Metabolic syndrome and effects of conjugated linoleic acid in obesity and lipoprotein disorders: the Québec experience\textsuperscript{1–4}

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ABSTRACT

The health hazards of obesity are well established. However, the fact that all obese individuals are not at equal risk of developing a disease is being increasingly recognized. The regional distribution of body fat has been identified as an important component of the obesity-related health hazards. Among obese individuals, those who accumulate fat predominantly in the abdominal area are more likely to present several metabolic perturbations of the metabolic syndrome, such as increased plasma triacylglycerol and apolipoprotein B concentrations, an elevated ratio of total cholesterol to HDL cholesterol, reduced plasma HDL-cholesterol concentrations, and small, dense LDL particles. This short review focuses on the risk associated with specific features of metabolic syndrome with use of data from the Québec Cardiovascular Study, an ongoing prospective study of traditional and nontraditional risk factors for ischemic heart disease in men. Recent data on the effect of conjugated linoleic acid on risk factors associated with metabolic syndrome are briefly reviewed. Data available to date suggest that conjugated linoleic acid might not be an appropriate dietary alternative for the treatment of metabolic syndrome and its complications. Am J Clin Nutr 2004; 79(suppl):1149S–52S.

KEY WORDS Metabolic syndrome, conjugated linoleic acids, obesity, dyslipidemia

INTRODUCTION

Although it is now clearly established that elevated plasma cholesterol concentrations contribute significantly to the risk of cardiovascular disease (CVD) (1, 2), other risk factors are being increasingly recognized to play a major role in the pathophysiology that leads to CVD (3). Reaven (4) introduced in 1988 the concept of the insulin resistance syndrome, a pluri metabolic disease which had as its cornerstone a dysregulation of glucose and insulin metabolism, along with hypertension and a typical dyslipidemic state that included elevated plasma triacylglycerol and low HDL-cholesterol concentrations.

The pioneer work of Reaven suggested that this insulin resistance syndrome, which was first referred to as syndrome X and later as metabolic syndrome (MS), plays a key role in the etiology of CVD. The characterization of MS has been the topic of intense research over the past 15 y, leading to the identification of a series of other metabolic disturbances that are most frequently found in combination rather than in isolation in individuals with MS (5). Thus, an increased number of reduced size LDL particles, impaired fibrinolytic activity, a proinflammatory state, impaired postprandial metabolism, abdominal obesity, and a pro-oxidative state were all identified as important features of MS (5, 6).

The objective of this short review is first to discuss some of the clinical aspects related to MS. We briefly discuss the role of obesity in contributing to perpetuating metabolic abnormalities that are associated with MS. We then focus on describing the unique role of hypertriacylglycerolemia as an important component of the multifaceted risk profile that leads to an increased risk of CVD in patients with MS. Finally, we briefly review recent work undertaken to investigate the effect of conjugated linoleic acids (CLAs) on specific risk factors for MS.

CLINICAL CONSIDERATIONS

The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) proposed in 2001 a definition for MS that could be used readily in clinics to identify individuals with this syndrome (7). According to this definition, an individual is classified as having MS if 3 of 5 criteria are present (Table 1). On the basis of this definition, it was suggested that approximately one-quarter of the adult American population would be classified as having MS (8). This figure increases to almost 45% in adult individuals older than age 65 y (8). The increasing prevalence of obesity among industrialized countries suggests that the prevalence of MS and its contribution to the global effect of CVD will evolve dramatically over the next decades. In their recent statement for the prevention and treatment of CVD, the NCEP ATP III has, therefore, emphasized the importance of considering MS as a secondary target for therapy in high-risk patients (7).

Obesity and metabolic syndrome

The hypothesis proposed by Reaven (4) in 1988 on MS implied that the metabolic and physiologic alterations accumulating in individuals with this syndrome were attributable to the presence of a systemic insulin resistance state. Interestingly, the

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initial concept of MS did not include obesity as one of its components. Since then, however, it has been clearly shown that obesity, and particularly abdominal obesity, was one of the key features that accompanies insulin resistance and its dysmetabolic state (9–11). The concept that obesities were not all created equal has been around for more than half a century when the French investigator Vague documented that men and women with a preponderance of fat accumulation in the abdominal area were more susceptible to having diabetes, CVD, and gout than were individuals accumulating fat in the gluteofemoral area (12). Several groups have since contributed to our more in-depth knowledge of how abdominal obesity could worsen the cardiovascular and diabetes risk profile. It is beyond the scope of this paper to review these mechanisms, which are the topic of excellent previous reviews (13–16). Also, whether it is abdominal obesity that precedes the onset of insulin resistance or vice versa is an issue that has yet to be elucidated (17). It is also beyond the scope of this paper to comment on this controversy. However, we can state that abdominal obesity and insulin resistance are hardly dissociable; both contribute to the increased risk of CVD and type 2 diabetes through several shared metabolic perturbations.

