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CARDIAC BIOMARKERS AND ATHEROGENIC INDICES IN HYPERTENSIVE POSTMENOPAUSAL WOMEN WITH CO-MORBIDITIES

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Abstract: Postmenopausal women are susceptible to various non-communicable diseases. Hypertension and hyperlipidemia contribute significantly to atherosclerotic cardiovascular disease. Hence, the present study was carried out to assess cardiac biomarkers and atherogenic indices in four groups of postmenopausal women namely normotensive postmenopausal women, hypertensive postmenopausal women, hypertensive postmenopausal women with diabetes and hypertensive postmenopausal women with renal insufficiency. Total cholesterol, HDL-cholesterol, triglyceride, VLDL-cholesterol and LDL-cholesterol were assessed in the subjects. Atherogenic index (LDL-C/HDL-C), cardiac risk ratio (TC/HDL-C), atherogenic coefficient ((TC-HDL)/HDL) and atherogenic index of plasma (log (TG/HDL-C)) were calculated in the participants of the study. One way ANOVA and Kruskal-Wallis test were performed. Statistical analysis was performed using SPSS16.0 statistical software. Total cholesterol was significantly increased in hypertensive postmenopausal women compared to the other groups namely hypertensive postmenopausal women with diabetes, hypertensive postmenopausal women with renal insufficiency and normotensive postmenopausal women. HDL-cholesterol was significantly decreased in hypertensive postmenopausal women with renal insufficiency compared to the other three groups. Triglycerides and VLDL-cholesterol were significantly increased in hypertensive postmenopausal women compared to the control group. LDL-cholesterol was significantly increased in experimental groups compared to normotensive control group. Atherogenic index, atherogenic coefficient, cardiac risk ratio and atherogenic index of plasma were significantly increased in experimental groups compared to normotensive postmenopausal women. Reduced levels of HDL-cholesterol and elevated levels of other cardiac biomarkers and atherogenic indices reflected the onset/progression of atherosclerotic cardiovascular disease in hypertensive postmenopausal women with and without co-morbidities.

Keywords: Hypertension, diabetes, menopause, lipid profile, cardiac risk ratio, atherogenic index of plasma



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INTRODUCTION

In a women's life, the years proximal to menopause are escorted by a dramatic rise in the prevalence of hypertension, a predominant risk factor for coronary heart disease ^[1]. The walls of the arterioles are lined with endothelial cells and play a crucial role in maintaining vascular homeostasis, vascular tone, cardiovascular and microvascular health ^[2]. Atherosclerotic plaque formation results in stiffer and narrower arteries. Ultimately, the harder the heart has to pump, more damage occurs in the inner walls of the arteries, leading to heart attack, cardiovascular failure and hypertension ^[3].

Type 2 diabetes mellitus is characterised by reduced uptake of glucose into muscle and adipose tissue, which leads to hyperglycemia, in turn resulting in tissue damage and pathophysiological complications. Heart disease and atherosclerosis are the most common cause of disability and death in diabetic patients ^[4]. Cardiovascular disease is the prime cause of morbidity and mortality in postmenopausal women with chronic renal failure ^[5].

The elderly people constitute the most rapidly growing population group. In this group of population, hypertension is considered as an important risk factor for cardiovascular morbidity and mortality. Treatment for hypertension in the elderly population reduces the incidence of stroke, heart failure and all-cause mortality ^[6]. Menopausal women had significantly elevated total cholesterol levels as compared to premenopausal women. Lipid profile parameters are considered to predict the development of coronary artery disease ^[7]. Atherogenic indices are more appropriate markers of lipid profile than individual lipid concentrations, hence can be employed in cardiovascular risk prediction ^[8]. Yang *et al* suggested atherogenic index as a major risk factor for atherosclerosis ^[9].

Postmenopausal women constitute a vulnerable group that needs special medical attention, since they are susceptible to numerous non-communicable diseases. Cardiovascular complications are considered to be the leading cause of mortality in this segment of population. Hence, the present study was carried out to assess cardiac biomarkers and atherogenic indices in four groups of postmenopausal women namely normotensive postmenopausal women, hypertensive postmenopausal women, hypertensive postmenopausal women with diabetes and hypertensive postmenopausal women with renal insufficiency. To the best of our knowledge, no such comparative studies were carried out in these four groups of postmenopausal women.

MATERIALS AND METHODS

Postmenopausal women who visited KTVR Hospital, Coimbatore, Tamilnadu were selected for the study. Institutional Human Ethics Committee clearance (HEC.2011.25) was obtained for the

study. A written informed consent was obtained from the subjects. Questionnaire was distributed to elicit personal details, medical history and personal habits of the participants. Participants with blood pressure $\geq 140/90$ mm Hg or those taking antihypertensive medications were categorized as hypertensive. Menopause was confirmed by the absence of menstruation for more than two years. Exclusion criteria consisted of those having congenital heart disease, thyroid abnormalities, infectious diseases, jaundice, cancer, undergone hysterectomy and who received/receiving hormone replacement therapy. 240 postmenopausal women were selected and categorized into four groups - normotensive postmenopausal, hypertensive postmenopausal, hypertensive postmenopausal with diabetes and hypertensive postmenopausal with renal insufficiency. Normotensive postmenopausal women constituted the control group.

