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ORIGINAL ARTICLE

Evolving our understanding of vitamin D, periostin levels and cardiovascular risk in the elderly: a cross sectional study

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Abstract

Summary This cross-sectional study explored how vitamin D and the protein periostin are related to the risk of heart disease in elderly individuals. Lower levels of both were linked to higher risk of heart disease. The findings suggest these markers may help identify cardiovascular (CV) risk as people age.

Purpose Given that both vitamin D and periostin are implicated in CV health, understanding their interrelationship could provide insights into the mechanisms influencing CV risk in aging populations.

Methods This was a cross-sectional analysis in a subgroup of elderly people from the InCHIANTI Biobank in Italy. Serum concentrations of 25-hydroxyvitamin D (25(OH)D), 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), and periostin were measured, and their associations with both an arbitrary CV risk score and the European Society of Cardiology's 10-year CV risk estimate (SCORE2/SCORE2-OP) were assessed through univariate and multivariate regression.

Results Serum levels of 25(OH)D, $1,25(OH)_2D$, and periostin were analyzed in blood samples from 299 individuals (aged 72.8 ± 15.7 years). A significant positive correlation was found between periostin and both $1,25(OH)_2D$ ($r = 0.39$, $p < 0.0001$) and 25(OH)D ($r = 0.76$, $p < 0.0001$) . Individuals with low periostin (< 150 pmol/L) had significantly higher CV risk scores (2.9 ± 1.4) and SCORE2/SCORE2-OP values ($21.1 \pm 12.5\%$) compared to those with high periostin levels (2.2 ± 1.4 and 14.7 ± 11.7, respectively; $p < 0.0001$). Logistic regression revealed that periostin levels < 150 pmol/L were significantly associated with 25(OH)D levels < 20 ng/mL (OR: 22.4, $p < 0.0001$), age ≥ 75 years (OR: 2.7, $p = 0.006$), and dyslipidemia (OR: 3.26, $p = 0.0003$). Low levels of vitamin D metabolites and low periostin were significantly associated with higher CV risk, but in a multivariate model only low $1,25(OH)_2D$ levels (< 41 pg/mL) remained significantly associated with high CV risk (OR: 3.0–3.45, $p < 0.0001$).

Conclusion This analysis identified a significant association between periostin and serum vitamin D levels, both linked to increased CV risk in the elderly, suggesting their potential role in CV disease.

Keywords $25(OH)D \cdot 1,25(OH)_2D$ · Cardiovascular risk · Elderly people · Periostin · Vitamin D

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Introduction

Vitamin D is a crucial regulator of calcium homeostasis and normal levels of vitamin D can help prevent and cure bone diseases, such as rickets osteomalacia, and osteoporosis [1–3]. Beyond its primary role in calcium and bone metabolism, vitamin D has also been shown to reduce inflammation, modulate cell growth, and regulate immune, neuromuscular, and glucose metabolism [4]. Chronic vitamin D deficiency can predispose individuals to various diseases.

Vitamin D status is evaluated through serum levels of 25-hydroxyvitamin D (25(OH)D). According to the Endocrine Society [1], deficiency is defined as levels below 20 ng/ml, while insufficiency is between 20 and 29 ng/ml. Vitamin D deficiency and insufficiency are prevalent worldwide, affecting 30–50% of the global population across all demographics [5, 6], particularly the elderly [7–9] due to limited sunlight exposure, decreased skin synthesis, and reduced intestinal absorption [10, 11]. Vitamin D deficiency can also occur in older individuals without these risk factors [9].

Recent observational studies and Nonlinear Mendelian analyses suggest that insufficient or deficient vitamin D status may increase the risk of cardiovascular diseases (CVD), demonstrating an inverse nonlinear relationship between vitamin D levels and CVD events and mortality [12, 13].

Periostin is a matricellular vitamin-K dependent protein primarily involved in tissue remodelling and repair [14, 15]. Similar to other matrix Gla proteins (MGP), periostin is post-translationally binded with γ-carboxylated glutamic acid residues in a vitamin K-dependent manner [16]. Among MGPs secreted by mesenchymal stem cells, periostin has been identified as the most abundant [16]. Initially recognized for its role in bone metabolism, periostin is now also being explored for its cardiovascular implications [17].

Previous studies have also demonstrated increased periostin expression in the hearts of diabetic rats, indicating its role in the development of diabetic cardiomyopathy [18, 19]. Furthermore, a significant association has been noted between periostin overexpression and cardiac remodelling in humans [20].

There are several lines of evidence showing crosstalk between vitamin K-dependent protein expression such as periostin and vitamin D in bone and cardiovascular health [21–23], however few clinical studies have examined the interrelationship between periostin and vitamin D.

