ORIGINAL ARTICLE

ASSOCIATION OF HYPERTENSION WITH APOE4 AND LIPID PROFILE IN WOMEN WITH DIFFERENT MENOPAUSAL STATUS

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Background: An association between ApoE4 and ApoE2 alleles with high blood pressure in relation to different menstrual phases has been observed. **Objectives:** To examine the association between lipid profile, ApoE polymorphism and hypertension in a group of peri- and postmenopausal women. **Methods:** Study included 63 hypertensive female patients having age range of 45–80 years. Patients were divided into two groups based on their menopausal status. Group A included 43 hypertensive peri-menopausal women and Group B included 21 hypertensive post-menopausal women. Thirty age-matched normal healthy subjects were taken as controls. Patients were taken from medical out-door of Sir Ganga Ram Hospital, and Services Hospital, Lahore. ApoE4 and lipid profile were measured in all subjects. **Results:** In peri-menopausal women E2/2 was 42% and it was 60% in postmenopausal women. E4/4 was 58% and 40% in peri- and postmenopausal women respectively. Level of serum cholesterol and the carrier lipoproteins LDL-c and VLDL-c were increased in peri-menopausal women as compared to postmenopausal women but significant difference ($p<0.05$) was only observed in case of LDL-cholesterol. The levels of serum triglyceride and carrier lipoprotein HDL cholesterol were decreased in peri-menopausal women compared to postmenopausal women but significant difference ($p<0.05$) was only observed in case of triglyceride. **Conclusion:** Both, peri- and postmenopausal conditions are associated with APOE genotypes and altered serum lipid profile and thus an independent risk factor for developing cardiovascular diseases especially in postmenopausal women.

Keywords: Lipid profile, ApoE4, ApoE2, Menstrual status

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INTRODUCTION

Hypertension is a major global health burden due to its high prevalence (61.3%) and is associated with increased risk of cardiovascular disease. Hypertension was defined as a systolic blood pressure >140 mmHg and/or a diastolic blood pressure >90 mmHg, or the use of anti-hypertensive medication.[1] Hypertension is determined by both genetic and environmental factors and their complex interactions.[2]

The allelic variation of Apolipoprotein E (ApoE) influences serum lipid levels including serum cholesterol triglyceride but its association with arterial hypertension is controversial.[3,4] Few studies observed an effect of ApoE genotype on hypertension in older individuals.[5] An association between the ApoE4 and E2 alleles with high blood pressure, and especially, with high systolic blood pressure has been observed.[6] However, lack of association with high blood pressure has also been reported.[7] The plasma concentrations of lipoproteins are also modulated by ApoE, present on the surface of these lipid-rich particles. It binds with high affinity to receptors in the liver and extrahepatic cells, mediating the uptake of lipoproteins.[8]

ApoE polymorphism affects plasma cholesterol level. ApoE2 allele is associated with lower levels of cholesterol, whereas the ApoE4 allele has opposite effects. In a cross-sectional study, the association between the ApoE genotype and cholesterol concentration has been found to be weaker in pre-menopausal compared with postmenopausal women[9], suggesting that oestrogen affects the influence of the ApoE genotype on cholesterol level. In postmenopausal women, apolipoprotein E (ApoE) 4 allele had significantly higher levels of serum testosterone and dehydroepiandrosterone. These hormones are thought to be associated with increased risk factors for coronary heart disease in women.[10]

Lipid profile abnormalities in the menopausal women are common health hazard all over the world. There is derangement of lipoproteins profile independent of age.[11] However a study observed that menopausal women have higher plasma lipid levels and their carriers when compared with pre-menopausal women.[12] It has been shown consistently that menopause causes an increase in serum cholesterol, but the effects of peri- and post-menopause on blood pressure remain unclear.[13]

Hormonal changes associated with menopause, play an important role in most cardiac disorders. Hypercholesterolemia in menopause is a key factor in the pathophysiology of atherosclerosis.[14,15] After menopause, there is loss of ovarian function. This results in adverse changes in glucose and insulin metabolism, body fat distribution, coagulation, fibrinolysis, vascular endothelial dysfunction and also derangement of lipoprotein profile. All these changes may be due to the lower level of serum oestrogen.[11]

MATERIAL AND METHODS

This study included 63 hypertensive female patients with age range of 45–80 years. Patients were divided into two groups based on their menopausal status. Group A included 43 hypertensive peri-menopausal women and Group B included 21 hypertensive postmenopausal women. Thirty age-matched normal healthy subjects were taken as controls. Patients were taken from medical Outdoor Department of Sir Ganga Ram Hospital, and Services Hospital, Lahore. Informed consent was taken from all the participants of the study.

Women with age <45 and >80 years were not included in the disease. Women who had any other disease besides hypertension were also excluded.

