Frequency of Vitamin D receptor (VDR) gene polymorphisms in the UAE population and their associations with 25-hydroxy vitamin D levels, obesity, diabetes and hypertension

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Abstract

Background: Although vitamin D levels and underlying vitamin D receptor (VDR) genetic polymorphisms have been linked to many common diseases including obesity, the association remains unclear. We aimed to determine the genotypes & allele percentage frequency distribution of four polymorphisms FokI, BsmI, ApaI and TaqI in the VDR gene in healthy Emirati individuals and their association with vitamin D levels and chronic conditions including diabetes mellitus, hypertension and
obesity

Methods: 277 participants who were part of a randomized controlled trial had their assessment that included clinical and anthropometric data. Whole blood samples were taken for measurements of vitamin D [25(OH) D], four vitamin D receptors gene polymorphism SNPs including BsmI, FokI, TaqI and ApaI, metabolic and inflammatory markers and related biochemical variables. Multiple logistic regression analysis used to assess the influence of vitamin D receptors gene SNPs on vitamin D status after adjusting for clinical parameters known to influence vitamin status in the study
population.

Results: Overall, 277 participants with a mean (±SD) age of 41±12 and 204 (74%) female were included in the study. There were statistically significant differences in vitamin concentrations between different genotypes of the 4 VDR gene polymorphisms ($p<0.05$). There were however no statistically significant differences in vitamin concentrations between subjects with and those without the 4 VDR gene polymorphisms genotype and alleles except for AA and AG and allele G in ApaI SNP ($p<0.05$). Multivariate analysis revealed no significant independent associations between vitamin D status and the 4 VDR gene polymorphisms after adjusting for dietary intakes, physical activity, sun exposure, smoking and body mass index. In addition, no significant differences found in the frequency of the genotypes & alleles of the 4 VDR genes among patients with obesity, diabetes and hypertension compared to those without these medical
conditions.

Conclusion: Although we found statistically significant differences in vitamin concentrations between different genotypes of the 4 VDR gene polymorphisms, however multivariate analysis revealed no association after adjusting for clinical parameters known to influence vitamin D status. Furthermore, no association found between obesity and related pathologies and the 4 VDR gene polymorphisms.

Introduction

Vitamin D an active hormone is essential for both bone and muscle health[1]. There is also mounting evidence that vitamin D can convey other health benefits because of the discovery that most cells and tissues in the human body contain vitamin D receptors[1]. Vitamin D elicits its biological action through binding to the vitamin D receptor (VDR)[1]. A number of loss-of-function mutations of the VDR gene have been identified which result in hereditary vitamin-D-resistant rickets[2]. In addition, several subtle allelic polymorphisms have been identified in the VDR gene, which have been linked to diseases such as osteoporosis and metabolic bone disorders[3]. However, the effects of these single nucleotide polymorphisms (SNPs) are not well understood[4]. Nevertheless, due to the large size of the VDR gene it is expected that many more SNPs will be identified and

of those already known some have been reported to influence susceptibility to some diseases such as type 1 and type 2 diabetes, rheumatoid arthritis, multiple sclerosis and many other autoimmune, metabolic and infectious conditions[5-8]. Furthermore associations between vitamin D and its VDR receptor polymorphism with obesity and associated diseases have been reported [9,10]. Both obesity and vitamin D deficiency are highly prevalent in UAE citizens, however their combined health implications are not yet clear. At present, BsmI, FokI, TaqI and ApaI are the four common single nucleotide polymorphisms in the VDR gene that have been most frequently studied[11-12]. Although numerous studies have reported the frequency of VDR gene SNPs and their association to different disease in different ethnic groups mostly Caucasian populations, very few studies have been conducted in the Middle East namely the UAE. And, many of those studies conducted in the Middle East suffer from methodological flaws including selection bias and small sample size[12-14]. Mutations of the VDR gene and allelic polymorphisms may influence disease susceptibility and responses to levels of circulating vitamin D especially in areas where D deficiency is highly prevalent such as Asian and Middle Eastern populations. However, results of the studies which have been published so far on the relationship between low vitamin D status and its health Implications in non- Caucasian population yielded conflicting results[15,16]. For example, a cross-sectional study evaluated whether Pakistanis living in the city of Oslo, have increased bone turnover compared with ethnic Norwegians due to their high prevalence of vitamin D deficiency[15]. The results revealed only minor ethnic differences in bone turnover, despite a striking difference in prevalence of secondary hyperparathyroidism with no differences observed in bone mineral density between the two groups [15]. Another study from the UK on vitamin D status and markers of bone turnover in Caucasian and South Asian postmenopausal women found that although South Asian women had significantly higher serum parathyroid hormones and lower 25(OH) D concentrations there were no significant differences between the two groups for biochemical markers of bone turnover [16]. An interesting speculative explanation for this paradox is that altered metabolism of vitamin D due ethnic and/or genetic difference in the Asian women may protect their skeleton from bone loss [17-19]. This is clearly an area for research. In summary vitamin D deficiency and obesity and related pathologies are highly prevalent in UAE citizens, but their combined health implications are not yet clear. Mutations of the VDR gene and presence of SNPs may account for variation in individual responses to levels of circulating vitamin D. The overall objective of this study is to investigate the genotypes & allele percentage frequency distribution of four common polymorphisms FokI, BsmI, ApaI and TaqI in the VDR gene in healthy Emirati individuals and their association with Vitamin D levels and chronic conditions including diabetes mellitus, hypertension and obesity

