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Vitamin D and Subclinical Cardiovascular Damage in Essential Hypertension

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Abstract: Vitamin D deficiency is linked to cardiac dysfunction, vascular remodeling, metabolic syndrome and insulin resistance (IR). The aim of the present study was to evaluate the association between vitamin D levels and cardiovascular (CV) organ damage in a large cohort of newly diagnosed treatment-naïve hypertensive patients, and the role of IR in this context. We enrolled 500 Caucasian individuals, without CV or renal complications. Subjects underwent a complete evaluation and measurements of vitamin D, standard laboratory determinations and instrumental examination, including echocardiography and applanation tonometry. Linear regression analyses were performed to assess the correlation between pulse wave velocity (PWV) and left ventricular mass index (LVMI) with different covariates. PWV was significantly correlated with age ($p < 0.0001$), LDL cholesterol ($p < 0.0001$), BMI ($p = 0.001$), pulse pressure (PP) ($p = 0.005$) and high sensitivity C-reactive protein (hs-CRP) ($p = 0.006$), while an inverse correlation was observed with vitamin D levels ($p < 0.0001$), Matsuda index ($p < 0.0001$) and estimated glomerular filtration ratio (e-GFR) ($p = 0.006$). LVMI significantly correlated with PP ($p < 0.0001$), hs-CRP ($p < 0, 0001$) and age ($p = 0.001$), while an inverse relationship was observed with vitamin D levels ($p < 0.0001$), Matsuda's insulin sensitivity index (ISI) ($p < 0.0001$) and e-GFR ($p < 0.0001$). Vitamin D was the strongest predictor of PWV and LVMI, explaining, respectively, 28.3% and 19.1% of their variation. Our study suggests that low vitamin D might be a biomarker of end-organ damage.

Keywords: vitamin D; organ damage; arterial stiffness; hypertension

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1. Introduction

Vitamin D exists in two forms: vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) [1]. Vitamin D3 is present in a biologically inactive form and, due to hydroxylation reactions in liver and kidney, is transformed into the active form 1,25(OH) vitamin D, calcitriol [2]. Vitamin D promotes intestinal and renal absorption of calcium and is essential for development and maintenance of bone mass [1]. Vitamin D receptors (VDRs) are present in different body tissues, including adipose, breast, smooth muscle, heart muscle and organs such as the pancreas. Therefore, $1,25(OH)_2D$ has autocrine and paracrine effects, and 25-hydroxyvitamin D represents the stable circulating form of vitamin D. The distribution of VDRs and the enzymatic system for metabolization of vitamin D in the cardiovascular (CV) site, led us to hypothesize cardioprotective, anti-inflammatory and antiatherosclerotic actions directly exerted by this vitamin.

Recently, many studies have indicated a strong association between hypovitaminosis D and cardiometabolic disorders, such as impaired glucose tolerance, insulin resistance (IR) and vascular damage [3,4]. Vitamin D deficiency may influence CV risk factors by affecting blood pressure (BP), inflammation and vascular calcification [5]. At the cardiac level, vitamin D deficiency is involved in promoting left ventricular hypertrophy (LVI),

increased telesystolic diameters and higher levels of atrial natriuretic peptide (ANP) [6]. Hypovitaminosis D is associated with metabolic syndrome and IR, independently of the amount of adipose tissue present in the body [4]. Experimental data, conducted in animal models and humans, demonstrated that vitamin D deficiency causes a reduction in insulin receptor expression and insulin secretion, which, associated with a proinflammatory state and hyper activation of the renin angiotensin-aldosterone system (RAAS), represent the pathogenetic background for the genesis of IR. Moreover, the link between hypovitaminosis D and IR may further contribute to explaining vascular damage. In fact, hyperinsulinemia contributes to smooth muscle cell proliferation and reduces nitric oxide (NO) production, leading to arterial stiffness [7]. Arterial stiffness, expressed by pulse wave velocity (PWV), is an independent predictor of coronary heart disease and stroke. Elevated PWV can induce arterial remodelling, increasing wall thickness and plaque development [8].

Furthermore, low levels of vitamin D are contributors to mortality. In a study conducted by Melamed et al., involving 13,331 nationally representative adults $\geq$ 20 years old from the Third National Health and Examination Survey (NHANES III), vitamin D deficiency was associated with a 26% higher risk of all causes of mortality, independent of traditional and nontraditional CV risk factors [9].