Hypertriacylglycerolemia and cardiovascular disease risk: evidence from the Québec Cardiovascular Study

We believe that hypertriacylglycerolemia is a key component that relates many of the metabolic perturbations seen in MS. The relation between hypertriacylglycerolemia and the risk of CVD has been a topic of intense debate over the years. This debate is partly because several epidemiologic studies were not able to observe an independent relation between plasma triacylglycerol concentrations and a risk of CVD, particularly after multivariate adjustment for plasma HDL-cholesterol concentrations. In 1996, a meta-analysis by Hokanson and Austin (18) provided strong evidence that hypertriacylglycerolemia should indeed be considered as an important and independent risk factor for CVD. When combining data from 17 studies in men and 5 studies in women, which comprised overall >55 000 subjects followed for an average of ≈9 y, they found that a 1-mmol/L increase in plasma triacylglycerol concentrations was associated with a significantly increased risk of CVD in both men (14%) and women (37%) even after adjustment for plasma HDL-cholesterol concentrations.

Analyses from the Québec Cardiovascular Study concur with these observations (19). Those analyses are based on a cohort of 1870 nondiabetic men free of ischemic heart disease (IHD) at baseline and followed for a period of 5 y, during which 91 first events of IHD were recorded. We found that moderate hypertriacylglycerolemia (triacylglycerol >1.6 mmol/L) was associated with a metabolic risk profile that was consistent with the presence of MS. Indeed, healthy men at baseline with plasma triacylglycerol concentrations >1.6 mmol/L were more obese and had lower plasma HDL-cholesterol concentrations, higher apolipoprotein B (apo B) and insulin concentrations, as well as smaller LDL particles, compared with men having plasma triacylglycerol concentrations <1.6 mmol/L. Moderate hypertriacylglycerolemia was also characterized by a 3-fold increase in the risk of IHD over 5 y, which remained highly significant even after adjustment for plasma HDL-cholesterol, apo B, or insulin concentrations (20). We also found that the various components of MS interacted with plasma triacylglycerol concentrations to modulate IHD risk. Thus, men with marginally elevated plasma triacylglycerol concentrations had a 3.4-fold increase in risk if they had relatively normal apo B, HDL-cholesterol, and insulin concentrations but had a 13.6-fold increase in the risk of IHD if they had all of these abnormalities simultaneously.

The debate on whether plasma triacylglycerol concentrations as part of MS should be considered seriously as a clinical tool in strategies for CVD prevention is an important one. It is essential, however, that this debate goes beyond statistical considerations. Indeed, it is rather difficult to dissociate the contribution of triacylglycerol and other metabolic disorders to the risk of CVD because they are tightly linked to one another. Thus, it is possible that marginally elevated plasma triacylglycerol concentrations could represent for the moment the best proxy for several interrelated metabolic perturbations that also predict an increased risk of CVD (20), including small dense LDL particles (20), reduced plasma HDL-cholesterol concentrations (21), and insulin resistance (22, 23).

Most features of MS are associated individually with an increased risk of CVD. In that regard, these data from the Québec Cardiovascular Study have allowed us to gain valuable expertise in our understanding of the relation between small dense LDL particles (24–26), hyperinsulinemia (27), hyperapobetalipoproteinemia (28, 29), inflammation (30, 31), and the risk of CVD. We have also documented the risk attributable to reduced plasma HDL cholesterol (32) and variability in HDL subfractions (33), 2 aspects of the lipid profile that are intrinsically related to hypertriacylglycerolemia. We also proposed that accumulation of specific features of MS, namely the simultaneous presence of small dense LDL particles and of elevated plasma apo B and insulin concentrations, was associated with a remarkable 20-fold increase in the risk of CVD in men over a 5-y period (34). It is fully recognized that the small dense LDL phenotype, apo B concentrations, and hyperinsulinemia cannot be readily quantified and obtained in day-to-day clinical practice. This practicality is another argument to give more consideration to plasma triacylglycerol concentrations when assessing the risk of CVD associated with MS. Plasma triacylglycerol concentrations are available to most general physicians. They may also be particularly useful when combined with a waist girth measure to reflect the presence of the highly atherogenic metabolic triad, ie, small dense LDL particles, hyperapobetalipoproteinemia, and hyperinsulinemia (35).