Methods

Details of the subjects' recruitment and methods were published before[20]. Briefly, healthy community free-living Emirati (UAE citizens) and expatriates Arabian men and women from other countries in the Middle East who were part of a randomized, double-blind placebo-controlled placebo intervention trial were included in this study. Subjects aged 18 years and over were recruited by advertisement through the local press, from community health centers and from hospital outpatient clinic. Individuals with renal disease or stones, hypercalcaemia, on calcium and/or vitamin D supplementation, bisphosphonates, steroid medications, hormones or diuretics or unable to give an informed written consent were excluded. Following informed written consent, eligible subject's blood samples were taken for measurements of vitamin D and inflammatory

and metabolic risk markers. Clinical assessment that includes demographic and baseline characteristics, general and self-rated health and physical activity were performed at baseline. Information on other important variables likely to influence vitamin D status were also collected.

The measurements

Face-to-face questionnaire data collected on lifestyle and health factors that are of interest in this study of the health implications of vitamin D deficiency in UAE citizens. A common set of questions on education and socio-economic status; current and past occupation; history of previous illness or surgical operations; tobacco smoking; consumption of beverages; physical activity, use of herbal medicine, vitamin supplements, exogenous hormones for contraception and postmenopausal replacement therapy were collected.
Anthropometric data including body weight, height and BMI were measured using Tanita body composition analyzer. Using WHO sex-adjusted cut-of-points for BMI, subjects with BMI =18-25 classified as normal, BMI=25.1-29.9 as overweight and those with BMI 30 as obese.

Biochemical and urine analysis

Patients provided a fasting morning blood sample. Biochemical analysis of 25(OH) D was measured using fully automated COBAS e411 analyzer that uses a patented Electro Chemiluminescence (ECL) technology for immunoassay analysis from ROCHE diagnostics, Manheim .

DNA preparation and VDR SNPs genotyping analysis

Genomic DNA was extracted from whole blood collected from study participants using a QIAamp DNA Mini Kit (QIAGEN, Valencia, CA, USA) according to the manufacturer's instructions. The extracted genomic DNA analyzed using agarose gel electrophoresis and quantitatively determined by spectrophotometry, and stored at 80oC until use. The four VDR SNPs (BsmI, FokI, TaqI and ApaI) evaluated using TaqMan SNP genotyping assay which consists of a predesigned mix of unlabeled polymerase chain reaction (PCR) primers and the TaqMan® minor groove binding group (MGB) probe (FAM™ and VIC® dye-labeled). All TaqMan SNP genotyping assays are designed to work with TaqMan® Universal PCR Master Mix which contains DNA polymerase, dNTPs and optimized mix components and uses the same thermal conditions (Applied Biosystems, USA). The PCR consisted of a hot start at 95°C for 10 min followed by 40 cycles of 94°C for 15s and 60°C for 1min. Fluorescence detection performed at 60°C. All assays were performed in 10-25µl reactions, using TaqMan Genotyping Master Mix on 96-well plates using Genetic Analyzer (Applied Biosystems, Foster City, CA, USA) according to the manufacturer's instructions.

Statistical analysis was performed with SPSS software, version 25.0 (SPSS Inc., Chicago). One-way ANOVA or the nonparametric Kruskal-Wallis H test was used to test for between-group differences, and a p value < 0.05 was considered significant. Multiple regression analyses were used to assess the independent association between vitamin D status (deficiency vs. insufficiency/optimal) and the 4 VDR gene after adjusting for other clinical parameters including, age, gender, dietary intakes, physical activity, sun exposure, smoking and body mass index.

Results

Baseline characteristics

Overall 277 participants with a mean (±SD) age of 41±12 and 204 (74%) female were included in the study. Among the 277 subjects recruited 46 (17%) had type 2 diabetes and 41(15%) had hypertension. Using WHO cut-of-points for BMI 65 (24%) subjects had normal BMI, 93 (34) overweight and 108 (39%) obesity at baseline (Table 1).

Distribution of 4 VDR gene polymorphism in 277 Emirati population

Figure 1 shows genotypes & allele percentage frequency distribution of 4 VDR gene polymorphism in 277 Emirati population. The frequencies of VDR genotypes for Bsml is: GG=37%, AG=44%, AA=20.7%. For Taql VDR genotype our result agree with another study findings from the UAE and France[12,21].

Vitamin D concentrations according to distribution and presence or absence of genotypes & allele of 4 VDR gene polymorphism

Table 2 shows vitamin D concentrations according to genotypes distribution of the 4 VDR gene polymorphism. There were statistically significant differences in vitamin concentrations between different genotypes of the 4 VDR gene polymorphisms ($p<0.05$). Table 3 shows vitamin D concentrations according to presence or absence of genotypes & allele distribution of 4 VDR gene polymorphism. There were statistically significant difference in vitamin concentrations between subjects with or without genotypes AA and AG and allele G in ApaI VDR gene polymorphism only ($p<0.05$).