In a previous cross-sectional study, performed by our Research Group on a subpopulation of 299 individuals from the InCHIANTI database, we observed a significant inverse correlation between vitamin D levels and cardiovascular risk [24].

To follow up on those findings, in this paper we explored the relationship between circulating levels of 25-hydroxyvitamin D (25(OH)D) and 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), along with periostin, and their independent and joint association with cardiovascular (CV) risk.

Methods

Study design

The InCHIANTI ("Invecchiare in Chianti") study, initiated in 1998, aimed to assess factors contributing to mobility decline in older adults in two small towns in Chianti, Tuscany, Italy[25]. Baseline assessments (1998–2000) and follow-up visits were conducted every three years through 2014.

Here, we present a cross-sectional analysis that included 299 InCHIANTI participants. This study adhered to Italian legislation on non-interventional studies [26] and the Declaration of Helsinki. All participants provided written informed consent for anonymous data use per European Legislative Decree 2016/679. The study was approved by the Regional Ethics Committee for Clinical Trials of Tuscany (protocol number: 13929_bio, 08/07/2019).

Study population and sample collection

We retrospectively retrieved available clinical, biochemical and therapeutic data from the InCHIANTI database and obtained blood and urine samples stored in the InCHIANTI Biobank from 299 elderly individuals collected during the fourth follow-up (from June 2013 to July 2014).

Intravenous blood samples were initially collected (in the absence of anticoagulants) after an overnight 8 h fasting from the InCHIANTI population, delivered to the laboratory within 2 h for harvesting of serum and plasma that was then stored, in 0.3 ml aliquots, at −80 °C in the InCHIANTI Biobank, at the Piero Palagi Hospital, Florence, prior to undertaking biochemical assays.

Laboratory assays

Assays for 25(OH)D, $1,25(OH)_2D$, parathyroid hormone (PTH), and creatinine were performed at the central laboratory of Azienda Ospedaliero-Universitaria Careggi (AOUC) in Florence, Italy. Vitamin D binding protein (VDBP) was measured at Fondazione FIRMO Onlus (FirmoLab), Florence, Italy via Enzyme-Linked Immuno Assay (ELISA) by R&D Systems. Serum levels of calcium, magnesium, total cholesterol, LDL, HDL, triglycerides, and glucose were retrieved from the InCHIANTI study database.

Serum $1,25(OH)_2D$ and 25(OH)D were measured by radioimmunoassay (Liason, DiaSorin). PTH was analyzed via electrochemiluminescence immunoassay (ECLIA) on the

Elecsys 2010 platform (Roche Diagnostics). Creatinine was measured enzymatically, calibrated to isotope dilution-mass spectrometry, on a Cobas 8000.

Serum periostin levels were measured using the Human Periostin ELISA Kit according to the manufacturer's protocol (Thermo Fisher Scientific, Cleveland, OH, USA).

For all assays, the mean value of duplicate measurements was used for analysis. Coefficients of variation for intra- and inter-assays were never greater than 12%. Investigators who performed immunoassays were blind to the characteristics of the participants until the final analysis.

Estimate of CV risk

To assess the association between vitamin D metabolites, periostin, and CV risk, we used two independent scoring systems: an arbitrary CV risk measure and the SCORE2/SCORE2-OP model proposed by the 2021 ESC Guidelines on Cardiovascular Disease Prevention [27, 28].

The arbitrary CV risk score, previously described [24, 29–31], considered eight clinical risk factors, each stratified as high/low or absent/present. These included age (≥ 75 years), BMI (≥ 30 kg/m^2), smoking, dyslipidemia, diabetes, hypertension, a prior CV event (e.g., myocardial infarction or stroke), and male gender, with a maximum score of 8 indicating highest CV risk.

As previously described [24], we also used the SCORE2/SCORE2-OP model from the 2021 ESC Guidelines to estimate 10-year CV event risk. SCORE2, calibrated for moderate-risk European populations, and SCORE2-OP, for those over 70 years, calculated individual CV risk (%) based on age, sex, smoking, systolic blood pressure (SBP), total cholesterol, and high-density lipoprotein (HDL) cholesterol. We have previously shown that both the arbitrary CV risk score and ESC-based SCORE2/OP algorithms correlated with each other in this patient cohort ($r = 0.52$, $p < 0.0001$) [24].

Statistical analysis

Continuous variables were summarized as mean ± standard deviation (SD), while categorical data were presented as numbers and percentages. The Kolmogorov–Smirnov test, along with skewness and kurtosis values, was used to assess data normality. Normally distributed variables were compared using the Student's t-test, while categorical data were compared using the $\chi 2$ or Fisher's exact test. Pearson's correlation coefficient was used for univariate correlations, presented in a correlation matrix. Skewed biochemical data were log-transformed for further analyses.

