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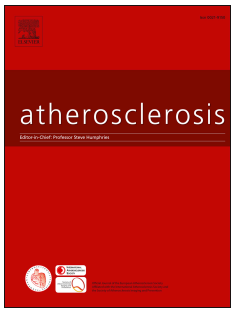

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Subclinical impairment of myocardial and endothelial functionality in very early psoriatic and rheumatoid arthritis patients: Association with vitamin D and inflammation

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ABSTRACT

Background and aims: Cardiovascular (CV) morbidity is increased in inflammatory joint diseases (IJD), as rheumatoid (RA) and psoriatic arthritis (PsA). Whereas increased prevalence of subclinical atherosclerosis has been reported in these conditions, whether an early myocardial functionality is also impaired remains unknown. The aim of this study was to evaluate the myocardial functionality by speckle-tracking echocardiography (STE) in recent onset RA and PsA patients and its potential associations with the levels of circulating CD34+ cells, vitamin D, and with disease activity.

Methods: STE was used to assess the myocardial functionality in patients with very early RA (n=41) and PsA (n=35) without traditional CV risk factors, and 58 matched healthy controls (HC). Global longitudinal and circumferential strain (GLS and GCS) were estimated. Pulse wave velocity (PWV), carotid intima-media thickness (cIMT) were measured as surrogate markers of atherosclerosis. Circulating CD34+ counts were evaluated by flow cytometry and vitamin D levels were quantified by HPLC. Disease activity was assessed by Disease Activity Score-28 (DAS28).

Results: RA patients exhibited impaired GLS and GCS (both $p<0.001$) as compared to HC, GLS being also altered in PsA ($p=0.020$ *vs*. HC). DAS28 was correlated to GLS ($r=0.908$, $p<0.001$) and GCS ($r=0.868$, $p<0.001$) in RA, these findings being confirmed by multivariate regression analyses adjusted for confounders and Principal Component Analyses. GLS and GCS were impaired in PsA patients with high disease activity as compared to HC, and GLS was found to be a predictor of cIMT in this condition. On the other hand, vitamin D was negatively associated with cIMT in HC ($r=-0.308$, $p=0.026$) but not in PsA or RA, although decreased levels were observed (both $p<0.001$). Vitamin D was an independent predictor of decreased CD34+ levels in PsA and RA. CD34+ counts negatively correlated DAS28, GLS and GCS in RA.

Conclusions: Subclinical myocardial dysfunction is observed in IJD patients with preserved left-ventricular function and without traditional CV risk factors. Subclinical myocardial dysfunction was found to be a very early event in IJD. Disease activity was the main predictor of myocardial strain impairment. Interestingly, myocardial function was altered and associated with cIMT also in PsA patients with high disease activity.

Keywords: rheumatoid arthritis, inflammatory joint diseases, speckle-tracking echocardiography, vitamin D

INTRODUCTION

Patients with inflammatory joint diseases (IJD), including rheumatoid arthritis (RA) and psoriatic arthritis (PsA), exhibit increased rates of cardiovascular disease (CVD) morbidity and mortality [1,2], especially heart failure and myocardial infarction. Traditional CV risk factors cannot fully account for this increased risk, and chronic inflammation and immune dysregulation are thought to play a substantial role [3,4].

The involvement of traditional and non-traditional CV risk factors in IJD has two main consequences. First, the CVD have a premature development in these patients. Second, the assessment of CV risk solely based on traditional CV risk factors, as implemented for the general population, is obviously insufficient. Therefore, there is a clear need for early and appropriate methods for CV risk assessment in IJD [5,6], which may benefit patient stratification and facilitate the establishment of earlier therapeutic interventions, in order to improve clinical outcomes.

Several non-invasive imaging techniques allows an adequate estimation of CV risk by evaluating atherosclerosis burden and cardiac function. Although most of the studies have focused on atherosclerosis, less attention has been paid to myocardial systolic functionality. Two dimensional speckle tracking echocardiography (STE) is a recent method for detecting ventricular dysfunction by echocardiographic assessment of myocardial deformation (strain). Strain refers to the deformation or the relative change of muscle from its original length, expressed as a percentage of change. This technique provides information about both regional and global myocardial function. It is a very sensitive, load- and angle-independent technique, which make it superior to angle-dependent 2D Doppler echocardiography [7,8]. Moreover, strain abnormalities have been reported in a broad range of CV conditions, from heart failure with preserved EF to myocardial infarction and ischemia-reperfusion lesions [9–12]. Therefore, impaired ventricular strain can be suited for early detection of CVD in PsA and RA [7,13].

