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The effect of vitamin D supplementation on tobacco-related disorders in individuals with a tobacco use disorder: a randomized clinical trial

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ABSTRACT

Vitamin D deficiency in cigarette smokers (CS) might associate with several complications, including metabolic deficits, depression and anxiety. This study evaluated the effects of vitamin D on mental health symptoms, nicotine misuse, and biomarkers of metabolic diseases in individuals with a tobacco use disorder. A randomized, double-blind, placebo-controlled trial was conducted with 60 CS subjects receiving either 50,000 IU vitamin D supplements ($n=30$) or placebo ($n=30$) every 2 weeks for 24-weeks. Nicotine misuse, mental health scale, and metabolic parameters were measured before and after the intervention in the CS subjects. Compared with the placebo-group, after the 24-weeks intervention, serum 25 (OH) vitamin D levels increased in the intervention group (β 2.96; 95% CI, 0.91, 5.01; $P=0.006$). In addition, vitamin D supplementation significantly improved Beck Depression Inventory (BDI) (β −2.06; 95% CI, −3.84, −0.28; $P=0.02$). In addition, vitamin D administration significantly decreased fasting plasma glucose (FPG) (β −4.56; 95% CI, −8.94, −0.19; $P=0.04$), insulin (β −0.50; 95% CI, −0.88, −0.13; $P=0.009$), and homeostasis model of assessment-estimated insulin resistance (HOMA-IR) levels (β −0.21; 95% CI, −0.33, −0.08; $P=0.001$). Furthermore, vitamin D resulted in a significant elevation in total antioxidant capacity (TAC) (β 81.20; 95% CI, 18.30, 144.11; $P=0.01$), and plasma glutathione (GSH) levels (β 73.05; 95% CI, 18.56, 127.54; $P=0.01$), compared with the placebo-group. Administration of vitamin D for 24-weeks to CS subjects had beneficial effects on symptoms of depression and several metabolic biomarkers. While this preliminary study suggests that vitamin D might have beneficial effects, its clinical efficacy in individuals with a tobacco use disorder should be further validated in future clinical trials.

KEYWORDS

Vitamin D supplementation; cigarette smokers; nicotine misuse; mental health; metabolic biomarkers

Introduction

Cigarette consumption is one of the major causes of mortality, public health concern, and numerous diseases, both indirectly and directly. However, this risk factor can be controlled, and its harmful effects can be reduced with proper regulation and education.[1] In 2010, World Health Organization (WHO) reported the prevalence of cigarette smoking to be 18.5% among adult men and 0.2% among women in Iran. Furthermore, they estimated that these figures would reach 19% among men and 10% among women in 2025. it is anticipated that by 2025, 9% of the total population in Iran will be smoking.[2,3] Annually, nearly six million people die from cigarette smoking, and this figure will reach beyond eight million by 2030 if the current trend persists.[4] Cigarette smoke exposure has a suppressive effect on several inflammatory cytokines, resulting in tissue damage by degradation products of extracellular matrix proteins, and increased lipid peroxidation.[5,6] In addition, cigarette consumption is a risk factor for coronary artery disease,[7] suicidal ideation, anxiety, and depressive symptoms.[8]

Cigarette smoking has an independent, dose-dependent effect on bone loss, and hypovitaminosis D, which enhances fracture risk.[9,10]

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Clinical trial registration: This study was retrospective registered in the Iranian website (www.irct.ir; IRCT20170420033551N7) for clinical trials registration. Registration date: 15 July 2019.

Hypovitaminosis D has been linked to impaired mental health, oxidative damage, and increased levels of inflammatory markers.[11,12] Several studies have established a beneficial role for vitamin D on metabolic biomarkers, and mental health parameters in non-CS cases. We have previously found that vitamin D administration at a dosage of 50,000 IU among subjects under methadone maintenance treatment for 24-weeks had beneficial effects on depression scores, but did not affect anxiety.[13] In addition, vitamin D3 (200,000 IU) increased total antioxidant capacity, and decreased inflammatory cytokines in elderly women with vitamin D insufficiency.[14] In addition, consuming vitamin D (50,000 IU) down-regulated interleukin-1 (IL-1), and increased peroxisome proliferator-activated receptor gamma (PPAR-γ) expression.[15] A prior meta-analysis indicated that consuming vitamin D supplements by women diagnosed with polycystic ovary syndrome (PCOs) beneficially improved markers of inflammation and oxidative stress.[16] However, in another meta-analysis study, Gowda et al.[17] found that vitamin D supplementation resulted in no significant reduction in depressive symptoms. Vitamin D might improve score of depression and anxiety via regulation of calcium homeostasis, synthesis of serotonin 5-hydroxyltryptamine (5HT), increasing the expression of neurotrophic factors, and stimulation of adult neurogenesis.[18–20] The ability of vitamin D to reduce its inflammatory reactions may result from inhibitory effects on nuclear kappa-β (NF-kB) signaling and mitogen-activated protein (MAP) kinase as well as the regulation of prostaglandin metabolism. In addition, vitamin D promotes metabolic homeostasis by enhancing antioxidant system function, beta-cell function and insulin transduction.[21,22]

