

Insulin resistance–associated cardiovascular disease: potential benefits of conjugated linoleic acid^{1–4}

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ABSTRACT

Type 2 diabetes and associated cardiovascular disease have reached global epidemic proportions. Recent data from the World Health Organization Multinational Study of Vascular Disease in Diabetes indicate that cardiovascular disease is the leading cause of mortality (52% of deaths) in individuals with type 2 diabetes. Although insulin resistance plays a critical role in the pathogenesis of type 2 diabetes–related cardiovascular disease, other related risk factors often cluster in a single patient; the combination of insulin resistance and these risk factors is known as the metabolic syndrome. According to the World Health Organization definition, this constellation of risk factors includes hypertension, elevated plasma triacylglycerol, reduced HDL cholesterol, central obesity, and microalbuminuria. The Multiple Risk Factor Intervention Trial showed that, although diabetes or insulin resistance is an independent risk factor for cardiovascular disease mortality, these other components of the metabolic syndrome confer additive risk. Thus, to effectively address cardiovascular disease in persons with diabetes, intervention would ideally target all these factors. Conjugated linoleic acid could represent a candidate agent. The therapeutic potential of conjugated linoleic acid against insulin resistance–associated cardiovascular disease is discussed on the basis of the reported effects of conjugated linoleic acid on individual components of the metabolic syndrome. *Am J Clin Nutr* 2004;79(suppl):1159S–63S.

KEY WORDS Conjugated linoleic acid, metabolic syndrome, type 2 diabetes, cardiovascular disease, insulin resistance

INTRODUCTION

The number of people diagnosed with diabetes is growing rapidly worldwide and has reached epidemic status. As of 2002, the estimated number of individuals with diabetes is 151 million; this number is expected to rise to 221 million by the year 2010 and to 300 million by the year 2025 (1). Of these cases, type 2 diabetes (that is, diabetes characterized by insulin resistance) is the most prevalent in both developing and developed countries. Populations that currently account for >90% of diabetes cases globally (1) and most at risk of developing this disease are those undergoing rapid socioeconomic development such as American Pima Indians, Micronesians and other Pacific Islanders, indigenous Australians, Asian Indians, and Mexican Americans (2). It is also very alarming that the number of children and adolescents predicted to develop type 2 diabetes in the next 10–20 y is increasing significantly (2). This increase is a new aspect to the epidemic, because, historically, this disease was not commonly found in children or adolescents.

The global diabetes epidemic that we face today is largely attributed to the changes in human behavior and lifestyle that have occurred over the past century (2). Type 2 diabetes is associated with physical inactivity, poor nutrition, and obesity. It is characterized by impaired insulin action (insulin resistance), by impaired β cell function or insulin secretion, or by both. Generally, insulin resistance develops first when tissues are unable to respond to normal circulating concentrations of insulin. This reduced sensitivity in body tissues to the action of insulin consequently limits glucose disposal in muscle and fat. In response, to maintain glucose homeostasis, β cells in the pancreas secrete more insulin, which eventually results in pancreatic β cell exhaustion, decompensation, and failure.

TYPE 2 DIABETES, INSULIN RESISTANCE, AND CARDIOVASCULAR DISEASE

A most disconcerting endpoint of type 2 diabetes is cardiovascular disease (CVD). In fact, the most common cause of mortality in these patients is CVD, accounting for at least 50% of deaths according to the World Health Organization Multinational Study of Vascular Diabetes in Diabetes (3). Therefore, studies have reported that the rising incidence of diabetes is, as expected, accompanied with significant increases in CVD (2). Individuals with type 2 diabetes have increased risk of CVD compared with individuals without diabetes. The risk of CVD in individuals with diabetes was shown to increase by 2–4-fold compared with individuals without diabetes (4). It was also accordingly associated with increasing health care costs and socioeconomic burden (1).

As the major underlying abnormality in patients with type 2 diabetes mellitus, insulin resistance is considered to be the main link between diabetes and CVD, even in the absence of glucose

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intolerance. Insulin resistance is a strong predictor of coronary artery disease (5). As reported by Fontbonne and Eschwege (5), elevated plasma insulin concentrations after an oral glucose tolerance test served as an independent predictor of coronary artery disease in the Paris Prospective Study, as did blood pressure, smoking, and plasma cholesterol concentration. This prediction is not necessarily surprising, considering that insulin resistance is commonly associated with the development of risk factors for CVD, including an atherogenic lipid profile, endothelial dysfunction, and increased risk of thrombosis. For example, individuals with insulin resistance commonly have increased triacylglycerol concentrations and elevated total cholesterol concentrations, with increased concentrations of small dense LDL and decreased concentrations of HDL (6).