In initial multiple logistic regression models, we wanted to evaluate the association between low serum periostin levels (< 150 pmol/L versus ≥ 150 pmol/L) as the dependent variable and clinical/laboratory variables (age, gender, BMI, diabetes, dyslipidemia, hypertension, smoking, and vitamin D status) as independent (predictor) variables.

Since there is no clinically recognised cut-off value for "low" or "high" periostin levels, we used the median value to divide the cohort into "low" and "high" groups, also maintaining similar sample size for the two groups. Results were reported as odds ratios (OR) with 95% confidence intervals (CI).

Additional logistic regression models assessed associations between periostin, vitamin D levels as predictor variables with CV risk scores (SCORE2/SCORE-2-OP $\geq 20\%$ or CV risk score ≥ 3) as dependent variables. These cut-off values were based on median scores but also reflect individuals at high CV risk. The interaction between periostin and vitamin D to explain CV risk variability were explored using linear and ordinal logistic regression.

A p-value ≤ 0.05 was considered statistically significant. Statistical analyses were conducted using MedCalc software (Mariakerke, Belgium).

Results

Clinical and biochemical characteristics

Blood samples from 299 individuals (mean age 72.8 ± 15.7 years) were analyzed and clinical data are summarized in Table 1. Comorbidities were prevalent, including dyslipidemia (48.2%), hypertension (47.5%), falls/fractures (29.4%), and obesity (18.7%). Antihypertensive (52.2%) and antithrombotic (34.8%) treatments were the most frequent.

Characteristics of individuals stratified as having low or high periostin levels

Clinical characteristics were compared between participants according to periostin levels: low (< 150 pmol/L) and high (≥ 150 pmol/L). Significant differences in clinical and biochemical variables were observed between these groups (Table 1). Individuals with lower periostin levels had significantly lower vitamin D ($p < 0.0001$) and higher parathyroid hormone (PTH) levels ($p < 0.0001$) compared to those with higher periostin. Participants in the low periostin group were older (76.3 ± 15.0 vs. 69.2 ± 15.7 years, $p < 0.0001$). Comorbidities were more frequent in the low periostin group, notably dyslipidemia (55.9% vs. 40.1%, $p = 0.009$) and CVD (19.1% vs. 8.8%, $p = 0.017$). Medication use was generally higher among low periostin individuals, except for vitamin D supplementation and antifracture treatments, which were more common in the high periostin group.