Accordingly, vitamin D need to be seriously considered in future studies for the treatment of an individual with a tobacco use disorder. These findings underscore the need to use vitamin D for the improvement of mental health agents, and metabolic biomarkers. The hypothesis of this research is that nicotine misuse, mental health and metabolic biomarkers might improve among individuals with a tobacco use disorder. A literature review revealed limited information about the effects of vitamin D on nicotine misuse, mental health, and metabolic profiles in individuals with a tobacco use disorder. The current study was designed to evaluate the effects of vitamin D on nicotine misuse, mental health (depression and anxiety), and metabolic biomarkers among individuals with a tobacco use disorder.

Methods

Participants

The study was conducted in Gholabchi Clinic between July 2019 and December 2019. This randomized, double-blind, placebo-controlled trial was registered in the Iranian Clinical Trials Registration of clinical trials (IRCT20170420033551N7). Informed consents were obtained from all participants prior to the enrollment, all of which were reviewed by the research ethics committee.

Inclusion/exclusion criteria

Inclusion criteria: Tobacco smoking misuse, and aged 17 to 60 years. Exclusion criteria: Metabolic diseases such as diabetes and neurological diseases such as epilepsy, unwillingness to cooperate, current severe depression, mania, psychosis, current opioid, alcohol or sedative physical dependence or cocaine dependence, suicide attempts within the past 12 months or either suicidal ideations or psychotic symptoms in the past 6 months, taking multivitamin-mineral, vitamin D and antioxidant drug during the last 3 months before the intervention.

Study design

In this randomized, double-blinded, placebo-controlled trial, participants were assigned to receive either 50,000 IU of vitamin D ($n=30$) or placebo ($n=30$) every 2 weeks for 24-weeks. To ensure adherence, participants received a message on their cell phones to consume the supplements. Due to lack of data about the appropriate dosage of vitamin D for individuals with a tobacco use disorder, we used the above-mentioned dose of vitamin D based on previous evidence in chronic liver diseases.[23] Supplements and placebos were produced by Zahravi, and Barij Essence Company

(Iran). Randomization was done with balanced block randomization and random numbers generated with computer software (Stat Trek software) by a trained staff. Randomization and allocation were concealed from the researchers and patients until the final analyses are completed. Placebo has been used to achieve masking of participants and investigators. Another person who is not involved in the trial and not aware of random sequences assigned the participants to specific dosages of supplements.

Assessment of outcomes

Mental health (BDI, and BAI Inventory), and nicotine misuse (NDSS) were considered as the primary outcomes, and metabolic biomarkers (secondary outcome).

Clinical signs

In the present study, Beck's Depression (BDI), Anxiety (BAI), and Nicotine Dependence Syndrome Scale (NDSS) inventories were used to assess level of depression, anxiety, and nicotine misuse, respectively.[24–26] BDI is a 21-question and BAI is a 20-queston inventory that each question scored between 0 to 4 and higher scores indicate the higher levels of depression and anxiety, respectively. The Persian versions of both inventories were validated in the previous studies.[27,28] NDSS is a new multi-dimensional measure of nicotine misuse, yielding five scores for different aspects of nicotine misuse (Drive, Priority, Tolerance, Continuity, and Stereotypy), as well as a total score.[26]

Biochemical assessment

At baseline and after the 24-week intervention, fasting blood was collected from each participant. Serum insulin levels were measured through applying an ELISA kit (DiaMetra, Milano, Italy) with intra- and inter assay CVs below 5%. The homeostasis model of assessment, QUICKI, and HOMA-IR were assessed using the established formulas.[29] Enzymatic kits (Pars Azmun, Tehran, Iran) with inter- and intra-assay CVs of less than 5% were applied to measure FPG, and lipid profiles. Hs-CRP status was determined by commercial ELISA kit (LDN, Nordhorn, Germany) with inter- and intra-assay CVs below 7%. In addition, total nitrite status was assessed using Griess method.[30] Furthermore, TAC was assessed using ferric reducing antioxidant power method developed by Benzie and Strain.[31] GSH and MDA status were evaluated using Beutler et al. method, and thiobarbituric acid reactive substances spectrophotometric test, respectively.[32,33] CVs for plasma MDA, GSH, and TAC were less than 5%.