Genotype distribution based on gender, BMI and diabetes, hypertension

Multiple logistic regression analysis revealed significant and independent association between vitamin D status and age and sex only ($p<0.05$), [Table 4]. We found no statistically significant independent associations between the VDR gene polymorphisms assessed and vitamin D status (deficiency vs. insufficiency/optimal) after adjusting for clinical parameters known to influence vitamin D status including age, sex, dietary intakes, physical activity, sun exposure, smoking and body mass index of study population (Table 4).

Figures 2, 3 & 4 show the genotypes & allele percentage frequency distribution of all 4 VDR gene polymorphism, Bsml,Taql, ApaI and Fok1 among subjects with and those without diabetes, HTN and obesity[GAA1] . There were no statistically significant differences in the frequency of the genotypes & alleles of Bsml,Taql, ApaI and Fok1 VDR genes among patients with diabetes and hypertension compared to those without these medical conditions except in Fok1 AA genotype and G alle (Figures 2 & 3). No statistically significant differences found in the frequency of the genotypes & alleles of Bsml, Taql, ApaI and Fok1 VDR genes in obese and overweight subjects compared to normal weight subjects (Figure 4). Furthermore, no statistically significant difference found in BMI between subjects with and those without the genotype & alleles of all 4 VDR genes.

Discussion

We examined the prevalence of the common four single nucleotide polymorphisms in the VDR gene including BsmI, FokI, TaqI and ApaI in a large sample of UAE population and compared vitamin D concentrations between subjects with and those without the genotypes & alleles of all 4 VDR genes. In addition, we compared their association with chronic diseases common in the UAE society including diabetes, hypertension and

obesity. Although we found statistically significant differences in vitamin concentrations between different genotypes of the 4 VDR gene polymorphisms, however, no assocaition found after adjusting clinical parameters known to influence vitamin D status. We also found no association with chronic diseases known to be prevalent in the UAE society such as obesity and its associated pathologies including diabetes and hypertensin, except in Fok1 AA genotype and G alle.

Genotypes & allele percentage frequency distribution compared to previous studies

The prevalence of some of the genotypes & allele is in agreement with previous studies from the UAE community and other societies. For example, the frequency distribution of Bsml is in agreement with a previous study from the UAE (Saadi et.al)[14]. (Saadi et al findings: GG=37%, AG=42%, AA=20%; our findings: GG=37%, AG=44%, AA=20.7%)[14]. For Taql VDR genotype our result agree with another study findings from the UAE and a study from France [12, 21]. Although not many studies in the UAE have reported the frequency distribution of the SNP3 ApaI however studies from the Middle East have reported the relationship between SNP3 ApaI and vitamin D and occurrence of cardiovascular disease (CVS) from around the world [22]. Our results of SNP4 Fok1 genotypes & allele percentage frequency distribution are different from previous studies including one from the UAE [12]. A study from India of the frequency of Fok I and Taq I variants in healthy Indian individuals and its association with 25-OH-Vitamin D levels reported that the distribution of the polymorphic loci Fok I and Taq I vary considerably not only in different populations, but also within India [23]. Overall the reasons for the difference in in vitamin D genotypes & allele nucleotide polymorphisms percentage frequency distribution appears to be difference in sample size and sampling methods used between different studies. The unrepresentative or biased samples made it difficult to make valid generalization about vitamin D genotypes & allele percentage frequency distribution within and between different populations.

Vitamin D concentrations according to presence or absence of genotypes & allele

distribution of 4 VDR gene polymorphism

Although we found statistically significant differences in vitamin concentrations between different genotypes of the 4 VDR gene polymorphisms, however no statistically significant independent associations found between 4 VDR gene polymorphisms assessed and D status after adjusting for clinical parameters known to influence vitamin D status such as dietary intakes, physical activity, sun exposure, smoking and body mass index. Another previous study from the UAE found no association between vitamin D levels and bone turnover markers and Bsml VDR gene polymorphism[14]. In contrast a study from India reported a significant association between vitamin D levels, and Taq 1 SNP but not with the Fok I [23].

Genotypes & allele percentage frequency distribution in subjects with and those without chronic conditions including obesity, diabetes mellitus and hypertension

Circulating vitamin D levels, action and underlying vitamin D receptor VDR genetic polymorphisms have been linked to many common diseases such as obesity and associated pathologies including diabetes, hypertension and CVS diseases. This is important because of the co-existence of pathologically high proportions of obesity and vitamin D deficiency in our population. Many vitamin D genetic and alleleic polymorphism have been identified and their effects on VDR protein function and consequently vitamin D

