ORIGINAL ARTICLE
https://doi.org/10.1590/1806-9282.20210492

An evaluation of the relationship between vitamin D level and CTRP-9, tumor necrosis factor-alpha, thiol-disulfide hemostasis in women

Muharrem Kiskac[1]*, Abdusselam Sekerci[1], Eray Metin Güler[2], Muhammed Tunc[1], Mustafa Cakirca[1], Cumali Karatoprak[1], Mehmet Zorlu[1]

SUMMARY

OBJECTIVE: Many chronic diseases such as malignancy, cardiovascular diseases, endothelial dysfunction, and autoimmune diseases, which have been shown to be related to vitamin D in various studies; have similar relations with CTRP-9, TNFα, and thiol-disulfide hemostasis. We aimed to contribute to the literature by evaluating the relationship between CTRP-9, TNFα, and thiol-disulfide hemostasis and vitamin D levels, which we thought may have some effects on the pathogenesis of vitamin D deficiency.

METHODS: In our study, 78 female volunteers older than 18 years were included. Volunteers were divided into three groups according to the reference values of vitamin D levels. Biochemical parameters, CTRP-9, TNFα, and thiol/disulfide hemostasis tests taken from all volunteers were studied.

RESULTS: In this study, there was a significant difference in CTRP-9, TNFα, total thiol (TT), native thiol (NT), DIS (disulfide), TT/DIS, and NT/DIS levels in vitamin D groups ($p<0.05$). There was a significant negative correlation between vitamin D and TNFα and DIS, while a significant positive correlation was found with CTRP-9, TT, NT, TT/DIS, and NT/DIS ($p<0.05$).

CONCLUSIONS: It was determined that vitamin D deficiency causes a significant decrease in CTRP-9 level and a significant increase in TNFα level, as well as an increase in thiol/disulfide hemostasis in favor of disulfide, which may be a risk factor for increased oxidative stress. We considered that these changes may play mediator roles for many chronic diseases and metabolic disorders that are increasing in frequency due to vitamin D deficiency.

KEYWORDS: Vitamin D. CTRP-9. TNFα. Total Thiol. Native Thiol. Disulfides.

INTRODUCTION

It was originally thought that vitamin D had effects mainly on calcium and bone metabolism. In preclinical studies, it has been determined that vitamin D exerts its effects through vitamin D receptors. It has been shown that these receptors are found not only in bone structure but also in many tissues and organs[1-3]. In recent years, vitamin D deficiency and insufficiency has been found to be associated with many chronic diseases, including a number of cancers, cardiovascular diseases, endothelial dysfunction, metabolic syndrome, infectious and autoimmune diseases[4,5]. Vitamin D deficiency is likely to be a risk factor for many acute and chronic diseases[6]. It is significantly higher in women than in men[7]. Risk factors for vitamin D deficiency include advanced age, genetic factors, living in a traditionally closed society, being in a closed environment, use of protective sunscreen, physical inactivity, smoking, air pollution, kidney

[1]Bezmialem Vakif University, Faculty of Medicine, Department of Internal Medicine – Istanbul, Turkey.
[2]University of Health Sciences Turkey, Hamidiye Medical Faculty, Department of Medical Biochemistry – Istanbul, Turkey.
*Corresponding author: muharremkiskac@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on June 12, 2021. Accepted on June 14, 2021.

disease, liver disease, anticonvulsants, and glucocorticoids, affecting vitamin D metabolism. including the use of drugs[8].

CTRP-9 (the C1q TNF-related protein) is a newly described adipokine secreted from adipose tissue, which shares the highest amino acid sequence (54%) as well as being the closest paralogue of adiponectin. The metabolic roles of CTRP-9 functionally overlap with those of adiponectin. CTRP-9 is produced at higher levels in women than in men[9]. Its anti-inflammatory and anti-atherosclerosis properties led it to play a cardioprotective role in the coronary artery disease process. CTRP-9 inhibits the expression of adhesion molecules in endothelial cells and reduces the secretion of proinflammatory cytokines such as tumor necrosis factor alpha (TNFα). It increases the production of nitric oxide in the atherosclerotic plaque, leading to vasodilation, decreasing endothelial dysfunction, also inhibiting the inflammatory responses of macrophages and consequently increasing the stability of the atherosclerotic plaque[10,11]. Due to the reduced neointimal formation of CTRP-9 following vascular injury with treatments that can increase CTRP-9 production, it is thought that the frequency of vascular restenosis can be reduced after angioplasty[12].

