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Visceral Obesity

The Link Among Inflammation, Hypertension, and Cardiovascular Disease

Patrick Mathieu, Paul Poirier, Philippe Pibarot, Isabelle Lemieux, Jean-Pierre Després

The worldwide epidemic of obesity, fostered by the modern lifestyle characterized by the lack of physical activity and an energy-dense diet, has contributed to create an unprecedented condition in human history where a majority of overfed individuals will soon surpass the number of malnourished.¹ Obesity-associated disorders, such as diabetes mellitus, an atherogenic dyslipidemia, and hypertension, have undoubtedly contributed to create an atherosclerosis-prone environment and thereby the development of cardiovascular disease (CVD), a leading cause of mortality in Westernized societies. A growing body of evidence indicates that obesity is a heterogeneous condition in which body fat distribution is closely associated with metabolic perturbations and, thus, with CVD risk.² In this regard, accumulation of visceral (intra-abdominal) fat is strongly associated with insulin resistance and with a typical atherogenic dyslipidemic state.³

The adipose tissue, once considered a simple energy warehouse, is now regarded as a complex organ not only contributing to the management of energy flux within the body but also interacting with the inflammatory system and the vascular wall. Furthermore, recent studies have underlined that there are intricate interplays among adipocytes, the sympathetic nervous system (SNS), and the renin-angiotensin system (RAS), which participate in the obesity-associated dysmetabolic state. Thus, the adipose tissue is believed to play an important role in the development of both hypertension and other complications related to insulin resistance. However, it should be pointed out that different fat depots have distinct metabolic characteristics, leading to individual differences in the impact of obesity on cardiometabolic risk. Herein, we reviewed the complex links among visceral adiposity, inflammation, and hypertension, along with an attempt to address the clinical implications of these interactions.

Visceral Fat and Metabolism

Small, Dense Low-Density Lipoprotein

By its peculiar location, the expanded visceral fat depot has easy access to the liver via the portal circulation, where it could influence metabolism and promote insulin resistance. It has been suggested that the hyperlipolytic state of the expanded visceral adipose depot leads to the delivery of large

amounts of nonesterified free fatty acid (FFA) to the liver. According to the FFA drainage hypothesis, the delivery of FFA to the liver would contribute to the synthesis of very low-density lipoproteins (VLDLs) enriched with triglycerides (TGs).⁴ Then, after the activity of cholesteryl ester transfer protein, which promotes the exchange of TGs from VLDLs to LDLs and the reverse transport of cholesteryl esters to VLDLs, TG-enriched LDL particles are produced in large amounts. By the action of hepatic lipase, TG-enriched LDLs become smaller and denser. However, it should be pointed out that, although experimental animal models support the portal FFA hypothesis, this issue is unsettled in humans. For instance, although a correlation between portal FFA levels and visceral fat has been reported, evidence indicates that most FFA delivered to the liver comes from the systemic circulation.⁵ Thus, other factors than FFA could explain the relation of visceral obesity to altered liver TG metabolism. In this regard, the release of proinflammatory substances by large intra-abdominal adipocytes combined to reduced secretion of an important cytokine, adiponectin, could also contribute to impair hepatic lipoprotein metabolism.⁶

Small, dense LDL is 1 key feature of visceral obesity and is closely associated with the hypertriglyceridemic state of insulin resistance. Studies have shown that small, dense LDL particles have a greater ability to penetrate within the vascular wall and have a high susceptibility to oxidation and are thereby potentially highly atherogenic.⁶ In line with this, population prospective studies have generally reported that a high proportion of small, dense LDLs is predictive of an increase risk of developing coronary artery disease (CAD).⁷ In fact, in the Quebec Cardiovascular Study, men having some of the key metabolic features of visceral obesity, eg, fasting hyperinsulinemia, small, dense LDLs, and high apolipoprotein B (Apo B) concentrations, were at a very high risk of having a first coronary event.⁸ Of note, in the same study, men having the small, dense LDL phenotype were at increased risk only in the presence of a high level of plasma Apo B. Thus, these results suggest that measurement of the number of LDL particles, which can be estimated by the Apo B concentration, is critical to properly assess the CVD risk associated with small, dense LDLs. Thus, although it is presently unclear whether small LDL particles predict CAD

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risk beyond classic lipid variables, a high proportion/number of small LDL particles is clearly associated with an increased CAD risk.

