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ORIGINAL ARTICLE

Cardiovascular risk in adult hypopituitaric patients with growth hormone deficiency: is there a role for vitamin D?

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Abstract Hypovitaminosis D represent an environmental risk factors for cardiovascular (CV) disease. To investigate the prevalence of hypovitaminosis D and the correlation between GH/IGF-I deficiency and hypovitaminosis D with CV risk in GH deficiency (GHD) patients. A link between these hormones has been shown. Forty-one hypopituitaric patients with GHD (22 males, age 18–84 years) and 41 controls were enrolled in the study. Anthropometric parameters, blood pressure, glucose and lipid profile, parathyroid hormone (PTH), 25(OH) vitamin D (vitamin D), metabolic syndrome (MS), GH peak after GHRH + ARG, IGF-I, and standard deviation score (SDS) of IGF-I (zIGF-I) were assessed. Vitamin D levels were lower in patients than in controls (21.3 ± 12.3 vs. 28.2 ± 9.4, $p = 0.006$). Deficiency was found in 51 % of patients versus 14.6 % of controls ($p < 0.01$), insufficiency in 26.8 versus 41.4 % ($p = 0.269$) and normal vitamin D levels in 21.9 versus 43.9 % ($p = 0.060$). The prevalence of dyslipidemia was 51.2 % in patients versus 12.1 % in controls ($p < 0.001$), type 2 diabetes mellitus (DM) was 7.3 versus 17 % ($p = 0.292$), hypertension was 44 versus 22 % ($p = 0.060$), and MS was 17 versus 14.6 % ($p = 0.957$). In patients, an association was found between the presence of hypovitaminosis D and the prevalence of dyslipidemia, hypertension and MS and between zIGF-I and the prevalence of hypertension. Hypovitaminosis D was the most powerful predictor of the prevalence of dyslipidemia and hypertension. GHD patients have an increased prevalence of hypovitaminosis D compared with controls. The presence of hypovitaminosis D was the most powerful predictor of the prevalence of dyslipidemia and hypertension in GHD patients, suggesting the involvement of both factors in the CV risk in these patients.

Keywords Hypovitaminosis D · Vitamin D · Environmental risk factors · GH–IGF-I axis · GH deficiency · Cardiovascular risk

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Introduction

Currently, vitamin D deficiency represents one of the environmental risk factors for the onset and progression of various diseases. Thus, in addition to the well-known role of vitamin D in the regulation of calcium and phosphorus homeostasis and consequences of vitamin D deficiency on the musculoskeletal system, nonskeletal effects of vitamin D have been recognized [1]. More specifically, a growing body of evidence suggests that vitamin D deficiency may represent an important cardiovascular (CV) risk factor [1–3]. The relationship between vitamin D and the CV system is confirmed by evidence that vitamin D receptors are present in most tissues including endothelium [4], vascular smooth muscle [5], and myocardium [6]. Low vitamin D status has been associated with an increase in blood pressure (BP), adverse lipid profiles, impaired insulin metabolism, and an increase in CV risk [7]. Low serum vitamin D levels have been documented in patients with myocardial infarction [8], stroke [9], congestive heart failure [10], peripheral vascular insufficiency [11], type 2 diabetes mellitus (DM), insulin resistance, obesity, and metabolic syndrome (MS) [12, 13]. Several mechanisms have been

proposed to explain the link between vitamin D and CV disease [14], although this association remains to be confirmed [15]. On the other hand, abnormalities of the growth hormone (GH)/insulin-like growth factor-I (IGF-I) axis contribute in determining CV disease, as reported by several clinical studies. Increased risk for CV morbidity and mortality has been evidenced both in GH deficiency (GHD) and excess [16, 17]. Epidemiological studies in the general population have suggested that IGF-I levels in the lower normal range are associated with an increased risk of ischemic heart disease [18, 19], ischemic stroke [20, 21], atherosclerosis [22, 23], severe hypertension, and type 2 DM [24]. Patients with hypopituitarism are known to have reduced life expectancy with a 2-fold higher risk of death for CV disease compared with healthy controls and GHD has been considered the underlying factor of the increased mortality when appropriate standard replacement of the other pituitary hormones deficiencies is given [25, 26].

