Letter to the Editor

Interactions of Vitamin D Receptor Polymorphisms with Hypertriglyceridemia and Obesity in Chinese Individuals Susceptible to Hypertension and Diabetes Comorbidity*

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Hypertension (HTN) and type 2 diabetes mellitus (T2DM) are interconnected metabolic diseases[1,2] that considerably increase susceptibility to microvascular and macrovascular disorders. In many patients, HTN and diabetes comorbidity (HDC) is caused by mutual pathogenic pathways, such as endothelial dysfunction, atherosclerosis, oxidative stress, and vascular inflammation[1]. Hence, it is crucial to identify risk factors, especially ones that can be treated, for HDC and provide essential information for further health management. Based on previous research, generalized and abdominal obesity are linked to a higher risk of HDC. In individuals with obesity, adipocyte dysfunction can lead to vascular and systemic insulin resistance and renin-angiotensin-aldosterone system and sympathetic nervous system dysfunction[2]. A possible indicator of HDC is dyslipidemia, which includes hypertriglyceridemia (HTG), and abnormal levels of high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and total cholesterol (TC).

In addition to modifiable indicators of HDC, including unhealthy diet, low levels of physical activity, and overweight or obesity, nonmodifiable risk factors, such as genetic polymorphisms and family history, should be addressed. One example is the vitamin D receptor (*VDR*) gene, which consists of 14 exons and is situated on human chromosome 12q13.11. Previous studies[3] found that *VDR* mutations may hasten the disease process of HTN and T2DM. However, few studies have focused on the relationship between *VDR* single nucleotide polymorphisms (SNPs) and HDC predisposition. Therefore, this study aimed to assess the potential correlations between *VDR* SNPs, HTG, abnormal waist-hip ratio (WHR), and HDC to show the physiological relevance of the combined effects. This can aid in the development of new treatment approaches to prevent HDC in Chinese populations.

Stratified random cluster sampling was used to recruit a total of 1,364 individuals in this cross-sectional study (Figure 1). The Zhengzhou University Life Science Ethics Committee approved the study protocol. We collected demographic and anthropometric data from the subjects and conducted a biochemical analysis (Supplementary Table S1, available in www.besjournal.com). We chose four associated SNPs based on the selection criteria of the minor allele frequency (MAF) > 0.01, linkage disequilibrium (r^2 > 0.8), and position in major gene functional and nonfunctional areas (rs2228570, rs3847987, rs2239179, and rs739837). Assuming additive, dominant, and recessive models of inheritance, logistic regression models were used to appraise the associations between *VDR* or metabolic factors (i.e., obesity and dyslipidemia) and HDC susceptibility. In the dominant model, the additive interaction model was applied to evaluate the effect of interaction between gene and

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environmental factors on HDC risk.

Multiple logistic regression analysis showed that rs3847987 and rs7398379 polymorphisms were associated with HDC risk after adjusting for age, sex, smoking, drinking, and family history of diabetes and HTN (Table 1). Participants with the "CA" and "AA" genotypes of rs3847987 were more likely to develop HDC (1.559, 95% *CI* 1.133–2.146 and 1.972, 95% *CI* 1.043–3.730) when compared with the "CC" genotype. Furthermore, subjects with the "GT+TT" genotype of rs7398379 had higher HDC susceptibility compared with the "GG" genotype (*OR* = 1.451, 95% *CI* 1.072–1.963). Our findings are in line with numerous studies[3,4] that found a correlation between *VDR* mutations and an increase in the prevalence of T2DM and HTN. The 3' untranslated region of *VDR* is where the SNPs rs3847987 and rs739837 are both found. This region has little effect on the amino acid sequence and is unlikely to affect gene function. However, through the modification of mRNA stability, this region is implicated in the control of gene expression. Variations in rs739837 may affect the levels of *VDR* mRNA and protein, which may be linked to a decreased risk of developing diabetes.

