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ORIGINAL ARTICLE

Levels of 25-hydroxyvitamin D_3, biochemical parameters and symptoms of depression and anxiety in healthy individuals

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Abstract

Growing evidence support the role of vitamin D in brain function and behavior. This study investigated the relationship between 25-hydroxyvitamin D_3 [25(OH)D_3] levels, biochemical profile and symptoms of depression and anxiety in healthy individuals. Symptoms of depression were assessed by the Beck Depression Inventory (BDI) and anxiety was evaluated with the State-Trait Anxiety Inventory (STAI). Our sample included 36 individuals, mostly women 27(75%), 36.39 ± 9.72 years old, non-smokers 31(86.1%), body mass index of 26.57 ± 3.92 kg/m^2, 27.95 ± 7.50% body fat. Participants were divided into those with 25(OH)D_3 levels lower than 40 ng/mL (mean 28.16 ± 7.07) and equal or higher than 40 ng/mL (mean 53.19 ± 6.32). Those with lower 25(OH)D_3 had higher levels of triacylglycerol, triacylglycerol/high density lipoprotein (HDL) ratio, high glucose and homeostatic model assessment of insulin resistance (HOMA-IR) index. No changes were observed in sociodemographic variables, body composition, inflammatory parameters and cortisol. Additionally, in the groups with low and high 25(OH)D_3 levels, STAI state, STAI trait and BDI scores were not statistically different. Levels of 25(OH)D_3 were inversely and independently associated with glucose and HOMA-IR, but not associated with triacylglycerol, depression and anxiety scores. Lower levels of 25(OH)D_3 were associated with dysfunction in glucose metabolism but not with depression and anxiety in healthy individuals.

Keywords Anxiety · Depression · Glucose · Lipid profile · Vitamin D

Abbreviations

[25(OH)D_3]	25-hydroxyvitamin D_3
[1,25(OH)$_2$$D_3$]	1,25-dihydroxyvitamin D_3
BDI	Beck Depression Inventory
BMI	body mass index
CNS	central nervous system
CRP	C-reactive protein
ELISA	Enzyme-Linked Immunosorbent Assay
HOMA-B	homeostatic model assessment of beta cells function
HOMA-IR	homeostatic model assessment of insulin resistance
HDL	high density lipoprotein
LDL	low density lipoprotein
S.D.	standard deviation
STAI	State-Trait Anxiety Inventory
SPSS	Statistical Program for Social Sciences

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Introduction

Vitamin D is a steroid hormone consumed in the diet as either ergocalciferol (D_2), from plant, fungi and yeast, or cholecalciferol (D_3), mainly from animal sources. Additionally, vitamin D is endogenously produced when the skin 7-dehydrocholesterol is converted into vitamin D_3 after sun exposure (Nair and Maseeh 2012). In the liver, vitamins D_2 and D_3 are hydroxylated to 25-hydroxyvitamin D [25(OH)D] and then, to the biologically active metabolite, 1,25-dihydroxyvitamin D_3 [1,25(OH)$_2$$D_3$] in the kidney and in other tissues, including the brain (Christakos et al. 2007). The actions of vitamin D are classically mediated through binding of its active metabolite, 1,25(OH)2D3, to the vitamin D

receptor (VDR) leading to either induction or repression of over 1000 genes in different tissues (Eelen et al. 2004).

The classical function attributed to vitamin D is related to the maintenance of musculoskeletal health as it has a direct association with calcium-phosphate homeostasis (Masuyama 2014). However, the ubiquitous expression of the machinery responsible for its bioactivation and biological effects, provides a mechanistic basis for the link between vitamin D deficiency and different disorders. In fact, over the past few decades, it has been found that vitamin D_3 is an essential micronutrient as it is associated with non-musculoskeletal health conditions including type 1 and type 2 diabetes, autoimmune diseases, cardiovascular disease, cancer, Alzheimer's disease and vascular dementia (Wang et al. 2008; Kayaniyil et al. 2010; Maki et al. 2012; Vacek et al. 2012; Song et al. 2013; Afzal et al. 2014; Maddaloni et al. 2018).