Recent findings suggested a relationship between GH/IGF-I axis and vitamin D and this interplay occurs both at endocrine and paracrine/autocrine levels [27, 28]. Vitamin D regulates gene expression of the GH/IGF-I axis and may promote the action of IGF-I by increasing IGF-I receptors, and both GH and IGF-I can elevate vitamin D concentrations by stimulating the hydroxylation in active hormone form [27–30]. Probably, GH effects on modulating vitamin D metabolism may be mediated by IGF-I and may be independent of PTH [31]. Additionally, vitamin D may enhance GH-dependent stimulation of IGF-I synthesis [32].

Few data are available regarding relationship between GH/IGF-I axis and vitamin D in healthy subjects. However, a positive association between vitamin D and IGF-I levels has been found [33, 34]. Data in Italian healthy population reported a clear relationship between vitamin D and serum IGF-I levels, independent of confounding factors [35].

On the basis of these findings it can be assumed that a state of hypovitaminosis D might contribute to increase the CV risk in hypopituitaric patients with GHD. The aims of the present study were first, to assess the prevalence of hypovitaminosis D in hypopituitaric patients with GHD; second, to correlate the hypovitaminosis D and GH/IGF-I deficiency with CV risk parameters; lastly, to evaluate which variable between presence of hypovitaminosis D and GH/IGF-I deficiency was more strongly associated with CV risk parameters.

Subjects and methods

Study population

Forty-one consecutive hypopituitaric patients with GHD (22 males, 19 female, aged 18–84 years, mean age: 54.7 ± 15.4 years) admitted to the Department of Gastroenterology, Endocrinology and Surgery of the University 'Federico II' of Naples, Italy (latitude 40°N) were included in the study. Thirty-six patients had been previously operated on via the transsphenoidal and/or transcranic route for non functioning pituitary adenoma (27 patients), craniopharyngioma (two patients), or other types of pituitary tumor (two Ratke's cleft cyst, two arachnoid cyst, one ependymoma, one medulloblastoma, one melanocytoma), and five patients had also been irradiated. Five patients had idiopathic GHD. A variable degree of pituitary insufficiency was found in our patients. The patients with a previous diagnosis of acromegaly or Cushing's disease were excluded from the study. Before being enrolled, in all patients hormone replacement therapy with levothyroxine (50–100 mg/day), cortisone acetate (25–37.5 mg/day), desmopressin acetate (5–20 mg/day), testosterone-enanthate (250 mg i.m. monthly) in men and oral or transdermal estrogens associated with progesterone in premenopausal females was given as appropriate. Adequacy of hormone replacement therapy was periodically assessed by serum-free thyroid hormones, testosterone, cortisol, urinary free cortisol, and serum and urinary sodium and potassium measurements. At study entry, these hormonal parameters were in the normal range for age in all patients. None of the patients had ever received recombinant human growth hormone (rhGH) treatment. Dyslipidemia was found in 51.2 % of patients, type 2 DM in 7.3 % and hypertension in 44 %. In addition, 17 % of patients had MS according to the criteria by IDF [36].

Forty-one controls (22 males, 19 female, aged 21–84 years, mean age: 53.2 ± 16.0 years) comparable to patients by sex, age, and body mass index (BMI), were also included in the study. In all controls, GHD was excluded by arginine (ARG) + GH releasing hormone (GHRH) test. Dyslipidemia was found in 12.1 % of controls, type 2 DM in 17 %, hypertension in 22 % and MS in 14.6 %. The clinical characteristics of patients and controls are shown in Table 1.

Clinical assessment

At study entry, height, weight, waist circumference, BMI, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were evaluated by standard methods in all patients and controls. Waist circumference was measured to the nearest 0.1 cm by using nonstretchable measuring tape with the subjects standing in a relaxed position and arms at the side. The measurement was taken at the midpoint between the lower rib margin (12th rib) and the iliac crest. BP was measured at the right arm, with subjects in a relaxed sitting position. The average of two measurements with a mercury sphygmomanometer was used.

