Lifestyle modification and endothelial function in obese subjects

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Metabolic syndrome is a cluster of metabolic and vascular abnormalities that include central obesity, insulin resistance, hyperinsulinemia, glucose intolerance, hypertension, dyslipidemia, hypercoagulability and an increased risk of coronary and cerebral vascular disease. These metabolic and vascular abnormalities are the main cause of cardiovascular mortality in western societies. Endothelial dysfunction, an early step in the development of atherosclerosis, has been reported in obese nondiabetic individuals and in patients with Type 2 diabetes. It has also been observed in individuals at high risk for Type 2 diabetes, including those with impaired glucose tolerance and the normoglycemic first-degree relatives of Type 2 diabetic patients. Recent evidence points to adipocytes as a complex and active endocrine tissue whose secretory products, including free fatty acids and several cytokines (i.e., leptin, adiponectin, TNF-α, interleukin-6, and resistin) play a major role in the regulation of human metabolic and vascular biology. These adipocytokines have been claimed to be the missing link between insulin resistance and cardiovascular disease. Interventions designed to improve endothelial and/or adipose-tissue functions may reduce cardiovascular events in obese individuals with either metabolic syndrome or Type 2 diabetes. Lifestyle modification in the form of caloric restriction and increased physical activity are the most common modalities used for treating those individuals at risk and is unanimously agreed to be the initial step in managing Type 2 diabetes. Several recent studies have demonstrated favorable impacts of lifestyle modifications in improving endothelial function and insulin sensitivity, in addition to changing levels of adipocytokines in serum and possibly reducing cardiovascular events. This review discusses current knowledge of the role of lifestyle modifications in ameliorating cardiovascular risk in obese subjects with either the metabolic syndrome or Type 2 diabetes.

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Obesity and insulin resistance are often associated with hyperinsulinemia, glucose intolerance, hypertension, dyslipidemia, coagulation abnormalities and an increased risk of coronary and cerebral vascular disease [1]. This cluster of abnormalities has recently been named the metabolic syndrome [2]. Although there is no doubt regarding the existence of this expanding interconnected web of metabolic and vascular abnormalities, the accurate clinical definition of this syndrome is still evolving. Using the World Health Organization criteria, the frequency of the metabolic syndrome in nondiabetic individuals varied between 7 and 36% for men aged 40 to 55 years, and between 5 and 22% for women of the same age in a large European cohort. In the same cohort, the frequency of the insulin resistance syndrome, as defined by the European Group for the Study of Insulin Resistance, is 1 to 22% in men and 1 to 14% in women aged 40 to 55 years [3]. Using the Adult Treatment Panel III clinical guidelines developed by the National Cholesterol Education Program, the age-adjusted prevalence of the metabolic syndrome is approximately 23.7% of all adults in

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the USA above the age of 20 years [4]. This population has an overall excess coronary artery disease (CAD) risk of approximately 70% [5]. Although several medications may be useful in managing this syndrome, lifestyle modification in the form of weight reduction through caloric restriction and increased physical activity is still the most common modality used in managing this high-risk population. More recently, the Diabetes Prevention Program (DPP) demonstrated that lifestyle modification that resulted in approximately 7% weight reduction, sustained for an average duration of 2.8 years, reduced the risk of developing Type 2 diabetes by 58% among individuals with impaired glucose tolerance compared with the control group [6]. Further studies showed that similar intervention improves endothelial function [7]; adipocytokine profile [8] and possibly reduces cardiovascular risk. This review demonstrates current knowledge of the impact of lifestyle modifications through either caloric restriction, exercise, or both, in ameliorating cardiovascular risk in obese individuals with either the metabolic syndrome or Type 2 diabetes.

Increased cardiovascular risk in obese subjects & in Type 2 diabetic patients

The risk for CAD is two- to three-times higher in obese nondiabetic individuals and three- to four-times higher in Type 2 diabetic patients in comparison with nondiabetic lean individuals [9,10]. It is quite clear that endothelial dysfunction (ED) is an early step in the atherosclerotic process, which eventually leads to CAD [11,12]. Numerous studies have shown that ED occurs in patients with Type 2 diabetes, whether evaluated *in vivo* or in isolated arteries *in vitro* [13–15]. A similar vascular abnormality was also observed in obese nondiabetic individuals [16] and in subjects at high risk for developing diabetes, including subjects with impaired glucose tolerance and normoglycemic first-degree relatives of patients with Type 2 diabetes [17].