In Table 1, we found that rs2228570 polymorphisms were not associated with HDC risk after adjusting for confounding factors. The rs2228570 is located at the 5' end of the gene, close to the promoter region. The T→C mutation at this position will result in a mutation of the first start codon from ATG to ACG, which may interfere with the binding effectiveness of vitamin D and *VDR* and restrict the complete function of vitamin D. Ultimately, this may affect the course of T2DM by influencing the function of vitamin D. However, rs2228570 and HDC were not found to be associated in this study. One study[5] discovered that the rs2228570 was not related to diabetes in the Chinese Han population. Conversely, another study[6] indicated an inverse association between rs2228570 and a greater chance of developing HTN. Thus, further research is required to establish the correlation between rs2228570 and HDC. Another gene, Rs2239179, is located in the *VDR* coding region, where the variation from A to G may impact the amino acid sequence. Similarly, we discovered no connection between rs2239179 and HDC risk.

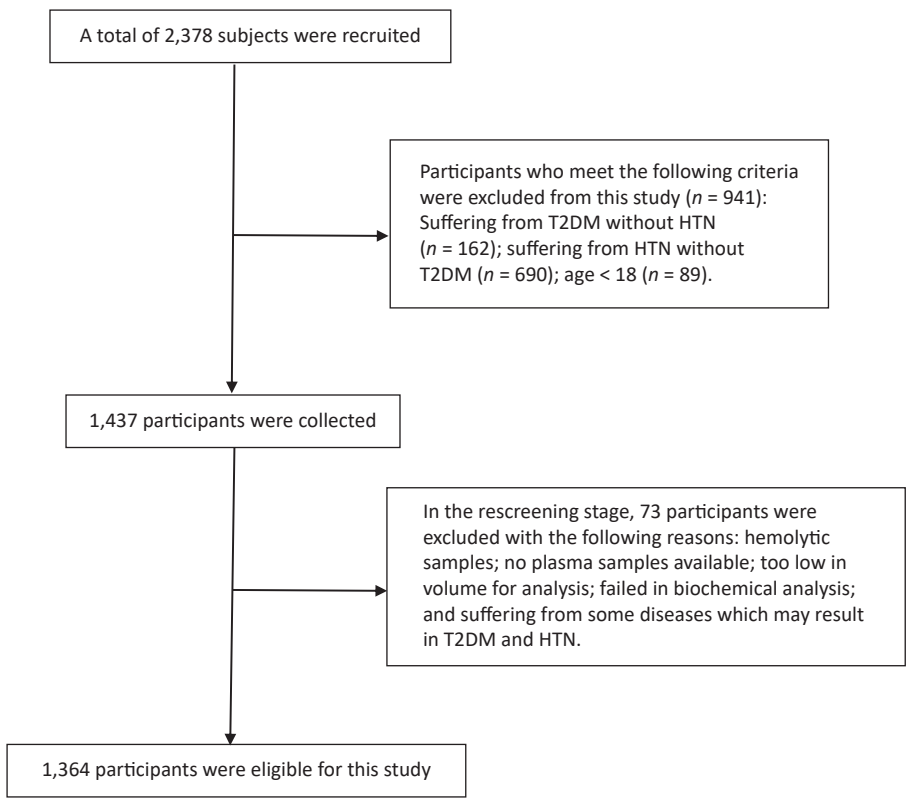

Figure 1. Flow diagram of the screening process. A total of 1,014 subjects who met the exclusion criteria were excluded, and 1,364 participants were finally included in this study. HTN, Hypertension; T2DM, type 2 diabetes mellitus.

Future research should verify the findings and investigate the mechanisms of activation.

We used logistic regression analysis to examine the relationships between metabolic indicators (TC, TG, HDL-C, BMI, WC, and WHR) and HDC risk (Supplementary Table S2, available in www.besjournal.com). Except for the level of HDL-C, significant associations between other indicators and HDC susceptibility were found after adjusting for confounding factors. Compared with participants with normal weight, those with overweight and obesity presented an elevated risk of HDC (*OR* = 3.396, 95% *CI* 2.258–5.106 and *OR* = 7.553, 95% *CI* 4.799–11.889, respectively). HDC susceptibility was positively correlated to TG level with an *OR* of 3.673 (95% *CI* 2.676–5.041). Similarly, abnormal WC, WHR, and TC increased the risk of HDC (*OR* = 4.368 [3.004–6.352], 4.138 [2.724–6.284], and 1.710 [1.230–2.378], respectively; $P < 0.001$). Consistent with other findings[7], high blood pressure and decreased sensitivity to insulin are linked to complicated and uncomplicated obesity.