The involvement of non-traditional risk factors in IJD is supported by mechanistic insights and may represent a source of biomarkers and therapeutic targets. Common immune mediators [14–17] drive both atherosclerosis and joint progression. Chronic activation of immune pathways leads to endothelial dysfunction, vascular repair failure [18], atherosclerotic plaque formation and, ultimately, CVD development. Among reparative mechanisms, the case of circulating proangiogenic haematopoietic cells (CD34+) must be noted. CD34+ precursors are bone marrow-derived, multipotent cells with the ability to differentiate into different cell types [19,20] that participate in the turnover of damaged endothelium, likely delaying CVD development [20]. CD34+ cells have been described to improve myocardial neovascularization and function [21,22], and their number is associated with LV remodeling [23]. Several factors are known to modulate the number and activity of progenitor cells in rheumatic diseases [18]. Recently, vitamin D receptor has been detected in progenitor CD34+ cells [23], and vitamin D3 has been described to promote the functionality of endothelial colony-forming cells [24], hence pointing to a role for

the vitamin D-CD34+ cells axis in CV homeostasis. Actually, vitamin D levels have been related to arterial stiffness and progenitor cell numbers in RA [25].

Whether myocardial dysfunction can be detected in patients with IJD free of traditional CV risk factors already in the early phases of the disease remains unknown. Moreover, although circulating CD34+ cells and vitamin D have been related to ventricular remodelling [23,26] and have been described to be altered in rheumatic conditions, the associations between STE, circulating CD34+ cells and vitamin D in IJD have not been investigated so far. Therefore, in the present study, we aimed (i) to evaluate the subclinical myocardial dysfunction by STE, as well as surrogate markers of subclinical CVD, in patients with very early IJD without traditional CV risk factors, (ii) to evaluate the associations of STE markers with disease activity, and (iii) to analyze the associations between myocardial dysfunction and the levels of circulating CD34+ cells and vitamin D.

MATERIALS AND METHODS

Ethics statement

Written informed consent was obtained from all subjects according to the Helsinki declaration and the retrospective observation was approved by the Ethics Committee of the University of Messina (Prot. N. 11/17).

Subjects

Between October 2015 and May 2016, 514 outpatients were examined for the first time at the Rheumatology Division of the University of Messina and were referred for a clinical and instrumental screening.

To be selected for the study, subjects needed to fulfill the following inclusion criteria: (i) to be newly diagnosed, (ii) not being exposed to immunomodulatory treatments, (iii) to be free of traditional CV risk factors, and (iv) to meet the classification criteria for PsA or RA [27,28]. Extended definition of traditional CV risk factors and exclusion criteria can be found in the Supplementary Materials. After applying inclusion and exclusion criteria, only 35 subjects with PsA and 41 RA patients were considered eligible for this study. A group of 58 gender- and age-matched healthy subjects were enrolled (institution-based recruitment) using identical inclusion and exclusion criteria (where applicable) and were studied as the healthy control (HC) group.

Patients undergone a complete clinical examination during the clinical appointment, including DAS28-CRP calculation. In PsA patients, cutaneous lesions were examined and the Psoriasis Area and Severity Index (PASI) was calculated to assess the severity [29]. The cut-off for low disease activity was established in 2.9 according to the literature [30].

At the first clinical evaluation, patients and controls underwent blood sampling by venipuncture and instrumental examination. Extensive chemical analyses were performed at the medical center after an overnight fasting in all subjects. Plasma lipids, glucose, fibrinogen, rheumatoid factor (RF) and ACPA were determined by routine methods. CRP was determined by a commercially available ELISA kit. The levels of 25-hydroxyvitamin D3 (25-OH D) were measured by using high-performance liquid chromatography (Bio-Rad).

CD34+ cell count

Flow cytometry was used for the quantification of CD34+ frequency in peripheral blood samples as previously described [25,29]. Briefly, 50 µL of peripheral blood was incubated with 10 µL of PE-conjugated anti-human CD34 antibody (BD) in TRUCOUNT tubes (BD) for 15 minutes. Sample acquisition and analysis were performed by in a FACSCalibur cytometer using CELLQuest as software. Non-viable cells were excluded according to 7-amino-actinomycin D (7-AAD; BD Pharmingen) staining. Circulating

cells that expressed the stem cell antigen CD34 were defined as progenitor haematopoietic CD34+ cells, and estimated and counted (cells/μL) as absolute count as previously described [25,29].