Although the exact pathogenesis of ED in these populations is not yet fully understood, multiple mechanisms are likely to be involved. Several components of the metabolic syndrome such as dyslipidemia, insulin resistance, hyperinsulinemia, hyperglycemia and hypertension may be central to the development of ED [18]. It has been hypothesized that ED could be a consequence, either of decreased synthesis of nitric oxide (NO), increased inactivation of NO or decreased arterial smooth muscle responsiveness to NO. There is some evidence that decreased NO production results from diabetes-related endothelial cell injury [19,20]. Similarly, there is evidence that degradation of NO by oxygen-derived free radicals and advanced glycation end products may be augmented in the hyperglycemic state [21–23].

Several reports demonstrated an elevation of markers of endothelial activation in diabetic patients, including vascular and intercellular adhesion molecules [24,25]. They also pointed to their association with the development of atherosclerosis [24–26]. Adhesion molecules are expressed on the endothelial surface of arterial blood vessels in response to inflammatory stimuli [24] and can also be detected in soluble form in the circulation. The intercellular adhesion molecules (ICAMs) and vascular cell-adhesion molecules (VCAMs) are thought to play a role in the early stages of vascular disease by facilitating the adhesion of circulating monocytes to, and their transmigration through, the endothelium [27].

Diabetic patients also have a higher plasma level of plasminogen activator inhibitor (PAI)-1 than nondiabetic subjects – a cytokine known to be associated with an increased risk of coronary artery thrombosis [28]. Through several postulated mechanisms, elevated PAI-1 levels causes an increase in thrombotic tendency [29]. PAI-1 inhibits the fibrinolytic action of plasminogen activator and thus inhibits the dissolution of fibrin deposits on the luminal sides of the vessel wall. In addition, it decreases vascular smooth muscle cell migration and expression of urokinase within the blood vessel wall and atherosclerotic plaque.

Role of adipocytokines in increasing cardiovascular risk

Obesity, and in particular increased central-fat accumulation, is a prominent feature of the metabolic syndrome. Increasing evidence points to the important role of adipocytes as a complex and active endocrine tissue whose metabolic and secretory products, including free fatty acids, leptin, adiponectin, PAI-1, interleukin (IL)-6, tumor necrosis factor (TNF)-α, resistin and others [30–32], play a major role in whole-body metabolic and vascular homeostasis. It remains controversial as to whether all adipose tissue has exactly the same endocrine role or whether its endocrine function is solely dependent on its anatomic location. Although there is no doubt that intra-abdominal fat has a significant impact on cardiovascular and metabolic biology, the metabolic role of peripheral fat remains controversial. In contrast to the view that all fat accumulation increases cardiovascular risk, a recent report demonstrated that peripheral fat may have an antiatherogenic effect [33].

The cardiovascular effect of adipose tissue, particularly that accumulated in a visceral location, probably occurs via alterations in lipoprotein profile (low high-density lipoprotein [HDL]), increased free fatty acids and alteration of other adipocyte secretory products. For example, the PAI-1 mentioned above is expressed in, and secreted by, adipocytes [34]. Although adipose tissue is not the major source of PAI-1, adipose tissue contributes significantly to the increase in PAI-1 plasma levels in obese individuals [34].

Adiponectin is another adipokine that has been implicated in the regulation of whole-body insulin sensitivity [35]. Levels are reduced as a function of obesity, increased amounts of visceral fat and insulin resistance. A reduction in both adiponectin gene expression and secretion with weight gain was claimed to contribute to the development of cardiovascular disease [36]. *In vitro*, human recombinant adiponectin suppresses endothelial expression of adhesion molecules, proliferation of vascular smooth muscle and the transformation of macrophages into foam cells [37]. In human aortic endothelial cells, adiponectin was also shown to inhibit TNF-α-induced monocyte adhesion and to suppress the mRNA levels of VCAM-1 [10]. Okamoto

and colleagues demonstrated that adenovirus-mediated increase of plasma adiponectin significantly suppressed the progression of atherosclerotic lesions in apoE-/- mice [38]. In another study, adiponectin overexpression attenuated TNF-α-mediated growth factor expression in endothelial cells [39]. These data may explain the association between decreased plasma adiponectin concentration and a higher risk of CAD [40].

Leptin, which is predominantly secreted by subcutaneous adipose tissue, has also been implicated in the etiology of hypertension and cardiovascular disease through its effects on the sympathetic nervous system in adipose tissue, the kidney and the adrenal gland [41].

Meanwhile, adipose tissue is an important determinant of low-level chronic inflammatory status, which is believed to link obesity and insulin resistance to ED and CAD [42]. It is known that adipose tissue is an important source of TNF-α and IL-6. These proinflammatory cytokines are related to all measures of obesity and are strongly related to insulin resistance [43]. Increased expression and secretion of TNF-α in obese individuals may contribute to adipocyte insulin resistance [44]. TNF-α is also increased in individuals with premature cardiovascular disease independent of insulin sensitivity [45]. TNF-α acts as a higher-order cytokine that influences the synthesis, secretion and activity of other adipokines that affect the endothelium, such as IL-6, PAI-1 and leptin [46]. Local infusion of TNF-α was found to impair endothelium-dependent vasodilation [47]. At a molecular level, TNF-α has been shown to:

- Increase the adhesion of monocytes to vascular endothelium [48]
- Activate nuclear factor (NF)-κB-dependent proinflammatory pathways [49]
- Induce endothelial expression of VCAM-1 [50]
- Induce smooth muscle expression of matrix metalloproteinase-1

These effects contribute to ED and plaque destabilization/rupture [51]. Conversely, a reversal or reduction of TNF-α effects along the downstream I-κB kinase/NF-κB inflammatory pathway improves insulin sensitivity [52].

On the other hand, IL-6 stimulates lipolysis and increases hepatic production of triglycerides [53]. IL-6 also controls hepatic production of C-reactive protein (CRP), which is a strong independent predictor of CAD [54]. Interestingly, CRP was found to correlate with fasting insulin concentration and various measures of body fat [54]. IL-6 is also known to promote the release of endothelial adhesion molecules and other chemokines [55]. It was recently shown that IL-6 plasma concentration is a strong predictor of future myocardial infarction in healthy men [56].

The interlink between these proinflammatory cytokines is complex, as where TNF-α stimulates IL-6 production and consequently hepatic CRP production, IL-6 exerts a feed-back inhibition of TNF-α [57]. Interventions that mainly increases IL-6, such as exercise, may have an anti-inflammatory effect through suppression of TNF-α, which is a major inducer of inflammation [58].

Link between obesity, insulin sensitivity & cardiovascular risk in obese & in Type 2 diabetic patients

Earlier studies demonstrated that both obese and Type 2 diabetic individuals have blunted endothelium-dependent vasodilation, and that the association between endothelial function and insulin resistance is independent [16,59]. In addition, obese/insulin-resistant people do not experience normal endothelium-dependent vasodilation in the presence of euglycemic hyperinsulinemia [16]. In obese Type 2 diabetes mellitus patients, Baldeweng and colleagues found that obesity appeared to relate to endothelial function more than diabetes [59]. However, the relative roles of hyperglycemia and insulin resistance in the regulation of endothelial function remain to be thoroughly ascertained.

On the other hand, increased circulating cytokines and growth factors, and their consequent subclinical inflammation, is currently viewed by many researchers as a possible key player in the etiology of atherosclerosis and diabetes [52,60]. Of particular interest, a low adiponectin serum concentration was observed in obesity, Type 2 diabetes and CAD both in mice and humans [31]. This observation attracts attention to this particular adipokine as the possible link between the three conditions. Although it is unclear how adiponectin affects insulin resistance, some evidence indicates that adiponectin improves the peripheral action of insulin by accelerating β-oxidation of free fatty acids in skeletal muscle [61].

On the other hand, levels of the proinflammatory cytokines IL-6 and TNF-α were shown to be correlated with all measures of obesity and were strongly related to insulin resistance [62–65]. Increased gene expression and protein production of TNF-α and its receptors 1 and 2 in adipose tissue were observed in an obese insulin-resistant rodent model and in obese subjects [44]. In humans, TNF-α levels inversely correlate with insulin sensitivity, as assessed by euglycemic hyperinsulinemic clamp [61]. Several studies in obese mice with a homozygous null mutation at TNF-α, or its receptor loci, demonstrated that the genetic absence of TNF-α signaling leads to a significant improvement in insulin-receptor signaling capacity and consequently insulin sensitivity [66]. The mechanism by which TNF-α induces insulin resistance is still not fully understood. Evidence suggests that TNF-α is associated with the downregulation of glucose transporter (GLUT)-4 mRNA in adipose tissue and skeletal muscles, and a reduction in insulin receptor substrate-1 [61,63]. Similarly, elevated levels of IL-6 reduce insulin sensitivity by inhibiting GLUT-4 [64]. Pradhan and colleagues recently demonstrated that elevated IL-6 doubles the risk of developing diabetes [65]. The link between adipose tissue mass and insulin resistance and ED is illustrated in FIGURE 1.

Although metformin and thiazolidinediones are extensively used in Type 2 diabetic patients to improve insulin sensitivity, neither of them are currently approved by the US Food and Drug Administration to be used in subjects with the metabolic syndrome without diabetes. The DPP demonstrated that metformin has partial success in preventing progression to Type 2 diabetes among the impaired glucose-tolerence population.

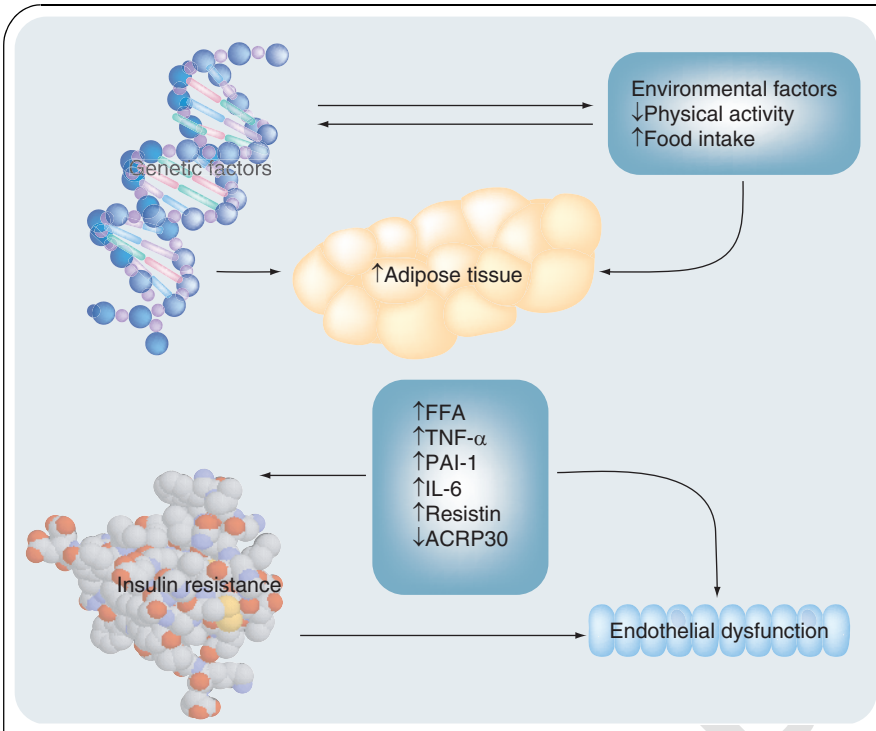

Figure 1. The link between adipose tissue mass and both insulin resistance and endothelial dysfunction.
Adapted from: Aldhahi W, Hamdy O. Curr. Diab. Rep. 3(4), 293–298 (2003).

However, it is much less effective than lifestyle modification. The lack of strong longitudinal studies that are primarily designed to study the cardiovascular effect of metformin in the prediabetic population, together with controversy concerning its possible anti-atherogenic effect, renders metformin a poor choice in subjects with the metabolic syndrome. Data on thiazolidinediones are also vague, despite several recent clinical studies demonstrating their favorable effect on circulating cytokines [67,68]. Additionally, a recent study showed that the anti-atherogenic effect of pioglitazone is independent of its hypoglycemic effect [69]. Pending the results of the ongoing prospective trials to evaluate their effect on cardiovascular outcome in the prediabetic population, lifestyle modification in the form of dietary caloric restriction and increased physical activity remains the only known effective tool in subjects with the metabolic syndrome, and is recommended as the first choice for obese Type 2 diabetic patients before beginning any oral medications.

Effect of lifestyle modification on endothelial function & vascular reactivity

Exercise has been demonstrated to improve endothelial function, usually in conjunction with a significant increase in exercise capacity, in people with chronic coronary occlusion, coronary heart disease or hypertension [70–73]. Hambrecht and colleagues reported that exercise training improves endothelium-dependent vasodilatation both in epicardial coronary vessels and in resistance vessels in nondiabetic patients with CAD [74]. A moderate exercise training program (including arm exercise and running) for 10 weeks in young, healthy men enhanced endothelium-dependent dilation measured in the forearm [75]. Also, 4 weeks' leg cycling exercise training in healthy males improved measures of endothelial function [76].

The authors' group recently demonstrated that a 6-month program of lifestyle modification in the form of caloric restriction and moderate-intensity physical exercise in obese subjects with insulin resistance significantly improved endothelium-dependent vasodilation of the brachial artery [6]. This improvement was observed across the entire spectrum of glucose tolerance and was strongly associated with the percentage weight reduction. This effect was also associated with a significant reduction in the plasma levels of soluble ICAM. The latter change is consistent with a similar recent observation by Ziccardi and colleagues in obese premenopausal women after a year of weight reduction [77]. Circulating soluble adhesion molecules are valuable markers of atherosclerosis and, in particular, elevated ICAMs was found to be associated with an increased risk of future myocardial infarction in healthy men [78]. A similar effect of combined energy-restricted diet and physical activity on endothelial function was also observed in obese healthy women using the acetylcholine-stimulated vasodilation technique [79], and also by measuring the blood pressure and platelet aggregation responses to an intravenous bolus of L-arginine – the natural precursor of NO [80]. Very recently, the author's group also found that longer-term weight reduction for 1 year through intensive lifestyle modification improved endothelial function, HDL-cholesterol and HbA1c in obese Type 2 diabetic patients in comparison with the control group that followed the standard diabetes care [UNPUBLISHED DATA].

Meanwhile, weight reduction for 6 months did not improve endothelium-independent vasodilation of the brachial artery and did not change endothelium-dependent or -independent vasodilation of the forearmskin microcirculation [6]. One possible explanation for this observation is that conduit vessels have different characteristics in sensitivity to insulin compared with microcirculation [81]. Further studies are clearly needed to evaluate this observation.

It is not yet clear whether the effects of lifestyle modification on endothelial function is predominantly related to the increase in physical activity or whether it is a result of the metabolic changes associated with weight reduction through diet restriction. A recent experimental study attempted to answer this question using two groups of the Otsuka Long–Evans Tokushima fatty rats – a model of spontaneous Type 2 diabetes. Rats

on a regime of exercise training and food restriction were compared with a matched group of sedentary rats. Interestingly the authors found that exercise training, but not food restriction, prevented ED in Type 2 diabetic rats, although both interventions significantly suppressed plasma levels of glucose, insulin and cholesterol. They also reduced the accumulation of abdominal fat and improved insulin sensitivity to a comparable extent. This study also found that urinary excretion of nitrite was significantly decreased in sedentary and food-restricted rats compared with nondiabetic rats and was significantly increased in exercise-trained rats. Based on these findings they presumed that the improvement in ED in exercised rats is due to the exercise-induced increase in the production of NO [82]. A similar study in humans is still lacking, and the currently available data are inconclusive.

Balkestein and colleagues evaluated the effect of 3 months' weight reduction with and without exercise on the vessel-wall properties of the brachial and common carotid arteries in obese healthy men [83]. Using a vessel-wall movement detector, this study demonstrated that weight reduction increased carotid artery distensibility. However, no additional benefit was found from adding an exercise component to the weight-loss program. In contrast to this study, improvement in macrovascular endothelium-dependent vasodilation was reported after acute [84] and chronic exercise programs in two studies [85,86] that did not include a weight-reduction component. The first found that 3 months' physical training enhanced brachial artery flow-mediated dilation (FMD) in patients with the metabolic syndrome [85]; the second observed that 12 weeks' aerobic and resistance training improved brachial artery FMD in subjects with Type 2 diabetes [86]. A similar favorable effect of exercise training on FMD was recently observed in a group of long-standing Type 1 diabetic patients [87].

On the other hand, weight loss alone, through gastric bypass surgery, was associated with a reduced rate of progression of carotid intima-media thickness over 4 years [88]. Similarly, dietary caloric restriction without exercise enhanced the response of forearm blood flow to acetylcholine in obese hypertensive Japanese subjects [89]. The intra-arterial infusion of NG-monomethyl-L-arginine, a NO-synthase inhibitor, decreased the acetylcholine-induced blood-flow response induced by caloric restriction [89]. More recently, Raitakari and colleagues demonstrated that weight reduction with a very low-calorie diet also improved flow-mediated vasodilation in obese individuals [90]. The authors suggested that this improvement was related to a reduction in plasma glucose, and that the changes in glucose metabolism may determine endothelial vasodilatory function in obesity.

It is of particular interest that macronutrient modifications may also have an impact on endothelial function. Carluccio and colleagues found that olive oil at nutritionally relevant concentrations transcriptionally inhibits endothelial adhesion-molecule expression, thus partially explaining atheroprotection from Mediterranean diets [91]. Yildirir and colleagues also found that a soy-protein diet significantly improved endothelial function, as determined by flow-mediated endothelium-dependent dilatation and plasma thrombomodulin levels [92]. Very recently, Miyashita and colleagues compared two hypocaloric diets different in their carbohydrate/fat ratio for 4 weeks [93]. Although both diets resulted in a comparable weight and total fat loss, only the diet lower in carbohydrates (~40%) resulted in a significant reduction in basal insulin level and visceral fat, and significant improvement of lipid profile.

Together with the results of the DPP [6] and the other lifestyle-intervention studies [94,95], it can be strongly assumed that weight reduction through diet and exercise not only decreases the risk of developing Type 2 diabetes, but also improves endothelial function and vascular reactivity. However, it is not clear from all previously mentioned studies if this effect would be maintained following cessation of the intervention program. Only one study demonstrated that the vascular effects from exercise training were abrogated 8 months after cessation of exercise [96]. The positive results of the DPP are difficult to duplicate outside research settings. In clinical practice, weight reduction achieved through nonsurgical interventions is difficult to maintain and remains a major challenge to current diabetic practice.

Effect of lifestyle modification on cytokines & insulin sensitivity

Weight reduction has been shown to improve several hemostatic factors associated with cardiovascular disease, including PAI-1 and tissue-type plasminogen activator (t-PA) [77]. As mentioned before, PAI-1 is expressed in both adipose tissue and vascular endothelium and was shown to be elevated in the insulin-resistant state. Furthermore, it has been shown to correlate with the degree of visceral adiposity [97]. Its elevation in obesity, insulin resistance and CAD indicates a possible link between the three [98]. In humans, it has been shown that an improvement in insulin sensitivity, by either weight reduction or medication, lowers circulating levels of PAI-1 [99]. McGill and colleagues also found that the decrease in PAI-1 correlates with the amount of weight lost and the decrease in plasma triglycerides [77]. Meanwhile, weight reduction has also been shown to improve t-PA antigen [77]. In a recent study, the authors' group also observed a significant reduction in the plasma PAI-1 after 6 months of combined caloric reduction and moderate-intensity physical exercise, but did not find any change in t-PA in obese individuals with insulin resistance [6]. Likewise, Rissanen and colleagues observed a significant reduction in PAI-1 after 6 months' weight reduction in obese healthy women [100]. They also found that this reduction correlated with the magnitude of weight reduction and tended to rise with weight rebound, but remained below the 6-month values if the weight loss was sustained or continued [100]. These observations indicate an improvement in the fibrinolytic system with weight reduction.

Weight reduction in combination with exercise was also associated with a reduction in TNF-α and IL-6 [38,49,101]. In a recent study, a long-term multidisciplinary approach aimed at inducing a sustained weight reduction in obese women for 1 year, also resulted in a reduction of circulating TNF-α and

IL-6 [80]. The reduction in circulating levels of TNF-α following weight reduction was parallel to the improvement in endothelial function [39]. Recently, the author's group also demonstrated that a shorter program of weight reduction, for 6 months, significantly reduced TNF-α in the impaired glucose-tolerence population [102]. Although IL-6 plasma levels decreased following lifestyle modification [103], it is still not known whether modifications of the IL-6 system are involved in the improvement of insulin sensitivity.

In experimental animals, Milan and colleagues found that adiponectin gene expression is significantly lower in the visceral fat of genetically obese Zucker (fa/fa) rats in comparison with lean rats, and that weight reduction increases adiponectin gene expression [104]. In humans, while one study showed that plasma adiponectin levels do not change with a 6-month moderate-weight-reduction program, even when accompanied by aerobic or resistive exercise training in overweight and obese postmenopausal women [105], two other studies found that plasma adiponectin increased after weight reduction following bariatric surgeries [105,106]. The first found a significant elevation of adiponectin following gastric bypass surgery that resulted in a 36.4 ± 9.6% weight reduction in severely obese subjects. It also found that adiponectin was the best predictor of improved insulin sensitivity [106]. The second showed that gastric partition surgery that resulted in a 21% reduction in the mean body mass index (BMI) was associated with a 46% increase in mean plasma adiponectin level [107].

While weight reduction is associated with an increase in plasma adiponectin, exercise that is not associated with weight reduction only improved insulin sensitivity without increasing adiponectin. Although one single study showed that exercise increases adiponectin levels in association with an improvement of insulin sensitivity in humans [108], several others did not show any change in plasma adiponectin despite improved insulin sensitivity [109–111]. Kraemer and colleagues found that acute continuous or intermittent exercise was not associated with increased adiponectin production in healthy middle-aged adults [109]. Hulver and colleagues also found that 6 months' physical training resulted in a 98% improvement in insulin sensitivity, but did not change plasma adiponectin levels [110]. Similarly, in Type 2 diabetic patients, an intensive training program for 8 weeks resulted in a reduction of abdominal fat, by 44%, and improved insulin sensitivity, by 58%, but was not associated with a significant variation in leptin or adiponectin levels [111]. Although the overall training program in the latter was not associated with a significant reduction in total body weight – probably due to an increase in lean-muscle mass – the change in adiponectin correlated with the change in total body weight but not with insulin sensitivity or the variation in abdominal adiposity. The only explanation for this observation is that exercise also increases β-adrenergic and glucocorticoid activities, which may suppress adiponectin expression. The exact mechanism through which exercise improves insulin sensitivity is not well understood, but it may involve an increase in total and plasma-membrane GLUT-4 content as well as GLUT-4 translocation in response to insulin [112–114].

The reduction in the amount of visceral fat, particularly in response to exercise [115,116], may explain the observed changes in circulating cytokines and insulin sensitivity. However, the differential effect of different types or intensity of exercise on circulating cytokines is a controversial point. Although surgical removal of visceral fat has not been attempted in humans, two interesting studies in experimental animals showed that removal of visceral fat improved glucose tolerance and insulin sensitivity, and reduces hepatic glucose production and circulating free fatty acids [117,118]. A recent pilot study evaluated visceral-fat reduction in connection with bariatric surgery, where either adjustable gastric banding alone, or adjustable gastric banding plus surgical removal of the total greater omentum were compared [119]. The study showed no statistical difference between the two groups regarding weight change and changes in waist–hip ratio and sagital diameter; however, the improvements in oral glucose tolerance, insulin sensitivity and fasting plasma glucose and insulin were two- to three-times greater in the omentectomized compared with the control subjects. This was statistically independent of the loss in BMI.

It has long been known that aerobic exercise reduces blood pressure in both hypertensive and normotensive people – a fact that encouraged experts to suggest that aerobic physical activity should be considered as an important component of lifestyle modification for the prevention and treatment of high blood pressure [120]. It was recently found that visceral fat is an independent predictor of systolic blood pressure in obese Type 2 diabetic patients, while VO_{2max} and insulin sensitivity are independent predictors of diastolic blood pressure [121]. A recent study found that the reduction in blood pressure caused by daily exercise in obese men significantly correlates with the reduction in the visceral fat area [122]. However, it is not yet clear if that effect is mainly related to cytokine changes following reduction of visceral fat or that other factors modulate the relationship between visceral fat and blood pressure. The role of cytokines in regulating blood pressure supports this assumption [123].

Expert opinion

The cytokines produced by adipose tissue and the adipose tissue-resident macrophages play a major role in linking obesity to insulin resistance and endothelial function in obese Type 2 diabetic patients and in individuals with the metabolic syndrome. The reduction in adiponectin, the increase in PAI-1 and the proinflammatory cytokines such as TNF-α and IL-6 are frequently seen in obese people, in Type 2 diabetic patients, in individuals with the metabolic syndrome and in patients with CAD. Lifestyle changes in the form of caloric restriction and increased physical activity were found to modify gene expression and production of these cytokines, and to improve insulin sensitivity, lipid profile and blood pressure. Weight reduction, particularly the reduction of central adiposity, is associated with an improvement in endothelial function and is assumed to reduce cardiovascular events in this high-risk population. Although it is not clear how the effect of exercise differs from the effect of weight reduction by diet, the combination of both seems to be more effective than each one separately. Longer-term studies are

needed to clarify whether sustained weight reduction through lifestyle modifications will definitely reduce cardiovascular events and overall cardiovascular mortality.

Five-year view

Several new parameters will be used in the future to better identify those individuals at high risk for CAD, including the volume of visceral fat, the serum level of adiponectin and TNF-α – a quantitative measure of insulin sensitivity and a noninvasive measure of endothelial function. Drugs that modify body-fat distribution or that specifically reduce visceral-fat volume may be available in the future. Thiazolidinediones have shown that modification of fat distribution is pharmaceutically possible. Specific and potent β-3 adrenergic agonists are the second comers. As lifestyle modifications in the form of weight reduction by caloric restriction and modest intensity exercise are found to be more effective in reducing cardiovascular risk than most of the available pharmaceutical interventions, it is expected that researchers will try exploring the additional benefits of combining pharmaceutical drugs with specific lifestyle interventions. For example, a combination of a thiazolidinedione with exercise may be found to be more effective than either one alone because of their complementary mechanisms on visceral fat volume and cytokine production; or a combination of metformin with diet that is modestly lower in carbohydrates may be more beneficial for weight reduction and for improving insulin sensitivity. The molecular pathway through which exercise modifies visceral fat or cytokine production has many potential target points for pharmaceutical interventions. Newer anti-inflammatory medications or other pharmaceutical products that specifically target the NF-κB-dependent proinflammatory pathways will modify or minimize the TNF-α effect of increasing monocyte adhesion to the vascular endothelium, and thus slow the progression of atherosclerosis. Meal replacements with specific macronutrient ratios – specifically higher in protein and mono- and polyunsaturated fat – in combination with a low glycemic load and glycemic-index carbohydrates, will be used by the high-risk population, not only to help them lose weight but also to help them modify their metabolic profile that includes serum lipids, plasma glucose, insulin sensitivity and blood pressure.

Key issues

- Cytokines produced from adipose tissue and from the adipose tissue-resident macrophages link obesity to insulin resistance and endothelial function in obese patients with the metabolic syndrome and Type 2 diabetes.
- In Type 2 diabetic patients, patients with coronary artery disease and individuals with the metabolic syndrome, adiponectin is reduced, and other cytokines including plasminogen activator inhibitor-1 and the proinflammatory cytokines such as tumor necrosis factor-α and interleukin-6 are increased.
- Short-term lifestyle changes through weight reduction, particularly the reduction of central adiposity, caloric restriction and increased modest-intensity physical activity modify the gene expression and production of these cytokines and therefore improve endothelial function, insulin sensitivity, lipid profile and blood pressure. The longer-term effect is not yet known.
- Although the combination of diet and exercise seems to be more effective than each one separately, it is not clear how the effect of exercise differs from the effect of weight reduction by diet on endothelial function and cardiovascular risk.
- The molecular pathway through which diet and exercise modifies visceral fat or cytokine production has many potential target points for future pharmaceutical interventions.

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