Lipolysis, which triggers the release of free fatty acids and causes metabolic irregularities, oxidative stress, and vascular dysfunction, is not prevented by postprandial hyperinsulinemia. In earlier research, abdominal obesity increased the risk of HDC more than general obesity, presumably due to the significant link between visceral and abdominal obesity[8]. Two mechanisms may be at play in the connection between obesity, metabolic syndrome, and their sequelae[9]. First, increased free fatty acids

Table 1. Genotypic distribution of vitamin D receptor polymorphisms and their association with HDC risk

SNPs	No-HDC	HDC	χ^2	*P*	*OR* (95% *CI*)[a]	*P*	HWE
rs2228570			0.276	0.871			0.267
TT	236 (20.92%)	53 (22.46%)			1		
CT	580 (51.42%)	119 (50.42%)			0.874 (0.597–1.279)	0.487	
CC	312 (27.66%)	64 (27.12%)			0.766 (0.497–1.182)	0.228	
TT/CT+CC					0.835 (0.582–1.198)	0.328	
TT+CT/CC					0.843 (0.599–1.186)	0.327	
rs3847987			10.108	0.006			0.805
CC	725 (64.27%)	128 (54.24%)			1		
CA	357 (31.65%)	91 (38.56%)			1.559 (1.133–2.146)	0.006	
AA	46 (4.08%)	17 (7.20%)			1.972 (1.043–3.730)	0.037	
CC/CA+AA					1.610 (1.186–2.185)	0.002	
CC+CA/AA					1.664 (0.893–3.100)	0.109	
rs2239179			0.095	0.954			0.342
AA	685 (60.73%)	144 (61.02%)			1		
AG	395 (35.02%)	83 (35.17%)			0.940 (0.683–1.294)	0.706	
GG	48 (4.26%)	9 (3.81%)			0.946 (0.433–2.068)	0.889	
AA/AG+GG					0.941 (0.691–1.281)	0.699	
AA+AG/GG					0.967 (0.446–2.097)	0.932	
rs739837			6.232	0.044			0.691
GG	637 (56.47%)	113 (47.88%)			1		
GT	418 (37.06%)	102 (43.22%)			1.412 (1.029–1.937)	0.033	
TT	73 (6.47%)	21 (8.90%)			1.681 (0.954–2.962)	0.072	
GG/GT+TT					1.451 (1.072–1.963)	0.016	
GG+GT/TT					1.441 (0.834–2.488)	0.190	

Note. *CI*, confidence interval; HWE, Hardy-Weinberg equilibrium; *OR*, odds ratio. [a]Adjusted for age, sex, smoking, alcohol drinking, family history of HTN, and family history of diabetes.

may cause insulin resistance by favoring highly sensitive visceral adipose tissue lipolysis in hypertrophied areas. Second, higher levels of free testosterone and lower levels of sex hormone-binding globulin may stimulate the accumulation of belly fat and decrease the proportion of insulin extracted by the liver. Consequently, the increased visceral fat depot that drains free fatty acids into the portal vein and systemic circulation may influence the relationship between adiposity and HDC. In other words, weight control is of great importance for patients with T2DM and HTN, especially those with abdominal obesity.