From each of the subjects 2ml blood was drawn through venipuncture. Blood was collected in serum separator tubes and serum was separated for the analysis of cardiac biomarkers. Blood pressure was recorded using mercury sphygmomanometer in sitting position. Height and weight of the subjects were measured and body mass index (BMI) was calculated from the formula:

$$\text{BMI} = \text{Weight in kg} / (\text{Height in meter})^2$$

Lipid profile was assessed by kit method in the participants of the study. Total cholesterol level was assessed by spectrophotometry by the method of Allain *et al* ^[10]. High density lipoprotein cholesterol (HDL-cholesterol) was assessed by the method of Gordon *et al* ^[11]. Triglyceride was estimated by the method of Jacobs and VanDemark ^[12]. The levels of low density lipoprotein cholesterol (LDL-cholesterol) and very low density lipoprotein cholesterol (VLDL-cholesterol) were calculated by using Friedewald equation ^[13]:

$$\text{VLDL-cholesterol} = \text{Triglycerides}/5$$

$$\text{LDL-cholesterol} = \text{Total cholesterol} - (\text{HDL-cholesterol} + \text{VLDL-cholesterol})$$

Atherogenic index (LDL-C/HDL-C), Cardiac risk ratio (TC/HDL-C), Atherogenic coefficient ((TC-HDL)/HDL) and Atherogenic index of plasma (log (TG/HDL-C)) were calculated in the participants of the study.

One way ANOVA and Kruskal-Wallis test were performed to compare selected biochemical parameters among the four groups of participants. Statistical analysis was performed using SPSS16.0 statistical software.

RESULT AND DISCUSSION

Hypertensive postmenopausal women (group 2) and hypertensive postmenopausal women with diabetes (group 3) belonged to significantly increased age group compared to the control group. Systolic blood pressure (SBP) was significantly increased whereas weight and body mass index were significantly reduced in hypertensive postmenopausal women with renal insufficiency (group 4) compared to the other three groups. Diastolic blood pressure (DBP) was significantly increased in experimental groups compared to normotensive control group. A significant decrease in height was observed in hypertensive postmenopausal women with renal insufficiency (group 4) compared to hypertensive postmenopausal women and hypertensive postmenopausal women with diabetes (group 3) (Table–1).

Table 1 Anthropometric profile of the participants of the study

Parameters	Control	Experimental groups		
	Group 1 (n=60) (a)	Group 2 (n=60) (b)	Group 3 (n=60) (c)	Group 4 (n=60) (d)
Age (yrs)	58±10	65±11 ^a	63±9 ^a	60±10 ^b
Systolic Blood Pressure (mmHg)	125±5.7	134±11 ^a	132±17 ^a	142±20 ^{abc}
Diastolic Blood Pressure (mmHg)	81±5.5	89±7.3 ^a	85±10 ^{ab}	84±8.5 ^{ab}
Weight (kg)	65.4±7.7	61.1±6.4 ^a	60.6±8.9 ^a	55.4±9.7 ^{abc}
Height (cm)	160±7.4	157.6±6.4	155.5±6.6 ^a	152.8±10 ^{ab}
Body Mass Index (kg.m ⁻²)	25.5±2.1	24.6±1.8 ^a	24.9±2.5	23.6±2.7 ^{abc}

Values are Mean ± SD

The superscript alphabets of a specific group mean denote the statistically significant difference of that group at 5% level

Group 1 - normotensive postmenopausal women as control

Group 2 - hypertensive postmenopausal women

Group 3 - hypertensive postmenopausal women with diabetes

Group 4 - hypertensive postmenopausal women with renal insufficiency

The study conducted by Ejike *et al* revealed an insignificant increase in SBP and DBP with age among hypertensive subjects while among normotensive subjects aged between 60-69 years, SBP was dropped and DBP was increased slightly with age, suggesting age as a factor affecting blood pressure elevation ^[14]. A study on postmenopausal women reported the significant increase in both SBP and DBP to be independent of age and BMI ^[15]. A hypertension follow-up study in men and women reported an increase in blood pressure in menopausal women than in premenopausal women ^[16]. A significant increase in systolic and diastolic blood pressure was also reported in diabetic hypertensive patients as compared to diabetic normotensive and non-diabetic normotensive control. Their study revealed significantly high BMI values in diabetic normotensive and diabetic hypertensive patients as compared to non-diabetic normotensive control ^[17]. Another study suggested that menopause is accompanied by slight increase in blood pressure that may be contributed by aging, BMI and augmented cardiovascular risk factors ^[18]. In the present study, a significant increase in systolic and diastolic blood pressure was found in hypertensive postmenopausal women with diabetes compared to normotensive postmenopausal women.

Total cholesterol was significantly increased in hypertensive postmenopausal women (group 2) compared to the other groups namely hypertensive postmenopausal women with diabetes, hypertensive postmenopausal women with renal insufficiency and normotensive postmenopausal women (Figure-1). HDL-cholesterol was significantly decreased in hypertensive postmenopausal women with renal insufficiency (group 4) compared to the other three groups (Figure-2). Triglycerides and VLDL-cholesterol were significantly increased in hypertensive postmenopausal women (group 2) compared to the control group (Figure-3 and 4). LDL-cholesterol was significantly increased in experimental groups compared to normotensive control group (Figure-5).

