Lower levels of TSH in vitamin D sufficient Graves patients and higher rates of vitamin D deficiency in graves patients: a case-control study

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Abstract

Vitamin D deficiency is associated with an increased incidence of autoimmune thyroid diseases. Its association with Hashimoto has previously been discussed in several studies, but its role in Graves' disease is yet to be elucidated; the aim of this study was to evaluate the effect of vitamin D on hyperthyroid patients regardless of the cause (autoimmune, non-autoimmune and control) . A total of 187 patients were divided into three groups: 74 patients with autoimmune hyperthyroidism (Graves), 43 non-immune patients (Toxic thyroid adenoma and goiter multi-nodular) and 70 healthy patients as the control group. The primary outcome was the frequency of vitamin D deficient patients and the level of vitamin D in each group. The secondary outcomes were measured as the values of anti-thyroid antibody and anti-thyroglobulin antibodies, TSH, T3, and T4. Based on the results, higher levels of TSH were observed in Graves patients who were vitamin D sufficient in comparison to Graves subjects with moderate vitamin D deficiency (P=0.022). Also, vitamin D sufficient control subjects had higher TSH levels than subjects with severe (p<0.0001) and moderate (P<0.0001) vitamin D deficiency. Vitamin D deficiency was more frequent in Graves patients, however the difference was not significant (P-value>0.05). Vitamin D deficiency as an effective factor in thyroid autoimmune diseases is more frequent in autoimmune hyperthyroid disease patients. Moreover, vitamin D sufficient Graves' participants had higher TSH levels compared with vitamin D deficient ones, probably protecting them from developing osteoporosis. Low TSH levels in hyperthyroid patients are one of the osteoporosis risk factors.

Background

Study design and settings:

The present case-control study was performed in Jahrom Peymaniyeh Hospital from 2016 to 2017. The hyperthyroidism was confirmed by the endocrinologist according to thyroid function tests, physical exams, thyroid auto-antibodies levels, and thyroid scintigraphy with technetium. Thyroid ultrasonography were also used as a complementary test to confirm the etiology of the hyperthyroidism and differentiate Toxic Multi-Nodular goiter from Graves (GD) and Toxic adenoma. The exclusion criteria of the present research were Type 1 diabetes, rheumatoid arthritis, lupus, collagen vascular, celiac diseases, and also the patients who had received supplementary vitamin D and interacting drugs with vitamin D (such as antacids, corticosteroids, Orlistat, diabetes medications, anti-hypertensive drugs, Cholestyramine, antiepileptics, calcium supplements). The three groups were matched in terms of age and gender intervention variables. Sampling was carried out in same season of year(spring).

Study population:

All patients with hyperthyroidism who referred to clinic, including GD and non-immune hyperthyroid (toxic adenoma and toxic multinodular goiter) patients were selected as the case group, and healthy people were considered as the control one (Figure1).

All patients with clinical hyperthyroidism were examined by serum levels of 25OHD vitamin D at the end of summer that participants had enough sun exposure. TSH, T3, T4, TPOAb, and TGAb were evaluated at first

visit for diagnosis. The level of vitamin D was then interpreted and compared with the causes of hyperthyroidism. In addition, healthy people in terms of thyroid function were selected as the control group (with ages and genders similar to the case group). The vitamin D level of the control group (who were not receiving supplementary vitamin D) was also measured same time at the end of the summer and compared with the case group (GD and non-immune patients). Another comparison was further made between GD and non-immune patients.

Moreover, written informed consent was obtained from all patients, and no harmful interventions were done. The study was performed during the routine endocrine follow-ups, where no personal information was obtained. The results will not be disseminated back to the study participants.

Laboratory measurements:

Blood samples were taken from all participants after at least 8 hours of fasting. T3, Free T4, and TSH were measured by Cobas ECLIAs (Roche Diagnostics GmbH, Mannheim, Germany). Thyroid peroxidase antibody (TPOAb) was determined by chemiluminiscenta IMMULITE 2000 XPi (Siemens, Eschborn, Germany). TPOAb values more than 40 IU/ml were considered for the presence of TPOAb in Iranian subjects [20]. Thyroid globulin antibody (TGAb) levels were analyzed by Enzyme-Linked Immunosorbent Assay (ELISA kit, Diesel), with values more than 100 IU/ml considered as positive [21]. Vitamin D levels were measured by LIAISON vitamin D chemiluminescence immunoassay (DiaSorin, Saluggia, Italy).