Preclinical studies provided strong evidence that vitamin D_3 plays an important role in glucose homeostasis since adequate vitamin D_3 concentrations in association with VDR functioning are essential for insulin secretion and pancreatic β-cells normal activity (Alvarez and Ashraf 2010; Sung et al. 2012; Manchanda and Bid 2012; Bikle 2014). Moreover, clinical studies have shown that low serum levels of vitamin D increase the risk of developing diabetes, neuropathy and retinopathy (Patrick et al. 2012; Afzal et al. 2013, Schöttker et al. 2013, Tsur et al. 2013; Afzal et al. 2014).

Despite the absence of a clear association between Vitamin D receptor knockout mice and diabetes susceptibility or changes in glucose homeostasis (Bouillon et al. 2008), several studies showed behavioral impairments in these mice associated with anxiety, including aggression, reductions in grooming, nest building, and maternal behaviors, but not a depressive-like phenotype in the tail suspension test (Minasyan et al. 2007). Animal studies suggest that despite the reduced uptake of $1,25(OH)_2D_3$ in the brain, some metabolites, including $25(OH)D_3$ can cross the blood-brain barrier and serve as substrate for conversion to $1,25(OH)_2D_3$ within the brain (Upadhyay 2014). Notably, the enzymes responsible for $25(OH)D_3$ conversion into its $1,25(OH)_2D_3$, as well as the receptors, are widely expressed in the central nervous system (CNS), in areas controlling mood and behavior, including the cortex and the limbic system (Upadhyay 2014). Vitamin D deficiency in rats during development or in utero results in brain abnormalities, including thinner neocortices, greater cell proliferation and decreased apoptosis (Féron et al. 2005). Among its other activities, $1,25(OH)_2D_3$ has neuroprotective properties and modulates the production and release of neurotrophic factors (Dicou 2009; Hua et al. 2012; Tang et al. 2013, 2015; Chabas et al. 2013), the expression of genes associated with GABAergic signaling, and stimulates the biosynthesis of catecholamines (Jiang et al. 2013). Moreover, antioxidant and anti-inflammatory properties were also described in preclinical studies (Hayes et al. 2003).

Nevertheless, clinical studies evaluating the relationship between vitamin D or its metabolites in depression and anxiety are mostly inconclusive (Bertone-Johnson 2009). The most convincing clinical evidence for the ability of vitamin D to modulate mood and behavior comes from a randomized clinical trial including 441 participants that exhibited a modest improvement in depressive symptoms after vitamin D supplementation for one year (Jorde et al. 2008). However, while evidence suggests that vitamin D has important functions both in the periphery and in the CNS, it remains unclear whether these functions may be related to the occurrence of biochemical and behavioral alterations relevant to metabolic and psychiatric disorders. Thus, the present work investigates if changes in $25(OH)D_3$ levels are associated with different biochemical parameters and symptoms of depression and anxiety in healthy individuals.

Methods

Participants and behavioral evaluation

This is a cross-sectional study including 36 patients who attended a nutrition clinic in the city of Garopaba, SC, Brazil, from November 2017 to February 2018. The study protocol was approved by the Ethics Committee of the Federal University of Santa Catarina (protocol 56227816.0.0000.0121) and it follows the provisions of the Declaration of Helsinki. After the informed consent, a detailed sociodemographic and clinical history was obtained, including information on age, gender, physical activity habits (more than twice a week), health habits (tobacco use, medication or previous clinical or psychiatric disease), and body composition (body mass index – BMI, % of body fat, visceral fat, lean mass and waist-to-rip ratio). The Bristol scale was used to analyze bowel habits and feces type (Martinez and de Azevedo 2012).

The behavioral evaluation was performed using the Beck Depression Inventory (BDI), a 21-item self-reported instrument that evaluates key symptoms of depression including changes in mood, anhedonia, pessimism, sense of failure, self-dissatisfaction, guilt, suicidal ideas, irritability, social withdrawal, indecisiveness, body image change, work difficulty, insomnia, fatigability, changes in appetite and weight and loss of libido. The total score ranges from 0 to 63, with scores from 0 to 9 being an indicative of none to minimal depressive symptoms; 10 to 18, mild depressive symptoms; 19 to 29, moderate depressive symptoms; and 30–63, severe depressive symptoms (Beck et al. 1988).