Tumor necrosis factor alpha has important properties in the initiation and maintenance of inflammation in autoimmune diseases. It has also multiple effects on inflammation, infection, immunity, cytotoxicity, endothelial dysfunction, oxidative stress, cardiovascular events, and tissue remodeling. Due to these versatile effects, anti-TNF drugs have been developed which are used in the treatment of many diseases[13].

Oxidative stress is defined as the impairment of molecular and cellular functions as a result of the loss of the balance between the production of free radical or reactive oxygen species and the antioxidant system. Reactive oxygen radicals are primary molecules that cause oxidative damage when they exceed physiological levels. Dynamic thiol/disulfide balance state has critical roles in antioxidant defense, detoxification apoptosis, regulation of enzyme activities, transcription and cellular signal transduction mechanisms. Abnormal thiol/disulfide balance levels is involved in the pathogenesis of various diseases such as diabetes mellitus, cardiovascular diseases, endothelial dysfunction, malignancy formation, rheumatoid arthritis, chronic renal failure, Parkinson's and Alzheimer's diseases[14-16].

In the literature review, there are a limited number of studies evaluating vitamin D level, thiol-disulfide hemostasis, and TNFα separately in some diseases. However, there was no study examining the relationship between CTRP-9 and vitamin D. Also, no study was found in which all these parameters were evaluated together. We aimed to contribute to the literature by evaluating the relationship between CTRP-9, TNFα, and thiol-disulfide hemostasis and vitamin D levels, which we thought may have some effects on the pathogenesis of vitamin D deficiency.

METHODS

After the approval of the ethics committee of Bezmialem Vakıf University, dated 18/12/2019 and decision number 24/17, 78 female volunteers over the age of 18 years, who applied to the internal medicine outpatient clinic of our hospital between May 2020 and November 2020, were included in our study. Patients with a known chronic disease, pregnancy, or surgery in the last 6 months were not included in our study. Also, patients who used antioxidant drugs, vitamin supplements, lipid-lowering drugs, smoking, alcohol use, and those who used vitamin D in the last 1 month were excluded from the study. Patients with normal C-reactive protein (CRP) levels were included in our study. If vitamin D level is <20 ng/mL, it indicates deficiency, if it is 20–30 ng/mL, it indicates insufficiency, and if it is above 30 ng/mL, it indicates sufficient level[17]. Volunteers were divided into three groups according to the reference values of vitamin D levels. For biochemical parameters (glucose, creatinine, aspartate aminotransferase [AST], alanine aminotransferase [ALT], calcium, magnesium, phosphorus, free tetraiodothyronine [fT4], thyroid-stimulating hormone [TSH], parathyroid hormone [PTH], total cholesterol, triglyceride, low-density lipoprotein-cholesterol [LDL-K], high-density lipoprotein-cholesterol [HDL-K]), CTRP-9, TNFα, and thiol/disulfide hemostasis tests from all volunteers, venous blood samples, were taken into a gel tube between 8:00 a.m. and 9:00 a.m. after 12 h of fasting and centrifuged at 3,600 rpm for 10 min and the serums were separated. After the serums of all volunteers were transferred to Eppendorf tubes, they were stored at -80°C until the day of the study.

Measurement of dynamic thiol/disulfide homeostasis

Serum thiol/disulfide homeostasis was determined with a recently developed measurement method by using the Thermo Scientific Varioskan Flash multimode reader. DIS was mathematically determined according to the formula (TT–NT)/2[14].

Measurement of CTRP-9 and TNFα

Concentrations of CTRP-9 and TNFα in the serum were measured by a specific commercial ELISA kit according to the manufacturer's instructions (CTRP-9: E3848Hu and TNFα: E0082Hu, Bioassay Technology Laboratory, China). Concentrations were determined with a spectrophotometric microtiter plate reader (Varioskan Flash Multimode Reader, Thermo, Waltham, USA) at 450 nm optical density[18].