Statistical analysis:

In order to compare the TPOAb level in different groups, Kruskal–Wallis nonparametric test was performed based on vitamin D. The chi-square test was further conducted to evaluate the distribution of people with positive antibody titers. In order to evaluate the relationship between vitamin D concentration and study factors, the Pearson correlation and linear regression were employed. U Mann-Whitney non-parametric test was also applied to compare the vitamin D concentration between males and females. Additionally, U Mann-Whitney test was used to compare the serum vitamin D level between people with positive and negative TPOAb. Data were reported in the form of mean ± standard deviation. The significance was considered at P=0.05. The results of abnormal and normal data are illustrated in the tables in the form of mean±SD and median (first quartile, third quartile), respectively.

Methods

The flowchart of the study population and design are presented in Fig. 1.

Fig. 1. Flowchart of the study population and the study design

In the present study, the paraclinical data of 187 patients were analyzed in three groups, including 74 patients with autoimmune hyperthyroidism (GD), 43 non-autoimmune patients (toxic adenoma and multinodular goiter), and 70 healthy subjects. With a mean age of 36.74 ± 13.76, the participants aged between 40 and 74 years. Anti-thyroid antibody (TPOAb) and anti-thyroglobulin antibodies (TGAb) were also utilized to detect the type of hyperthyroidism along with other paraclinical tests (Table1).

Table 1. Basal characteristic of study subjects

The results of this study showed that 22 non-autoimmune thyroid patients (%51.16), 50 GD patients (%67.56) and 41 controls (%58.57) were vitamin D deficient. Vitamin D deficiency was more frequent in GD patients. However, the differences were not statistically significant (P-value>0.05)(Figure 2).

Figure2. Vitamin D deficiency rate in study groups

The levels of vitamin D in female and male subjects were 13.05(7.4-24.03) and 23.4(17.98-30.35) respectively (P<0.05). Moreover, the levels of TSH in female and male subjects were 0.81(0.01-2.75) and 0.03(0.00-1.43) respectively (P<0.05).

There was no significant difference between patients with autoimmune and non-autoimmune hyperthyroid diseases in terms of the serum concentration of 25OHD (P=0.608). Patients with GD had significantly higher levels of TPOAb and TGAb compared with control and non-autoimmune hyperthyroid disease groups (P<0.001) (Figure 3).

Figure3. Rate of Positive autoantibodies in study subjects

According to Table 2, we found positive TPOAb and TGAb in 51 (%45.13) and 30 (%26.54) patients, respectively among vitamin D deficient individuals (Vitamin D<20 ng/mL). However, TPOAb and TGAb rates among vitamin D sufficient patients (Vitamin D>20 ng/mL) were 27 (%36.48) and 16 (%21.62), respectively.

Table2: comparing between vitamin d sufficient and deficient subjects

As seen in Table 3, there were no significant differences concerning TSH, T3, T4, and autoantibodies. In GD patients, on the other hand, individuals with sufficient vitamin D levels had significantly higher levels of TSH compared with subjects suffering from moderate vitamin D deficiency (P=0.022); no differences were observed as far as T3 and T4 levels are concerned. In the control group, subjects with normal 25OHD levels had higher TSH levels than subjects with severe vitamin D deficiency (p<0.0001) and moderate vitamin D deficiency (P<0.0001) (Table 3). However, there was no significant difference among different levels of vitamin D regarding T3 and T4 concentrations.

Table 3. Vitamin D ranges and paraclinical tests

Discussion

Autoimmune thyroid diseases such as Hashimoto's thyroiditis and GD are among the most common autoimmune disorders. The onset of these diseases occurs by lymphocytic penetration into the thyroid gland and the production of anti-thyroid antibodies. These lymphocytes produce antibodies that bind to thyroid TSH receptor. Vitamin D plays an important role in regulating the immune system and has an inhibitory effect on the specific immune system [16]. GD is also an autoimmune disorder in which autoantibodies bind to thyrotropin receptors (TSH-Rs), causing excessive production and secretion of thyroid hormones, independent of the thyrotropin feedback regulation [19]. It seems that vitamin D inhibits the production of anti-thyroid

antibodies by binding to VDR and activating VDR-relate genes. The VDR gene polymorphism is associated with autoimmune thyroid disease (AITD) [17].

