The Pathophysiology of Obesity and Its Clinical Manifestations

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Abstract: Obesity is an exaggeration of normal adiposity and is a central player in the pathophysiology of diabetes mellitus, insulin resistance, dyslipidemia, hypertension, and atherosclerosis, largely due to its secretion of excessive adipokines. Obesity is a major contributor to the metabolic dysfunction involving lipid and glucose, but on a broader scale, it influences organ dysfunction involving cardiac, liver, intestinal, pulmonary, endocrine, and reproductive functions. Inflammatory, insulin-resistant, hypertensive, and thrombotic-promoting adipokines, which are atherogenic, are counterbalanced by anti-inflammatory and anti-atherogenic adipocyte hormones such as adiponectin, visfatin, and acylation-stimulating protein, whereas certain actions of leptin and resistin are pro-atherogenic. Adiponectin is protective against liver fibrosis due to its anti-inflammatory effect, whereas inflammatory cytokines such as tumor necrosis factor-α are detrimental for both fatty liver and pancreatic insulin release. Obesity contributes to immune dysfunction from the effects of its inflammatory adipokine secretion and is a major risk factor for many cancers, including hepatocellular, esophageal, and colon. Because of the accelerating effects that obesity has on the worsening of metabolic syndrome and cancer, it has the potential to be profoundly detrimental to our species if major methods of prevention and/or effective treatment are not realized. It is essential then to institute major educational efforts aimed at promoting better eating habits and physical exercise.

Keywords
Pathophysiology, obesity, lipotoxicity, inflammatory cytokines, clinical correlations

General Considerations

Much has been learned in the past decade regarding the regulation of obesity as it relates to the molecular regulation of appetite that affects energy homeostasis, particularly as positive energy balance upsets lipid and glucose metabolism.[1,2] Furthermore, obesity appears to play a central role in the dysregulation of cellular metabolism that accounts for insulin resistance in diabetes mellitus type 2. Excess adipocytes secrete numerous cytokines that contribute to

vascular dysfunction in hypertension and dyslipidemia, as manifested by hypercholesterolemia and triglyceridemia. These conditions eventually contribute to significant atherosclerosis, and when associated with obesity and/or diabetes and insulin resistance, they constitute the metabolic syndrome.[3,4] New knowledge related to fatty liver and its association with inflammation, as well as visceral adiposity's effect on gastroesophageal reflux, gallstone disease, and cancer of the bowel, also make the liver and gut vulnerable to comorbidities of obesity.[4-7] A detailed explanation of the pathophysiology of obesity, or excess adiposity, and its comorbidities follows.

Dysregulation of Lipid and Glucose Metabolism: Lipotoxicity and Insulin Resistance in Obesity

The abundance of stored fat is required for survival during nutritionally deprived states such as starvation. In times of prolonged abundance of food, however, very efficient fat storage results in the excessive storage of fat, eventually resulting in obesity.[8-10] It has been hypothesized that the storage of fatty acid as triacylglycerol within adipocytes protects against fatty acid toxicity; otherwise, free fatty acids would circulate freely in the vasculature and produce oxidative stress by disseminating throughout the body. However, the excessive storage that creates obesity eventually leads to the release of excessive fatty acids from enhanced lipolysis, which is stimulated by the enhanced sympathetic state existing in obesity. The release of these excessive free fatty acids then incites lipotoxicity, as lipids and their metabolites create oxidant stress to the endoplasmic reticulum and mitochondria. This affects adipose as well as nonadipose tissue, accounting for its pathophysiology in many organs, such as the liver and pancreas, and in the metabolic syndrome.[11,12] The free fatty acids released from excessively stored triacylglycerol deposits also inhibit lipogenesis, preventing adequate clearance of serum triacylglycerol levels that contribute to hypertriglyceridemia. Release of free fatty acids by endothelial lipoprotein lipase from increased serum triglycerides within elevated β lipoproteins causes lipotoxicity that results in insulin-receptor dysfunction. The consequent insulin-resistant state creates hyperglycemia with compensated hepatic gluconeogenesis. The latter increases hepatic glucose production, further accentuating the hyperglycemia caused by insulin resistance. Free fatty acids also decrease utilization of insulin-stimulated muscle glucose, contributing further to hyperglycemia.[13,14] Lipotoxicity from excessive free fatty acids also decreases secretion of pancreatic β-cell insulin, which eventually results in β-cell exhaustion (Figure 1).[15]