Sitting BP (mmHg) was measured on the left arm after a sufficient sedentary period, standing height (m) and body weight (Kg) were measured and a fasting blood sample was drawn to measure ApoE4 and lipid profile in all subjects.

The last menstrual period was recorded for all female subjects. When amenorrhea was observed for more than 12 months, except for pregnancy, the last menstrual period was defined as the time of menopause. Total serum cholesterol, high density lipoproteins (HDL), low density lipoproteins (LDL) and triglycerides were quantified by enzymatic techniques. ApoE genotyping was performed using a combination of the polymerase chain reaction (PCR) and solid-phase mini sequencing technique.

RESULTS

The genotypes and their percentage for ApoE gene in hypertensive peri- and postmenopausal women are presented in Table-1. It was observed that the percentage of E2/2 was 42% and E4/4 was 60% in peri- and postmenopausal women respectively. On the other hand E4/4 was 58% and 40% in peri- and postmenopausal women respectively.

Biochemical characteristics of peri- and postmenopausal women are tabulated as Table-2. It was observed that the level of serum cholesterol and the carrier lipoproteins LDL-C and VLDL-C were increased in peri-menopausal women as compared to postmenopausal women but significant difference (p<0.05) was only observed in case of LDL-C. The level of serum triglyceride and carrier lipoprotein HDL-C were decreased in peri-menopausal women compared to postmenopausal women but significant difference (p<0.05) was only observed in case of triglyceride.

Table-1: Genotypic distribution of ApoE gene in hypertensive peri- and postmenopausal women

Genotypes	Peri-menopausal women (n=41)	Postmenopausal women (n=22)
E2/2	42%	60%
E4/4	58%	40%

Table-2: Biochemical characteristics of peri- and postmenopausal women

Variables	Peri-menopausal women (mg/dl) (n=41)	Postmenopausal women (mg/dl) (n=22)
Total cholesterol	281.06±83.52	272.55±100.31
Triglycerides	209.68±101.89	232.44±147.16*
HDL-C	36.46±9.93	40.99±24.85
LDL-C	205.09±97.94	185.07±88.79*
VLDL-C	47.98±36.32	46.49±29.43

*p<0.05

DISCUSSION

Present study observed that the percentage of E2/2, levels of serum triglyceride and HDL-cholesterol were increased in postmenopausal women compared to the parameters of peri-menopausal women. Our study is in line to other studies which observed the same results. It is stated that the association of the ApoE alleles with plasma lipid levels is a direct consequence of the role of ApoE protein in lipid metabolism. ApoE2 is metabolically impaired when compared to ApoE3 and ApoE4, due to its reduced interaction with cellular receptors, resulting in delayed clearance and accumulation of chylomicrons and VLDL remnants in the plasma. The net effect is an up-regulation of LDL receptors, higher plasma concentrations of triglyceride- and cholesterol-containing remnant particles, and lower plasma levels of cholesterol-rich LDL particles.[16] However, a study reported that postmenopausal women have higher serum cholesterol levels than premenopausal women. Study suggested that the level of cholesterol is associated in menopause with oestrogen deprivation.[17]

Our study observed that the level of ApoE4/4 was decreased in postmenopausal women compared to the level of E4/4 in peri-menopausal women. Among lipids and lipoproteins the level of total serum cholesterol, level of LDL and VLDL cholesterol was decreased in postmenopausal women as compared to the level of these parameters in peri-menopausal women. Number of studies observed the effect of ApoE4 allele on lipid profile. According to a study, women with the ApoE4 allele benefit the most, while the lipid profile could worsen in women without the ApoE4 allele.[18]

Another study reported that the combination of hypertension and E4 was associated with a significant deterioration in cognitive function during the 3-year follow-up. Findings of a study suggested that an interaction between ApoE and HDL is facilitated by ApoE4, and is possibly linked with a protective effect on cognitive decline in later life. The findings also indicate a synergistic effect of an ApoE4 allele and hypertension on the acceleration of cognitive decline.[19]

An association was observed between greater LDL cholesterol levels and the presence of the ApoE4 allele, as well as between lower LDL cholesterol levels

and the presence of the ApoE2 allele. However study observed that hypertension, was not associated with the ApoE genotype. Additionally it is reported that ApoE genotype affects serum cholesterol and LDL-levels in the very elderly. However, there was no association between ApoE genotype and some other cardiovascular risk factors such as systolic or diastolic blood pressure, and serum triglycerides.[17]

CONCLUSION

Both peri- and post-menopause are associated with ApoE genotypes and altered serum lipid profile and thus an independent risk factor for developing cardiovascular diseases, especially in postmenopausal women. It is important to consider both peri- and postmenopausal woman to undergo screening for ApoE genotypes and abnormal lipid profile.