High-Density Lipoprotein

Epidemiological prospective studies have conclusively shown that low plasma levels of high-density lipoprotein (HDL) cholesterol are associated with an increased CVD risk. In the Quebec Cardiovascular Study, a prospective longitudinal study of 2103 middle-aged men followed over a period of 5 years, it was found that subjects with low HDL levels were at an increased risk of developing a first ischemic heart event.⁹ It is noteworthy that, in the same study, a low HDL concentration was a better predictor of ischemic heart disease than LDL levels. From a clinical standpoint, it should be stressed that a decreased HDL concentration is rarely an isolated finding in patients. Rather, low HDL levels are often found in association with high TG, high Apo B, and insulin resistance, which are, incidentally, also associated with a high proportion of small, dense LDL. At this point, it should also be emphasized that, in a majority of studies, the independent effect of TG as a predictor of CAD is at best weak when HDL variation is taken into account. In this regard, the physiological interactions between TG and HDL should not be overlooked and may explain the confusion among clinicians with regard to proper interpretation of hypertriglyceridemia. In fact, plasma TG concentration shows a strong negative correlation with HDL level and is a marker of visceral obesity and insulin resistance. Rather, hypertriglyceridemia should be considered as a simple and convenient marker of a cluster of metabolic abnormalities conferring a high CVD risk, particularly when accompanied by intra-abdominal obesity. Incidentally, in the Prospective Cardiovascular Munster and Helsinki Heart studies, the groups of patients having both a high plasma TG and low HDL levels were at the highest risk of developing CAD.^{10,11}

In the viscerally obese individual, through the successive actions of cholesteryl ester transfer protein and hepatic lipase, HDL levels are decreased, and, more important perhaps, the particles become smaller and more dense. *In vitro* studies have found that small, dense HDLs are less efficient at quenching reactive oxygen species, and, moreover, these particles have been found in some situations to even act as proinflammatory agents.¹² In 1 study of 238 patients, we have documented that HDL size was negatively correlated with the amount of visceral fat and was closely associated with the features of the metabolic syndrome.¹³ Of particular significance, a high proportion (66%) of the men in the lowest tertile of HDL size had the atherogenic features of the metabolic syndrome (elevated Apo B, insulin resistance, and small, dense LDL). Thus, it is important to stress that the biology of HDL is far more complex than initially thought. In this regard, although a low level of HDL, which is incidentally often associated with a dysmetabolic state, has been consistently related to a higher CVD risk, it is still unknown whether it represents a mere marker or an active player. Indeed, conclusive proof in humans indicating that specific therapy-induced elevation of HDL reduces CVD risk is still lacking.

Endocannabinoid System: A New Player in the Control of Body Fat Distribution and Related Metabolism

In the early 1990s, the discovery of the cannabinoid (CB) receptors was a landmark finding, which has fuelled a tremendous interest for the discovery of endogenous ligands. Then onwards, a series of ligands for CB receptors, termed endocannabinoids (ECs) were discovered, and found to be derived from the metabolism of arachidonic acid. Soon it appeared that ECs were important mediators having fundamental regulatory activities in the brain, the adipose tissue, and the liver, where a high density of CB1 receptors (the receptor subtype with metabolic functions) is documented.⁶ In the brain, stimulation of CB1 receptors has been shown to promote food consumption. In addition to this central activity, ECs are also involved in lipid metabolism. To this effect, a high density of CB1 receptors is found in the liver, where ECs upregulate transcription factors involved in lipogenesis.¹⁴ Interestingly, knockout mice lacking the CB1 receptor and fed a high-fat diet remain lean without hepatic steatosis. In humans, levels of 2-arachidonoylglycerol, a major EC, were found to be elevated in obese subjects, particularly in those with excess visceral fat. Of foremost importance, circulating levels of 2-arachidonoylglycerol have been shown to be positively correlated with plasma TG and insulin levels and negatively correlated with adiponectin and HDL levels.¹⁵ Although further studies will be needed to confirm the direct role played by ECs in the regulation of body fat distribution, these recent observations suggest that the activity of the EC system is related not only to energy balance but also to insulin resistance and to atherogenic dyslipidemic states. Mechanistic studies in this area are, therefore, clearly warranted.