Sample size

The main focus of this study was to evaluate the efficacy of vitamin D in attenuating mental health symptoms (depression, and anxiety), and nicotine misuse in individuals with a tobacco use disorder. To estimate the sample size, we used a randomized clinical trial sample size formula where type one (α) and type two (β) errors were 0.05 and 0.20 (power = 80%), respectively. Based on a previous study,[34] we used a standard deviation (SD) of 7.8 and 4.5 for vitamin D and placebo groups, and a difference in mean (d) of 4.3, considering anxiety (BAI) as the key variable. The calculation shown 35 persons were needed in each group. Assuming a dropout of 5 persons per group, the final sample size was determined to be 30 persons per group.

Statistical analysis

The normality of data was assessed by Shapiro–Wilk test using the Statistical Package for Social Science version 22[35] (SPSS Inc., Chicago, Illinois) and all data had a normal distribution. Therefore, categorical data and quantitative data were analyzed using Chi square (Fisher's exact test) and *t*-test, respectively. Multiple linear regression models were used to assess treatment effects on study outcomes after adjusting for baseline levels of variables. $P < 0.05$ was considered significant.

Results

Out of 92 screened subjects with CS, 60 subjects were enrolled in the study and randomly assigned to either intervention or control group to receive vitamin D or placebo, respectively (30 people to

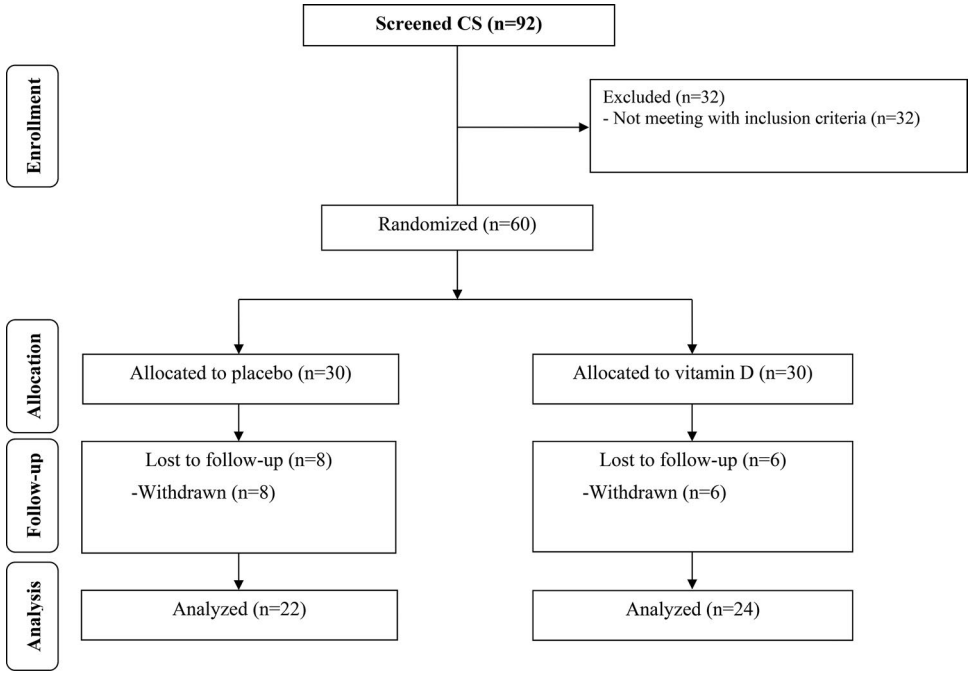

Figure 1. Summary of patient flow diagram.

each group). In the placebo group, eight people discontinued intervention due to personal reasons. In the intervention group six people revoked their consents. Therefore, data from a total of 46 people [intervention ($n=24$), and placebo ($n=22$)] were analyzed. CONSORT flow diagram regarding the enrollment of people in the present study has been showed in Figure 1. No side effects were shown following the administration of vitamin D supplements in CS. The general characteristics of subjects were similar between the two groups (Table 1).

After the six months intervention, 25(OH) vitamin D status significantly increased in the intervention group (β 2.96; 95% CI, 0.91, 5.01; $P=0.006$). In addition, vitamin D supplementation significantly decreased BDI score (β −2.06; 95% CI, −3.84, −0.28; $P=0.02$) compared with the placebo group (Table 2). There was no significant effect of vitamin D administration on anxiety inventory and nicotine misuse. Changes in vitamin D levels, NDSS, BAI, and BDI score in subjects with CS receiving vitamin D and placebo are presented in Figure 2.