Anxiety was evaluated with the State-Trait Anxiety Inventory (STAI), divided in anxiety trait of anxiety, which is related to how the person feels most of the time and anxiety state (S-anxiety), a section related to how the person feels at

the time of the assessment. The instrument measures the presence and severity of current symptoms of anxiety and a generalized propensity to be anxious (Spielberger et al. 1970). The questionnaire was adapted and validated in Brazil (Biaggio et al. 1977; Gorenstein and Andrade 1996). T-anxiety and S-anxiety scales include 20 items with 4 Likert responses; score ranges from 20 to 80; the higher the scores the higher the anxiety trait or state.

Biochemical analysis

Vitamin D status was measured by assessing circulating levels of 25(OH)D_3, which is the major circulating metabolite and is considered as the main biomarker of vitamin D3 status of the patient (Caprio et al. 2017). The biochemical evaluation was performed in fasting samples in a laboratory in the city of Garopaba, Brazil. Serum levels of 25(OH)D_3, insulin and cortisol were measured by chemiluminescence immunoassay, C-reactive protein (CRP) and complete blood count were determined by automated analyzers, glucose was measured by the hexokinase method, lipid profile was determined by enzymatic methods. HOMA-IR and HOMA-B index were calculated using HOMA calculator © developed by the University of Oxford in 2013 and based on glucose and insulin levels. Although there is no formal consensus on the optimal levels of 25(OH)D_3, serum 25(OH)D_3 levels <40 ng/ml were considered vitamin D insufficiency and ≥ 40 ng/ml were considered adequate levels, according to a previous study (Jorde et al. 2008).

Statistical analysis

Statistical analysis was performed with the Statistical Program for Social Sciences (SPSS) 21.0. Normality was tested using the Shapiro-Wilk test. All sociodemographic and clinical variables including levels of vitamin D ($p = 0.73$), glucose ($p = 0.716$), HDL ($p = 0.127$) and LDL levels ($p = 0.843$), mood ($p = 0.539$) and anxiety trait ($p = 0.264$) and anxiety state scores ($p = 0.599$) were normally distributed, with exception of triglycerides (0.010), HOMA-IR ($p = 0.005$) and HOMA-B index ($p = 0.008$).

Sociodemographic characteristics according to 25(OH)D_3 levels were analyzed by *Student t* test (for parametric variables) or Mann-Whitney U test (for non-parametric variables) and expressed as mean ± standard deviation (S.D.) for continuous variables. For categorical variables, results were expressed as number and %, and compared with the χ^2-test. Comparative analyses were carried out using the Pearson correlation (for parametric variables) or Spearman correlation (for triglycerides, HOMA-IR and HOMA-B). Multilinear regression was used for adjustment for the confound variables. *p*-values ≤0.05 were considered statistically significant.

Results

A total of 36 young subjects were included in this report. The gender distribution was 27 (75%) female, and 9 (25.5%) male subjects. The mean age among the subjects was 36.39 ± 9.72 years, body mass index (BMI) of 26.57 ± 3.92 kg/m^2 and 27.95 ± 7.50% body fat. Concerning the use of substances, only 6 subjects (13.9%) were habitual smokers and none of the individuals used any medication.

Serum 25(OH)D_3 levels were determined in 34 patients. Participants were divided into those with sufficient and insufficient 25(OH)D_3 levels (<40 vs. ≥ 40 ng/mL). The levels of 25(OH)D_3 were 28.16 ± 7.07 in the group with <40 ng/ml ($n = 27$) and 53.19 ± 6.32 in the group ≥40 ng/mL ($n = 07$). Table 1 shows the distribution of sociodemographic and body composition measures of the sample according to the levels of 25(OH)D_3. No differences were observed according to age, gender, BMI, % of body fat, visceral fat, lean mass, waist-to-rip ratio, Bristol scale, self-reported physical activity or tobacco use between groups with low and high levels of 25(OH)D_3. Table 2 shows metabolic parameters and mood symptoms according to levels of 25(OH)D_3. Regarding the blood count, levels of CRP and cortisol, no differences were found between groups. However, individuals with 25(OH)D_3 levels <40 ng/mL had some changes in lipid profile, characterized by higher levels of triglycerides ($p = 0.015$) and high ratios of high

Table 1 Sociodemographic information and body composition according to 25(OH)D_3 levels

