


The Associations Between Vitamin D Receptor BsmI and ApaI Polymorphisms and Obesity in Korean Patients with Type 2 Diabetes Mellitus

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Background: Vitamin D receptor (*VDR*) polymorphisms are associated with osteoporosis, diabetes, immunological diseases, and cancers. However, the association of obesity with *VDR* polymorphisms has shown inconsistent results, and perhaps it depends upon the characteristics of a population. Therefore, we evaluated the association between BsmI (rs1544410) and ApaI (rs7975232) polymorphisms of *VDR* and obesity in Korean patients with type 2 diabetes mellitus (T2DM).

Methods: A total of 506 patients with T2DM participated in the study. Polymerase chain reaction-restriction fragment length polymorphism was used to analyze BsmI and ApaI polymorphisms; the genotypes were presented as BB, Bb, or bb for BsmI and AA, Aa, or aa for ApaI. Obesity was defined using the body mass index (BMI) with a cutoff level of 25 kg/m².

Results: The prevalence of obesity was higher in patients with the bb genotype than in those with BB or Bb genotypes (48.4% vs 33.9%, $P = 0.031$). The mean BMI was 25.2 ± 3.5 kg/m² in patients with bb genotype and 24.1 ± 3.1 kg/m² in patients with BB or Bb genotypes. Patients with Aa or aa genotypes showed a higher prevalence of obesity than patients with AA genotype (47.6% vs 26.1%, $P = 0.043$). Glycemic control parameters and lipid profiles did not show significant differences with either polymorphism.

Conclusion: To our knowledge, this is the first study to assess the association between *VDR* polymorphisms and obesity in Korean patients with T2DM. Further studies in larger populations and multiethnic cohorts are needed to validate our findings.

Keywords: type 2 diabetes mellitus, obesity, vitamin D, vitamin D receptor gene, polymorphism

Introduction

Obesity is a common metabolic disorder and its prevalence is increasing worldwide.¹ In Korea, the prevalence of obesity is rapidly increasing because of westernized diet and sedentary lifestyle; consequently, it has become a serious socioeconomic problem.² According to an obesity fact sheet of Korea, the occurrence of obesity in adults increased from 29.7% in 2009 to 35.7% in 2018.³ Further, obesity is closely associated with increased risks of various chronic metabolic disorders, including diabetes mellitus (DM), hypertension, dyslipidemia, and cardiovascular diseases.¹ According to the diabetes fact sheet in Korea, half of the patients with DM suffer from obesity.⁴ Therefore, the assessment and management of obesity is important to reduce obesity-related complications in a population.

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Obesity results from the interactions between environmental and genetic factors. A previous study reported that genetic factors are responsible for approximately 40–70% of the etiology of obesity.⁵ Moreover, advanced technologies such as genome-wide association studies have led to the identification of some candidate obesity-related genes.⁶

The vitamin D endocrine system plays a central role in bone and calcium homeostasis. Apart from its classical involvement, vitamin D also plays an important role in other metabolic pathways in immune system, cancers, and other endocrine systems.⁷ Although vitamin D deficiency has been associated with obesity,^{8,9} the exact underlying mechanisms leading to obesity have not been fully determined yet; regardless, some possible explanations, such as insulin resistance and lipolysis have been suggested.¹⁰

Vitamin D receptor (VDR; a member of the steroid/thyroid hormone receptor superfamily)¹¹ in complex with vitamin D serves as a transcription activator and regulates gene transcription by binding to vitamin D responsive elements, which are located in the promoter region of the target genes. Therefore, genetic alterations of *VDR* gene can alter gene activation, and lead to various diseases.⁷ Furthermore, *VDR* gene is also expressed in adipocytes and pancreatic beta cells linked to insulin resistance and therefore it might be associated with body composition as well.^{12,13} More than 470 *VDR* polymorphisms have been identified in the *VDR* gene.¹⁴ Among them, the well-established *VDR* polymorphisms are as follows: FokI (rs2228570 C > T), BsmI (rs1544410 A > G), ApaI (rs7975232 C > T), TaqI (rs731236 T > C), and Cdx2 (rs11568820 A > G).¹⁵ A previous study has demonstrated that TaqI and BsmI polymorphisms are associated with obesity in French patients with type 2 diabetes mellitus (T2DM).¹⁶ In another study performed in the Thai population, the Cdx2 polymorphism was associated with a higher waist circumference; however, the four common polymorphisms (FokI, BsmI, ApaI, and TaqI) of the *VDR* gene did not show any association with BMI.¹⁷ In contrast, the VDR BsmI polymorphism has shown a significant association with vitamin D deficiency but not with the obesity phenotype in adolescents residing in Malaysia.⁸

