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ORIGINAL RESEARCH

Protective Association of Single Nucleotide Polymorphisms rs1861868-FTO and rs7975232-VDR and Obesity in Saudi Females

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Background: Obesity is a major health threat worldwide. It predisposes individuals to diabetes, cardiovascular complications, and cancer. Genetic and environmental factors are responsible for the increasing incidence of obesity. In this study, we investigated the genetic factors associated with obesity in young Saudi women.

Subjects and Methods: In this cross-sectional study, 131 young Saudi female students were recruited. Body mass index (BMI), waist–hip ratio, blood glucose, triglyceride, cholesterol, HDL, LDL, and vitamin D3 levels of the subjects were determined. Twelve SNPs of different genes that showed a correlation with obesity in different population were tested, namely GNPDA2 (rs10938397), TCF7L2 (rs10885409), FTO (rs1477196), ADIPOQ (rs1501299), MC4R (rs17782313), ABCA1 (rs1800977), FTO (rs1861868), VDR (rs2228570), VDR (rs731236), VDR (rs7975232), ADIPOQ (rs266729), and PFPK (rs6602024). Student's *t*-test was conducted for all parameters. Pearson correlation was performed to identify the correlated variables. The frequencies of different risk alleles were determined by direct counting of the test allele divided by the total number of alleles and compared.

Results: Only two SNPs, rs1861868 of *FTO* and rs7975232 of *VDR*, of the twelve tested SNPs showed significant protective associations with the BMI with odds ratio 0.3886 (0.1761–0.8572); p 0.0192 and odds ratio 0.4563 (0.2343–0.8888); p 0.0211, respectively.

Conclusion: The current study showed that minor alleles, "T" of *FTO* and "A" of *VDR*, might be protective factors against increased BMI in young Saudi female subjects. To elucidate this association, further studies with larger sample size involving both sexes are required.

Keywords: BMI, obesity, body weight, *FTO* gene, *VDR* gene, polymorphism

Introduction

Obesity is increasingly becoming a debilitating and threatening condition worldwide. It is also among the top concerns of all world health systems.[1] Accumulating evidence has revealed a strong association of obesity with chronic diseases such as diabetes mellitus, cardiovascular diseases, neurological impairments, and cancer.[2] Life expectancy is shorter in obese individuals owing to its association with high morbidity and mortality.[3]

A large-scale population-based study conducted in 2018 in Saudi Arabia reported the prevalence of obesity, particularly that of morbid obesity (body mass index (BMI) ≥ 30 kg/m^2), which is higher in women compared to that in men (36.5% versus 29.4% ($p < 0.001$)).[4] An earlier study performed by Al-Nozha et al

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in Saudi Arabia showed similar findings with the prevalence of morbid obesity is 44% in females and 26.4% in males.[5] Furthermore, the increase in the incidence of obesity in the population started at an early age. It has been found that the prevalence of obesity has increased in Saudi school boys from 3.4% to 24.5% in the period from 1988 to 2005.[6,7] Noteworthy, less attention has been given to studies of obesity in young and adolescent females in Saudi Arabia.[8]

Obesity is defined in general as an absolute increase in the fat mass. Central accumulation of fat has recently attracted the interest of the medical field, due to the strong association with all-cause mortality. Obesity is also associated with abnormal biochemical blood markers such as increased total blood triglycerides and cholesterol.[9] Furthermore, some studies demonstrated a correlation between vitamin D deficiency and obesity. In a randomized controlled study, vitamin D supplement for obese and overweight ladies with vitamin D deficiency enhanced their anthropometric data.[10]