Vitamin D supplementation significantly decreased FPG (β −4.56; 95% CI, −8.94, −0.19; $P=0.04$), insulin (β −0.50; 95% CI, −0.88, −0.13; $P=0.009$), and HOMA-IR levels (β −0.21; 95% CI, −0.33, −0.08; $P=0.001$), compared with the placebo-group. In addition, vitamin D resulted in a significant increase in plasma TAC (β 81.20; 95% CI, 18.30, 144.11; $P=0.01$), and GSH levels (β 73.05; 95% CI, 18.56, 127.54; $P=0.01$) (Table 3). No significant effect was recorded for vitamin D supplementation on QUICKI, lipid profile, hs-CRP, total nitrite, and malondialdehyde.

Discussion

We determined the impacts of vitamin D administration on nicotine misuse, mental health, and metabolic biomarkers for 24-weeks to an individual with a tobacco use disorder. Our study supported that taking vitamin D supplements, compared with the placebo, for 24-weeks among CS improved 25 (OH) vitamin D levels, BDI score, FPG, insulin, HOMA-IR, TAC, and GSH levels, but did not affect anxiety, nicotine misuse, QUICKI, lipid profile, hs-CRP, total nitrite, and malondialdehyde levels. Vitamin D plays an important role in regulating cell proliferation, immune response, regulating serum calcium and phosphorus levels.[36,37] There is growing evidence of the negative effects of CS on calcium metabolism and 25-hydroxyvitamin D.[38] CS has been

Table 1. Patients characteristics[a].

	Placebo ($n=22$)	Vitamin D ($n=24$)	P[b]
Age (year)	34.9 ± 12.3	35.4 ± 12.8	0.88
Age first experience of cigarette smoking (year)	19.9 ± 3.8	19.2 ± 3.9	0.54
Height (cm)	174.5 ± 5.6	173.1 ± 5.0	0.40
Weight at study baseline (kg)	76.7 ± 10.2	75.3 ± 9.7	0.63
Weight at the end-of-trial (kg)	77.6 ± 10.6	74.4 ± 8.8	0.26
Weight change (kg)	0.9 ± 3.1	−0.9 ± 4.2	0.10
BMI at study baseline (kg/m2)	25.2 ± 3.9	25.1 ± 3.2	0.89
BMI at the end-of-trial (kg/m2)	25.5 ± 3.9	24.8 ± 2.9	0.46
BMI change (kg/m2)	0.2 ± 1.0	−0.3 ± 1.4	0.11
Education (%)			
Illiterate	1 (4.5)	1 (4.2)	
Elementary	4 (18.2)	5 (20.8)	
Intermediate	6 (27.3)	6 (25)	0.99[c]
Diploma	2 (9.1)	3 (12.5)	
University Education	9 (40.9)	9 (37.5)	
Marital status (%)			
Single	13 (59.1)	12 (50)	
Married	9 (40.9)	9 (37.5)	0.22[c]
Widow/Divorced	0 (0)	3 (12.5)	
Job (%)			
Unemployed	2 (9.1)	1 (4.2)	
Employed	8 (36.4)	8 (33.3)	0.74[c]
Others	12 (54.5)	15 (62.5)	
Frequency of cigarette smoking			
One pack of cigarettes	15 (68.2)	19 (79.2)	0.39[c]
Two pack of cigarettes	7 (31.8)	5 (20.8)	
Duration of cigarette smoking (year)	14.3 ± 10.3	15.2 ± 10.4	0.77

[a]Data are mean ± SDs and percentage.
[b]Obtained from independent *t*-test.
[c]Obtained from Pearson Chi-square test.

demonstrated to augment the risk for vitamin D deficiency by impairing the enzymes involved in vitamin D synthesis, enhancing the activity of enzymatic markers of liver damage and other mechanisms.[39,40] Recently meta-analysis demonstrated that differences in vitamin D status among nonsmokers and smokers, with smokers likely to have lower vitamin D levels.[41] To our knowledge, this evidence is the first study to evaluate the effects of vitamin D on nicotine misuse, mental health, and metabolic biomarkers in individuals with a tobacco use disorder.

Effects on nicotine misuse

Available interventions for tobacco-related disorders, such as pharmacological treatments, psychological or behavioral interventions including physical training can only be helpful temporally.[42] So the relapse rate is still high. Therefore, looking for a safe, simple, and inexpensive supplementation to ease the nicotine withdrawal signs experienced by subjects when they quit CS is essential for continuous abstinence from tobacco-related disorders. We indicated that vitamin D supplementation to CS subjects for 24-weeks did not affect the nicotine misuse. Data documenting the effects of supplementation of vitamin D on nicotine misuse in individuals with a tobacco use disorder are limited. In the study by Wu et al.,[43] showed that dietary supplementation with vitamin D3 ameliorated nicotine withdrawal-induced anxiety, which might related to downregulation of NR2A expression in hippocampus. Vitamin D3 might provide a new intervention with the easy access for smoking cessation. Vitamin D can decrease the level of extracellular Ca2+ in hippocampal and downregulate the expression of L-type calcium channels. Also, it has neuroprotective effect and can prevent excitotoxicity injury caused by overexpression of NMDA receptors.[44] It has been demonstrated that nicotine, and marijuana stimulate neurons in nucleus accumbens (NA), while opiates, alcohol, and sedative-hypnotics stimulate neurons in the ventral tegmental area (VTA); however, all of them share a commonality in enhancing dopamine levels. In animals studies, vitamin D has been shown to afford a neuroprotective effect on dopaminergic system, as well as on nicotine misuse.[45,46]