The Specific Role of Adipocyte Inflammatory Secretagogues (Adipocytokines), Including Effects of Hypertension, Macrophage, and Immune Functions

Sites and Function of Adipokines

Adipocytes, consisting of over one billion cells, not only store triacylglycerol in fat depots in various body sites to provide energy reserves, but in aggregate constitute the largest endocrine tissue that constantly communicates with other tissues by adipocyte-released secretagogues, such as the proteohormones lectin, adiponectin, and visfatin. Along with insulin, these proteohormones help regulate body-fat mass.[16,17] Other gene groups that contribute to adipocyte adipokines include cytokines, growth factors, and complement proteins.[17] These include the inflammatory adipokines tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6 that cause local steatonecrosis, but are also distributed by the vascular system and cause inflammation elsewhere.[18] The enhanced fat content in muscle becomes so significant in severe obesity that whole-body magnetic resonance imaging reveals cumulative fat depots in muscle sites similar in size to that of total visceral adipose tissue.[19] Buttock fat appears to be largely inert with respect to endocrine function, as this fat is used largely for long-term energy reserves.[20] Visceral fat depots release inflammatory adipokines, which, along with free fatty acids, provide the pathophysiologic basis for comorbid conditions associated with obesity such as insulin resistance and diabetes mellitus type 2.[21] Visceral adipokines are transported by the portal vascular system to the liver, enhancing nonalcoholic steatohepatitis (NASH), and also by the systemic circulation to other diverse sites. Along with fatty-acid lipotoxicity, visceral adipokines also contribute to the adipokine inflammatory injury that leads to pancreatic β-cell dysfunction, which, in turn, decreases insulin synthesis and secretion.

Role of Specific Adipokines

Dyslipidemia, hypertension, and atherogenesis are comorbid conditions, in addition to insulin resistance, that are associated with obesity and adversely influenced by the secretion of diverse inflammatory adipokines, particularly from white adipose tissues (WAT) in visceral fat depots.[22] Specific adipokines enhance endothelial vasomotor tone by secreting renin, angiotensinogen, and angiotensin II, which are similar to those within the renal renin-angiotensin system (RAS), but when secreted from adipocytes, enhance hypertension in obese patients.[23] TNF-α secretion increases in proportion to increased total body-fat mass and enhances inflammation in fatty livers and fat depots elsewhere, particularly in pancreas, mesentery, and gut visceral sites.[24] Inflammatory markers that are