Statistical analyses

IBM SPSS statistics 22.0 program was used for statistical analysis in the study. While evaluating study data, descriptive

statistical methods (mean, standard deviation, and frequency) were used. Skewness and kurtosis values were used together with the Shapiro-Wilk test to evaluate the normal distribution of the data. While the one-way ANOVA test was used to compare more than two normally distributed variables, the Kruskal-Wallis test was used to evaluate more than two non-normally distributed variables. In order to evaluate the correlation between data, Pearson's correlation analysis was used for normally distributed data, and Spearman correlation analysis was used for non-normal distribution data. Results were evaluated at 95% confidence interval and significance level of $p<0.05$.

RESULTS

The mean age of 78 women who joined the study was 34.06±10.89 (20–61) years, while their average body mass index (BMI) was 24.57±4.60 (16.8–35.0) kg/m^2. When we divided volunteers according to their vitamin D levels into three groups (Group 1: vitamin D<20 ng/mL; Group 2: vitamin D between 20 and 30 ng/mL; Group 3: vitamin D>30 ng/mL): Group 1: age and BMI average were 32.26±10.06 years, 24.76±4.86 kg/m^2; Group 2: 35.86±12.95 years, 24.03±4.74 kg/m^2; and Group 3: 35.15±9.92 years, 24.85±4.13 kg/m^2. There was no statistically significant difference between the groups in terms of age and BMI ($p>0.05$) (Table 1).

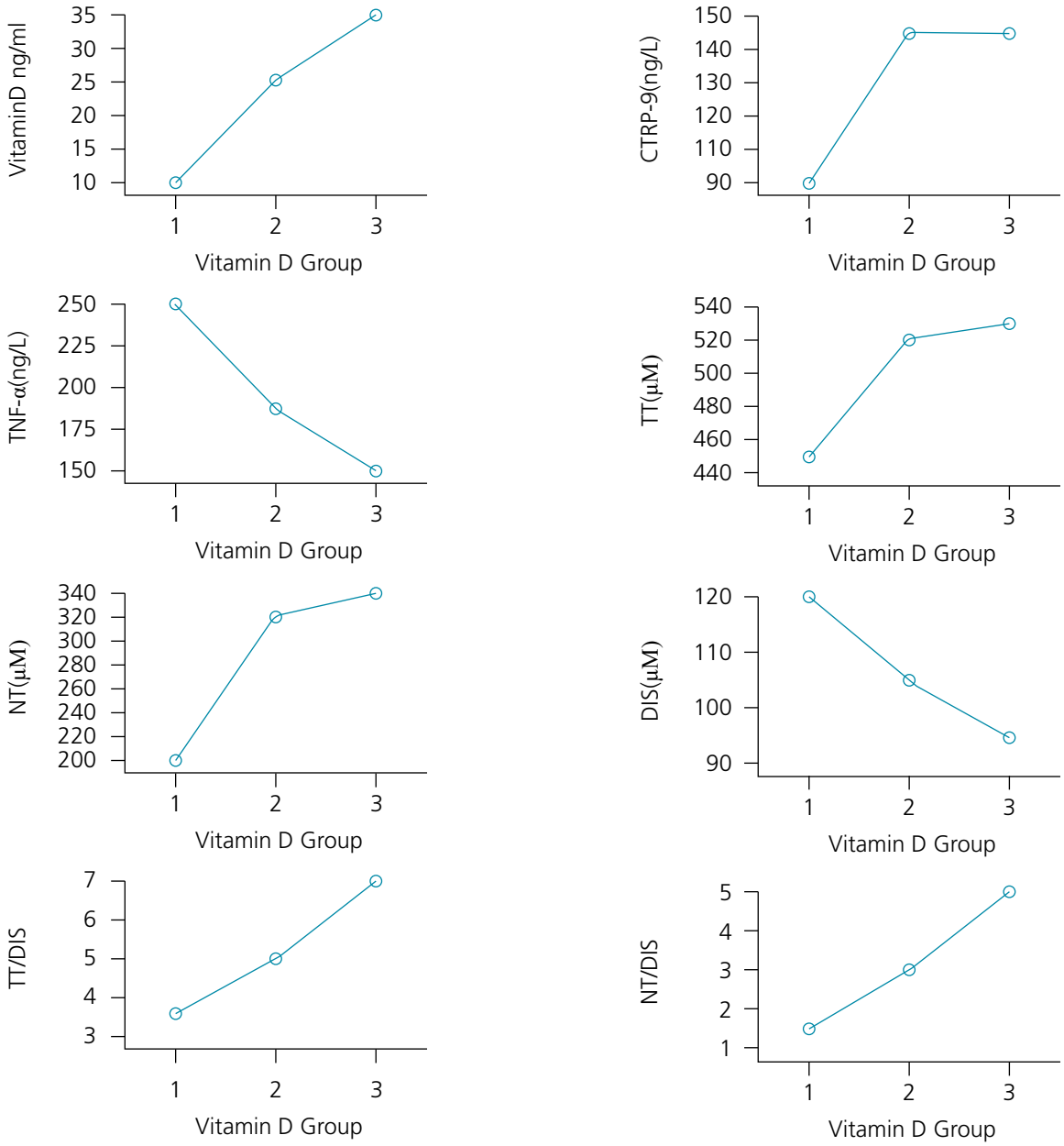
Table 1. Evaluation of age, body mass index, the C1q TNF-related protein, tumor necrosis factor-alpha, total thiol, native thiol, disulfide, total thiol/disulfide, native thiol/disulfide, and biochemical parameters levels in vitamin D groups.