As a dietary factor, vitamin D is also crucial for the development of HDC. Theoretically, vitamin D can affect insulin sensitivity in several ways. The expression of insulin receptors appears to be stimulated by $1,25(OH)_2D$ and, therefore, influences insulin sensitivity. In insulin-responsive cells, $1,25(OH)_2D$ enters and interacts with *VDR*, boosting the transcriptional activity of insulin receptor genes and the number of insulin receptors overall without changing their affinity. As $1,25(OH)_2D$ activates the peroxisome-activated receptor delta, it may also improve insulin sensitivity. Patients with 25(OH)D levels of < 21 ng/mL in the National Health and Nutrition Examination Survey had a 1.3-fold increased risk of developing HTN than those with levels of ≥37 ng/mL. Currently, no experimental trials support a correlation between vitamin D intervention and HDC risk. Additionally, we were unable to detect a significant relationship between 25(OH)D3 level and HDC risk (Supplementary Table S2).

Both HTN and T2DM are chronic systemic disorders caused by the combination of various genes and environmental risk factors[10]. In both T1DM and T2DM, only a minority of cases are caused by either genetic or environmental factors alone. Moreover, 95% of these cases are multifactorial, induced by the interaction of environmental, genetic, and behavioral risk factors. Individuals with genetic susceptibility are more likely to develop T2DM owing to metabolic factors, such as obesity, reduced physical activity, high-sucrose diet, and low physical activity. In this study, the interaction of *VDR* with obesity and dyslipidemia was analyzed (Supplementary Table S3, available in www.besjournal.com), and we found that the interaction of rs3847987 with TG and WHR can increase the risk of developing HDC.

HDC risk in participants with HTG having the "CC" allele of rs3847987 increased by 203% (*OR* = 3.026, 95% *CI* 1.913–4.788; *P* < 0.001), whereas HDC risk in those carrying the mutational allele of rs3847987 increased by 675% (*OR* = 7.749, 95% *CI* 4.685–12.817; *P* < 0.001, Table 2). For participants

Table 2. Interactions between *VDR* variants and HTG and abdominal obesity and HDC risk

SNPs	Status	*OR* (95% *CI*)	*P*
rs3847987			
CC	Normal TG[a]	1	
AA+CA	Normal TG	1.338 (0.911−1.966)	0.137
CC	HTG	3.026 (1.913−4.788)	< 0.001
AA+CA	HTG	7.749 (4.685−12.817)	< 0.001
RERI		2.666 (0.045−5.286)	
AP		0.475 (0.183−0.766)	
SIrs3847987		2.367 (1.106−5.065)	
CC	Non-abdominal obesity	1	
AA+CA	Non-abdominal obesity	0.849 (0.382−1.890)	0.689
CC	abdominal obesity[b]	3.028 (1.800−5.094)	< 0.001
AA+CA		5.742 (3.355−9.828)	
RERI	abdominal obesity	2.544 (0.534−4.554)	< 0.001
AP		0.412 (0.179−0.644)	
SI		1.964 (1.137−3.392)	

Note. RERI, relative excess risk due to interaction; AP, attributable proportion due to interaction; SI, synergy index. [a]Normal TG (< 2.26 mmol/L); HTG (≥ 2.26 mmol/L). [b]Abdominal obesity was diagnosed as having a waist-hip ratio (WHR) of ≥ 0.90 for men and ≥ 0.85 for women.

with abdominal obesity, those who carried "CC" or "TT+TC" of rs3847987 showed an increased risk of HDC by 203% (*OR* = 3.028, 95% *CI* 1.800–5.094; *P* < 0.001) or 474% (*OR* = 5.742, 95% *CI* 3.355–9.828; *P* < 0.0001) compared to wild-type gene carriers with regular WHR. The additive interaction analysis provided more proof that *VDR*-HTG or gene-WHR interaction may be a crucial factor in the rising HDC susceptibility among the Chinese population. Although we conducted a gene-environment interaction study, future research should confirm the interactions of other genes and environmental variables on HDC risk.

No potential conflicts of interest were disclosed.

SUN Hua Lei and ZHAO Tong substantially contributed to the study design, gathered the data, and wrote the manuscript; ZHANG Dong Dong conducted data collection and established the methodology; FENG Ming Ming, XU Ze, HUANG Hao Yue, and ZHANG Luo Ya conducted data collection; LI Wen Jie, LI Xing, and DUAN Jia Yu supervised the study and contributed to data curation. Li Jia and DUAN Jia Yu reviewed and revised the manuscript.

