OSA-free subjects, suggesting that elevated levels of proinflammatory cytokines upregulate NF- $\kappa$ B in neutrophils and monocytes of sleep apnea patients, which upregulates ROS production and causes oxidative stress in this pathophysiology.<sup>173</sup>

**Obesity, oxidative stress, and liver dysfunction.** *In vivo studies.* Obesity is associated with an increased risk of hepatic dysfunction, known as nonalcoholic fatty liver disease (NAFLD), which is characterized by an increase in intrahepatic lipid accumulation due to increased inflow of FFA and/or *de novo* lipogenesis.<sup>174,175</sup> A serious consequence of NAFLD is nonalcoholic steatohepatitis (NASH), which can progress to liver fibrosis, cirrhosis, and eventually hepatocellular carcinoma. The prevalence of NAFLD increases with the increase in BMI.<sup>176</sup> Among nonobese subjects, the rates of occurrence of steatosis and steatohepatitis were ~15% and

3%, respectively; however, in subjects with BMI between 30 and 39.9, the prevalence rates were 65% and 20%, respectively, and in extremely obese subjects with BMI  $\geq 40$ , the rates were 85% and 40%, respectively.<sup>175</sup> Racial/ethnic background and genetic variation in specific genes can influence the relationship between BMI and NAFLD.<sup>177–179</sup> NAFLD has become an important public health issue because it is associated with a high risk of developing type 2 diabetes, cardiovascular complications, and dyslipidemia.<sup>180</sup> An increase in intrahepatic triglyceride content is associated with alterations in glucose, fatty acids, and lipoprotein metabolism, leading to hepatic insulin resistance in association with serious cardiovascular dysfunction.

**Mechanistic studies.** Oxidative stress has been implicated in the pathogenesis of NAFLD/NASH.<sup>181</sup> Mitochondrial, peroxisomal, microsomal, and ER oxidative stress plays an important role in the pathogenesis of NAFLD.<sup>182</sup> Elevated fatty acid catabolism in hepatocytes causes excessive electron flux in the mitochondrial electron transport chain, which impairs the oxidative capacity of the mitochondria and stimulates the peroxisomal and microsomal pathways of fat oxidation. The consequent overproduction of ROS and reactive aldehyde derivatives causes oxidative stress and cell death by reducing cellular ATP, NAD, and glutathione levels and causing DNA, lipid, and protein damage.<sup>183</sup> ER stress-induced cell death is mediated through calcium perturbations, ROS production, and activation of JNK-dependent signaling cascade. Hyperglycemia is also an important contributor to hepatic lipid accumulation; apart from the stimulation of increased ROS production and the consequent development of oxidative stress, it also causes activation of carbohydrate responsive element-binding protein (ChREBP), which stimulates the transcription of L-type pyruvate kinase (L-PK) and various lipogenic genes.<sup>184</sup>

**Obesity, oxidative stress, and renal dysfunction.** In vivo studies: Although obesity has long been recognized as an independent risk factor for CVD and diabetes mellitus, recent studies in the literature have reported that obesity is also an important risk factor for chronic kidney diseases (CKD).<sup>185–187</sup> In 1974, Weisinger et al. first reported an association between massive obesity and nephrotic syndrome.<sup>188</sup> Subsequent studies in the literature demonstrated that obesity could induce renal dysfunction, namely, obesity-related glomerulopathy (ORG).<sup>189–191</sup> In the Framingham Offspring cohort study, a single-unit increase in BMI was found to be associated with a 20% increase in kidney disease over a period of 20 years of follow up.<sup>192</sup> In a large-scale clinicopathologic study, Kambham et al. found a progressive increase in ORG from 0.2% in the years between 1986 and 1990 to 2% in the years between 1996 and 2000.<sup>191</sup> Kambham et al. suggest that this 10-fold increase in incidence of ORG over 15 years is a newly emerging epidemic.<sup>191</sup>

**Mechanistic studies.** Oxidative stress has been increasingly linked to a higher incidence of CKD.<sup>193</sup> A significant imbalance between pro-oxidants and antioxidants has been observed among patients with renal dysfunction.<sup>194</sup> Serum TAS is inversely associated with the glomerular filtration rate (GFR).<sup>195</sup> Impaired lymphocytic function has been described in chronic renal failure.<sup>196</sup> Tepel et al. demonstrated that elevated ROS production may cause impaired lymphocytic function in patients with renal dysfunction.<sup>194</sup>