Table 1 Clinical and laboratory characteristics of individuals stratified by periostin levels

Characteristic	Total (*N*=299)	Periostin <150 pmol/L (*N*=152)	Periostin ≥150 pmol/L (*N*=147)	*p*-value
General				
Age, years	72.8 ± 15.7	76.3 ± 15.0	69.2 ± 15.7	**< 0.0001**
Male gender, *n* (%)	134 (44.8)	67 (44.1)	67 (45.6)	0.89
BMI (kg/m^2)	26.8 ± 4.4	27.2 ± 4.6	26.3 ± 4.2	0.09
Smoking, *n* (%)*	140 (46.8)	67 (44.1)	73 (49.7)	0.39
Biochemical parameters				
Periostin (pmol/L)	342.1 ± 363.5	105.3 ± 15.6	583.7 ± 389	-
1,25(OH)$_2$D (pg/ml)	43.7 ± 17.0	39.3 ± 16.5	48.2 ± 16.3	**< 0.0001**
25(OH)D (ng/ml)	20.2 ± 12.1	13.7 ± 6.0	27.0 ± 12.9	**< 0.0001**
PTH (pmol/L)	5.6 ± 3.1	6.2 ± 3.6	4.9 ± 2.2	**< 0.0001**
VDBP (mg/L)	698.2 ± 200.9	687.5 ± 168.6	709.3 ± 229.7	0.35
Creatinine (mg/dL)	0.89 ± 0.5	0.8 ± 0.5	1.0 ± 0.6	**0.05**
Total calcium (mg/dL)	9.2 ± 0.4	9.2 ± 0.4	9.3 ± 0.4	**0.04**
Magnesium (mg/dl)	2.1 ± 0.2	2.1 ± 0.2	2.1 ± 0.2	1.0
Total cholesterol (mg/dL)	216.7 ± 46.9	217.9 ± 52.1	215 ± 41	0.64
LDL-cholesterol (mg/dL)	135.4 ± 41.1	135.8 ± 45.5	135.1 ± 36.2	0.89
HDL-cholesterol (mg/dL)	58.1 ± 15.1	57.4 ± 15.3	58.8 ± 14.8	0.43
Triglycerides (mg/dL)	115.4 ± 75.4	123.5 ± 91.9	107.0 ± 52.4	0.06
Plasma glucose (mg/dL)	96.8 ± 19.5	99.2 ± 19.7	94.4 ± 19.1	**0.032**
Comorbid diseases, n (%)				
Dyslipidemia	144 (48.2)	85 (55.9)	59 (40.1)	**0.009**
Hypertension	142 (47.5)	79 (51.9)	63 (42.9)	0.14
Fall/fracture/hospitalisation	88 (29.4)	50 (32.9)	38 (25.9)	0.23
Obesity	56 (18.7)	34 (22.4)	22 (15.0)	0.14
Osteoporosis	48 (16.1)	20 (13.2)	28 (19.0)	0.22
Cardiovascular disease	42 (14.0)	29 (19.1)	13 (8.8)	**0.017**
Type-2 diabetes mellitus	39 (13.0)	24 (15.8)	15 (10.2)	0.21
Asthma and/or bronchitis	18 (6.0)	12 (7.9)	6 (4.1)	
Treatment, n (%)				
Antihypertensive	156 (52.2)	90 (59.2)	66 (44.9)	**0.018**
Antithrombotic	104 (34.8)	67 (44.1)	37 (25.2)	**0.0009**
Psychotropic	82 (27.4)	42 (27.6)	40 (27.2)	0.94
Lipid lowering	73 (24.4)	43 (28.3)	30 (20.4)	0.15
Cardiac	42 (14.0)	24 (15.8)	18 (12.2)	0.47
Anti-diabetic	33 (11.0)	21 (13.8)	12 (8.2)	0.17
Vitamin D supplementation	28 (9.4)	4 (2.6)	24 (16.3)	**0.0001**
Anti-fracture	15 (5.0)	3 (2.0)	12 (8.2)	**0.029**