Table 1 Clinical characteristics of patients and controls

	Patients	Controls	*p*
Male/female	22/19	22/19	
Age (years)	54.7 ± 15.4	53.2 ± 16.0	0.668
BMI (Kg/m^2)	27.6 ± 6.3	26.8 ± 5.8	0.881
GH peak after GHRH + ARGININE (mcg/L)	2.5 ± 2.4	30.6 ± 6.3	<0.001
IGF-I (μg/L)	74.5 ± 37.2	158.4 ± 44.8	<0.001
Type 2 diabetes mellitus	7.3 %	17 %	0.292
Hypertension	44 %	22 %	0.060
Dyslipidemia	51.2 %	12.1 %	<0.001
Metabolic syndrome	17 %	14.6 %	0.957
Multiple anterior pituitary deficiencies:			
FSH/LH	46.3 %	–	
TSH	60 %	–	
ACTH	63 %	–	
Diabetes insipidus	22 %	–	

BMI body mass index, *GH* growth hormone, *GHRH* growth hormone releasing hormone, *IGF-I* insulin-like growth factor-I

Use of specific treatment for dyslipidemia, type 2 DM and hypertension was also recorded. Dyslipidemia was considered when subjects had least two of the following lipid alterations: high serum levels of total cholesterol and/or high serum levels of low density lipoprotein (LDL) cholesterol and/or high levels of triglycerides and/or specific treatment for lipid abnormalities. MS was evaluated by the IDF criteria [36]. Then, MS was considered when the subject had central obesity, as assessed by waist circumference >94 cm in males e > 80 cm in female, in addition at least two of the following factors: triglycerides levels >150 mg/dL or specific treatment for this lipid abnormality, high density lipoprotein (HDL) cholesterol levels <40 mg/dL in males and <50 mg/dL in female or specific treatment for this lipid abnormality, blood pressure values >130/85 mm/Hg or treatment of previously diagnosed hypertension; fasting glucose levels >100 mg/dL or previously diagnosed type 2 DM.

Biochemical assessment

In all patients and controls, routine blood tests including total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, glycemia, glycated hemoglobin (HbA1c), insulin, creatinine, albumin, total alkaline phosphatase (ALP), calcium, and phosphorus were determined on serum samples at fasting by automated techniques (Roche Modular System). Urinary calcium, phosphorus, and creatinine were also measured on 24-h urine samples. Intact parathyroid hormone (PTH) was measured by immunometric assay (Immulite iPTH; Diagnostic Products, Los Angeles, CA). 25(OH) vitamin D (vitamin D) is the vitamin D metabolite that is measured to assess a patient's vitamin D status. Serum levels of vitamin D were measured with chemiluminescence (Liaison, DiaSorin, Saluggia, Italy). Vitamin D deficiency was defined as a serum concentration of vitamin D <20 ng/mL (50 nmol/L), insufficiency between 21 and 29 ng/mL (52.5–72.5 nmol/L) and normal levels for values >30 ng/mL (>75 nmol/L) [37]. We defined as hypovitaminosis D when subjects had vitamin D deficiency or vitamin D insufficiency defined by serum vitamin D levels <30 ng/mL. In order to avoid seasonal influences on vitamin D, the study has been carried out from the beginning of November, 2013 to the end of February, 2014. All patients and controls were tested with ARG + GHRH test. ARG (arginine hydrochloride, SALF, Bergamo, Italy) was administered at the dose of 0.5 g/kg, up to a maximal dose of 30 g slowly infused from time 0–30 min while GHRH (GHRH Ferring, Milan, Italy) as given at the dose of 1 μg/kg as i.v. bolus at time 0. Blood samples were taken every 30 min from 0 up to 60 min. The GH response after ARG + GHRH was classified according with appropriate diagnostic cut-off limits related to BMI [38]. Serum GH levels were measured by immunoradiometric assay using commercially available kits. The sensitivity of the assay was 0.2 μg/L. The intra- and inter-assay coefficients of variation (CVs) were 4.5 and 7.9 %, respectively. Plasma IGF-I was measured by immunoradiometric assay after ethanol extraction. The normal ranges in 20–30, 31–40, 41–50, and over 50-yr-old subjects were 110–502, 100–494, 100–303, and 78–258 mg/L, respectively. The sensitivity of the assay was 0.8 mg/L. The intra-assay CVs were 3.4, 3.0, and 1.5 % for the low, medium, and high points of the standard curve, respectively. The inter-assay CVs were 8.2, 1.5, and 3.7 % for the low, medium, and high points of the standard

