ORIGINAL PAPER

Diffuse idiopathic skeletal hyperostosis is associated with greater complexity of coronary artery disease burden on coronary angiography

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SUMMARY

Objective. Diffuse idiopathic skeletal hyperostosis (DISH) is a common disorder characterized by ossification of tendons and ligaments. DISH has been largely associated with an increased risk of metabolic syndrome and type 2 diabetes. The objective of the present study is to investigate the role of DISH in the risk of coronary artery disease (CAD).

Methods. We conducted an observational cross-sectional study of patients without a history of rheumatic musculoskeletal diseases who underwent coronary angiography between March 2016 and April 2021. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) score was calculated based on coronary angiography images. DISH diagnosis was based on standard X-ray images and computed tomography scans (Resnick criteria). Demographic and clinical characteristics were retrieved from electronic medical records. Multinomial and binary logistic regression models were employed to determine the association between SYNTAX score (dependent variable) and DISH (independent variable).

Results. The study included 187 patients, 82.9% of whom were men, with valid radiological imaging. 83 (44.4%) patients had a confirmed radiological diagnosis of DISH. Diagnosis of DISH was associated with a higher SYNTAX score [adjusted odds ratio (aOR) 34.1, 95% confidence interval (CI) 1.41-79.2 p=0.049], independently from traditional cardiovascular risk factors. In patients aged <70 years, DISH was associated with a 7-fold higher risk of belonging to the highest category of SYNTAX (≥34), compared to non-DISH (aOR 7.23, 95% CI 1.08-48.4; p=0.041). The extension of vertebral calcification was significantly associated with SYNTAX score (r2 0.378, p<0.0001).

Conclusions. DISH diagnosis is common in patients at high risk of cardiovascular disease or with definitive CAD. DISH was independently associated with higher CAD complexity.

Key words: *Diffuse idiopathic skeletal hyperostosis, cardiovascular disease, SYNTAX score.*

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INTRODUCTION

Diffuse idiopathic skeletal hyperostosis (DISH) is characterized by prominent ossification of soft tissues, such as ligaments and enthesis, affecting both the peripheral and axial skeleton. DISH is highly prevalent in the general population aged over 50 years old (1). DISH is a common incidental finding in patients with metabolic diseases such as type 2 diabetes and obesity (2). Despite being usually asymptomatic, patients with DISH have an increased risk of fragility fractures, restrictive respiratory syndrome, and troubles during intubation procedures (3, 4). DISH is diagnosed based on the Resnick criteria that require flowing ossification of at least four vertebral bodies with the preservation of the intervertebral disc space without apparent degenerative disc disease as well as the absence of apophyseal or sacroiliac joints' erosions, sclerosis, or ankylosis (5).

The etiology of the disease is unclear; however, it probably involves inflammatory as well as metabolic mechanisms, which are,

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at least in part, shared with coronary artery disease (CAD) (4). Indeed, patients with DISH had a greater burden of coronary artery calcification on computed tomography (CT) scans (6). Coronary angiography is the diagnostic standard for CAD and provides a visual estimate of the stenosis as well as a more precise characterization of the burden of the disease. Multiple scoring systems have been developed to objectively quantify CAD severity. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) score is among these and has been endorsed by current myocardial revascularization guidelines (7). The SYNTAX score is based on a visual evaluation of angiography to describe CAD in terms of complexity and predict clinical outcomes. The SYNTAX score-II includes also clinical variables in the angiographic evaluation and predicts mortality four years after coronary revascularization (8-11). The aim of our study is to determine the association between CAD and DISH in a cohort of patients at high risk of cardiovascular disease undergoing coronary angiography.

MATERIALS AND METHODS

We conducted an observational cross-sectional study of patients who underwent a diagnostic or therapeutic coronary angiography between March 2016 and April 2021. We retrieved clinical, demographic, radiographic, and laboratory data from electronic medical records of the University of Verona Hospital Trust. Inclusion criteria were: age ≥18 years old, availability of coronary angiography images for proper SYNTAX score estimation, and a 2-projection chest X-ray or CT-scan in the 6 months prior to the coronary angiography.