**Obesity, oxidative stress, and infertility.** In vivo studies: Elevated body weight can influence various aspects of reproduction in both men and women, from sexual activity to

conception.<sup>197</sup> The relationship between obesity and reproductive disturbances in women was recognized a long time ago.<sup>198</sup> More recently, in the Nurses' Health Study, a classic U-shaped relationship was observed between obesity and infertility, primarily anovulatory infertility; women with BMIs between 20 and 24 showed the lowest infertility, but infertility increased with both lower and higher BMIs.<sup>199</sup> Several other cross-sectional and prospective studies have reported similar findings.<sup>200,201</sup> Furthermore, weight loss in obese women improves fertility and increases the likelihood of ovulation and conception.<sup>202,203</sup> A study by Hammoud et al. showed an increased incidence of low sperm count (from 5.3% to 15.6%) and poor sperm motility (from 4.5% to 13.3%) in obese men compared to those in normal weight men.<sup>204</sup> Chavarro et al. also found major differences in reproductive hormone levels with increases in body weight.<sup>205</sup> The effect of obesity on the development of sexual dysfunction has also been observed among obese men and women compared with normal weight individuals.<sup>206–209</sup>

**Mechanistic studies.** Oxidative stress also plays a significant role in infertility. Elevated steroid production in the growing follicle causes an increase in P450, resulting in ROS formation. Oxidative stress in the follicular fluid environment of ovaries is detrimental in several ways, causing poor development of both oocytes and embryos, and adversely affecting the overall outcome of pregnancy.<sup>210–213</sup> Oxidative stress is associated with several female reproductive diseases, such as endometriosis, polycystic ovary syndrome (PCOS), and preeclampsia.<sup>214</sup> In addition to the effects of obesity on female fertility, its effect on male infertility is also gaining attention worldwide.<sup>215</sup> Various studies reported a decrease in sperm count and concentration, sperm motility, DNA fragmentation, and normal sperm morphology among obese men.<sup>215</sup> Recent evidence suggests that ROS-mediated damage to sperm is a significant contributing factor to male infertility.<sup>216–218</sup> ROS causes male infertility through two principal mechanisms: first, ROS damage the sperm membrane, which in turn reduces the sperm's motility and ability to fuse with the oocyte, and second, ROS can directly damage sperm DNA, compromising the paternal genomic contribution to the embryo.<sup>219</sup>

## Obesity and Dysfunctional Adipose Tissue

In the human body there are two types of adipose tissue, brown adipose tissue (BAT) and WAT, which differ structurally and functionally.<sup>220</sup> BAT, mainly found in small and discrete regions of newborn humans, is responsible for the production of heat by a process called thermogenesis.<sup>220</sup> However, more recently, a significant amount of BAT has also been found in adults.<sup>221</sup> WAT, in contrast, is the predominant form of adipose tissue found in adults and is responsible for fat storage in the body.<sup>220</sup> In addition to energy storage, it is now well established that WAT also functions as an endocrine organ that secretes various bioactive substances, commonly known as adipokines, involved in glucose metabolism (e.g., adiponectin, resistin), lipid metabolism [e.g., cholesteryl ester transfer protein (CETP)], inflammation [e.g., TNF- $\alpha$ ; IL-6, IL-8, C-reactive protein (CRP), monocyte chemoattractive protein (MCP-1)], coagulation [plasminogen activator inhibitor-1 (PAI-1)], blood pressure regulation (e.g., angiotensinogen, angiotensin II), and feeding behavior (leptin).<sup>222–224</sup> Obesity is mainly



**FIG. 3.** Role of dysfunctional adipose tissue in the development of obesity associated health risks.

characterized by an increase in body fat or WAT and is associated with marked changes in the secretory function of WAT.<sup>225</sup> In humans, it has been observed that the tissue expression, as well as the circulating concentration of many adipokines, increases with an increase in adiposity, as is the case for leptin, TNF- $\alpha$ , IL-6, IL-8, CRP, MCP-1, PAI-1, heptoglobin, and angiotensinogen.<sup>226</sup> An exception is adiponectin, the concentration of which is inversely related to body weight.<sup>226</sup> Similar findings have also been observed in animal studies.<sup>65</sup> The deposition of excess fat in the WAT perturbs its normal endocrine function, causing dysregulated expression of secreted factors, which has been linked to the pathogenesis of various obesity-related diseases.<sup>226–228</sup> Herein we discuss the role of dysfunctional adipose tissue in the development of obesity-associated health risks (Fig. 3).