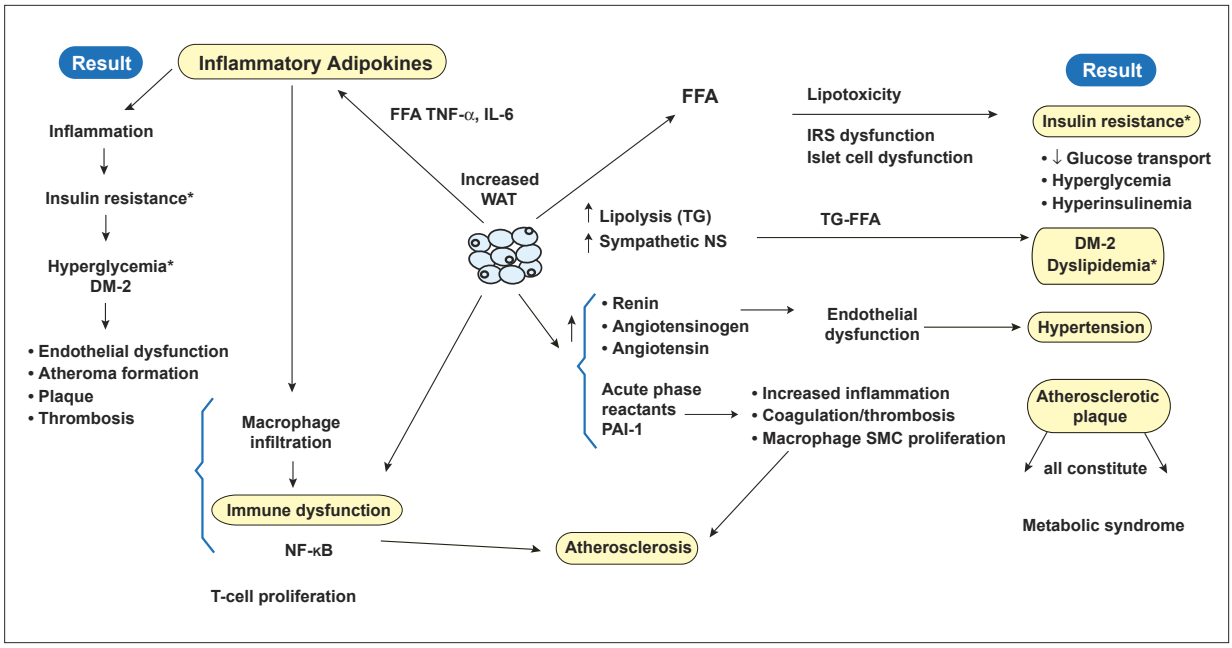

Figure 1. Role of lipotoxicity and inflammation on obesity. White adipose tissue (WAT) releases pre–fatty acids and adipokines, which are lipotoxic and inflammatory and result in diverse effects, outlined in the left-hand columns. Their correlation to the metabolic syndrome is shown on the right-hand column, whereas all the effects culminate in atherosclerosis on the bottom of the figure.

*Perturbed glucose and lipid metabolism.

DM-2=diabetes mellitus-2; FFA=free fatty acids; IL=interleukin; IRS=insulin receptor substrate; NF-κB=nuclear factor kappa beta; NS=nervous system; PAI-1=plasminogen activator inhibitor-1; SMC=smooth muscle cell; TG=triglyceride; TNF=tumor necrosis factor.

increased in obesity commonly contribute to inflammatory conditions such as NASH[25] and in the bronchial tree of patients with obstructive sleep apnea.[26] These markers include not only TNF-α and IL-6, but also acute-phase reactants such as C-reactive protein, α1 acid glycoprotein, and the specific amyloid antigen, particularly in the fatty liver.[23] The acute-phase reactants are important inflammatory markers that are also upregulated in the insulin-resistant state associated with diabetes mellitus type 2 and NASH.[25,27] Adipocytes also stimulate fat-associated macrophages that also secrete monocyte chemoattractant protein 1 (MCP-1), macrophage migration inhibiting factor (MMIF), and resistin, all of which decrease insulin sensitivity (ie, enhance insulin resistance).[23,24,28-30] These macrophages contribute to the enhanced inflammatory state and, as immune stimulators, enhance the mitogen-activated protein kinase family (C-Jun N-terminal Kinase, inhibitor of nuclear factor kappa beta [NF-κB] Kinase b, and phosphatidylinositol 3-Kinase), inducing the transcription factor NF-κB that allows dephosphorylation of the IRS-1 and -2 docking proteins. The latter inhibits the GLUT4 transporter of glucose, resulting in insulin resistance (Figure 2).[31,32]

The progressive proinflammatory state resulting from increased obesity that promotes insulin resistance also perpetuates atherogenesis throughout its development, from early endothelial fatty streaks to late-plaque formation, rupture, and thrombosis. Endothelial modulators—such as vasoactive endothelial growth factor,[33] plasminogen activator inhibitor-1,[34] angiotensinogen, renin, and angiotensin II[31]—are secreted by white fat cells, in particular by perivascular fat tissues that contribute to vasomotor dysfunction and cause hypertension and endothelial injury.[35] This process is followed by the formation of foam cells following the enhanced endothelial uptake of oxidized low density lipoproteins, free fatty acids, and other lipid metabolites that accumulate as a result of fatty acid peroxidation—all of which originate from dyslipidemic β-lipoproteins. Both endothelial and adipose cell lipoprotein lipase activity are also decreased by inflammatory cytokines such as IL-6, so that by inhibiting lipolysis they increase serum triacylglycerol levels accentuating hyper-triglyceridemia.[32,36-38] Later, as atherosclerosis progresses with macrophage and smooth–muscle cell infiltration, there is additional secretion of other cytokines, such as MCP-1, MMIF, and endothelin-1,

