



RESEARCH ARTICLE

Role of VDR gene polymorphisms and vitamin D levels in normal and overweight patients with PCOS

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Abstract. Polycystic ovary syndrome (PCOS) is one of the most common endocrine diseases in women. In recent years, the effects of vitamin D receptor (VDR) gene variants and VitD3 levels on clinical features of PCOS have been frequently described. In this study, we aimed to determine the relationship between VDR *Apal*, *Taq1* and *Cdx2* gene variants and VitD3 levels in PCOS patients. Patients were divided into two groups: BMI<25 and BMI≥25. VDR genotypes were determined by real-time polymerase chain reaction (PCR) and serum VitD3 levels were examined by ELISA. We observed that frequencies of the *Apal* AC genotype, C allele and *Cdx2* T allele are increased in the BMI≥25 group compared to BMI<25 group. Also, the *Apal* C allele, *Taq1* AA genotype and A allele, *Cdx2* CC genotype and C allele are associated with increased triglyceride, total cholesterol, LDL-cholesterol levels in patients with BMI≥25. When examining the relationship between VitD3 levels and clinical profiles in all PCOS patients, regardless of BMI distinction, it is determined that there is a positive correlation between LDL-cholesterol and testosterone levels. The present findings suggest that VDR variants are one of the most important risk factors for PCOS, especially for patients with BMI≥25.

Keywords. vitamin D receptor; 1,25-dihydroxyvitamin D3; polycystic ovary syndrome; lipids.

Introduction

Polycystic ovary syndrome (PCOS), the most common gynecological endocrinopathy characterized by chronic anovulation and hyperandrogenism, is a multigenic disease. In recent years, several genes have been involved in the insulin signalling pathway (Hahn *et al.* 2006), and gonadotropin secretion (Li *et al.* 2011). Vitamin D is a steroid hormone and its continuity in the organism turns into an active formula as 1,25-dihydroxyvitamin D3 (VitD3) after different synthesis stages. There are many articles on vitamin D that say PCOS plays a role in the female reproductive system during the day (Grundmann and von Versen-Hoynck 2011; Anagnostis *et al.* 2013). VitD3 shows its functions in metabolism via VDRs. These receptors are found in many tissues in the organism. Vitamin D deficiency is common and associated with metabolic risk factors in patients with PCOS have been investigated in association with increased susceptibility to PCOS; yet, none of them are strong enough

to correlate with disease susceptibility alone (Gaasenbeek *et al.* 2004). The prevalence of obesity in PCOS is reported to be 40–60%. Depending on the general prevalence of obesity in the population, the prevalence of obesity in PCOS patients in different countries may differ. Obesity is the central type of obesity, in which the waist/hip ratio increases, and it brings additional risks to patients with PCOS. Waist/hip ratio increased in PCOS patients with normal body weight compared to weight-matched healthy controls. It was shown that lipid profiles have an effect on endocrine diseases. It was reported that the lipid profile in women with anovulation was seen as an increase in LDL-cholesterol and triglyceride levels, but a decrease in HDL-cholesterol levels, similar to the metabolic syndrome (Newman 2023).

It is known that obesity is an important risk for pregnancy and related complications in women with PCOS (Peeva *et al.* 2022). Although obesity is not the sole cause of PCOS, it does contribute to the vicious circle. In obese women with PCOS, it has been observed that insulin levels improve to a

large extent with weight loss and ovulation occurs due to a decrease in androgen level (Costello *et al.* 2012; Setji and Brown 2014). Another study indicated that increased serum lipids were negatively associated with the reproductive outcomes of PCOS women undergoing ovulation induction with clomiphene with or without acupuncture (Cai *et al.* 2022). VDR polymorphisms are involved in the pathogenesis and development of PCOS. *Apal*, *TaqI*, *Cdx2*, *Bsm-1*, and *Fok-1* polymorphisms on the VDR gene are associated with the metabolic features of PCOS (Dasgupta *et al.* 2015; Shi *et al.* 2019; Abouzid *et al.* 2021).

This study sought to investigate the relationship among the VDR gene *Apal* (rs7975232), *TaqI* (rs731236) and *Cdx2* (rs11568820) variants, serum VitD3 levels, and PCOS susceptibility in normal and overweight patients.