	25(OH)D_3 < 40	25(OH)D_3 ≥ 40	*p* value
Age (years)	34.52 ± 8.55	38.86 ± 10.88	0.266
25(OH)D_3 (ng/mL)	28.16 ± 7.07	53.19 ± 6.32	0.000*
Gender			0.883
Female	20 (74.11%)	6 (85.7%)	
Male	7 (25%)	1 (14.3%)	
Tobacco use			0.670
No	23 (46.7%)	7 (23.3%)	
Yes	4 (100%)	0 (0%)	
Physical activity			1.000
No	1 (100%)	0(0%)	
Yes	26 (78.8%)	7 (21.2%)	
BMI (kg/m^2)	27.37 ± 3.75	24.19 ± 4.14	0.059
Body fat (%)	29.21 ± 7.32	23.52 ± 7.84	0.080
Visceral fat (kg)	24.26 ± 2.50	19.99 ± 2.37	0.079
Lean mass (kg)	51.46 ± 1.83	47.97 ± 9.69	0.355
Waist-to-hip ratio	0.77 ± 0.014	0.75 ± 0.011	0.443
Bristol scale	3.37 ± 0.152	3.71 ± 0.184	0.284
Total (n)	27	07	–

Results are expressed as mean ± S.D. or n (%) and analyzed by Student t test for continuous variables or χ^2-test for categorical variables. *$p < 0.05$. BMI: body mass index

Table 2 Biochemical information and mood symptoms according to $25(OH)D_3$ levels

	$25(OH)D_3 < 40$	$25(OH)D_3 \geq 40$	*p* value
Immune markers			
CRP (mg/L)	3.03 ± 4.84	1.60 ± 2.58	0.460
Hematocrit (%)	40.08 ± 2.80	39.28 ± 4.17	0.551
Leukocytes (mm^3)	6345.41 ± 1991.65	5360.28 ± 1339.40	0.227
Segmented (mm^3)	3358.75 ± 1163.25	2649.00 ± 1050.78	0.153
Eosinophils (mm^3)	218.14 ± 187.07	121.00 ± 41.49	0.186
Basophils(mm^3)	28.74 ± 28.78	36.45 ± 23.42	0.518
Lymphocytes (mm^3)	2364.27 ± 577.08	2105.00 ± 672.72	0.313
Monocytes (mm^3)	405.64 ± 109.62	443.71 ± 123.58	0.430
Platelets (mm^3)	246.14 ± 62.31	221.71 ± 26.17	0.322
Lipid profile			
Cholesterol (mg/dL)	188.36 ± 31.70	173.710 ± 36.53	0.298
HDL (mg/dL)	55.04 ± 12.29	55.57 ± 9.36	0.917
LDL (mg/dL)	115.59 ± 27.84	108.77 ± 30.69	0.575
Triglycerides (mg/dL)	86.29 ± 36.86	49.28 ± 15.11	0.015*
Triglycerides/HDL	1.59 ± 0.64	0.93 ± 0.41	0.015*
Glucose metabolism			
Cortisol	16.06 ± 62.42	15.83 ± 5.15	0.930
Glucose (mg/dL)	85.45 ± 7.43	78.00 ± 5.29	0.019*
HOMA-IR	1.02 ± 0.44	0.54 ± 0.10	0.008*
HOMA-B (%)	108.85 ± 38.87	86.78 ± 15.86	0.155
Mood symptoms			
BDI	10.04 ± 5.05	7.86 ± 7.98	0.375
STAI trait	40.56 ± 8.26	40.57 ± 5.85	0.996
STAI state	39.67 ± 8.91	41.57 ± 7.87	0.610
Total (n)	27	07	–

Results are expressed as mean ± S.D. and analyzed by Student t test (for parametric variables) or Mann-Whitney U test (for non-parametric variables) *$p < 0.05$. BDI: Beck Depression Inventory; CRP: C-reactive protein; HOMA-B: homeostatic model assessment of beta cell function; HOMA-IR: homeostatic model assessment of insulin resistance; HDL: high density lipoprotein; LDL: low density lipoprotein; STAI: State-Trait Anxiety Inventory

density lipoprotein triglycerides/HDL ($p = 0.015$), but no changes in the levels of total cholesterol, HDL and low-density lipoprotein (LDL). In addition, participants with $25(OH)D_3$ levels <40 ng/mL had significant changes in glucose homeostasis, with higher levels of glucose ($p = 0.019$) and high homeostatic model assessment of insulin resistance index (HOMA-IR, $p = 0.004$), but not homeostatic model assessment of beta cell function (HOMA-B, $p = 0.191$) when compared with individuals with higher $25(OH)D_3$ levels (≥ 40 ng/mL). Regarding the behavioral evaluation, the scores in BDI ($p = 0.375$), STAI state ($p = 0.996$) or STAI trait ($p = 0.610$) were not significantly different in individuals with lower and higher $25(OH)D_3$ levels.