curve. Since IGF-I levels are related to age, to analyze the relationships between IGF-I levels and the other variables we calculated the standard deviation score (SDS) of IGF-I (zIGF-I) levels according to age [39]. To this aim, we calculated the mean and SD of IGF-I levels in our subjects. The zIGF-I for age and gender was also calculated according to our population reference values. For the purpose of this study, IGF-1 levels were classified as "normal" when higher than −1.5 SD, "insufficient" when were between −1.5 and −2 SD and "deficient" when lower than −2 SD [39–41]. In patients, serum testosterone, estradiol, free thyroid hormones, TSH, FSH, LH, PRL, and free urinary cortisol were measured by commercially available immunoassays.

Statistical analysis

The statistical analysis was performed by SPSS for Windows version 17 (SPSS Inc., Chicago, IL). Data were expressed as mean ± standard deviation. ANOVA followed by Newman-Keuls test for comparison between groups has been used. The normality was assessed with Kolmogorov–Smirnov test. The correlation analysis by Pearson's coefficient was assessed to study the correlation between numerical data. The percentage of hypovitaminosis, dyslipidemia, type 2 DM, hypertension and MS in patients and controls were compared using χ^2-test. Using glucocorticoid replacement and age as covariates, a linear logistic regression analysis model (enter method) was performed to determine if the categorical values of zIGF-I and the presence of hypovitaminosis D were associated with the presence of dyslipidemia, type 2 DM, hypertension and MS. A multinomial logistic regression analysis model was also performed to evaluate which variable between categorical values of zIGF-I and the presence of hypovitaminosis D was more strongly associated with the presence of dyslipidemia, hypertension, and MS. The limit of significance was considered 5 %.

Results

IGF-I and vitamin D

Serum IGF-I concentrations were lower in patients than in controls ($p < 0.001$, Table.1), as expected. Particularly, zIGF-I was between −1.5 and −2 SD in 19 patients (46.3 %), below −2 SD in seven patients (17 %), and in none of controls ($p < 0.001$). The vitamin D levels were lower in patients than in controls (21.3 ± 12.3 ng/mL versus 28.2 ± 9.4, $p = 0.006$). In particular, vitamin D deficiency (<20 ng/mL) was found in 51 % of patients versus 14.6 % of controls ($\chi^2 = 9.07$, $p < 0.01$), insufficiency (21–29 ng/mL) in 26.8 versus 41.4 % ($\chi^2 = 0.03$, $p = 0.269$) and normal vitamin D levels (>30 ng/mL) in 21.9 versus 43.9 % ($\chi^2 = 3.53$, $p = 0.060$) (Table 2). Serum levels of PTH and serum and urinary levels of calcium and phosphorus were similar in two groups (data not shown).