Exclusion criteria were:

1) history of cirrhosis, active cancer, and end-stage renal disease (defined as estimated glomerular filtration rate <15 mL/min/1.73 m^2 or dialysis);
2) history of hyperthyroidism or hypothyroidism;
3) history of osteoporosis, osteoporotic fractures (including vertebral fractures), treatment with anti-osteoporotic agents;
4) diagnosis of rheumatic musculoskeletal diseases (including spondylarthritis or other axial spinal disease other than DISH);
5) chest X-ray or CT scan ordered for back pain or suspected rheumatic musculoskeletal disease (such as DISH itself or suspected vertebral fracture).

We collected clinical, angiographic, and radiological characteristics [including chest X-rays, CT scans and echocardiography conducted by a skilled cardiologist (GP, MP, RS)]. Chest X-rays and/or CT scans were requested by the treating cardiologist for various reasons, including pre-angiography screening for heart failure or coronary CT for pre-angiography study. We considered DISH as a dichotomic variable (present *versus* not present) as well as a semiquantitative variable based on the vertebral extension of the flowing ossification (number of metamers involved). Two expert operators (GA and AF) examined independently X-ray images and CT scans for the diagnosis of DISH. Patients' coronary angiography indications were stratified in acute coronary syndrome (ACS) and stable disease. Two skilled cardiologists (SZ and MP) independently examined the angiography images and calculated the SYNTAX score.

Patients were then stratified according to SYNTAX score I tertiles as in the original SYNTAX trial (low complexity ≤22, intermediate complexity 23-32, high complexity ≥33) (9). We then calculated the SYNTAX score-II which adds clinical variables to the anatomic coronary lesions score. Patients were also stratified according to SYNTAX score-II tertiles (low tertile ≤21, intermediate tertile 22-28, high tertile ≥29) (12).

Normally distributed variables were stated as mean (standard deviation) and non-normally distributed variables as median (interquartile range). Demographic and clinical features were summarized by descriptive statistic methods: the Student's *t*-test for normally distributed continuous variables and the Mann-Whitney U test or Chi-square test for categorical variables, as appropriate. Multinomial and binary logistic regression models were used to determine

the association between SYNTAX score (dependent variable) and DISH (independent variable) independently from age, sex, body mass index (BMI), creatinine clearance (Cockroft-Gault formula), family history of CVD in up to 2nd degree relatives, hypertension, dyslipidemia, smoke, and diabetes (covariates). In addition, we applied further models, including interaction terms between age and DISH, to investigate how the relationship between DISH and the SYNTAX score varies across different age groups. Further, we did a bootstrapping with resampling 1000 times using simple sampling. The Spearman Rho correlation model was used to evaluate the correlation between the ossified metamers involved and the SYNTAX score. The chi-square test was used to discriminate different indications for coronary angiography, such as ACS indication or stable disease, and to evaluate the presence of valvular calcification on echocardiographic imaging. Statistical analyses were performed using SPSS version 26 (SPSS, Inc., Chicago, IL, USA), considering a 5% level of significance and 95% confidence intervals (CI).

RESULTS

This study consecutively included 200 patients undergoing coronary angiography. Among the overall cohort, 187 patients (82.9% men) with valid spine radiological imaging, obtained for reasons other than chronic back pain or ruling out rheumatological musculoskeletal diseases, in the 6 months before the coronary angiography were eventually included in the study. Twelve patients were excluded because of

Table I - General characteristics of the study population stratified by the presence of diffuse idiopathic skeletal hyperostosis.

Characteristic	No DISH (n=104)	DISH (n=83)	p value
Age (SD)	61 (11)	73 (9)	<0.0001
Weight, kg (SD)	78.5 (14.7)	78.4 (12.4)	NS
Height, cm (SD)	172 (9)	171 (7)	NS
BMI (SD)	26.3 (3.8)	27.0 (4.3)	NS
Sex, male (%)	83 (79.8)	72 (86.7)	NS
Syntax score II (SD)	22.5 (14.9)	28.9 (19.4)	0.008
ACS (%)	58 (55.8)	33 (39.8)	0.03
Smoking (%)	33 (31.7)	16 (19.3)	NS (0.054)
Echocardiographic valvular calcification (%)	13 (12.5)	25 (30.1)	0.003
Family history of CVD (%)	51 (49.0)	25 (30.9)	0.013
Dyslipidemia (%)	65 (63.1)	51 (63.0)	NS
Hypertension (%)	74 (71.2)	67 (82.7)	NS (0.067)
COPD (%)	5 (4.8)	6 (7.4)	NS
Stroke (%)	3 (2.9)	5 (6.3)	NS
Diabetes (%)	23 (22.1)	28 (33.7)	NS
Glomerular filtration rate, mL/min (SD)	91.8 (35.5)	73.9 (28.1)	<0.0001
Total cholesterol, mg/dL (SD)	168 (47)	158 (41)	NS
LDL, mg/dL (SD)	98 (42)	85 (38)	NS
HDL, mg/dL (SD)	44 (12)	48 (17)	NS
Triglycerides, mg/dL (SD)	121 (51)	121 (54)	NS