The results depicted in Fig. 1 show that levels of $25(OH)D_3$ were inversely associated with levels of glucose ($r = -0.354$, $p = 0.040$) using Pearson correlation. This association remained significant after adjusting by age, gender, tobacco use, physical activity, BMI and levels of triglycerides ($B = -0.268$, $p = 0.024$) using multilinear regression. No association was found between levels of glucose and triglycerides ($r = 0.132$, $p = 0.443$) using Spearman's correlation. Additionally, levels of $25(OH)D_3$ were inversely associated with HOMA-IR index ($r = -0.363$, $p = 0.035$), but not HOMA-B ($r = -0.111$, $p = 0.533$) using Spearman's correlation. Levels of $25(OH)D_3$ were not associated with behavioral scores in the BDI ($r = -0.199$, $p = 0.259$), STAI state ($r = 0.227$, $p = 0.197$) and STAI trait ($r = 0.103$, $p = 0.561$) using Pearson correlation.

Discussion

In this cross-sectional study, we found that lower $25(OH)D_3$ levels were significantly associated with prejudicial effects in the biochemical profile, including increased levels of glucose, increased HOMA-IR index, triglycerides and triglycerides/

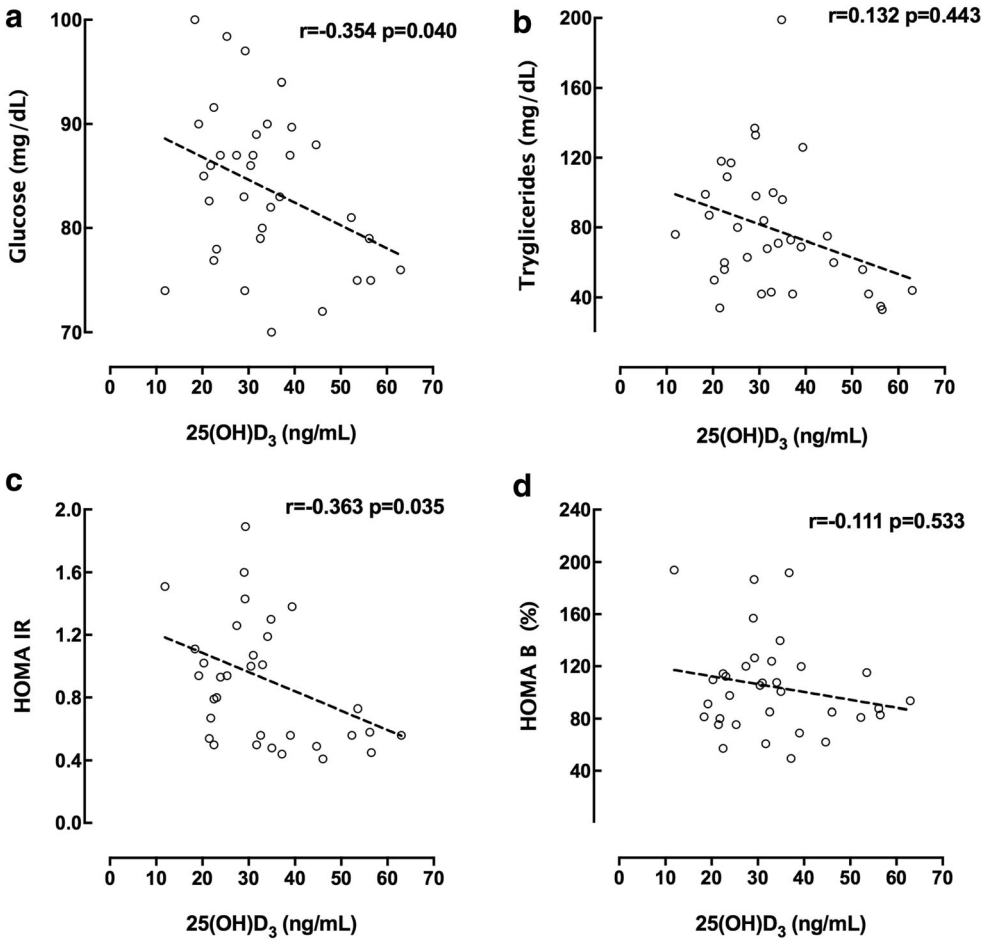

Fig. 1 Correlation between serum levels 25(OH)D_3 and glucose levels (**a**), triglycerides (**b**), HOMA-IR (**c**) and HOMA-B (**d**). Each dot represents an individual and correlation was calculated using Pearson's correlation coefficient for glucose or Spearman's correlation for triglycerides HOMA-IR and HOMA-B values. $p < 0.05$ was considered significant ($n = 34$)

HDL ratio. However, changes in these biochemical parameters were not associated with symptoms of depression or anxiety in young and healthy individuals.

There is increasing evidence suggesting that vitamin D deficiency is associated with risk for cardiovascular disease (Wang et al. 2008; Maki et al. 2012; Vacek et al. 2012) insulin resistance, and type-2 diabetes (Kayaniyil et al. 2010; Song et al. 2013). We found that lower levels of 25-(OH)D_3 were significantly associated with worse cardiovascular and metabolic factors, including higher fasting