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Original Article

The association of LRP5 (rs556442) polymorphism with body composition and obesity in postmenopausal women

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ABSTRACT

Aim: The main of this study was to investigate the association between the rs566442 (V1119V) coding polymorphism of Low-density lipoprotein receptor-related protein 5 (*LRP5*) with obesity and basal metabolic rate in Iranian postmenopausal women.
Methods: This cross-sectional study was performed on 350 postmenopausal women with a mean age of 57.8 years (SD ± 6.14). Body composition was analyzed by bioelectrical impedance analysis (BIA) resistance. Obesity was defined based on Body mass index (BMI) ≥30 kg/m2. To determine the genotype of SNP (rs556442), PCR-RFLP assay was performed and confirmed by sequencing. DNA samples from participants were genotyped using the RFLP-PCR method.
Results: Among the study population 37.1% (130) were obese. G allele had minor-allele frequency of 0.38% in our population. The frequency of genotypes in our study population was 12.9% (45 person) GG, 35.7% (125 person) AA and 51.4% (180) GA. After adjusting age and menopausal age, only basal metabolic rate showed significantly higher in GG group compare to other groups ($p = 0.02$). Our data showed basal metabolic rate was higher in obese women with GG genotype in comparison to obese women with AG and AA genotypes.
Discussion: The findings of this study suggest that the GG genotype of SNP (rs556442) could protective role in obese women through the association with BMR.
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1. Introduction

Hormonal alterations during menopause cause different changes and affect regulation of postmenopausal women bodies; one of the important effects of menopausal status is on body composition [1], which includes an increase in body fat and accumulation of fat trunk and a decrease in muscle mass. These alterations in total body fat will increase the risk of metabolic disorders associated with obesity including type 2 diabetes mellitus (T2DM), coronary heart disease, arthritis and hypertension. They are also considered as a risk factor in augmenting the severity of these disease conditions [2,3]. On the other hand, due to these alterations menopause women are highly prone to musculoskeletal impairments like osteoporosis and sarcopenia, and these two conditions are among the most significant health challenges - in postmenopausal women [4].

Recently, several studies have shown relations between musculoskeletal disorders and different candidate genes in genetic pathways [5,6]. It also has been shown that genetic factors can play

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a crucial role in pathogenesis of osteoporosis [7,8]. Notably, among all these cellular pathways, some are common among these conditions, such as Wnt signaling pathway, which is involved in progression of disease conditions, including diabetes, heart disease, and osteoporosis [9]. Wnt signaling pathway regulates a wide variety of cellular processes in adult tissues, including tissue homeostasis and organs through cell to cell signaling, tissue maintenance and remodeling processes. Wnt is involved in progression of disease conditions, including diabetes, obesity and even cancer. All of these conditions require notable remodeling of adult tissue and as a result, differentiation in metabolic status of the cells [10,11]. Despite the fact that Wnt pathway plays a role in the regulation of the cellular metabolism and tissue remodeling, it is not clear how Wnt signaling pathway senses and responds to metabolic alterations of the cells. So, it seems to be mandatory to clarify how Wnt signaling activity in regulating the metabolic status of the cell can prevent or lead to obesity. Frizzled molecules are known to be the primary receptors of Wnts. These receptors consist of 7 *trans*-membrane proteins with a long cysteine rich domain at amino terminus known as CRD, that Wnts binds to the frizzled CRD; it is also known that besides Frizzled receptors, Wnts require co-receptors to efficiently bind CRDs [12]. low-density lipoprotein (LDL)-receptor-related proteins (LRP) including LRP5 and LRP6 in human bind to Wnts to act as co-receptors of this proteins to bind frizzled molecules [13,14]. Among all the genes present in this pathway, the LRP5 is our candidate gene in this study, because of its role in diabetes, obesity, osteoporosis and muscle mass. LRP5 also regulates cholesterol metabolism and glucose-induced insulin secretion [15]; this suggests that Wnts may play a significant role in signaling tissue-specific and whole-body carbohydrate and lipid homoeostasis. Hence, polymorphisms in LRP5, may lead to metabolic disorders.

In previous studies the impact of *LRP5* polymorphism (rs556442) on body composition and TG levels have been investigated [16]. In this study, we hypothesized that the rs566442 (V1119V) coding polymorphism in exon 15 in *LRP5* may have an association with obesity in menopause woman. Since the LRP5 mutations have a relation to the muscle mass, and as muscles are considered as metabolism site in the body, we assumed these mutations will cause decreasing in the basal metabolic rate.

