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Obesity Prevention

Obesity, weight loss and conditional cardiovascular risk factors

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Summary

Obesity is a pathological condition aggregating a substantial number of proatherogenic factors, such as insulin resistance, type 2 diabetes mellitus, dyslipidaemia and hypertension. In addition to these classic cardiometabolic risk factors, atherosclerosis may be aggravated by other non-classic factors, which are characterized as conditional, including homocysteine, fibrinogen, lipoprotein(a), LDL particle size and high-sensitivity CRP. Some of these biomarkers are disturbed in obesity because of a combination of dietary factors, hypertrophic adipose tissue, low-grade inflammation, insulin resistance and other parameters under investigation. For the reduction of these risk factors, weight loss exceeding 10–20% of the initial body weight is probably necessary, achieved through either conventional lifestyle measures or more drastic interventions such as bariatric surgery. It has been shown that certain well-balanced diets, such as the Mediterranean diet, constitute a means of improving in a concerted manner the levels of CRP, fibrinogen, homocysteine and small dense LDL particles, regardless of weight loss. The significance of considering these factors in weight management intervention is an issue that needs further investigation.

Keywords: Atherosclerosis, conditional risk factors, obesity, weight loss.

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Introduction

Obesity is a proatherogenic condition that predisposes to cardiovascular disease (CVD) via its major associated risk factors such as dyslipidaemia, hypertension, insulin resistance and type 2 diabetes mellitus. These established risk factors appear to explain less than 50% of the variability in the quantitative measures of atherosclerotic vascular disease, and it is well known that a substantial proportion of cardiovascular events occur in individuals who exhibit none of these classic risk factors (1).

For these reasons, there has been considerable interest in identifying novel biomarkers that might improve the global risk prediction of cardiovascular disease These novel factors may well be causative and/or drive conventional risk factors, hence the term *conditional*. Conditional cardiovascular risk factors include homocysteine, fibrinogen, lipoprotein(a) [Lp(a)], low-density lipoprotein (LDL) of small dense particle size (sdLDL) and high-sensitivity C-Reactive Protein (hs-CRP) (2). In addition, recent studies have identified new 'emerging' factors of which the association with coronary heart disease (CHD) needs further confirmation (2). Most of conditional risk factors can now be accurately measured in routine clinical practice, and specific cut-off values have been proposed for the European population (3). It is debatable, however whether they should be added to the Framingham scoring, in particular for the classification of subjects at intermediate cardiovascular risk (i.e. 10–20% over 10 years) (3,4).

In the case of obesity, which represents a state of enlarged adipose tissue, low-grade inflammation and insulin resistance, some of these conditional vascular risk factors are often disturbed and weight loss, can eventually ameliorate their profile. This review article presents the

state of knowledge on the role of obesity in the conditional risk factors for atherosclerosis and the effects on them of weight loss through different therapeutic modalities.

Fibrinogen

Fibrinogen, an acute-phase reactant, is synthesized in the liver. It is an important component of the coagulation pathway and a major determinant of plasma viscosity (2). The Framingham study and other epidemiological studies have shown that fibrinogen is a powerful and independent risk factor for CVD(5). The precise role of fibrinogen in the atherosclerotic process is not yet completely clear; possible explanations include regulation of cell adhesion and proliferation, vasoconstriction at the site of vessel wall injury, stimulation of platelet aggregation and determination of blood viscosity. Plasma levels of fibrinogen appear to be, at least partly, genetically determined, and they are also influenced by various environmental factors, smoking being the strongest known determinant of its levels (2,6).

Fibrinogen and obesity

Clinical studies yield strong evidence that fibrinogen levels are increased in obese and overweight individuals and a positive correlation has been observed between Body Mass Index (BMI) and fibrinogen (7,8), but it is not clear whether these associations reflect a cause-and-effect relationships (6). Higher levels of fibrinogen have been reported in subjects with abdominal fat distribution (9). A case–control study suggests that this increase, along with other rheological disturbances, are associated with insulin resistance and the metabolic syndrome (8). In a recent kinetic study in non-diabetic obese males using an euglycaemic, euaminoacidaemic, hyperinsulinaemic clamp, an increased production of fibrinogen was associated with hyperinsulinaemia and/or insulin resistance (10).