The pathophysiology of obesity is not well understood. However, it has been determined that multiple genetic and environmental factors are involved. The interaction of these multiple factors is the most essential element involved in the precipitation of the condition.[11] Genetic predisposition can be related to the imbalance between food consumption and energy expenditure. These two important parameters are regulated by multiple neural and hormonal pathways involved in appetite, satiety, and metabolism.[12] Several studies conducted among different populations have identified some specific gene variants that are significantly associated with obesity. Most of the studied genes demonstrated functional influence on either the hypothalamic nuclei that regulate the appetite, and satiety, or related to the hormonal influence of the metabolism. Some other genes were related to physical activity and energy expenditure.[13] According to these studies, some variants of prominent genes, such as *FTO, MC4R, ABCA1, VDR, ADIPOQ, GNPDA2, PFKP, and TCF7L2*, were found to play an inevitable role in scoring the genetic background for obesity.[14] Polymorphisms in *FTO, MC4R*, ABCA1, and *ADIPOQ* were reported to be significantly associated with obesity and Type 2 diabetes mellitus (-T2DM).[15–18] Similarly, *VDR* variants, another set of most-studied SNPs, have been identified to be associated with many diseases, including obesity and increased adiposity.[19,20] *GNPDA2, PFKP, and TCF7L2* showed a strong association with BMI, body weight, and waist circumference in genome association studies in Europe and Indian Asian.[21]

Identification of different genes related to obesity is essential for the elaboration of the underlying pathophysiological mechanisms of obesity, which might help in designing an effective management plan of the global and local increase of obesity. On the other hand, evidence from multiple studies revealed that the frequency of those gene variants is not consistent in different populations. Wide variations were demonstrated in different population.[22] Therefore, we aim in the present study to elucidate the status of some prominent obesity-related gene variants in young Saudi female subjects recruited from the Imam Abdulrahman Bin Faisal University, Dammam, and compare the association of these variants with body indices and some biochemical markers related to adiposity.

Subjects and Methods

Eligibility and Recruitment of Subjects

This cross-sectional study included 131 Saudi female students recruited randomly from different colleges of Imam Abdulrahman Bin Faisal University in the period March–September 2015. Simple random selection was performed using a Microsoft Excel sheet including all female students in the campus. Demographic data, including age, marital status, parity, medical history, medications, and family history of diabetes, hyperlipidemia, hypertension, and coronary artery disease, were collected. All subjects were of Saudi origin. Pregnancy or lactation during the last six months were reasons for exclusion from the study. The study followed the ethical considerations approved by the declaration of Helsinki. All the participants signed a written informed consent. The protocol of the study was reviewed by the Institutional Review Board of Imam Abdulrahman Bin Faisal University and given the certificate number (IRB-2015-01-096).

Anthropometric Data

Bodyweight and height for each subject were measured using a weight scale that is rounded to the nearest 0.1 kg, and a height scale adjusted to the nearest 0.25 cm. Then, the BMIs of all subjects were calculated as weight in kg/height in m^2. Central obesity was assessed by measuring the waist and hip circumferences (WC, HC) and calculating waist/hip (W/H) and waist/stature (W/S) ratios.

Blood Parameter Analysis

Blood investigations included total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, random blood glucose (RBG), vitamin D3 level, alkaline phosphatase, calcium, and phosphorus. These tests were performed through chemiluminescent magnetic microparticle immunoassay techniques using (CMIA) kits from ABBOTT, USA.

Mutation Detection by TaqMan SNP Genotyping Assay

The first step of the genetic analysis was the genomic DNA isolation. It was performed using Promega DNA isolation kit (Promega, Madison, USA). Guidelines provided by the manufacturer were followed. Later, the concentration and purity of the isolated DNA were estimated by a Nanodrop spectrophotometer (Thermo Fisher Scientific, CA, USA). The isolated DNA was then stored at −20°C. The analysis of multiple SNPs was run using TaqMan technique for Real-Time PCR. The targeted SNPs were GNPDA2 (rs10938397), TCF7L2 (rs10885409), FTO (rs1477196), ADIPOQ (rs1501299), MC4R (rs17782313), ABCA1 (rs1800977), FTO (rs1861868), VDR (rs2228570), ADIPOQ (rs266729), PFPK (rs6602024), VDR (rs731236), and VDR (rs7975232). Each SNP probe (Thermo Fisher Scientific, CA, USA) detects both the wildtype allele and mutant allele, respectively, using FAM and VIC dyes. A master mix was prepared by addition of primer probe mix, Taqman genotyping master mix (Thermo Fisher Scientific, CA, USA), and the DNA. Total volume of the MIX was 25 µL, which is loaded on to the real-time PCR (ABI 7500, Thermo Fisher Scientific, USA) and the thermal profile was adjusted based on the manufacturer recommendations. The Interpretation of the genotype was carried out using proprietary software of the real-time PCR (Thermo Fischer Scientific, CA, USA). The genotyping of the studied SNPs showed 100% success rate.