A prospective study revealed that the levels of total cholesterol, triglyceride and LDL-cholesterol were significantly elevated whereas HDL-cholesterol was significantly reduced in hypertensive patients as compared to normotensive control. This elevation in total cholesterol, triglyceride and LDL-cholesterol levels might be due to increased dietary animal fat intake, metabolic syndrome, physical inactivity, genetic factors, stress and aging ^[19]. Similar results obtained in another study suggested that most of the hypertensive patients were taking treatment irregularly and recommended the reinforcement of the use of lipid profile in routine clinical tests conducted on hypertensives in order to prevent adverse cardiovascular events ^[20]. In the present study also most of the hypertensive postmenopausal women participants were taking antihypertensive medications irregularly. This along with lack of exercise and age can be attributed to the significant elevation in total cholesterol, triglycerides and VLDL-cholesterol in hypertensive postmenopausal women.

In the present study, there was no significant difference in triglycerides whereas HDL-cholesterol exhibited a significant decline in hypertensive postmenopausal women compared to normotensive control. In contrast to the present study, there was a significant increase in triglyceride and significant decrease in HDL-cholesterol in diabetic postmenopausal women compared to non-diabetic postmenopausal women. Total cholesterol and LDL-cholesterol exhibited no significant difference among diabetic postmenopausal women and non-diabetic postmenopausal women ^[21].

Total cholesterol and LDL-cholesterol levels were significantly increased while HDL-cholesterol was significantly decreased in hypertensive postmenopausal women with renal insufficiency compared to normotensive control. No significant difference was seen in triglycerides and VLDL-cholesterol between the two groups. The study conducted on chronic kidney disease patients revealed that total cholesterol levels were decreased and LDL-cholesterol levels were increased in chronic kidney disease patients. There was no significant difference in HDL-cholesterol in chronic kidney disease patients compared to that of controls ^[22]. Similar studies were carried out, but with contrasting results. Total cholesterol, triglycerides and LDL-cholesterol were increased significantly, but no significant difference was seen in the levels of HDL-cholesterol ^[23].

Atherogenic index (LDL-C/HDL-C), atherogenic coefficient ((TC-HDL)/HDL), cardiac risk ratio (TC/HDL-C) and atherogenic index of plasma (log (TG/HDL-C)) were significantly increased in experimental groups compared to normotensive postmenopausal women (Figure-6, 7 and 8). There was no significant difference in LDL-cholesterol and atherogenic index of plasma between hypertensive postmenopausal women (group 2) and hypertensive postmenopausal women with diabetes (group 3).

Idemudia *et al* reported increase in atherogenic index in hypertensive patients compared to normotensive patients ^[24]. Total cholesterol, triglycerides, LDL-cholesterol, cardiac risk ratio and atherogenic index, except HDL-cholesterol were increased in patients with hypertension, ischemic heart disease and cerebrovascular disease/stroke compared to their healthy counterparts ^[25]. In the present study also total cholesterol, triglycerides, LDL-cholesterol along with atherogenic index and cardiac risk ratio were significantly increased, indicating the onset of atherosclerotic cardiovascular events in hypertensive postmenopausal women. Hence the present study reports are in agreement with these statements.

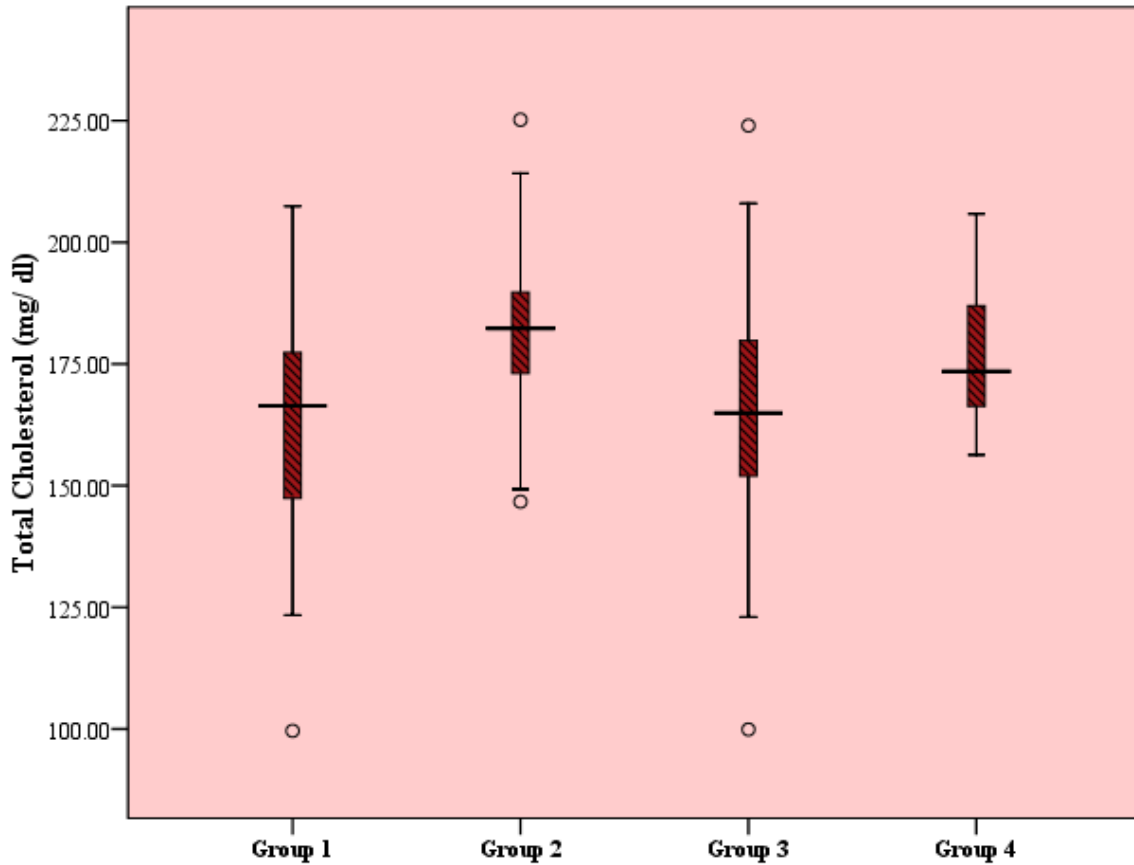
Atherogenic index, cardiac risk ratio, atherogenic coefficient and atherogenic index of plasma were significantly increased in hypertensive postmenopausal women with renal insufficiency compared to the other groups namely hypertensive postmenopausal women with diabetes, hypertensive postmenopausal women with renal insufficiency and normotensive