	Group 1 Vitamin D <20 ng/mL n:36	Group 2 Vitamin D 20–30 ng/mL n:22	Group 3 Vitamin D >30 ng/mL n:20	p
Age (years)	32.36±10.06	35.86±12.95	35.15±9.92	0.438
BMI (kg/m^2)	24.76±4.86	24.03±4.74	24.85±4.13	0.809
CTRP-9 (ng/L)	90.45±25.57	145.20±13.98	145.42±22.76	0.001
TNFα (ng/L)	249.29±29.59	182.23±22.97	142.35±19.13	0.001
TT (μM)	449.66±53.58	524.48±56.40	530.11±52.47	0.001
NT (μM)	205.95±37.96	316.03±57.10	342.20±43.64	0.001
DIS (μM)	121.85±15.39	104.22±2.58	93.95±38.30	0.001
TT/DIS	3.70±0.35	5.03±0.57	6.89±3.77	0.001
NT/DIS	1.70±0.35	3.03±0.57	4.89±3.77	0.001
Glucose (mg/dL)	92.11±7.43	91.04±8.81	90.40±5.64	0.693
Creatinine (mg/dL)	0.69±0.05	0.69±0.04	0.71±0.08	0.354
AST (U/L)	17.05±4.88	16.86±3.79	17.05±3.61	0.153
ALT (U/L)	17.72±8.84	14.81±5.01	14.40±4.61	0.225
Calcium (mg/dL)	9.34±0.30	9.42±0.44	9.36±0.39	0.726
Magnesium (mg/dL)	1.94±0.14	1.95±0.15	1.90±0.11	0.415
Phosphorus (mg/dL)	3.55±0.43	3.38±0.35	3.63±0.51	0.177
PTH (ng/L)	63.22±21.31	60.79±15.31	47.61±17.02	0.012
fT4 (pg/mL)	12.29±1.39	12.89±1.59	12.65±1.21	0.280
TSH (mU/L)	1.65±0.71	1.50±0.61	1.46±0.55	0.518
Total cholesterol (mg/dL)	181.50±34.17	171.13±21.89	189.85±38.50	0.179
Triglyceride (mg/dL)	79.86±44.33	74.63±29.80	77.06±35.01	0.878
LDL-K (mg/dL)	105.41±31.68	90.57±29.57	115.69±31.95	0.036
HDL (mg/dL)	60.46±14.85	60.36±13.62	57.52±15.14	0.745

BMI: body mass index; CTRP-9: the C1q TNF-related protein; TNFα: tumor necrosis factor-alpha; TT: total thiol; NT: native thiol; DIS: disulfide; AST: aspartate aminotransferase; ALT: alanine aminotransferase; PTH: parathormone; fT4: free tetraiodothyronine; TSH: thyroid-stimulating hormone; LDL-K: low-density lipoprotein-cholesterol; HDL-K: high-density lipoprotein-cholesterol.