Visceral Fat and Inflammation

Studies have highlighted that, in addition to its metabolic activity, visceral adipose tissue produces large amount of interleukin-6 and by doing so promotes the secretion of acute-phase proteins by the liver, eg, C-reactive protein (CRP).⁶ Clinical studies have demonstrated that CRP levels are associated with coronary events. Whether there is a cause-and-effect relationship between CRP and coronary heart disease event remains unclear, but studies have shown that CRP levels are markedly increased in individuals with abdominal obesity, particularly among subjects with a selective excess of visceral adipose tissue.⁶ Therefore, the expanded intra-abdominal fat depot may contribute to a proinflammatory state, which, in turn, is linked to clinical events. Although it is still unclear whether CRP is a marker or a component of the atheroinflammatory process, it is believed that it may help identify individuals at higher risk.¹⁶

Adiponectin, an adipocyte-specific peptide, has been reported to be involved in an array of functions in different target organs, including the brain, the liver, the skeletal muscle, and the vascular wall. Moreover, adiponectin has been identified as having a potent anti-inflammatory role.^{2,6} In peripheral tissues, adiponectin promotes the oxidation of FFA and favorably affects insulin sensitivity. Thus, it appears that adiponectin could be at the center stage in having

multiple metabolic effects along with anti-inflammatory and antiatherosclerotic properties.

In humans, circulating adiponectin levels have been documented to be decreased in obese individuals. Of special interest, adiponectin plasma levels have been found to be more closely related to the amount of visceral than total fat.⁶ In one study, low plasma adiponectin levels were associated with the progression of a coronary artery calcification score.¹⁷ Paradoxically, in a recent study, Schnabel et al¹⁸ reported in a cohort of 1890 patients with CAD that plasma adiponectin concentration was positively associated with future cardiovascular events. Thus, from this study it appears that, in contrast to patients without CAD, where a high adiponectin level may be cardioprotective, increased adiponectin concentration in patients with CAD may reflect a rather deleterious process. Among other hypotheses, adiponectin could increase during atherosclerosis as an adaptive response, which could be seen as an attempt to slow the atherosclerotic process or as a sign of peripheral resistance to its action. Hence, further studies are needed to properly assess the role of adiponectin in atherosclerosis.

Visceral Obesity and Hypertension

Renin-Angiotensin System

Hypertension, a major cardiovascular risk factor, is closely associated with obesity. Indeed, it is estimated that between 65% and 78% of cases of hypertension could be attributed to obesity.¹⁹ Activation of the RAS in hypertension is well known and is suspected of having a role in insulin resistance (Figure 1). Importantly, the discovery that adipose tissue is, in addition to the liver, an extra source of angiotensinogen (AGN), has contributed to the heralding of intense research efforts aiming at uncovering specific mechanisms involved in the obesity-associated hypertension. In fact, renin produced by the kidney allows the transformation of AGN to angiotensin (Ang) I and then, through the action of angiotensin-converting enzyme (ACE), Ang I is transformed to Ang II, a powerful vasoconstrictor. Of note, angiotensin II type 1 receptor (AR-1) is expressed by adipocytes, where it exerts potential important functions. In fact, differentiation of preadipocyte to adipocyte is hampered by Ang II.²⁰ Thus, it is likely that, by interfering with preadipocyte differentiation, Ang II contributes to the formation of large and dysfunctional adipocytes. In turn, expression of AGN is increased in large adipocytes and, therefore, suggests that a vicious circle between the RAS and the dysfunctional adipose tissue is involved in obesity-associated hypertension. Increasing evidence indicates that large adipocytes are producing elevated levels of leptin, reactive oxygen species, and proinflammatory cytokines.²¹ Furthermore, accumulation of ectopic fat and development of insulin resistance are abetted by the insufficient capacity of oversized adipocytes to appropriately handle excess energy intake.^{6,22} Importantly, adipose depots with large adipocytes are infiltrated by macrophages, which have reciprocal communications with fat cells. Accordingly, FFAs released by adipocytes promote the production of tumor necrosis factor- α by macrophages, which, in turn, induce the production of interleukin-6 by fat cells.²³ Interest-