postmenopausal women. The study conducted on nephrotic syndrome patients also found that cardiac risk ratio, atherogenic index of plasma and atherogenic coefficient were significantly increased in controlled nephrotic syndrome patients compared to normal healthy subjects. Cardiac risk ratio, atherogenic index of plasma and atherogenic coefficient were significantly increased in uncontrolled nephrotic syndrome patients compared to controlled nephrotic syndrome patients. Atherogenic index of plasma can be easily calculated from lipid profile values, hence can be a better predictor for atherosclerosis than the common lipid parameters, TC/LDL-C and LDL-C/HDL-C ratios ^[26].

Similar studies suggested that atherogenic index of plasma, a triglyceride based index can be a potential tool for assessing the pathogenesis of atherosclerosis. In their study postmenopausal women exhibited elevated levels of total cholesterol, triglycerides, LDL-cholesterol, VLDL-cholesterol and atherogenic index of plasma and the levels increased with the duration of menopause ^[27]. There was a significant increase in total cholesterol, LDL-cholesterol and atherogenic index of plasma in hypertensive postmenopausal women compared to hypertensive premenopausal women ^[28].

Figure 1

Total cholesterol levels in normotensive and hypertensive postmenopausal women with and without diabetic and renal insufficiency



Group 1 -normotensive postmenopausal women as control

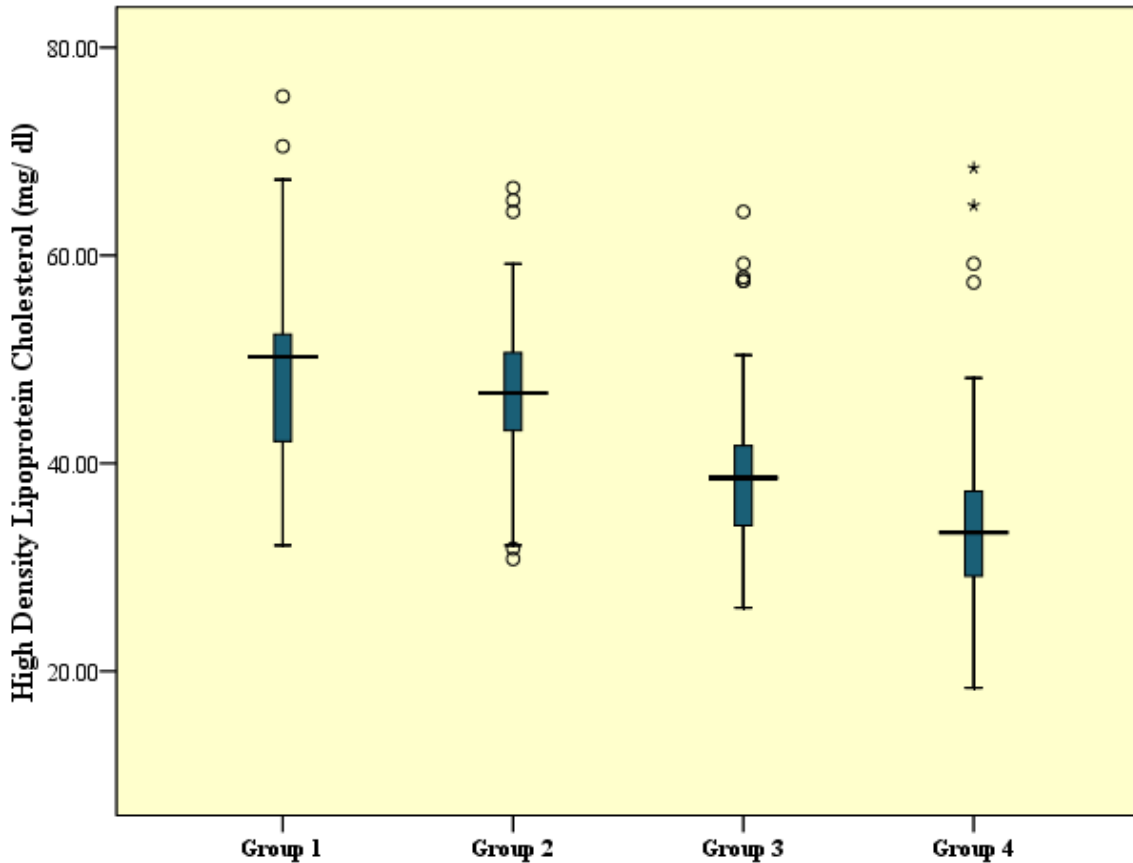
Group 2 -hypertensive postmenopausal women

