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Regular paper

Interleukin-6 genotype is associated with high-density lipoprotein cholesterol responses to exercise training

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Abstract

Background: High-density lipoprotein cholesterol (HDL-C) and its subfractions are modifiable with exercise training and these responses are heritable. The interleukin-6 (IL6)-174G/C polymorphism may be associated with HDL-C levels. We hypothesized that the IL6-174G/C polymorphism would be associated with plasma HDL-C response to exercise training.
Methods and results: Sixty-five 50- to 75-year-olds on a standardized diet were studied before and after 24 weeks of aerobic exercise training. Significant differences existed among genotype groups for change with exercise training in HDL-C, HDL_3-C, integrated $HDL_{4,5NMR}$-C, and HDL_{size}. The CC genotype group increased HDL-C more than the GG (7.0 ± 1.3 v. 1.0 ± 1.1 mg/dL, $p = 0.001$) and GC groups (3.3 ± 0.9 mg/dL, $p = 0.02$); for HDL_3-C, the CC group increased more than the GG (6.1 ± 1.0 v. 0.9 ± 0.9, mg/dL $p < 0.001$) and GC groups (2.5 ± 0.7 mg/dL, $p = 0.006$). Integrated $HDL_{4,5NMR}$-C increased more in the CC than GG group (6.5 ± 1.6 mg/dL v. 1.0 ± 1.3 mg/dL, $p = 0.01$), as did HDL_{size} compared to the GG (CC: 0.3 ± 0.1 v. GG: 0.1 ± 0.1 nm, $p = 0.02$) and GC (0.0 ± 0.0 nm, $p = 0.007$) groups.
Conclusions: IL6 genotype is associated with HDL-C response to exercise training.

Keywords: Lipid; Lipoprotein; Genetic; Exercise; Risk factor

1. Introduction

Cardiovascular (CV) disease is currently the leading cause of morbidity and mortality in the developed world and will soon be the most critical health problem across the globe [1]. For over 30 years, plasma lipoprotein-lipids have been known to be major physiological contributors to the pathophysiology of atherosclerotic vascular disease and have been classified as a major CV disease risk factor [1,2]. However, recent evidence suggests that chronic inflammation, mediated by elevated levels of the inflammatory cytokine interleukin-6 (IL-6), is one underlying mechanism that regulates the atherosclerotic process [2–4]. Elevated IL-6 levels have been associated with many CV disease risk factors including obesity, diabetes, and dyslipidemia [5–7]. Endurance exercise training has been shown to reduce CV disease risk by improving CV disease risk profiles, including producing positive increases in high-density lipoprotein cholesterol (HDL-C) levels [8].

IL-6 and other inflammatory cytokines produce pro-atherogenic changes in lipid metabolism and lipoproteins that include alterations in the enzymes and apolipoproteins associated with HDL-C [9–11]. These enzymatic and structural changes may reduce HDL-C levels and impair HDL anti-inflammatory, anti-oxidant, and reverse cholesterol transport functions, thus inhibiting its normally protective role in CV disease prevention [9–11]. IL-6 inhibits adipose lipoprotein lipase and stimulates increased lipolysis, free fatty acid (FFA) levels, and secretion of

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triglycerides (TG) by the liver, all of which can lead to increased TG, LDL-C, and FFA in the blood and reduced HDL-C [9–11]. IL-6 may also act indirectly on lipoprotein and lipid metabolism through its stimulation of other acute phase reactants known to contribute to low HDL-C and altered HDL [11].

There are several potentially functional promoter polymorphisms in the IL6 gene 5′ flanking region, including the -597G/A, -572 G/C, -373A_nT_n, and -174G/C promoter polymorphisms, that may influence IL6 gene transcription and IL-6 production [12–15]. Previous work indicates there is strong linkage disequilibrium among these polymorphisms and that the -174G/C polymorphism serves as a marker for haplotype combinations at these loci [12,13,15]. For example, the -174G/C polymorphism characterizes 94% of the possible haplotype combinations for the three single nucleotide polymorphisms [13] and occurs 95% of the time in association with the A8T12 allele [15]. Furthermore, associations have been found between the −174G/C polymorphism and various health related phenotypes, including insulin sensitivity and plasma lipoprotein lipid levels [6,16–19].