CV risk parameters

No significant difference was found in glucose, insulin, HbA1c and total cholesterol levels between patients and controls (Table 2). HDL cholesterol levels were lower ($p = 0.002$), whereas LDL cholesterol ($p = 0.021$) and triglycerides ($p = 0.002$) levels were higher in patients than in controls (Table 2). No significant difference was

Table 2 Cardiovascular risk parameters and vitamin D status in patients and in controls

	Patients	Controls	*p*
Glycemia (mg/dL)	91.9 ± 16.1	87.6 ± 8.3	0.127
Insulin (μU/mL)	11.1 ± 7.5	12.2 ± 8.2	0.528
HbA1c (%)	5.8 ± 0.7	6.0 ± 1.2	0.359
Total cholesterol (mg/dL)	198.0 ± 38.0	185.5 ± 27.8	0.103
HDL cholesterol (mg/dL)	54.9 ± 18.2	75.1 ± 35.9	0.002
LDL cholesterol (mg/dL)	118.4 ± 25.9	106.3 ± 20.9	0.021
Triglycerides (mg/dL)	142.7 ± 65.5	103.5 ± 44.5	0.002
SBP mm/Hg	134.9 ± 18.7	136.7 ± 17.1	0.653
DBP mm/Hg	78 ± 8.7	78.4 ± 10.7	0.854
Vitamin D status:			
Deficiency (<20 ng/mL)	51 %	14.6 %	<0.01
Insufficiency (21–29 ng/mL)	26.8 %	41.4 %	0.269
Normal (>30 ng/mL)	21.9 %	43.9 %	0.060

HbA1c glycated hemoglobin, *HDL* high density lipoprotein, *LDL* low density lipoprotein, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

found in SBP and DBP between patients and controls (Table 2).

The prevalence of dyslipidemia was 51.2 % in patients versus 12.1 % in controls ($\chi^2 = 12.67$, $p < 0.001$), type 2 DM was 7.3 versus 17 % ($\chi^2 = 1.02$, $p = 0.292$), hypertension was 44 versus 22 % ($\chi^2 = 3.53$, $p = 0.060$) and MS was found 17 % versus 14.6 % ($\chi^2 = 0.00$, $p = 0.957$) (Table 1).

Correlation study

A significant correlation was found between IGF-I and vitamin D levels in patients and controls ($r = 0.695$, $p < 0.001$ and $r = 0.492$, $p = 0.001$, respectively). In addition, in both patients and controls IGF-I and vitamin D levels were correlated with age (IGF-I: $r = -0.475$, $p = 0.002$; $r = -0.863$, $p < 0.001$; vitamin D: $r = -0.295$, $p = 0.051$; $r = -0.333$, $p = 0.036$; respectively) and SBP (IGF-I: $r = -0.609$, $p < 0.001$; $r = -0.608$, $p = 0.001$; vitamin D: $r = -0.412$, $p = 0.009$; $r = -0.427$, $p = 0.033$; respectively). In patients, at linear regression analysis, the presence of hypovitaminosis D and the prevalence of dyslipidemia, hypertension and MS were significantly associated, whereas no association was found between the presence of hypovitaminosis D and the prevalence of type 2 DM (Table 3). In addition, using glucocorticoid replacement and age as covariates, the presence of hypovitaminosis D and the prevalence of dyslipidemia (Exp(B):3.45, p:0.039), hypertension (Exp(B):6.30, p:0.048) and MS (Exp(B):1.10, p:0.012) remained significantly associated. A significant association was also found between categorical value of zIGF-I and the prevalence of hypertension (Table 3). No associations were found between the presence of hypovitaminosis D and categorical value of zIGF-I with the prevalence of dyslipidemia, hypertension, MS, and type 2 DM in controls (Table 3). At multinomial logistic regression analysis, in a model including as dependent variables the prevalence of dyslipidemia, hypertension, and MS and as covariates the categorical value of zIGF-I and the presence of hypovitaminosis D in patients, the most powerful predictor of the prevalence of dyslipidemia and hypertension was the presence of hypovitaminosis D (Table 4).

