Effect of APOE polymorphism on obesity and lipid profile in women of differing reproductive status

Lenka Luptákova*, Daniela Siváková, Marta Cvíčelová

Department of Anthropology, Faculty of Natural Sciences, Comenius University, 842 15 Bratislava, Slovakia

Abstract: The aim of this study was to investigate whether the effect of apolipoprotein E polymorphism (APOE) on somatic and lipid risk parameters varies in women of differing reproductive status. We analyzed 447 Slovak women aged between 39 and 90 years. APOE genotypes were determined by PCR-RFLP. Regression analysis confirmed the effect of the APOE genotype on the levels of LDL-cholesterol, apolipoprotein B (apoB), non-HDL-cholesterol and on the three atherogenic indices: apoB-to-apoA1, TC-to-HDL-cholesterol, LDL-C-to-HDL-cholesterol. Here, lower mean levels were registered in the E2 carriers than in the E3 and E4 subgroups. However, the impact of menopausal status on lipid parameters was not confirmed. Bonferroni correction showed that systolic blood pressure was significantly lower in the E4 carriers compared to the E3 group (P=0.017). Univariate analysis of covariance revealed a significant interaction between the menopausal group and the APOE group, and their common effect on waist-to-hip-ratio (WHR). Bonferroni correction in early postmenopausal women showed that the mean WHR values were significantly different between E2 and E4 groups (P=0.008). This study demonstrates that the E*2 allele has a protective effect against higher blood lipid levels. Moreover, the results suggest that E*2 could have a partial negative effect on WHR in early postmenopausal Slovak women.

Keywords: Apolipoprotein E gene • Menopause • Anthropometric parameters • Lipid levels

© Versita Sp. z o.o.

1. Introduction

Menopause is the permanent cessation of menstruation resulting from the loss of ovarian follicular activity [1]. It is estimated that perhaps 50 million women worldwide will reach menopause annually [2]. Menopause has been shown to contribute to development of central obesity, insulin resistance and impaired glucose and lipid metabolism which all increase the risk of cardiovascular disease in women [3]. Postmenopausal health consequences are believed to be related to low oestrogen levels, which characterize the hormonal milieu of postmenopausal women. However, the fact that postmenopausal complications are not universal in the female population illustrates the multifactorial nature of these disorders, where environmental and genetic factors contribute to the phenotypic expression of a given complication [2].
Apolipoprotein E gene (APOE) codes a glycoprotein that plays a central role in lipid metabolism. ApoE binds with high affinity to the low density lipoprotein (LDL) receptor and facilitates endocytosis of the associated lipoprotein particle [4]. The human APOE gene is located on chromosome 19q13.2 and consists of 3.7 kb DNA including 4 exons and 3 introns encoding for a polypeptide of 299 amino acids [5]. A single nucleotide polymorphism (SNP) in the APOE gene (rs429358, rs7412) is characterized by a single base substitution of the two nucleotides, T→C and C→T, which cause amino acid substitution of cysteine (Cys) and arginine (Arg). The E3 is the most common of the three protein isoforms, and is distinguished by Cys at position 112 and Arg at position 158 in the receptor-binding region of the apoE. The E2 isoform has Cys in both positions, while the E4 isoform has Arg in both positions [6].

The APOE*4 allele is associated with increased levels of LDL cholesterol (LDL-C) and apolipoprotein B (apoB), and decreased levels of apolipoprotein A1 (apoA1) and high density lipoprotein cholesterol (HDL-C) [7]. This increases susceptibility to heart disease and atherosclerosis [8]. Almeida et al. [9] have suggested that the influence of hormonal replacement therapy (HRT) on total cholesterol (TC) and LDL-C is modulated by APOE genotypes, as total-C and LDL-C concentrations in postmenopausal APOE*4 carriers who used HRT were similar to those in the postmenopausal homozygote APOE*3 and APOE*2 carriers who did not use HRT. Although Oh et al. [10] and Lee et al. [11] report positive associations between APOE genotypes and obesity phenotypes, no such associations were observed by Nicklas et al. [12] and Guerra et al. [13]. Kee et al. [14] showed that subjects carrying at least one APOE*4 allele had a significantly reduced response to weight loss through decreasing total cholesterol and apolipoprotein serum levels. Lee et al. [11] observed that APOE*3/4 genotype led to a higher prevalence of metabolic syndrome and obesity than the other APOE genotypes in postmenopausal Korean women. The APOE*4 allele has been found to be a major genetic risk factor for Alzheimer’s disease [15] and it has also been associated with osteoporosis in postmenopausal females [16]. Niculescu et al. [17] propose that the combination of APOE*2 and CETP B2 (cholesteryl ester transfer protein) alleles may play a protective role in successful ageing and longevity.

There have been no previous reports on the APOE polymorphism related to obesity and metabolic parameters in Slovak women with respect to their menopausal status. Therefore, we investigated how various isoforms of the APOE polymorphism influence these variables in women with respect to their menopausal status.

2. Experimental Procedures

2.1 Study sample

This study was based on data collected during cross-sectional surveys in Slovakia between 2004 and 2011, in order to analyze the effect of genetic variants of some candidate genes on biomarkers of health in Slovak women. The complete sample was composed of 447 women ranging in age between 39 and 90 years, with a mean age of 56.37±12.72. The participants provided all the required anthropometrical, genetic and biochemical data. From this sample, 427 participants were also typed for HDL-C, LDL-C, apoA1 and apoB.

Participants were recruited from different localities in the western, southern and middle parts of Slovakia via an invitation letter regarding the study which was circulated and distributed prior to data collection with the help of local medical doctors. Volunteers were then interviewed during their routine health check and, after giving written Informed Consent for this study, they were investigated in regard to their medical, anthropometrical and lifestyle aspects at local Health Centres. However, only selected variables were considered for the purpose of this paper. Women who had undergone acute disorders such as cancer, myocardial infarction, or stroke were not included in the survey. All included women, and particularly those above 60 years, were assessed as free from serious physical handicaps or Alzheimer’s and Parkinson’s diseases at the time of their recruitment. This entire sample was divided into three subgroups; premenopausal and perimenopausal women (n=175, 39–56 years, 45.57±3.93); early postmenopausal women, 1-10 years after the final menstrual period (FMP) (n=129, 41–70 years, 53.40±4.73) and late postmenopausal women, 11 and more years after FMP (n=143, 53–90 years, 72.26±7.96). The women in this study were considered to be perimenopausal if they reported that their menstrual cycle length had become more irregular in the preceding 12 months or that they had stopped menstruating for between 3 and 12 months, and women were considered to be postmenopausal if they reported 12 consecutive months of amenorrhoea for which there was no other obvious pathological or physiological cause, in accordance with the definition of WHO [1].

2.2 Anthropometric and blood pressure analysis

Anthropometrical measurements of body height, body weight, waist (WC) and hip (HC) circumferences were carried out according to the technique of Knussmann [18]. Body height was measured at the head level, with 0.5 cm accuracy, with a Sieber and Hegner anthropometer with the participant standing barefoot with feet together.