DISH, diffuse idiopathic skeletal hyperostosis; SD, standard deviation; BMI, body mass index; ACS, acute coronary syndrome; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; LDL, low-density lipoproteins; HDL, high-density lipoproteins; NS, not significant.

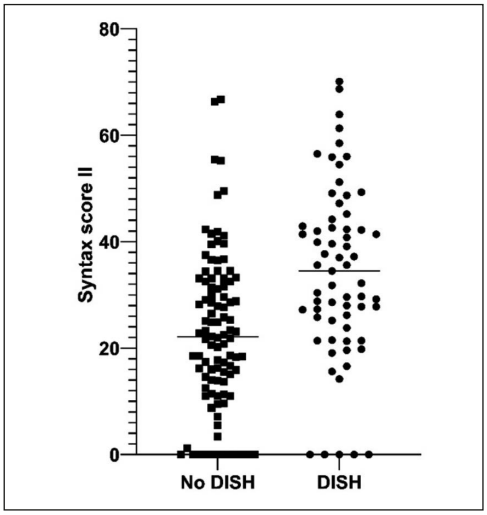

Figure 1 - The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) score II in patients with and without diffuse idiopathic skeletal hyperostosis (DISH).

low-quality imaging and one patient because of insufficient clinical information.

The mean age of the cohort was 67.2±11.3 years, and 83 (44.4% of the overall cohort) patients had a confirmed radiological diagnosis of DISH. It was obtained with CT scans in 52 patients out of 73 with available CT scan images and with standard X-rays in 31 patients out of 114 with available X-ray images. Table I shows the general characteristics of the study population stratified for the presence of DISH.

SYNTAX score was similar between groups, but SYNTAX score-II was significantly higher in the DISH group compared to non-DISH (29.0±19.4 *versus* 22.5±14.9; p=0.012) (Figure 1), and 60.2% of DISH patients belonged to the highest SYNTAX score-II tertile, compared to 39.4% of non-DISH (p=0.015). Echocardiographic valvu-

Table II - Multinomial logistic regression and binary logistic regression.

Multinomial logistic regression (SYNTAX score-II 1st tertile versus 3rd tertile, comparisons with 2nd tertile is not shown)				
Covariate	**β**	**SE**	**p-value**	**aOR**
Age	0.060	0.086	0.481	1.062
Creatinine clearance	0.000	0.023	0.998	1.000
BMI	-0.106	0.114	0.352	0.899
DISH diagnosis	3.531	1.760	0.049	34.149
Familiy history of CVD	1.453	1.264	0.250	4.278
Hypertension	-2.463	1.318	0.062	0.085
Dyslipidemia	0.095	1.259	0.940	1.099
Smoking status	1.019	1.350	0.450	2.771
Sex	-0.948	1.396	0.497	0.387
Diabetes	1.211	1.125	0.282	3.357
Binary logistic regression (SYNTAX score-II as a dichotomous variable, threshold 29 points)				
Covariate	**β**	**SE**	**p-value**	**aOR**
Age	0.155	0.115	0.178	1.168
Creatinine clearance	0.002	0.280	0.994	1.001
BMI	-0.049	0.186	0.792	0.952
DISH diagnosis	0.900	4.821	0.045	2.460
Family history of CVD	-0.061	1.687	0.971	0.941
Hypertension	-3.194	2.949	0.279	1.331
Dyslipidemia	-0.130	1.586	0.935	0.878
Smoking status	0.580	3.828	0.880	1.787
Sex	-0.913	0.957	0.340	0.394
Diabetes	-1.007	0.656	0.125	0.365

SYNTAX, SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery; BMI, body mass index; CVD, cardiovascular disease; SE, standard error; aOR, adjusted odds ratio.

lar calcification was detected more often in DISH patients compared to non-DISH [30.1% *versus* 12.5% - odds ratio (OR) 3.017; p=0.003]. Patients with DISH had a lower incidence of ACS compared to non-DISH (OR 0.52, 95% CI 0.29-0.94). Indeed, a total of 91 patients had ACS and, among those, 33 (39.8%) had DISH while 58 (55.8%) did not have DISH (p=0.03). In contrast among the 96 patients without ACS, 50 (52.1%) had DISH, and 46 (47.9%) did not have (p-value NS).