Although synthesis of fibrinogen by the adipose tissue has not been described, the release of adipocytokines in the portal circulation by dysfunctional adipose tissue could influence the production of fibrinogen and other coagulation factors in the liver. In this respect, elevated fibrinogen levels could reflect a proinflammatory state closely associated with insulin resistance and obesity. Visceral adipose tissue, in particular, is known to increase the biosynthesis of fibrinogen through its secretion of the proinflammatory cytokine IL-6 (11).

Fibrinogen and weight change

The findings of studies investigating the effect of weight loss on fibrinogen levels are not conclusive, with a few studies demonstrating a positive effect of weight loss on fibrinogen levels (12,13) and others finding no effect (8). A probable explanation could be that a substantial weight loss, exceeding 10% of initial weight, is needed to produce a significant reduction in fibrinogen levels (6) Accordingly, in studies with variation in the macronutrient content of the diet, fibrinogen levels did not change significantly in the cases in which substantial weight loss was not achieved (14,15). Similar findings are reported in studies examining the effect of weight loss through bariatric surgery (16). However, some bariatric surgery procedures may affect biomarkers, including fibrinogen not only via weight loss but also by inducing malabsorption and altering a host of metabolic parameters.

Data on the effects of anti-obesity drugs on fibrinogen levels are insufficient. It appears that orlistat, at least, did not influence any haemostatic factor beyond its effect on weight loss, suggesting that even using anti-obesity medication, a substantial weight loss is required to obtain a significant effect on fibrinogen levels (17,18).

High-sensitivity C-reactive protein

C-reactive protein is a protein produced by hepatocytes in the presence of inflammation, but may also be synthesized in the adipose tissue (2,19). Inflammation is thought to play a major role in the pathophysiological mechanisms of CVD and minor elevations in its levels are considered to be a strong, independent predictor of cardiovascular events (20).

Large prospective studies showed that increased hs-CRP levels in metabolic syndrome confer greater cardiovascular risk, and thus measurement of hs-CRP could add prognostic information in these patients (19). It appears that hs-CRP may be directly involved in atherosclerosis by mechanisms including amplification of the inflammatory response through complement activation, tissue damage and endothelial cell activation (21).

C-reactive protein and obesity

Various different large, cross-sectional community cohort studies have reported a positive correlation between plasma hs-CRP levels and BMI or waist circumference (2). Mechanistically, the increase of CRP in obesity state could be explained by the infiltration of the expanded adipose tissue by macrophages which are responsible for both the generation of inflammatory signals and the production of cytokines such as IL-6 and TNF-α; IL-6, in particular, stimulates the liver to produce CRP in large quantities (22). hs-CRP appears to be increased particularly in abdominal obesity, possibly because visceral adipose tissue is more infiltrated with inflammatory cells than subcutaneous adipose tissue (23). This low-level, chronic inflammatory state may induce insulin resistance and endothelial dysfunction and provides a model linking obesity and cardiovascular disease (24).

C-reactive protein and weight change

It has been shown that in obese patients dietary restriction and weight loss at least 10% leads to a significant reduction in inflammation and hs-CRP levels (17,25). Many reports suggest that the weight loss *per se*, rather than the macronutrient composition of the diet, is the driving force underlying the reduction in inflammatory markers (26,27).

Weight loss via physical activity can influence hs-CRP levels to a variable degree. It has been observed that obese women receiving a low-energy, Mediterranean-style diet combined with increased physical activity for 2 years showed a greater reduction in hs-CRP levels than controls who received general information about healthy food choices and exercise (28). Aerobic exercise can decrease both body weight and hs-CRP levels; however, a transient increase in its levels and other inflammatory markers due to muscle damage has been observed (29,30).

More consistent decreases in hs-CRP levels have been observed after bariatric surgery (31,32). The reduction in CRP and other proinflammatory cytokines and adipocyte hormones after Roux-en-Y gastric bypass could contribute to the long-term resolution of insulin resistance (33).