Table 3 Linear regression analysis in patients and controls

Dyslipidemia	Patients		Controls	
	Exp (B)	p	Exp (B)	p
Versus				
Hypovitaminosis D	10.2	0.016	0.99	0.970
zIGF-I	0.26	0.084	1.02	0.129
Hypertension	**Patients**		**Controls**	
	Exp (B)	p	Exp (B)	p
Versus				
Hypovitaminosis D	8.00	0.004	0.47	0.339
zIGF-I	7.33	0.020	1.00	0.363
Metabolic syndrome	**Patients**		**Controls**	
	Exp (B)	p	Exp (B)	p
Versus				
Hypovitaminosis D	0.18	0.020	0.88	0.894
zIGF-I	0.26	0.123	0.98	0.319
Type 2 Diabetes mellitus	**Patients**		**Controls**	
	Exp (B)	p	Exp (B)	p
Versus				
Hypovitaminosis D	2.0	0.580	1.60	0.576
zIGF-I	0.92	0.950	1.02	0.794

zIGF-I standard deviation score (SDS) of IGF-I (zIGF-I)

Table 4 Multinomial logistic regression analysis in patients

Dyslipidemia	Patients	
	Exp (B)	p
Versus		
Hypovitaminosis D	4.58	0.046
zIGF-I	0.57	0.511
Hypertension	**Patients**	
	Exp (B)	p
versus		
Hypovitaminosis D	0.195	0.037
zIGF-I	0.279	0.177

zIGF-I standard deviation score (SDS) of IGF-I (zIGF-I)

Discussion

The results of our study indicate that there is a high prevalence of hypovitaminosis D (<30 ng/mL) in a representative sample of 41 hypopituitaric patients with GHD, in appropriate standard replacement for all pituitary hormones deficiencies, except that GHD. In particular, vitamin D deficiency was found 51 % in patients versus 14.6 % in controls ($p < 0.01$), insufficiency in 26.8 versus 41.4 % ($p = 0.269$) and normal vitamin D levels in 21.9 versus 43.9 % ($p = 0.060$). In GHD patients, the presence of hypovitaminosis D is the most powerful predictor of the prevalence of dyslipidemia and hypertension.

Recent findings report a relationship between GH/IGF-I axis and vitamin D [27–32]. However, only few data are available regarding relationship between GH/IGF-I axis and vitamin D in general population [33–35]. Data collected from 6810 British white subjects in the 1958 cohort, surveyed during 2002–2004 (aged 45 years), evidenced a positive association between vitamin D and IGF-I, with a linear increase in IGF-1 until vitamin D concentrations reached 75–85 nmol/L (30–34 ng/mL), after which this effect reached a plateau [34]. More recently, data on a cohort of Italian healthy adults showed a clear relationship between vitamin D and serum IGF-I levels, independent of confounding factors, including age, suggesting that vitamin D status may contribute to circulating IGF-I levels in this population [35]. The possible role of vitamin D on IGF-I levels was supported by lower IGF-I levels in subjects with severe vitamin D deficiency than in those with mild-to-absent deficit, defined in this study by serum vitamin D levels <20 ng/mL and ≥ 20 ng/mL, respectively [35]. In line with this study, we also found a significant positive correlation between vitamin D and IGF-I in both patients and controls ($r = 0.695$, $p < 0.001$ and $r = 0.492$, $p = 0.001$; respectively). In this context, recent data in GHD patients on replacement therapy with rhGH, evidenced that a better vitamin D status may ease the achievement of normal IGF-I values, allowing the use of lower doses of rhGH [42].

In our study, we also correlated the GH/IGF-I deficiency and hypovitaminosis D with CV risk factors. As expected, the prevalence of dyslipidemia was higher in patients than in controls, while there were no differences in the prevalence of type 2 DM, hypertension and MS between patients and controls. A possible explanation might be that both patients and sex, age, and BMI-matched controls have been recruited consecutively in this study and were all resident in southern Italy, where the prevalence of type II DM, overweight/obesity and MS is higher than in other regions.