Table II details the multinomial logistic and binary logistic regressions. In the multinomial logistic analysis, the presence of DISH was associated with a 34 times higher risk of falling into the SYNTAX higher tertile, compared to the lower tertile, independently from traditional cardiovascular risk factors (age, sex, BMI, family history of CVD, hypertension, dyslipidemia, smoke, diabetes, and creatinine clearance) [adjusted OR (aOR) 34.1, 95% CI 1.41, 79.2; p=0.049]. In the binary logistic regression analysis (dependent variable SYNTAX score-II as a dichotomous variable, threshold 29 points), DISH patients had a 2-fold higher risk of falling into the poor prognostic category than non-DISH (aOR 2.46, CI 95%: 1.02-5.94; p=0.045), regardless of traditional cardiovascular risk factors (age, sex, BMI, family history of CVD, hypertension, dyslipidemia, smoke, and diabetes). In sensitivity analyses, increasing the threshold of SYNTAX score-II to 34 points yielded similar results (aOR 2.97, 95% CI 1.58-5.60; p <0.001). Of note, even in patients aged <70 years, diagnosis of DISH was associated with a 7-fold higher risk of belonging to the highest SYNTAX score-II category (≥34), compared to non-DISH (aOR 7.23, 95% CI 1.08-48.4; p=0.041).

The extension of vertebral calcification correlated with SYNTAX score-II (r2 0.378, p<0.0001) (Figure 2). This result remained significant even when selecting patients under 70 years with DISH (r2 0.255, p=0.012). We introduced an interaction term between DISH and age in both the multinomial logistic analysis for the SYNTAX score tertiles and the binary logistic regression analysis with the SYNTAX score-II as a dichotomous outcome. This additional analysis aimed to assess whether the impact of DISH on CAD risk varies significantly across different age groups. In the multinomial logistic model, the interaction term between DISH and age did not significantly change the risk of falling into the higher SYNTAX score tertile (aOR for DISH*age interaction not statistically significant, p>0.05), indicating that the association between DISH and an increased risk of complex CAD remains robust across different age groups, independent of traditional cardiovascular risk factors. Similarly, in the binary logistic regression analysis, the addition of the DISH*age interaction term did not substantially modify the previously observed 2-fold higher risk of poor prognosis in DISH patients (aOR for DISH*age interaction not statistically significant, p>0.05). These findings suggest that while age is an important factor in cardiovascular risk assessment, it does not significantly modify the relationship between DISH and the severity of CAD as measured by the SYNTAX score. The bootstrap analysis, which involved resampling our data 1000 times with replacement, yielded a slightly changed adjusted p-value, moving from p=0.045 in our

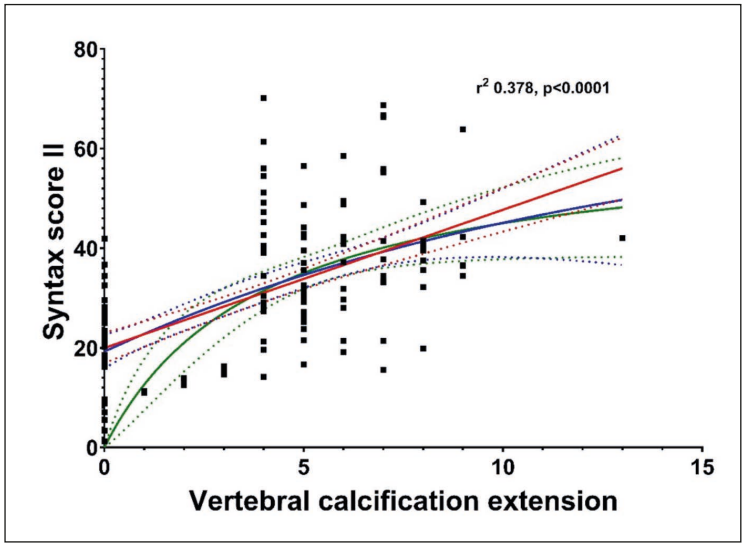

Figure 2 - Correlation between the SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) score and vertebral ossification extension. In red linear regression, in blue exponential with plateau interpolation, in green hyperbola interpolation.

original analysis to p=0.048 in the bootstrap analysis (binary logistic regression SYNTAX-II threshold 29).