Group 3 - hypertensive postmenopausal women with diabetes

Group 4 - hypertensive postmenopausal women with renal insufficiency

Figure 2

HDL-cholesterol levels in normotensive and hypertensive postmenopausal women with and without diabetic and renal insufficiency



Group 1 -normotensive postmenopausal women as control

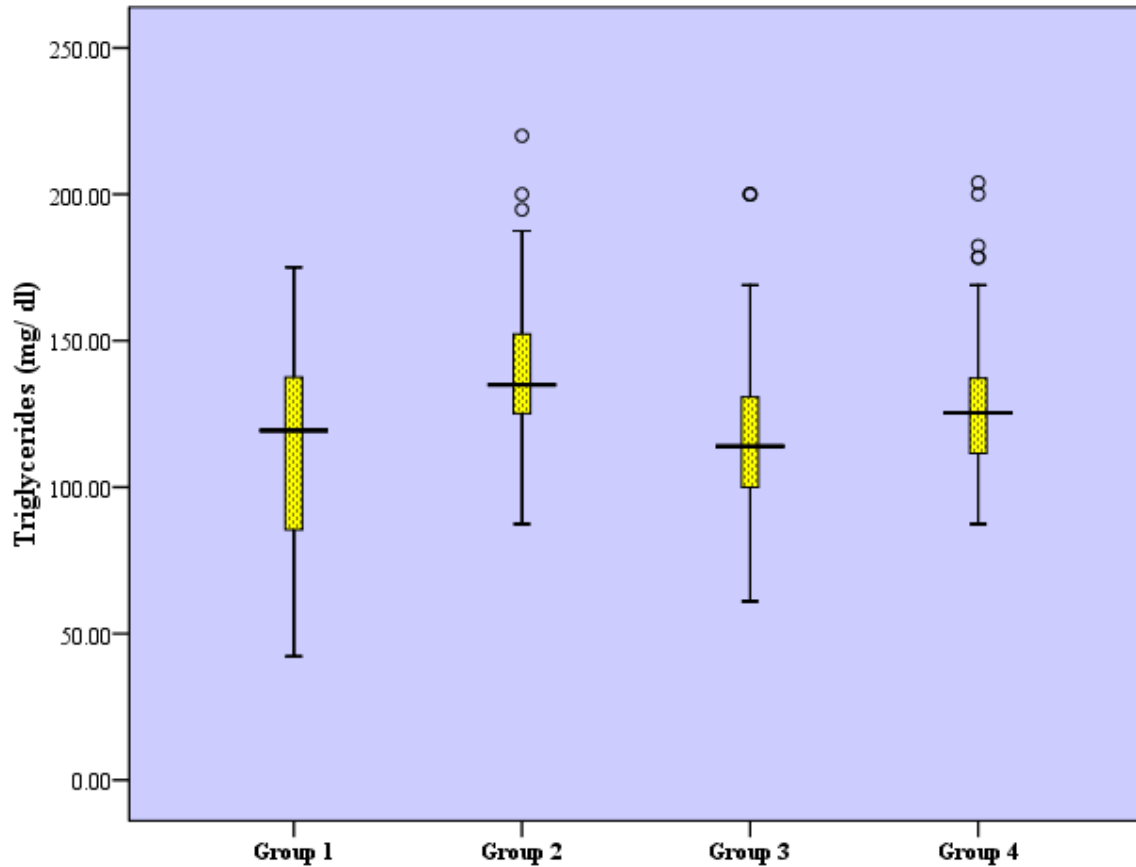
Group 2 -hypertensive postmenopausal women

Group 3 - hypertensive postmenopausal women with diabetes

Group 4 - hypertensive postmenopausal women with renal insufficiency

Figure 3

Triglyceride levels in normotensive and hypertensive postmenopausal women with and without diabetic and renal insufficiency



Group 1 -normotensive postmenopausal women as control

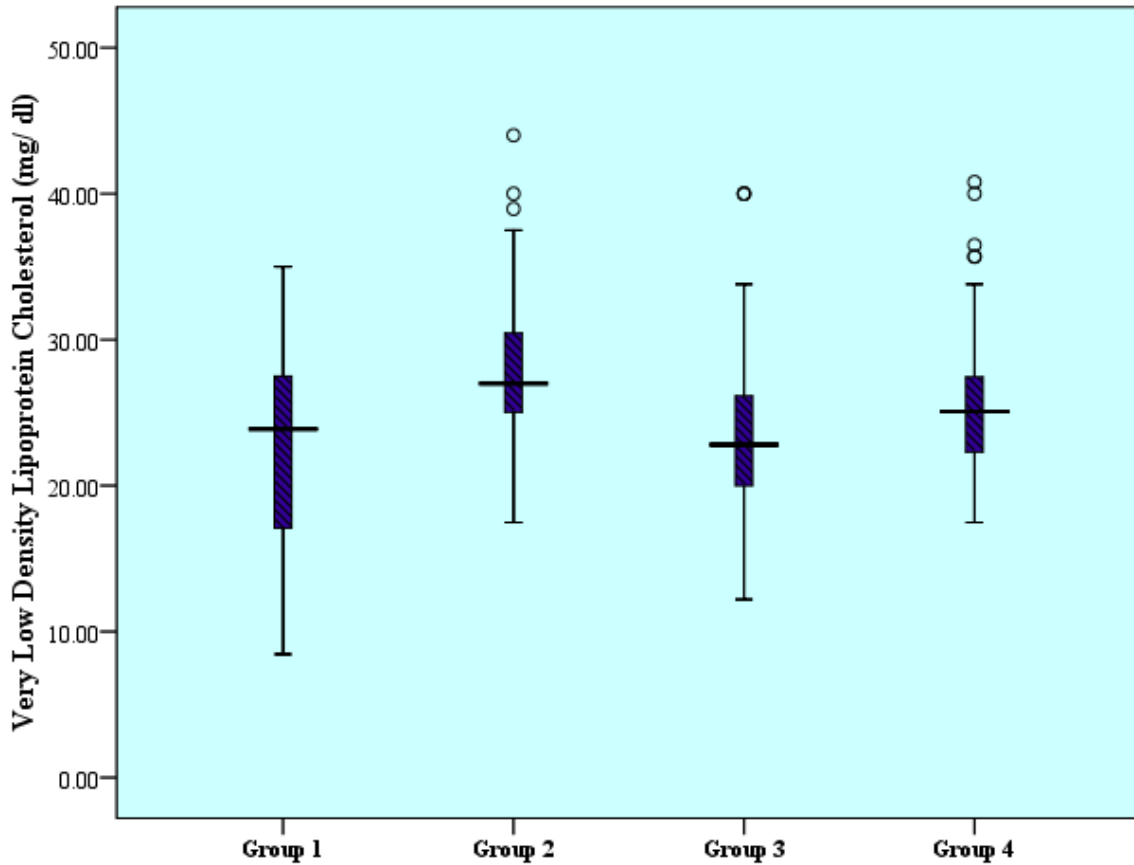
Group 2 -hypertensive postmenopausal women

Group 3 - hypertensive postmenopausal women with diabetes

Group 4 - hypertensive postmenopausal women with renal insufficiency

Figure 4

VLDL-cholesterol levels in normotensive and hypertensive postmenopausal women with and without diabetic and renal insufficiency



Group 1 -normotensive postmenopausal women as control

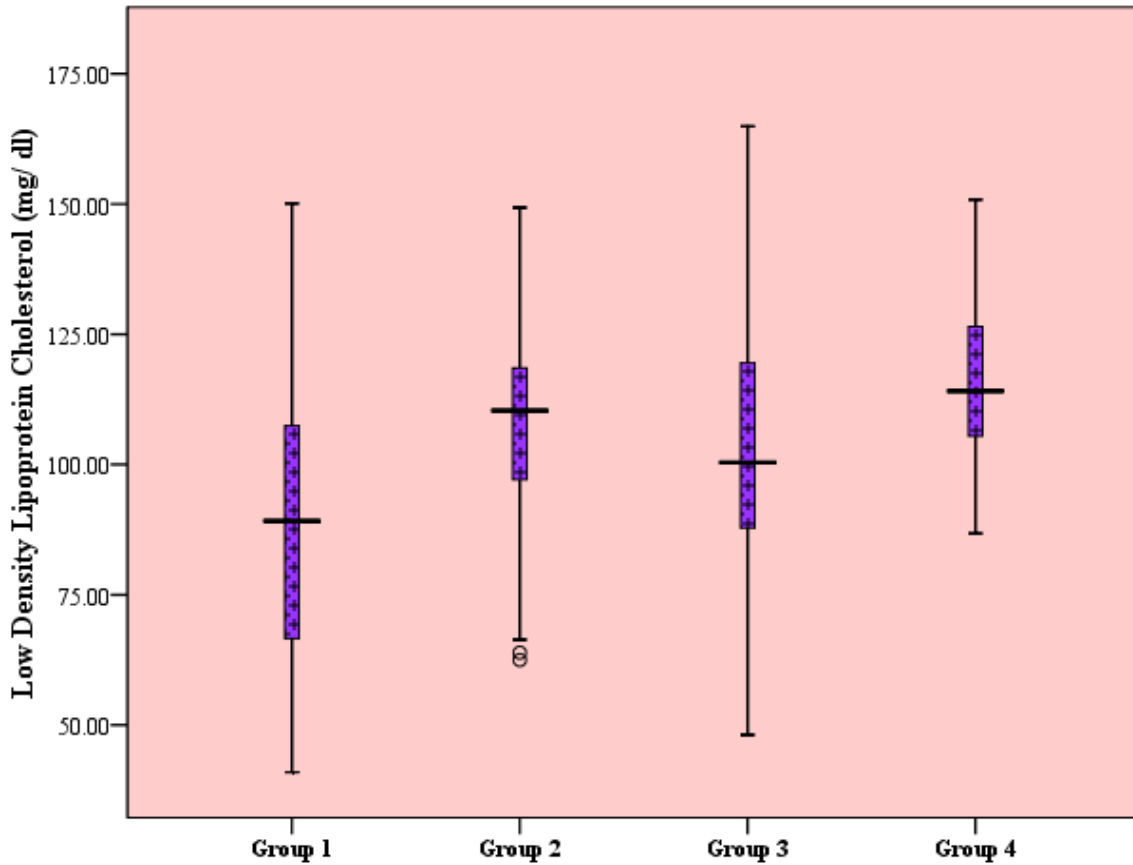
Group 2 -hypertensive postmenopausal women

Group 3 - hypertensive postmenopausal women with diabetes

Group 4 - hypertensive postmenopausal women with renal insufficiency

Figure 5

LDL-cholesterol levels in normotensive and hypertensive postmenopausal women with and without diabetic and renal insufficiency