The association between serum vitamin D levels and autoimmune diseases has generally been accepted by researchers [18]. In the present case-control study, the level of 25OHD has been evaluated in hyperthyroid patients, and compared with control subjects. Anti-thyroid antibody (TPOAb), anti-thyroglobulin antibodies (TGAb), TSH, T3, and T4 were also measured. In our study there was a high incidence of vitamin D deficiency. Among the 187 subjects, 113 (60.42%) patients were suffering from vitamin D deficiency.

The results of the present research indicated that positive TPOAb and TGAb incidences were more frequent in patients with vitamin D deficiency, yet the differences were not statistically significant. In terms of serum levels, despite the lower median of TGAb and TPOAb serum levels in individuals with sufficient vitamin D level compared to those with vitamin D deficiency, no significant differences were observed. Apparently, determining the cut-off measurement of these autoantibodies plays a role in these differences [22]. Tehran thyroid study, in which the median of TPOAb level of individuals with positive titer was considered to be 177 (79-366), was used as a measurement reference in specifying the diagnostic levels in the present research [20]. Accordingly, the subjects enrolled in the research as TPOAb positive had a median equivalent to 269 (143-489). The difference between these two values can occur due to the following reasons :(1) In the present study, most patients were diagnosed with known thyroid diseases; however, in Tehran's study population, only the families living in Tehran were included. Therefore, the higher median level of TPOAb was foresighted in our study. (2) The difference in the number of participants can be yet another reason. In Tehran study, as a cohort study, the number of subjects were higher, yet no study has ever determined the natural courses of TGAb level in Iranian subjects.

Kivity et al. [15], as a pioneer in this field, reported the relationship between the lower levels of vitamin D and autoimmune thyroid disease. They also demonstrated the role of vitamin D in the pathogenesis of autoimmune diseases through considering anti-thyroid antibodies. The meta-analysis of Xu et al. showed that the deficiency of vitamin D increased the risk of GD disease, which is in agreement with the present findings [23].

No relationship was observed between serum vitamin D levels and hyperthyroid disease (non-autoimmune hyperthyroid disease or GD), meaning there was no significant difference in vitamin D levels of GD, non-autoimmune thyroid disease patients and healthy subjects. However, vitamin D deficiency was more frequent in GD patients.

Thyroid autoantibodies existed for several years prior to the onset of thyroid disease [24]. Of course, thyroid antibodies can be positive in people without thyroid dysfunction [7]. In our study, in the control group, 20 (28.57%) and 2 (2.85%) patients were reported as positive TPOAb and TGAb, respectively. Since the incidence of positive TPOAb was very high, the comparison of the relationship between TPOAb and vitamin D was affected by high positive antibody titers in the control subjects. In the study of Kohno et al. [23], 6.4% of the subjects were positive for autoantibodies. Their age range, being 17 to 23 years, is different from the present research. TPOAb of healthy people does not hinder the activity of TPO enzymes. These findings suggest that the properties of anti-TPO antibodies can be different for patients with pathological conditions of the thyroid [25].

Chaudhary et al. used vitamin D supplements to treat routine autoimmune diseases and reported the reduction of TPOAb titer following the treatment. On the other hand, vitamin D levels in our study were not able to predict TPOAb levels. Such difference can be due to the fact that their study was on 100 patients with newly diagnosed ATID. Besides, no differentiation was considered between the types of patients with autoimmune hyperthyroid diseases [24]. On the other hand, Wang et al. showed the relationship between lower serum levels of vitamin D and the presence of TGAb[26]. They further observed that the relationship between TGAb and vitamin D was more potent in female subjects. Apparently, sex differences play a major role in determining the relationship between Vitamin D and thyroid diseases. In the present study, vitamin D levels were higher in male subjects, while females had higher levels of TSH. Goswami et al. reported a weak correlation between TPOAb titers and Vitamin D levels [27]. In the present study, no correlation was observed between these two variables.

According to Choi et al., in pre-menopause women, TPOAb positive subjects had a lower level of vitamin D comparisons with TPOAb negative group [16]; however, in our study no differences were observed. In addition to the fact that Choi et al. did not measure the level of TgAb, the difference between the results of our study and them could be due to the difference in gender and age distribution of patients.