Data are presented as number and % or mean and SD. *BMI* body mass index; *HDL* high-density lipoprotein; *LDL* low-density lipoprotein; *PTH* parathyroid hormone; *VDBP* vitamin D binding protein

*Smoking status refers to in the previous 3 years or current cigarette smoker

Association between periostin with biochemical and clinical variables by univariate analysis

Statistically significant correlations were observed for a range of different variables Supplementary Table S1. Periostin was observed to be negatively correlated with age ($r=-0.20$, $p=0.0004$) and PTH levels ($r=-0.29$, $p<0.0001$). Weaker but still statistically significant negative correlations were also observed for periostin levels with BMI ($r=-0.16$, $p=0.004$), glucose ($r=-0.16$, $p=0.004$) and triglyceride levels ($r=-0.14$, $p=0.014$). Periostin levels were also observed to be strongly correlated with both 1,25(OH)$_2$D ($r=0.39$, $p<0.0001$) and 25(OH)D ($r=0.76$, $p<0.0001$) (Fig. 1) even after adjusting for age and gender ($r=0.35$, $p<0.0001$ for 1,25(OH)$_2$D and $r=0.74$, $p<0.0001$ for 25(OH)D).

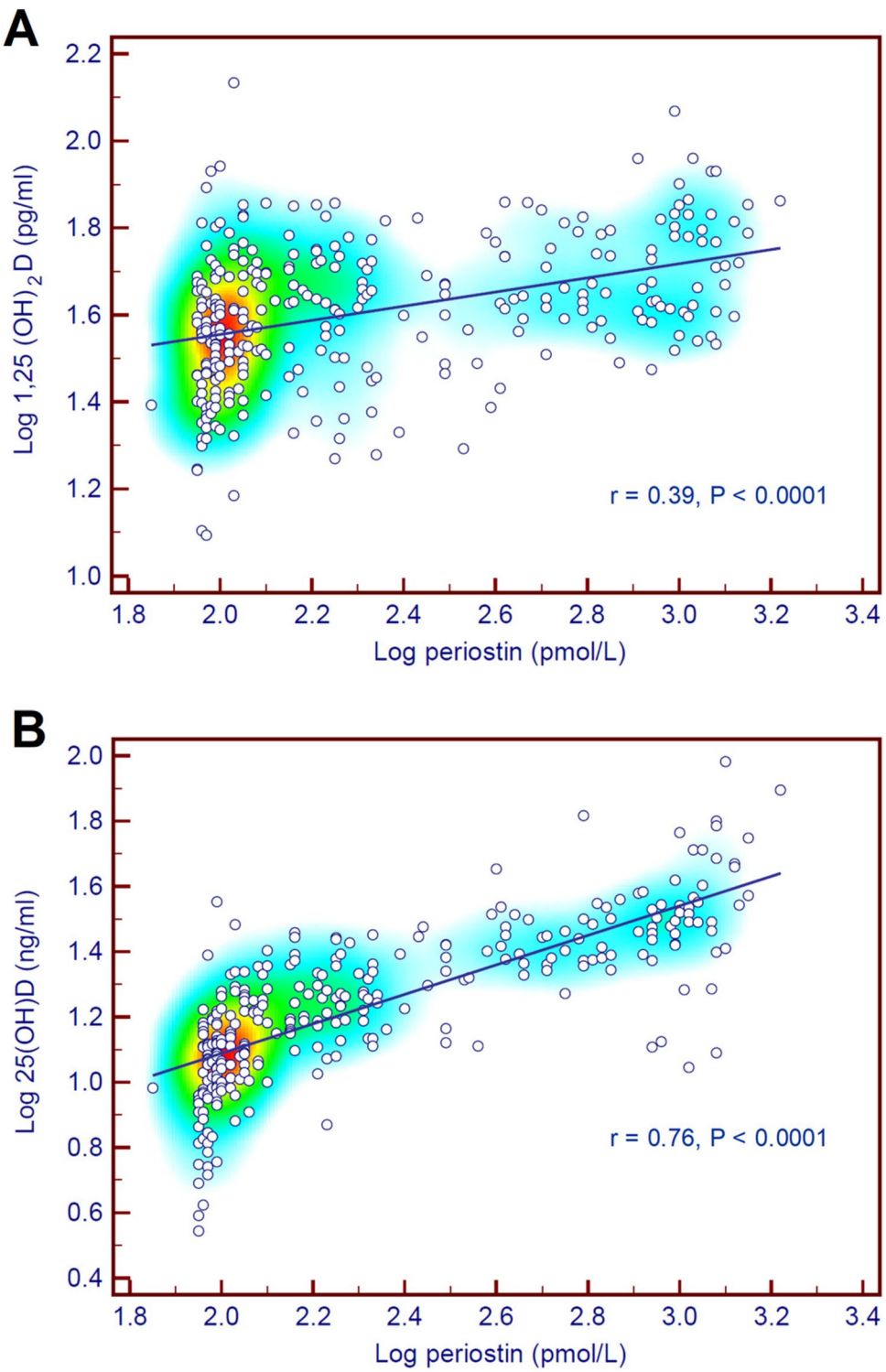

Fig. 1 Scatterplot depicting correlation between periostin and vitamin D levels. **A**, correlation between log $1,25(OH)_2D$ levels and log periostin levels. **B**, correlation between log 25(OH)D levels and log periostin levels. Heatmap represents the distribution of individual datapoints where red represents highest density and light blue (cyan) represents lowest density. Regression coefficient and p values are shown

CV risk and periostin levels

The mean CV risk score for the entire cohort was 2.6 ± 1.4. Individuals with low periostin levels (< 150 pmol/L) had a significantly higher CV risk score compared to individuals with periostin levels ≥ 150 pmol/L (2.9 ± 1.4 vs. 2.2 ± 1.4, $p < 0.0001$) (Fig. 2A). Using the SCORE2/SCORE2-OP, the estimated average 10-year percent risk of a CV event for the entire cohort was $17.95 \pm 12.5\%$ (95% CI: 16.5–19.4%). Participants with low periostin levels (< 150 pmol/L) had significantly higher 10-year risk of a CV event compared to individuals with high periostin levels (≥ 150 pmol/L;