Based on data present in literature, the aim of the present study was to evaluate the possible association between vitamin D levels and CV organ damage in a large cohort of hypertensive patients at first diagnosis, and to investigate the potential role of IR.

2. Materials and Methods

2.1. Study Populations

We enrolled 500 Caucasian, newly diagnosed hypertensive patients (267 men and 233 women, mean age of 54.7 $\pm$ 10.9 years), without CV or renal complications, participating in the Catanzaro Metabolic Risk Factors Study (CATAMERI) study [10]. All subjects underwent medical history and physical examinations. Causes of secondary arterial hypertension were excluded with appropriate clinical and laboratory evaluations. Other exclusion criteria were history or clinical evidence of coronary and/or valvular disease, congestive heart failure, hyperlipidemia, peripheral vascular disease, chronic gastrointestinal diseases associated with malabsorption, chronic pancreatitis, positive history of any malignant disease, history of alcohol or drug abuse, hepatic or renal insufficiency, treatment with drugs that interfere with glucose metabolism or diagnosis of diabetes mellitus. None of the recruited patients had previously been treated with antihypertensive drugs. All subjects underwent anthropometric evaluation of weight, height and body mass index (BMI).

2.2. Blood Pressure Measurements

Measurements of blood pressure (BP) were executed in the left arm of supine patients with an aneroid sphygmomanometer after 5 min of rest. A minimum of three BP records were performed on three dissimilar measurements at least two weeks apart. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded at the first appearance (phase I) and the disappearance (phase V) of Korotkoff tone. Baseline values of BP were acquired from the average of the last two of three successive recordings performed at three minutes intervals. Patients with SBP > 140 mmHg and/or DBP > 90 mmHg were defined hypertensive in conformity with current guidelines [11]. Pulse pressure (PP) was correlated as the SBP-DBP difference.

2.3. Laboratory Determinations

The glucose tolerance status was defined based on the Oral Glucose Tolerance Test (OGTT) results. After 12 h fast, an oral load of 75 g of glucose was administered with sampling of plasma glucose and insulin values at 0, 30, 60, 90 and 120 min. Insulin sensitivity was assessed by Matsuda's insulin sensitivity index (ISI) calculated as 10,000/square root

of (fasting blood glucose expressed in millimoles per liter * fasting insulin expressed in milliunits per liter) * (mean blood glucose * mean insulin during OGTT) [12].

Concentrations of plasma glucose were assessed by glucose oxidation (Beckman Glucose Analyzer II; Beckman Instruments, Milan, Italy). Triglycerides, high- (HDL), low-density lipoprotein (LDL) and total cholesterol concentrations were estimated by enzymatic methods (Roche Diagnostics GmbH, Mannheim, Germany). High sensitivity C reactive protein (hs-CRP) was determined by an immunological method. The concentration of plasma insulin was assessed by a chemiluminescence-based assay (Roche Diagnostics). Creatinine was measured using Jaffe's methodology. Renal function, evaluated by estimated glomerular filtrate rate (e-GFR), was calculated according to the equation suggested by the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration group [13]. Serum levels of 25(OH)D were measured in the same seasonal period (Spring) by a competitive chemiluminescence immunoassay (CLIA) through the Liaison-Diasorin test. For the determination of 25(OH)D, venous blood samples were taken in the morning after at least 12 h of fast. A sample (2.5 mL) of venous blood was collected and subsequently introduced into a disposable test tube equipped with separator gel. The blood sample was centrifuged for 5 min at 2500 rpm and 500 µL of the obtained serum was collected. During the first incubation, 25(OH)D was dissociated from its binding protein and bound to a specific antibody. After 10 min, an isoluminol tracer was added and incubated for a further 10 min, then the unbound material was removed with a wash cycle. In the last step, the reagents for the chemiluminescence reaction were added. The signal was measured by a photomultiplier as a relative light unit (RLU) and was inversely correlated with the 25(OH)D concentration in each sample [14]. Vitamin D status was classified as deficiency (<20 ng/mL), insufficiency ($\geq$20 to <30 ng/mL) and normal ($\geq$30 ng/mL).