The prevalence of obesity in menopause woman is also of major importance. Although it is not clear which factors are contributing to this increase after menopause, hormonal changes and aging disorders are claiming factors [17]. In the current study the polymorphism of the rs566442 was analyzed in a group of menopause woman.

2. Materials and methods

2.1. Study population

The population for the present study included 350 Iranian postmenopausal women. Participants with serious and/or chronic illnesses, especially those with diabetes mellitus, coronary artery disease and pregnant women were excluded. At baseline, all study participants were subjected to a thorough screening program that included an assessment of detailed personal and family history, physical examination, determination of anthropometric indices and measurement of various biochemical parameters. The study was approved by the research council and ethics committee of the Tehran University of Medical Sciences and written informed consent was obtained from all participants prior to their inclusion in the study.

2.2. Phenotype measurement

BMI was calculated as body weight (kg) divided by the square of height (m). Weight was measured in light indoor clothing, using a calibrated balance beam scale, and height was measured using a calibrated stadiometer. We defined obesity as a dichotomous trait using the World Health Organization criterion, BMI >30 kg/m2. In all participants, body height, body weight, waist circumferences and hip circumferences were measured for calculation of BMI, and waist to hip ratio (WHR).

Body composition of all participants were assessed by BODY COMPOSITION ANALYZER BC-418MA—Tanita (United Kingdom), strictly following the techniques, procedures, and precautions of the manufacturer's protocol. The precisions of the measurement of weight, height and fat mass, as reflected by the coefficient of variation, were 1.2%, 0.9% and 2.2%, respectively. The device calculates body-fat percentage, fat mass, and fat-free mass, BMR and predicts muscle mass. Percentage Fat Mass (PFM) was calculated as the ratio of fat mass to body weight. The muscle mass index was calculated by the following equation: skeletal muscle mass (kg) divided by the square of height (m2).

2.3. Laboratory analysis

After a 12-14 hours overnight fast, blood samples were collected. The sera were kept at -80 ^{o}C until analysis. Serum glucose and lipid profile [total cholesterol (TC), high-density lipoprotein (HDL), low density of lipoprotein (LDL), and triglyceride (TG)] were measured by enzymatic colorimetric assay (Pars-Asmun kits, Iran) using an auto analyzer (Hitachi 902, Japan).

2.4. Genotyping

DNA samples were isolated from peripheral blood using High Pure PCRT Template Preparation Kit (GeneAll Biotechnology Co. Ltd, Korea). The quality and quantity of DNA were assessed using a Nanodrop ND-1000 (Thermo Fischer Scientific, USA) and agarose gel electrophoresis was used to evaluate the integrity of DNA. The PCR-RFLP assay was used to determine the genotype of SNP (rs556442). PCR was carried out in a DNA thermal cycler (Biometra, Goettingen, Germany) using the primers: forward-AGTATAGAATGTGACCTGTCAGC reverse: GCTGCTGCTGCCATTACT-GAC. PCR was performed after the first denaturation at 96 °C for 10 min; followed by 35 cycles of 96 °C for 75 s, 62 °C for 75 s, and 73 °C for 75 s, and a final elongation step of 72 °C for 5 min. To assess genotyping reproducibility, randomly selected 10% DNA samples were sequenced with 100% concordance. The PCR generated a 399-bp fragment. PCR products were digested with restriction enzyme *Acc*I, digestion yielded 260bp and 139bp fragments. G allele resulted 260bp fragments and 139. A allele yielded 399bp fragments.

2.5. Statistical analysis

Statistical analysis was performed using SPSS 20.0 (SPSS Inc., Chicago, IL). Data are expressed as number (%) for categorical values and mean ± standard deviation for continues variables. Data normality was analyzed by using the Shapiro–Wilk test. Because of skewed distributions, blood triglycerides (TG) and HDL were Ln-transformed for analyses and back transformed to mean ± coefficient of variation (CV%). The Hardy-Weinberg equilibrium (HWE) and linkage disequilibrium (LD) test of SNP were assessed. Demographics and clinical measures were reported using descriptive statistics. Comparisons between genotypes were performed using the Student's t-test for continuous variables and χ^2 test for

categorical variables. Further, a Univariate analysis was used to examine the relative predictive value of gene loci for the risk of obesity. A p-value of less than 0.05 (2-tailed) was used for statistical significance.