Between vitamin D groups, while there was no significant difference found (p>0.05) in terms of glucose, creatinine, AST, ALT, calcium, magnesium, phosphorus, fT4, TSH, total cholesterol, triglyceride, HDL-K, there was a significant difference (p<0.05) found in terms of CTRP-9, TNFα, total thiol (TT), native thiol (NT), disulfide (DIS), TT/DIS, NT/DIS, PTH, and LDL-K (Table 1). The change of vitamin D, CTRP-9, TNFα, TT, NT, DIS, TT/DIS, and NT/DIS levels were shown in vitamin D groups (Figure 1).

In the evaluation of the correlation between vitamin D and age, BMI, CTRP-9, TNFα, TT, NT, DIS, TT/DIS, NT/DIS, and other biochemical parameters, a significant negative correlation was found with TNFα, DIS, PTH, while a significant positive correlation was found with CTRP-9, TT, NT, TT/DIS, and NT/DIS (p<0.05; Table 2).



CTRP-9: the C1q TNF-related protein; TNFα, tumor necrosis factor-alpha; TT, total thiol; NT, native thiol; DIS, disulfide.

Figure 1. Evaluation of vitamin D, the C1q TNF-related protein, tumor necrosis factor-alpha, total thiol, native thiol, disulfide, total thiol/disulfide, and native thiol/disulfide levels in vitamin D groups.

Table 2. Evaluation of the correlation between vitamin D level and levels of age, body mass index, the C1q TNF-related protein, tumor necrosis factor-alpha, total thiol, native thiol, disulfide, total thiol/disulfide, native thiol/disulfide and biochemical parameters.

	r	p
Age (years)	0.144	0.209
BMI (kg/m^2)	-0.002	0.983
CTRP-9 (ng/L)	0.781	0.001
TNFα (ng/L)	-0.815	0.001
TT (μM)	0.805	0.001
NT (μM)	0.852	0.001
DIS (μM)	-0.245	0.031
TT/DIS	0.459	0.001
NT/DIS	0.459	0.001
Glucose (mg/dL)	-0.072	0.695
Creatinine (mg/dL)	0.119	0.298
AST (U/L)	0.039	0.736
ALT (U/L)	-0.184	0.107
Calcium (mg/dL)	0.053	0.644
Magnesium (mg/dL)	-0.116	0.351
Phosphorus (mg/dL)	0.012	0.918
PTH (ng/L)	-0.372	0.002
fT4 (pg/mL)	0.163	0.154
TSH (mU/L)	-0.115	0.318
Total cholesterol (mg/dL)	0.026	0.822
Triglyceride (mg/dL)	0.014	0.906
LDL-K (mg/dL)	0.072	0.531
HDL (mg/dL)	-0.170	0.137

r: correlation coefficient; BMI: body mass index; CTRP-9: the C1q TNF-related protein; TNFα: tumor necrosis factor-alpha; TT: total thiol; NT: native thiol; DIS: disulfide; AST: aspartate aminotransferase; ALT: alanine aminotransferase; PTH: parathormone; fT4: free tetraiodothyronine; TSH: thyroid-stimulating hormone; LDL-K: low-density lipoprotein-cholesterol; HDL-K: high-density lipoprotein-cholesterol.

DISCUSSION

In addition to the fact that vitamin D deficiency is a very important hormone for bone and calcium metabolism, various studies have shown that it is associated with many important diseases including some cancers, cardiovascular diseases, endothelial dysfunction, metabolic syndrome, infectious and autoimmune diseases. This has led to an increase in the relevant awareness of vitamin D and therefore the use of vitamin D preparations[4,5,17,19]. Despite this, as a result of the decrease in the exposure to sunlight due to reasons such as living in a closed environment, the use of high factor creams that protect against the harmful effects of the sun, clothing style, seasonal characteristics, decrease in food quality, insufficient and short-term use of vitamin D preparations for treatment. Vitamin D deficiency is still a common occurrence today[20].