#### *Role of dysfunctional adipose tissue in obesity-associated health risks*

**Adipokines and type 2 diabetes.** During the progression from normal weight to obesity, changes in the circulating levels of adipocyte-derived factors play an important role in the pathogenesis of  $\beta$ -cell dysfunction and insulin resistance.<sup>229–231</sup> It has been observed that some adipokines have beneficial effects, whereas others have detrimental properties; however, the overall contribution of the changed concentrations of adipokines is highly dependent on the balance between these effects and the interactions between the adipokines, which act on the  $\beta$ -cell and insulin-sensitive organs such as the liver and muscle tissues by means of a number of intersecting intracellular signaling cascades.<sup>229–231</sup>

**Effects of adipokines on the  $\beta$ -cell function:** The biological effects of adipokines such as leptin, adiponectin, TNF- $\alpha$ , and IL-6 on  $\beta$ -cell function, including insulin synthesis and secretion, cell survival, and cell death, have been well documented in the literature.<sup>230,231</sup> Leptin inhibits the secretion of insulin from human and murine islets, as well as the pancreatic  $\beta$ -cell lines, through the activation of  $K_{ATP}$  channels,<sup>232–234</sup> reduction in the cellular concentration of cAMP,<sup>235</sup> alteration in the PLC-PKC pathway,<sup>236</sup> and activation of the PI3K pathway.<sup>230,236</sup> Leptin also reduces insulin mRNA expression by inhibiting the action of the insulin promoter and suppresses  $\beta$ -cell apoptosis through reduction of triglyceride accumulation,<sup>237,238</sup> inhibiting NO production,<sup>230,239</sup> and activating the antiapoptosis transcription factor, Bcl-2.<sup>240</sup>

The protective effects provided to  $\beta$ -cells by adiponectin have been reported in the literature. A defect in insulin se-

cretion has been observed in adiponectin knockout mice.<sup>241</sup> Globular domain adiponectin (gAd) is the functional adiponectin protein. The gAd transgenic *ob/ob* mice (a cross between the gAd transgenic mice and leptin-deficient *ob/ob* mice) exhibit higher plasma insulin levels, along with increased insulin sensitivity, compared to those seen in *ob/ob* litter-mates, indicating that adiponectin protects  $\beta$ -cells.<sup>242,243</sup> A direct effect of adiponectin has also been observed when gAd strongly inhibited palmitic acid- and cytokine-induced suppression of glucose, stimulated insulin secretion, and attenuated apoptosis of INS-1 cells.<sup>244</sup> Adiponectin also inhibits the accumulation of lipids through the activation of AMP protein kinase (AMPK) pathways in both rodent pancreatic  $\beta$ -cells and MIN6 cells.<sup>245</sup>

Data derived from various cell culture studies showed that TNF- $\alpha$  decreased glucose-induced insulin secretion from  $\beta$ -cells.<sup>246,247</sup> TNF- $\alpha$  increases expression of  $Ca^{2+}$ -independent adhesion molecules, which perturbs the segregation between  $\beta$ -cells and non- $\beta$ -cells; this alteration in the islet architecture may influence insulin secretion.<sup>248</sup> Activation of caspases and reduction in Bcl-2 expression have also been reported to play an important role in TNF- $\alpha$ -mediated apoptosis in  $\beta$ -cells.<sup>249–252</sup> A line of studies in the literature demonstrated the beneficial effect of IL-6 on insulin secretion from pancreatic islets.<sup>253–255</sup> Involvement of the PLC-IP3-dependent pathway plays an important role in IL-6-induced insulin secretion from pancreatic  $\beta$ -cells.<sup>253</sup> Moreover, IL-6 also increased the insulin secretion and the expression of preproinsulin mRNA through the  $Ca^{2+}$ -dependent pathway.<sup>254</sup>

**Role of adipokines on insulin resistance.** The adipokine leptin enhances the action of insulin on both the inhibition of hepatic glucose production and on glucose uptake,<sup>256</sup> which may perhaps explain the role of insulin in relation to insulin sensitivity.<sup>257</sup> It has been observed that plasma leptin concentrations are independently associated with insulin sensitivity.<sup>258</sup> The effect of leptin on insulin sensitivity in the liver and skeletal muscle is mediated through phosphorylation and activation of AMPK and inhibition of the activity of acetyl-CoA carboxylase.<sup>259,260</sup> Leptin-induced stimulation of the PI3K signaling pathway appears to be important for the regulation of glucose metabolism.<sup>261</sup> Leptin has also been shown to be effective in regulating feeding behavior through the central nervous system.<sup>262</sup> Leptin-deficient mice (*ob/ob*) show abnormally increased feeding, obesity, and insulin resistance, and the administration of leptin to these *ob/ob* mice reverses these changes.<sup>263</sup> However, high levels of leptin have been observed among obese individuals without any anorexic responses, indicating the occurrence of leptin resistance.<sup>263</sup>