So far, the previous studies have shown inconsistent results pertaining to the associations between *VDR* polymorphisms and obesity. Furthermore, there is a lack of data regarding the same in the Korean population, especially the data of patients with T2DM who have a higher risk of obesity. Therefore, in this study, we evaluated the

association between BsmI and ApaI polymorphisms of the *VDR* gene and obesity in Korean patients with T2DM.

Patients and Methods

Study Design and Participants

This was a single-center, case–control study. Patients who were diagnosed with T2DM and treated at the Chungbuk National University Hospital, Korea, were included in the study. The diagnosis of T2DM was performed by the World Health Organization criteria. Patients with type 1 DM and other types of DM were excluded from this study. The demographic data including age, sex, height, weight, BMI, duration of DM, and family history of DM were collected through reviewing of medical records. Further, the laboratory data, such as fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), C-peptide, insulin, and liver function, kidney function, and lipid metabolism parameters, were also investigated for each patient.

Definition of Obesity

BMI was used to evaluate obesity. The BMI (kg/m^2) was calculated as baseline body weight (kg) divided by the square of the height (m^2). Obesity was defined as a cutoff value of $25 \text{ kg}/\text{m}^2$ BMI, according to Asian-Pacific guidelines.¹⁸

Genotyping of VDR Gene Polymorphic Variants

The two polymorphisms of *VDR*, BsmI and ApaI, were analyzed in this study. Peripheral leukocytes were isolated from ethylenediaminetetraacetic acid-treated whole blood obtained from each patient. Then, the genomic DNA was extracted for subsequent polymerase chain reactions (PCR). All the included T2DM patients were genotyped using PCR-restriction fragment length polymorphism method, for two restriction sites in the *VDR* gene, BsmI and ApaI using specific primer sequences. The following BsmI and ApaI primers were used for amplification: (BsmI) forward 5'-CAA CCA AGA CTA CAA GTA CCG CGT CAG TGA-3' and reverse 5'-AAC CAG CGG AAG AGG TCA AGG G-3'. (ApaI) forward 5'-GGG ACG CTG AGG GAT GGC AGA GC-3' and reverse 5'-GGA AAGGGGTTAGGTTGGACAGGA-3'. The primers of the *VDR* gene were designed based on previous literature.¹⁹ The PCR condition used for BsmI as followed: an initial denaturation of 3 min at 94°C , followed by denaturation of 30 s at 94°C , annealing of 30

s at 62 °C, and extension of 1 min at 72 °C for 30 cycles, and a final extension of 5 min at 72 °C. The PCR condition used for amplification of *Apa1* as follows; 94 °C for 10 min, and 30 cycles using the following temperature profile: 94 °C for 1 min, 62 °C for 1 min, 72 °C for 1 min, and final elongation for 5 min. The PCR products were digested overnight at 37 °C by Fermentas restriction enzymes, and then resolved in 1.5% agarose gel electrophoresis for the genotype analysis. We analyzed three genotypes for each polymorphism: BB, Bb, and bb for BsmI and AA, Aa, and aa for ApaI.

Statistical Analysis

The probability of Hardy–Weinberg equilibrium was tested using the chi-squared test. The data were expressed as the mean \pm standard deviation or as percentages for the categorical variables. The baseline characteristics were compared using Student's *t*-test for the continuous variables and chi-squared test for categorical parameters. Multiple logistic regression analyses were performed to evaluate the relationship between obesity and the following variables: genotype, sex, age, duration of DM, hypertension, dyslipidemia, and HbA1c. All statistical analyses were performed using SPSS for Windows software 22.0 (IBM Corp., Armonk, NY, USA). The significance was set at $P < 0.05$.