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Supplementary Table S1. Demographic and clinical characteristics of the study participants

Characteristics	Non-HDC (*n* = 1,128)	HDC (*n* = 236)	*P*
Male	513 (45.48%)	82 (34.75%)	0.003
Age (years)	48.00 (37.00–60.00)	61.00 (54.50–68.00)	< 0.001
Smoking	386 (34.22%)	60 (25.42%)	0.009
Alcohol drinking	252 (22.42%)	33 (14.04%)	0.004
Family history of diabetes	214 (18.97%)	43 (18.22%)	0.932
Family history of hypertension	391 (34.66%)	83 (35.17%)	0.833
FPG (mmol/L)	4.66 (4.14–5.15)	8.37 (6.59–10.62)	< 0.001
SBP (mm Hg)	116.67 (108.33–123.33)	143.17 (133.33–153.33)	< 0.001
DBP (mm Hg)	75.67 (70.00–80.00)	86.00 (80.00–91.67)	< 0.001
TC (mmol/L)	4.27 (3.68–4.97)	4.71 (4.07–5.52)	< 0.001
TG (mmol/L)	1.14 (0.76–1.79)	1.87 (1.26–2.94)	< 0.001
HDL-C (mmol/L)	1.24 (1.04–1.46)	1.17 (1.00–1.39)	0.018
LDL-C (mmol/L)	2.40 (1.89–2.93)	2.57 (2.00–3.17)	0.028
BMI (kg/m^2)	24.16 (21.65–26.60)	26.86 (24.93–28.98)	< 0.001
WHR	0.88 (0.83–0.93)	0.94 (0.90–0.98)	< 0.001
WC (cm)	83.00 (75.90–90.50)	92.00 (86.00–98.00)	< 0.001
25(OH)D3			0.080
VDD (< 20 ng/mL)	550 (48.76%)	133 (56.36%)	
VDI (20–30 ng/mL)	279 (24.73%)	54 (22.88%)	
VDS (> 30 ng/mL)	299 (26.51%)	49 (20.76%)	

Note. HDC, hypertension and diabetes comorbidity; FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BMI, body mass index; WHR, waist–hip ratio; WC, waist circumference; VDD, vitamin D deficiency; VDI, vitamin D insufficiency; VDS, vitamin D sufficiency. Data are given as the mean ± SD, *n* (%) or median (interquartile range), with the significance of differences between groups evaluated using *t* test, the χ^2 test, or Wilcoxon ranks teat, respectively.

Supplementary Table S2. Results of association analysis of metabolic indicators with HDC risk

Indicator	*OR* (95% *CI*)[a]	*P*
BMI		
< 18.50	0.873 (0.192−3.974)	0.861
18.50−23.99	1	
24.00−27.99	3.396 (2.258−5.106)	< 0.001
≥ 28.00	7.553 (4.799−11.889)	< 0.001
HTG[b]	3.673 (2.676−5.041)	< 0.001
Abnormal WC[c]	4.368 (3.004−6.352)	< 0.001
Abnormal WHR[c]	4.138 (2.724−6.284)	< 0.001
Abnormal TC[d]	1.710 (1.230−2.378)	0.001
Abnormal HDL-C[e]	1.352 (0.972−1.879)	0.073
25(OH)D3[f]		
VDD (< 20)	1.204 (0.820−1.768)	0.343
VDI (20−30)	0.827 (0.527−1.299)	0.411
VDS (> 30)	1	

Note. [a]Adjusted for age, sex, smoking, alcohol drinking, family history of HTN, and family history of diabetes. [b]HTG, hypertriglyceridemia (TG ≥ 2.26 mmol/L). [c]WC > 85 cm or waist-hip ratio WHR ≥ 0.90 for men and > 80 cm or ≥ 0.85 for women are defined as abnormal WC and abnormal WHR. [d] TC ≥ 5.18 mmol/L was determined to be abnormal TC. [e]HDL-C < 1.04 mmol/L was defined as abnormal HDL-C. [f]VDD-vitamin D deficiency (< 20 ng/mL); VDI-vitamin D insufficient (20−30 ng/mL); VDS-vitamin D sufficient (≥ 30 ng/mL).