While endurance exercise training is a proven intervention for improving plasma HDL profiles, the response of plasma lipoprotein lipids to even standardized exercise training is highly variable [8,20–25]. For example, while Williams et al. [23] found average increases in HDL-C of 4.2 mg/dL in 46 men with a 1 year exercise training program, the individual training-induced changes in HDL-C ranged from a 10 mg/dL decrease to a 20 mg/dL increase in HDL-C. Durstine et al. [25] reviewed current studies and established that 15–20 miles of brisk walking or jogging per week was associated with increases in HDL-C ranging from 2 to 8 mg/dL. Additionally, Leon et al. [20] showed that while 20 weeks of endurance exercise training significantly increased HDL-C levels on average by 3.6%, the HDL response to training ranged from a mean 9.3% decrease in the lowest 25% of responders to a mean 18% increase in the top 25% of responders. Strong evidence suggests that this variability in plasma HDL-C response to exercise training may be due to genetic factors [20–22,26,27]. For example, Rice et al. [22] recently found that heritable factors accounted for 25–38% of the variance in lipid response to exercise training, with heritability for HDL_2-C change with exercise training in whites as high as 60%. Leon et al. [20] also found that genetic contributors accounted for 26–29% of the variance in HDL-C changes with training. These studies support the role of exercise training in improving plasma lipoprotein lipid profiles and demonstrate that the variability in lipid levels and response to training is partially accounted for by a genetic component.

With endurance exercise training and the Il-6-174G/C gene polymorphism independently influencing lipid metabolism, investigation of the potential interaction of endurance exercise training and the IL6-174G/C gene polymorphism on plasma lipoprotein-lipid levels is warranted [4,6,7,9,11,18,25,28]. We hypothesized that the IL6-174G/C gene polymorphism would be associated with variation in plasma HDL-C, its subfractions, and their response to exercise training.

2. Materials and methods

The study population consisted of sixty-five healthy sedentary Caucasian women and men participating in the Gene Exercise Research Study at the University of Maryland, College Park. The Institutional Review Board at the University of Maryland College Park and Baltimore approved all study procedures. Written informed consent was obtained on all subjects. Eligibility for the study required subjects to be healthy, sedentary (regular aerobic exercise ≤2 times/wk and <20 min/session, sedentary occupation), 50–75 years old, not on lipid- or glucose-lowering medications, normotensive or hypertension controlled (BP<160/99 mm Hg) with medications not affecting lipid metabolism (no thiazides, α-or β-blockers, etc), non-diabetic, non-smoking, no history of CV disease, body mass index (BMI) <37 kg/m^2, no other medical conditions that would preclude vigorous exercise, and to have at least one National Cholesterol Education Program lipid abnormality. All female participants were required to be >2 years past menopause and agree to maintain their hormone replacement therapy (HRT) status (on or not on HRT) constant for the duration of the study. Subjects underwent 1) health and inclusion criteria screening, 2) 6 weeks of dietary stabilization classes to ensure compliance with the American Heart Association Step I Diet, 3) baseline testing, 4) 6 months of standardized exercise training, and 5) final testing.

3. Screening

3.1. Screening visit 1

Medical histories were reviewed and BMI confirmed to be <37 kg/m^2. A fasted blood sample was drawn for genotyping and plasma lipoprotein-lipid profile analysis. Subjects had to have ≥one National Cholesterol Education Program lipid abnormality (cholesterol>200 mg/dL, LDL-C>130, HDL-C<40 mg/dL, TG>200 but<400 mg/dL); total cholesterol and low-density lipoprotein cholesterol (LDL-C) must have been <90th and HDL-C>20th percentile for their age and gender to exclude subjects with the possibility of a familial dyslipidemia.

3.2. Screening visit 2

Each subject had fasting blood samples drawn and underwent a 2-h 75-g oral glucose tolerance test to assess study eligibility (fasting glucose levels<126 mg/dL and 2-h glucose levels <200 mg/dL).