levels health impact have been studied. The BsmI, FokI, TaqI and ApaI polymorphisms in the VDR gene have been the most studied. In this study we found no statistically significant differences in the percentage frequency distribution of all 4 VDR gene polymorphism, Bsml,TaqI, ApaI and Fok1 among subjects with and those without obesity, diabetes mellitus and hypertension except in Fok1 AA genotype and G alle in subjects with diabetes and hypertension compared with those without these conditions. The association between vitamin D receptor VDR polymorphism and the risk of chronic diseases including obesity, hypertension, diabetes and other cardiovascular diseases therefore remains unclear. A recent preliminary study assessed the relationship between the VDR genotypes, plasma concentrations of vitamin D metabolites, and the occurrence of cardiovascular and metabolic disorders in 58 patients treated for various cardiological diseases. Among patients with the TT genotype, frequency of hypertension was higher than among carriers of other ApaI genotypes ($p < 0.01$). In addition, carriers of the TT ApaI, TC TaqI, and GA BsmI genotypes had an increased risk of obesity, while the presence of the FokI TT genotype was associated with a higher incidence of heart failure and hypertension. In conclusion, this study reported that the BsmI AA genotype can be protective against CVS, but this observation needs to be confirmed on a larger group of patients. Particular VDR genotypes were associated with 25-hydroxyvitamin-D levels, and the mechanism of this association should be further investigated [22]. Another cross-sectional study investigated relationships of vitamin D receptor gene VDR polymorphisms to the components of metabolic syndrome (MetS) including obesity, hypertension, diabetes and dyslipidemia among 198 (148 females, 50 males) Arabs adult residing in the United Arab Emirates reported that VDR gene polymorphisms were not associated with MetS. However, the authors reported that it may affect the severity of some of components of MetS, namely the association of BsmI with obesity, FokI and BsmI with dyslipidemia and FokI with systolic blood pressure [24]. Another cross-sectional study from the UAE investigated the association between VDR polymorphisms and type 2 diabetes (T2DM) among 264 patients with T2DM and 91 healthy controls were enrolled. The TaqI variant was shown to be associated with high cholesterol and LDL-cholesterol levels in T2DM patients, while BsmI was associated with lower BMI and lower LDL cholesterol levels. Their results implied that alleles and haploypes of the VDR gene are associated with the susceptibility to T2DM in the Emirati population [25]. A meta-analysis of 14 studies of the association of four polymorphisms FokI, BsmI, ApaI and TaqI in the VDR gene with the susceptibility to T2DM reported no significant associations between BsmI, ApaI and TaqI variants and T2DM risk. The report did suggest and increased with of T2DM in subjects with FokI VDR gene polymorphism in Asian population [26]. The association of low vitamin D level and its receptor polymorphism with obesity was studied in 300 Saudi men reported that both bb of BsmI and tt of TaqI genotypes were higher in the obese group compared with lean group and that low vitamin D level and VDR BsmI and Taq1 genotypes may be a risk factor of obesity [27]. A study from Iran which looked at the association of the VDR gene ApaI, BsmI, and TaqI polymorphisms with obesity in 348 obese and 320 non-obese subject reported an increased risk of obesity in subjects with VDR ApaI polymorphism. In particular the A allele and the AA genotype in ApaI were associated with the obesity phenotypes [28].

A systematic review of the association between genetic polymorphisms and obesity in the Arab world included 59 studies with a total 15,488 cases and 9,760 controls in the final analysis. A total of 76 variants located within or near 49 genes were reported to be significantly associated with obesity. Among the 76 variants, two were described as unique to Arabs, as they have not been previously reported in other populations, and 19 were reported to be distinctively associated with obesity in Arabs but not in non-Arab populations. The authors

concluded that there appears to be a unique genetic and clinical susceptibility profile of obesity in Arab patients [29].

Strength & weakness

Our study is one of the very few studies to measure the four single nucleotide polymorphisms in the VDR gene including BsmI, FokI, TaqI and ApaI in a large sample of UAE population with a high prevalence of overweight & obesity (76%), diabetes (17%) and hypertension (15%). We used BMI as a measure of adiposity in our study. Although BMI is an easily accessible measure of excessive body weight in the general population, it cannot differentiate between fat and lean body mass. Individuals with normal weight can still demonstrate harmful adiposity traits[30]. Nevertheless, and similar to most previous studies reported on the relationship between vitamin D VDR genetic polymorphisms and risk or severity of chronic diseases our sample selection and size may not be representative of the whole UAE population. Most previous studies reported in this area however, have major heterogeneity and weaknesses in relation to study design, sample size, variables measured and control for confounders. In this study we have made an attempt to identify a potential independent effect of the four single nucleotide polymorphisms on vitamin D status by adjusting for a number of clinical parameters likely to affect vitamin D status.

Conclusion

Although we found statistically significant differences in vitamin concentrations between different genotypes of the 4 VDR gene polymorphisms, however, no independent associations found between VDR gene polymorphisms assessed and D status (deficiency vs. insufficiency/optimal) after adjusting for clinical parameters known to influence vitamin D status. We also found no association with chronic diseases known to be prevalent in the UAE society such as obesity, diabetes and hypertensin. There is still however the need to study the relationships between VDR gene polymorphisms and obesity related diseases in an appropriate representative sample of the target population to which the findings will be referred. This is because of the co-existence of pathologically high proportions of obesity and vitamin D deficiency conditions in our society and the Middle East at large.