According to our results, the increase in the levels of vitamin D in patients with GD can be associated with improved treatment outcomes such as increased TSH levels. Nonetheless, this relationship between vitamin D and TSH levels could be affected by patient's age. Qingqing et al. reported the relationship between high serum vitamin D level and the lower level of TSH in old men [28]. Contrary to our results, Colbay et al. [29] showed that vitamin D levels had a negative relationship with the serum TSH level and no correlation with thyroid antibodies. Chailurkit et al. reported the association between the higher level of vitamin D in younger people and the increase in TSH levels [30]. In a study by Barchetta [31], lower Vitamin D levels were associated with higher TSH levels. In the present study, the median of GD patients age was lower than the other two groups (Table 1), which is in accordance with the aforementioned studies in terms of age and the effect of vitamin D on thyroid function.

Review of recent research indicated that thyroid autoimmunity is the consequence of an interaction of inflammatory cytokines, the immune modulating effect of vitamin D, and thyrocyte reactions to environmental factors [32]. Also, as Ferrari et al.[33] stated in a review study, low sun exposure and dietary vitamin D intake as environmental factors can be associated with autoimmune thyroid disease. Women’s clothing in Islamic countries as Iran causing low sun exposure could be one of the vitamin D deficiency reasons but regarding the Tabrizi et al.[34] systematic review study, other environmental reasons such as dietary habits, lifestyle, and air pollution affecting the prevalence of vitamin D deficiency should be considered.

One of the limitations of the present study, which does not allow for a generalization of the results, is the small size of the research community. Based on Effraimidis et al. study, the onset of autoimmune thyroid disease is not related to a lower vitamin D level [35]. So, examining the role of vitamin D in the GD autoimmune hyperthyroidism patients and even non-autoimmune hyperthyroid disease patients in the long-term is further recommended. Although there was no relationship between the vitamin D levels and non-autoimmune hyperthyroid disease, our results showed that non-autoimmune hyperthyroid disease patients had a higher mean age. Higher ages and low TSH levels are related to osteoporosis [36]. There is a high risk of

osteoporosis in non-autoimmune hyperthyroid disease patients, hence, analyzing vitamin D levels and prescribing vitamin D supplements are needed.

Conclusions

Vitamin D deficiency is more frequent in autoimmune hyperthyroidism disease patients than non-autoimmune ones. Considering the prevalence of vitamin D deficiency, the use of vitamin D supplements should be placed on the health system agenda.

Abbreviations

TGAb: Thyroid globulin antibody

TPOAb: Thyroid globulin antibody

GD: Graves

TSH: Thyroid stimulating hormone

Vit: vitamin

Declarations

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none.

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the research has been endorsed by the Ethics Committees of the Jahrom University of Medical Sciences.

Contributors:

All writers have read and approved the manuscript. All individuals mentioned as writers have contributed to the preparation of the manuscript. SA intended the survey and the collection of the sample was performed by SA and MK. SA and NH carried out evaluation of the information and wrote the manuscript.

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Tables

Table 1. Basal characteristic of study subjects

P-value	control	GD	non-autoimmune hyperthyroid disease	
-	70	74	43	number
0.013	35.13±13.67	35±14.15	41.95±12.08	age
0.44	6(18.18%)	16(48.48%)	11(33.3%)	Gender (male) n (%)
0.748	2.78(1.91-3.825)	0.02(0.01-0.2775)	0.1(0.01-0.56)	TSH
0.150	0.58(0.455-0.725)	0.74(0.6-1.04)	0.73(0.6-1.02)	T3
0.652	0.58(0.5-0.67)	0.67(0.51-0.89)	0.68(0.6-0.86)	T4
0.608	15.685(7.51-25.2725)	15.925(8.815-22.79)	18.2(8.855-28.795)	25OHD
< .00001	0(0-24.25)	238.9(45.75-574)	19.5(14-41.5)	TGAb
< .00001	12.1(6.525-50.75	233.8(48.95-468.15)	9.3(5.14-19.6	TPOAb
<0.05	3 (%2.85)	43 (%52.70)	0 (%0)	TGAb(+) n (%)
<0.05	21 (%30)	56(%75.67)	1 (%2.32)	TPOAb (+) n(%)

