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Atherosclerosis 194 (2007) 169–174

ATHEROSCLEROSIS

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Codon 54 polymorphism of the fatty acid binding protein (FABP) 2 gene is associated with increased cardiovascular risk in the dyslipidemic diabetic participants of the veterans affairs HDL intervention trial (VA-HIT)

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Received 14 February 2006; received in revised form 14 July 2006; accepted 20 July 2006
Available online 30 August 2006

Abstract

The threonine (Thr) for alanine (Ala) codon 54 polymorphism of the fatty acid binding protein (FABP) 2 gene, when compared to the wild type, is associated with dyslipidemia. Since dyslipidemia is common in diabetes and is associated with increased cardiovascular risk, we tested the hypothesis that Thr-54 is associated with increased cardiovascular risk in patients with diabetes. The secondary prevention veterans affairs HDL intervention trial (VA-HIT) was carried out in patients with dyslipidemia. The DNA of trial participants ($n = 776$) was screened for the Thr-54 polymorphism and cardiovascular endpoints were monitored. The polymorphism was detected in 370 (47.7%). For first occurrence of the primary endpoint [myocardial infarction (MI) or coronary heart disease (CHD) death] the hazard ratio (HR) and confidence intervals (Cox proportional hazards model) was 2.5 (1.2, 5.3) $p = .02$ in diabetic carriers of Thr-54 versus carriers without diabetes or fasting glucose >7 mmol/L. For the expanded endpoint (stroke, MI or CHD death), the corresponding HR was 3.0 (1.4, 5.4) $p = .0003$ and for the stroke alone the corresponding HR was 3.5 (1.4–8.9) $p = .01$. The higher cumulative incidence of the expanded endpoint in diabetic participants carrying the FABP2 polymorphism versus non-diabetic carriers was consistently present throughout the 5 years of the study ($p = .0002$). We conclude that based on the VA-HIT data, the Thr-54 polymorphism of the FABP2 gene is associated with a 2–3.5-fold increase in cardiovascular risk in dyslipidemic men with diabetes compared to their non-diabetic counterparts.
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Keywords: Polymorphisms; FABP2; Diabetes; Cardiovascular risk

1. Introduction

Fatty acid binding protein (FABP) 2 is a 15 kDa protein that binds long chain fatty acids [1]. It is present only in the intestine [1]. The Thr-54 polymorphism of FABP2 replaces an alanine for a threonine [2] and is present in around 30–40% of Caucasian, Japanese and Native American individuals [2–4]. This polymorphism is functional and results in greater affinity of the protein for fatty acids and increased secretion of triglycerides in *in vitro* studies using Caco-2 cells, a human intestinal cell line [5] and human intestinal explants [6]. Therefore, the polymorphism could serve as a model for the effects of increased intestinal input of triglyceride-rich lipoproteins into the body.

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0021-9150/$ – see front matter © 2006 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.atherosclerosis.2006.07.022

We have recently reported that patients with type 2 diabetes and the Thr-54 FABP2 polymorphism have dyslipidemia and increased levels of fasting and postprandial triglyceride-rich lipoproteins, compared to diabetic non-carriers of the polymorphism [7]. Fasting dyslipidemia is the most common lipoprotein phenotype present in diabetes. In addition to the fasting dyslipidemia, as we and others have reported, diabetes is associated with abnormalities in the metabolism of postprandial triglyceride-rich lipoproteins [8] that could contribute to the 2–4-fold higher risk of atherosclerotic cardiovascular disease in diabetes [9,10]. The present study is addressing the question whether diabetic carriers of the Thr-54 polymorphism of FABP2 are at increased risk for cardiovascular events when compared to non-diabetic carriers. This was investigated by screening for the Thr-54 polymorphism participants of the Veteran Affairs HDL Intervention Trial (VA-HIT), a randomized placebo-controlled secondary prevention trial of gemfibrozil in dyslipidemic patients with low HDL who had a relatively high prevalence of diabetes (25%) [11].