Table 2. Nicotine misuse and mental health scale at baseline and after 24 weeks of the intervention in CS.

	Placebo group ($n=22$)		Vitamin D group ($n=24$)		Difference in outcome measures between vitamin D and placebo treatment groups[a]	
Variables	Baseline	Week 24	Baseline	Week 24	β (95% CI)	P[b]
Vitamin D (ng/mL)	24.5 ± 11.3	23.7 ± 11.8	23.3 ± 10.5	25.6 ± 10.1	2.96 (0.91, 5.01)	0.006
NDSS	54.8 ± 10.4	55.2 ± 10.4	55.2 ± 13.8	54.5 ± 13.8	−1.08 (−3.03, 0.85)	0.26
BAI	22.0 ± 9.3	21.5 ± 8.5	19.6 ± 10.2	18.1 ± 9.7	−1.24 (−2.64, 0.15)	0.08
BDI	26.4 ± 11.7	25.6 ± 11.5	25.8 ± 10.2	23.0 ± 10.7	−2.06 (−3.84, −0.28)	0.02

Data are mean ± SDs.
BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; NDSS, Nicotine Dependence Syndrome Scale.
[a]"Outcome measures" refers to the change in values of measures of interest between baseline and week 24. β [difference in the mean outcomes measures between treatment groups (vitamin D group = 1 and placebo group = 0)].
[b]Obtained from multiple regression models (adjusted for baseline values of each clinical variables).