3. Results

3.1. Study population and characteristics

Our study population was 350 Iranian postmenopausal women with a mean age of 57.8 ± 6.14 years. Among them, 37.1% (130) were obese. Average BMI (Body Mass Index) of obese women compared to non-obese women was 33.18 ± 2.8 (mean ± SD) versus 25.94 ± 2.5 (mean ± SD) respectively. Base on obesity, study population was divided in two groups (obese and non-obese). The characteristics of the study participants are shown in Table 1. Our data showed that there was no significant difference in age, menopausal age, serum levels of LDL, and total cholesterol and between two groups. While FAT%, visceral fat, Fat Mass, BMR, Muscle Mass, waist, Hip, HDL and TG were higher in obese women. The mean difference of FAT% was 6.6% between obese and non-obese women (Table 1).

3.2. Frequency of rs556442 polymorphism

The frequency of minor-allele (G allele) was 0.38% in our population. The distribution of studied genotypes is shown in Table 2. The observed genotype frequencies were consistent with Hardy-Weinberg equilibrium in all participants ($p = 0.11$), in obese women ($p = 0.16$) and in non-obese women ($p = 0.4$). Also, there was no significant difference in the genotype's frequencies between obese and non-obese women ($p = 0.95$) (Table 2).

3.3. Association between rs556442 genotypes and body composition analyses

Body composition analysis showed that only basal metabolic rate was higher in women with GG genotype compared to women with other genotypes (Table 3). Univariate analysis of variants showed that after adjusting for age and menopause age, there was a significant association between GG genotype and BMR (rs556442, $p = 0.02$). However, such association was not observed between the genotypes and other factors including; BMI and Fat% ($p = 0.3$, $p = 0.4$).

Our data indicated that there was a significant correlation between the levels of BMR with Fat% (r: 0.7 $p = 0.0001$) and BMI (r: 0.68 $p = 0.0001$). In order to further clarify the role of genotype in association between BMR and BMI, Fig. 1 shows that in women with GG genotype, increase in BMI results in increase in BMR with lower intensity compared to GA and AA groups (Fig. 1).

Table 2
Genotype frequency of LRP5 (rs556442) based on obesity.

Genotype	Total	Obese	Non-obese	*P*-value
rs556442				0.957
GG	45 (12.9%)	28 (12.7%)	17 (13.1%)	
AA	125 (35.7%)	78 (35.5%)	47 (36.2%)	
AG	180 (51.4%)	114 (51.8%)	66 (50.8)	

The genotyping was based on PCR products- AA: 399-bp fragment. GG: 260bp and a 139bp fragments. AG: 399-bp, 260bp and 139 fragments.

4. Discussion

In this study, we examined the influence of LRP5 (rs556442) polymorphism on obesity in postmenopausal Iranian women. WNT/β-catenin signaling has a significant role in metabolism and adipocyte biology and it is considered as the main signaling pathway regulating adipogenesis [18]. While candidate gene association studies related to gene variations of LRP5 and obesity risk did not show consistent results [19,20]. Our data showed no direct association between this variation and obesity. This discrepancy is likely due to underlying study population as well as different SNPs of LRP5 which they may have different functions. In the study of association of three polymorphic variations of the *LRP5* gene (Q89R, N740N, and A1330V) and obesity in young Chinese men, no associations were found [20]. While in another study a significant association was found between SNP4 (*rs4988300*) and SNP6 (*rs634008*) located in block 2 (intron 1) with obesity and BMI in a family-based study. The allele A for SNP4 and minor allele G for SNP6 were responsible for the increased risk of obesity [21]. Koay et al. found no association between LRP5 (rs556442) polymorphism and either height or weight in British children [18,19]. We also investigate the impact of LRP5 polymorphism on body composition in Iranian menopausal women. Our data revealed that LRP5 (rs556442) had significant influence on basal metabolic rate. BMR was higher in obese women with GG genotype in comparison to obese women with AG and AA genotypes. Our data showed GG genotype had a protective role in obese persons while this correlation was not seen in other factors like BMI and Fat%.

Table 1
Study population characteristics.