Abbreviations

BMI
body mass index
CVS
cardiovascular disease
ECL
chemiluminescence
LDL
Low density lipoprotein
SNPs
single nucleotide polymorphism
T2DM

type 2 diabetes mellitus
UAE
United Arab Emirates
VDR
vitamin D receptor
MetS
metabolic syndrome

Declarations

Ethics approval and consent to participate: Al Ain Medical District Human research ethics committee approved the study. An informed written consent was obtained from all patients recruited to this study.

Consent to publish: Not applicable

Availability of data and material: Data is available upon request to the corresponding author

Competing interest: The authors declare that they have no financial or non-financial competing interest or conflict of interest

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Authors' contribution: SG wrote the first draft, SG, & JY contributed to the design, running of study, analysis and presentation of data. GA contributed data management and analysis. All authors contributed to the writing of the manuscript and the discussion and approved the final manuscript.

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Tables

Table 1. Baseline clinical, metabolic characteristics of the study population

Variables		Mean (SD unless otherwise stated (n=277)
Age (years)		41 (12)
Sex, female n(%)		204 (74)
Smoking n (%)		
	Current	35 (13)
	Ex-smoker	12 (4)
	Never smoked	225 (81)
Body mass index (BMI) n(%)		
	Normal weight (BMI 18.5-25)	65 (24)
	Overweight (BMI 25.1-29.9)	93 (34)
	Obese (BMI ≥30)	108 (39)
Physical activity n(%)		
	Not active	32 (12)
	Moderately active	146 (53)
	Very active	96 (35)
Diabetes n(%)		46 (17)
Hypertension n(%)		41 (15)
Hs CRP (mg/L)*		3.5 mg (3)
Glucose (mmol/L) *		6.3 (2,5)
Total cholesterol (mmol/L) *		4.9 (0.9)
Urea (mmol/L) *		4.1 (1.5)

*All values fall within normal limits

Table 2: Vitamin D concentrations (ng/ml) according to genotypes distribution of 4 VDR gene polymorphism

	AA	GG	AG	P value
RS1544410_SNP1_BsmI	24.5 (11)	22.1 (11)	23.9 (10)	0.046
RS731236_SNP2_TaqI	22.0 (11)	24.0 (11)	23.9 (10)	0.054
RS7975232_SNP3_ApaI	25.0 (11)	22.3 (11)	21.7 (9)	0.008
RS2228570_SNP4_Foak1	24.0 (10)	23.9 (12)	22.6 (9)	0.007

Table 3: mean (SD) vitamin D concentrations (ng/ml) according to presence or absence of genotypes & allele distribution of 4 VDR gene polymorphism

	AA		GG		AG		A		G	
	Yes	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
RS1544410_SNP1_BsmI	25.5 (11)	23.2 (10)	22.1 (11)	24.2 (10)	23.9 (10)	23.1 (11)	23.9 (10)	22.7 (12)	23.0 (10)	25.0 (12)
RS731236_SNP2_TaqI	22.0 (11)	24.1 (10)	24.0 (11)	23.3 (11)	23.9 (10)	23.0 (11)	23.2 (11)	24.5 (11)	23.9 (11)	22.3 (11)
RS7975232_SNP3_ApaI	25.1 (11)	22.1* (10)	22.3 (11)	23.7 (11)	21.7 (9)	24.5* (11)	23.6 (10)	22.9 (12)	21.9 (10)	25.3* (12)
RS2228570_SNP4_Foak1	23.9 (10)	23.4 (11)	22.6 (9)	24.1 (11)	23.9 (12)	23.0 (10)	22.9 (10)	24.1 (12)	23.3 (11)	24.6 (11)

*P<0.05 for difference between those with and those without the genotypes & allele 4 VDR gene polymorphism

Table 4. Multiple logistic regression analysis of the influence of 4 VDR gene polymorphism and some clinical prognostic variables on vitamin D status (deficiency vs. insufficiency/optimal) of study population

	Standardized Coefficients B	Standard error	p value	Exp(B)	95.0% Confidence Interval for B	
					Lower bound	Upper bound
Age (years)	.018	.008	.022	1.018	1.003	1.034
Gender (male/female)	-.763	.241	.002	.466	.291	.748
BMI	-.006	.008	.443	.994	.978	1.010
Sun exposure	.009	.044	.838	1.009	.926	1.099
Diet	.010	.036	.782	1.010	.941	1.083
Physical activity	.050	.154	.748	1.051	.777	1.422
Smoking	.071	.142	.616	1.074	.813	1.417
RS1544410_SNP1_Bsm	.179	.146	.221	1.196	.898	1.593
RS731236_SNP2_TaqI	-.067	.127	.598	.935	.730	1.199
RS7975232_SNP3_ApaI	-.079	.064	.217	.924	.815	1.047
RS2228570_SNP4_	-.156	.144	.279	.855	.645	1.135