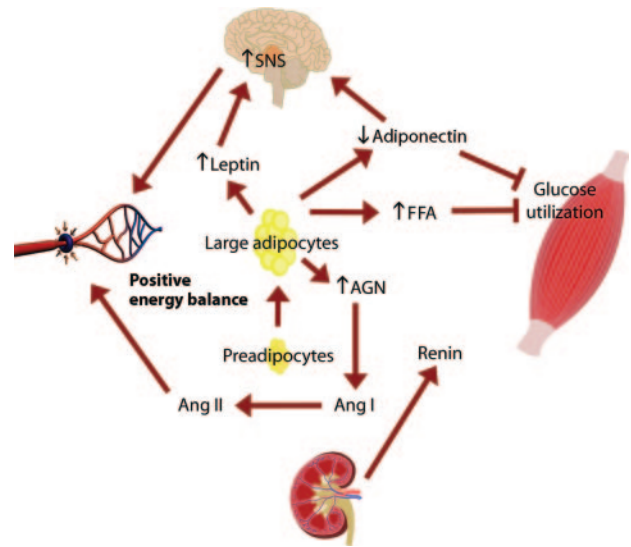


Figure 1. Physiopathologic relationships between obesity and hypertension. Chronic positive energy balance promotes the accumulation of excessive ectopic/visceral fat, which in turn synthesizes AGN and thereby contributes to the activation of the RAS. In addition, Ang II hampers the development of preadipocytes and, therefore, promotes the accumulation of large dysfunctional adipocytes, which produce an increased amount of leptin and nonesterified FFAs, as well as reduced quantity of adiponectin. In turn, a decreased level of adiponectin and increased load of FFA impede glucose use by the skeletal muscle. Furthermore, higher levels of leptin and lower amounts of circulating adiponectin activate the SNS, a key component of the hypertensive response.

ingly, although the causal relationship is not clearly delineated yet, an experimental study has demonstrated a blunted hypertensive response to psychosocial stress in interleukin-6 knockout mice.²⁴

Atherosclerosis clearly has an inflammatory component, and to this effect coronary artery plaques are infiltrated with macrophages and T cells producing cytokines such as tumor necrosis factor- α and interferon- γ . In an elegant study, Mazzolai et al²⁵ have conclusively shown in the apolipoprotein E knockout mice that, when compared with the 1-kidney, 1-clip model resulting in hypertension with normal Ang II blood levels, mice having hypertension with high circulating Ang II levels (2-kidney, 1-clip model) developed vulnerable atherosclerotic plaques characterized by a larger lipid core and higher inflammatory cell content. Thus, at least from an experimental standpoint, hypertension associated with the activation of the RAS could be linked to the development of unstable plaques. Of particular interest, infusion of Ang II in rats resulted in a significant increase of T-helper 1 cytokines, which could be explained by the presence of AR-1 receptors on immune cells.²⁶ Therefore, these mechanistic studies may explain, at least in part, the links among adaptive immunity, hypertension, obesity, and cardiovascular events.