plasma glucose and higher HOMA-IR, but not HOMA-B index and triglycerides levels. These results are in agreement with literature data, which show that higher circulating levels of 25-(OH)D_3 are related to reduced risk of higher fasting plasma glucose levels (Pittas et al. 2007). In addition, several intervention studies have shown a significant reduction in insulin resistance, assessed by HOMA-IR in healthy subjects or subjects with impaired glucose tolerance after supplementation with vitamin D (Pittas et al. 2007; Nikooyeh et al. 2011; Kampmann et al. 2014).

The mechanisms involved in the relationship between 25-(OH)D_3 and glucose metabolism are not well established. However, in several studies the effects of vitamin D on glucose homeostasis was not dependent on the adiposity or BMI, but rather related to its effect on the control of calcium levels, up-regulation of the insulin receptor gene, and regulating insulin secretion from pancreatic beta-cell and maintenance of islet viability, as well as preventing insulin resistance as indicated in Fig. 2 (Sergeev and Rhoten 1995; Maestro et al. 2002). Considering that insulin inhibits gluconeogenesis and glycogenolysis and stimulates muscle glucose uptake, the ability of vitamin D to increase insulin levels and sensitivity could be important to afford beneficial effects for glucose homeostasis, as depicted in Fig. 2.

Our results also reinforce the notion that vitamin D deficiency is associated with an unfavorable lipid profile, high levels of triacylglycerol and triglycerides/HDL ratio. In a review including 22 cross-sectional studies, low 25(OH)D_3 levels were associated with high serum levels of triglycerides and low high-density lipoprotein (HDL), which possibly explain the relationship between 25(OH)D_3 and cardiovascular disease (Jorde and Grimnes 2011). The mechanisms involved in the effects of vitamin D on lipid profile are not well understood. In our study, despite the unfavorable lipid profile in individuals with levels of vitamin D lower than 40 ng/mL, triglycerides triacylglycerol and triglycerides/HDL ratio were