Figures

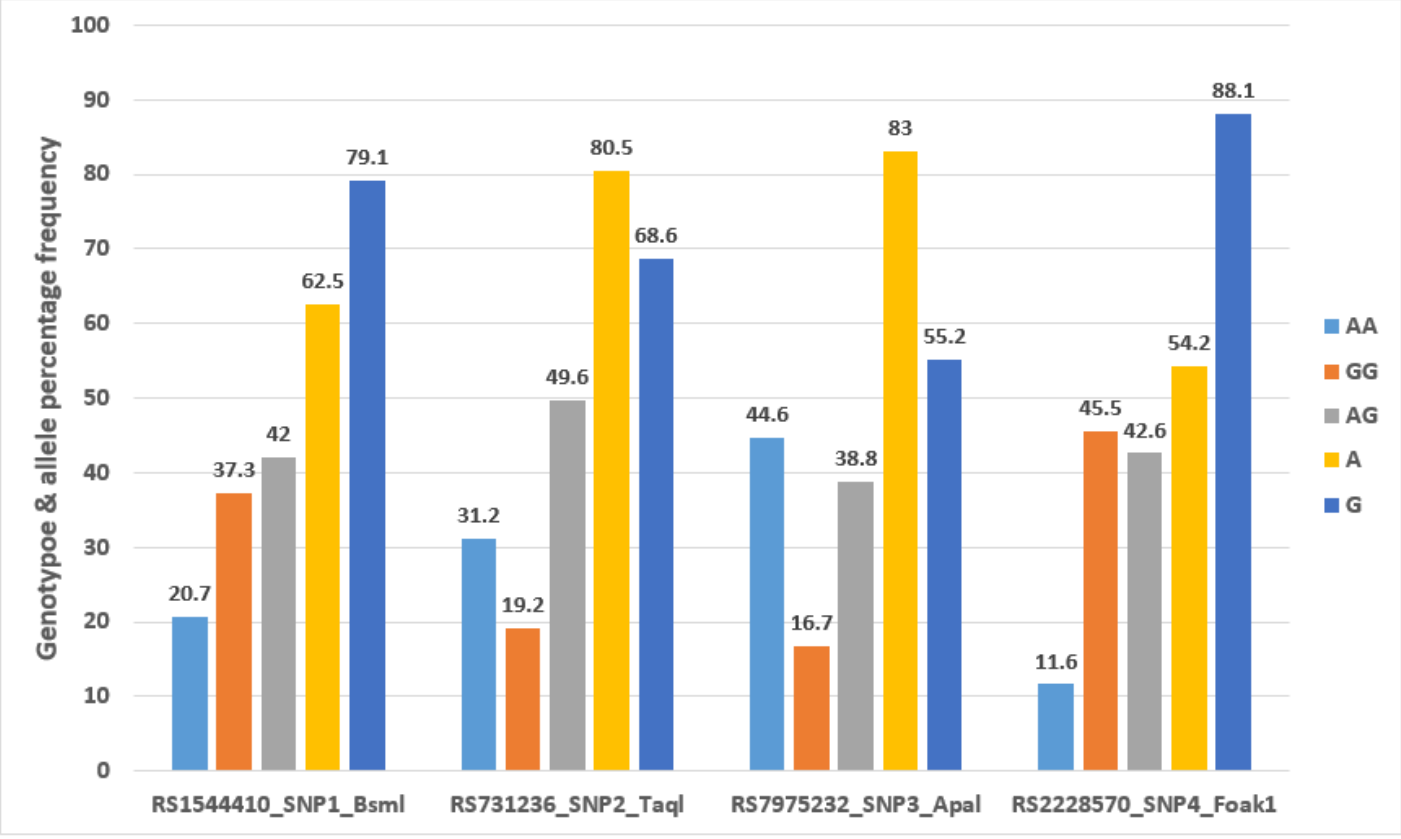
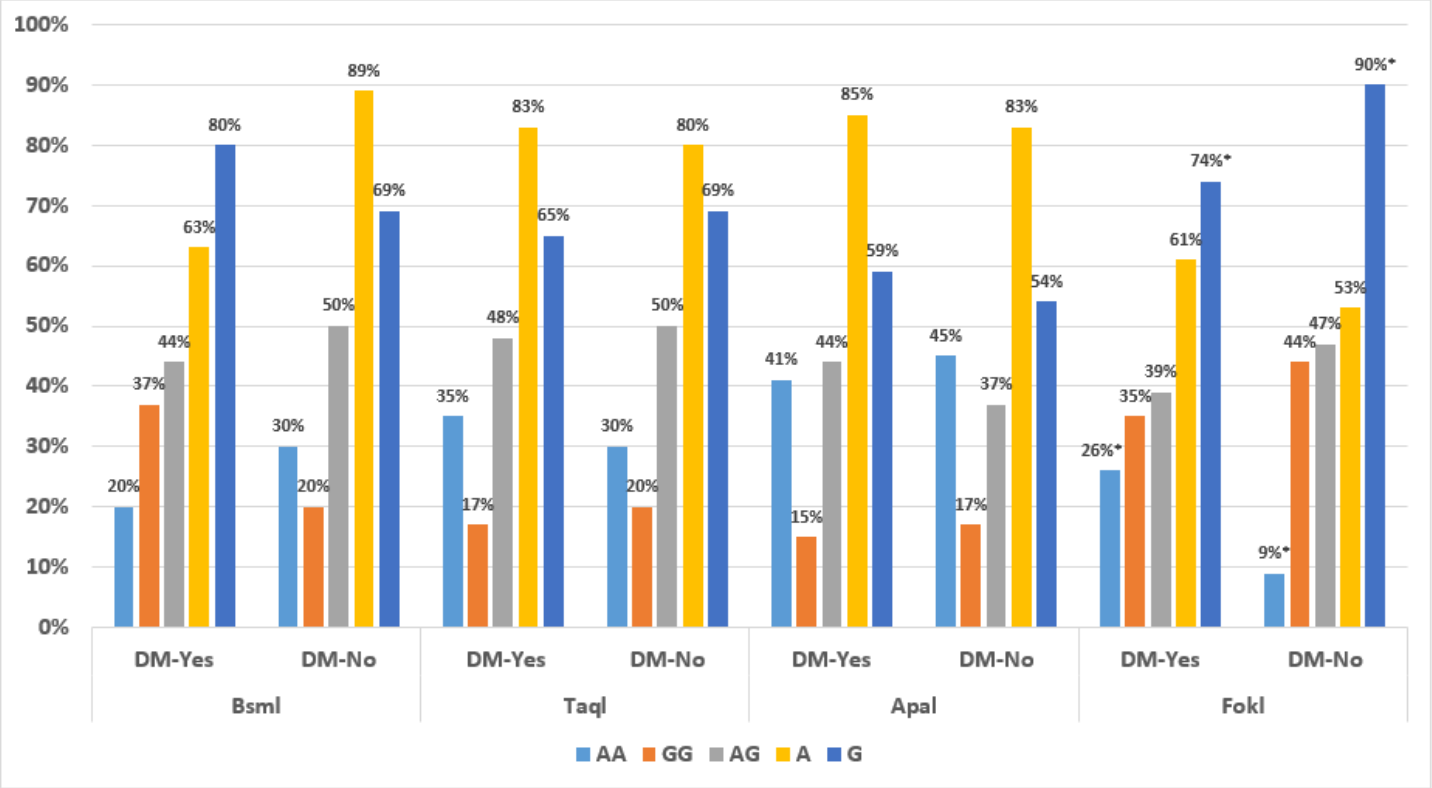