Adipokines and Hypertension: A Link Between the Adipose Tissue and the Autonomic Nervous System

Activation of the SNS, a regulatory component responsive to different stress stimuli, has been unequivocally associated

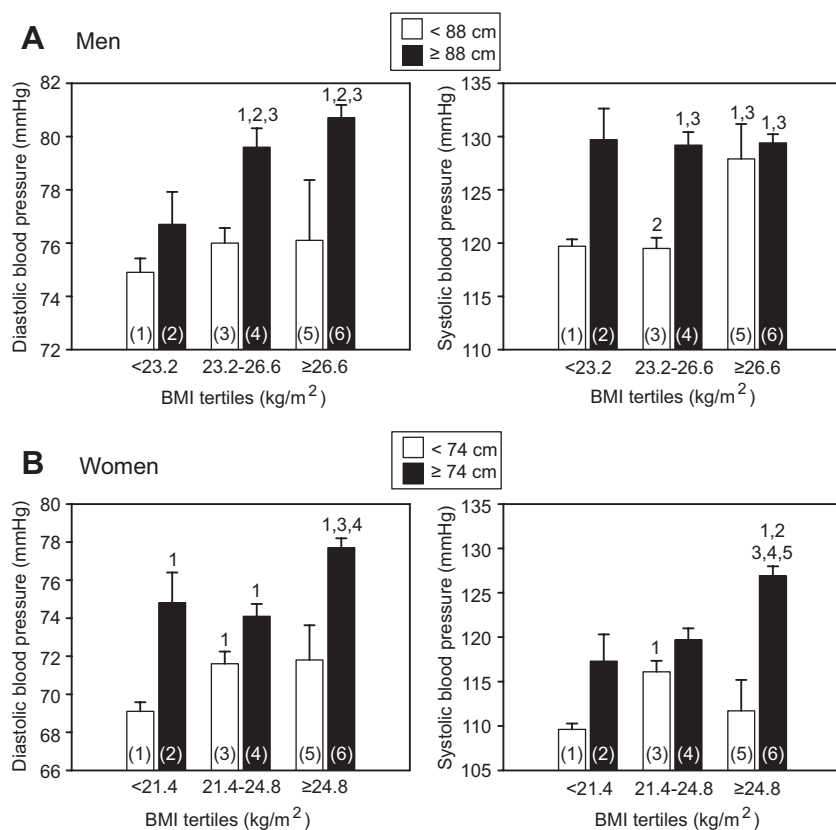


Figure 2. Diastolic and systolic blood pressures according to waist circumference and body mass index (BMI) among men (A) and women (B) of the Quebec Health Survey. 1, 2, 3, 4, and 5 indicate significantly different from the corresponding subgroup. Men (A), all $P < 0.0001$; age-adjusted all $P < 0.03$; women (B), all $P < 0.0001$; age-adjusted all $P < 0.05$. From Reference 38, with permission from the American Heart Association.

with the initiation and maintenance of hypertension. On the one hand, increased sympathoactivation to the blood vessels leads to a peripheral vasoconstriction, and on the other hand, augmented sympathetic flux to the kidneys is promoting the production of renin, as well as increasing sodium reabsorption.²⁷ Molecular mechanisms leading to the activation of the SNS have been elucidated recently, and leptin has been identified as a key component linking adipose tissue and sympathetic activity. In fact, in addition to decreasing appetite, leptin has been shown to increase sympathetic outflow through a melanocortin-dependent pathway within the hypothalamus.²⁸ Furthermore, in rats, insulin is also known to elevate the sympathetic outflow to the blood vessels, adrenal glands, and the kidneys.²⁹ Hence, evidence suggests that an exquisitely regulated system controls the autonomic activity of the nervous system, in which metabolic activities have intimate connections and feedback loops.

Mounting evidence also suggests that, beyond the blood pressure reduction properties exerted by angiotensin receptor blockers, beneficial effects on insulin sensitization occur with the inhibition of the RAS pathway. In fact, clinical studies indicate that treatment with RAS blockers increases adiponectin levels, an insulin sensitizer.³⁰ Of great interest, administration of Ang II in rats has been shown to reduce circulating adiponectin levels. It is believed that, by increasing the production of reactive oxygen species, Ang II is suppressing adiponectin production by adipocytes.³¹ In addition, adiponectin has been found to inhibit the activation of SNS, and, conversely, stimulation of the SNS would restrain adiponectin expression. Apart from the centrally mediated

effect of adiponectin, another mechanism could explain its role in hypertension, because it has been proposed as a critical regulator of endothelial activity. After its binding to endothelial receptors, adiponectin exerts, through multiple downstream signaling pathways, a net increase of endothelial NO synthase activity. Accordingly, investigations in humans have indicated that adiponectin is inversely related to the endothelial vasodilatory response.³²

Visceral Obesity: A New Target in Hypertension?