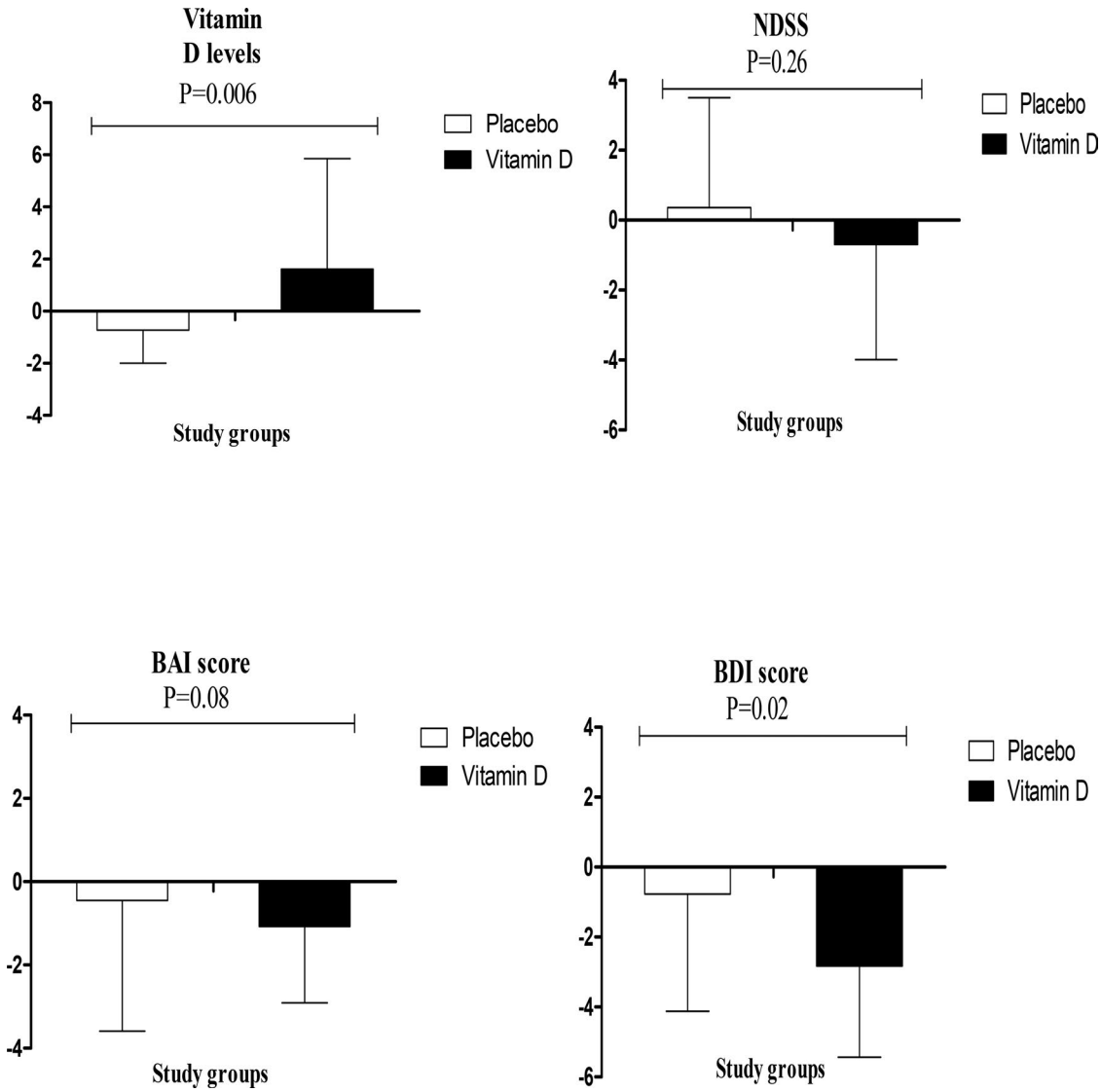

Figure 2. Fold change (means ± SDs) in nicotine misuse, mental health scale, and vitamin D levels of NDSS, BAI and BDI in CS who were candidate for receiving vitamin D supplements and placebo.

Table 3. Metabolic biomarkers at baseline and after 24 weeks of the intervention in CS.

	Placebo group ($n=22$)		Vitamin D group ($n=24$)		Difference in outcome measures between vitamin D and placebo treatment groups[a]	
Variables	Baseline	Week 24	Baseline	Week 24	β (95% CI)	P[b]
FPG (mg/dL)	84.2 ± 11.5	83.5 ± 10.7	89.1 ± 11.7	82.5 ± 11.7	−4.56 (−8.94, −0.19)	0.04
Insulin (μIU/mL)	7.4 ± 1.6	7.5 ± 1.3	7.7 ± 1.7	7.2 ± 1.2	−0.50 (−0.88, −0.13)	0.009
HOMA-IR	1.4 ± 0.3	1.5 ± 0.3	1.6 ± 0.5	1.4 ± 0.4	−0.21 (−0.33, −0.08)	0.001
QUICKI	0.36 ± 0.01	0.35 ± 0.01	0.35 ± 0.02	0.36 ± 0.01	0.005 (−0.003, 0.01)	0.18
Triglycerides (mg/dL)	163.0 ± 62.4	164.7 ± 65.9	166.6 ± 73.5	163.2 ± 58.1	−4.43 (−18.02, 9.14)	0.51
VLDL-cholesterol (mg/dL)	32.6 ± 12.4	32.9 ± 13.1	33.3 ± 14.7	32.6 ± 11.6	−0.88 (−3.60, 1.83)	0.51
Total cholesterol (mg/dL)	207.9 ± 22.8	216.3 ± 42.0	185.3 ± 39.5	181.1 ± 38.3	−14.22 (−30.02, 1.56)	0.07
LDL-cholesterol (mg/dL)	136.3 ± 26.8	145.1 ± 44.1	117.2 ± 32.6	112.8 ± 33.1	−13.98 (−29.71, 1.74)	0.08
HDL-cholesterol (mg/dL)	39.0 ± 8.3	38.1 ± 8.5	34.7 ± 6.1	35.6 ± 5.6	0.84 (−1.83, 3.50)	0.52
Hs-CRP (mg/L)	4.3 ± 1.1	4.6 ± 1.2	4.7 ± 1.3	4.7 ± 1.2	−0.26 (−0.57, 0.03)	0.08
Total nitrite (μmol/L)	66.0 ± 9.1	67.0 ± 9.4	67.3 ± 9.2	66.2 ± 9.3	−1.56 (−6.39, 3.27)	0.51
TAC (mmol/L)	766.4 ± 113.1	776.4 ± 128.1	679.2 ± 97.6	779.6 ± 133.5	81.20 (18.30, 144.11)	0.01
GSH (μmol/L)	701.7 ± 187.2	720.4 ± 160.2	680 ± 160.4	777.6 ± 170.8	73.05 (18.56, 127.54)	0.01
MDA (μmol/L)	3.0 ± 0.8	3.0 ± 0.6	2.5 ± 0.5	2.4 ± 0.5	−0.20 (−0.46, 0.06)	0.13

Data are mean ± SDs.

