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Cholesterol metabolism in cardiac sarcoidosis☆

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ABSTRACT

Background and aims: Patients with cardiac sarcoidosis (CS) suffer from myocardial inflammation, but atherosclerosis is not infrequent in these patients. However, the classical atherosclerotic risk factors, such as perturbed serum lipids and whole-body cholesterol metabolism, remain unravelled in CS.
Methods: We assessed serum non-cholesterol sterols, biomarkers of whole-body cholesterol synthesis and cholesterol absorption efficiency, with gas-liquid chromatography in 39 patients with histologically verified CS and in an age-adjusted random population sample (n = 124).
Results: CS was inactive or responding to treatment in all patients. Concentrations of serum, LDL, and HDL cholesterol and serum triglycerides were similar in CS patients and in control subjects. Cholesterol absorption markers were higher in CS patients than in controls (eg serum campesterol to cholesterol ratio in CS 246 ± 18 vs in controls 190 ± 8 10^2 x μmol/mmol of cholesterol, p = 0.001). Cholesterol synthesis markers were lower in CS patients than in controls (eg serum lathosterol to cholesterol ratio in CS 102 ± 8 vs in controls 195 ± 5 10^2 x μmol/mmol of cholesterol, p = 0.000). In CS patients, cholesterol absorption markers significantly correlated with plasma prohormone brain natriuretic peptide (proBNP), a marker of hemodynamic load.
Conclusion: High cholesterol absorption efficiency, which is suggested to be atherogenic, characterized the metabolic profile of cholesterol in CS patients. The association between cholesterol absorption efficiency and plasma proBNP concentration, which suggests a link between inflammation, cholesterol homeostasis, and hemodynamic load, warrants further studies in order to confirm this finding and to reveal the underlying mechanisms.

1. Introduction

Sarcoidosis is a multisystem inflammatory disease characterized by the formation of non-caseating granulomas in several tissues. Cardiac sarcoidosis (CS) may accompany the systemic sarcoidosis or, alternatively, may exist as an isolated form of disease. The baseline pathogenesis of the inflammation is unknown, but it is speculated that the chronic antigenic stimulation of unknown origin enhances the expression of T helper cell cytokines and chemokines [1]. Serum and lipoprotein lipid concentrations and their metabolism is in general affected by the activation of the acute phase response caused by inflammation. Changes in lipoproteins towards atherogenicity and an increased risk of atherosclerosis are well documented consequences of inflammation eg in rheumatoid arthritis [2]. In addition to myocardial inflammatory involvement, simultaneous coronary artery disease (CAD) can also occur in sarcoidosis [3–5]. The lesions in the coronary arteries can result from the sarcoidosis-caused vasculitis, but the possible role of atherosclerosis cannot be ruled out [5]. Very little is known about serum and lipoprotein lipids or their atherogenicity in sarcoidosis. In the few studies which have been carried out in patients with active systemic sarcoidosis, LDL cholesterol concentration was not elevated compared with control subjects [6–8]. HDL cholesterol concentration was reduced in patients with active sarcoidosis, but it was normalized during the corticosteroid therapy [9]. However, nothing is known about the whole-body cholesterol metabolism, whose profile may contribute to the development of atherosclerosis and CAD [10]. Accordingly, we were interested to see, whether serum and lipoprotein lipids and cholesterol metabolism are

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disturbed in patients with CS to find out, if the risk of atherosclerosis is increased in these patients. We assessed the hypothesis that cholesterol absorption and synthesis are abnormal in CS. Thus, we evaluated cholesterol metabolism by determining serum non-cholesterol sterols, valid biomarkers of cholesterol synthesis and cholesterol absorption efficiency [11–20] in patients with CS and in an age-adjusted random population sample from the Finnish Population Register Centre.

2. Materials and methods

2.1. Study population

The study population consisted of 39 patients with histologically verified CS and of 124 controls of similar age randomly selected from the Finnish Population Register Centre and living in Helsinki. All CS diagnoses were made in our hospital after year 2008 using the criteria described in our previous works [21,22]. In brief, a histology of non-caseating granulomatous inflammation in endomyocardial biopsy or in extracardiac tissue sample associated with clinical manifestations and findings at cardiac imaging compatible with CS was mandatory for the diagnosis. The clinical data of these patients including demographics, medical history and symptoms, laboratory tests, electrocardiogram, imaging results, and histopathological analyses of biopsy material were retrospectively reviewed and analysed in detail for the present study. These patients were followed up regularly as ambulatory outpatients in our hospital. The use of lipid lowering medication was an exclusion criteria for both CS patients and control subjects. Any immunosuppressive medication had to remain unchanged for one month before the study.