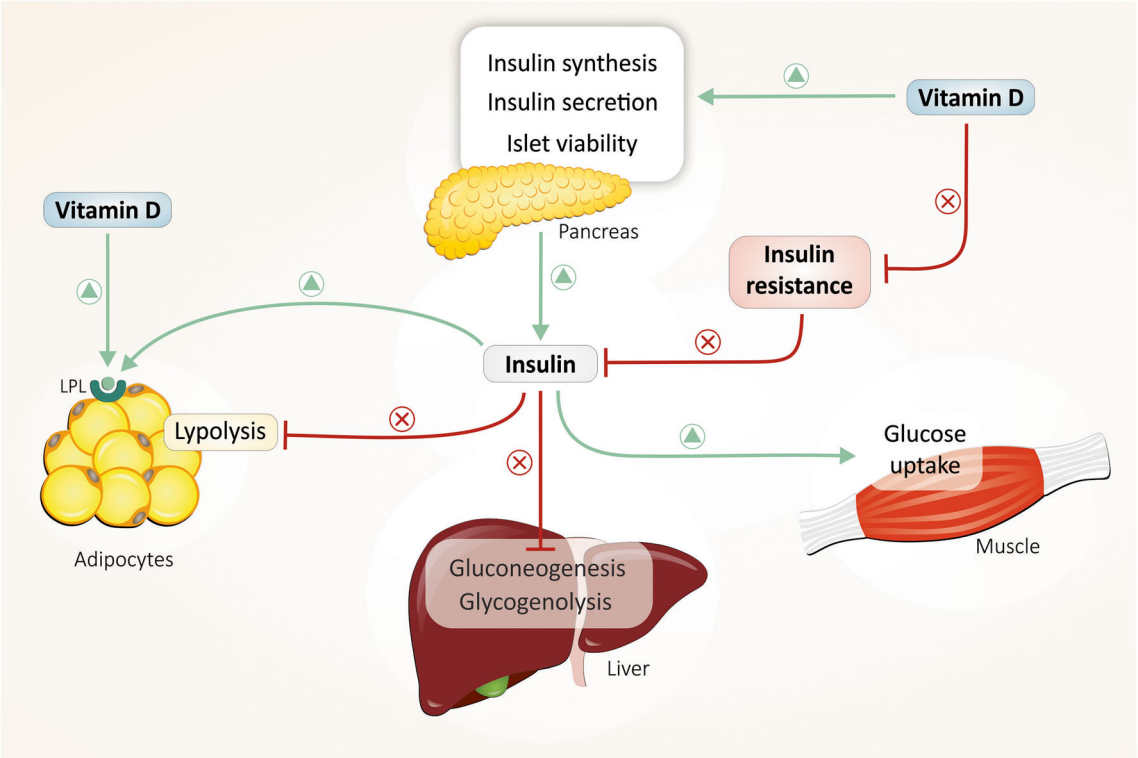

Fig. 2 Proposal mechanisms underlying the beneficial effects of vitamin D for glucose homeostasis and lipid metabolism. Vitamin D is able to promote insulin synthesis and secretion and islet viability through its binding to VDR in pancreatic β cells. Vitamin D is also proposed to decrease insulin resistance, therefore contributing to the maintenance of insulin effects on glucose and lipid metabolism, i.e., inhibition of gluconeogenesis and glycogenolysis (consequently decreasing hepatic glucose production and release to blood circulation), stimulation of muscle glucose uptake and decrease of lipolysis in adipocytes. (Adapted from Van Belle et al. 2013)

not associated with vitamin D levels in correlation analysis. These results might indicate indirect effects of vitamin D on lipid profile and metabolism. In fact, vitamin D may indirectly improve the lipid profile by enhancing insulin sensitivity, as indicated in Fig. 2, reducing the secretion of parathyroid hormone, and increasing calcium absorption, which in turn, might result in increased fat absorption (Maestro et al. 2002; Reid 2004). However, preclinical data have found both positive and negative effects of vitamin D on lipid profile (Wong et al. 2009; Wang et al. 2012) and the genetic depletion of vitamin D receptors in mice was associated with less body fat and reduced plasma triglycerides when compared to wild type, even after high fat diet (Ross et al. 2011). In addition, despite the potential beneficial role for vitamin D in the regulation of glucose homeostasis and lipid profile, studies evaluating vitamin D supplementation and protection against metabolic and cardiovascular diseases obtained inconclusive results (Altay et al. 2012).

Regarding the behavioral evaluation, our results showed no correlation between levels of vitamin D and symptoms of depression and anxiety, evaluated by the BDI and STAI scores. Results evaluating peripheral levels of 1,25(OH)D_3 or the metabolite 25(OH)D_3 and their association with psychiatric symptoms are divergent. Several authors failed to find an association between 25(OH)D_3 levels and symptoms of depression (Khoraminya et al. 2012; Williams et al. 2016). However, lower levels of 1,25(OH)D_3 were observed in 25 patients with major depression when compared with 31 healthy controls (Sheline et al. 2006). Furthermore, in a study including 40 elderly individuals with mild Alzheimer's disease and 40 controls, symptoms of depression were more prevalent in individuals with levels of 25(OH)D_3 lower than 20 ng/mL (Jorde et al. 2006). In line with this, serum 25(OH)D_3 levels have been inversely associate with the severity of depressive symptoms (Hoogendijk et al. 2008; Milaneschi et al. 2014). Moreover, 25(OH)D_3 levels were significantly lower in 89 premenopausal women with major depression as compared to 44 controls. Hoogendijk and colleagues (Hoogendijk et al. 2008) evaluated 25(OH)D_3 levels and depression in elderly men and women and found that depression severity was significantly associated with low levels of 25(OH)D_3 even after adjustment.

