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Impact of a 1-year lifestyle modification program on plasma lipoprotein and PCSK9 concentrations in patients with coronary artery disease

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BACKGROUND: Patients with coronary artery disease (CAD) are characterized by an impaired cardiometabolic risk profile including high levels of atherogenic apolipoprotein (apo) B-containing lipoprotein levels. Genetic studies have highlighted a critical role for proprotein convertase subtilisin/kexin type 9 (PCSK9) in lipoprotein metabolism and CAD risk.

OBJECTIVE: To determine whether improving dietary quality and increasing physical activity levels improve parameters of the cardiometabolic risk profile such as plasma apoB and PCSK9 levels in patients with CAD.

METHODS: We recruited 86 men aged between 39 and 80 years (82 of them on statins) undergoing coronary artery bypass graft (CABG) surgery. These patients participated in a 1-year lifestyle modification program aiming at achieving a minimum of 150 minutes/week of physical activity and improving diet quality by following dietary guidelines. We used magnetic resonance imaging to measure visceral adipose tissue and a modified Bruce protocol to measure fitness levels before and after the intervention.

RESULTS: Plasma apoB and low-density lipoprotein cholesterol levels were not modified by the intervention (-3.0%, $P = .08$ and 1.3%, $P = .56$, respectively), whereas non-HDL cholesterol decreased by 4.5% ($P = .04$) and triglycerides by 13% ($P = .002$). In contrast, PCSK9 levels increased by 5.2% after the intervention ($P = .05$). HDL cholesterol and apolipoprotein A-I levels also increased ($+12\%$, $P < .0001$ and $+ 6\%$, $P < .0001$, respectively). PCSK9 levels increased with improvements in fitness ($r = 0.23$, $P = .04$) and visceral fat mobilization ($r = -0.23$, $P = .04$).

CONCLUSION: In post-CABG patients, a lifestyle modification program lead to significant improvements in some parameters of the lipoprotein profile but unexpectedly increased plasma PCSK9 levels.

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Introduction

An elevated proportion of patients with coronary artery disease (CAD) are characterized by an altered cardiometabolic risk profile, which includes ectopic visceral fat accumulation (even within the normal body mass index [BMI] range) and a poor cardiorespiratory fitness.[1,2] Also, despite being treated with potent statins and achieving targeted low-density lipoprotein (LDL) cholesterol levels, these patients often present elevated triglyceride, apolipoprotein (apo) B, non-high-density lipoprotein (HDL) cholesterol levels, and low levels of HDL cholesterol and apoA-I, which contribute to the so-called residual risk in these patients.[3] Several studies have shown that patients with CAD who become physically active and/or who improve their diet could ameliorate their lipoprotein-lipid profile and hence, reduce their risk of cardiovascular disease (CVD).[4–8] Mounting evidence suggests that lifestyle modification therapy should be integrated in the therapeutic armamentarium to reduce residual CVD risk.[9,10]

Large-scale genetic association studies and family-based investigations have identified a pivotal role for proprotein convertase subtilisin/kexin type 9 (PCSK9) in the regulation of blood cholesterol levels.[11–14] PCSK9 is secreted by the liver, binds to and target the LDL receptor for lysosomal degradation, thereby decreasing LDL receptor density on hepatocytes.[15,16] The biological factors that regulate PCSK9 expression and secretion are not well understood. We and others have shown that plasma PCSK9 levels can be influenced by insulin levels in humans.[17] Although the association between insulin and PCSK9 has been confirmed *in vitro* and in animal models,[18,19] whether this association is causal in humans is unknown.[20,21] Several studies have also shown that statin therapy increases PCSK9 levels, as recently explored in the meta-analysis of Sahebkar et al.[22] The influence of lifestyle modification program on plasma PCSK9 is currently unknown. In a study that included 67 healthy hospital employees, who participated in a 6-month intervention promoting active use of stairs instead of elevators, plasma PCSK9 levels were found to drop 20% at 3 months, but there were no differences in PCSK9 levels between the baseline and 6-month time points.[23] In a population of abdominally obese sedentary men with dyslipidemia but without CAD, we have recently shown that a 1-year lifestyle modification program that included both improvements in physical activity levels and dietary quality failed to change plasma PCSK9 levels.[17] However, the impact of such an intervention in patients with CAD treated with statins is currently unknown.

The objective of our study was to determine the impact of a 1-year lifestyle modification program on plasma lipoprotein and PCSK9 levels in post-CABG patients. We also explored the association between plasma PCSK9 levels and markers of lipoprotein-lipid metabolism before and during the lifestyle intervention program.

Material and methods

Study participants

A total of 86 men, aged between 39 and 79 years, were recruited at the Institut universitaire de cardiologie et de pneumologie de Québec (IUCPQ), after CABG surgery. All selected patients had severe CAD that required a CABG procedure according to current ACC/AHA practice guidelines.[17] Exclusion criteria for the 1-year lifestyle modification program included greater than moderate systolic dysfunction (left ventricular ejection fraction $<40\%$), impaired renal function (creatinine >150 mmol/L), inflammatory, or a known autoimmune disease and/or lung disease. Patients with significant valvular disease that may eventually require surgery were excluded as were active smokers and patients under weight loss medication. Each participant provided signed informed consent approved by the IUCPQ institutional review board.

Intervention

This study is an uncontrolled analysis of 86 men who completed a 1-year lifestyle modification program consisting in a personalized healthy eating strategy combined with physical activity counseling. The intervention began at least 6 weeks after the CABG procedure (86 days on average). Cardiometabolic risk parameters were assessed at baseline and after the 1-year lifestyle modification program. Physical activity counseling was performed by kinesiologists, and nutritional follow-up was done by registered dietitians, most of the time at the same visits. Frequency of the one-to-one visits was once a week for the first month, twice a month for the next 3 months, and finally once every 3 to 4 weeks for the rest of the intervention. The physical activity program aimed at achieving a minimum of 150 minutes of aerobic physical activity weekly at moderate-to-vigorous intensity (50%–80% of their maximum heart rate measured during maximal treadmill test) and was based on patients' preferences. The personalized nutritional recommendation aimed at improving dietary quality in all participants and included a moderate caloric restriction for overweight patient (-500 kcal daily). All patients were asked to increase daily consumption of fruits, vegetables, fibers, fish, whole grains as well as more proteins from vegetables, poultry, or fish. Patients were also advised to reduce saturated fatty acids intake and to decrease the consumption of food and beverages with added sugars and sodium.

Body composition

At baseline and follow-up, each patient underwent anthropometric measurements with standardized procedures (weight, height, and waist circumference). In brief, waist circumference was obtained in standard standing anatomic position, and measurement was made at the end of normal expiration at the midpoint between the last rib and the iliac crest. BMI was calculated (weight in kg/height in m^2).