2.4. Echocardiographic Measurements

Echocardiography was performed 24–48 h after clinical and laboratory evaluations with the patient in a partial left lateral decubitus using a E-95 (GE Technologies, Milwaukee, WI, USA) ultrasound system with a 2.5 MHz transducer. Echocardiography examinations were performed in random order by the examiner, who was unaware of the patient's blood pressure or other related clinical information. Only the projection with the best visualization of cardiac structures was considered for reading. The values of all parameters for each patient were obtained from the average of at least five measurements. Examinations were performed by a single skilled operator, in a dimly lit and quiet environment, optimizing the reproducibility of measurements. The coefficient of variability was 3.85% for the thickness of the posterior wall (PW), 3.70% for the thickness of the interventricular septum (IVS), 1.5% for the internal diameter of the left ventricle (LVID), 5.10% for left ventricular mass (MVS). Acquisitions were made in two-dimensional mode, and M-mode measurements were made at or just below the mitral valve. Measurements of the thickness of IVS, PW and LVID were recorded in the end-diastolic and end-systolic phases. MVS was calculated using the Devereux formula and subsequently indexed to the patient's body surface area (LVMI) [15].

2.5. Central BP and Pulse Wave Reflection Measurements

All evaluations were conducted using a validated system (Sphygmocor™; AtCor Medical, Sydney, Australia) based on high-fidelity applanation tonometry (Millar) and estimated by specific software for the analysis of pressure waves (Sphygmocor™), as previously reported [16]. Pressure calibration was obtained with a supine subject through noninvasive, automatic recording of brachial artery BP in the dominant arm, (Dinamap Compact T; Johnson & Johnson Medical Ltd., Newport, UK), after a 30 min rest. BP was recorded five times at 10 min intervals, and the average value of the last three measurements was considered for the calibration. The pulse wave was evaluated at the radial artery of the dominant arm with the wrist softly hyperextended, and the considered value was the average of single pressure waves registered consecutively for eight seconds. Pulse wave

recordings were accepted only if the change of the peak and bottom values of single waves was <5%. The central pressure wave was derived from the radial pressures with a built-in generalized transfer function. Furthermore, pressure waves were also measured at the right carotid artery, given that central augmentation index (AI) has been reported to be more accurate when obtained from this vascular area [16]. Central pulse waves were also examined to recognize the time to peak/shoulder of the first (T1) and second (T2) pressure wave components during the systolic phase. The pressure at the peak/shoulder of T1 was defined as outgoing pressure wave height (P1) and the pressure at the peak/shoulder of T2 was identified as the reflected pressure wave height (P2), either absolutely or as percent of ejection duration. Augmentation pressure (AP) was recognized as the difference between P2 and P1, and AI as (AP/pulse pressure (PP)) × 100. Aortic pulse wave velocity (PWV) was derived from carotid and femoral pressure waveforms. Carotid to femoral transit time (ΔT) was evaluated from the foot-to-foot time difference between carotid and femoral waveforms. The distance between the landmark of the sternal notch and femoral artery was employed to estimate the path length between the carotid and femoral arteries (L), and PWV was measured as L/ΔT [17]. The gold standard to evaluate aortic stiffness is the carotid-femoral PWV and, in hypertensive patients, a threshold of >10 m/s has been suggested as a conservative estimate of increased arterial stiffness [18,19].

2.6. Statistical Analysis

Normally distributed data is represented as mean ± standard deviation (SD), while data not normally distributed as median and interquartile range.

For continuous variables, an ANOVA test for unpaired data was performed to assess differences between three groups: patients with vitamin D deficiency (<20 ng/mL), patients with vitamin D insufficiency (20–30 ng/mL) and patients with normal vitamin D levels (>30 ng/mL). The χ^2 test was used for categorical variables. Variables not normally distributed were expressed as a logarithmic parameter (log10) before the correlational analyses. A linear regression analysis was performed considering first the LVMI and then the PWV as dependent variables and testing different covariates. Subsequently the variables that reached statistical significance, and smoking and gender as dichotomous variables, were inserted in a stepwise multiple regression model to identify independent predictors of LVMI and PWV. The differences were considered significant at $p < 0.05$. The analysis was performed with the SPSS 20.0 program for Windows (SPSS Inc., Chicago, IL, USA).

2.7. Ethical Approval

All investigations were made according to the Declaration of Helsinki. The study was approved by the local Ethical Committee and written informed consent was obtained from each subject (code protocol number 2012.63).