Measurement of cIMT and arterial stiffness indices

Carotid echo Doppler scan and arterial stiffness assessments were performed using a Vivid 3 Expert ultrasound machine equipped with a 7–15 MHz linear array transducer (GE Healthcare) according to ESC/ESH guidelines [31] (see Supplementary Materials). The intraobserver/interobserver variability of IMT and PWV measurements were 1.13/3.51% and 1.23/3.86%, respectively. Intraclass Correlation Coefficient (ICC) for PWV yielded a value of 0.993 (95% CI: 0.991 – 0.995).

Echocardiography study

Echocardiography examination was performed using a VIVID-7 ultrasound machine (GE Vingmed Ultrasound) equipped with a phased-array transducer, and stored on a dedicated workstation (EchoPAC, version 8.0.0) for off-line analyses. All measurements (LV, E/A ratio, LVMI and LV mass) were performed according to the recommendations of the American Society of Echocardiography on three averaged cardiac cycles [29] (see Supplementary Materials for detailed definitions). To complete the analysis of LV systolic function, myocardial deformation was assessed by speckle tracking echocardiography and automated function imaging for the evaluation of global and regional longitudinal (GLS) and circumferential (GCS) strain, as previously described [29]. Automated function imaging was performed on apical long-axis, 4-chamber, and 2-chamber views, following an on-screen guided workflow. The results are presented as a bull's-eye display showing color-coded and numeric values for peak systolic GLS and GCS. A detailed technique was previously described [29]. A frame rate >70 fps was employed. Strain analysis was performed offline by using Echopac. Endocardial border was manually traced from apical views, automatically obtaining the calculation of a region of interest comprised between endocardial and epicardial layers. Tracking quality was verified for each segment and low quality images were excluded. Global values of longitudinal strain from each apical view were calculated through an Automated Function Imaging analysis. LV twist was defined by the difference (in degrees) between apical rotation and basal rotation at isochronal time points. The intraobserver/interobserver variability of GLS and GCS measurements were 0.90/3.49% and 1.78/5.97%, respectively. ICC analyses for GLS yielded a value of 0.982 (0.975 – 0.987) whereas that of GCS was 0.971 (0.960 – 0.979).

Statistical analysis

Variables were summarized as mean ± standard deviation or n(%), unless otherwise stated. Variables were checked for normality by the Kolmogorov-Smirnov test, and non-parametric tests (Mann-Withney U and Kruskal-Wallis tests) were used to analyze differences among groups. Correlations were assessed by the Spearman's test. Multivariate regression analyses were performed to assess the contribution of different independent covariates to the dependent variable. Non-normal variables were log-transformed

prior to be included in the models. A Principal Component Analysis (PCA) was performed as an integrative approach to avoid any potential collinearity bias and to retain the maximum of the variance from the demographical, clinical and traditional risk-related variables. The number of components (correlation method) retained was based on eigenvalues (>1) and loadings greater than 0.5 were used to identify the variables comprising a component. Principal component scores were calculated for each patient and used for multivariate regression analysis. Intraclass Correlation Coefficients (ICC) were computed to further assess the reproducibility of the imaging parameters made by different observers. ICC estimates and their 95% confident intervals were calculated based on a mean-rating (k = 3), absolute-agreement, two-way mixed-effects models. A $p<0.050$ was used to denote statistical significance. SPSS 17.0 and R v. 3.3.1 statistical packages were used to perform statistical analyses.

RESULTS

Subclinical CV disease and myocardial dysfunction in early RA and PsA

The characteristics of the subjects recruited for this study are summarized in Table 1. No differences were observed in age (p=0.170), gender (p=0.130) or BMI (p=0.787) among study groups. Although slight differences in HDL-cholesterol in RA, the total/HDL-cholesterol ratio (atherogenic index) did not differ among groups and all individuals were free of previously diagnosed traditional CV risk factors (hypercholesterolemia/dyslipidemia, hypertension, diabetes, smoking habit and obesity). Similarly, no differences in creatinine levels and estimated GFR were noted. Finally, both PsA and RA patients were recruited at onset and they were not exposed to any medication at the time of sampling.

cIMT was found to be increased in RA (Table 1): 25 (60.9%) of the RA patients exhibited a cIMT>0.90 mm, compared to 4 (11.4%) and 8 (13.7%) of the PsA and HC groups, respectively (p<0.0001). Additionally, the PWV was found to be impaired in both PsA and RA (Table 1). Moreover, PWV was correlated with DAS28 (r=0.322, p=0.055), CRP (r=0.446, p=0.007) and BASDAI (r=0.340, p=0.049) in PsA. Similarly, it was found to parallel DAS28 (r=0.371, p=0.017), ESR (r=0.456, p=0.003), CRP (r=0.384, p=0.013) and duration of the symptoms (r=0.337, p=0.036) in the RA group.