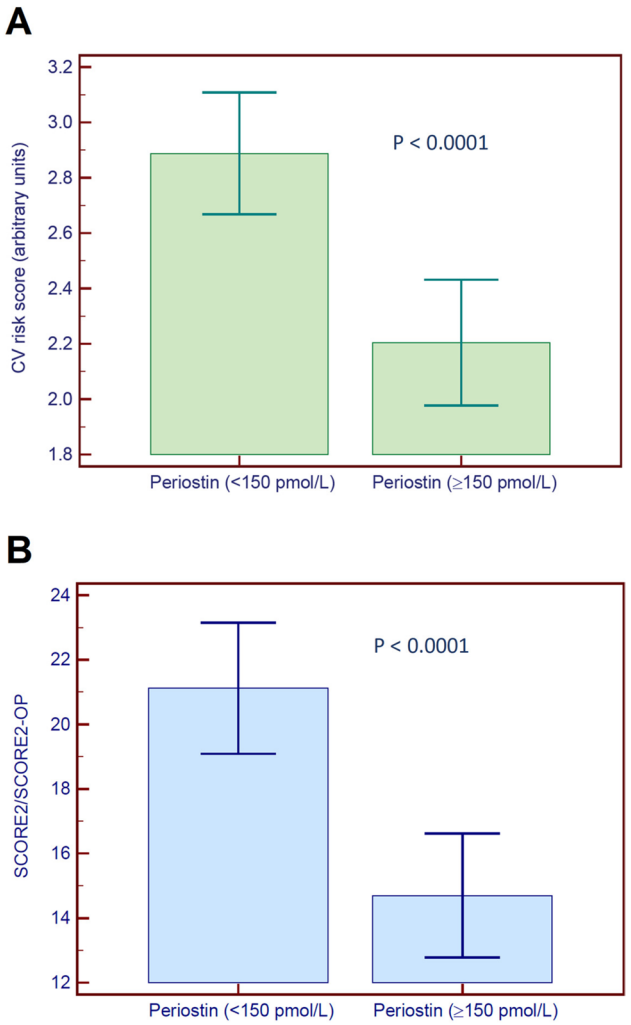

Fig. 2 Comparison between levels of cardiovascular risk after stratifying periostin levels. **A**, Elderly individuals with periostin levels ≥ 150 pmol/L were observed to have a significantly lower CV risk ($p < 0.0001$). Similarly, **B**, Elderly individuals with periostin levels ≥ 150 pmol/L were observed to have a significantly lower SCORE2/SCORE2-OP scores ($p < 0.0001$). Data are presented as mean and standard deviation

21.1 ± 12.5% vs14.7 ± 11.7%, $p < 0.0001$) (Fig. 2B). Confirming these results, we also observed that both CV risk score and SCORE2/SCORE2-OP were inversely correlated with perisotin levels ($r = -0.22$, $p = 0.0001$ and $r = -0.24$, $p = 0.0001$ respectively; Supplementary Figure S1.

Predictor variables associated with low periostin levels

Multivariate logistic regression analysis was next used to determine the whether periostin could be a risk factor for CVD, independent of vitamin D levels. In a multivariate analysis with low periostin level as the dependent variable, 25(OH)D levels < 20 ng/mL (odds ratio [OR]: 22.4, $p < 0.0001$) was the strongest significant correlate of periostin levels (Model #1; Table 2). Older age (≥ 75 years, OR: 2.7, $p = 0.006$) and dyslipidemia (OR: 3.26, $p = 0.0003$) were positively and independently associated with low periostin levels (Table 2).

Association of vitamin D and periostin with CV risk score ≥ 3 and SCORE2/SCORE2-OP ≥ 20%

Next, we evaluated the association between vitamin D metabolites and periostin with very high CV risk. For this analysis we categorized CV risk score and SCORE2/SCORE2-OP by their median values (i.e. 3 and 20%, respectively).

In separate models (models #2–4), deficient levels of 25(OH)D, $1,25(OH)_2D$ levels of < 41 pg/ml and low levels of periostin (< 150 pmol/L) were significantly associated with a CV risk score of ≥ 3 (Table 3). In a fifth model and sixth model, the predictive effect of 25(OH)D or $1,25(OH)_2D$ together with periostin was examined and only $1,25(OH)_2D$ (< 41 pg/ml) remained statistically significant ($p < 0.0001$). In a final model (model #7), considering both vitamin D forms and periostin together, again only $1,25(OH)_2D$ (< 41 pg/ml) was observed to be associated with increased CV risk (OR = 3.45, 95% CI: 2.1–5.8, $p < 0.0001$). Results were consistent, regardless of what measure of CV burden was used in the analysis. While all three variables (low vitamin D metabolites and low periostin levels) were associated with very high SCORE2/SCORE2-OP (i.e. ≥ 20%) (models #8–10; Table 4), only the effect of $1,25(OH)_2D$ levels of < 41 pg/ml remained statistically significant when these three variables were considered together (OR = 3.05, 95% CI: 1.82–5.1, $p < 0.0001$)) (Model #13; Table 4).

Table 2 Multivariate logistic regression analysis of variables associated with serum periostin levels < 150 pmol/L

Variable	OR (95% CI)	*p*-value
Model #1		
$1,25(OH)_2D$ (< 41 pg/ml)	1.29 (0.67–2.5)	0.45
25(OH)D (< 20 ng/ml)	22.4 (10.7–46.7)	**< 0.0001**
Age (≥ 75 years)	2.7 (1.3–5.4)	**0.006**
Gender (male)	0.7 (0.39-1.3)	0.28
BMI (≥ 30 kg/m^2)	0.81 (0.38–1.75)	0.59
Diabetes (yes/no)	1.06 (0.44–2.5)	0.90
Dyslipidemia (yes/no)	3.26 (1.72–6.19)	**0.0003**
Hypertension (yes/no)	0.82 (0.77–2.97)	0.56
Smoking (yes/no)	1.69 (0.50–5.71)	0.40

BMI body mass index

Table 3 Multivariate linear regression analysis of variables associated with CV risk score ≥ 3