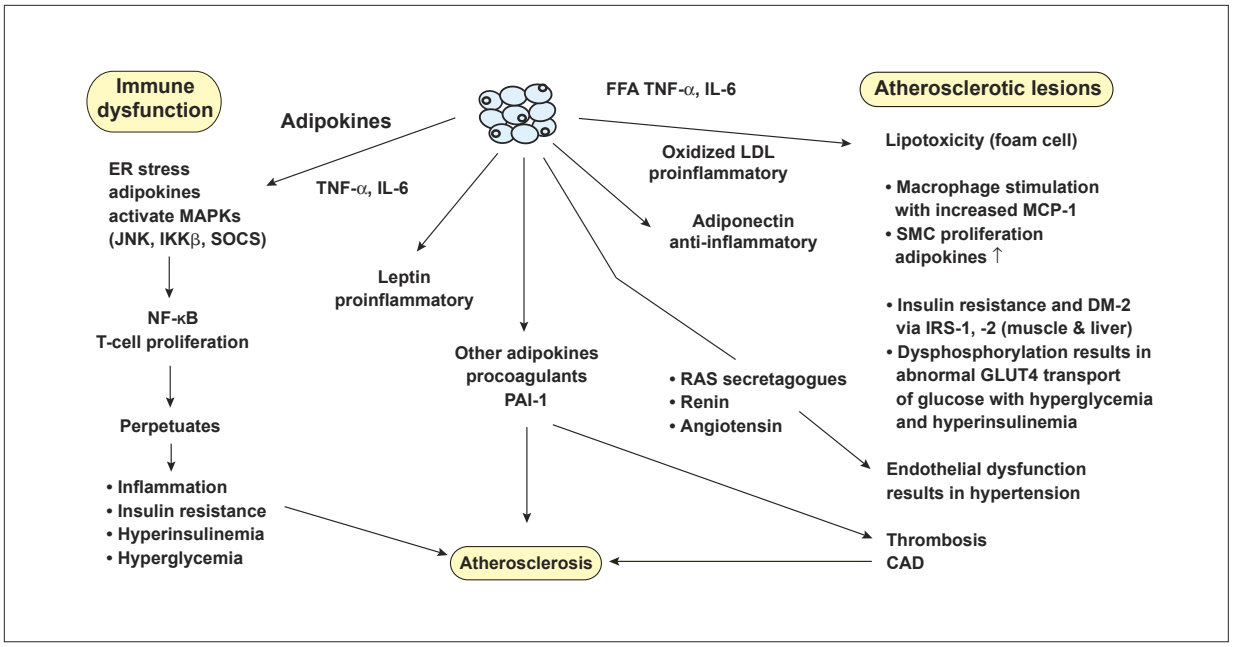

Figure 2. Role of inflammation and immune dysfunction in obesity. The immune dysfunction (left column) and inflammation (center column with arrows) are correlated with atherosclerotic lesions (right column).

CAD=coronary artery disease; DM=diabetes mellitus; ER=endoplasmic reticulum; FFA=free fatty acids; IKKβ=inhibitor of NF-κB kinase b; IL=interleukin; IRS=insulin receptor substrate; JNK=Jun N-terminal kinase; LDL=low-density lipoproteins; MAPK=mitogen-activated protein kinase; MCP-1=monocyte chemotactic protein; NF-κB=nuclear factor kappa beta; PAI-1=plasminogen activator inhibitor-1; RAS=renin angiotensin system; SMC=smooth muscle cell; SOCS=suppressor of cytokine signaling; TNF=tumor necrosis factor.

that enhance the evolving inflammatory lesions of atherosclerotic plaques within the vascular wall.[4,28] Other adipokine procoagulants include plasminogen activator inhibitor-1, IL-6, tumor growth factor-β, and TNF-α, which cause thrombosis, particularly from ruptured atherosclerotic plaques.[6,34] Progression of atherosclerosis with plaque formation and remodeling of collagen results from the action of matrix metalloproteinases also secreted by adipocytes.[39] This activity causes atheroma cap thinning and plaque rupture that precipitates release of the tissue factor, also promoting intravascular thrombosis.[39] Adipokines also enhance angiogenesis and promote adipogenesis by neovascularization enhancement of WAT.[34] Figure 2 shows immune and inflammatory mediator effects on the comorbidities of obesity, including atherosclerosis.