In our study, there was a significant difference between vitamin D groups in terms of CTRP-9 level, and a significant positive correlation was found between vitamin D level and CTRP-9 level ($p<0.05$). CTRP-9 is the closest paralog of adiponectin and shows a high level of amino acid sequence similarity. Both molecules have antiatherogenic, anti-inflammatory, and antiproliferative effects. Additionally, both molecules prevent insulin resistance and endothelial dysfunction[21]. In the literature scan that has been carried out, we did not come across a study that examined the relationship of CTRP-9 and vitamin D. However, there are a limited number of studies examining the relationship between vitamin D and adiponectin, Rambhojan et al., in their study on 117 adolescents, found that adiponectin levels were significantly lower in patients with vitamin D deficiency compared with those without vitamin D deficiency[22]. However, in the study Mohammedi et al. conducted to the first-degree relatives of 64 type 2 diabetic patients, a significant decrease in adiponectin levels was found after the vitamin D replacement treatment done on the patients[23]. In our study, CTRP-9, whose relationship with vitamin D was examined, has high similarities with adiponectin both structurally and functionally, as well as being a different molecule; again in the study of Mohammedi et al.[23], since the effects of vitamin D replacement treatment are evaluated, it may be thought that the results are different. The lower levels of CTRP-9 in vitamin D deficient patients in our study suggest that it may play some mediator roles for increased atherogenesis, endothelial dysfunction, cardiovascular, and inflammatory events as a result of vitamin D deficiency. However, these possible mechanisms should be supported by some comprehensive studies.

In our study, there was a significant difference between vitamin D groups in terms of TNFα level as well as a significant negative correlation between vitamin D level and TNFα level ($p<0.05$). TNFα has multiple effects on the initiation and maintenance of inflammation, endothelial dysfunction, cytotoxicity, oxidative stress, and cardiovascular events[13]. El Hajj et al. have carried out the study on 88 type 2 diabetics patients after the vitamin D replacement treatment. TNFα levels were found to be significantly lower than before replacement[24]. In the study conducted by Azizieh et al. on 112 healthy women, participants were divided into two groups according to their vitamin D levels (above and below of 25 nmol/l [10 ng/ml]). Although TNFα level was found to be lower in the group with

vitamin D level below 25 nmol/l, no significant difference was detected between the groups[25]. In terms of TNFα level, the results of our study are similar to the results of the study conducted by El Hajj et al. However, we considered that the difference between the results of the study by Azizieh et al.[25] and this study may be due to the fact that different patient groups have been studied in terms of vitamin D levels. In our study, a significant negative correlation was found between CTRP-9 and TNFα ($p<0.05$). This suggests that molecules such as CTRP-9 and adiponectin may exert their anti-inflammatory effects by decreasing the level of TNFα.

In our study, while there was a significant difference between vitamin D groups in terms of TT, NT, DIS, TT/DIS, and NT/DIS levels, and a significant positive correlation was found between vitamin D level and TT, NT, TT/DIS, and NT/DIS level, a significant negative correlation was found with DIS level ($p<0.05$). Dynamic thiol/disulfide balance state has critical roles such as antioxidant defense, detoxification, and apoptosis. It has been determined that oxidative stress, which occurs as a result of the deterioration of this balance in favor of disulfide, plays a role in the pathogenesis of various diseases such as diabetes mellitus, cardiovascular diseases, endothelial dysfunction, and malignancy[14-16]. In the literature scan, we came across very few studies examining vitamin D and thiol/disulfide hemostasis in different patient groups. In the results of the study that Mertoglu et al. carried out on 203 healthy children to examine the relationship between vitamin D level and thiol/disulfide, it was found that thiol/disulfide hemostasis was impaired in patients with severe vitamin D deficiency, but this disorder did not improve with vitamin D replacement. As a result of their studies, they stated that it may be more beneficial to increase the endogenous production of vitamin D[26]. In the study conducted by Alvarez et al. on 693 adults, it was found that vitamin D deficiency was associated with oxidative stress by causing disruption in glutathione and cysteine thiol/disulfide balance[27]. The results of our study are also similar to both studies. We considered that the triggering role of vitamin D deficiency in the increase of oxidative stress may be effective in its risk factor for many chronic diseases and metabolic disorders. In addition to the benefits of vitamin D replacement therapy, it is thought that increasing endogenous vitamin D production may provide additional benefits in reducing oxidative stress. However, more accurate results can be obtained with more comprehensive studies on this subject.