Ethics Statement

The study was approved by the International Review Board of Chungbuk National University Hospital (IRB No. 2018–03–034–001) and conducted in accordance with the Declaration of Helsinki. All procedures were carried out with adequate understanding, and all patients gave their informed consent prior to being included in the study.

Results

Clinical Characteristics of the Study

Subjects

A total of 506 patients (266 males and 240 females) were included in this study. The demographic and biochemical characteristics of the patients are shown in [Table 1](#). The mean age and BMI of the patients were 62.6 ± 10.6 years and 25.1 ± 3.5 kg/m², respectively. The mean duration of DM was 14.7 ± 7.5 years and approximately 51% of the patients had a family history of DM. The mean HbA1c and FPG values were $7.6 \pm 1.4\%$ and 145.1 ± 55.4 mg/dL, respectively. The patients were categorized into “obesity group” and “normal weight group” depending upon their BMI

values. The mean BMI was 27.9 ± 2.9 kg/m² in the obesity group and 22.7 ± 1.7 kg/m² in the normal weight group ($P < 0.001$). The proportion of females and prevalence of hypertension and dyslipidemia were higher in the obesity group than in the normal weight group. The duration of DM was shorter in the obesity group than in the normal weight group; however, family history of DM and serum HbA1c levels did not show significant differences between the two groups. The serum triglyceride levels were 172.6 ± 120.3 mg/dL in the obesity group and 146.0 ± 78.0 mg/dL in the normal weight group ($P = 0.004$). Finally, the liver enzymes, including aspartate aminotransferase (AST) and aspartate aminotransferase (ALT), were significantly higher in the obesity group than in the normal weight group.

Various Parameters According to BsmI Genotypes

[Table 2](#) presents various parameters according to BsmI genotypes. Patients with the bb genotype (bb group) showed significantly higher BMI (25.2 ± 3.5 kg/m²) than patients with BB or Bb genotypes (BB + Bb group; 24.1 ± 3.1 kg/m²; $P = 0.034$). However, no significant differences were observed between the glucose metabolism, lipid metabolism, and liver enzyme parameters of the two groups.

Various Parameters According to ApaI Genotypes

The clinical parameters according to ApaI genotypes are shown in [Table 3](#). The mean BMI was 25.1 ± 3.5 kg/m² in patients with the Aa or aa genotypes (Aa + aa group) and 24.1 ± 2.4 kg/m² in patients with AA genotype (AA group); however, the difference was not significant ($P = 0.180$). Other laboratory findings were not significantly different between these two groups.

VDR Polymorphisms and Obesity

The frequencies of BsmI genotypes in the patients were as follows: BB, 2.0% ($n = 10$); Bb, 10.3% ($n = 52$); and bb, 87.7% ($n = 444$). The frequencies of the ApaI genotypes in the patients were as follows: AA, 4.5% ($n = 23$); Aa, 46.8% ($n = 237$); and aa, 48.6% ($n = 246$; [Supplementary Table 1](#)). The bb group was significantly associated with a higher prevalence of obesity compared with the BB + Bb group (48.4% vs 33.9%; $P = 0.031$; [Table 4](#)). Moreover, the Aa + aa group showed a higher prevalence of obesity than the AA group (47.6% vs 26.1%; $P = 0.043$; [Table 4](#)). Furthermore, we performed a logistic regression analysis of the risk factors