Anti-inflammatory Secretagogues

To counter these injurious inflammatory secretagogues, adipose cells also secrete anti-inflammatory hormones, such as adiponectin, visfatin, and the complement-related acylation-stimulating protein, which exert beneficial effects inhibiting inflammatory adipokines. In this fashion, protective hormones and complement proteins become both anti-inflammatory and anti-atherogenetic in action, as they concomitantly enhance insulin sensitivity and improve vascular endothelium dysfunction. This effect is most obvious when these anti-inflammatory adipokines become deficient, as when adiponectin levels decrease with increasing obesity.[17] It is probable that adiponectin receptor deficiency, inflammatory adipokines, as well as excessive fatty acids, all contribute to insulin resistance and other comorbidities of obesity—including hypertension, dyslipidemia, and atherosclerosis—as obesity is the common cause of these disorders. Interestingly, leptin may act as both an anti-inflammatory and pro-inflammatory secretagogue, in that it enhances insulin sensitivity for glucose uptake in muscle but promotes inflammation and angiogenesis at other sites (Table 1).

In summary, inflammatory, insulin-resistant, hypertensive, and thrombotic-promoting adipokines that are atherogenic are counterbalanced by anti-inflammatory and anti-atherogenic adipocyte hormones, such as adiponectin, visfatin, and acylation-stimulating protein, whereas certain actions of leptin and resistin are pro-atherogenic.

Table 1. Adipocyte Secretagogues—Mechanism of Action

Adipokine Promoters	Inhibitors or Atheroprotective
Inflammatory	**Anti-inflammatory**
IL-1, IL-6, TNF-α, IFN-α, IFN-β IL-8, IP-10, MCP-1, TGF-β, leptin Resistin, RANTES, markers of inflammation,* immune regulators†	IL-10, IL-4, TGF-β
Hypertensive	**Antihypertensive**
Renin, angiotensin system, angiotensinogen, angiotensin II	Angiotensin II receptor blocker
Insulin resistance	**Insulin sensitivity**
TNF-α, IL-6, resistin	Adiponectin, leptin, AgRP, MMIF, acylation-stimulating protein (stimulates glucose transport)
Procoagulant	**Anticoagulant**
Plasminogen activator inhibitor-1, tissue factor TNF-α, IL-6, TGF-β	Adiponectin
Angiogenetic	**Atheroprotective**
Leptin, IL-8, VEGF, FGF-2, MCP-1, IP-10, VCAM, ICAM-1, monobutyrin	Adiponectin
Lipogenetic (adipogenesis)	**Lipolysis**
Agouti protein insulin-like growth factor 1, angiotensinogen, angiotensin II, acylation-stimulating protein, visfatin	TNF-α, IL-6

*Markers of inflammation: CRP, SAA, fibrinogen (acute phase reactants).

†Immune regulators: IL-6, IL-8, MMIF, leptin.

AgRP=agouti-related protein; CRP=C-reactive protein; FGF=fibroblastic growth factor; ICAM=intercellular adhesion molecule; IFN=interferon; IL=interleukin; IP-10=interferon γ inducible protein-10; MCP=monocyte chemoattractant protein; MMIF=macrophage migration inhibiting factor; RANTES=regulate upon activation of novel T-cell expression sequences; SAA= serum amyloid A; TGF=tumor growth factor; TNF=tumor necrosis factor; VCAM=vascular cell adhesion molecule; VEGF=vascular endothelial growth factor.