Relatively less number of patients and the fact that it was performed only in women were the limitations of this study, whereas the evaluation of several interrelated parameters together was the strength.

CONCLUSIONS

As a result of this study, it was determined that vitamin D deficiency causes a significant decrease in CTRP-9 level and a significant increase in TNFα level, as well as an increase in thiol/disulfide hemostasis in favor of disulfide, and could be a risk factor for increased oxidative stress. These changes might play an intermediary role in many chronic diseases and metabolic disorders that occur in vitamin D deficiency, as well as contributing to the formation of the multifactorial effects of vitamin D. However, these possible roles need to be supported by some comprehensive studies.

AUTHORS' CONTRIBUTIONS

MK: Conceptualization, Investigation, Project administration, Writing – original draft. **AS:** Data curation ,Writing – review & editing. **EMG:** Formal analysis, Methodology. **MT:** Resources, Validation. **MC:** Validation, Visualization. **CK:** Data curation, Software. **MZ:** Supervision, Writing – review & editing

REFERENCES

1. Kanikarla-Marie P, Jain SK. 1,25(OH) 2D3 inhibits oxidative stress and monocyte adhesion by mediating the upregulation of GCLC and GSH in endothelial cells treated with acetoacetate (ketosis). J Steroid Biochem Mol Biol. 2016;159:94-101. https://doi.org/10.1016/j.jsbmb.2016.03.002
2. Bischoff HA, Borchers M, Gudat F, Duermueller U, Theiler R, Stähelin HB, et al. In situ detection of 1,25-dihydroxyvitamin D3 receptor in human skeletal muscle tissue. Histochem. J. 2001;33(1):19-24. https://doi.org/10.1023/a:1017535728844
3. Kim DH, Meza CA, Clarke H, Kim JS, Hickner RC. Vitamin D and endothelial function. Nutrients. 2020;12(2):575. https://doi.org/10.3390/nu12020575
4. Holick MF. Vitamin D: a D-lightful health perspective. Nutr Rev. 2008;66(10 Suppl 2):S182-94. https://doi.org/10.1111/j.1753-4887.2008.00104.x
5. Hyppönen E, Boucher BJ, Berry DJ, Power C. 25-hydroxyvitamin D, IGF-1, and metabolic syndrome at 45 years: a cross-sectional study in the 1958 British birth cohort. Diabetes. 2008;57(2):298-305. https://doi.org/10.2337/db07-1122