All subjects gave their written informed consent. The study was performed according to the principles of the Declaration of Helsinki. The Ethics Committee for the Department of Medicine, Hospital District of Helsinki and Uusimaa approved the study protocol.

2.2. Study design

All subjects were studied on their normal habitual diet. Fasting blood samples were drawn after a 12- hour fast. The subjects were weighed and their height was measured, and a history of previous diseases and current drug treatment was recorded. The CS patients were also medically evaluated as part of their regular ambulatory clinical follow-up.

2.3. Laboratory methods and measurements

Laboratory measurements of the CS patients included assessments of blood count, serum creatinine, serum alanine aminotransferase, thyroid stimulating hormone, serum thyroxine, plasma high-sensitive C-reactive protein (hsCRP), plasma troponin T, plasma prohormone brain natriuretic peptide (proBNP), and plasma glucose, and they were analysed with routine standardized methods at the Central Laboratory of Helsinki University Central Hospital (HUSLAB). Serum total, LDL, and HDL cholesterol and serum triglycerides were determined both from the CS patients and control subjects, and they were analysed enzymatically by using an automated analyzer system (HUSLAB).

Serum cholesterol, cholesterol precursors (squalene, cholestenol (5α-cholest-8-en-3β-ol), desmosterol, and lathosterol), plant sterols (sitosterol and campesterol), and cholestanol, a metabolite of cholesterol, were quantified with capillary gas-liquid chromatography (GLC) with a 50-m Ultra 2 capillary column, as described previously [23]. Serum concentrations of non-cholesterol sterols were expressed in μg/dl and also as the ratio to cholesterol (10^2 x μmol/mmol of cholesterol) by adjusting the non-cholesterol sterol concentrations to the cholesterol value of the same GLC run, and multiplying the ratio by 10^2 in order to get rid of the decimals. Because the assessment of absolute whole-body cholesterol metabolism is difficult and laborious, it is generally accepted that the ratios of serum non-cholesterol sterols to cholesterol are valid biomarkers of cholesterol metabolism [24,25]. Accordingly, the ratios of serum cholesterol precursors to cholesterol reflect cholesterol synthesis [11–16], while the ratios of plant sterols and cholestanol reflect cholesterol absorption efficiency [14,16–20]. We also calculated the lathosterol/campesterol ratio, which reflects the whole-body cholesterol metabolism [14], and campesterol/cholestanol ratio, which is a biomarker of dietary plant sterol intake [26].

2.4. Statistics

Statistical analyses were performed with SPSS for Windows 19.0 statistics program (SPSS, Chicago, IL, USA). The normality and the homogeneity of variance assumptions were checked before further analyses. The comparisons for continuous variables between CS patients and control subjects were performed with Student's t-test. The variables not normally distributed even after logarithmic transformation, non-homogenous in variance, or non-continuous were tested with Mann-Whitney *U* test and Fisher exact test. Spearman correlation coefficients were calculated. A *p*-value of <0.05 was considered statistically significant. The results are given as mean ± SEM.

3. Results

3.1. Demographics and clinical characteristics

The main clinical characteristics of the study population are demonstrated in Table 1. The CS patients comprised 31 women and 8 men, and the mean age of the patients was 53.1 years (range, 37–69 years). The control group consisted of 124 subjects (61 women, 63 men), who were randomly selected from population cohorts. The CS patients did not differ from the controls regarding age or body mass index (BMI), but the female preponderance in the CS patients was statistically significant ($p = 0.0009$). However, there was no difference in demographics and clinical characteristics between men and women in the CS group.

The inflammatory and cardiac/hemodynamic markers and plasma glucose were not analysed in the control subjects, because they were clinically in good health, and only one subject had type 2 diabetes with oral hypoglycemic treatment.

CS with clinically isolated cardiac involvement, defined as cardiac involvement with neither previous history or any current signs or symptoms of evident extracardiac sarcoidosis according to clinical examination, chest x-ray and laboratory tests, was observed in 28/39 patients (72%), whereas the remaining 11 patients had already known extracardiac sarcoidosis (mainly pulmonary sarcoidosis; skin or extrathoracic lymph nodes were affected in solitary cases, and liver was affected in one patient). The demographic and clinical characteristics and medication were similar in patients with isolated CS and CS with extracardiac manifestations.

The histology of sarcoidosis had been confirmed by endomyocardial biopsy ($n = 20$) or by biopsy of mediastinal lymph nodes ($n = 11$), lungs ($n = 5$), skin ($n = 2$) or liver ($n = 1$).

The mean duration of CS from diagnosis was 28 months (range 5–52 months) at the time of our study. The mean ejection fraction was 50.7 ± 1.8% in the CS patients (reference value > 50.0%). Blood count, kidney function and liver enzymes were normal in all CS patients. Troponin T was elevated in six patients, whereas hsCRP