Material and methods

Study population

One hundred and twenty patients aged between 18 and 45 years old who applied to the Haseki Training and Research Hospital Gynecology and Obstetrics Clinic with PCOS were included in this study. Diagnosis of PCOS was based on the Rotterdam criteria (Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group 2004). Ethics committee approval was received for this study from the Ethical Committee of the Istanbul Faculty of Medicine. Patients were divided into two groups: BMI<25 ($n=77$) and BMI \geq 25 ($n=43$). Peripheral blood samples were taken from patients after all participants gave written informed consent. Biochemical and clinical parameters were obtained from Haseki Training and Research Hospital.

DNA isolation

Genomic DNA was extracted from blood samples using an Invitrogen purelink genomic DNA kit.

SNP analysis

VDR *Apal* (rs7975232), *TaqI* (rs731236), and *Cdx2* (rs11568820) gene polymorphisms were analysed by real-time polymerase chain reaction (PCR) device (StepOne and StepOnePlus Real-Time PCR Systems). The real-time PCR protocol of VDR *Apal* (rs7975232), *TaqI* (rs731236), *Cdx2* (rs11568820) gene polymorphisms are shown in table 1.

Determination of vitamin D3 levels

Blood samples, 5–10 cc taken into gel tubes were centrifuged at 3000 rpm for about 5 min, then the serum part

Table 1. PCR mix content and real-time PCR conditions.

1 × PCR mix		Concentration
TaqMan® Universal PCR Master Mix (2×)		5 μ L
TaqMan® Genotyping Assay Mix (40×)		0.25 μ L
DNase-free water		3.75 μ L
cDNA		1 μ L
Total volume		10 μ L
Temperature	Duration	Cycle
95°C	5 min	1
95°C	10 s	40
60°C*	1 min	

*Plate read.

was taken into a separate tube and stored at -20°C . Serum VitD3 levels were studied by the ELISA method (Enzo Life Sciences).

Statistical analysis

The SPSS 21.0 program was used to evaluate the data in this study. The difference between the frequencies of VDR *Apal* (rs7975232), *TaqI* (rs731236), *Cdx2* (rs11568820) gene polymorphisms in patients and healthy controls were evaluated with chi-square and Fisher exact tests. The significant difference between the clinical parameters and VitD3 levels of the patients with PCOS was compared with the Student *t*-test and Mann–Whitney U test. Statistical significance was accepted as $P<0.05$.

This study was conducted with the approval of the Ethical Committee of the Istanbul Faculty of Medicine, Istanbul University (596/2018).

Results

The demographical and clinical parameters of study groups are shown in table 2. BMI ($P=0.001$), waist/hip ratio ($P=0.008$), fasting blood glucose ($P=0.015$) and triglyceride levels ($P=0.035$) are elevated in BMI \geq 25 group. Estradiol level ($P=0.04$) and infertility ratio ($P=0.003$) are increased in the BMI<25 group. Table 3 shows the genotype and allele distributions of VDR gene variants in study groups. Frequencies of *Apal* AC genotype ($P=0.027$), C allele ($P=0.011$) and *Cdx2* T allele ($P=0.048$) are increased in the BMI \geq 25 group compared to the BMI<25 group. Besides, *Apal* AA genotype ($P=0.011$) and *Cdx2* CC genotype ($P=0.048$) frequencies are elevated in the BMI<25 group.

The relationship between VDR gene variants and lipid parameters is evaluated in table 4. According to the *Apal* variant; total cholesterol level is increased in carrying AA genotype in the BMI<25 group ($P=0.009$), total cholesterol

Table 2. Demographical and clinical parameters of study groups.

Parameters	BMI<25 (n= 77)	BMI≥25 (n= 43)
Age	24.08±3.91	26.16±5.58
Body mass index (kg/m ²)	21.90±1.90	28.21±3.03*
Waist/hip ratio	0.75±0.05	0.80±0.05**
Fasting blood glucose (mg/dL)	84.18±6.94	87.51±7.08***
Insulin (IU)	6.92±2.73	7.51±2.80
HOMA-IR	1.45±0.60	1.62±0.60
High-density lipoprotein (mg/dL)	52.25±11.37	50.14±10.63
Low-density lipoprotein (mg/dL)	91.55±19.09	96.26±24.66
Cholesterol (mg/dL)	158.59±23.33	162.05±34.59
Triglyceride (mg/dL)	82.71±31.87	96.37±34.05****
1,25 VitD ₃ (ng/mL)	14.24±9.47	16.21±15.99
Dehydroepiandrosterone (mg/dL)	239.53±84.34	244.16±94.32
Testosterone (mg/dL)	0.65±0.18	0.63±0.18
Ftestosterone (mg/dL)	2.69±0.92	2.98±1.22
C-reactive protein (mg/dL)	2.33±2.16	2.87±2.18
Follicle-stimulating hormone (mg/dL)	6.66±1.28	6.61±1.19
Luteinizing hormone (mg/dL)	11.75±3.89	10.59±3.90
Estradiol (mg/dL)	49.94±16.00*****	43.51±16.23
Thyroid-stimulating hormone (mg/dL)	2.23±0.96	2.23±1.21
Prolactin (mg/dL)	15.03±5.00	14.00±5.81
Anovulation (%)	81.8	81.4
Hirsutism (%)		
Less	55.8	39.5
Widespread	44.2	60.5
Infertility (%)	92.2*****	64.5
Infertility duration (week)	35.89±22.40	44.05±39.96
Menstruation cycle frequency (day)	55.55±32.97	60.40±48.34

* $P=0.001$, 95%CI=5.42–7.20; ** $P=0.008$, 95%CI=0.01–0.08; *** $P=0.015$, 95%CI=0.66–5.99; **** $P=0.035$, 95%CI=1.00–26.32; ***** $P=0.04$, 95%CI=0.30–12.53; ***** $P=0.003$, 95%CI=1.08–1.87.

($P=0.01$) and LDL-cholesterol level ($P=0.02$) are elevated in the BMI≥25 group compared to the BMI<25 group. Also, carrying C allele may be a risk factor for total cholesterol ($P=0.041$), LDL-cholesterol ($P=0.044$) and triglyceride ($P=0.028$) levels in the BMI≥25 group compared to the BMI<25 group. According to *TaqI* variant; AA genotype ($P=0.020$) and A allele ($P=0.041$) are associated with elevated triglyceride level in the BMI≥25 group compared to the BMI<25 group. When we evaluate the *Cdx2* variant, triglyceride levels are observed to be higher in the BMI≥25 compared to BMI<25 in those carrying CC genotype ($P=0.048$) and C allele ($P=0.030$). Besides, HDL-cholesterol level is elevated in patients having T allele in the BMI≥25

Table 3. Genotypes and alleles distribution of VDR gene variants in study groups.

	BMI<25 (n= 77)	BMI≥25 (n= 43)
<i>Apal</i>		
Genotypes		
AA	38 (49.4%)*	11 (25.6%)
CC	12 (15.6%)	8 (18.6%)
AC	27 (35.1%)	24 (55.8%)**
Alleles		
A	103 (66.8%)	46 (53.4%)
C	51 (33.2%)	40 (46.6%***)
<i>TaqI</i>		
Genotypes		
AA	28 (36.4%)	20 (46.5%)
CC	16 (20.8%)	5 (11.6%)
AC	33 (42.9%)	18 (41.9%)
Alleles		
A	89 (57.7%)	58 (67.4%)
C	65 (42.3%)	28 (32.6%)
<i>Cdx2</i>		
Genotypes		
CC	51 (66.2%****)	21 (48.8%)
TT	5 (6.5%)	4 (9.3%)
CT	21 (27.3%)	18 (41.9%)
Alleles		
C	123 (79.8%)	60 (69.7%)
T	31 (20.2%)	26 (30.3%*****)

* $P=0.011$, $\chi^2=6.45$, OR=1.92, 95%CI=1.10–3.37; ** $P=0.027$, $\chi^2=4.86$, OR=2.33, 95%CI=1.09–5.01; *** $P=0.011$, $\chi^2=6.45$, OR=2.83, 95%CI=1.25–6.42; **** $P=0.048$, $\chi^2=3.91$, OR=1.39, 95%CI=0.97–1.98; ***** $P=0.048$, $\chi^2=3.91$, OR=2.15, 95%CI=1.00–4.65.

compared to the BMI<25 ($P=0.027$). Haplotypes were evaluated for association with PCOS. No evidence of association between VDR genes and PCOS was observed between study groups (table 5).

When examining the relationship between VitD3 levels and clinical profiles in all PCOS patients, regardless of BMI distinction. It is determined that there is a positive correlation with LDL-cholesterol ($P=0.028$) and ftestosterone levels ($P=0.037$) (table 6; figure 1).

Discussion

Impaired lipid and insulin metabolism inhibit the proliferation and differentiation of follicular cells or promote their apoptosis. This adversely affects the follicular maturation and ovulation process. PCOS is a common endocrine disease characterized by hypovitaminosis D, which may adversely affect the steroidogenesis process, and reproductive and metabolic dysfunction. Vitamin D is a steroid hormone synthesized by the skin mainly under ultraviolet type B radiation. Besides its role in maintaining calcium

Table 4. Lipid parameters according to VDR genotypes and alleles.

Groups	BMI < 25 (n = 77)						BMI ≥ 25 (n = 43)					
	AA n = 38	AC n = 27	CC n = 12	A n = 65	C n = 39	AA n = 11	AC n = 24	CC n = 8	A n = 35	C n = 32		
Triglyceride (mg/dL)	86.00±33.05	79.88±31.20	78.67±31.17	83.48±32.18	79.50±30.77	95.64±40.14	94.67±33.62	102.50±29.76	94.97±35.20	96.62±32.41 ^f		
Total cholesterol (mg/dL)	161.00±21.21 ^a	149.96±23.88	169.83±23.67	156.44±22.83	156.24±25.29	136.09±27.66	172.58±34.05 ^c	166.12±28.58	161.11±36.12	170.97±32.45 ^e		
HDL-cholesterol (mg/dL)	51.11±11.40	52.27±11.29	55.75±11.73	51.59±11.27	53.37±11.39	46.55±8.99	51.67±11.44	50.50±10.18	50.06±10.87	51.38±10.99		
LDL-cholesterol (mg/dL)	93.14±17.97	85.69±20.97	99.33±15.48	90.06±19.45	90.00±20.24	82.18±20.80	102.12±26.63 ^b	98.00±16.35	95.86±26.37	101.09±24.29 ^d		
<i>TaqI</i>	AA n = 28	AC n = 33	CC n = 16	A n = 61	C n = 49	AA n = 20	AC n = 18	CC n = 5	A n = 38	C n = 23		
Triglyceride (mg/dL)	84.68±34.42	80.52±27.10	83.50±37.29	82.49±30.59	81.53±30.57	102.45±29.98 ^a	89.17±34.30	98.00±49.82	96.16±32.36 ^b	91.09±37.07		
Total cholesterol (mg/dL)	167.89±24.83	150.61±20.29	157.75±21.43	158.81±23.99	153.04±20.73	170.75±30.76	156.94±38.47	145.60±30.72	164.21±34.85	154.48±36.58		
HDL-cholesterol (mg/dL)	56.64±10.52	49.84±11.92	49.25±9.84	53.07±11.70	49.64±11.15	52.50±11.03	47.39±9.81	50.60±11.69	50.08±10.65	48.09±10.05		
LDL-cholesterol (mg/dL)	98.46±20.48	84.81±17.22	92.50±16.28	91.29±19.90	87.43±17.13	100.30±25.25	92.61±25.41	93.20±21.44	96.66±25.28	92.74±24.13		
<i>Cdx2</i>	CC n = 51	CT n = 21	TT n = 5	C n = 72	T n = 26	CC n = 21	CT n = 18	TT n = 4	C n = 38	T n = 22		
Triglyceride (mg/dL)	83.58±32.21	81.45±28.07	79.00±47.92	82.97±30.90	80.96±31.74	102.40±35.49 ^a	93.17±35.02	84.75±26.96	98.03±35.10 ^b	91.64±33.28		
Total cholesterol (mg/dL)	161.38±23.11	152.95±24.21	153.20±21.34	158.97±23.56	153.00±23.23	158.30±34.79	169.56±34.69	159.50±31.48	163.63±34.74	167.73±33.64		
HDL-cholesterol (mg/dL)	54.34±11.35	47.75±9.62	49.40±14.39	52.46±11.23	48.08±10.41	44.55±8.36	54.28±8.77	58.25±17.23	49.16±9.77	55.00±10.35 ^c		
LDL-cholesterol (mg/dL)	91.64±20.75	91.85±16.24	89.40±14.45	91.70±19.45	91.36±15.64	95.30±24.75	99.83±25.14	91.00±27.16	97.45±24.70	98.23±25.08		