Figure 1

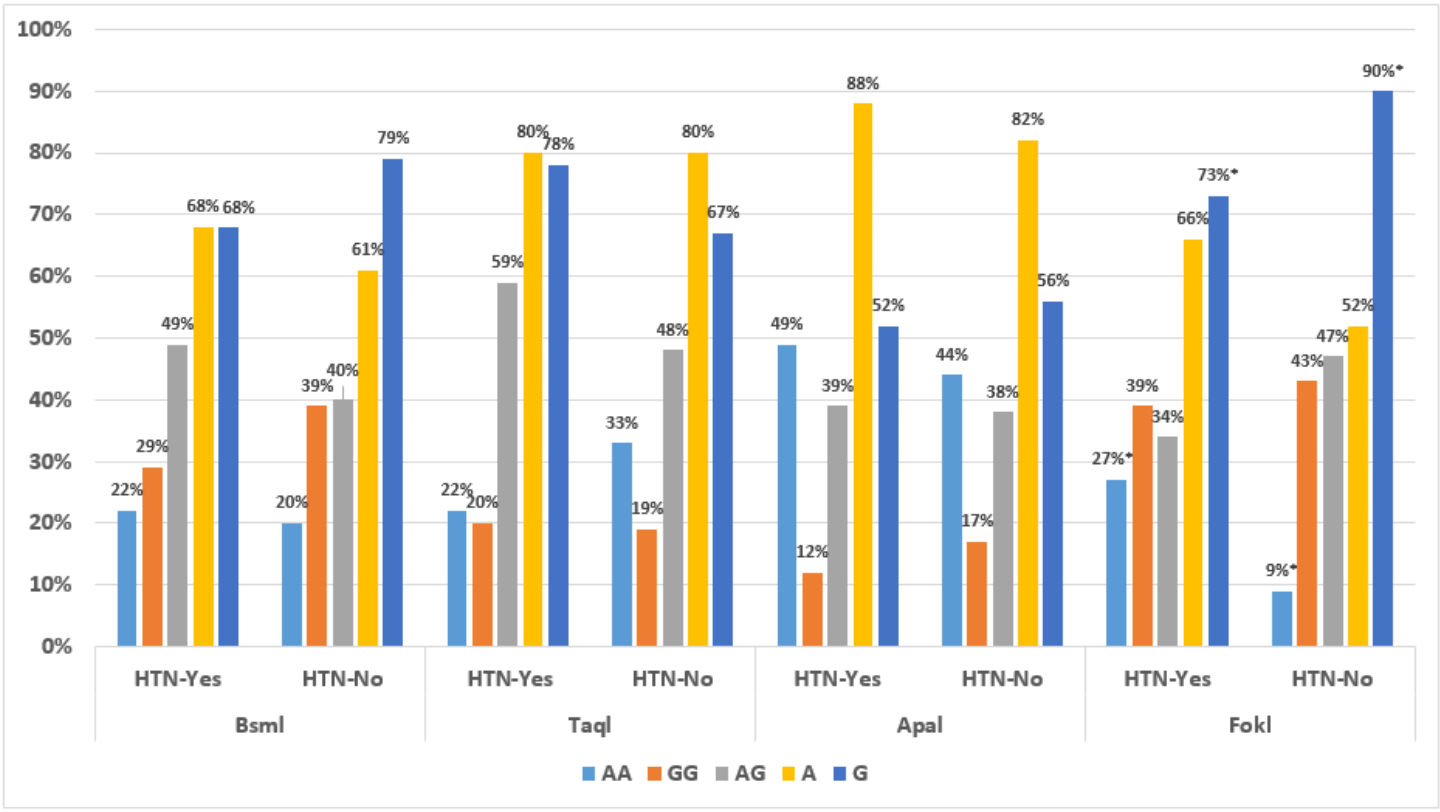
Genotypes & allele percentage frequency distribution of 4 VDR gene polymorphism in Emirati population