Group 1 -normotensive postmenopausal women as control

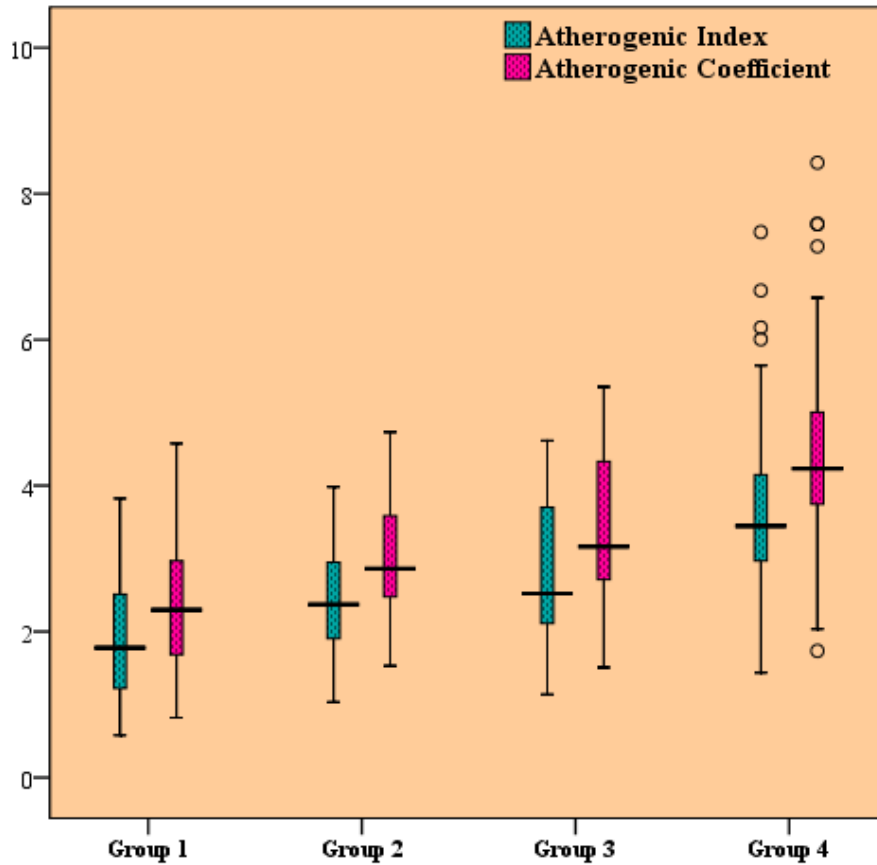
Group 2 -hypertensive postmenopausal women

Group 3 - hypertensive postmenopausal women with diabetes

Group 4 - hypertensive postmenopausal women with renal insufficiency

Figure 6

Atherogenic index and atherogenic coefficient in normotensive and hypertensive postmenopausal women with and without diabetic and renal insufficiency



Group 1 -normotensive postmenopausal women as control

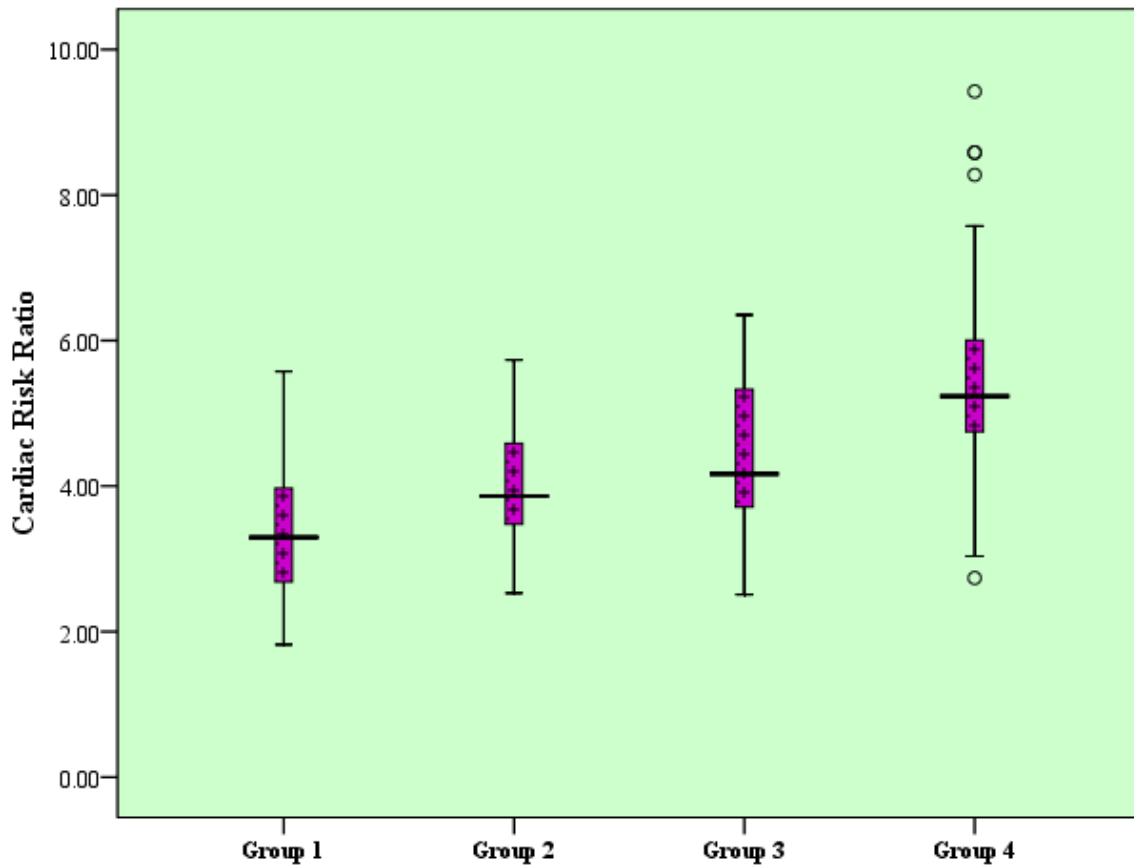
Group 2 -hypertensive postmenopausal women