FPG, fasting plasma glucose; GSH, total glutathione; HOMA-IR, homeostasis model of assessment-estimated insulin resistance; HDL-cholesterol, high density lipoprotein-cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-cholesterol, low density lipoprotein-cholesterol; MDA, malondialdehyde; QUICKI, quantitative insulin sensitivity check index; TAC, total antioxidant capacity; VLDL-cholesterol, very low density lipoprotein-cholesterol.

[a]"Outcome measures" refers to the change in values of measures of interest between baseline and week 24. β [difference in the mean outcomes measures between treatment groups (vitamin D group = 1 and placebo group = 0)].

[b]Obtained from multiple regression model (adjusted for baseline values of each biochemical variables).

Effects on mental health

The high co-occurrence of cigarette smoking and mental disorder is a major public health concern, and cigarette smoking accounts for the reduction in life expectancy associated with mental disorders. Several studies demonstrated a positive association between mental disorders and cigarette smoking, with smoking rates increasing the severity of the disease.[47,48] Cigarette smoking has a significant effect on vitamin D and calcium metabolism. Higher score of depression and anxiety in CS may be associated with lower vitamin D levels induced by smoking.[10,49] Herein, we found that vitamin D administration to CS subjects for 24-weeks improved BDI indices, but did not affect anxiety inventory. The effects of vitamin D supplementation on mental health indices in nonsmoker subjects are inconsistent. For example, it was recently reported that 50,000 IU vitamin D administration every 2 weeks for 24-weeks in MMT programs had beneficial effects on BDI score, but did not affect BAI score.[13] We have previously observed that taking 50,000IU vitamin D for 3-months had favorable effects on sleep disorder, and depression indexes in people under MMT.[34] The current meta-analysis demonstrated that vitamin D supplements in patients with psychiatric disturbance had beneficial effects on BDI, as well as the Pittsburgh Sleep Quality Index (PSQI).[50] In addition, the study by Huang et al.[51] indicated that vitamin D supplementation at a dosage of 50,000 IU/week improved various aspects of quality of life in veterans with multiple areas of chronic pain. Moreover, two clinical trials have shown a significant effect of vitamin D intake on anxiety and depression symptoms.[52,53] On the other hand, high-dose vitamin D 3 supplementation (50,000 IU/week) for 52-weeks did not reduce the depressive symptoms in dialysis people with vitamin D 3 insufficiency.[54] In addition, two meta-analyses failed to show any beneficial effects of vitamin D supplementation on depressive signs in subjects with different health conditions.[17,55] Vitamin D modulates the expression of several calcium pumps, which results in attenuated intracellular calcium levels and calcium-regulated signaling pathways. In addition, vitamin D induces the transcription of serotonin synthesizing gene tryptophan hydroxylase 2, which contains a vitamin D response element (VDRE), and contributes to improved depression and anxiety symptoms.[56,57]

Effects on metabolic biomarkers

Smoking is a major risk factor for many diseases (e.g., cancer and inflammatory diseases). Tobacco smoke contains a compound of chemicals (e.g.,

ROS, RNS, and other), that can damage sub-cellular and cellular targets, such as proteins, lipids, and nucleic acids. Several studies have demonstrated a key role for smoking-induced ROS and the resulting oxidative stress in carcinogenesis and inflammation.[58] A review of the literature identified the acute effects of cigarette smoking on oxidative stress and inflammation in human and animal models.[5] Our study supports the notion that vitamin D administration for 24-weeks in CS subjects resulted in significant decreases in HOMA-IR, insulin values, FPG, and increases in TAC and GSH levels, but no significant change in QUICKI and lipid profiles, hs-CRP, NO, and MDA levels, compared with the placebo. It has been indicated that vitamin D deficiency could play an important role in inflammation and immune activation.[59] Moreover, vitamin D might prevent damage to pancreatic beta-cells and reduce the incidence of autoimmune diabetes mellitus, possibly due to attenuated production of inflammatory cytokines.[60] Several clinical trials have identified efficacy of vitamin D supplementation on inflammatory and oxidative stress parameters in psychiatric disturbance; others did not show such effect. However, the sample size of these clinical trials was small, the frequency and dosage of supplementation were diverse, and the quality of evidence was variable; accordingly, the results were inconsistent. In the study by Ghaderi et al.,[34] it was noted that consuming vitamin D for 12-weeks improved lipid profiles except HDL-cholesterol, glycemic control, hs-CRP, GSH and TAC levels in people under methadone maintenance treatment (MMT). In addition, GSH and TAC concentration were significantly enhanced as a result of high-dose vitamin D supplementation (every 2 weeks) among gestational diabetes women.[61] Another study indicated that vitamin D administration in individuals with endometriosis resulted in a significant improvement in total-/HDL-cholesterol, TAC and hs-CRP levels, but did not affect other metabolic parameters.[62] A meta-analysis study by Jamilian et al.,[50] showed that vitamin D supplementation in psychiatric disorders improved TAC, GSH and CRP concentration, but did not affect other biomarkers of oxidative stress and inflammation. Another meta-analysis by Mansournia et al.[63] showed that vitamin D administration enhanced GSH, NO and TAC and reduced MDA concentrations in diabetic patients. In addition, the current meta-analysis revealed that administration of vitamin D supplements for polycystic ovary syndrome resulted in an improvement in MDA, hs-CRP and TAC levels, but did not affect GSH and NO concentrations.[16] In contrast, another meta-analysis study has shown that vitamin D supplementation failed to a significantly affect inflammatory indices in overweight and obese people.[64] In addition, a systematic review by Rodriguez et al.,[65] failed to find any significant improvement in CRP concentrations in heart failure upon vitamin D administration. Other studies have reported that vitamin D might enhance gene expression of several antioxidants (e.g., superoxide dismutase, glutathione peroxidase, and GSH) by binding to VDRE. Moreover, vitamin D administration might improve inflammation and oxidative stress via its antioxidant properties, and attenuated production of pro-inflammatory cytokines and ROS.[66–68]