Table 1 Baseline Characteristics of the Patients

	Total (n = 506)			Obesity Group (n = 236)			Normal Weight Group (n = 270)			P value
Age (years)	62.6	±	10.6	61.6	±	11.0	63.5	±	10.1	0.040
Sex (male/female)	266	/	240	105	/	131	161	/	109	0.001
Height (cm)	162.2	±	9.1	160.8	±	9.8	163.4	±	8.3	0.002
Body weight (kg)	66.1	±	11.4	72.4	±	11.8	60.7	±	7.7	<0.001
Maximum body weight (kg)	74.1	±	12.7	80.4	±	12.3	69.7	±	11.1	<0.001
Body mass index (kg/m ²)	25.1	±	3.5	27.9	±	2.9	22.7	±	1.7	<0.001
Duration of DM (years)	14.7	±	7.5	13.7	±	7.0	15.5	±	7.9	0.008
Family history of DM (n, %)	258		(51.0)	114		(48.3)	144		(53.3)	0.209
Hypertension (n, %)	339		(67.0)	172		(72.9)	167		(61.9)	0.008
Dyslipidemia (n, %)	291		(57.5)	150		(63.6)	141		(52.2)	0.010
FPG (mg/dL)	145.1	±	55.4	138.5	±	43.9	150.9	±	63.2	0.010
PP2 (mg/dL)	208.0	±	77.4	210.9	±	79.8	205.4	±	75.2	0.448
HbA1c (%)	7.6	±	1.4	7.6	±	1.5	7.5	±	1.3	0.739
C-peptide (ng/mL)	2.6	±	2.0	2.8	±	1.9	2.4	±	2.1	0.034
Insulin (μU/mL)	13.1	±	20.2	14.9	±	27.3	11.6	±	11.0	0.086
HOMA-IR	4.8	±	8.7	5.3	±	11.9	4.4	±	4.7	0.273
Total cholesterol (mg/dL)	170.3	±	33.7	170.4	±	33.4	170.1	±	34.0	0.916
Triglycerides (mg/dL)	158.4	±	100.8	172.6	±	120.3	146.0	±	78.0	0.004
HDL-cholesterol (mg/dL)	45.5	±	11.9	44.2	±	11.2	46.6	±	12.3	0.023
LDL-cholesterol (mg/dL)	96.5	±	28.3	97.4	±	28.0	95.8	±	28.6	0.526
AST (IU/L)	27.7	±	14.3	29.4	±	15.8	26.2	±	12.7	0.014
ALT (IU/L)	31.0	±	22.8	33.2	±	22.3	29.0	±	23.2	0.036
BUN (mg/dL)	16.5	±	8.4	16.4	±	8.6	16.5	±	8.2	0.843
Creatinine (mg/dL)	1.1	±	0.8	1.1	±	0.7	1.2	±	0.9	0.343
Urine ACR (mg/g)	122.5	±	330.9	147.8	±	361.0	98.9	±	300.0	0.146

Notes: Data are expressed as mean ± standard deviation (SD). The P values were calculated using Student's t-test for continuous data and chi-square test for categorical data between the obesity and normal weight groups.

Abbreviations: DM, diabetes mellitus; FPG, fasting plasma glucose; PP2, post-prandial 2 h glucose; HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment for insulin resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; ACR, albumin to creatinine ratio.

associated with obesity, and the related data are shown in Table 5. The non-B allele of BsmI was significantly associated with obesity, and the odds ratio (OR) was 2.132 ($P = 0.014$). The a-allele of ApaI also showed a significantly high risk of obesity (OR was 2.711, $P = 0.048$). Among other parameters, female sex, hypertension, and dyslipidemia were identified as the risk factors for obesity.

Discussion

In this study, we investigated the association between BsmI and ApaI polymorphisms in *VDR* gene and obesity in Korean patients with T2DM. We found that patients with T2DM carrying the bb genotype of *VDR* BsmI polymorphism were associated with higher BMI and increased risk of obesity than the BB or Bb genotypes. Although patients with the Aa or aa genotypes did not show significant differences in BMI (compared with the patients with AA genotype), the a-allele showed a significant correlation with obesity in the study population.

Recently, non-classical roles of vitamin D such as regulation of hormone secretion, immune function, cellular proliferation, and differentiation have emerged.²⁰ Interestingly, previous studies have associated the effects of vitamin D with obesity. For instance, in a study of mixed-ethnicity participants, the individuals with obesity and those who were overweight showed a significant inverse correlation of serum 25-hydroxyvitamin D (25(OH)D) level with body weight, BMI, and waist circumference.²¹ Another study demonstrated that vitamin D affects energy expenditure through the upregulation of leptin gene expression.²² Further, the previous meta-analysis has reported that vitamin D deficiency is associated with obesity.²³ Moreover, vitamin D improves insulin sensitivity; therefore, vitamin D deficiency may lead to the development of T2DM.^{24,25} Thus, these studies imply that vitamin D may play a possible role in obesity and obesity-related metabolic disorders.