The effect of weight reducing drugs on hs-CRP needs further investigation. There are some reports of a lowering effect of orlistat on hs-CRP levels, but it is not clear whether this effect could be attributed directly to the drug or is because of the associated weight reduction (34).

Lipoprotein(a)

Lipoprotein(a) is a LDL-like particle, synthesized by the liver, that consists of an apolipoprotein B100 molecule covalently linked to a unique glycoprotein known as apolipoprotein(a) which resembles to plasminogen (35). The physiological function of Lp(a) remains obscure, although a role in wound healing and tissue repair has been proposed (2).

Plasma levels of Lp(a) vary widely among individuals and appear to be hereditary. Recently, two Lp(a) variants have been identified that were strongly associated with both an increased level of Lp(a) and an increased risk of CHD(36). Elevated plasma levels of Lp(a) increase the risk for developing CVD through both proatherogenic and prothrombotic properties (1) and this risk appears to be more important when plasma levels exceed 20 to 30 mg dL^{-1}. The findings of a recent review support a causal association of Lp(a) with CHD (37).

Lipoprotein(a) and obesity

Only few studies have examined the relationship between Lp(a) and obesity. Some investigators have reported a significant inverse (38) or positive (39) association between Lp(a) and BMI while others have not identified any relationship (40). In a random sample of Mexican population, plasma Lp(a) concentrations were similar in obese and non-obese individuals, but the obese normoinsulinaemic subjects had higher Lp(a) levels than the obese hyperinsulinaemic subjects (41). More research is needed to clarify the relationship and the possible mechanisms linking obesity and Lp(a).

Lipoprotein(a) and weight loss

It is generally considered that standard diet, exercise therapy and hypolipidaemic drugs known to alter plasma levels of other lipoproteins, have little or no effect on Lp(a) (2).

Although studies have shown no change in the mean Lp(a) levels in obese patients following weight loss (42), some authors reported that the response of Lp(a) to a dietary induced weight loss could possibly be dependent on the initial Lp(a) levels (40,43). In a study of obese women with high baseline levels of Lp(a), a low-calorie low-fat diet produced weight loss and a significant reduction in the plasma level of Lp(a) (44). Conversely, a significant elevation in the Lp(a) levels after reduction of the saturated fat intake was reported (45). The implication of dietary fat modulation in Lp(a) levels needs further investigation. Finally, the efficacy of intestinal bypass surgery for obesity to lower mean serum Lp(a) level was reported in one study (46).

Further analyses of large cohorts are needed to identify the molecular basis and more precisely the role of apo(a) isoform size on the potential modulation of levels of Lp(a) by weight loss.

Low-density lipoprotein particle size

Low-density lipoprotein particles differ in size and density, and gradient gel electrophoresis has been commonly used to characterize the distribution of LDL particles by size. Two distinct phenotypes have been described: pattern B, with a predominance of sdLDL, and pattern A, with a higher proportion of large, more buoyant LDL particles (47). sdLDL tend to coexist with elevated triglyceride and low high-density lipoprotein cholesterol levels, a trait called 'atherogenic dyslipidaemia' which appears to be highly heritable (47). sdLDL are more susceptible to oxidation and are therefore highly atherogenic. LDL diameter may improve the ability to predict CVD risk overuse of the classic lipid variables, although prospective studies have not consistently shown LDL particle size to be an independent risk factor after adjustment for triglyceride levels (48).

Low-density lipoprotein particle size and obesity

One of the most common lipid abnormalities observed in obese individuals, and particularly in those with central fat distribution, is the presence of sdLDL(49). Patients with metabolic syndrome exhibit significantly higher concentrations of dense LDL particles and lower mean LDL particle size than control subjects, and serum triglyceride concentration is a good determinant of the presence of sdLDL particles (50). In such patients, Apolipoprotein B (ApoB) measurement has to be considered for assessing risk because this protein largely reflects LDL particle concentration and the presence of other proatherogenic particles including very-low density lipoprotein (VLDL), intermediate density lipoprotein (IDL) and Lp(a), as each particle contains one molecule of ApoB(51).