DISCUSSION

Herein we conducted an observational study on the association between DISH and CAD. Overall, we found that the diagnosis of DISH was associated with greater complexity of CAD independently from age and other traditional cardiovascular risk factors. Moreover, we found that the degree of flowing ossification at the thoracic vertebrae was positively associated with the complexity of the CAD on angiography.

Oudkerk *et al.* previously investigated the correlation between DISH and coronary artery calcification using a CT scan with calcium calibration and the Agatston score (6). The authors found that patients with DISH had a greater burden of coronary artery calcification. However, a CT scan can only give a rough estimate of the atherosclerosis extension and it cannot describe with accuracy the CAD burden, especially as regards soft plaque stenosis, stenosis entity, and clinical significance or prognosis.

In contrast, we utilized invasive coronary angiography, the diagnostic gold standard for CAD, which can provide a detailed visual estimate of the stenosis (13). Moreover, we used a validated score for CAD complexity, which has been shown to effectively predict the mortality of patients with CAD after revascularization (10, 12). The SYNTAX score is commonly applied by cardiologists to guide treatment strategy in patients with relevant coronary stenosis on diagnostic angiography (7). Patients with higher SYNTAX scores are more commonly treated with surgical aorto-coronary bypass (7).

In our analysis, we found that DISH patients had a lower incidence of ACS compared to non-DISH. To date, it is unclear whether calcified plaques that develop in DISH patients tend to be more stable and less liable to rupture. However, based on our findings, we could speculate that DISH patients are more prone to develop chronic heart disease with complex, calcific, and stable plaques rather than ACS with unstable plaques.

Dan Lantsman *et al*. recently published a study that appears to contrast with our findings, specifically investigating the association between DISH and CAD using the coronary artery calcification score (CACS) and the CAD Reporting and Data System (CAD-RADS) score in patients with symptomatic chest pain (14). This study, which included a cohort of 268 individuals, found that while DISH was associated with higher CACS in univariate analysis, the association did not persist after adjusting for known atherosclerotic risk factors. Similarly, a positive trend toward higher CAD-RADS scores in the DISH group was observed, but this trend was not statistically significant after adjustment for age, male sex, and family history of CVD. The discrepancy between these findings and ours could be due to several methodological differences in evaluating coronary burden. First, our study, as already mentioned, employed a more precise assessment of CAD complexity that broader measures like CACS and CAD-RADS may overlook. Second, our analysis, which considered additional cardiovascular risk factors and utilized specific statistical techniques, may have further defined the intricate association between DISH and CAD. Third, patient selection criteria and study design differed significantly, particularly regarding the symptomatic status of the participants and the direction of screening for disease associations. The study in question focused on a cohort that included both symptomatic and asymptomatic patients, with a general emphasis on lower CV disease burden, and primarily screened for the presence of DISH among individuals evaluated for CAD. This approach might inherently bias the study towards a population with less pronounced coronary pathology, potentially diluting the observable impact of DISH on CAD severity as measured by CACS and CAD-RADS scores. In contrast, our study adopted an opposite approach by selecting patients with established or high risk for CAD and subsequently screening for the presence of DISH. This methodology was

likely selected for a population with a higher baseline risk and prevalence of CAD, which could enhance the sensitivity of our study to detect associations between DISH and CAD severity.

The pathogenesis of DISH is complex and involves various mechanisms. Osteoblasts seem to play a crucial role in its development (15, 16). Interestingly, the differentiation of smooth muscle cells into osteoblast-like cells, mediated by the osteo-metabolic axis disruption, appears to be the first step in the process of calcification of the vessel wall, which represents the last stage of atherosclerosis (17, 18). Therefore, the dysregulation of the osteoblastic lineage might represent the link that connects diffused coronary artery calcification and DISH. Sclerostin, a bone formation inhibitor, has been found to be low in DISH patients (2, 19) as well as in patients with calcific atherosclerosis (20). In contrast, sclerostin serum levels have been found elevated in patients with acute cardiovascular events (21, 22). Overall, these results are somehow in line with our findings. Indeed, we found that DISH patients were more prone to have diffuse coronary calcifications, but they were somewhat protected from acute events.