Supplementary Table S3. The interactions between *VDR* variants and environment indicators on the HDC risk

SNPs	RERI	AP	SI
rs2228570			
BMI	−3.27 (−9.03−2.48)	−0.42 (0.99−0.14)	0.67 (0.44−1.04)
WC	−2.39 (−6.19−1.40)	−0.44 (−1.04−0.17)	0.65 (0.40−1.06)
WHR	−0.80 (−3.51−1.90)	−0.16 (−0.67−0.35)	0.83 (0.49−1.41)
TC	−0.04 (−1.59−1.50)	−0.02 (−0.76−0.72)	0.96 (0.25−3.71)
TG	0.61 (−1.43−2.65)	0.19 (−0.41−0.79)	1.37 (0.43−4.41)
HDL-C	−0.08 (−0.99−0.82)	−0.11 (−1.34−1.12)	1.49 (0.01−281.05)
25(OH)D3	0.18 (−0.53−0.88)	0.18 (−0.61−0.97)	0.13 (0.01−1.91)
rs3847987			
BMI	−0.58 (−3.28−2.12)	−0.08 (−0.48−0.31)	0.91 (0.60−1.39)
WC	0.96 (−1.04−2.97)	0.17 (−0.15−0.48)	1.25 (0.78−2.01)
WHR	2.54 (0.53−4.55)	0.41 (0.18−0.64)	1.96 (1.14−3.39)
TC	1.33 (−0.04−2.69)	0.43 (0.11−0.75)	2.76 (0.85−8.97)
TG	2.67 (0.05−5.29)	0.48 (0.18−0.77)	2.37 (1.11−5.07)
HDL-C	−1.10 (−3.12−0.93)	−0.42 (−1.13−0.29)	0.60 (0.30−1.19)
25(OH)D3	−0.59 (−1.97−0.78)	−0.28 (−0.92−0.36)	0.65 (0.29−1.46)
rs2239179			
BMI	−1.03 (−3.05−0.98)	−0.23 (−0.69−0.23)	0.77 (0.49−1.23)
WC	−1.47 (−3.63−0.69)	−0.32 (−0.81−0.18)	0.71 (0.45−1.13)
WHR	−2.82 (−6.23−0.60)	−0.43 (−0.94−0.07)	0.66 (0.44−0.99)
TC	−1.33 (−2.68−0.01)	−0.79 (−1.81−0.24)	0.34 (0.10−1.21)
TG	−0.34 (−2.30−1.61)	−0.10 (−0.72−0.51)	0.87 (0.40−1.91)
HDL-C	0.01 (−0.88−0.91)	0.01 (−0.63−0.65)	1.03 (0.10−10.48)
25(OH)D3	0.17 (−0.55−0.89)	0.13 (−0.41−0.66)	1.93 (0.02−152.78)
rs739837			
BMI	−1.44 (−4.58−1.71)	−0.19 (−0.60−0.23)	0.82 (0.55−1.22)
WC	0.58 (−1.48−2.64)	0.10 (−0.23−0.43)	1.13 (0.72−1.77)
WHR	1.70 (−0.22−3.63)	0.28 (0.01−0.55)	1.50 (0.92−2.45)
TC	1.10 (−0.18−2.38)	0.38 (0.03−0.73)	2.40 (0.74−7.76)
TG	2.01 (−0.37−4.38)	0.38 (0.05−0.72)	1.91 (0.92−3.97)
HDL-C	−0.10 (−2.96−0.97)	−0.36 (−1.01−0.28)	0.64 (0.34−1.20)
25(OH)D3	−0.58 (−1.90−0.74)	−0.28 (−0.88−0.33)	0.66 (0.31−1.40)

Note. SNPs: Single nucleotide polymorphisms; RERI, relative excess risk due to interaction; AP, attributable proportion due to interaction; SI, synergy index; BMI, body mass index; WC, waist circumference; WHR, waist–hip ratio; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol.