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Original Article

Vitamin D receptor (*Bsm*I) genotypes influence inflammatory and oxidative stress responses to altered vitamin D intake in subjects with Type 2 diabetes: A randomized controlled trial

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A B S T R A C T

Background: The purpose of our study was to investigate the possible effect of *Bsm*I vitamin D receptor (VDR's) polymorphism on changes of the inflammatory and oxidative stress (OS) biomarkers in response to daily intake of vitamin D-fortified yogurt drink (*doogh*) in subjects with type 2 diabetes (T2D).

Methods: In a randomized controlled trial, 100 T2D subjects were allocated to two groups to receive either plain *doogh* (PD; n = 50, containing 170 mg calcium and no vitamin D/250 ml) or vitamin D3-fortified *doogh* (FD; n = 50, containing 170 mg calcium and 500 IU/250 ml) twice a day for 12 weeks. 25(OH)D, glycemic status, inflammatory as well as OS biomarkers were evaluated before and after the intervention. VDR-*Bsm*I genotypes in an extended number of T2D subjects in the FD group (n = 140) were determined as BB, Bb, and bb.

Results: After 12 weeks, in FD compared to PD, serum 25(OH)D increased (+30.0 nmol/l vs. −4.8 nmol/l, $p < 0.001$). The 25(OH)D, parathyroid hormone, highly sensitive C-reactive protein (hs-CRP), malondialdehyde (MDA), and glutathione (GSH) in patients with the BB genotype were more responsive to vitamin D intake in which the maximum increment in 25(OH)D was in BB (31.8 nmol/l) compared with Bb (24.4 nmol/l) and bb (20.8 nmol/l) (p for trend < 0.001), and the difference in BB, compared to Bb and bb was significant [Bb ($p = 0.024$) and bb ($p = 0.037$)]. This difference was accompanied by a significant difference for other biomarkers including fasting serum glucose (p trend = 0.039), fat mass % (p trend < 0.001), interleukin 6 (p trend = 0.033), hs-CRP (p trend < 0.001), and MDA (p trend = 0.028) which significantly all decreased in BB genotype except for GSH which significantly increased (p trend = 0.035).

Conclusion: Daily intake of vitamin D-FD for 12 weeks improved the inflammatory and OS biomarkers in T2D subjects, and the improvement was more pronounced in the carriers of BB genotype of VDR-*Bsm*.

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Introduction

The prevalence of type 2 diabetes (T2D) is increasing worldwide and has been shown that diabetes is accompanied by greater risk factor for several chronic diseases such as cardiovascular disease and fracture [1]. In addition, vitamin D deficiency is also a worldwide epidemic that affects both the elderly and children, particularly it was shown that it prevalent in T2D [2], and leading to a wide range of extra-skeletal conditions, such as cardiovascular diseases, hypertension, diabetes and insulin metabolism, autoimmune disorders, metabolic syndrome, and obstructive sleep apnea. The mechanism by which vitamin D deficiency affects cardiovascular health is still unclear.

Oxidative stress (OS) is a major feature in obesity and diabetes which result in the development and progression of diabetes and its complications. Some evidence indicates that persistent hyperglycemia, augments production of excess reactive free radicals and causes OS, which is linked to the development of adverse metabolic effects, causing dysregulation of adipokines and inflammation [3]. Vitamin D can also have a role in inflammation status through diverse effects on inflammatory cells [4]. Association studies have shown that low 25(OH)D3 levels are associated with higher levels of systemic inflammation, glycoxidation, and lipoxidation biomarkers [5, 6]. The production of adipokines and the inflammatory response in adipose tissue is influenced by vitamin D [7]. Moreover, vitamin D regulates genes encoding pro-inflammatory cytokines, down-regulates toll-like receptors expression [8, 9], and counteracts the inflammatory effects induced by cytokines [10].

An inverse association between serum concentrations of 25(OH)D and OS biomarkers has recently been reported [11]. In addition, animal studies have shown that vitamin D can modulate activities of the antioxidant enzymes in diabetes [12].

Vitamin D receptor (VDR) can be express in a wide range of extrarenal cells including adipocytes and cells of the immune system, which result in synthesizing of 1,25(OH)2D3. This local production of vitamin D is responsible for extraskeletal modulation of various physiological processes by regulating gene expression of as many as 2000 genes [13].

The VDR rs1544410 is an adenine/guanine substitution located in the 3′UTR region of intron 8 that does not alter the structure and function of the VDR but is strongly related to the poly (A) tail, potentially affecting the stability of mRNA [14]. Epidemiologic data show an inverse association of this polymorphism as a possible genetic marker in several important clinical conditions such as type 1 diabetes mellitus [15], obesity [16], and some specific cancers [17]. Polymorphisms of the VDR gene, including *Bsm*I, are also associated with different responses to vitamin D supplementation [18].

de Medeiros Cavalcante et al. [19] noted that vitamin D supplementation contributes to a beneficial reduction of inflammatory markers and increased the total antioxidant capacity in elderly women. Given the potential risk of vitamin D deficiency for variety of non-skeletal diseases and conditions such as metabolic syndrome, T2D, cardiovascular disease and obesity, and role of VDR genetic variants in diabetes outcome, we conducted a clinical trial on subjects with T2D to evaluate the possible effects of regular intake of vitamin D-fortified Persian yogurt drink (*doogh*) on inflammatory, as well as OS biomarkers. The findings on the effects of vitamin D on endothelial and systemic inflammation biomarkers have been reported elsewhere [20-22]. This study aimed to evaluate the influence of improvement of vitamin D status on some selected markers of OS and to investigate the interactive effect of VDR *Bsm*I polymorphism and vitamin D intake on inflammatory and OS biomarkers. We hypothesized that vitamin D supplementation would ameliorate OS, and subjects with different VDR variants might respond differently to vitamin D intake in terms of selected OS biomarkers.

Methods

This was a 12 weeks randomized clinical trial (RCT) and a part of a larger trial on the evaluation of efficacy of vitamin D-fortified *doogh* (FD) on diabetes outcomes in T2D patients. The protocol of this trial has been published in detail previously [20]. The RCT was conducted collaboratively by National Nutrition and Food Technology Research Institute (NNFTRI) and Tehran University of Medical Sciences (TUMS) in Tehran, the capital of Iran. Full information on the study design and objectives were given to all participants before they signed an informed consent. The study protocol was approved scientifically and ethically by both NNFTRI and TUMS. The trial

registration number at ClinicalTrials.gov is NCT01236846.

Participants were recruited from the Iranian Diabetes Society and Gabric Diabetes Society members. Volunteers were invited to attend the Laboratory of Nutrition Research at NNFTRI while they were fasting for 12-14 hours.

The inclusion criteria were: (a) fasting blood glucose more than 126 mg/dl, (b) aged 30-60 years old, (c) willingness to participate, and (d) no intake of vitamin, dietary, herbal, or omega-3 supplements since at least 3 months prior to the intervention. Exclusion criteria were: (a) history of cardiovascular, gastrointestinal, renal, and other endocrinological diseases, (b) pregnancy or lactation, (c) receiving insulin, and (d) treatment for weight reduction.

A run-in period was considered for 2 weeks during which the subjects were instructed to have a weight maintenance diet according to the American Diabetes Association guidelines including 2 servings of low-fat dairy products (milk and yogurt), 2-3 servings of fruits and 2-3 servings of vegetables a day. The clinical trial comprised two parts. In the first part (intervention study), the effects of daily intake of two servings of vitamin D3-FD as compared to plain *doogh* (PD) on obesity indices were evaluated in T2D patients. To do this, participants were randomly assigned to one of the treatment groups of either FD (FD, containing 170 mg calcium and 500 IU vitamin D3/250 ml; $n_1 = 50$) or PD (PD, containing 170 mg calcium and no vitamin D/250 ml; $n_2 = 50$). Participants were instructed to consume a bottle of yogurt drink with both lunch and dinner, i.e. 500 ml/day equaling 1000 IU vitamin D3 a day in FD group. In the second part (nutrigenetic study), number of patients in FD group was extended (n = 140) to investigate the possible role of VDR single nucleotide polymorphisms, *Bsm*I, on the response of inflammatory and OS biomarkers to vitamin D intake.

Every 2 weeks, all subjects were visited to evaluate their compliance and to provide a new package of *doogh*. Yogurt drinks were identical in color, size, taste, and packaging. Therefore, participants were not aware of their group, nor were all the interviewers and laboratory staff. Compliance was evaluated by checking the consumption tables, counting the empty bottles, and direct inquiry both on biweekly visits and weekly follow-up phone calls. The composition (including vitamin D) of *dooghs* was determined immediately after production, in the middle and at the end of the storage period, to ensure the stability of the components. The measurements were done at Maad Laboratory of Foods, Drinks and Cosmetics, accredited by the Food and Drug Organization of the Iran Ministry of Health.

We assessed dietary intakes by employing a 24 hours recall questionnaire for 3 days (including a weekend) in the beginning and in the end of the intervention period, as described earlier [22]. To translate dietary intake data to the actual amounts of energy and nutrients, US Department of Agriculture food composition tables with some modifications for Iranian foods were used.

Weight was measured with light clothing and without shoes using a digital scale (Seca 808, Hamburg, Germany) to the nearest of 0.1 kg. Height was measured without shoes using a stadiometer (Seca, Hamburg, Germany) to the nearest of 0.1 cm. Circumferences of the waist and hip were evaluated by a measuring tape to the nearest of 0.1 cm. Body mass index (BMI) was calculated using the equation:

$BMI = \text{weight (kg)}/\text{height}^2 \text{ (m)}$.

To evaluate the percentage of body fat mass (FM), bioelectrical impedance analysis (Quadscan 4000 system, Bodystat, UK) was employed. All participants were requested to abstain from any food or liquid intake and from any intensive exercise for at least 4 hours before evaluation. They were also instructed not to wear any metallic object for the tests.

Blood samples were collected after 12 hours overnight fasting and were divided into two tubes either with or without the anticoagulant, EDTA. The anti-coagulated tube was used to extract genomic DNA while the sera recovered from clot samples were used for biochemical analyses. Glycemic status was determined as previously described [23]. Fasting serum glucose (FSG) was determined using an enzymatic method by commercial kits (Pars Azmoon, Iran) and an auto-analyzer system (Selectra E, Vitalab, the Netherlands). Glycated hemoglobin (HbA1c) was determined using colorimetric method after an initial chromatographic separation (BioSystems, Spain). Fasting serum insulin was assayed by immunoradiometric assay (IRMA) (Biosource, Belgium) and a gamma-counter system (Gamma I, Genesys, USA). The intra- and inter-assay variations for all tests were < 7% and 9%, respectively. Insulin sensitivity was evaluated by Quantitative Insulin Check Index (QUICKI) calculated as [24]:

QUICKI index: $1/[\log (\text{insulin}) (\mu U/ml) + \log$

(glucose) (mg/dl)].

Circulating 25(OH)D and intact parathyroid hormone (iPTH): Briefly, serum 25(OH)D was assayed using high-performance liquid chromatography (HPLC) as described earlier [23]. Serum iPTH (DRG, Marburg, Germany) was measured by the enzyme immunoassay (EIA) method using a semi-automatic system (microplate enzyme-linked immunosorbent assay reader, STATFAX 3200; Awareness, Palm City, FL, USA). The intra- and inter-assay variations were < 3%.

Inflammatory status was evaluated using determination of both circulating and cellular biomarkers. Highly sensitive C-reactive protein (hs-CRP) and serum amyloid A were measured using immunoturbidimetric assay (Pars Azmoon, Iran) and EIA (IBL International, Germany). interleukin 6 (IL-6) and tumor necrosis factor-α were determined in peripheral blood mononuclear cells culture media. Cell separation and culture was performed as described elsewhere [25] with minor modifications. Cell number was set as ~2 × 10^6 in 2 ml RPMI 1640. After 24 hours, supernatants were transferred to clean microtubes in aliquots and kept at −80° C until the day of analysis. Cytokine assay was performed using EIA (all from Bender Medsystems, Austria) with the aid of a microplate reader (Statfax 3200, Awareness, USA).

Endothelial function was evaluated by determination of serum levels of endothelin-1, E-selectin (both from IBL, Hamburg, Germany) and matrix metallopeptidase 9 (MMP-9) (e-Bioscience, Vienna, Austria). All enzyme-linked immunosorbent assay tests were performed with the aid of an automatic plate reader (StatFax 3200, Awareness, Palm City, USA). The intra- and inter-assay variations were < 8.1% and 8.5% for endothelin-1, 5.4% and 6.0% for E-selectin, and 7.3% and 10.2% for MMP-9, respectively.

Total antioxidant capacity (TAC) was determined with bovine serum albumin as a standard, as described elsewhere [20]. Malondialdehyde (MDA) was assayed as originally described with some minor modifications [26]. Serum concentrations of serum superoxide dismutase (SOD) and glutathione (GSH) were both determined using enzymatic immunoassay (all from Bender Medsystems, Austria) with the aid of a microplate reader (StatFax 3200, Q8 Awareness, USA).

DNA was extracted from anti-coagulated blood samples using Genet Bio DNA Isolation kit (Prime Prep, Chungnam, South Korea) according to the manufacturer's protocol. The *Bsm*I polymorphism was amplified with polymerase chain reaction (PCR) using primers 5'-ggC AAC CTg AAg ggA gAC gTA-3' and 5'-CTC TTT ggA CCT CAT CAC CgA C-3' based on the report of Ye et al. [27] and resulted in a 461-bp product.

PCR was performed for 30 cycles and at 62° C annealing temperature. DNA was digested with *Bsm*I restriction enzyme (Mva 1269I) (Fermentas; Thermo Scientific, Burlington, Ontario, Canada). *Bsm*I alleles were defined by capital letters in the absence of the restriction site and small letters in the presence of the restriction site. Accordingly, *Bsm*I VDR start codon genotypes were bb, Bb, and BB.

Data were expressed as mean ± standard deviation. Normal distribution of data was checked using Kolmogrov–Smirnov. Genotype frequencies of *Bsm*I were tested for Hardy–Weinberg equilibrium using χ^2 test. Independent sample t-test (for normally distributed variables) or Mann–Whitney U (for non-normally distributed variables) was used to test anthropometric and metabolic biomarkers between PD and FD groups. Repeated-measures analysis of variance (ANOVA) was used to evaluate time × group interactions, with time and group as factors. In case of significant time-group interaction, among group comparisons of changes at week 12 was done using ANOVA followed by Tukey post-hoc analysis with polynomial contrast analysis for trend when indicated. When time effect was significant, the within-group comparison of values was performed by paired samples t-test. All statistical analyses were done using Statistical Package for Social Sciences (SPSS, version 18; Chicago, IL, USA). $p < 0.050$ was considered significant.

Results

A flow chart of subject enrollment is shown in figure 1. The observed genotype frequency distributions for *Bsm*I were in Hardy–Weinberg equilibrium. Distribution of age, gender, and duration of disease and sun exposure did not differ significantly among the genotypic groups. The subjects included 73 womens and 67 mens aged 52.5 ± 7.7 years. Mean age (PD: 51.3 ± 7.7, FD: 54.1 ± 8.0 years), duration of disease (PD: 7.2 ± 5.8, FD: 8.6 ± 5.5 years) and sex ratio showed no significant difference between the groups (Table 1). Comparison of dietary data between PD and FD groups showed no

significant difference in the initial and final values of calcium intake (595.6 ± 270.0 vs. 530.8 ± 216.4 mg/day, p = 0.140 and 615.5 ± 311.0 vs. 640.4 ± 315.1 mg, p = 0.660, respectively). Nor was there any significant difference in the initial and final vitamin D intakes, excluding the amount consumed with the FDs in the FD group (15.5 ± 13.7 vs. 14.1 ± 13.9 IU, p = 0.607; 17.6 ± 22.0 vs. 16.0 ± 19.0 IU/day, p = 0.670, respectively).

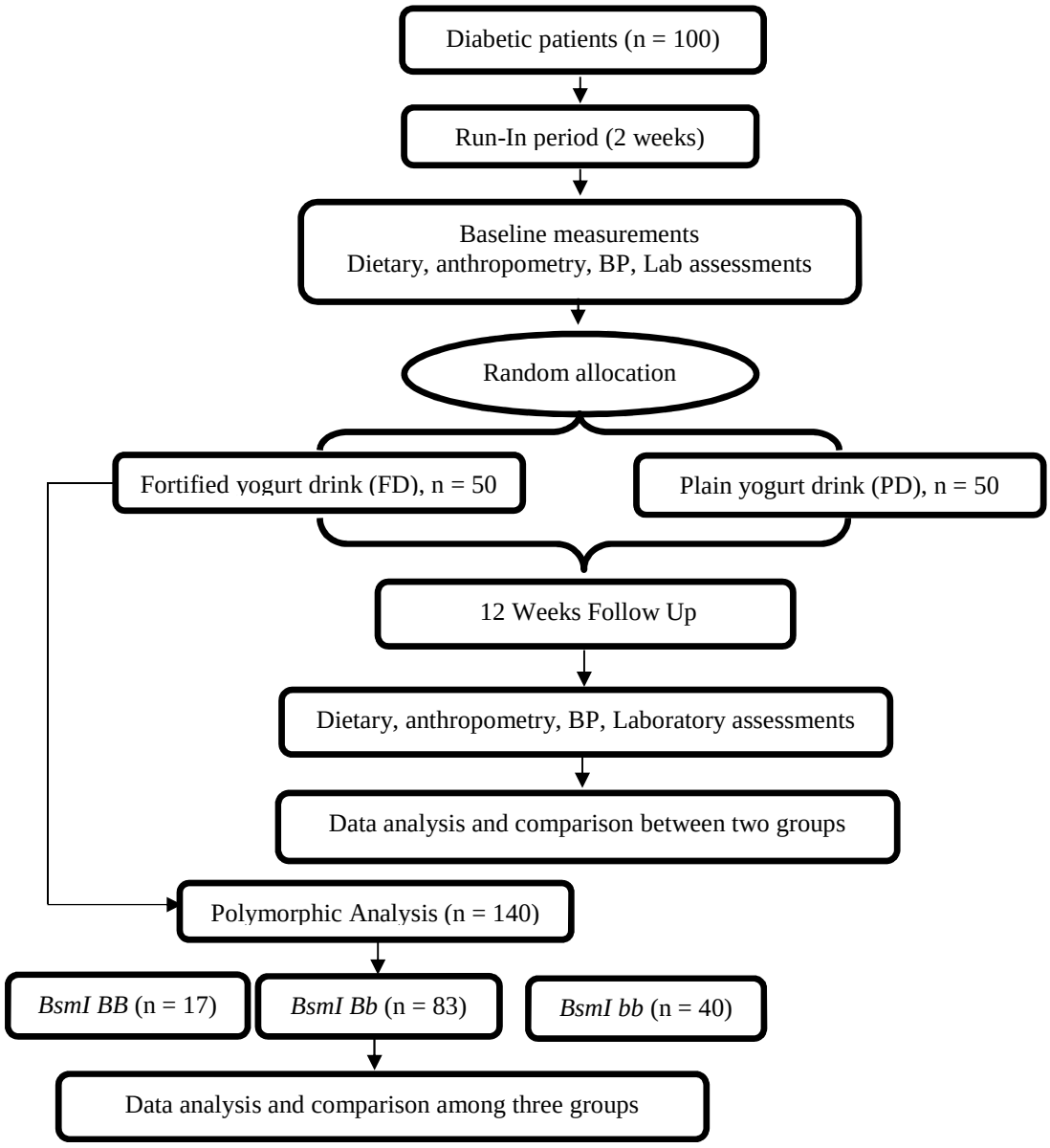

Figure 1. Protocol of the study

Table 1. Some selected individual characteristics of the subjects enrolled in the RCT study and *Bsm*I (rs1544410) genotypic groups for the nutrigenetic study

Variables	Treatment groups (n = 100)		p value	*Bsm*I genotypic groups (n = 140)			p value
	PD (n = 50)	FD (n = 50)		BB (n = 17)	Bb (n = 83)	bb (n = 40)	
Age (year)	52.4 ± 8.4	52.6 ± 6.3	0.860	51.6 ± 5.4	50.3 ± 5.8	51.3 ± 7.8	0.560
Sex (male/female)	19/31	24/26	0.280	10/7	39/44	18/22	0.680
Diabetes duration (year)	7.0 ± 5.2	8.3 ± 4.6	0.180	7.8 ± 5.7	8.7 ± 7.4	7.7 ± 6.6	0.470
Physical activity (%)[1]	1 (2.0)	5 (10.0)	0.180	9 (16.4)	4 (9.3)	3 (9.4)	0.680
Sun exposure (min/day)	53.7 ± 9.2	50.3 ± 8.2	0.220	75.3 ± 50.7	64.5 ± 63.2	65.3 ± 56.8	0.630

Data presented as mean ± SD or percentage unless stated otherwise. FD = Vitamin D-fortified *doogh*; PD = Plain *doogh*. [1]Very low physical activity. RCT = Randomized clinical trial

Intervention study

As reported elsewhere [4, 21, 22], at baseline, vitamin D concentrations and other biomarkers were not significantly different between two groups (Table 2). There were significant time effect between weeks 0 and 12 in serum 25(OH)D. Serum concentrations of 25(OH)D increased significantly in FD group compared to baseline ($p < 0.001$) and to PD (+30 nmol/L in FD vs. −4.8 nmol/L in PD, $p < 0.001$) (Table 2). Accordingly, vitamin D status in FD, as compared to PD, improved significantly after 12 weeks intervention**.** There were also significant time effects between weeks 0 and 12 for PTH, HbA1c, FM%, vascular and systemic inflammatory biomarkers and OS markers except for SOD. In the FD group, PTH ($p < 0.001$), HbA1c ($p < 0.001$), FM% ($p < 0.001$), inflammatory biomarkers ($p < 0.001$), MDA ($p = 0.004$) and GSH-peroxidase (GSH-Px) ($p < 0.001$) all decreased and TAC ($p < 0.001$) and GSH ($p = 0.007$) both increased significantly after 12 weeks, while in the PD group these variables tended to increase except for HbA1c ($p = 0.030$) and GSH-Px ($p < 0.001$) that significantly decreased. There were also significant time × treatment interaction for 25(OH)D, QUICKI, waist circumference (WC), FM%, inflammatory and OS biomarkers except for SOD and GSH-Px. Analysis of changes within groups revealed a significant decrease in WC ($p = 0.020$), waist-hip ratio ($p = 0.050$), FM% ($p < 0.008$), inflammatory biomarkers, TAC ($p = 0.030$), MDA ($p < 0.001$) and GSH ($p = 0.002$) in FD group compared to the PD group while 25(OH)D, QUICKI significantly increased in FD group compared to PD group ($p < 0.001$ for both) (Table 2). Weight, BMI, and FSG did not change significantly either within or between groups after 12 weeks (Table 2).

Nutrigenetic study

Vitamin D intake resulted in a significant time effect between weeks 0 and 12 for serum 25(OH)D. Serum 25(OH)D increased significantly after 12 weeks in all genotypes groups ($p < 0.001$ and $p = 0.025$ and $p = 0.043$ for BB, Bb, and bb, respectively) which was more pronounced in BB versus Bb and bb groups (31.8 vs. 24.4 and 20.8 nmol/l) (Table 3). There were also significant time effects between weeks 0 and 12 for FSG, HbA1c, FM%, IL-6, hs-CRP, MDA, TAC and GSH. Though changes in the BB group, FSG ($p < 0.035$), HbA1c ($p = 0.006$), FM% ($p = 0.037$), IL-6 ($p = 0.004$), hs-CRP ($p < 0.001$), MDA ($p = 0.005$), TAC ($p = 0.003$) and GSH ($p = 0.032$) were significant after 12 weeks, in Bb and bb groups, these variables did not change significantly (Table 3). There were significant time × treatment interaction for 25(OH)D, FSG, FM%, IL-6, hs-CRP, MDA and GSH among *Bsm*I genotypes (Table 3). Post-hoc Tukey test revealed that the BB group had significantly higher 25(OH)D compared with Bb ($p = 0.024$) and bb ($p = 0.037$) after 12 weeks. This difference was accompanied by a significant difference for other biomarkers such as FSG ($p_{trend} = 0.039$), FM% ($p_{trend} < 0.001$), IL-6 ($p_{trend} = 0.033$), hs-CRP ($p_{trend} < 0.001$), and MDA ($p_{trend} = 0.028$) which significantly all decreased in BB genotype except for GSH which significantly increased ($p_{trend} = 0.035$).

Discussion

This study demonstrated that 12 weeks of 1000 IU vitamin D intake resulted in a significant difference in the diabetic host response in terms of inflammatory and OS biomarkers according to *Bsm*I VDR variants. The high prevalence of poor vitamin D status reported in several populations [28], specially T2D patients [22], indicate that to reach adequate levels of serum vitamin D food sources and sun exposure are not sufficient. Moreover, it is demonstrated that poor vitamin D status is an independent risk factor for several chronic disease such as cardiovascular disease and T2D.

According to previous reports vitamin D supplementation can ameliorate OS [21], vascular and systemic inflammation [4, 22, 29] which may partly contribute to improvement of insulin resistance and reducing blood pressure [22, 30]. Accumulating data suggest that excessive synthesis of pro-inflammatory cytokines may be mediated leading to impairment of insulin sensitivity in T2D [31]. Considering the anti-inflammatory effects of cholecalciferol [32], modifying poor vitamin D status may improve systemic inflammation and thereby other metabolic derangements including insulin resistance and raised blood glucose. There is too much discrepancy about the effect of vitamin D supplementation on the metabolic, inflammatory and OS process. For example although some studies were not able to show any association between 25(OH)D and inflammatory status [33], evidence from other studies suggest that insulin resistance and beta cell function may be modulate by vitamin D [34].

Table 2. Comparison of the initial and final values of the variables under study in the RCT [20-23]

Variables	PD (n = 50)			FD (n = 50)			Time	Group	Time × Group
	Before	After	Change	Before	After	Change	p_1	p_2	p_3
25(OH)D (nmol/L)	41.1 ± 20.5	36.2 ± 23.6	-4.8 ± 16.6	41.6 ± 15.9	77.1 ± 19.7	35.4 ± 18.3	< 0.001	< 0.001	< 0.001
PTH	55.0 ± 22.5	59.1 ± 18.2	4.3 ± 58.3	52.5 ± 24.1	40.1 ± 15.6	-11.7 ± 20.6	0.001	0.120	0.070
FSG (mg/dL)	159.6 ± 52.0	167.6 ± 52.5	8.0 ± 48.2	166.5 ± 43.2	152.5 ± 42.8	-14.0 ± 49.8	0.630	0.700	0.080
HbA1c (propotional)	8.9 ± 1.7	8.3 ± 1.6	-0.71 ± 1.70	8.9 ± 2.4	7.4 ± 1.6	-1.5 ± 2.0	< 0.001	0.240	0.120
QUICKI	0.28 ± 0.20	0.28 ± 0.02	-0.009 ± 0.020	0.28 ± 0.02	0.29 ± 0.02	0.02 ± 0.02	0.670	0.700	< 0.001
Weight (kg)	78.8 ± 13.2	79.7 ± 13.8	0.86 ± 2.60	73.7 ± 13.8	73.5 ± 11.5	-0.2 ± 2.7	0.320	0.130	0.160
BMI (kg/m^2)	29.6 ± 4.2	30.0 ± 4.1	0.33 ± 1.00	27.8 ± 4.6	27.7 ± 4.6	0.06 ± 1.0	0.320	0.110	0.160
WC (cm)	101.1 ± 9.8	102.2 ± 10.8	1.6 ± 4.4	96.8 ± 11.4	95.8 ± 8.9	-1.3 ± 5.0	0.800	0.046	0.028
WHR	0.94 ± 0.05	0.95 ± 0.05	0.02 ± 0.04	0.93 ± 0.05	0.92 ± 0.05	-0.05 ± 0.04	0.270	0.070	0.051
FM%	38.9 ± 9.6	40.3 ± 9.4	0.60 ± 3.30	36.7 ± 10.6	33.3 ± 9.6	-5.1 ± 5.5	< 0.001	0.025	< 0.001
IL-6 (pg/ml)	561.8 (105.3)	632.7 ± 135.4	+76.8 ± 172.0	638.3 (90.4)	552.0 ± 213.5	-51.3 ± 220.2	0.001	0.058	0.076
TNF-α (pg/ml)	108.6 (427.3)	263.6 ± 278.0	29.6 ± 439.1	200.2 (341.4)	211.6 ± 216.0	-28.1 ± 257.5	0.001	0.009	0.290
Hs-CRP (mg/L)	1.6 (1.8)	2.7 ± 1.6	0.06 ± 3.7	2.0 (2.7)	1.7 ± 1.1	-0.76 ± 3.70	0.001	0.001	< 0.001
SAA (pg/ml)	87.5 (48.6)	93.6 ± 28.7	+7.3 ± 36.8	87.6 (56.0)	77.1 ± 35.8	-16.7 ± 43.6	0.001	0.024	0.012
Endothelin (µg/L)	0.80 ± 0.40	0.88 ± 0.41	0.35 ± 0.63	0.95 ± 0.38	0.75 ± 0.64	0.03 ± 0.55	0.001	0.060	0.028
E-selectin (µg/L)	16.1 ± 6.5	17.1 ± 6.9	+0.95 ± 8.30	18.1 ± 7.1	14.4 ± 5.7	-3.8 ± 7.3	0.001	0.035	0.003
MMP-9 (µg/L)	9.2 ± 5.3	9.6 ± 4.7	+0.44 ± 7.10	10.6 ± 4.2	8.3 ± 3.7	-2.3 ± 3.7	0.001	0.120	0.020
MDA (µmol/L)	3.0 ± 1.0	3.2 ± 1.1	0.17 ± 1.10	3.20 ± 0.78	2.70 ± 0.76	-0.54 ± 0.82	0.004	0.001	< 0.001
TAC (mmol/L BSA Eq)	1.90 ± 0.35	1.90 ± 0.40	0.02 ± 0.45	1.90 ± 0.28	2.30 ± 0.40	0.14 ± 0.43	< 0.001	0.310	0.030
SOD (ng/L)	0.73 ± 0.56	0.56 ± 0.56	-0.15 ± 0.81	0.73 ± 0.69	0.72 ± 0.70	-0.03 ± 0.94	0.200	0.160	0.670
GSH (µg/ml)	62.0 ± 25.0	47.5 ± 23.4	-13.1 ± 29.4	65.3 ± 30.2	72.0 ± 24.4	8.4 ± 40.1	0.007	0.018	0.002
GSH-Px (U/ml)	123.1 ± 180.0	16.2 ± 23.0	-107.0 ± 182.2	90.7 ± 174.2	18.8 ± 41.6	-71.8 ± 181.5	< 0.001	0.680	0.250

p_1 = Probability level by repeated-measures ANOVA for difference in time course; p_2 = Probability level by repeated-measures ANOVA for difference between types of yogurt drink; p_3 = Probability level by repeated-measures ANOVA for interaction between time course and type of yogurt drink. Groups: PD = Plain doogh; FD = Vitamin D-fortified doogh; PTH = Parathyroid hormone; FSG = Fasting serum glucose; HbA1c = Glycated hemoglobin; BMI = Body mass index; WC = Waist circumference; WHR = Waist-hip ratio; FM = Fat mass; IL-6 = Interleukin 6; TNF = Tumor necrosis factor; hs-CRP = Highly sensitive C-reactive protein; SAA = Serum amyloid A; MMP-9 = Matrix metallopeptidase 9; MDA = Malondialdehyde; TAC = Total antioxidant capacity; SOD = Serum superoxide dismutase; GSH = Glutathione; GSH-Px = Glutathione-peroxidase; RCT = Randomized clinical trial

Table 3. Comparisons of the variables among the *BsmI* (rs1544410) genotypic groups with T2D before and after 12 weeks intervention in the nutrigenetic study (n = 60)