Table2: comparing between vitamin d sufficient and deficient subjects

p-value	Vit D>20	Vit D<20	
-	74	113	number
0.631	18.75(8.26-195.42)	27(6.9-257.25)	TPOAb
0.896	35.5(10.5-59)	24(0-128)	TGAb
0.255	27 (%36.48)	51 (%45.13)	TGAb(+) n (%)
0.324	16 (21.62%)	30 (%26.54)	TPOAb (+) n(%)

Table 3. Vitamin D ranges and paraclinical tests

	severe Vit d deficiency (0-8)	moderate Vit d deficiency (8-15)	mild Vit d deficiency (20-15)	sufficient (>20)	P value
n	50	38	27	72	-
TGAb(IU/ml)	0.17(0-1.17)	0.22(0-1.68)	0.44(0.17-0.84)	0.39(0.1525-0.62)	>0.05
TPOAb (IU/ml)	19.1(6.7-325.05)	25.6(5.9125-258)	29.73(8.7-210)	18.75(8.605-193.6)	>0.05
TGAb(+) n (%)	13(%26)	10(%26.31)	7(%25.92)	16(%22.22)	>0.05
TPOAb (+) n(%)	22(%44)	17(%44.73)	13(%48.14)	26(%36.11)	>0.05
TSH	1.335(0.027-2.55)	0.24(0.01-2.72)	0.06(0.01-1.83)	0.725(0.01-2.57)	>0.05
T3	0.7(0.6-0.9175)	0.675(0.5525-0.805)	0.845(0.6175-1.085)	0.72(0.57-1.035)	>0.05
T4	0.61(0.53-0.755)	0.61(0.49-0.79)	0.44(0.17-0.84)	0.67(0.5525-0.8)	>0.05