Statistical Analysis

All data were expressed as mean ± SD for the whole group. Then, the subjects were stratified into two groups according to their BMI. A comparison of all the data was run between the two stratified groups using Student's *t*-test. The frequencies of different risk alleles were determined by direct counting of the test allele divided by the total number of alleles. SPSS (The statistical package of social sciences) software version 19 was used for the statistical analysis. P values < 0.05 were considered significant.

Results

Body Indices and Blood Parameters - Before and After Stratification

All participants were women of Saudi origin with a mean age of 20.77 ± 2.37 years and a mean BMI of 22.22 ± 3.94 kg/m^2. The study subjects were stratified to form two groups according to the BMI, <25 kg/m^2 and ≥25 kg/m^2. There was a statistically significant difference (p <0.05) between the two groups concerning their anthropometric characteristics, including BMI, WC, HC, W/H, and W/S, as well as in their blood parameters, such as vitamin D_3, triglyceride, HDL, uric acid, and phosphorus levels (Table 1).

Genotypic Characteristics - Before and After Stratification

Allele frequencies of all SNPs are listed in Table 2 for all subjects and for each group. The minor allele T of SNP rs1861868 on *FTO* and minor allele A of SNP rs7975232 on *VDR* showed significant protective associations, [Odds ratio 0.3886 (0.1761–0.8572); p 0.0192] and [Odds ratio 0.4563 (0.2343–0.8888); p 0.0211], respectively, with BMI. All other alleles of the studied SNPs did not show any significant association between the groups.

Discussion

Despite the expected environmental risk of obesity, possible genetic predisposition and enhancement might be present. Therefore, in this study, we aim to explore the association of obesity with some SNPs and to discover the most related alleles and variants. This study includes 131 young Saudi women, 16 of whom had BMI above 25 kg/m^2. Significant differences were observed in their anthropometric features, blood triglycerides, HDL, and vitamin D3 levels concerning their increased BMI.

We examined the association of 12 obesity-related SPNs and found 2 of the concerned SNPs demonstrated an association with BMI in the studied sample; those are FTO rs1861868 and VDR rs7975232. The minor allele T of FTO and A of VDR demonstrated a protective effect against obesity in young Saudi females with an Odd's ratio of 0.3886 (0.1761–0.8572) and 0.4563 (0.2343–0.8888), respectively.

Table 1 Body Indices and Blood Parameters of the Study Subjects Before and After Stratification

Parameter	Mean ± Standard Deviation	Mean ± Standard Deviation After Stratification		p-value
	Without Stratification (n=131)	<25 (n=115)	≥25 (n=16)	
Age (years)	20.77 ± 2.37	20.72 ± 2.41	20.92 ± 2.28	0.37296
BMI kg/m^2	22.22 ± 3.94	20.96 ± 1.90	29.21 ± 4.49	<0.00001[a]
Waist circumference (cm)	72.24 ± 10.84	67.89 ± 6.81	83.83 ± 11.17	<0.00001[a]
Hip circumference (cm)	97.50 ± 11.46	92.55 ± 6.88	110.71 ± 10.81	<0.00001[a]
Waist–hip ratio	0.73 ± 0.05	0.72 ± 0.05	0.75 ± 0.06	0.01408[a]
Waist–height ratio	0.45 ± 0.06	0.42 ± 0.04	0.52 ± 0.06	<0.00001[a]
Vitamin D3 (ng/mL)	15.24 ± 7.22	14.43 ± 6.15	17.47 ± 9.37	0.04642[a]
Random glucose (mg/dL)	89.86 ± 12.75	88.80 ± 13.05	93.00 ± 11.58	0.12305
Triglycerides (mg/dL)	80.37 ± 46.39	74.46 ± 31.49	97.80 ± 73.36	0.02692[a]
LDL (mg/dL)	64.32 ± 16.91	63.88 ± 15.62	65.60 ± 20.68	0.33214
HDL (mg/dL)	48.67 ± 8.55	49.92 ± 8.92	45.00 ± 6.20	0.01069[a]
Cholesterol (mg/dL)	167.57 ± 29.79	167.39 ± 27.71	168.10 ± 36.03	0.47737
Alkaline phosphatase (µkat/L)	2.56 ± 1.24	2.54 ± 1.12	2.60 ± 1.57	0.44110
Uric acid (mg/dL)	3.49 ± 0.98	3.30 ± 0.71	4.08 ± 1.38	0.00603[a]
Calcium (mmol/L)	2.00 ± 0.00	2.00 ± 0.00	2.00 ± 0.00	0.50000
Phosphorous (mg/dL)	3.52 ± 0.45	3.47 ± 0.40	3.66 ± 0.58	0.03975[a]

Note: [a]*P*-value < 0.05 for significant test.