Variable	BB (n = 17)			p	Bb (n = 83)			p	bb (n = 40)			p	Time	Group	Time × group
	Before	After	Change		Before	After	Change		Before	After	Change		p_1	p_2	p_3
25(OH)D (nmol/L)	31.4 ± 13.2	76.1 ± 18.5	31.8 ± 15.3	< 0.001	33.7 ± 12.7	59.0 ± 13.5	24.4 ± 15.0	0.025	35.4 ± 24.5	55.2 ± 22.4	20.8 ± 9.5	0.043	0.001	< 0.001	< 0.001
FSG (mmol/L)	166.5 ± 43.2	152.3 ± 42.8	-13.8 ± 36.8	0.035	170.8 ± 47.1	165.4 ± 50.3	-6.7 ± 36.1	0.130	158.3 ± 21.0	150.4 ± 22.6	11.8 ± 33.2	0.180	0.045	0.690	0.039
HbA1c (%)	8.7 ± 2.5	7.6 ± 1.3	-1.3 ± 2.1	0.006	8.8 ± 1.6	8.5 ± 1.6	-0.35 ± 2.00	0.540	8.8 ± 2.1	8.5 ± 1.9	-0.44 ± 0.71	0.340	0.042	0.650	0.430
QUICKI	0.28 ± 0.02	0.28 ± 0.02	0.002 ± 0.020	0.350	0.28 ± 0.02	0.28 ± 0.02	-0.006 ± 0.020	0.270	0.29 ± 0.02	0.28 ± 0.01	-0.002 ± 0.020	0.120	0.260	0.780	0.210
Weight (kg)	74.0 ± 11.4	74.0 ± 11.8	-0.33 ± 2.50	0.570	75.6 ± 14.6	76.3 ± 14.0	1.1 ± 2.4	0.15	76.3 ± 11.2	76.1 ± 10.8	0.16 ± 2.20	0.770	0.500	0.480	0.430
BMI (kg/m^2)	27.6 ± 4.6	27.8 ± 4.5	-0.06 ± 1.20	0.660	27.4 ± 3.2	28.2 ± 3.4	0.56 ± 1.10	0.19	28.5 ± 3.6	29.5 ± 3.2	0.07 ± 0.95	0.640	0.350	0.120	0.420
WC (cm)	96.1 ± 11.4	95.0 ± 9.8	-1.2 ± 6.5	0.350	99.0 ± 9.8	98.2 ± 8.9	0.98 ± 6.50	0.530	98.2 ± 8.7	99.0 ± 11.6	1.1 ± 5.3	0.350	0.540	0.670	0.170
FM (%)	34.9 ± 10.7	32.7 ± 10.5	-2.2 ± 2.5	0.037	34.4 ± 8.5	33.8 ± 7.9	-0.6 ± 2.2	0.170	35.4 ± 9.1	34.9 ± 8.5	-0.5 ± 4.0	0.640	0.026	< 0.001	< 0.001
IL-6 (pg/ml)	552.6 ± 26.4	512.7 ± 30.4	-29.9 ± 21.2	0.041	567.5 ± 28.7	578.2 ± 21.7	+12.3 ± 24.5	0.480	547.0 ± 24.6	548.0 ± 33.6	1.9 ± 21.1	0.780	0.047	0.570	0.033
TNF-α (pg/ml)	286.5 ± 38.2	278.3 ± 31.8	-8.5 ± 37.7	0.460	293.1 ± 39.3	279.0 ± 36.8	-14.5 ± 32.1	0.520	293.3 ± 34.6	294.7 ± 35.8	1.4 ± 31.7	0.490	0.670	0.490	0.371
hsCRP (mg/l)	2.80 ± 0.16	1.50 ± 0.10	-1.30 ± 0.15	< 0.001	2.40 ± 0.23	2.00 ± 0.20	-0.46 ± 0.18	0.005	2.70 ± 0.33	2.30 ± 0.25	-0.42 ± 0.21	0.008	0.001	0.003	< 0.001
SAA (pg/ml)	85.7 ± 43.4	84.6 ± 35.4	-5.5 ± 32.3	0.720	87.8 ± 45.1	85.5 ± 40.8	-6.3 ± 25.1	0.240	88.1 ± 26.3	84.2 ± 6.2	-6.1 ± 26.1	0.120	0.560	0.410	0.230
Endothelin (µg/L)	1.20 ± 0.06	0.83 ± 0.07	-0.11 ± 0.10	0.100	1.10 ± 0.11	0.91 ± 0.10	-0.15 ± 0.15	0.220	1.10 ± 0.12	0.96 ± 0.06	-0.04 ± 0.24	0.310	0.310	0.380	0.320
E-selectin (µg/L)	15.80 ± 0.83	14.60 ± 0.66	-1.70 ± 0.76	0.120	16.9 ± 1.3	16.10 ± 0.88	-1.3 ± 1.4	0.320	17.3 ± 1.2	16.6 ± 1.3	-0.37 ± 1.1	0.750	0.350	0.180	0.240
MMP-9 (µg/L)	10.7 ± 0.8	9.9 ± 0.5	-0.80 ± 0.89	0.190	10.50 ± 0.52	9.60 ± 0.33	-0.49 ± 0.66	0.460	10.5 ± 0.9	11.1 ± 0.7	-0.59 ± 1.00	0.060	0.370	0.530	0.630
MDA (µmol/L)	3.30 ± 0.66	2.50 ± 0.76	−0.81 ± 0.33	0.005	3.20 ± 0.72	2.80 ± 0.73	-0.45 ± 0.46	0.001	3.10 ± 0.67	2.80 ± 0.32	-0.30 ± 0.32	0.510	0.022	0.041	0.028
TAC (mmol/L BSA Eq)	1.80 ± 0.28	2.30 ± 0.45	−0.06 ± 1.10	0.003	1.90 ± 0.35	1.90 ± 0.38	-0.01 ± 0.81	0.420	1.80 ± 0.32	2.10 ± 0.28	0.04 ± 0.74	0.620	0.510	0.280	0.990
SOD (ng/L)	0.74 ± 0.69	0.75 ± 0.69	4.2 ± 31.5	0.690	0.80 ± 0.80	0.75 ± 0.75	-3.9 ± 30.1	0.470	0.77 ± 0.67	0.65 ± 0.67	-4.7 ± 40.0	0.700	0.620	0.450	0.990
GSH (µg/ml)	64.28 ± 28.6	68.3 ± 30.6	2.6 ± 30.1	0.032	67.2 ± 30.5	68.6 ± 34.5	1.3 ± 38.4	0.72	65.0 ± 34.6	66.0 ± 36.6	0.93 ± 38.4	0.46	0.67	0.54	0.035
GSH-Px (U/ml)	84.8 ± 143.8	54.5 ± 89.0	−21.2 ± 87.8	0.520	101.1 ± 178.7	89.5 ± 98.7	-39.5 ± 106.6	0.041	92.8 ± 78.2	80.3 ± 40.5	-10.4 ± 58.3	0.210	0.490	0.760	0.180