2. Methods

2.1. Study population and experimental design

The design and major results of the VA-HIT have been published [11–13]. Men less than 74 years were enrolled if they had CHD, an HDL of $\leq$1.04 mmol/L an LDL $\leq$3.63 mmol/L and a triglyceride of $\leq$3.39 mmol/L. A total of 2531 signed the consent form approved by the Human Rights and Evaluation Committees of the Coordinating Center of the Cooperative Studies Program and by each of the 20 participating centers institutional review board. Participants were randomized to gemfibrozil or placebo and followed for an average of 5.1 years. Demographic and clinical parameters were collected at baseline [11]. An average of 2 fasting lipoprotein profiles drawn 1–2 weeks apart was used for baseline. A single fasting plasma glucose was measured at the local clinical laboratories of the participating veterans affairs medical centers. All cardiovascular endpoints were adjudicated by blinded endpoint committees, according to standardized predefined algorithms [11,12]. The primary endpoint was CHD death or nonfatal myocardial infarction (MI) and the expanded endpoint included CHD death, non-fatal MI and stroke. Gemfibrozil was associated with a 22% reduction in the primary endpoint and a 24% reduction in the expanded endpoint [13].

A consent form for genetic screening was generated later in the study and some of the patients ($N = 776$) consented to DNA harvesting. All 776 consented participants were included in the present study. Our study participants differed ($p < .0001$) from those who were not screened in the following parameters: fewer were non-whites (7% versus 10%) and more were better compliers (85% versus 75%); the baseline total and low density lipoprotein cholesterol in those consented were slightly higher than in those who refused, i.e. total cholesterol 4.60 mmol/L versus 4.47 mmol/L and low density lipoprotein cholesterol 2.94 mmol/L versus 2.84 mmol/L.

There were no differences between the two groups in the following parameters: age, waist girth, smoking, alcohol intake, congestive heart failure, diabetes, history of hypertension, systolic and diastolic blood pressure, glucose, insulin, high density lipoprotein cholesterol and triglyceride.

DNA was used for screening for the Thr-54 polymorphism of FABP2, which was detected by PCR and restriction enzyme digestion according to the method of Galluzzi and Ordovas [14]. The diagnosis of diabetes was made by history of the disease.

2.2. Statistical analysis

The data were analyzed by intention to treat. The relationship of the Thr-54 polymorphism and diabetes with baseline lipids was assessed by a 2×2 ANOVA. Cox proportional hazards models [15] were used to obtain hazard ratios (HRs) for diabetes (relative to normal fasting glucose) in the presence and absence of the Thr-54 FABP2 polymorphism. All analyses were adjusted for risk factors: BMI, age, smoking, hypertension and baseline HDL cholesterol. The proportional hazard assumptions were tested and found valid.

3. Results

The Thr-54 polymorphism was present in 370 participants or 47.7% of the 776 individuals screened. Both heterozygous and homozygous carriers were grouped together, since the number of homozygous was small ($n = 43$) and the comparisons included 4 groups and a small number of endpoints. The characteristics of the study participants screened for the Thr-54 polymorphism of FABP2 are shown in Table 1. There were no significant differences in any of the variables listed between those on placebo or gemfibrozil, so the data of both groups were pooled together. Table 2 shows the hazard ratio (HR) and 95% CI for endpoints in participants with and without diabetes in the presence or absence of the polymorphism. Columns 1 and 2 represent the primary endpoint (combined cardiac death or MI); columns 3 and 4 the expanded endpoint (cardiac death, MI or stroke) and columns 5 and 6 the stroke alone endpoint. Participants with the polymorphism are in columns 1, 3 and 5 and those without in columns 2, 4 and 6. Two comparisons are included: participants with versus those without a history of diabetes (A versus B); and participants with a history of diabetes versus those without either a history of diabetes or an elevated fasting glucose (A versus C). This comparison was done, since some of the patients who had no history of diabetes were found to have an elevated fasting glucose of $\geq$7 mmol/L at baseline. The incidence of death was not different between the study groups; therefore, myocardial infarction and stroke accounted for the results. No subgroup

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