Figures

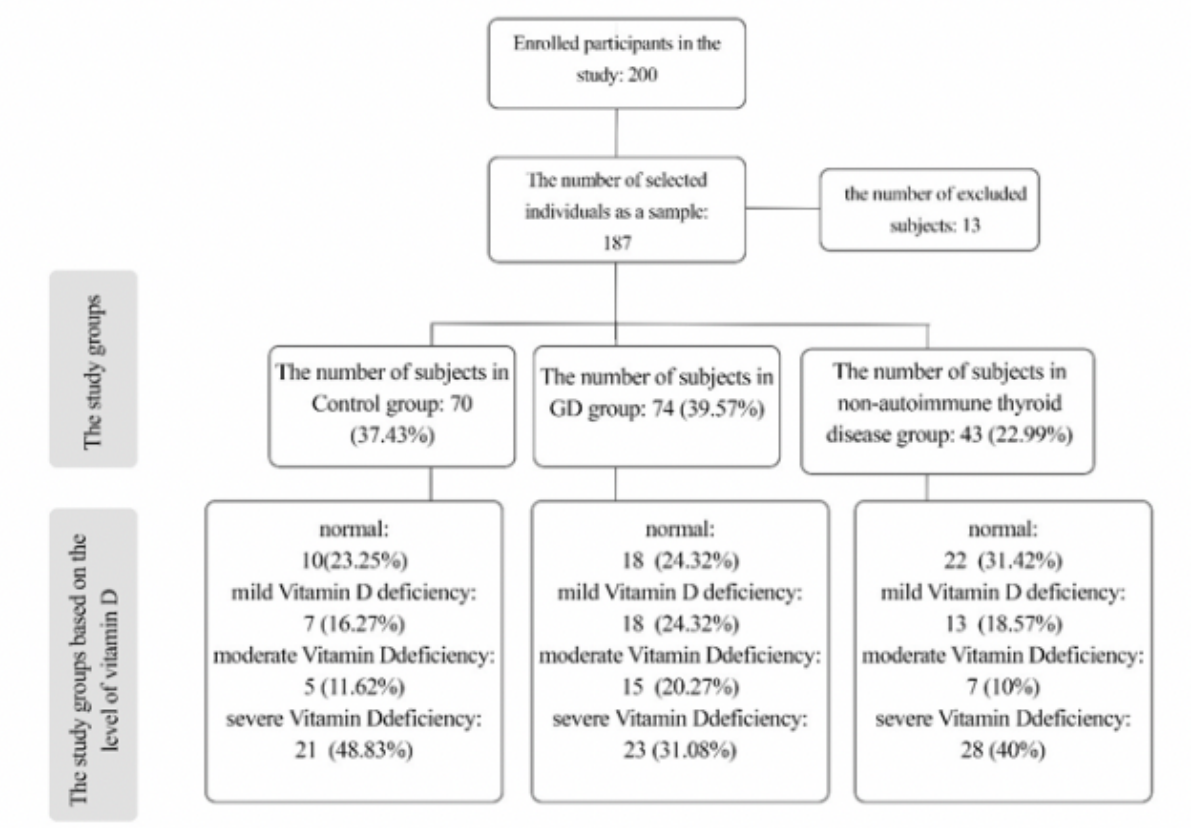

Figure 1

Flowchart of the study population and the study design

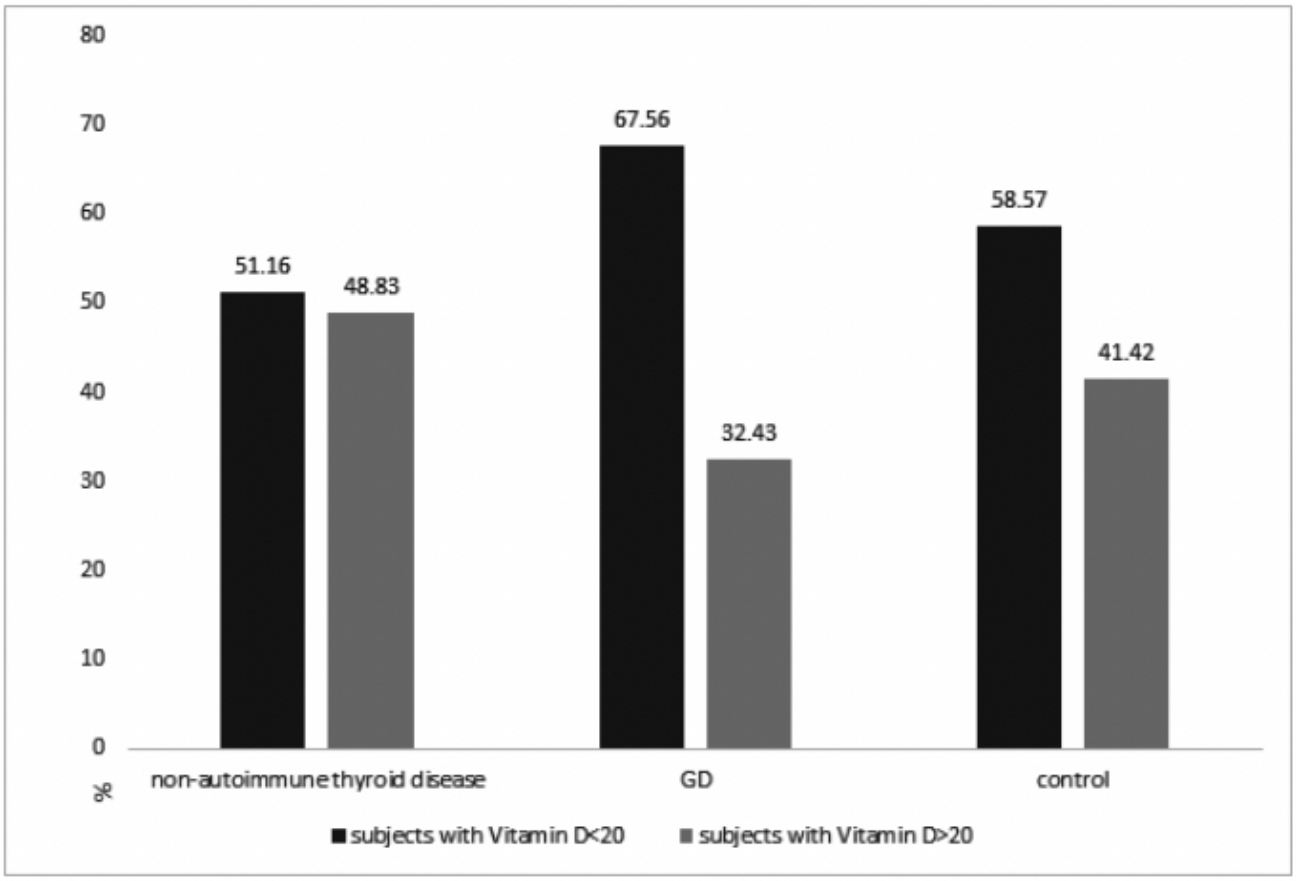