In our patients a significant association was found between the presence of hypovitaminosis D and the prevalence of dyslipidemia, hypertension and MS, whereas no association was found between the presence of hypovitaminosis D and the prevalence of type 2 DM. As well known, age is tightly related to vitamin D status, while corticosteroids are able to increase the catabolism of vitamin D [43, 44]. However, also after adjusting for age and glucocorticoid replacement, the association between the presence of hypovitaminosis D and the prevalence of dyslipidemia, hypertension, and MS remained significant, being the presence of hypovitaminosis D the most powerful predictor of the prevalence of dyslipidemia and hypertension. Regarding zIGF-I, a significant association was found only with the prevalence of hypertension. It is known that abnormalities of the GH/IGF-I axis contribute in determining CV disease, as reported by several clinical studies. IGF-I levels in the lower normal range are associated with an increased risk of ischemic heart disease [18, 19], ischemic stroke [20, 21], atherosclerosis [22, 23], severe hypertension and DM [24]. Patients with hypopituitarism are known to have reduced life expectancy, with a 2-fold higher risk of death for CV disease compared with healthy controls, and GHD has been considered the underlying factor of the increased mortality also when appropriate standard replacement of the other pituitary hormones deficiencies is given [25, 26].

On the other hand, it has been suggested that low vitamin D status may represent an important CV risk factor [1–4, 7]. Low serum levels of vitamin D have been associated with an adverse lipid profile, with lower HDL cholesterol, higher triglycerides, higher apolipoprotein E levels, and hypercholesterolemia [45–47]. However, data on association between vitamin D status and lipid profile are still lacking and this association remains unclear. In a recent large clinical trial in postmenopausal women, using data from the Women's Health Initiative, the authors evaluated the long-term effect of calcium and vitamin D supplementation on circulating concentrations of lipid and found no significant effects on changes in lipid concentrations [48].

Vitamin D has been also reported to be involved in BP regulation. Patients who live at higher latitudes and are considered to be at higher risk of vitamin D deficiency are more likely to develop hypertension [49]. Lower vitamin D levels have been associated with high BP and hypertension risk [7, 50, 51]. The finding that vitamin D negatively regulates the renin-angiotensin axis could explain the link between hypovitaminosis D and BP [52]. However, some studies have failed to find an association [53]. Recent trial data have shown no significant effect of vitamin D supplementation on blood pressure, even at high doses, low vitamin D levels and in patients with high baseline blood pressure [54].

Finally, hypovitaminosis D also appears to be related to the MS and its component, such as obesity and insulin resistance [55]. Interestingly, Hypponen et al. [34] examined the associations of both vitamin D status and IGF-I with MS and its individual components (abdominal obesity, HbA1c, high BP, low HDL cholesterol, high triglycerides) in nearly 7000 participants at age 45 years. The examination of the interactions between these factors further suggested that vitamin D was inversely associated with MS, regardless of IGF-I concentration, whereas the inverse association with IGF-1 was found only among those without hypovitaminosis D, suggesting that individual's vitamin D status was essential for the metabolic effects of IGF-I.

There are some limitations in the present study. In particular, from an epidemiological point of view, GHD is a rare disease. This limits the number of available patients

and there is need for caution in the interpretation of the results of this study. Moreover, the group of hypopituitaric GHD patients enrolled in this study is heterogenous and include patients with previous radiotherapy and patients on multiple hormonal replacement therapies which may affect the CV risk.

Conclusion

In summary, the results of the present study indicate that the GHD hypopituitaric patients have an increased prevalence of hypovitaminosis D compared with controls. The presence of hypovitaminosis D is the most powerful predictor of the prevalence of dyslipidemia and hypertension. Although in GHD hypopituitaric patients, CV risk and mortality are influenced by other factors, such as excessive glucocorticoids or T4 replacement, gonadal steroids underreplacement, and previous radiotherapy, the hypovitaminosis D might be also considered as adjunctive CV risk factor in these patients.

Nonetheless, due to paucity of intervention studies, a causal link between vitamin D status and CV disease in GHD hypopituitaric patients is far from be proven, thus no guidance can be provided for or against recommending vitamin D supplementation for prevention or treatment of CV disease in these patients. Ongoing and future trials are expected to provide answers to whether vitamin D supplementation holds promise for the prevention of CV disease in GHD hypopituitaric patients and for a better management of these patients.

Compliance with ethical standards

Conflict of interest None of the authors have any conflict of interest.

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