Although both adiposity and insulin resistance influence concentrations of the LDL subclass (52), hyperinsulinaemia and peripheral insulin resistance are more closely associated with an unfavourable lipoprotein profile and increased number of sdLDL particles (53). The clustering of elevated triglycerides and sdLDL particles in the context of insulin resistance and obesity could be mediated by adiponectin, which is typically reduced in this clinical situation (54).

Low-density lipoprotein particle size and weight change

Weight loss achieved by low-calorie diet has been shown to beneficially modulate LDL size and distribution (28). Conversion of the LDL subclass pattern B to pattern A, and reversal of the atherogenic phenotype can be achieved in a high proportion of overweight men by normalization of adiposity (55).

It has been postulated that the specific diet composition could also play a role. Study findings suggest that LDL particle size shifts from larger to smaller in direct proportion to the degree to which dietary fat is replaced by carbohydrates (56). Dietary carbohydrates, especially simple sugars, can promote metabolic syndrome and atherogenic dyslipidaemia, in a large part because of effects on the metabolism of plasma triacylglycerol-rich lipoproteins (57). Recent studies show that moderate carbohydrate restriction and weight loss provide an equivalent effect in improving atherogenic dyslipidaemia (58,59).

Sedentary behaviour appears to have a negative effect on lipoprotein metabolism but the effect of exercise on LDL particle size remains controversial. Many studies that examined this relationship reported either an increase in the mean particle size in response to exercise (60) or no effect (61). In general, an intensive lifestyle programme for at-risk patients can effectively alter plasma lipoprotein subclasses and may reduce the risk of cardiovascular events (62).

Beneficial results have also been reported in studies examining weight loss as a result of bariatric surgery, e.g. after gastroplasty (63) and laparoscopic gastric banding (64), which, however need further confirmation by larger studies. Finally, orlistat, taken either alone or in combination with fenofibrate, has also been shown to lower plasma sdLDL concentrations in obese subjects with the metabolic syndrome (65).

Homocysteine

Homocysteine is a thiol-containing amino acid intermediate formed during the metabolism of methionine, an essential amino acid (2). Three micronutrients are important co-factors in homocysteine metabolism: folate and vitamin B12 are co-factors for the methylation of homocysteine to methionine, and vitamin B6 is involved in its catabolism.

Substantial evidence has been accumulated from observational studies linking homocysteine in plasma and serum to the risk of CVD(66). Homocysteine promotes atherothrombogenesis via a variety of mechanisms: It increases the oxidation of LDL and the production of free radicals, impairs the metabolism of nitric oxide and provokes endothelial injury or dysfunction (2).

Homocysteine and obesity

Reports about a possible correlation between homocysteine levels and obesity status are few and provide conflicting data. The data from the Framingham Offspring Study showed a weak positive correlation between homocysteine and the BMI(67). Plasma homocysteine level has been reported to be linked with indices of childhood obesity and insulin resistance (68), but other studies found no such association (69).

Elevated fasting homocysteine levels are particularly associated with dietary factors such as lower intake and circulating concentrations of folate and vitamin B-12 (70) and are amenable to treatment with these vitamins (71).

Homocysteine and weight change

Most studies have reported an increase in homocysteine concentrations during weight reduction, changes that have been ascribed to inadequate folate or B12 intake (72), whereas vitamin supplementation caused a decrease in the homocysteine levels.

The macronutrient content of the diet can also influence the level of homocysteine during weight loss. For example, homocysteine increased after a low-carbohydrate diet, perhaps because of the low concentration of folate in such diets (73). Other factors that could modulate homocysteine levels during weight loss are the protein content of the diet, the reduction of the lean or fat mass, related metabolic effects, etc (74).

Table 1 Conditional cardiovascular risk factors in obesity

Risk factor	Levels in obesity	Modulators
Fibrinogen	Increased	Visceral fat, inflammation, insulin resistance
High sensitivity CRP	Increased	Visceral fat, inflammation, insulin resistance
Lipoprotein(a)	Unclear	Genetic factors
Small dense LDL	Increased	Visceral fat, triglycerides, insulin resistance
Homocysteine	Probably increased (weak association)	Dietary factors, adipose tissue, hyperinsulinism

CRP, C-reactive protein; LDL, low-density lipoprotein.