The fat mass and obesity-associated *FTO* is considered the first and most robust obesity susceptibility gene of the genome-wide association study era. It was first discovered in 2007. *FTO* is a large gene with nine exons spanning more than 400 kb located on chromosome 16 in humans.[14] It was proposed that FTO gene plays an important role in the adipose tissue development and the precipitation of obesity.[23] Furthermore, the FTO rs1861868 was reported to be linked to leptin, fat mass ratio, thyrotropin, and basal energy expenditure. The T allele of FTO rs1861868 is expected to be related to less leptin and thyrotropin, which is in concordance with the finding of this study.[24] Association of obesity with SNPs of the *FTO* gene has been reported in several populations globally.[25] Specifically, the SNP, rs1861868, is regarded as one of the African-American ethnic-specific polymorphisms of the *FTO* gene.[26] A significant association of rs1861868 with BMI was reported among European populations, Old Order Amish communities with low physical activity,[27] Sorbs from Eastern Germany,[28] and Portuguese children.[29] Interestingly, one regional study of 213 overweight and obese subjects in UAE reported similar finding of association of FTO gene rs1861868 and BMI.[30] However, to date, there is limited information on the relationship between SNP rs1861868 and BMI, and to our knowledge, no previous report on the Saudi population is available.

Many studies revealed that gene polymorphisms with obesity predisposition may vary with differences in the ethnic background,[31] gender variability,[32] or the age of the subjects.[33] In the current study, we observed a protective effect of rs1861868 against obesity in young Saudi females at an odds ratio of 0.4.

1,25 OH-Vitamin D and its receptors (VDR) are widely distributed in many tissues. It is believed that vitamin D plays multiple roles in the body including the development of adipose tissue. VDRs are abundant in adipose tissue, and it has been found that it mediates the action of vitamin D supplements to inhibit adipogenesis in 3T3-L1 preadipocyte cell line.[34] In Animal studies, VDR knockout mice demonstrate resistance to diet-induced obesity.[35] Vitamin D deficiency is highly prevalent in Saudi Arabia and more in females,[36] as it was manifested in this study furthermore, a correlation was found between vitamin D deficiency and obesity in Saudi females.[37] In a local study in Saudi Arabia, it has been found that vitamin D supplements to obese and overweight ladies with vitamin D deficiency enhanced their anthropometric parameters.[38] Therefore, it becomes inevitable to study VDR gene polymorphisms and its association with obesity and body adiposity in young Saudi females. In the current study, we found a protective effect of VDR rs7975232 against obesity. The A allele of VDR rs7975232 showed a protective effect with an Odd's ratio of 0.4563.

Table 2 Allelic Distribution of Study Subjects Before and After Stratification into Groups Based on Their BMI