3. Results

3.1. Study Population

Table 1 shows the anthropometric and biochemical characteristics of the whole study population according to serum levels of vitamin D. In the whole study population, 219 (43.8%) patients had vitamin D deficiency, 89 (17.8%) had vitamin D insufficiency and 192 (38.4%) had normal vitamin D levels. The median vitamin D was 20.7 ng/mL (15.0–34.0). There were no significant differences between groups for gender, SBP, DPB, PP and LDL cholesterol, hs-PCR, levels of calcium and phosphorus and prevalence of smokers. Patients with vitamin D deficiency were significantly older and had higher insulin, triglycerides, hs-CRP and PTH, and significantly reduced Matsuda index values. In addition, patients with vitamin D levels < 20 ng/mL had significantly higher LVMI and PWV values. In the Bonferroni's post hoc analysis, vitamin D < 20 ng/mL vs. vitamin D > 30 ng/mL the p value was <0.05 for BMI, Matsuda Index, glucose, insulin, TG, LVMI and PWV.

The median vitamin D was 20.7 ng/mL (15.0–34.0).

Table 1. Anthropometric, hemodynamic and biochemical characteristics of study population according to Vitamin D levels.

	All	Vitamin D < 20 ng/mL	Vitamin D 20–30 ng/mL	Vitamin D > 30 ng/mL	*p*-Value
	(n = 500)	(n = 219)	(n = 85)	(n = 196)	
Gender, M/F	267/233	121/98	47/38	99/97	0.453 *
Age, years	54.7 ± 10.9	57 ± 10.4	55.8 ± 12.5	51.5 ± 9.9	<0.0002
BMI, Kg/m^2	28.7 ± 4.8	29.7 ± 4.9	28.1 ± 4.3	27.7 ± 4.8	<0.0001
SBP, mmHg	144.0 ± 14	145.6 ± 15.9	142.4 ± 13	142.8 ± 12.1	0.071
DBP, mmHg	90.5 ± 7.0	90.4 ± 7.6	90 ± 6.4	90.9 ± 6.4	0.58
PP, mmHg	53.4 ± 15.4	55.1 ± 16.4	52.4 ± 16.4	51.9 ± 13.6	0.083
Matsuda Index	68.8 ± 40.5	53 ± 31.1	70.7 ± 36.6	88.4 ± 43.4	<0.0001
Glucose, mg/dL	94.2 ± 9.0	96.3 ± 8.9	94.1 ± 7.4	91.9 ± 9.2	<0.0001
Insulin, mU/L	13.1 ± 5.9	15.1 ± 6.1	12.2 ± 6	11.2 ± 4.8	<0.0001
Serum LDL, mg/dL	134.8 ± 35.3	137.9 ± 36	131.4 ± 35.5	132.9 ± 34.2	0.207
Serum hdl, mg/dL	51.5 ± 13.9	50 ± 13.3	55.1 ± 14.4	51.6 ± 14.2	0.015
Serum Triglycerides, mg/dL	127.2 ± 54.4	135.1 ± 59	127.5 ± 55.4	118 ± 46.9	0.006
e-GFR, mL/min/1.73 m^2	96.6 ± 22.7	93.1 ± 22.4	92.9 ± 23.4	102.4 ± 21.6	<0.0001
PTH, pg/ml	59.4 ± 37.0	75.5 ± 37.2	51.4 ± 33.4	44.27 ± 30.6	<0.0001
Calcium, mg/dL	9.5 ± 0.5	9.5 ± 0.6	9.5 ± 0.4	9.5 ± 0.4	0.862
Phosphorus, mg/dL	3.3 ± 0.5	3.2 ± 0.5	3.2 ± 0.4	3.3 ± 0.5	0.520
hs-CRP, mg/L	2.6 ± 1.9	2.7 ± 2.0	2.6 ± 2.0	2.4 ± 1.8	0.099
Smokers, n (%)	122 (24.4)	51 (23.3)	17 (20)	55 (26.6)	0.295 *
LVMI, g/m^2	115.3 ± 39.0	128.1 ± 39.0	110.7 ± 40.3	102.8 ± 33.9	<0.0001
PWV, m/s	6.9 ± 2.4	8.1 ± 2.7	6.4 ± 1.5	5.7 ± 1.4	<0.0001

* χ^2 test. BMI: Body Max Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; PP: pulse pressure; e-GFR: Estimated Glomerular Filtration Ratio; hs-CRP: high sensitivity C-Reactive Protein; LVMI: Left Ventricular Mass Index; PWV: Pulse Wave Velocity.