The Clinical Manifestations of Obesity

The Associated Inflammatory State in Obesity as a Major Contributor to the Metabolic Syndrome X

The understanding of the pathophysiology of obesity and its comorbidities reveals the central role that obesity plays as a result of the action of inflammatory adipokines in metabolic syndrome X. These comorbidities include diabetes mellitus type 2, whereby insulin resistance is worsened by TNF-α and other inflammatory adipocyte secretagogues[21]; endothelial dysfunction and hypertension, which results from the activity of RAS-secreting adipokines[33,40]; and dyslipidemia, which is caused by hypercholesterolemia and hypertriglyceridemia. These comorbidities and the effects of fatty acid lipotoxicity[41] culminate to promote atherogenesis, including coronary artery disease. All these disorders are adversely affected by enhanced upregulation of NF-κB from visceral WAT inflammatory adipokines.[3,42,43] Other conditions that appear to contribute to metabolic syndrome include chronic renal disease,[44] obstructive sleep apnea,[45] and non-alcoholic fatty-liver disease.[46] In each disorder, immune responses engendered by inflammation (Figure 2) accentuate the dysfunction of the involved tissue, whether in adipose tissue, muscle, or vascular endothelium, or in multiple organs such as the liver, heart, and kidney. In summary, the profound effect that these inflammatory adipokines have on obesity and its comorbidities, including atherosclerosis,[3,4,5,6] makes obesity the number one preventable public health problem in the United States and an increasing risk factor in the rest of the world.[47-50]

Obesity and Cancer

Besides the profound effect that obesity has on the manifestations of inflammation in many tissues and organs, it is a major risk factor for many forms of cancer, including breast, colon, endometrial, esophageal, hepatocellular, renal, and prostate cancer. A mechanism for this association was first realized when hyperinsulinemia was found to be a risk factor for colon cancer in obese patients.[51] The combined effects of diabetes, insulin resistance, and increased body-mass index (BMI) were all later determined to contribute to the pathogenesis of colorectal cancer.[51] Obesity accounts for 20–33% of the risk for breast, esophageal, endothelial, and kidney cancer.[52,53] Mechanisms of carcinogenesis or tumor growth include

perturbed cellular proliferation, dedifferentiation and/or apoptosis, angiogenesis, and chronic adipokine-associated inflammation, along with the effects of cancer genes and/or environmental toxins that enhance inflammation. Examples of adipose tissue adipokines that promote cancer include stimulating insulin-like growth factor-1 and other growth hormone secretagogues, such as leptin that enhance cellular proliferation and/or dedifferentiation.[54,55]

In a landmark paper, Calle and colleagues[56] determined that among men who did not initially have cancer and who were then followed for 16 years, those with BMIs of 30–34.9 had a 20% higher death rate from prostate cancer, whereas those with BMIs of 35–39.9 had a 34% higher death rate compared with men with normal BMIs. Although testosterone itself is a key prostate growth factor that may enhance cellular proliferation, it was speculated that enzymatic conversion of testosterone to estradiol within cells of benign prostatic hypertrophy caused them to dedifferentiate into prostate cancer cells.[57-59] A meta-analysis of multiple studies showed a relationship between obesity and advanced cancer but not early prostate cancer.[60,61]

Hepatocellular cancer is also linked to the associated comorbidity of fatty liver in obesity, which, after progressing from steatonecrosis to cirrhosis, becomes a risk factor for hepatocellular cancer. High leptin levels are also found in these obese patients and may be a growth-promoting factor for this cancer.[62] Pancreatic cancer may be linked to obesity as a result of associated inflammatory adipokines, which not only upset glucose transport, causing insulin resistance, but combined with hyperinsulinemia, hyperglycemia, and lipotoxicity, all may lead to pancreatic β-cell inflammation and their exhaustion. It is speculated that the pancreatic dysplasia resulting from chronic inflammation associated with chronic pancreatitis promotes progression to pancreatic adenocarcinoma.[7,63] Although depression and hypercoagulable states are features of pancreatic cancer, both conditions are enhanced in obese patients with pancreatic cancer.