p = Before and after study in each genotypic group; p_1 for trend = Between group comparison at baseline; p_2 for trend = Between group comparison after 12 weeks; P_3 for trend = Between group comparison of changes after 12 weeks. *Arbitrary unit. FSG = Fasting serum glucose; HbA1c = Glycated hemoglobin; BMI = Body mass index; WC = Waist circumference; WHR = Waist-hip ratio; FM = Fat mass; IL-6 = Interleukin 6; TNF = Tumor necrosis factor; hs-CRP = Highly sensitive C-reactive protein; SAA = Serum amyloid A; MMP-9 = Matrix metallopeptidase 9; MDA = Malondialdehyde; TAC = Total antioxidant capacity; SOD = Serum superoxide dismutase; GSH = Glutathione; GSH-Px = Glutathione-peroxidase; T2D = Type 2 diabetes; QUICKI = Quantitative Insulin Check Index

The variations in host response also exist in experimental models with homogenize samples. These conflicting results might be, at least partly, due to the effect of genetic polymorphisms that may modulate the response to vitamin D intake [35]. We previously reported the influence of VDR polymorphisms, *Fok*I and *Cdx*-2 on different aspects of T2D host. The absorption of both calcium and vitamin D has already been reported that is dependent to VDR genotypes [36].

Our results support previous findings of observational and molecular studies [37-39]. In a study, Elnenaei et al. [18] found that BB/Bb genotype in post-menopausal women were more responsive to vitamin D supplementation. Arabi et al. [40], have shown that this polymorphism results in lower response of the skeletal parameters of young healthy girls treated with vitamin D in the BB genotype. In addition, some studies have demonstrated that the VDR *Bsm*I genotype may influence the inflammatory marker profile and the anti-inflammatory response to treatment with vitamin D. In cachectic cancer patients, Punzi et al. showed that carriers of b allele had higher CRP levels. Moreover, in hemodialysis patients, Pacini et al. demonstrated that the presence of b allele was more frequent in patients with elevated serum CRP levels and suggested that the presence of this allele could be considered a risk factor in the pathogenesis of inflammation.

Recently, in de Medeiros Cavalcante et al. study [19] supplementation with a vitamin D3 megadose reduced inflammatory markers and increased the total antioxidant capacity in elderly women with vitamin D insufficiency. The 25(OH)D, PTH, ultra-sensitive CRP and AGPA levels of elderly patients with the BB/Bb genotype were more responsive to supplementation compared with those with the bb genotype. In another study with 25(OH)D3 supplementation, the differentiation of healthy and type 1 diabetes human monocytes into dendritic cells was inhibited and was increased the number of intermediate cells (IC) *in vitro*, demonstrating a dependent immunomodulatory effect to rs1544410 genotype in which bb genotype leads to a smaller increase in IC after supplementation with 25(OH)D compared to Bb and BB genotypes. Therefore, according to these results there is a dose response sensitivity to 25(OH)D which increases in the following order: bb, Bb, and BB.

Because VDR is involved in the regulation of many genes, different biological responses can be identified for its genotype [41]. Then, physiological impact of 1,25(OH)D is not restricted to the homeostasis of calcium and phosphate. VDR has been demonstrated to be involved in the decreased activation of the pro-inflammatory transcription factor nuclear factor-κB, which suggests that VDR plays an intrinsic inhibitory role in inflammation [42]. Then, the occurrence of VDR genotypes could, therefore, be pivotal in the outcome of any vitamin D intervention in a healthy as well as a patient population especially because differential activity of the VDR protein has been partially related to variations in the VDR gene [41].

Conclusion

Our findings indicated that those with VDR *Bsm*I bb genotype may be regarded as low responders to vitamin D intake in terms of circulating 25(OH)D and certain inflammatory and OS biomarkers. The prevalence of different VDR *Bsm*I variants among diabetes subjects could explain, at least in part, some discrepancies observed in the effect of vitamin D on various aspects of diabetes host response. However, further research is needed to replicate those findings in different populations, including populations of other racial and ethnic groups, to confirm the biological significance of *Bsm*I polymorphism in relation to diabetes host response.

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Conflict of interest

None of the authors had any personal or financial conflicts of interest.

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