Gene	SNP	Allele in Total Population (n=131) (Frequency)	BMI ≤ 25 (n=115) (Frequency)	BMI > 25 (n=16) (Frequency)	Odds Ratio	95% Confidence Interval	*p*-value
GNPDA2	rs10938397	A (0.66) G (0.34)	152 (0.58) 78 (0.30)	20 (0.08) 12 (0.05)	Ref 1.1692	0.5435–2.5152	0.6891
TCF7L2	rs10885409	C (0.51) T (0.49)	116 (0.44) 114 (0.45)	18 (0.07) 14 (0.05)	Ref 0.7914	0.3758–1.6667	0.5381
FTO	rs1477196	G (0.81) A (0.19)	186 (0.71) 44 (0.17)	25 (0.10) 7 (0.03)	Ref 1.1836	0.4811–2.9120	0.7136
ADIPOQ	rs1501299	G (0.69) T (0.31)	157 (0.60) 73 (0.28)	24 (0.09) 8 (0.03)	Ref 0.7169	0.3073–1.6722	0.4412
MC4R	rs17782313	T (0.71) C (0.29)	163 (0.62) 67 (0.26)	22 (0.08) 10 (0.04)	Ref 1.1058	0.4970–2.4606	0.8053
ABCA1	rs1800977	A (0.36) G (0.64)	82 (0.31) 148 (0.56)	13 (0.05) 19 (0.07)	Ref 0.8098	0.3805–1.7234	0.584
FTO	rs1861868	C (0.49) T (0.51)	106 (0.40) 124 (0.47)	22 (0.08) 10 (0.04)	Ref 0.3886	0.1761–0.8572	0.0192[a]
VDR	rs2228570	T (0.72) C (0.28)	162 (0.62) 68 (0.26)	26 (0.10) 6 (0.02)	Ref 0.5498	0.2165–1.3959	0.2082
ADIPOQ	rs266729	C (0.73) G (0.27)	166 (0.63) 64 (0.24)	25 (0.10) 7 (0.03)	Ref 0.7263	0.2993–1.7621	0.4794
PFPK	rs6602024	G (0.92) A (0.08)	214 (0.82) 16 (0.06)	27 (0.10) 5 (0.02)	Ref 2.4769	0.8403–7.3011	0.1001
VDR	rs731236	A (0.65) G (0.35)	147 (0.56) 83 (0.32)	23 (0.09) 9 (0.03)	Ref 0.693	0.3064–1.5677	0.3786
VDR	rs7975232	C (0.39) A (0.61)	87 (0.33) 143 (0.61)	24 (0.09) 18 (0.07)	Ref 0.4563	0.2343–0.8888	0.0211[a]

[a]**Note:** [a]Data with significant *p*-value < 0.05.

Our result was in consensus with the findings of an earlier Saudi study by Al-Daghri et al who showed positive association of the minor allele G of VDR SNPs rs731236 and negative association of the minor allele T of VDR SNPs rs1544410 with obesity and inflammatory reaction. The latter VDR SNP variant allele was associated with lower VDR expression.[39] In a Chinese study of 517 healthy adults, VDR rs7975232 gene polymorphisms showed an association with adiposity in the form of body fat percentage and triceps skinfold thickness and not with BMI.

In two-regional studies, one in UAE[30] and the other in Bahrain,[40] both showed no association of VDR polymorphisms of SNPs rs1544410 and rs731236, respectively, with BMI. These SNPs and the SNP examined in our study are in complete linkage disequilibrium. Despite the lack of association of VDR polymorphism in the Emirati study,[30] they have explained a tendency toward higher BMI in females with the A allele of rs1544410, which was further confirmed in a study of females in Qatar which demonstrated a significant association of VDR SNP rs1544410 and BMI in females.[41] Accordingly, we can propose that the association of the VDR polymorphisms and obesity is more pronounced in females, and this can explain the inconsistency in the studies' findings where males and females are combined. Moreover, the protective influence of the selected alleles in VDR polymorphisms might explain another phenomenon described between obesity and vitamin D deficiency in young Saudi females, which stated that obesity might carry a protective effect for

vitamin D deficiency in Saudi females.[42] Hence, these data further indicate the complexity of the interaction between vitamin D, VDR, and obesity which is not easily explained by the current available information and required extensive research and study.

In conclusion, the SNPs, rs1861868 of *FTO* and rs7975232 of *VDR*, showed a protective associative effect against increases in BMI among the study cohort. The two stratified groups of BMI showed significant differences in blood triglycerides, HDL, and vitamin D; however, these parameters were not associated with the SNP polymorphisms. Gene SNPs might vary between males and females and different age groups. Therefore, we believe that despite the small sample size of our study, it gains a strength from being focused on female gender only and young age group. However, we suggest a cross-sectional study that includes a larger number of female subjects from different regions of this country, to confirm this association.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethical and Consents Statement

All participants signed written informed consents following the recommendations of the Institutional Review Board of Imam Abdulrahman Bin Faisal University. The ethical approval certificate is (IRB-2015-01-096).

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no ethical or financial issues or conflicts of interests related to this research.

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