When compared with the subcutaneous adipose tissue, the gene expression profile indicates that visceral fat expresses more proinflammatory cytokines and more AGN.³³ Experimental evidence in mice has indicated that overexpression of 11- β hydroxysteroid dehydrogenase type 1, an enzyme allowing the recycling of inactive cortisone into active cortisol, was associated with the development of visceral obesity and hypertension.³⁴ Incidentally, the expression of 11- β hydroxysteroid dehydrogenase type 1 and glucocorticoid receptors is elevated in the visceral fat of obese patients.³⁵ Considering the fact that patients with Cushing syndrome have excessive accumulation of visceral fat, it is tempting to speculate that 11- β hydroxysteroid dehydrogenase type 1 might participate in ectopic fat accumulation. Thus, a question arises as to whether visceral fat is a mere marker of a generalized metabolic dysfunction or an essential component acting as a fulcrum on which metabolic perturbations originate. In this regard, in an animal experimental model, surgical removal of visceral fat has been associated with a reversal of insulin resistance.³⁶ Moreover, in a small cohort of severely obese patients undergoing a gastric banding procedure, the concom-

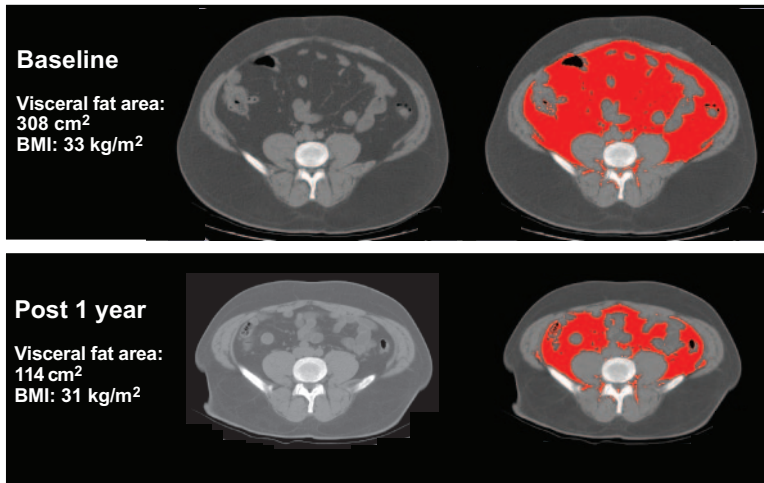


Figure 3. An illustrative case showing an individual having undergone a lifestyle intervention program with a modest weight loss (body mass index reduced from 33 to 31 kg/m²) but with a substantial reduction of visceral fat (66%) and, therefore, a significant improvement of the metabolic risk factors.

itant removal of the omentum at the time of the surgery was associated with a significant improvement of insulin sensitivity 2 years after the intervention, which was independent of weight loss.³⁷

Whether visceral obesity and/or hyperinsulinemia are related to the development of hypertension or not remain an open question, but a study investigating the relationships among waist circumference, insulinemia, and blood pressure has possibly shed some light on this issue. In a cohort of 1847 individuals, Poirier et al³⁸ have shown that insulin sensitivity was only a weak correlate of blood pressure, and after classifying subjects into tertiles of fasting insulinemia and waist circumference, insulin, per se, did not predict variations in blood pressure, whereas waist girth did. Equally important, in the same study, variations of waist circumference had a much greater impact than the body mass index on blood pressure (Figure 2). Although in this study the amount of visceral fat was not directly measured by imaging techniques, it is possible that most of the variations of blood pressure related to hyperinsulinemia were explained by the amount of intra-abdominal fat, which was crudely assessed with the measurement of waist circumference. However, these results do not necessarily imply that hyperinsulinemia does not contribute to hypertension. Rather they suggest that there could be important cross-talk among the visceral fat depot, the RAS, and insulin resistance in promoting the regulation of blood pressure. To this effect, in viscerally obese individuals, resistance to antilipolytic activity of insulin results in greater FFA flux, which, in turn, is significantly related to the mean blood pressure and vascular resistance.³⁹ To further support the role of visceral fat in hypertension, a study from Engeli et al⁴⁰ has demonstrated, in a small cohort of women undergoing weight loss, that the decline of blood pressure was explained by the reduction of waist circumference and not by the fall of the body mass index. Moreover, in patients having a weight loss of 5%, the decline of plasma AGN was, to a large extent, explained by the decrease of waist circumference.