REFERENCES

1. Fuzikawa AK, Peixoto SV, Taufer M, Moriguchi EH, Lima-Costa MF. Association of ApoE polymorphisms with prevalent hypertension in 1406 older adults: the Bambui Health Aging Study (BHAS). Braz J Med Biol Res 2008;41(2):89–94.
2. Zhao Q, Kelly TN, Li C, He J. Progress and future aspects in genetics of human hypertension. Curr Hypertens Rep 2013;15(6):676–86.
3. von Muhlen D, Barrett-Connor E, Kritz-Silverstein D. Apolipoprotein E genotype and response of lipid levels to postmenopausal estrogen use. Atherosclerosis 2002;161(1):209–14.
4. Volcik KA, Barkley RA, Hutchinson RG, Mosley TH, Heiss G, Sharrett AR, *et al*. Apolipoprotein E polymorphisms predict low density lipoprotein cholesterol levels and carotid artery wall thickness but not incident coronary heart disease in 12,491 ARIC study participants. Am J Epidemiol 2006;164(4):342–8.
5. Rastas S, Mattila K, Verkkoniemi A, Niinisto L, Juva K, Sulkava R, *et al*. Association of apolipoprotein E genotypes, blood pressure, blood lipids and ECG abnormalities in a general population aged 85+. BMC Geriatr 2004;4:1.
6. Stoumpos S, Hamodrakas SJ, Anthopoulos PG, Bagos PG. The association between apolipoprotein E gene polymorphisms and essential hypertension: a meta-analysis of 45 studies including 13,940 cases and 16,364 controls. J Hum Hyperten 2013;27(4):245–55.
7. Lea Correa Leite M, Lima-Costa MF, Moriguchi EH. Age-related trends of blood pressure levels by apolipoprotein E genotype: the Bambui Cohort Study of Ageing (1997–2008). Hypertens Res 2013;36(3):270–6.
8. Zende PD, Bankar MP, Kamble PS, Momin AA. Apolipoprotein e gene polymorphism and its effect on plasma lipids in arteriosclerosis. J Clin Diagn Res 2013;7(10):2149–52.
9. Schaefer EJ, Lamon-Fava S, Johnson S, Ordovas JM, Schaefer MM, Castelli WP, *et al*. Effects of gender and menopausal status on the association of apolipoprotein E phenotype with plasma lipoprotein levels. Results from the Framingham Offspring Study. Arterioscler Thromb Vasc Biol 1994;14:1105–13.
10. Haffner SM, Newcomb PA, Marcus PM, Klein BE, Klein R. Relation of sex hormones and dehydroepiandrosterone sulfate (DHEA-SO_4) to cardiovascular risk factors in postmenopausal women. Am J Epidemiol 1995;142(9):925–34.
11. Bales AC. In search of lipid balance in older women. New studies raise questions about what works best. Postgrad Med 2000;108(7):57–60,6,9–72.
12. Matthan NR, Jalbert SM, Lamon-Fava S, Dolnikowski GG, Welty FK, Barrett HR, *et al*. TRL, IDL, and LDL apolipoprotein B-100 and HDL apolipoprotein A-I kinetics as a function of age and menopausal status. Arterioscler Thromb Vasc Biol 2005;25(8):1691–6.
13. Bonithon-Kopp C, Scarabin PY, Darne B, Malmejac A, Guize L. Menopause-related changes in lipoproteins and some other cardiovascular risk factors. Int J Epidemiol 1990;19(1):42–8.
14. Igweh JC, Nwagha IU, Okaro JM. The effects of menopause on the serum lipid profile of normal females of South East Nigeria. Niger J Physiol Sci 2005;20(1-2):48–53.
15. Reddy Kilim S, Chandala SR. A comparative study of lipid profile and oestradiol in pre- and post-menopausal women. J clin diagn Res 2013;7(8):1596–8.
16. Mahley RW, Innerarity TL, Rall SC, Jr, Weisgraber KH. Plasma lipoproteins: apolipoprotein structure and function. J Lipid Res 1984;25(12):1277–94.
17. Syvanen AC, Sajantila A, Lukka M. Identification of individuals by analysis of biallelic DNA markers, using PCR and solid-phase minisequencing. Am J Hum Genet 1993;52(1):46–59.
18. Nicklas BJ, Ferrell RE, Bunyard LB, Berman DM, Dennis KE, Goldberg AP. Effects of apolipoprotein E genotype on dietary-induced changes in high-density lipoprotein cholesterol in obese postmenopausal women. Metabolism 2002;51(7):853–8.
19. Yasuno F, Tanimukai S, Sasaki M, Ikejima C, Yamashita F, Kodama C, *et al*. Effect of plasma lipids, hypertension and APOE genotype on cognitive decline. Neurobiol Aging 2012;33(11):2633–40.

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