Group 3 - hypertensive postmenopausal women with diabetes

Group 4 - hypertensive postmenopausal women with renal insufficiency

Figure 7

Cardiac risk ratio in normotensive and hypertensive postmenopausal women with and without diabetic and renal insufficiency



Group 1 -normotensive postmenopausal women as control

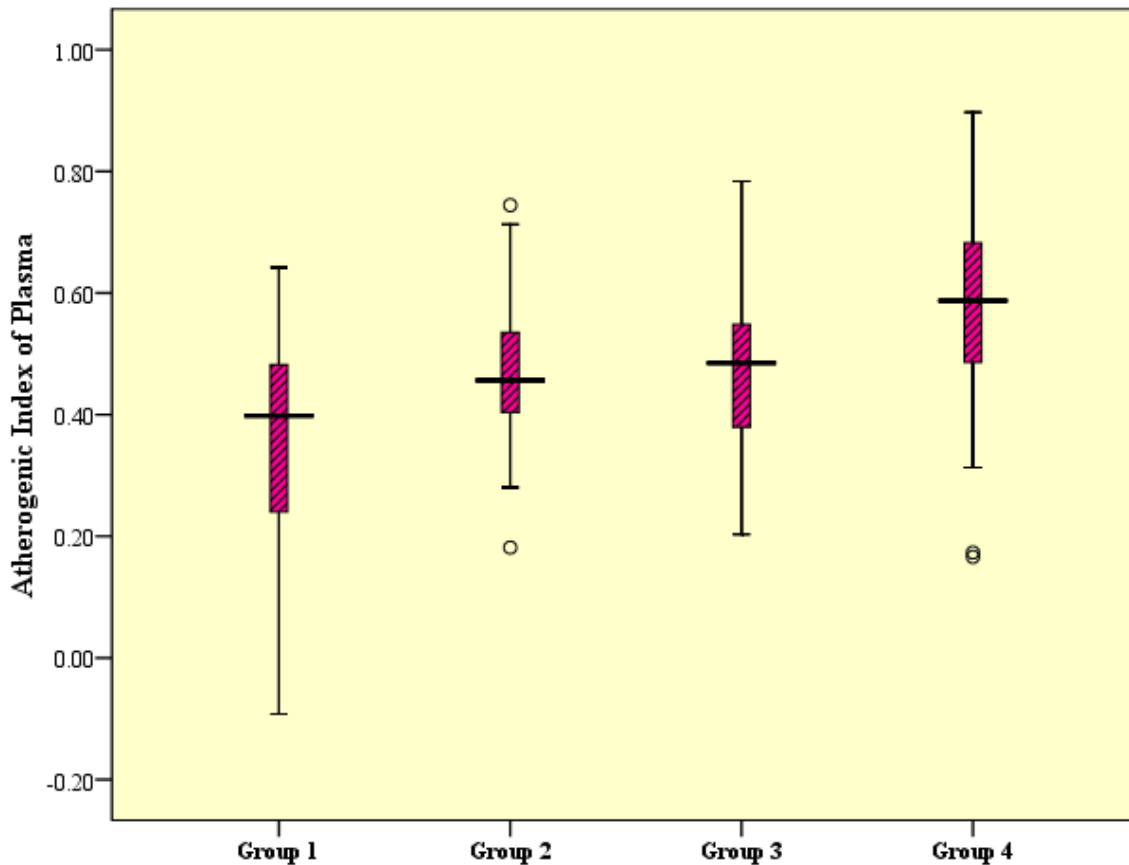
Group 2 -hypertensive postmenopausal women

Group 3 - hypertensive postmenopausal women with diabetes

Group 4 - hypertensive postmenopausal women with renal insufficiency

Figure 8

Atherogenic index of plasma in normotensive and hypertensive postmenopausal women with and without diabetic and renal insufficiency



Group 1 -normotensive postmenopausal women as control

Group 2 -hypertensive postmenopausal women

Group 3 - hypertensive postmenopausal women with diabetes

Group 4 - hypertensive postmenopausal women with renal insufficiency

CONCLUSION

The significant elevation in total cholesterol, triglycerides and VLDL-cholesterol in hypertensive postmenopausal women can be attributed to irregular intake of antihypertensive medications and unhealthy lifestyle, which adversely affect the quality of life.

Reduced levels of HDL-cholesterol and elevated LDL-cholesterol, atherogenic index, atherogenic coefficient, cardiac risk ratio and atherogenic index of plasma in hypertensive postmenopausal women with renal insufficiency might be indicative of onset and progression of atherosclerotic cardiovascular disease.

Hence, awareness programmes emphasizing the significance of routine medical check-ups and regular medications need to be organized.

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