Variable	OR (95% CI)	*p*-value
Model #2		
25(OH)D (< 20 ng/ml)	2.4 (1.4–3.6)	**0.0008**
Model #3		
$1,25(OH)_2D$ (< 41 pg/ml)	3.89 (2.39–6.3)	**< 0.0001**
Model #4		
Periostin (< 150 pmol/L)	2.2 (1.35–3.4)	**0.001**
Model #5		
Periostin (< 150 pmol/L)	1.62 (0.91–2.89)	0.10
25(OH)D (< 20 ng/ml)	1.62 (0.89–2.93)	0.11
Model #6		
Periostin (< 150 pmol/L)	1.57 (0.95–2.57)	0.078
$1,25(OH)_2D$ (< 41 pg/ml)	3.54 (2.15–5.83)	**< 0.0001**
Model #7		
Periostin (< 150 pmol/L)	1.46 (0.8–2.67)	0.22
25(OH)D (< 20 ng/ml)	1.14 (0.61–2.14)	0.69
$1,25(OH)_2D$ (< 41 pg/ml)	3.45 (2.1–5.8)	**< 0.0001**

BMI body mass index; *CV* cardiovascular

Table 4 Multivariate linear regression analysis of variables associated with SCORE2/SCORE2-OP ≥ 20%

Variable	OR (95% CI)	*p*-value
Model #8		
25(OH)D (< 20 ng/ml)	2.4 (1.5–3.9)	**0.0003**
Model #9		
$1,25(OH)_2D$ (< 41 pg/ml)	3.75 (2.3–6.1)	**< 0.0001**
Model #10		
Periostin (< 150 pmol/L)	2.42 (1.51–3.87)	**0.0002**
Model #11		
Periostin (< 150 pmol/L)	1.76 (0.98–3.13)	0.056
25(OH)D (< 20 ng/ml)	1.75 (0.96–3.19)	0.066
Model #12		
Periostin (< 150 pmol/L)	1.81 (1.09–2.99)	**0.02**
$1,25(OH)_2D$ (< 41 pg/ml)	3.19 (1.93–5.27)	**< 0.0001**
Model #13		
Periostin (< 150 pmol/L)	1.56 (0.87–2.92)	0.13
25(OH)D (< 20 ng/ml)	1.27 (0.67–2.39)	0.47
$1,25(OH)_2D$ (< 41 pg/ml)	3.05 (1.82–5.1)	**< 0.0001**

BMI body mass index; *CV* cardiovascular

Effect modification between vitamin D metabolites and periostin to explain CV risk

The effect modification between log transformed values of periostin and tertiles of log transformed values of $1,25(OH)_2D$ or 25(OH)D to explain CV risk score (≥ 3) and SCORE2/SCORE-2 (≥ 20%) was investigated by logistic regression analyses. These analyses revealed that no effect modification existed between periostin and $1,25(OH)_2D$ for explaining both the CV risk score ($p = 0.49$) and SCORE-2/SCORE2-OP ($p = 0.08$). The same analysis carried out according to 25(OH)D showed no effect modification by this variable as for the link between periostin and CV risk score ($p = 0.327$). Remarkably, 25(OH)D significantly modified the effect of periostin on SCORE-2/SCORE2-OP implying that the OR of SCORE-2/SCORE2-OP ≥ 20% associated to 1 log unit increase of periostin was lowest in patients of the first 25(OH)D tertile (OR: 0.19, 95% CI: 0.04–0.98), intermediate in those of the second 25(OH)D tertile (OR: 0.63, 95% CI: 0.24–1.65), and highest in patients of the third 25(OH)D tertile (OR: 2.06, 95% CI: 0.73–5.86) (*p* for effect modification = 0.017).

Discussion

This observational study is the first to report a strong correlation between periostin and vitamin D metabolites and their association with CV risk. In univariate analysis, lower periostin and levels of both vitamin D metabolites were associated with increased CV risk although only $1,25(OH)_2D$ remained a significant predictor of increased CV risk in combined multivariate analyses. Levels of 25(OH)D significantly modified the effect of periostin on SCORE-2/SCORE2-OP. There is extensive evidence supporting the interaction between vitamin K-dependent proteins, such as MGP, and vitamin D in maintaining bone and CV health [32]. Our study revealed a strong positive correlation between periostin and both $1,25(OH)_2D$ and 25(OH)D, with deficient 25(OH)D levels as the most robust predictor of low periostin levels. This is consistent with in-vitro studies showing that $1,25(OH)_2D$ significantly increases periostin expression in osteoblast-derived osteospheres [33].