Therapeutic Options for the Viscerally Obese Patient

Lifestyle Interventions

Keeping in mind the relevance of visceral obesity and related metabolic perturbations in the pathophysiology of CVD,

along with an expanding pool of patients, it is likely that interventions targeting the loss of visceral fat may significantly decrease global cardiovascular risk. However, until now, one has to acknowledge that most of the lifestyle interventions have focused on weight reduction as the primary objective. Nonetheless, intervention programs based on weight reduction have generally shown that reducing body fat mass is associated with substantial improvements in the metabolic profile. In this regard, a recent trial investigating diet-induced weight loss has shown that both during the weight loss and the maintenance phases, plasma levels of CRP decreased, whereas adiponectin increased.⁴¹ Daily energy deficits of ≈ 500 to 1000 kcal have been shown to be efficient to achieve significant weight reduction, but the ideal macronutrient composition of the diet remains an unresolved issue. Although a low-fat diet will provide a greater reduction of LDL level, a low-carbohydrate diet will be most efficient at increasing HDL concentration. It is worth bearing in mind that intervention programs based on both diet and exercise provide a greater and longer lasting weight reduction with less weight regain.⁴² In addition, exercise training, per se, is independently associated with blood pressure reduction. Thus, decreasing weight and, more importantly, the waistline are likely to yield significant improvements in the metabolic profile and a considerable reduction of CVD risk. In this regard, given the crucial links between visceral obesity and the atheroinflammatory process, it is likely that targeting a reduction of the waistline instead of body weight may provide a better assessment of the efficacy of the intervention; the point being that, in some individuals, regular exercise will increase the fat-free mass resulting in an apparent modest weight reduction, which may mask a very significant loss of visceral fat (Figure 3).

Pharmacological Treatment

In recent years, major discoveries have contributed to singling out some crucial molecular pathways involved in the regulation of energy metabolism. It is worth noting that some of these molecular targets are transcription factors having central roles in both energy homeostasis and inflammation. Understandably, these discoveries have fueled the development of new drugs of potential interest. The glitazones are a

class of drug that activates peroxisome proliferator-activated receptor (PPAR)- γ , a transcription factor regulating glucose homeostasis and having anti-inflammatory activities, as well as potentially antiatherosclerotic properties. No less significant is the observation that glitazones increase the deposition of subcutaneous fat and by doing so prevent the accumulation of harmful intra-abdominal fat, possibly the phenomenon explaining how this class of drugs improves insulin sensitivity. Although in some clinical trials glitazones have been associated with a reduction of all-cause mortality and composite cardiovascular end points, recent meta-analyses have emphasized that glitazones may precipitate heart failure in some patients.⁴³ In one meta-analysis, rosiglitazone was associated with an excess of cardiovascular mortality.⁴⁴ Whether the 2 molecules of this class, rosiglitazone and pioglitazone, have marked differences in their metabolic properties is unresolved and debated at this stage.