*** P < 0.05**

Figure 2

Genotypes & allele percentage distribution of 4 VDR gene polymorphism in subject with diabetes (DM) compared with those without diabetes.



*** P < 0.05**

Figure 3

Genotypes & allele percentage distribution of 4 VDR gene polymorphism in subject with hypertension (HTN) compared with those without hypertension.

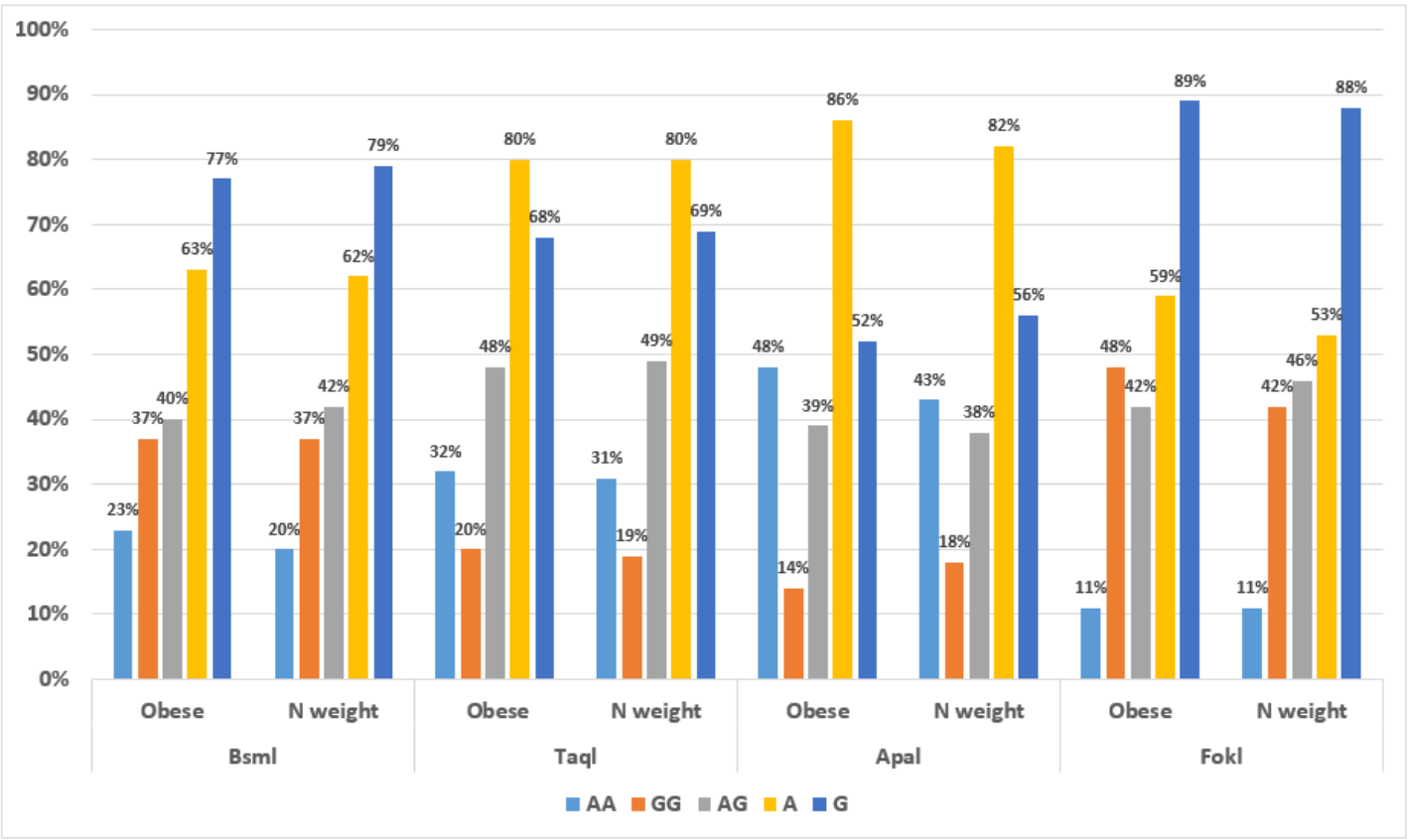


Figure 4

Genotypes & allele percentage distribution of 4 VDR gene polymorphism in obese subject compared to normal weight (N weight) subjects.