INSULIN RESISTANCE AND METABOLIC SYNDROME

Although insulin resistance is a strong predictor for CVD, it is rarely the only contributor to CVD in a patient. Very often, in a single patient's clinical profile, insulin resistance presents along with a constellation of several other risk factors for CVD. This constellation is referred to clinically as the metabolic syndrome but is also referred to as syndrome X, insulin resistance syndrome, and diabetes. Although the clinical parameters that define the metabolic syndrome could change as more is understood about this disease, in 1999 the World Health Organization defined metabolic syndrome by the following criteria: having 1) at least one manifestation of insulin resistance, whether insulin resistance per se, impaired glucose tolerance (IGT), glucose intolerance, or type 2 diabetes in combination with 2) at least 2 of the following CVD risk factors: hypertension, visceral obesity, hypertriacylglycerolemia, reduced HDL cholesterol, or microalbuminuria (2). As the common denominator in metabolic syndrome, insulin resistance not surprisingly confers with it the elevated risk of CVD (as discussed earlier). Indeed, in the Botnia study conducted by Isomaa et al (7), cardiovascular risk associated with metabolic syndrome was analyzed. Cardiovascular mortality was increased in subjects with metabolic syndrome (12% compared with 2%). The risk for coronary artery disease and stroke was also increased 3-fold in subjects with the syndrome (7).

TREATING METABOLIC SYNDROME: THERAPEUTIC APPROACH

As discussed earlier, epidemiologic studies that show the rapidly escalating number of patients with type 2 diabetes and metabolic syndrome strongly support the urgent need for lifestyle management and pharmacologic intervention, as well as the need to develop novel therapeutic approaches. Certainly, lifestyle intervention, in particular, that targets dietary and exercise habits can reduce the progression of IGT to fully developed type 2 diabetes in subjects by up to 58% (8).

As a cluster of clinical abnormalities, the best approach for treating metabolic syndrome was and is under some debate. In an attempt to prevent the development of CVD, it was unclear whether treatment should focus primarily on managing the insulin resistance component (as the common denominator of all patients with metabolic syndrome) or whether treatment regimens should instead focus on the other risk factors that clearly elevated risk of CVD (eg, hypertension or dyslipidemia). The

Multiple Risk Factor Intervention Trial (MRFIT) sought to address this issue. In the screening of $\approx 350\,000$ men with and without diabetes, CVD mortality was followed for an average of 12 y. Absolute risk of CVD death was much higher for men with diabetes than for men without diabetes of every age stratum, ethnic background, and risk factor concentration. Overall risk was 3 times higher, with adjustment for age, race, income, serum cholesterol concentration, systolic blood pressure, and cigarette smoking. Moreover, this study confirmed that insulin resistance is a strong independent risk factor for CVD mortality, and, accordingly, it is imperative that insulin resistance is addressed in any attempt to treat patients with metabolic syndrome. Importantly, the study also revealed that the presence of each additional risk factor, over and above insulin resistance, conferred with it an additive effect that, in turn, conferred a further, steeper rise in CVD risk profile. This finding underlined the importance of addressing the multiple risk factors for CVD, as present in patients with metabolic syndrome, in parallel (9). Accordingly, because of the results of the MRFIT and related trials, the American Diabetes Association and the European Diabetes Policy Group strongly recommend that effective management of diabetes and CVD should address all factors of metabolic syndrome.

NUTRACEUTICALS AND METABOLIC SYNDROME

Popular interest in alternative medicine and self-prescribed oral nutritional supplements has grown recently, particularly to treat chronic rather than acute life-threatening disease states (10). In fact, as early as 1990 in the United States, 34% of study respondents had resorted to nonconventional therapies within the past year (10). Although more than 200 pure phytochemicals are known to exert hypoglycemic activity, some of these effects can be attributable to metabolic or hepatic toxicity (11, 12). However, numerous nutraceutical, functional food, or natural health product regimens do yield therapeutically useful effects in diabetes. Examples are buckwheat (13), magnesium supplementation (14, 15), chromium picolinate (16), Caiapo (white sweet potato extract) (17), flaxseed extract (18), American ginseng (19), oat bran (20), oat gum (21), and vanadium (22).