More recent studies that used the NCEP-ATP III definition of MS or other organizations’ definition have provided further ev-

**Table 1**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cutoff</th>
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<tbody>
<tr>
<td>Waist girth (cm)</td>
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<tr>
<td>Men</td>
<td>102</td>
</tr>
<tr>
<td>Women</td>
<td>88</td>
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<tr>
<td>HDL cholesterol (mmol/L)</td>
<td></td>
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<tr>
<td>Men</td>
<td>1.1</td>
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<tr>
<td>Women</td>
<td>1.3</td>
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<tr>
<td>Triacylglycerols (mmol/L)</td>
<td>1.7</td>
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<tr>
<td>Blood pressure (mm Hg)</td>
<td>130/90</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol/L)</td>
<td>6.1</td>
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2 NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III.
C-reactive protein and urinary 8-iso-prostaglandin F2α compared with placebo (47). Results also indicated that the trans-10, cis-12 isomer of CLA was associated with an 3-fold increase in the 8-year risk of CVD. Most important, however, the increased risk of CVD in women with MS was significantly modified by the presence versus absence of concurrent elevations in plasma C-reactive protein levels (40).

No doubt, therefore, exists that more energy will have to be directed toward the identification of subjects at high risk of CVD because of the presence of MS. This challenge becomes particularly important in light of the worrisome increasing epidemic of obesity in industrialized countries. Another challenge is the identification of the most adequate and optimal treatment of the dyslipidemic state and other CVD risk factors associated with MS.

Conjugated linoleic acid and metabolic syndrome

CLAs identify various derivatives of linoleic acid containing conjugated double bonds (41). CLAs are mostly found in foods from ruminant sources, in relatively small amounts that range from 1 to 8 mg/g lipid in ruminant meats and dairy products (42, 43). Earlier work has indicated that intake of CLA in the form of supplements might reduce adiposity in humans and could have important other beneficial effects (these effects are reviewed in other papers in this supplement). However, more recent data indicated that the relation between CLA taken as supplements or as part of naturally occurring foods and CVD risk factors and insulin resistance could be more complex than initially thought.

In animal studies, the desirable effects of CLA on body composition are ascribed to the trans-10, cis-12 isomer rather than the cis-9, trans-11 isomer (44–46), the predominant isomer in foods (42, 43). In that regard, Risérus et al (47, 48) conducted a study to investigate insulin action in a group of 60 abdominally obese men with MS who were randomly assigned to 3 supplements containing either 3.4 g/d of a CLA isomer mixture, the purified trans-10, cis-12 isomer, or a placebo. The investigators reported that after 12 wk of supplementation, the trans-10, cis-12 isomer induced statistically significant deteriorations in insulin resistance, as determined by the hyperinsulinemic clamp technique, in glyceremia as well as in plasma HDL-cholesterol concentrations compared with placebo (47). Results also indicated that the trans-10, cis-12 isomer led to a marked increase in plasma C-reactive protein and urinary 8-iso-prostaglandin F2α compared with the placebo (48). Changes in these markers of inflammation and oxidative stress could be related to the increase in insulin resistance associated with CLA supplementation.

We conducted a randomized crossover study designed to compare the effects of a modified butter naturally enriched with CLA (4.22 g CLA/100 g butter fat) compared with a control butter low in CLA (0.38 g CLA/100 g butter fat) on plasma lipoproteins and body composition in men (49). Briefly, we found that the CLA-enriched butter induced no significant change in the CVD risk profile and had no effect on the distribution of body fat. Indices of insulin sensitivity and of inflammation were also not modified by the CLA-enriched butter compared with the control butter (unpublished observation, 2001). These results suggested that a 10-fold CLA enrichment of butter fat does not lead to beneficial metabolic effects in overweight or obese men. Taken together, recent results surprisingly suggest that supplementation with trans-10, cis-12 CLA synthetic isomer or with the cis-9, trans-11 isomer–enriched foods may not lead to the expected beneficial changes in the risk variables traditionally associated with MS.

**CONCLUSIONS**

MS is a clinical entity that will have to be considered seriously in the next decades when we are faced with designing new strategies to reduce the burden of CVD in industrialized countries. MS is associated with a significant elevation in the risk of CVD in both men and women. Although we better understand the molecular and physiologic mechanisms underlying this syndrome, the most appropriate and effective therapeutic approaches for the treatment of MS and its associated features have yet to be identified. The use of CLA in that context might not represent an appealing option. Indeed, the metabolic effects of CLA in humans are much more complex than initially thought, and further studies, especially of isomer-specific effects, with individuals characterized by MS and for longer time periods, are clearly warranted.

BL and SD contributed intellectually to this short review. BL provided the main ideas conveyed in this paper. SD also provided intellectual input and was responsible for the critical review as well as final preparation of the manuscript. None of the authors had any conflict of interest on the topic reviewed in this brief paper.

**REFERENCES**