Vitamin D binds to VDR to induce transcription pathways and gene expression. Therefore, genetic alterations of the *VDR*

Table 2 Various Parameters According to BsmI Genotypes

	BB + Bb (n = 62)			bb (n = 444)			P value
Age (years)	63.7	±	10.9	62.5	±	10.5	0.415
Height (cm)	161.7	±	9.4	162.2	±	9.1	0.652
Body weight (kg)	63.0	±	10.1	66.6	±	11.5	0.023
Body mass index (kg/m ²)	24.1	±	3.1	25.2	±	3.5	0.013
FPG (mg/dL)	147.6	±	75.0	144.8	±	52.2	0.713
PP2 (mg/dL)	205.2	±	72.6	208.4	±	78.1	0.769
HbA1c (%)	7.8	±	1.6	7.5	±	1.4	0.172
C-peptide (ng/mL)	2.5	±	1.8	2.6	±	2.1	0.743
Insulin (μIU/mL)	11.9	±	8.8	13.3	±	21.4	0.645
HOMA-IR	4.4	±	3.4	4.9	±	9.3	0.720
Total cholesterol (mg/dL)	171.3	±	37.8	170.1	±	33.2	0.795
Triglycerides (mg/dL)	140.5	±	76.1	160.9	±	103.6	0.142
HDL-cholesterol (mg/dL)	47.9	±	12.4	45.2	±	11.8	0.101
LDL-cholesterol (mg/dL)	96.7	±	31.4	96.5	±	27.9	0.948
AST (IU/L)	26.4	±	12.7	27.9	±	14.5	0.450
ALT (IU/L)	28.9	±	21.6	31.2	±	23.0	0.459

Notes: Data are expressed as mean ± standard deviation (SD). The P values were calculated using Student's *t*-test.

Abbreviations: FPG, fasting plasma glucose; PP2, post-prandial 2 h glucose; HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment for insulin resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 3 Various Parameters According to ApaI Genotypes

	AA (n = 23)			Aa + aa (n = 483)			P value
Age (years)	65.1	±	10.3	62.5	±	10.6	0.244
Height (cm)	161.2	±	8.5	162.2	±	9.2	0.606
Body weight (kg)	62.8	±	7.8	66.3	±	11.5	0.149
Body mass index (kg/m ²)	24.1	±	2.4	25.1	±	3.5	0.180
FPG (mg/dL)	163.6	±	39.9	144.2	±	55.9	0.102
PP2 (mg/dL)	214.8	±	43.2	207.7	±	78.5	0.505
HbA1c (%)	8.1	±	2.1	7.5	±	1.3	0.202
C-peptide (ng/mL)	3.1	±	4.0	2.6	±	1.9	0.589
Insulin (μIU/mL)	30.9	±	80.6	12.2	±	9.8	0.302
HOMA-IR	12.5	±	34.7	4.4	±	4.3	0.301
Total cholesterol (mg/dL)	170.0	±	32.0	170.3	±	33.8	0.965
Triglycerides (mg/dL)	154.1	±	61.6	158.7	±	102.4	0.832
HDL-cholesterol (mg/dL)	43.1	±	11.2	45.6	±	11.9	0.322
LDL-cholesterol (mg/dL)	100.3	±	22.3	96.3	±	28.6	0.511
AST (IU/L)	24.7	±	7.4	27.9	±	14.5	0.309
ALT (IU/L)	29.2	±	13.6	31.0	±	23.2	0.703

Notes: Data are expressed as mean ± standard deviation (SD). P values were calculated using Student's *t*-test.

Abbreviations: FPG, fasting plasma glucose; PP2, post-prandial 2 h glucose; HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment for insulin resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

gene may hinder the gene activation and functions.⁷ As *VDR* expression has been found in adipose tissues, the association between obesity and *VDR* polymorphisms has also been investigated.^{8,9,16} In a study performed in French subjects with T2DM, BsmI and TaqI polymorphisms were associated with obesity; whereas ApaI did not show any significant correlation.¹⁶ This is in accordance with the results of our study. Another study showed that BsmI polymorphism was

significantly associated with a higher BMI.²⁶ Interestingly, conflicting results have been observed with respect to the association of obesity and ApaI polymorphisms. In a Chinese population, positive associations were observed between ApaI polymorphism and obesity (assessed by body fat percentage and skinfold thickness).²⁷ In contrast, these associations were not observed in another study, which involved a study group of young Chinese males.²⁸ In adolescents and young adults from