Our study should be interpreted in light of strengths and limitations. The main strength is the utilization of angiography, the gold standard for CAD assessment, to visualize the coronary tree anatomy and characteristics. Moreover, we had access to a full set of clinical and radiological features of patients with established CAD. The main limitation comes from the retrospective nature of the study that might cause selection bias; indeed, the indication for coronary angiography was not pre-specified possibly inducing a referral bias for healthier or older patients, who are more likely to undergo coronary angiography for stable angina in contrast to ACS. Notwithstanding, correcting for age and several other clinical variables in the logistic regression analyses should have reduced such bias. Moreover, sensitivity analyses that excluded subjects older than 70 years old yielded similar results. In addition, to mitigate selection bias, we conduced bootstrap analyses of the regression models and additional model fitting (such as exponential with plateau and hyperbole) to strengthen the results. Misclassification bias might have also affected our findings. Indeed, CT scans and standard X-rays have different sensitivity and specificity for the diagnosis of DISH, and we might have missed some DISH patients with X-rays. However, the prevalence of DISH that we found in our study is highly consistent with other studies in similar populations (23).

Our findings highlight the importance of longitudinal and experimental studies to further explore the relationship between DISH and CAD. Future research should focus on tracking the progression of CAD in individuals with DISH over time to establish causality and explore the underlying biological mechanisms. This could involve both prospective cohort studies and laboratory investigations into the pathophysiological pathways linking DISH to cardiovascular risk.

CONCLUSIONS

In conclusion, we found a high prevalence of DISH in patients with CAD. Individuals with DISH had more complex CAD compared to non-DISH subjects, independent of age and other traditional cardiovascular risk factors. However, DISH appeared to be associated with stable CAD in contrast to ACS. Our study suggests that recognizing DISH in patients with CAD may necessitate tailored clinical management, emphasizing aggressive cardiovascular risk factor control. Identifying DISH could help stratify patients' risk profiles, guiding more personalized treatment strategies to mitigate the heightened risk of complex CAD. Longitudinal and confirmatory studies are needed to ascertain the prognostic role of DISH in CAD.

Contributions

GA, conceptualization, formal analysis; GA, SZ, data curation, writing – original draft; FLR, project administration; FLR, DG, supervision; GA, DG, validation. All authors contributed to the investigation and the review and editing of the manuscript.

Conflict of interest
GA has received advisory board honoraria, consultancy fees and/or speaker fees from Theramex, UCB, Lilly, Galapagos, Fresenius Kabi, Amgen, BMS, Abiogen and Pfizer. DG has received advisory board honoraria, consultancy fees and/or speaker fees from Abiogen, Celgene, Eli-Lilly, Neopharmed-Gentili, Pfizer, UCB. MR reports advisory board honoraria, consultancy fees and/or speaker fees from AbbVie, Amgen, BMS, Eli-Lilly, Galapagos, Menarini, Sandoz, Theramex, UCB, outside the submitted work. AF reports personal fees from Abiogen, Novartis, Neopharmed. All the other authors declare no potential conflict of interest.

Ethics approval and consent to participate
This study was conducted according to the protocol REUMABANK approved by the Ethics Committee of the University of Verona Hospital, in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent
This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient-relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

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Availability of data and materials
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REFERENCES