While several epidemiological and observational studies in humans have shown evidence of an association between vitamin D deficiency and the risk of CV diseases and related outcomes[34–47], randomized controlled trials and Mendelian randomization studies have largely failed to demonstrate significant reductions in reducing CV events in healthy or community-dwelling older adults [38, 48–54]. The lack of benefit in these studies may be due to short trial durations, suboptimal dosing, or inclusion of participants with sufficient baseline vitamin D as well as the influence of comorbidities that are frequent in aging populations [38, 50, 53–56].

Animal studies also suggest that vitamin D promotes the production of vitamin K-dependent proteins [57]. However, data in humans are limited. One study in 387 hemodialysis patients showed higher levels of bone Gla-proteins in vitamin D analog users [58], and another randomized,

double-blind, placebo-controlled trial demonstrated that vitamin D supplementation in 131 older participants increased MGP levels [59].

Periostin, originally recognized for its involvement in bone metabolism, is now also associated with CV health [17]. This is consistent with the notion that MGPs are synthesized by vascular smooth muscle cells and chondrocytes to prevent ectopic calcification [23]. In our analysis, we observed that lower serum periostin levels were associated with a higher risk of CVD. While, to our knowledge, no studies have directly investigated the correlation between serum periostin levels and CV risk, periostin is known to contribute to cardiac tissue repair after injury, such as myocardial infarction [60–62].

In animal models, treatment with periostin patches have been shown to improve cardiac function and to reduce fibrosis [60], while periostin ablation hinders myocardial regeneration [63]. However, the role of periostin in CV diseases is complex: while it aids myocardial regeneration, it can also promote pathological tissue remodeling, leading to heart failure in both mice and humans [64, 65]. A recent cross-sectional study found a positive correlation between circulating periostin levels and SCORE2-Diabetes values in type 2 diabetes patients [17]. Thus, it can be hypothesized that periostin's role in health and disease is context-dependent, beneficial in acute tissue repair but potentially maladaptive in chronic conditions.

Building on the dual roles of periostin in CV health and disease, our study further revealed that both low periostin and vitamin D serum metabolite levels were independently associated with very high CV risk. However, when considered together, only low $1,25(OH)_2D$ levels remained significantly associated with high CV risk. These findings highlight the robust predictive value of $1,25(OH)_2D$ for very high CV risk across various stratifications and align with existing literature linking vitamin D deficiency to increased CV risk [24, 41, 66].

Study limitations

This study has several limitations that should be considered. The cross-sectional design does not allow for establishing causal relationships between vitamin D metabolites, periostin levels, and CV risk, highlighting the need for longitudinal studies to clarify the directionality of these associations. In addition,, the sample consisted of a specific subgroup of elderly individuals from the InCHIANTI Biobank, limiting the generalizability of the findings to younger populations or other demographic groups. Despite multivariate analyses, the influence of unmeasured confounders, such as dietary habits, physical activity or genetic factors affecting vitamin D metabolism and periostin expression, cannot be excluded. The use of an arbitrary (non-validated) CV risk score alongside SCORE2/SCORE2-OP, while informative, may not capture CV risk comprehensively or be universally applicable.

This study also lacked information on participants' vitamin D supplementation, dietary intake, and sun exposure, which may influence vitamin D levels and the observed associations. Furthermore, while periostin revealed associations with CV risk, its role as a biomarker remains complex and context-dependent, requiring further studies to resolve conflicting evidence in other pathophysiological settings. The absence of direct measurements of vitamin K status and functional outcomes, such as incident CV events, limits the ability to fully understand the mechanisms underlying the observed relationships and their clinical implications.

Conclusion

This observational study provides novel insights into the interplay between periostin, vitamin D metabolites, and CV risk. It is the first to establish a strong correlation between periostin and both 25(OH)D and $1,25(OH)_2D$. Low periostin levels were observed to be independently associated with elevated CV risk, but when considered alongside vitamin D, $1,25(OH)_2D$ emerged as the strongest predictor. Taken together, these findings suggest that low vitamin D may serve more as a marker of frailty and ill health rather than a direct mediator of CV risk in older adults. Likewise, while periostin has emerged as a potential biomarker of CV remodelling, its prognostic use remains speculative and requires validation in large, prospective studies in addition to mechanistic studies to explore the relationship between this protein and vitamin D.

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Data availability Data can be provided by the corresponding author upon request.

Declarations

Ethics approval All participants provided written informed consent for anonymous data use per European Legislative Decree 2016/679. The study was approved by the Regional Ethics Committee for Clinical Trials of Tuscany (protocol number: 13929_bio, 08/07/2019).

Competing interests MLB has received honoraria/grants or speaker fees from Abiogen Pharma, Alexion, Amgen, Bruno Farmaceutici, Eli Lilly, Kyowa Kirin, MSD, NPS, Servier or Shire. All other authors declare no conflict of interest. F.N., RG, S.B. are employees of Abiogen Pharma Spa, Pisa, Italy.

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