Figure 2

Vitamin D deficiency rate in study groups

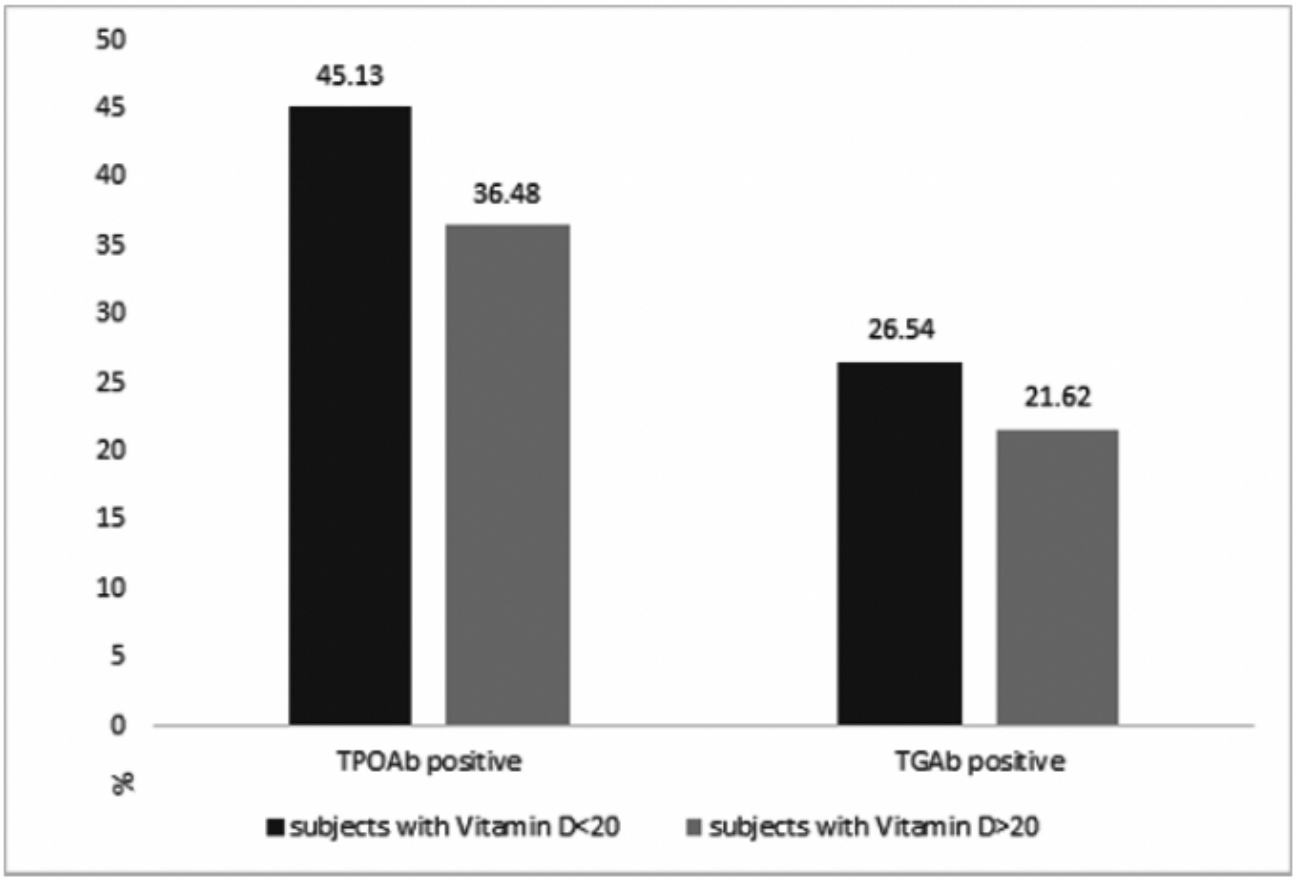

Figure 3

Rate of Positive autoantibodies in study subjects