Characteristic	Total N = 350	Obese N = 130	Non −Obese N = 220	*P*-Value
Age (year)	57.23 ± 5.8	57.4 ± 5.5	56.9 ± 5.8	0.44
Menopausal age (year)	47.9 ± 5.2	47.8 ± 5.5	48.2 ± 5	0.91
Waist (cm)	91.5 ± 12.1	101 ± 10	85 ± 9.2	0.0001
Hip (cm)	104.7 ± 8.9	111.5 ± 7.8	100.6 ± 6.9	0.0001
FAT percentage (%)	37.0 ± 5.7	41.1 ± 3.9	34.5 ± 5.2	0.0001
Fat mass (kg)	26.9 ± 7.5	32.9 ± 6.4	23.2 ± 5.5	0.0001
Viceral fat (kg)	8.9 ± 2.3	11 ± 1.7	7.7 ± 1.6	0.0001
BMR (Calorie)	1320.6 ± 131.34	5926 ± 504.4	5288.4 ± 423.8	0.0001
Muscle Mass Index (kg/m^2)	7.3 ± 0.77	8.05 ± 0.56	6.9 ± 0.53	0.0001
LDL (mg/dL)	109.35 ± 25.67	110.8 ± 25.8	108.4 ± 25.6	0.42
HDL* (mg/dL)	45.65 ± 10.25	40.44 ± 6.48	44.70 ± 5.52	0.0001
TG* (mg/dL)	112.59 ± 10.92	133.75 ± 9.84	101.63 ± 11.01	0.0001
TC (mg/dL)	209.19 ± 38.45	211.3 ± 39.3	207.9 ± 37.9	0.42

BMR, basal metabolic rate; TG, triglyceride; HDL, High density lipoprotein cholesterol; LDL, low density lipoprotein; TC, total cholesterol. Numerical variables were expressed as the mean ± standard deviation (SD). Categorical variables were presented as percentages. *Back transformed data were presented mean ± coefficient of variation (CV %).Student's t-test for numerical variables and Pearson Chi-Square test for categorical variables.

Table 3
Body composition analysis between three genotypes of LRP5 (rs556442).

	GG	AA	GA	*P*-value
BMI (kg/m^2)	29.32 ± 4.39	28.86 ± 4.62	28.34 ± 4.34	0.3
BMR (Calorie)	1363.31 ± 134.14^{abcd}	1318.66 ± 141.18^{ac}	1311.93 ± 123.28^{bd}	0.02*
Fat percentage (%)	38.1 ± 5.31	36.9 ± 9.14	36.81 ± 5.64	0.4
Fat mass (kg)	27.96 ± 7.76	27.11 ± 7.76	26.48 ± 7.38	0.4
Viceral fat (kg)	9.36 ± 2.35	8.93 ± 2.29	8.92 ± 2.32	0.5
Muscle mass index (kg/m^2)	7.33 ± 0.9	7.21 0.92	7.12 0.91	0.4

Significant Post Hoc tests; a: comparison between GG and AA groups, b: comparison between GG and GA groups, c: comparison between AA and GG groups, d: comparison between GA and GG groups.