CONJUGATED LINOLEIC ACIDS: CANDIDATE NUTRACEUTICAL APPROACH FOR TREATMENT OF METABOLIC SYNDROME

Conjugated linoleic acids (CLAs) are a group of naturally occurring fatty acids found predominantly in milk and animal fat that have gained ample attention for their numerous reported health benefits. They are formed as a first intermediate in the ruminal biohydrogenation pathway of linoleic acid to stearic acid and endogenously in mammary tissue from *trans* vaccenic acid, a precursor of rumen origin. CLAs are a mixture of positional and geometric isomers of linoleic acid (*cis*-9,*cis*-12-octadecadienoic acid) that contain a conjugated double bond system (23). The double bonds in CLA can be found in positions 9 and 11, 10 and 12, 11 and 13, 8 and 10, and 7 and 9 in all possible *cis* or *trans* configurations (24). CLA was first recognized for its anticarcinogenic activities. Later, it was found to have antiatherogenic properties (25) and functions in reducing body fat (26). Studies (27–29) have reported antidiabetic effects. Thus, on the basis of these reported findings it is speculated that CLA could serve as

a novel therapeutic approach for the prevention or treatment of type 2 diabetes and metabolic syndrome.

EFFECT OF CONJUGATED LINOLEIC ACID ON INSULIN SENSITIVITY

Insulin sensitivity can be defined as the ability of insulin-sensitive tissues such as skeletal muscle and adipose tissue to respond to normal physiologic concentrations of insulin circulating in the plasma to facilitate glucose uptake. Dietary CLA acts as an insulin-sensitizing agent. For example, Houseknecht et al (27) found that CLA normalized IGT, improved hyperinsulinemia, and lowered circulating free fatty acids in prediabetic Zucker diabetic fatty (ZDF) rats. The insulin-sensitizing effect of CLA is believed to be by activation of peroxisome proliferator-activated receptor (PPAR)- γ , in a manner comparable to that of thiazolidinediones such as rosiglitazone (PPAR γ agonists), which are used clinically as insulin sensitizers. This effect is in contrast to the ability of CLA to reduce plasma lipid concentrations, an effect which can be mediated by way of activation of hepatic PPAR α and thereby increasing fatty acid oxidation (27). The insulin-sensitizing actions of CLA were also reported by Ryder et al (28), whereby supplementing the diets of ZDF rats with 1.5% CLA (containing a mixture of 47% *cis*-9, *trans*-11 and 47.9% *cis*-10, *trans*-12 isomers, 50:50) reduced adiposity and improved glucose tolerance compared with control feedings. This antidiabetic effect in ZDF rats was mediated specifically by the *cis*-10, *trans*-12 CLA isoform. Furthermore, the 50:50 diet improved insulin-stimulated glucose transport in soleus skeletal muscles and insulin-stimulated glycogen synthase activity in soleus and extensor digitorum longus muscles. In addition to its agonist actions at PPAR γ , the effects of CLA on insulin sensitivity could be due to multiple mechanisms, some of which could be indirect. For example, a portion of its antidiabetic effect was attributed to its effect on lipid metabolism, including fatty acid oxidation, lipolysis, de novo lipogenesis, and the expression of enzymes involved in lipid metabolism (29).

Although CLA was shown as an insulin sensitizer repeatedly in animal models, whether it exerts similar actions in human patients with metabolic syndrome remains less clear. Instead, a mixture of CLA isomers had no effect on insulin sensitivity or plasma insulin concentrations (30, 31), and the *cis*-10, *trans*-12 CLA isoform actually worsened insulin resistance, resulting in significantly greater plasma insulin (hyperinsulinemia) (31). Thus, currently, the potential of CLA in addressing insulin resistance in human patients with metabolic syndrome remains questionable.

EFFECT OF CONJUGATED LINOLEIC ACID ON DYSLIPIDEMIA

Hypertriacylglycerolemia and elevated plasma cholesterol are major risk factors for atherosclerosis and CVD. Lipids are transported in the circulatory system with proteins, phospholipids, and carbohydrates in various forms as chylomicrons, VLDLs, LDLs, and HDLs. In general, high concentrations of serum LDL are associated with atherosclerosis, whereas HDL is inversely related to CVD. In addition, as aforementioned, hypertriacylglycerolemia and reduced plasma HDL were identified as major components of metabolic syndrome (2). Lee et al (25) found that CLA exhibits hypocholesterolemic and antiatherogenic proper-

ties. Rabbits fed high-cholesterol diets along with 0.5 g CLA/d had significantly lower total cholesterol and had reduced triacylglycerol concentrations compared with rabbits on high cholesterol in the absence of CLA. Furthermore, the aortas of these CLA-fed rabbits showed less atherosclerosis than the high-cholesterol-alone group. Similar results were also observed in CLA-fed hamsters (32, 33). Interestingly, HDL cholesterol was not affected by dietary supplementation in any of the animal model studies. Gavino et al (33) likewise observed a decrease in plasma triacylglycerol and total cholesterol in hamsters but found no effect in animals fed pure *cis*-9, *trans*-11 CLA. Thus, they concluded that the lipid-lowering effect in hamsters might be associated with the *trans*-10, *cis*-12 isomer or a synergistic effect from a combination of CLA isomers.