1. Liang H, Liu G, Lu S, Chen S, Jiang D, Shi H, et al. Epidemiology of ossification of the spinal ligaments and associated factors in the Chinese population: a cross-sectional study of 2000 consecutive individuals. BMC Musculoskelet Disord 2019; 20: 253.
2. Fassio A, Adami G, Idolazzi L, Giollo A, Viapiana O, Bosco E, et al. Diffuse idiopathic skeletal hyperostosis (DISH) in type 2 diabetes: a new imaging possibility and a new biomarker. Calcif Tissue Int 2021; 108: 231-9.
3. Guiot A, Estublier C, Gaude M, Szulc P, Chapurlat R. Relationship between diffuse idiopathic skeletal hyperostosis and fragility vertebral fracture: a prospective study in older men. Rheumatology 2021; 60: 2197-205.
4. Mader R, Verlaan JJ, Buskila D. Diffuse idiopathic skeletal hyperostosis: clinical features and pathogenic mechanisms. Nat Rev Rheumatol 2013; 9: 741-50.
5. Resnick D, Niwayama G. Radiographic and pathologic features of spinal involvement in diffuse idiopathic skeletal hyperostosis (DISH). Radiology 1976; 119: 559-68.
6. Oudkerk SF, Mohamed Hoesein FAA, PThM Mali W, Öner FC, Verlaan JJ, de Jong PA, et al. Subjects with diffuse idiopathic skeletal hyperostosis have an increased burden of coronary artery disease: an evaluation in the COPDGene cohort. Atherosclerosis 2019; 287: 24-9.
7. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J 2019; 40: 87-165.
8. Morice MC, Serruys PW, Kappetein AP, Feldman TE, Ståhle E, Colombo A, et al. Five-year outcomes in patients with left main disease treated with either percutaneous coronary intervention or coronary artery bypass grafting in the synergy between percutaneous coronary intervention with taxus and cardiac surgery trial. Circulation 2014; 129: 2388-94.
9. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP, et al. Assessment of the SYNTAX score in the Syntax study. EuroIntervention 2009; 5: 50-6.
10. Chichareon P, Onuma Y, van Klaveren D, Modolo R, Kogame N, Takahashi K, et al. Validation of the updated logistic clinical SYNTAX score for all-cause mortality in the GLOBAL LEADERS trial. EuroIntervention 2019; 15: e539-46.
11. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005; 1: 219-27.
12. Xu B, Généreux P, Yang Y, Leon MB, Xu L, Qiao S, et al. Validation and comparison of the long-term prognostic capability of the SYNTAX score-II among 1,528 consecutive patients who underwent left main percutaneous coronary intervention. JACC Cardiovasc Interv 2014; 7: 1128-37.
13. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American Col-

lege of Cardiology/American Heart Association task force on clinical practice guidelines: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. Circulation 2016; 134: e123-55.
14. Dan Lantsman C, Brodov Y, Matetzky S, Beigel R, Lidar M, Eshed I, et al. No correlation between diffuse idiopathic skeletal hyperostosis and coronary artery disease on computed tomography using two different scoring systems. Acta Radiol 2023; 64: 508-14.
15. Berthelot JM, Le Goff B, Maugars Y. Pathogenesis of hyperostosis: a key role for mesenchymatous cells? Joint Bone Spine 2013; 80: 592-6.
16. Xu L, Qian Z, Wang S, Wang R, Pu X, Yang B, et al. Galectin-3 enhances osteogenic differentiation of precursor cells from patients with diffuse idiopathic skeletal hyperostosis via Wnt/β-catenin signaling. J Bone Miner Res 2022; 37: 724-39.
17. Chiang HY, Chu PH, Chen SC, Lee TH. MFG-E8 promotes osteogenic transdifferentiation of smooth muscle cells and vascular calcification by regulating TGF-β1 signaling. Commun Biol 2022; 5: 364.
18. Gonçalves I, Oduor L, Matthes F, Rakem N, Meryn J, Skenteris NT, et al. Osteomodulin gene expression is associated with plaque calcification, stability, and fewer cardiovascular events in the CPIP cohort. Stroke 2022; 53: e79-84.
19. Niu CC, Lin SS, Yuan LJ, Chen LH, Yang CY, Chung AN, et al. Correlation of blood bone turnover biomarkers and Wnt signaling antagonists with AS, DISH, OPLL, and OYL. BMC Musculoskelet Disord 2017; 18: 61.
20. Golledge J, Thanigaimani S. Role of sclerostin in cardiovascular disease. Arterioscler Thromb Vasc Biol 2022; 42: e187-202.
21. He J, Pan M, Xu M, Chen R. Circulating miRNA-29b and sclerostin levels correlate with coronary artery calcification and cardiovascular events in maintenance hemodialysis patients. Cardiol Res Pract 2021; 2021: 9208634.
22. Shui X, Dong R, Wu Z, Chen Z, Wen Z, Tang L, et al. Association of serum sclerostin and osteoprotegerin levels with the presence, severity and prognosis in patients with acute myocardial infarction. BMC Cardiovasc Disord 2022; 22: 213.
23. Zincarelli C, Iervolino S, Di Minno MND, Miniero E, Rengo C, Di Gioia L, et al. Diffuse idiopathic skeletal hyperostosis prevalence in subjects with severe atherosclerotic cardiovascular diseases. Arthritis Care Res 2012; 64: 1765-9.