Anxiety evaluation was divided into trait anxiety and state anxiety. Trait anxiety can be defined as a predisposition to experience anxiety as a response to stress and psychological threats, characterizing a maladaptation under conflict circumstances (Reiss 1997; Endler and Kocovski 2001), whereas state anxiety measures the current symptoms of anxiety

(Moritz et al. 2017). Regarding the symptoms of anxiety trait and state, clinical data are scarce. Studies in animals have identified that mouse lacking the vitamin D receptors gene showed an increase in anxiety-like behavior (Kalueff et al. 2004; Fedotova et al. 2017). A recent study has showed a therapeutic effect of vitamin D on anxiety-like behavior in female rats with long-term estrogen deficiency (Han et al. 2018). Other authors reported that low serum levels of vitamin D are independently associated with anxiety among children and adolescents on dialysis (Chaowen et al. 2016) and that insufficient levels of vitamin D may represent an independent risk factor for the development of anxiety in acute stroke patients one month after the onset of brain injury (Kimball et al. 2018).

Several values for 25(OH)D_3 have been proposed in the scientific literature as adequate levels. In a report published in 2011, concentrations of 20 ng/ml were considered sufficient to meet the vitamin D requirements in 97.5% of the general population (Altay et al. 2012). However, according to the Kimball et al. (2018). serum 25(OH)D concentrations above 40 ng/mL positively influenced depression and anxiety outcomes. Additionally, core symptoms of autism spectrum disorder were remarkably improved in autistic children after vitamin D supplementation when 25(OH)D_3 levels reached over 40 ng/mL, suggesting that maintaining serum 25(OH)D_3 levels between 40 and 100 ng/ml might be beneficial for behavioral function (Jia et al. 2018). Despite the absence of significant depression or anxiety symptoms in the participants enrolled in the present study, it has been recognized for decades that metabolic conditions including metabolic syndrome, diabetes mellitus type 2 and cardiovascular diseases are common risk factors for psychiatric disorders, including major depression and anxiety (Jean-Louis et al. 2008).

It is important to highlight that in our sample of heathy young adults, no changes in immune markers or cortisol were observed according to the levels of vitamin D. In addition, the individuals enrolled in the present study had very low BDI and STAI scores, an indicative of low or absent symptoms of depression and anxiety, which might explain this observation. In fact, a meta-analysis reported no overall effect on depressive symptoms when analyzing all the studies with depression outcomes. However, in subgroup analysis enrolling only patients with clinically significant depression, vitamin D was associated with decreased depression severity (Shaffer et al. 2014).

There are several limitations that need to be acknowledged in our study. The study design was cross-sectional and therefore, a causal relationship between vitamin D and metabolic factors, body composition and psychiatric symptoms could not be established. Additionally, the relatively small sample size also raises the question of lack of power to detect smaller associations between 25(OH)D_3 and psychiatric symptoms. Finally, we acknowledge that our population included young and healthy individuals, without the diagnosis of major depression and anxiety disorders and with a small variation in 25(OH)D_3 levels. However, our study points to a strong and independent association between glucose metabolism and elevated triglycerides or triglycerides/HDL ratio in individuals with low levels of vitamin D, which suggest that vitamin D supplementation might prevent an exacerbation of metabolic dysfunction and possibly the development of type-2 diabetes or metabolic syndrome in healthy individuals. However, prospective studies are needed to evaluate the impact of this relationship on symptoms of depression and anxiety.

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Author contributions M.P.K and A.L.R. were involved in the conception and design of the study and drafting of the manuscript; G.A. and G.A.S.C. were responsible for acquisition and analysis of data and drafting the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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