Plasma adiponectin is another positive regulator of insulin sensitivity.<sup>264</sup> A significant negative correlation has been observed between age- and sex-adjusted HOMA IR levels and plasma adiponectin levels in a cross-sectional study of 2356 individuals (1998–2001).<sup>265</sup> It was observed that high-molecular-weight adiponectin may have a more insulin-sensitizing effect compared to its monomeric form.<sup>266</sup> Like leptin, adiponectin also enhances insulin sensitivity through the activation of AMPK.<sup>267</sup> Adiponectin also affects hepatic glucose production by regulating the mRNA expression of two essential gluconeogenesis enzymes: phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6PD).<sup>267</sup> Obesity-associated downregulation of adiponectin levels is a mechanism that might explain how obesity can cause insulin resistance and diabetes.<sup>267</sup>



TNF- $\alpha$ , the most widely studied cytokine, plays an important role in the modulation of insulin resistance. Deletion of TNF- $\alpha$  or the TNF- $\alpha$ -receptor resulted in significantly improved insulin sensitivity in both diet-induced obese mice and leptin-deficient *ob/ob* mice, suggesting a role for TNF- $\alpha$  in obesity-associated insulin resistance.<sup>268</sup> In the Framingham Offspring Study, it was observed that age- and sex-adjusted HOMA IR levels were positively associated with fasting plasma TNF- $\alpha$  levels.<sup>265</sup> In humans, adipose tissue TNF- $\alpha$  expression is associated with BMI, percentage of body fat, and hyperinsulinemia; a decrease in body weight reduces TNF- $\alpha$  levels.<sup>269</sup>

IL-6 is emerging as one of the potential mediators linking obesity-derived chronic inflammation with insulin resistance. Chronic exposure to IL-6 induces hepatic insulin resistance<sup>270,271</sup> and reduces glucose uptake in adipocytes.<sup>272</sup> Circulating IL-6 levels are elevated in obese and insulin-resistant subjects.<sup>273,274</sup> It can be speculated that a persistent increase in levels of IL-6, such as those that occur in a state of inflammation such as obesity and type 2 diabetes, may trigger insulin resistance. It has been observed that IL-6 can modulate insulin resistance through several distinct pathways, including JNK1-mediated serine phosphorylation of IRS1, I $\kappa$ B-mediated activation of NF- $\kappa$ B, and induction of suppressor of cytokine signaling-3 (SOCS-3).<sup>275</sup>

*Adipokines and cardiovascular dysfunction.* Abnormal production of the adipose tissue-derived factors, adipokines, has been implicated in the pathogenesis and progression of atherosclerosis, endothelial cell dysfunction, and altered expression of proangiogenic/proatherogenic factors such as vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs), leading to structural and functional changes in the endothelium.<sup>276,277</sup> In obese humans, elevated angiotensinogen is associated with the development of hypertension.<sup>278</sup> A decrease in body weight reduces the expression of WAT angiotensinogen expression and is thought to contribute to the concomitant fall in blood pressure.<sup>279</sup>

Various epidemiological studies demonstrate that reduced adiponectin levels correlate with increased risk of CVD in obese individuals.<sup>280,281</sup> Many experimental studies demonstrate that adiponectin ameliorates the progression of macrovascular disease and this is consistent with its correlation with improved vascular outcomes in epidemiological studies.<sup>281,282</sup> The mechanisms of adiponectin signaling vary among its cellular sites of action. In endothelial cells, adiponectin protects cells from high glucose or TNF- $\alpha$ -induced inflammation through the activation of AMP-activated protein kinase and cyclic AMP-dependent protein kinase signaling cascades.<sup>281,283,284</sup> In the myocardium, adiponectin-mediated protection from ischemia-reperfusion injury is linked to COX2-mediated suppression of TNF- $\alpha$  signaling, inhibition of apoptosis by the activation of AMPK signaling pathways.<sup>281</sup> Ox-LDL-induced alteration in adipokine secretion can also induce CVD complications.<sup>138</sup>

Numerous studies demonstrate the association between circulating levels of leptin and CVD.<sup>285,286</sup> Although many paradoxical effects have been reported, for the most part, elevated circulating leptin levels have been observed in the majority of obese individuals,<sup>287,288</sup> while a lack of leptin (as observed in the genetic animal model of leptin deficiency) has been associated with hypertension, atherosclerosis, stroke, and myocardial infarction.<sup>285,286</sup> Recently, it has been documented that circulating leptin levels significantly correlate with heart failure among obese individuals without pre-existing CHD.<sup>289</sup>

The effects of leptin on the cardiovascular system are not straight forward enough to definitively summarize, and it is important to consider other parameters such as aging, degree of hyperleptinemia, and the coexistence of other factors, which may also have an impact on cardiovascular function.