The current study had a number of strengths. Firstly, we focused on some interesting questions using a randomized, double-blind, placebo-controlled trial. The findings of improved depression symptoms and several metabolic biomarkers in the vitamin D supplementation group are interesting but need to be confirmed in a larger study. There were some limitations in this study. In the current study, we did not specify vitamin D intake through sun exposure. This should be considered in the interpretation of our findings as one of the limitations of this study. Also, the duration of the intervention in our study was short. Long-term interventions may have better effects on nicotine misuse, anxiety scale, and other metabolic profiles. In addition, vitamin D and placebo were provided by two various companies. This should be considered in the interpretation of our findings. Moreover, we did not evaluate dietary intakes of study participants; however, we requested participants not to change their regular physical activity, dietary intakes, and medication. We were not able to investigate the craving, relapse and cognitive functions in the CS. It seems that more assessments on craving, relapse and cognitive functions are needed in future studies. Also, assessment of the effect vitamin D administration on gene expression as well as finding new polymorphisms in the related-genes can open new sides in individuals with a tobacco use disorder.

Conclusions

Overall, we found that vitamin D administration for 24-weeks in CS subjects compared with the placebo group improved BDI score, FPG, insulin, HOMA-IR, TAC, and GSH levels, but did not affect nicotine misuse, the anxiety scale, lipid profile, QUICKI, hs-CRP, total nitrite and MDA levels. In conclusion, further well-controlled, randomized and blinded studies are needed to validate the efficacy of vitamin D in individuals with a tobacco use disorder.

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Disclosure statement

The authors declare that there are no conflicts of interest.

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Authors' contributions

Amir Ghaderi, Azam Mesdaghinia, and Hamid Reza Banafshe designed the study, provided oversight to the implementation, contributed to the interpretation and writing with input from Fatemeh Sadat Ghoreishi. Amir Ghaderi and Ahmad Reza Saghazade conducted the primary analysis with guidance from Samira Abbaszadeh-Mashkani and Azam Mesdaghinia. Soheil Bagheri, Ahmad Reza Saghazade, Samira Abbaszadeh-Mashkani, Fatemeh Sadat Ghoreishi, Hamid Reza Banafshe, Azam Mesdaghinia, and Amir Ghaderi contributed in data collection and manuscript drafting.

Ethics approval and consent to participate

At the beginning of the questionnaire distribution session, the purpose of the study was explained for the participants and they were assured about the anonymity and confidentiality of their responses. All participants gave their signed written informed consent letters. The study protocol was approved by the Ethics Committee of Kashan University of Medical Sciences "approval no. **IR.KAUMS.MEDNT.REC.1398.026"**. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available because the intellectual property is owned by the funding body. They may be available from the corresponding author on reasonable request containing the approval from the associated funding body.

Abbreviations

FPG	fasting plasma glucose
GSH	total glutathione
HOMA-IR	homeostasis model of assessment-insulin resistance
HDL-cholesterol	high density lipoprotein-cholesterol
Hs-CRP	high sensitivity C-reactive protein
LDL-cholesterol	low density lipoprotein-cholesterol
NO	nitric oxide
QUICKI	quantitative insulin sensitivity check index
VLDL-cholesterol	very low density lipoprotein-cholesterol
TAC	total antioxidant capacity
MDA	malondialdehyde
BDI	Beck Depression Inventory
BAI	Beck Anxiety Inventory
NDSS	Nicotine Dependence Syndrome Scale

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