6. Pludowski P, Holick MF, Pilz S, Wagner CL, Hollis BW, Grant WB, et al. Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality – a review of recent evidence. Autoimmun Rev. 2013;12(10)2 976-89. https://doi.org/10.1016/j.autrev.2013.02.004
7. Hekimsoy Z, Dinç G, Kafesçiler S, Onur E, Güvenç Y, Pala T, et al. Vitamin D status among adults in the Aegean region of Turkey. BMC Public Health. 2010;10:782. https://doi.org/10.1186/1471-2458-10-782
8. Lavie CJ, Lee JH, Milani RV. Vitamin D and cardiovascular disease will it live up to its hype? J Am Coll Cardiol. 2011;58(15):1547-56. https://doi.org/10.1016/j.jacc.2011.07.008
9. Wong GW, Krawczyk SA, Kitidis-Mitrokostas C, Ge G, Spooner E, Hug C, et al. Identification and characterization of CTRP9, a novel secreted glycoprotein, from adipose tissue that reduces serum glucose in mice and forms heterotrimers with adiponectin. FASEB J. 2009;23(1):241-58. https://doi.org/10.1096/fj.08-114991
10. Wang J, Hang T, Cheng XM, Li DM, Zhang QG, Wang LJ, et al. Associations of C1q/TNF-related protein-9 levels in serum and epicardial adipose tissue with coronary atherosclerosis in humans. Biomed Res Int. 2015;971683. https://doi.org/10.1155/2015/971683
11. Jung CH, Lee MJ, Kang YM, Lee YL, Seol SM, Yoon HK, et al. C1q/TNF-related protein-9 inhibits cytokine-induced vascular inflammation and leukocyte adhesiveness via AMP-activated protein kinase activation in endothelial cells. Mol Cell Endocrinol. 2016;419:235-43. https://doi.org/10.1016/j.mce.2015.10.023
12. Uemura Y, Shibata R, Ohashi K, Enomoto T, Kambara T, Yamamoto T, et al. Adipose-derived factor CTRP9 attenuates vascular smooth muscle cell proliferation and neointimal formation. FASEB J. 2013;27(1):25-33. https://doi.org/10.1096/fj.12-213744
13. Çayakar A. What is tumor necrosis factor alpha? Turkiye Klinikleri Journal of Internal Medicine. 2018;3(2):67-76. https://doi.org/10.5336/intermed.2018-61424
14. Ates I, Ozkayar N, Inan B, Yilmaz FM, Topcuoglu C, Neselioglu S, et al. Dynamic thiol/disulphide homeostasis in patients with newly diagnosed primary hypertension. J Am Soc Hypertens. 2016;10(2):159-66. https://doi.org/10.1016/j.jash.2015.12.008
15. Erel O, Neselioglu S. A novel and automated assay for thiol/disulphide homeostasis. Clin Biochem. 2014;47(18):326-32. https://doi.org/10.1016/j.clinbiochem.2014.09.026
16. Gurer H, Ercal N. Can antioxidants be beneficial in the treatment of lead poisoning? Free Radic Biol Med. 2000;29(10):927-45. https://doi.org/10.1016/s0891-5849(00)00413-5
17. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357(3):266-81. https://doi.org/10.1056/NEJMra070553
18. Guler EM, Gokce M, Bacaksiz A, Kocyigit A. Urotensin-II, oxidative stress, and inflammation increase in hypertensive and resistant hypertensive patients. Clin Exp Hypertens. 2020;43(3):211-6. https://doi.org/10.1080/10641963.2020.1847128
19. Holick MF. Vitamin D: a millenium perspective. J Cell Biochem. 2003;88(2):296-307. https://doi.org/10.1002/jcb.10338
20. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. Am J Clin Nutr. 2008;87(4):1080S-6S. https://doi.org/10.1093/ajcn/87.4.1080S
21. Wong GW, Krawczyk SA, Kitidis-Mitrokostas C, Ge G, Spooner E, Hug C, et al. Identification and characterization of CTRP9, a novel secreted glycoprotein, from adipose tissue that reduces serum glucose in mice and forms heterotrimers with adiponectin. FASEB J. 2009;23(1):241-58. https://doi.org/10.1096/fj.08-114991
22. Rambhojan C, Larifla L, Clepier J, Bouaziz-Amar E, Velayoudom-Cephise FL, Blanchet-Deverly A, et al. Vitamin D status, insulin resistance, leptin-to-adiponectin ratio in adolescents: results of a 1-year lifestyle intervention. Open Access Maced J Med Sci. 2016;4(4):596-602. https://doi.org/10.3889/oamjms.2016.131
23. Mohammadi SM, Eghbali SA, Soheilikhah S, Ashkezari SJ, Salami M, Afkhami-Ardekani M, et al. The effects of vitamin D supplementation on adiponectin level and insulin resistance in first-degree relatives of subjects with type 2 diabetes: a randomized double-blinded controlled trial. Electron Physician. 2016;8(9):2849-54. https://doi.org/10.19082/2849
24. El Hajj C, Walrand S, Helou M, Yammine K. Effect of vitamin D supplementation on inflammatory markers in non-obese lebanese patients with type 2 diabetes: a randomized controlled trial. Nutrients. 2020;12(7):2033. https://doi.org/10.3390/nu12072033
25. Azizieh F, Alyahya KO, Raghupathy R. Association between levels of vitamin D and inflammatory markers in healthy women. J Inflamm Res. 2016;9:51-7. https://doi.org/10.2147/JIR.S103298
26. Mertoglu C, Siranli G, Topal I, Gok G, Erel O. Vitamin D supplementation does not improve plasma thiol/disulfide homeostasis. Pediatr Int. 2018;60(11):1008-13. https://doi.org/10.1111/ped.13705
27. Alvarez JA, Chowdhury R, Jones DP, Martin GS, Brigham KL, et al. Vitamin D status is independently associated with plasma glutathione and cysteine thiol/disulphide redox status in adults. Clin Endocrinol (Oxf). 2014;81(3):458-66. https://doi.org/10.1111/cen.12449