For *Apal*: ^aP=0.009, 95%CI=5.47-44.34, ^bP=0.02, 95%CI=2.69-30.17, ^cP=0.01, 95%CI=5.69-39.55, ^dP=0.044, 95%CI=0.28-21.90, ^eP=0.041, 95%CI=0.61-28.85, ^fP=0.028, 95%CI=1.94-32.30. For *TaqI*: ^aP=0.020, 95%CI=1.05-36.59, ^bP=0.041, 95%CI=0.54-26.79. For *Cdx2*: ^aP=0.048, 95%CI=0.18-37.45, ^bP=0.030, 95%CI=1.51-28.60, ^cP=0.027, 95%CI=0.80-13.03.

Table 5. Frequencies of haplotypes of VDR genes in study groups.

Haplotype associations	Frequencies	Group ratios	χ^2	P value
CAC	0.331	0.321; 0.350	0.207	0.649
ACC	0.255	0.263; 0.241	0.140	0.708
AAC	0.170	0.177; 0.158	0.128	0.720
ACT	0.117	0.124; 0.102	0.257	0.612
AAT	0.067	0.058; 0.082	0.499	0.479
CAT	0.044	0.040; 0.052	0.190	0.663
CCT	0.010	0.015; 0.002	0.934	0.333

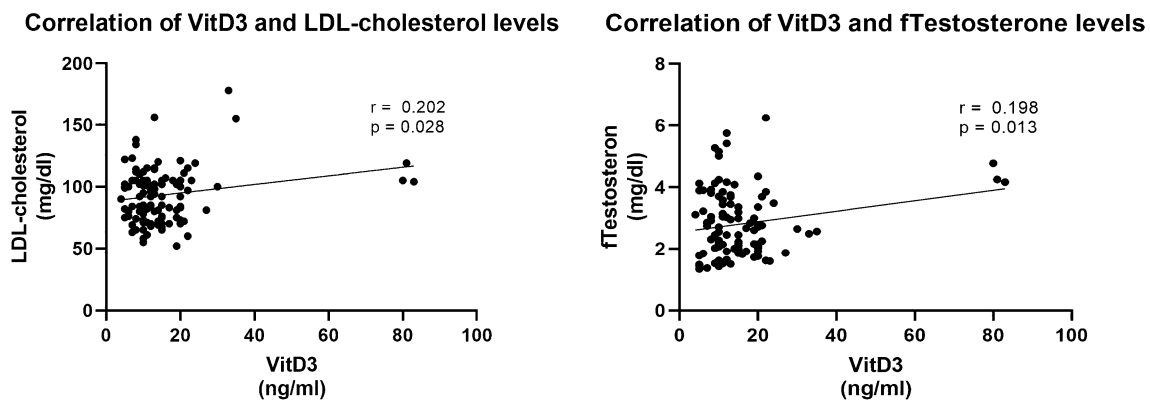
Table 6. Correlation of VitD3 levels and clinical profiles.

Parameters	r	P value
HDL-cholesterol	0.085	0.361
LDL-cholesterol	0.202	0.028
Total cholesterol	0.146	0.115
Triglyceride	-0.138	0.137
Ftestosterone	0.198	0.013
DHEA	0.001	0.995
BMI	0.048	0.601
Waist/hip ratio	0.035	0.82

homeostasis and bone mineralization, it has anti-inflammatory, antioxidant, immunomodulatory, antiangiogenic and antiproliferative properties. Evidence suggests that vitamin D status is closely related to the pathogenesis of insulin resistance and metabolic syndrome in PCOS. Although the relationship between vitamin D levels and PCOS has been extensively studied, the results are still controversial. Most of the links appear to be between the VDR polymorphism and PCOS (Reis *et al.* 2017; Vulcan *et al.* 2021).