A degree of cross talk has been observed between resistin and other cytokines: a linear relationship with leptin and a reciprocal relationship with adiponectin. Elevated plasma levels of resistin correlate with proatherogenic inflammatory markers,<sup>290</sup> increased cardiovascular risk, endothelial dysfunction (through promotion of adhesion molecules, endothelial migration, and proliferation), unstable angina, and poor prognosis with regard to coronary artery disease.<sup>291,292</sup> Resistin induces the proliferation of human aortic smooth muscle cells through the PI3K/AKT and MAPK (p42/44) signaling pathways.<sup>293</sup> Resistin also enhances the migration and proliferation of endothelial cells through the activation of p38 and p44/42 MAPKs.<sup>294</sup> Moreover, in isolated coronary artery rings, resistin can induce endothelial dysfunction.<sup>295</sup> Resistin has been shown to increase transcriptional events, leading to increased expression of several proinflammatory cytokines, including IL-1, IL-6, IL-12, and TNF- $\alpha$  in an NF- $\kappa$ B-mediated pathway.<sup>296,297</sup>

*Adipokines and cancer.* Various epidemiological studies demonstrate an association between obesity and a range of various cancer types, although the mechanisms by which obesity induces or promotes tumorigenesis vary from one cancer site to another.<sup>298</sup> These include insulin resistance and chronic hyperinsulinemia, a low-grade chronic inflammation, and increased bioavailability of steroid hormones.<sup>298</sup> Elevated leptin levels have been implicated in the pathogenesis of certain human cancers, including esophageal and hepatocellular carcinomas.<sup>299</sup> Leptin-induced stimulation of insulin-like growth factor-1 (IGF-1) and other growth hormone secretagogues may increase cellular proliferation and/or dedifferentiation,<sup>300</sup> and enhance angiogenesis, all of which may promote neoplasia.<sup>301</sup> Leptin also acts as a promoting factor for hepatocellular carcinoma,<sup>302</sup> as well as inhibiting apoptosis in esophageal cancer.<sup>303</sup> Adiponectin, in contrast, reduces the expression of adhesion molecules and provides some protection against carcinogenesis by inhibiting cancer cell growth and tumor-associated angiogenesis.<sup>304,305</sup> Lower levels of circulating adiponectin have been observed in patients with various types of cancers and may contribute to their severity.<sup>304,305</sup> Hyperinsulinemia, a pathological event common to obesity, has been associated directly with colon cancer in obese humans.<sup>306</sup> The inflammatory adipokines associated with obesity also contribute to the development of pancreatic adenocarcinoma.<sup>298</sup>

*Adipokines and respiratory disorders.* Obesity is associated with both sleep disorders and asthma, an association that might be partially explained by the physical impairment caused by the presence of fat on both the chest wall and diaphragm.<sup>307</sup> However, abdominal obesity is also associated with an increased prevalence of asthma.<sup>308</sup> It has been reported that both asthma and obesity were independently and synergistically associated with systemic inflammation.<sup>309</sup>

*Adipokines and asthma.* Many of the proinflammatory cytokines, whose levels are elevated in the plasma of obese subjects, also play an important role in the pathogenesis of asthma.<sup>310</sup> For instance, TNF- $\alpha$  can increase airway inflammation<sup>311</sup> and enhance airway contractility,<sup>312</sup> both TNF- $\alpha$  and IL-6 can modulate T-helper 2 cell immunity,<sup>153,313</sup> and leptin may facilitate airway hyper-responsiveness.<sup>314</sup>

*Adipokines and sleep disorders.* In normal subjects, secretion of adipokines such as TNF- $\alpha$  and IL-6 in a circadian rhythm is involved in the regulation of physiological sleep patterns.<sup>315-318</sup> Increased secretion of IL-6 is associated with excessive daytime sleepiness and fatigue,<sup>319</sup> while a decrease in overall secretion of IL-6 is associated with a good night's sleep and a sense of well-being the next day.<sup>315</sup> Both TNF- $\alpha$  and IL-6 are elevated in sleep apnea independently of obesity.<sup>320</sup> In a recent study it was observed that sleep disorder breathing is associated with elevated levels of CRP, independent of age, BMI, WC, or body fat percentage, suggesting an association between low-grade inflammation and sleep disorders.<sup>321</sup>

*Adipokines and liver dysfunction.* Animals lacking leptin due to leptin gene mutation or leptin receptor gene mutation are obese, insulin resistant, and have hepatic steatosis.<sup>322,323</sup> Leptin injections reduce their fatty livers and metabolic abnormalities<sup>324</sup> through the activation of hepatic stellate cells and the modulation of Kupffer cell function. In obese NAFLD patients, plasma leptin levels are elevated and directly correlated with the severity of hepatic steatosis,<sup>325</sup> suggesting that there exists a state of leptin resistance in obesity.<sup>326</sup>

Various studies have suggested a link between lower circulating levels of adiponectin and increased liver fat content and the degree of hepatic insulin resistance.<sup>327</sup> Administration of adiponectin decreased hepatic insulin resistance in a mouse model of obesity and diabetes through the activation of the AMPK signaling pathway.<sup>327</sup> Local production of IL-6 and TNF- $\alpha$  by Kupffer cells has been proposed to play an important role in the pathogenesis of NAFLD.<sup>328</sup> Both IL-6 and TNF- $\alpha$  are potent inhibitors of adiponectin expression and high levels of these cytokines in obesity and NAFLD explain this relationship.<sup>329</sup> IL-6 causes hepatic insulin resistance by the inhibition of IRS phosphorylation mediated by activating the SOCS-3 protein.<sup>271,330</sup>

*Adipokines and renal dysfunction.* Altered levels of adipokines, including leptin, adiponectin, resistin, and visfatin, are associated with obesity-related renal dysfunction because they increase the risk of developing albuminuria by alteration of the GFR and modulation of renal tubule function.<sup>331</sup>

Alteration in circulating leptin concentrations plays an important role in the development of renal dysfunction. Elevated levels of leptin cause hypertrophy in glomerular mesangial cells through the activation of the PI3K and ERK1/2 pathways<sup>332</sup>; glomerular mesangial hypertrophy increases the amount of filtered protein and albumin.<sup>333,334</sup> In addition, elevated leptin increases the accumulation of collagen and the secretion of TGF- $\beta$ 1 from glomerular endothelial cells. An increase in TGF- $\beta$ 1 is associated with thickening of the basement membrane, leading to the development of glomerulosclerosis.<sup>335</sup> Elevated leptin also increases the expression of matrix metalloproteinase-2 (MMP-2) in renal mesangial cells.<sup>336</sup> Patients with end-stage renal disorders have an estimated 4- to 7.5-fold higher plasma leptin concentrations compared to that of healthy control subjects, suggesting a link between elevated leptin levels and the development of CKD in the absence of obesity.<sup>337,338</sup>

Hypoadiponectinemia has been associated with the development of renal dysfunction and CKD.<sup>339,340</sup> It has been reported that adiponectin is an independent predictor of CKD.<sup>339,340</sup> Hypoadiponectinemia causes an increase in tubular inflammation by decreasing tubular AMPK activation and causing an accumulation of MCP-1.<sup>341</sup> Mice with

hypoadiponectinemia treated with adiponectin exhibit podocyte fusion leading to an improvement in glomerular podocyte foot processes through activation of AMPK.<sup>340</sup>

The circulating resistin level is also linked to the albumin-to-creatinine ratio and the GFR.<sup>342,343</sup> Plasma resistin levels are elevated in uremia, primarily because of reduced renal clearance and inflammation.<sup>344</sup> An increased resistin level is associated with a decrease in GFR, which may be due to the activation of macrophages and enhanced inflammatory responses.<sup>342,343</sup> Visfatin, a new adipokine, is significantly associated with inflammation/endothelial dysfunction in CKD.<sup>345</sup> Elevated visfatin levels have been observed in diabetic patients with CKD.<sup>346</sup> Visfatin has been shown to increase the secretion of the inflammatory cytokines such as TNF- $\alpha$ , IL-6, and IL-1 $\beta$ .<sup>345</sup> Exposure to elevated levels of visfatin in glomerular mesangial cells increased the mRNA expression of both renin and angiotensinogen; changes in renin and angiotensinogen levels are linked with alteration in GFR leading to renal dysfunction.<sup>347</sup>

*Adipokines and infertility.* Recent studies in the literature have reported that alterations in adipokine levels, or in their mechanism of action, are associated with fertility impairment and pregnancy diseases.<sup>348,349</sup> An increase in serum leptin levels has been observed among infertile obese men and women.<sup>350</sup> Excess levels of leptin have a deleterious effect on sperm production and the formation of androgens by Leydig cells.<sup>351</sup> Increased serum leptin concentrations have been observed in women with PCOS compared to those of weight-matched control subjects,<sup>352</sup> but these observations are dependent on ethnicity, heterogeneity of the PCOS group, or the different sampling methods used to get fat biopsies in the various studies.<sup>349</sup> Adiponectin, in contrast, is described as a beneficial adipokine in reproduction.<sup>353</sup> Women diagnosed with PCOS also have reduced adiponectin levels, independent of obesity.<sup>354,355</sup> Genomic studies support the observation that hypoadiponectinemia is a causative agent for PCOS.<sup>354,355</sup> Various experimental studies demonstrate that adiponectin can directly induce ovarian gene expression.<sup>356,357</sup>