Fibrates are weak activators of PPAR- α and are routinely used to treat hypertriglyceridemia. In mice, weight loss is associated with an increased expression of PPAR- α and PPAR- γ in the adipose tissue and atherosclerotic plaques, which is, in turn, inversely related to plaque volume, suggesting that PPARs are in some ways related to the burden of atheroma.⁴⁵ PPAR- α agonists activate lipoprotein lipase and thereby decrease TG level, along with the proportion of small, dense LDL. Moreover, Apo A-I secretion is increased by PPAR- α agonists and thus contributes to elevate HDL levels in the plasma. In one clinical trial, fibrates reduced coronary artery luminal narrowing and plaque volume.⁴⁶ However, in a larger randomized clinical trial in patients with type 2 diabetes mellitus, while reducing revascularization and myocardial infarction, fenofibrate failed at decreasing the primary end point of coronary events.⁴⁷ Thus, an ongoing trial in patients with type 2 diabetes will test, among other objectives, whether the association of a fibrate with a statin could decrease cardiovascular events.⁴⁸

In view of the recent discoveries of the EC system, rimonabant, a CB1 antagonist, has been developed and used in clinical randomized studies. In 3 investigations, rimonabant was more effective than the placebo for reducing weight, and possibly far more important, it was associated with a sizeable improvement of the metabolic profile.^{49–51} However, one drawback noted in clinical trials with rimonabant was that some individuals experienced depressive disorders. This adverse effect was particularly frequent among patients with a history of depressive disorders. Therefore, depending on the absence/presence of a history of depression symptoms, the incidence of anxiety and/or depression was reported to be quite variable according to studies, with figures varying from 1.7% to 28.4%. Discrepancies with regard to the incidence of mood disorders and/or depression symptoms in different reports may have come from the selection of patients in those studies. In a meta-analysis, rimonabant was found to increase the risk of depressive disorder by 2.5-fold.⁵² Being aware of this potentially important adverse effect and from monitoring of its use in Europe, rimonabant has been withdrawn from the market. Recently, the Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabant: The Intravascular Ultra-

sound Study (STRADIVARIUS) Trial, evaluating the cardiovascular effect of rimonabant over a period of 18 months, failed at showing a significant effect of the drug on the primary end point of change in the percentage of atheroma volume.⁵³ Thus, in light of these recent developments, the key question to be answered regarding the EC system and CB1 receptor antagonists is whether it will ever be possible in clinical practice to easily identify the subgroup of patients for whom this type of drug would have an overwhelmingly favorable benefit/risk ratio. Until such evidence becomes available, the future of this class of drugs remains uncertain.

A large proportion of viscerally obese individuals is resistant to insulin and suffers from hypertension. Insofar as hypertension, hyperinsulinemia, and the visceral adipose tissue are linked by complex reciprocal molecular interactions, it is logical to expect that blocking an interconnected pathway may provide multiscale benefits. In this regard, blocking the RAS, a key pathway regulating adipocyte differentiation, with either ACE inhibitors or angiotensin receptor blockers may offer promising avenues. Although not designed for this purpose, clinical trials have shown that RAS blockers significantly reduced new-onset diabetes mellitus.⁵⁴ On the other hand, investigations have underlined that, with regard to cardiovascular events, it appears that no major differences exist between different classes of antihypertensive medications.⁵⁵ Despite such findings, it should be stressed that many recent intervention trials comparing different antihypertensive drugs were not specifically designed to address the problem of obesity-related hypertension. Hence, in light of the devastating consequences of type 2 diabetes, future studies specifically investigating the role of RAS blockers in hypertensive, glucose intolerant, and viscerally obese subjects may provide important insights.

Conclusion

At the turn of the Second World War, Jean Vague, a French physician, had made a simple but important observation: android obesity (truncal obesity) was often associated with diabetes mellitus and CVD.⁵⁶ Since then, our understanding of the extraordinary complex links among visceral adipose tissue, inflammation, hypertension, and cardiovascular disorders has been extended up to the molecular level. Unfortunately, meanwhile, the mosaic of modifiable risk factors has changed at a startling pace in Westernized societies and now in developing countries, where obesity is considered by many authorities as the major public health problem. Then, it should be recognized that, in light of the havoc brought about by visceral obesity, a concerted approach to prevent and to treat afflicted patients is urgently needed. Hopefully more research will lead in the near future to widely applicable lifestyle intervention programs and/or to the discovery of new pharmacological targets to prevent or alter the course of CVD in viscerally obese patients.

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Disclosures

None.

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