Table 4 Association Between Genotypes of *VDR* Polymorphisms and Obesity

	Obesity (n, %)	Normal (n, %)	P value
<i>BsmI</i>			
BB + Bb (n = 62)	21 (33.9)	41 (66.1)	0.031
bb (n = 444)	215 (48.4)	229 (51.6)	
<i>Apal</i>			
AA (n = 23)	6 (26.1)	17 (73.9)	0.043
Aa + aa (n = 483)	230 (47.6)	253 (52.4)	

Note: P values were calculated by chi-square test.

Table 5 Logistic Analysis of Risk Factors to Determine Their Association with Obesity According to *VDR* Polymorphisms

	OR (95% CI)	P value
Non-B allele of <i>BsmI</i>	2.132 (1.164–3.903)	0.014
a-allele of <i>Apal</i>	2.711 (1.007–7.302)	0.048
Sex	2.082 (1.425–3.041)	0.001
Age ^a	0.854 (0.710–1.026)	0.093
Duration of DM ^b	0.655 (0.509–0.844)	0.001
Hypertension	2.168 (1.425–3.299)	0.001
Dyslipidemia	1.540 (1.053–2.253)	0.026
HbA1c ^c	1.030 (0.894–1.186)	0.686

Notes: ^aRisk associated with a 10 y increase in age. ^bRisk associated with a 10 y increase in duration of DM. ^cRisk associated with a 1% increase in HbA1c.

Abbreviations: OR, odds ratio; CI, confidence interval; HbA1c, hemoglobin A1c; DM, diabetes mellitus.

Spain and Malaysia, no significant associations were observed between the *VDR* gene polymorphisms and obesity-related phenotypes.^{8,9} In recently published data, *Apal* polymorphism appears to be correlated with overweightness and obesity in Chinese children.²⁹ There are many ongoing studies and new SNP in *VDR* gene (rs3847987) have been shown an association with obesity phenotypes.³⁰ Thus, to date, inconsistent results have been observed with respect to *VDR* polymorphisms and obesity. We believe that these differences may be attributed to different parameters such as sex, age, ethnicity, and behavioral characteristics. Further studies are needed and obesity is closely related to the development of T2DM and has been attributed to the progression of diabetic complications via various mechanisms.^{31,32} Therefore, it is possible that *VDR* polymorphisms, which are related to obesity, may be responsible for these complications in patients with T2DM. Previous studies have reported an association between *VDR* polymorphisms and diabetic complications.^{33,34} Results from the logistic regression analysis showed that *BsmI* and *Apal* polymorphisms were strong risk factors for obesity. Thus, our data imply a possible effect of *VDR* polymorphisms on obesity in patients

with T2DM, which is in accordance with the results of previous studies.^{16,26}

To our knowledge, this is the first study to assess the association between the *VDR* polymorphisms and obesity in Korean patients with T2DM. The present study was performed in relatively homogenous subjects with similar ethnicities and disease statuses. However, there are several limitations of our study. First, we did not evaluate the serum 25(OH)D level, therefore, we could not determine whether the patients had vitamin D deficiency. Second, the clinical characteristics related to obesity such as physical activity and diet were not evaluated. Moreover, other parameters assessing obesity including waist circumference and body composition could not obtain due to the retrospective study design. Third, there was no control group of individuals without T2DM. Finally, not all *VDR* polymorphisms were investigated. Thus, we cannot rule out that other *VDR* polymorphisms may also be associated with obesity in the studied population.

In conclusion, the present study demonstrated that *BsmI* and *Apal* polymorphisms of the *VDR* gene were associated with obesity in Korean patients with T2DM. However, further studies with larger multiethnic cohorts and experimental models are required to validate our results.

Presentation

Parts of this study were presented at the International Congress on Obesity and Metabolic Syndrome, Seoul, Korea, 6–9 September 2018.

Ethical Statement

All retrospective data involving human participants were in accordance with the ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval was obtained by the Local Ethics Committee.

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; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. Everyone participated in the final approval of the manuscript.

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