## Potential Strategies to Reduce the Pathogenesis of Obesity

A broad range of strategies are recommended to reduce the prevalence of obesity. Physical activity remains the most common therapy for the treatment of obesity and its associated health risks. There are several ways by which increased physical activity could be beneficial in reducing and preventing obesity.<sup>358</sup> Physical activity increases total energy expenditure and decreases total body fat, including fat around the waist, which can help people to reach and maintain a state of energy balance, as long as they are not taking in more food to compensate for the lost calories. Oh et al. reported that exercise training reduced the serum levels of inflammation and oxidative stress markers, ferritin and thiobarbituric acid reactive substances, and significantly increased the adiponectin levels among a total of 108 subjects who completed a 12-week exercise training program.<sup>359</sup>

*Ad libitum* food intake limiting to certain micronutrients is another important strategy for the regulation of obesity because of its relation to energy balance.<sup>360</sup> *Ad libitum* low-fat diets, high-protein diets, and low-carbohydrate diets are the proposed tools for facilitating weight loss.<sup>361,362</sup> Controlled food intake with variety in the composition of

macronutrients reduces a patient's feelings of being restricted to a particular diet, which might improve the weight loss program. A few long-term trials have demonstrated that maintenance of weight loss with *ad libitum* dietary programs achieved significant results compared to conventional energy-restricted diets.<sup>363,364</sup> The CARMEN trial also observed greater loss of weight and fat mass by the long-term intake of *ad libitum* low-fat, high-carbohydrate diets.<sup>365,366</sup>

Beside *ad libitum* food intake, a healthy dietary pattern is also necessary to regulate obesity and its associated health risks. However, adoption of healthy dietary habits is very difficult in an obesogenic environment, in which palatable, inexpensive, high-fat, and energy-dense foods are easily available. Dietary intake of macronutrients is gaining attention as an important factor in the regulation of obesity and its associated risk factors. A number of nutritional intervention studies using diets supplemented or enriched with different micronutrients have shown a variety of results regarding weight loss and weight management. Dietary supplementation with calcium has been shown to play an important role in the regulation of energy metabolism and obesity risk.<sup>367,368</sup> Supplementation with high calcium inhibited lipogenesis, stimulated lipolysis, lipid oxidation, and thermogenesis and thus prevented diet-induced obesity in mice.<sup>369</sup> One meta-analysis concluded that dietary calcium has the potential to increase fecal fat excretion, which is relevant for its potential contribution to weight loss.<sup>370</sup> Potassium and magnesium are two other well-known dietary micronutrients that could favor a decrease in blood pressure<sup>371</sup> and are the main components of the DASH diet, which is more effective for weight loss and metabolic variables.<sup>372,373</sup> Chromium, an essential trace element, is present in a wide variety of foods, including eggs, cereal, nuts, and vegetables.<sup>374</sup> A few clinical studies have reported the weight-lowering effect of chromium supplementation.<sup>375,376</sup>

Dietary consumption of more fruits and vegetables is also associated with a decrease in the prevalence of obesity.<sup>377</sup> The role of an increased consumption of fruits and vegetables in the prevention of overweight and obesity is linked to several features: high water content, relatively low-energy density, and high dietary fiber content.<sup>378</sup> Water has the greatest impact on energy density because it increases the weight of food without increasing calories and thus decreases energy density.<sup>379</sup> Consumption of whole apples (2.9% fiber) was associated with a higher satiety rating compared with the consumption of apple puree or fiber-free apple juice.<sup>380</sup> Similarly, whole oranges (2.5% fiber) versus orange juice (fiber free) and whole grapes (1.3% fiber) versus grape juice (fiber free) also confirmed that whole fruits provide more satiety than juice.<sup>381</sup> Dietary fibers, specially viscous dietary fibers, have also been shown to increase postprandial satiety and to decrease subsequent hunger in short-term studies.<sup>382</sup> In a review summarizing the effects of high- versus low-fiber diet interventions, it has been observed that participants on the high-fiber diets lost significantly more weight than those on the low-fiber diets.<sup>382</sup> Studies investigating the influence of vegetables on feeling full reported that adding at least 200 g of vegetables (carrot and spinach) to meals with equal calories enhanced the feeling of being full, suggesting a correlation between the dietary water and fiber content and the total weight of the meal.<sup>383–385</sup> These analyses support the importance of high water and fiber-rich foods, such as fruits and vegetables, in weight regulation.