The mechanism by which CLA lowers serum cholesterol is still poorly understood. However, it was suggested that CLA could reduce LDL particles by inhibiting the secretion of apolipoprotein B (34) or by enhancing the clearance rate of circulating LDL by way of increasing LDL receptor activity (35). More recently, Yeung et al (32) found that dietary CLA increased the fecal excretion of total neutral sterols. On the basis of their results they stipulated that the cholesterol-reducing effect of CLA is mediated in part by its inhibitory effect on cholesterol absorption by way of the down-regulation of intestinal sterol *O*-acyltransferase activity.

In humans, again the putative benefit of CLA is less clear than in animal models. Although CLA in human subjects with type 2 diabetes or healthy patients shows some indication of lowering serum triacylglycerol, it failed to improve HDL concentrations (30) and in some cases even further lowered them (31). Therefore, as with insulin resistance in human patients with metabolic syndrome, the therapeutic potential of CLA requires further study.

EFFECT OF CONJUGATED LINOLEIC ACID ON OBESITY

Abdominal obesity is associated with type 2 diabetes, CVD, and, by definition, metabolic syndrome. Indeed, obesity was identified as one of the main factors responsible for the growing diabetes epidemic in industrialized countries where consumption of caloric-rich diets and sedentary lifestyles prevail. It is well recognized that in itself the growing epidemic of obesity needs urgently to be addressed (1).

CLA reduces body fat and sagittal abdominal diameter in humans. Smedman and Vessby (36) found that supplementing CLA (4.2 g/d) in capsule form (containing 75.9% CLA with an equal mixture of *cis*-9, *trans*-11 and *trans*-10, *cis*-12 isomers) to healthy individuals for 12 wk significantly reduced body fat compared with the control group. In that study participants were requested not to change their habits regarding diet and physical activity. Another group of researchers, Riserus et al (37), reported that CLA supplementation (4.2 g mixed CLA isomers/d) for 4 wk significantly reduced sagittal abdominal diameter in obese middle-aged men with metabolic syndrome. The investigators of that study suggested that one of the possible mechanisms to explain the adiposity-reducing effect of CLA is its inhibitory effect on prostaglandin production. CLA increases lipolysis of adipose tissue by modulating the production of prostaglandins with antilipolytic effects. In a later study, Riserus et al (31) showed that CLA (3.4 g/d for 12 wk) again significantly reduced both sagittal abdominal diameter and body fat

percentage in obese middle-aged men with metabolic syndrome. In a more recent study, Belury et al (38) observed a correlation between CLA concentrations and degree of body weight loss as well as serum leptin (a hormone that plays a key role in body fat regulation) in patients with type 2 diabetes, which was attributable to the *trans*-10, *cis*-12 isomer of CLA.

EFFECT OF CONJUGATED LINOLEIC ACID ON MICROALBUMINURIA AND HYPERTENSION

Microalbuminuria and hypertension are 2 components of metabolic syndrome that are indeed major CVD risk factors. Microalbuminuria is associated with all components of metabolic syndrome, including insulin resistance with the exception of obesity. It is a marker for hypertension, as a result of endothelial permeability, and also signifies endothelial dysfunction (7). Microalbuminuria indicates an advanced stage of CVD and is a strong predictor of cardiovascular morbidity and mortality (7). In fact, as a marker of late CVD, its presence is associated with the greatest risk of CVD mortality compared with all the other components of metabolic syndrome (7).

Hypertension is estimated to contribute from 35% to 75% of diabetic complications (4). Findings from the MRFIT indicated that systolic blood pressure along with serum cholesterol and smoking are significant predictors of CVD mortality in men with or without diabetes (9). The United Kingdom Prospective Diabetes Study showed that tight blood pressure control reduced diabetes-related death by 32% (39). CLA was shown to have an effect on several components of metabolic syndrome. However, to our knowledge, no study has investigated the effect of CLA on hypertension or microalbuminuria. Such a study would be interesting, considering the significant implication with respect to vascular disease.

CONCLUSIONS

Type 2 diabetes-related CVD is rising worldwide, despite pharmacologic treatment that adequately achieves glycemic control. It has since become clear that to effectively address cardiovascular mortality, all components of metabolic syndrome must be addressed therapeutically. Aggressive research to identify such an intervention that would ideally target all these factors is ongoing. CLA might represent such a candidate agent that, as a nutraceutical agent, could be attractive to the general public. The therapeutic potential of CLA against insulin resistance-associated CVD according to its reported effects on individual components of metabolic syndrome, although promising, is yet to be fully determined.

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