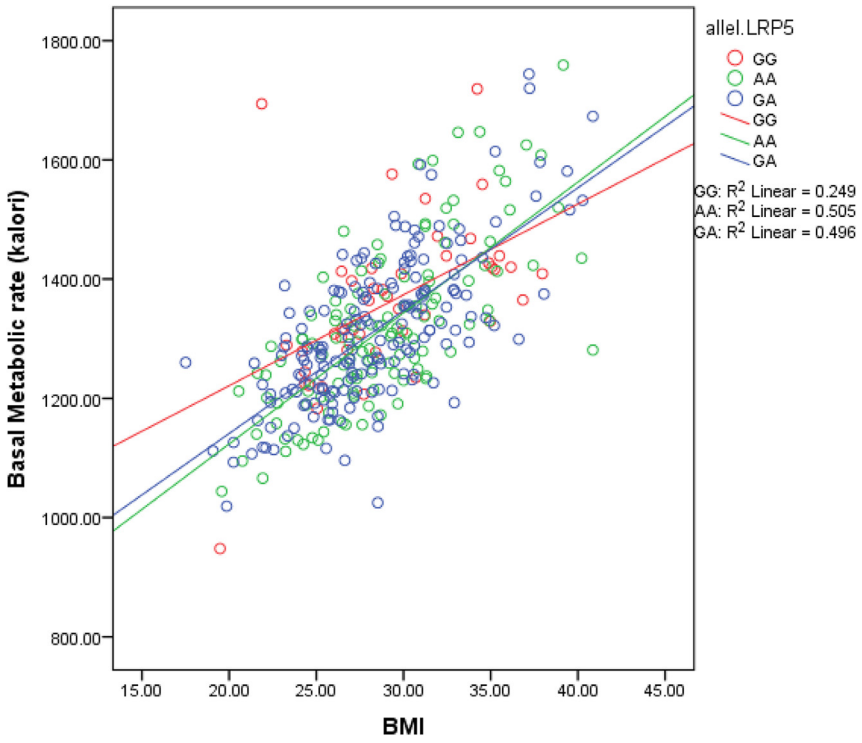

Fig. 1. Association of BMI and BMR in three different genotype groups of LRP5 (rs556442); increased BMI accompanied by increased BMR with higher intensity in women with GG genotype.

In a previous study that has investigated the role of LRP5 in metabolic disorders in Iranian children, LRP5 (rs556442) polymorphism has shown a significant influence on triglyceride levels in both unadjusted analysis and when adjusted for interacting factors [14]. The authors reported, higher TG levels in AA/AG genotype of rs566442 in comparison to GG genotype. But no association was found between rs566442 polymorphism and BMI, height, weight, waist circumference, hip circumference, android/gynoid ratio and fat mass index in their studied population [16]. The association of LRP5 polymorphism and body compositions reported by Ashouri et al. [22]. They showed that total lean mass was more in the GG genotype of rs556442 in Iranian children. In a recent study, Fei et al. found that LRP5 rs12363572 was associated with BMI and rs4930588 was associated with triglyceride levels in 507 newly diagnosed T2DM cases but not in healthy controls [23]. In our study, after adjusting for age and menopausal age, BMR was lower in the obese women with AG or AA genotype of the LRP5 polymorphism (rs556442) than in the obese with GG genotype. Our data suggest an association between LRP5 rs566442 polymorphism and metabolically healthy obesity.

People with BMI higher than 30 are considered obese but not all obese people are at the same risk of obesity-related complications like type 2 diabetes, insulin resistance, cardiovascular diseases, and several types of cancer. These obese people without metabolic abnormalities are considered metabolically healthy obese people and they are not at risk of obesity-related diseases compared to unhealthy obese people [24,25]. A previous study has shown that metabolically healthy obese people with higher basal metabolic rate had more favorable lipid profile, -lower insulin resistance, and lower total fat percentage and fat mass. BMR per BMI was 25% higher in the metabolically healthy obese group compared to the metabolically unhealthy obese people [26]. Thus lower basal metabolic rate is considered as a risk factor of obesity.

BMR is mainly determined by lean body mass, age and sex [27]. However, BMR varies considerably even among the people of the same weight and age, suggesting that BMR is partly genetically determined [28] and some genetic defects have been found to be associated with BMR [29]. This study confirms that BMR can be affected by genotype. We suggest that mutation in LRP5 gene alter the basal metabolic rate and may be a determining genetically factor in the metabolically healthy and unhealthy obesity conditions. Although the link between LRP5's variants and body composition has not been probed in the studied population, our study has some limitations which must be considered. In this study,

we showed that the obese individuals with GG genotype, had a higher BMR than other patients with AG and AA genotypes. Furthermore, we could not find a significant correlation between LRP5 polymorphism and obesity. However, to shed light on this polymorphism's relationship with obesity phenotypes, comprehensive studies that include both females and males and in diverse populations are needed.

5. Conclusion

The present research is the first of its kind to examine LRP5 gene variant's association with obesity, body composition and basic metabolic rate in Iranian population. Current evidence hints to a relationship between LRP5 gene variants and obesity and its phenotypes such as BMR and BMI. The LRP5's important role in glucose and cholesterol metabolism has been well demonstrated, thus investigating the related genetic factors in LRP5's performance can be helpful in gaining better understanding of obesity etiology and its complications.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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Compliance with ethical standards

Written informed consent was obtained from all study participants in accordance with procedures approved by the Ethical Committee of the Endocrinology and Metabolism Research Institute of Tehran University of Medical Science (IR.TUMS.EMRI.REC.1395.00103).

Authors contribution

Conceptualization of the project: Zhila Maghbooli.
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All authors read and approved the manuscript.

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