Meal-replacement strategy may be one important pathway to combat against the prevalence of obesity.<sup>386–388</sup> Weight loss programs based on meal replacement for one or two meals per day with a product of defined nutrient and calorie content have shown to improve compliance with an energy-restricted diet as well as weight management in overweight and obese individuals.<sup>387,388</sup> Smeets et al. showed that a high-protein replacement meal was more satiating and had a higher thermogenic effect compared to a low-protein replacement meal.<sup>389</sup>

Certain pharmacological treatments have also been recommended in the management of obesity. Antiobesity medications are categorized according to their mode of action, such as inhibitors of fat absorption, inhibitors of the endocannabinoid system, or modifiers of the central nervous system.<sup>390,391</sup> Orlistat is a pancreatic lipase inhibitor that binds to lipase in gut lumen and prevents the hydrolysis and absorption of ~30% of the dietary fat contained in a meal.<sup>392</sup> Sibutramine, a selective inhibitor of neurotransmitter (serotonin and norepinephrine) reuptake, acts centrally to reduce food intake.<sup>392</sup> Phentermine is a sympathomimetic amine that promotes the release of catecholamine.<sup>393</sup> Common adverse effects of these drugs include several gastrointestinal adverse effects, diarrhea, insomnia, anxiety, and other effects on the central nervous system.<sup>393</sup> Due to the numerous adverse side effects and the related safety issues, many antiobesity medications, including drugs in the field of pharmacotherapy, have been withdrawn even after licensing.<sup>394</sup>

BAT is emerging as an important antiobesity tissue in humans.<sup>395,396</sup> An experimental rodent study demonstrated the beneficial role of brown fat against diet-induced obesity.<sup>397</sup> Transgenic mice with decreased brown fat develop glucose intolerance and insulin resistance<sup>398</sup> and are susceptible to diet-induced obesity, diabetes, and hyperlipidemia,<sup>399</sup> suggesting a protective role of brown fat against energy-dense diet-induced obesity in rodents.  $\beta$ 3-Adrenergic receptors ( $\beta$ 3-AR) are found predominantly in BAT and treatment with  $\beta$ 3-AR selective agonists caused a significant increase in energy expenditure and a decrease in obesity in rodents.<sup>400</sup> The occurrence of BAT in adult humans varies from 2% to 100%.<sup>401,402</sup> Possible BAT-oriented therapeutic treatments to combat obesity, aimed at increasing energy expenditure, might work in one of two ways: first, by stimulating the activity of already existing BAT and, second, by upregulating the occurrence of brown adipocytes by inducing the specific gene expression program of brown fat cells through specific molecular switches.<sup>396</sup> Wijers et al. reported a link between BAT activity and diet-induced thermogenesis in humans.<sup>403</sup> Recent data suggest the role of thyroid hormone in the regulation of BAT thermogenic activity through modulation of hypothalamic fat metabolism.<sup>404</sup>

## Conclusion

Obesity is the one of the most prevalent metabolic disorders of the 21st century. The rising epidemic of obesity is a serious healthcare catastrophe due to its strong association with several major downstream health consequences such as diabetes, cardiovascular complications, cancer, asthma, sleep disorders, hepatic dysfunction, renal dysfunction, and infertility. Oxidative stress has been suggested as a critical factor linking obesity with its associated complications. There are various biochemical mechanisms by which

obesity can induce systemic oxidative stress, such as activation of NOX, oxidative phosphorylation, glyceraldehyde auto-oxidation, PKC activation, polyol and hexosamine pathways, hyperleptinemia, low antioxidant defense, chronic inflammation, and postprandial ROS generation. The deposition of excess fat in the WAT inhibits its normal endocrine function, leading to the dysregulated expression of secreted factors, elevated plasma lipid levels, increased formation of reactive intermediates, impaired mitochondrial function, inadequate cellular antioxidant defense, and development of oxidative stress. This has been linked to the pathogenesis of a variety of obesity-related diseases. The development of obesity is characterized by the interplay of nature and nurture. Moreover, current epidemiological studies indicate that a major cause of the global obesity problem lies in alterations in dietary and physical activity patterns, while genetic and metabolic studies reveal that there are individuals who are more susceptible to weight gain than others. On the basis of the currently identified predominant determinants of obesity, various effective strategies are recommended to regulate or manage the prevalence of obesity, including regular physical activity, *ad libitum* food intake limiting to certain micronutrients, increased dietary intake of fruits and vegetables, and activation of brown fat. Furthermore, while some pharmacological therapeutics have also been found to help regulate obesity, most of the commonly used pharmacotherapies are associated with serious adverse health effects. At present, modification of life style, increased physical activity and adoption of a healthy diet, including more fruits, vegetables, and balanced micronutrients, have been suggested as beneficial strategies to overcome or regulate the prevalence of obesity and its associated risk factors.

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