Similarly, multiple etiologies may contribute to both obesity and chronic inflammation that are risk factors for esophageal carcinoma. The chronic inflammatory state related to the chronic esophageal acid reflux common in obesity results in Barrett esophagus, whose pathologic hallmark is intestinal metaplasia. This may also be accentuated by chronic adipokine injury from visceral periesophageal adiposity appearing to enhance the progression of metaplasia to high-grade dysplasia, the premalignant precursor to esophageal carcinoma. Further complications of visceral adiposity include hiatal hernial formation and its associated decreased esophageal sphincter function, which, with increased abdominal pressure from visceral adiposity, further enhances gastric reflux.[64] In addition, increases in the leptin levels seen in obesity may also contribute to cellular proliferation, dedifferentiation, and inhibition of apoptosis in this cancer.[65]

Adipokine secretagogues such as unbound insulin-like growth factor also enhance angiogenesis, which promotes cancer growth in general.[66] Adiponectin, the adipocyte-secretory proteohormone, protects against angiogenesis, but decreased adiponectin levels in obesity allows the progression from enhanced angiogenesis to cancer.[67,68] Cancer-promoting factors enhanced by estrogenization occur in breast, endometrial, ovarian, and prostate cancers, whereas increased leptin levels have been found in renal, esophageal, and hepatocellular carcinomas. Much more information is needed to explain the molecular biology of obesity that would be responsible for the development of individual cancers, particularly those due to cancer genes and environmental toxins that could compound inflammation engendered by inflammatory adipokines in obesity.

Other Comorbidities Related to Obesity

Comorbidities also result from the burden of weight and space-occupying effects of obesity. These include enhanced degenerative joint disease that results from increased weight-bearing on joints due to increased adiposity and the injurious effects that inflammatory adipokines such as resistin have on joint synovia and muscle function.[69,70] Comorbidities involving the respiratory system include obstructive sleep apnea, which results from accumulation of extra adipose tissue within the confines of the upper respiratory tract, and hypopharynx, which adversely affects ventilation, with secondary hypoxia and even hypercapnia. Excessive bronchial and peribronchial adipose cells secrete inflammatory adipokines that enhance bronchial mucosal and submucosal inflammation, causing reactive airway disease including asthma in women.[26] Pulmonary embolism also occurs at higher rates in patients with obesity, particularly in those with decreased mobility.

Cholesterol gallstone disease is also associated with obesity, particularly in overweight women of child-bearing age. During fasting, there is enhanced mobilization of cholesterol from fat depots, which pass through the liver into the biliary ducts. This allows increased biliary cholesterol secretion and supersaturation of bile in the gallbladder, promoting gallstone formation.[71] Such gallstones invoke a local inflammatory state, which, when chronic, becomes a risk factor for gallbladder cancer.

Obesity is also a feature of polycystic ovarian syndrome, in which adipocyte secretagogues enhance the metabolic abnormalities of hyperandrogenemia, insulin resistance, and, along with inflammatory adipokines, increase the incidence of diabetes mellitus type 2 in this disorder.[72] Obesity is a risk factor for preeclampsia and

eclampsia of pregnancy, in which increased adipokines include RAS, prostaglandins, and other fatty-acid derivatives. Adipocytes also secrete these substances, which exacerbates hypertension and fluid retention in this syndrome. Endarteritis within the placenta may also be related to the increased inflammatory adipokines that contribute to preeclampsia.[73] Many of these disorders improve or even disappear with the elimination of obesity. Obesity in women causes a predisposition to depression, amenorrhea, menorrhagia, infertility, and urinary stress incontinence. Obesity is associated with poor wound-healing, which in morbid obesity is magnified by chronic renal failure and calcific necrosis or calciphylaxis.[74]

Summary

Obesity is an exaggeration of normal adiposity and is a central player in the pathophysiology of diabetes mellitus, insulin resistance, dyslipidemia, hypertension, and atherosclerosis, largely because of its secretion of excessive adipokines. Obesity is a major contributor to the metabolic dysfunction involving lipid and glucose, but on a broader scale, it influences organ dysfunction involving cardiac, liver, pulmonary, endocrine, and reproductive functions. Finally, obesity contributes to immune dysfunction from the effects of its secretion of inflammatory adipokines and is a major risk factor for many cancers. Because of the accelerating effects it has on the worsening of metabolic syndrome and cancer, obesity has the potential to be profoundly detrimental to our species if major methods of prevention and/or effective treatment are not realized.[47,48] It is essential then to institute major educational efforts aimed at promoting better habits of eating and physical exercise. These lifestyle changes may be complemented by pharmacologic therapy.

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