We aimed to examine the relationship among the VDR gene variants, serum VitD3 levels and PCOS susceptibility in normal and overweight patients. We observed that carrying of *Apal* C allele (as AC and C) and *Cdx2* T allele are increased in the BMI \geq 25 group compared to the BMI<25 group. Besides, *Apal* AA genotype and *Cdx2* CC genotype frequencies are elevated in the BMI<25 group. Zadeh-Vakili *et al.* (2013) found that the genetic variant of the VDR (rs757343) was found to have an association with severity of clinical features of PCOS, but none with disease risk. A meta analysis study demonstrated that VDR *Apal* (rs7975232) and VDR *BsmI* (rs1544410) polymorphisms are correlated with susceptibility to PCOS in the Asian population and VDR *TaqI* (rs731236), VDR *FokI* (rs2228570), VDR *Tru9I* (rs757343) did not reveal a relationship with the PCOS susceptibility (Shi *et al.* 2019). However, we observed no evidence of association between VDR genes and PCOS between study groups in haplotype analysis. Lone *et al.* (2020) suggested that no statistically significant association was observed between the genotype of any SNP investigated and risk of PCOS, either as a main effect or in interaction with vitamin D status (Lone *et al.* 2020).

Dyslipidemia is one of the most common symptoms of PCOS. In the present study, we observed only increased triglyceride levels in patients with a BMI \geq 25 compared to patients with normal weight. Bedel *et al.* (2022) found that fasting insulin level, HOMA-IR score, and triglyceride level were significantly higher in obese adolescents with PCOS compared to normal weights (Bedel *et al.* 2022). In this study, the relationship between lipid profiles and VDR gene variants was investigated in patient groups. According to laboratory analysis results, carrying *Apal* AA genotype is associated with elevated total cholesterol ($P=0.01$) and LDL-cholesterol level ($P=0.02$) in the BMI \geq 25 group compared to the BMI<25 group. Also, carrying C allele may be a risk factor for total cholesterol ($P=0.041$), LDL-cholesterol ($P=0.044$) and triglyceride ($P=0.028$) levels in the BMI \geq 25 group. According to *TaqI* variant; AA genotype ($P=0.020$) and A allele ($P=0.041$) are associated with elevated triglyceride level in the BMI \geq 25 group compared to the

**Figure 1.** Correlations among VitD3, LDL-cholesterol and ftestosterone levels in patients.

BMI<25 group. When we evaluate the *Cdx2* variant, triglyceride levels are observed to be higher in the BMI≥25 compared to the BMI<25 in those carrying CC genotype ($P=0.048$) and C allele ($P=0.030$). Besides, HDL-cholesterol level is elevated in patients having T allele in a BMI≥25 compared to a BMI<25 ($P=0.027$). Santos et al. (2018) suggested that *Apal* variant may be associated with metabolic syndrome in southern Brazilian women with PCOS, and with blood pressure, total cholesterol, and LDL-c in women with and without PCOS (Santos et al. 2018). In a VDR genotype analysis study conducted on 185 PCOS patients and 207 healthy women in Egypt, a positive association was found between the rs7975232 (*Apal*) variant and an increased risk of PCOS (Albahlol et al. 2023).

However, in our study, no significant relationship was observed between VitD3 levels and VDR variants in both study groups. Similarly, a Brazilian study suggested that *TaqI* and *BsmI* polymorphisms were associated with PCOS, but not VitD3 levels in Brazilian women with PCOS (Xavier et al. 2019).

Another finding in our study, when we looked at the correlation between VitD3 levels and clinical parameters in all PCOS patients, we found a positive correlation with LDL-cholesterol and testosterone levels. In a Turkish study, Gokosmanoglu et al. (2020) observed that negative correlation between serum VitD3 levels and BMI, fasting glucose, waist circumference, LH, serum testosterone and DHEAS in women with PCOS (Gokosmanoglu et al. 2020). Al Thomali et al. (2018) did not find any association between VitD3 levels and the clinical variables such as age, weight, height, BMI, LH in PCOS.

In conclusion, present findings showed that the incidence of VDR *Apal* and *Cdx2* gene variants were significantly increased in overweight PCOS patients. In addition to these variants, *TaqI* variant was also closely associated with lipid profiles in patients with BMI≥25. However, no correlation was found between weight gain and serum VitD3 levels. Besides, a positive correlation was found between VitD3 levels and serum LDL and testosterone levels, independent of BMI. Our findings confirm that VDR variants are one of the most important risk factors for PCOS, especially with weight gain.

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Authors' contributions

VLB and ZMIS: data processing, collection, perform experiment; ZMIS and MNA: study conception and/or design; AE: analysis and interpretation of results, critical revision or editing of the article.

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