Table 2 Effects of weight loss intervention on conditional risk factors for cardiovascular disease in obesity

Risk factor	Weight loss	Weight loss intervention			
		Diet	Exercise	Anti-obesity drugs	Bariatric surgery
Fibrinogen	↓ (WL > 10–20% needed)	→	→	?	↓
High sensitivity CRP	↓ (WL > 10–20% needed)	↓?	↓?	?	↓
Lipoprotein(a)	→ or↓	→ or ↓(dietary fat?)	→	?	?
Small dense LDL	↓	↓(low CHO)	→ or↓	?	↓
Homocysteine	↑	↑	→ or↓or↑	?	↑

CHO, carbohydrates; CRP, C-reactive protein; LDL, low-density lipoprotein; WL, weight loss; ↑, increased; ↓, decreased; →, stable; ?, unclear.

The effect of physical activity on homocysteine levels is equivocal and duration, intensity and mode of exercise appear to impact blood homocysteine levels differently (75). Finally, an elevation of plasma homocysteine levels is to be expected following bariatric surgery by the Lap-Band form of gastric restrictive surgery (76) or by gastroplasty (72). In these studies, the changes in levels of homocysteine were not explained by decreased folate or vitamin B-12 concentrations. However, subjects taking regular multivitamin supplements had significantly lower fasting homocysteine levels than those taking them intermittently or not at all (77).

The possibility that weight loss might increase one independent risk factor, such as homocysteine, raises some concerns and highlights the importance of well-balanced and correctly supplemented diets in the treatment of obesity. It should also be pointed out that beyond CVD risk, weight loss may increase the risk of folate-related neural tube defects.

The influence of obesity status on conditional risk factors and possible modulators is represented in Table 1, while the effects of various weight loss interventions on these factors are summarized in Table 2.

New emerging cardiovascular risk factors and obesity

Lipoprotein-associated phospholipase A_2, an enzyme associated primarily with LDL promoting atherothrombotic diseases has been shown decrease after low-fat low-calorie diet (78). *Lipid transfer proteins (Cholesteryl ester transfer protein, CETP and Phospholipid transfer protein, PLTP)* which are also involved in the atherosclerotic process may be reduced simultaneously, either by hypocaloric dietary manipulation or laparoscopic gastric banding surgery (79,80). Finally, *oxidative stress* which may be the unifying mechanism underlying the development of co- morbidities in obesity, can greatly be improved by several means of obesity treatment (81).

Conclusions

Obesity represents a unique pathological condition in which a substantial number of proatherogenic factors are aggregated. Most of the conditional cardiovascular risk factors, such as fibrinogen, CRP and the sdLDL phenotype appear to be disturbed in visceral-type obesity, essentially because of enlargement of the adipose tissue, low-grade inflammation and insulin resistance; in the case of Lp(a) and homocysteine the relationship is less clear. A small or moderate weight loss (5–10%) is sufficient to improve the classic risk factors, but not certain conditional ones, such as proinflammatory fibrinogen and CRP, for reduction of which a weight loss exceeding 10–20% of the initial body weight is probably necessary. Bariatric surgery, by producing substantial weight loss, has a beneficial effect on the conditional factors, with the exception of levels of homocysteine, which may increase significantly following surgery, possibly because of deficiency of vitamins and folic acid. Although it appears that weight loss is more impor-

tant than the variation of macro-nutrients for improving the conditional risk factors, investigation is currently under way to identify lifestyle measures which will produce a global improvement; e.g. the Mediterranean diet appears to provide relevant nutrition which improves in a concerted manner the levels of hs-CRP, fibrinogen, homocysteine and sdLDL, regardless of weight loss (82,83). The effect of anti-obesity drugs on the conditional risk factors needs further investigation. Studies are also needed to identify the mechanisms of interaction between the conditional risk factors and adipose tissue and to explore the effect of long-term improvement of these factors on the cardiovascular risk in obese individuals.

Conflict of interest statement

No conflict of interest was declared.

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