3.2. Correlational Analysis

In the entire study population, linear regression analysis was performed to assess the correlation between PWV and LVMI with different covariates (Table 2). PWV was significantly correlated with age (r = 0.280, $p < 0.0001$), LDL cholesterol (r = 0.188, $p < 0.0001$), BMI (r = 0.144, $p = 0.001$), PP (r = 0.116, $p = 0.005$), hs-CRP (r = 0.112, $p = 0.006$), while an inverse relationship was observed with vitamin D levels (r = −0.532, $p < 0.0001$), Matsuda index (r = −0.468, $p < 0.0001$) and e-GFR (r = −0.113, $p = 0.006$). Furthermore, LVMI was significantly correlated with PP (r = 0.231, $p < 0.0001$), hs-CRP (r = 0.229, $p < 0.0001$), age (r = 0.141, $p = 0.001$), BMI (r = 0.060, p = 0,09) and LDL cholesterol (r = 0.004, $p = 0.462$), while an inverse relationship was observed with vitamin D levels (r = −0.437, $p < 0.0001$), ISI (r = −0.390, $p < 0.0001$) and e-GFR (r = −0.164, $p < 0.0001$). The variables achieving statistical significance, and smoking and gender as dichotomous values, were inserted into a stepwise multiple regression model to determine independent predictors of PWV and LVMI (Table 3). Vitamin D was the strongest predictor of PWV, explaining 28.3% ($p < 0.0001$) of its variation. Furthermore, the other independent predictors were ISI, age, LDL cholesterol and smoking, justifying, respectively 6.8%, 2.7%, 3% and 0.8% of its variation. The whole model justified 41.6% of PWV variations.

Interestingly, vitamin D was also the strongest predictor of LVMI, explaining 19.1% ($p < 0.0001$) of its variation. Other independent predictors of LVMI were Matsuda index, PP and hs-CRP, justifying, respectively, 4.9%, 3.0% and 2.2% of its variation. The whole model justified 29.2% variation in mass.

Table 2. Linear regression analysis on pulse wave velocity (PWV) and left ventricular mass index (LVMI) as dependent variables.

	PWV		LVMI	
	R	***p***	**R**	***p***
log25(OH)D	−0.532	<0.0001	−0.437	<0.0001
Matsuda Index	−0.468	<0.0001	−0.390	<0.0001
Age, years	0.280	<0.0001	0.141	0.001
PP, mmHg	0.116	0.005	0.231	<0.0001
hs-CRP, mg/dL	0.112	0.006	0.229	<0.0001
Serum LDL, mg/dL	0.188	<0.0001	0.004	0.462
e-GFR, ml/min/1.73 m^2	−0.113	0.006	−0.164	<0.0001
BMI, Kg/m^2	0.144	0.001	0.060	0.09

BMI: Body Mass Index; PP: Pulse Pressure; e-GFR: Estimated Glomerular Filtration Ratio; hs-CRP: High Sensitivity C-Reactive Protein; LVMI: Left Ventricular Mass Index; PWV: Pulse Wave Velocity.

Table 3. Multiple stepwise regression analysis on pulse wave velocity (PWV) and left ventricular mass index (LVMI) as dependent variable.

	PWV		LVMI	
	Partial R^2 (%)	***p***	**Partial R^2 (%)**	***p***
log25(OH)D	28.3	<0.0001	19.1	<0.0001
Matsuda Index	6.8	<0.0001	4.9	<0.0001
Age, years	2.7	<0.0001	-	-
Serum LDL, mg/dL	3.0	0.001	-	-
Smokers, yes/no	0.8	0.010	-	-
PP, mmHg	-	-	3.0	<0.0001
hs-CRP, mg/dL	-	-	2.2	<0.0001
Total R^2 (%)	41.6		29.2	

PP: pulse pressure; hs-CRP: high sensitivity C-Reactive Protein; LVMI: Left Ventricular Mass Index; PWV: Pulse Wave Velocity.

4. Discussion

Literature data on the effects of vitamin D on arterial stiffness and endothelial dysfunction are scarce; therefore, the originality of our study was to demonstrate, in a large cohort of newly diagnosed nondiabetic hypertensive patients with normal renal function, that hypovitaminosis D is significantly correlated with the development of cardiac and vascular subclinical organ damage. Patients with hypovitaminosis D presented significantly increased arterial stiffness, expressed as PWV and PP, and LVMI, compared with subjects with normal vitamin D levels. Moreover, the multivariate analysis showed that vitamin D was the strongest predictor of PWV and LVMI, explaining 28.3% and 19.1% of their variations. In the hypertensive patient, the coexistence of both cardiac and vascular damage has a multiplicative effect on the risk of events, in fact the simultaneous presence of LVMI and vascular damage quintuples the risk of future CV events [20]. This result can be justified by the effect of vitamin D metabolites on RAAS regulation. In fact, vitamin D can directly suppress renin gene expression by downregulating activation of the RAAS with positive effects on the reduction of inflammatory burden, improvement of insulin sensitivity and CV protection [21,22]. In particular, vitamin D, by regulating RAAS, influences the vascular wall, exerting antiproliferative effects on vascular smooth muscle and playing an important role in immune modulation, regulating the differentiation of lymphocytes and monocytes/macrophages and the release of inflammatory cytokines.

This in turn, in a hypovitaminosis D state, could lead to the infiltration of monocytes and oxidized LDL cholesterol into the vascular wall, favoring proinflammatory conditions and vascular damage [23,24]. In fact, calcitriol is able to promote the action of anti-inflammatory factors such as IL-10 (Th2 mediated), and to inhibit proinflammatory factors such as IL-2, IL-6, TNF-α, INF-γ and MMP (Th1 mediated) [24].

Moreover, our study showed that CRP concentration was significantly higher in patients with levels of 25(OH)D < 30 mg/mL compared to subjects with normal levels, reflecting the anti-inflammatory role of Vitamin D [25]. Data obtained from the present study, showed that low levels of vitamin D are inversely correlated with the Matsuda index, which is reduced in patients with insufficient levels of 25(OH)D. Vitamin D is able to modulate, directly or indirectly, pancreatic β cell function and insulin sensitivity [4]. Many studies, conducted in animal models and human subjects, demonstrated that insufficient levels of vitamin D cause a reduction in insulin receptor expression and insulin secretion, and treatment with vitamin D improves β cells function and glucose tolerance [26,27].

Another mechanism potentially involved in this association is the regulatory effect of vitamin D on the activity of the RAAS [27], which interferes with insulin signaling in various tissues, reducing endothelial responsiveness [28]. In fact, at the molecular level, the activation of the PI3K/Akt/e-NOS axis is significantly reduced, while the MAPK signal, which induces proliferative and proinflammatory stimulation and endothelin-mediated vasoconstrictors that predispose to endothelial dysfunction and atherosclerosis, is enhanced [29].

As observed in our study, vitamin D deficiency is also associated with elevated levels of PTH that reproduce secondary hyperparathyroidism that can contribute, through the reduction of insulin sensitivity, to cardiac and vascular remodeling, development of glucose intolerance and cardiovascular complications [3].

However, the beneficial effect of vitamin D supplementation on arterial stiffness and LVM is currently controversial, as demonstrated by multiple reviews and meta-analysis studies carried out to obtain evidence on the effect of vitamin D supplementation on cardio-metabolic factors. The HYPODD study, a double-blind, multicenter, randomized trial to evaluate the effects of cholecalciferol supplementation on blood pressure control and progression of organ damage in patients with essential hypertension and hypovitaminosis D, did not lead to achievement of these cardiovascular endpoints [29]. However, recruited patients were already treated and well controlled; therefore, pharmacological treatment may have influenced the study results. In addition, patients were not subjected to an OGTT and it is thus possible that diabetic subjects were included.

This study has some limitations. First, it was a cross-sectional study; therefore, no causal relationship can be established. In addition, the study was conducted with a specific cohort of untreated hypertensive patients, which may not represent the general population. Finally, the study did not take into account some variables that influence 25(OH)D levels such as physical activity and social class. However, the study has many strengths including a large cohort of drug-naïve hypertensive individuals, use of OGTT to exclude diabetic individuals and inclusion of subjects with normal renal function. In addition, the association between vitamin D and CV organ damage continued to be significant despite correction for all possible confounding factors.

5. Conclusions

Even if further studies are needed to definitively conclude that vitamin D can offer preventive and therapeutic benefits in a wide range of physiological states and chronic diseases, our study suggests that low vitamin D status might be a marker of end-organ damage.

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