Finally, RA patients exhibited a significant impairment of GLS and GCS compared to HC, whereas GLS was also altered in PsA. Importantly, DAS28 was positively correlated to GLS (r=0.908, p<0.001) and GCS (r=0.868, p<0.001) in RA. Similar associations were retrieved for ESR, CRP and fibrinogen (data not shown). Of note, although GCS was not significantly different in PsA compared to HC, a positive correlation with DAS28 (r=0.438, p=0.008) was observed. Notably, standard echocardiographic examination showed no differences in LV diameters, volumes, wall thickness and EF among individuals (Table 1).

Overall, all these results confirm an increased prevalence of subclinical CV disease and myocardial dysfunction in the early stages of inflammatory joint diseases in the absence of established traditional CV risk factors. Surrogate markers of subclinical CV disease and myocardial dysfunction were strongly associated with the inflammatory burden, hence suggesting a role for inflammation in this scenario.

Subclinical myocardial dysfunction: role for disease features

Further analyses were conducted to evaluate the associations between the subclinical myocardial dysfunction and disease features in PsA and RA.

Because of the previous findings in relation to the disease activity, PsA patients were classified as low (DAS28<2.9) or high (DAS28>2.9) disease activity (Table 2). High disease activity was associated with altered GCS and PWV. Moreover, a trend towards an impaired GLS was also noted. PsA patients with high disease activity exhibited differences in GCS, GLS and PWV when compared to HC, but these

differences were not observed in their low disease activity-counterparts. Interestingly, GLS was found to be a predictor of cIMT in PsA patients (B[95% CI], p: 0.019 [0.002, 0.035], p=0.027) after adjusting for age, BMI, disease activity and inflammation parameters (ESR, CRP and fibrinogen), PWV and vitamin D.

Equivalent results were obtained when RA patients were stratified according to disease activity (Supplementary Table 1). The association between disease activity and subclinical myocardial dysfunction was analyzed by multivariate regression analyses in RA patients. Importantly, DAS28 was found to be the only predictor of GLS and GCS in RA, even after adjusting for potential confounders (Table 3). Therefore, in order to avoid any potential collinearity bias among the features analyzed, a PCA was conducted including age, BMI, DAS28, CRP, ESR, fibrinogen, total-, HDL- and LDL-cholesterol, SBP, DBP and duration on the symptoms (Table 4). PCA revealed a good adequacy of the data (KMO = 0.523, Barlett sphericity test $p=2.03 \cdot 10^{-26}$) and 4 components were obtained, explaining 69.2% of the total variance. Variables included in each component based on their loadings were as follows: component 1 (DAS28, CRP, ESR and fibrinogen), component 2 (age, BMI, total- and LDL-cholesterol), component 3 (SBP and DBP) and component 4 (HDL-cholesterol and duration of the symptoms). Then, a good separation between disease-related and other traditional risk-related factors was achieved. Finally, the association between these components and the myocardial dysfunction was studied by multivariate regression analyses. Interestingly, only disease-related features (component 1) were predictors of GLS and GCS in RA patients, hence confirming our previous findings.

All these results reinforce the relevance of the inflammatory burden in the subclinical impairment of the myocardial functionality in IJD already in the very early stage of these conditions. In addition to the strong association being observed in RA, where GCS and GLS were notably impaired, a clear link was also found in PsA patients with high disease activity. Moreover, GLS was found to be associated with cIMT in these patients. Overall, our findings clearly point to disease activity as the driver of STE impairment in IJD, independently of clinical diagnosis.

Altered CD34+ progenitor cells and vitamin D: associations with subclinical myocardial dysfunction

Finally, we studied whether altered circulating CD34+ progenitor cells or vitamin D levels may underlie the subclinical myocardial dysfunction in IJD.

Vitamin D was negatively associated with cIMT in HC (r=-0.308, p=0.026) but not in IJD patients, where decreased levels were found (Table 1), hence pointing to a link between vitamin D and subclinical atherosclerosis. This correlation was also observed in PsA patients with low disease activity (DAS28<2.9) (r=-0.636, p=0.035), but not in those with higher disease activity (r=0.185, p=0.387).

Moreover, vitamin D levels and DAS28 were independent predictors of CD34+ cells in PsA, whereas vitamin D and duration of the symptoms did in RA (Table 5). Circulating CD34+ cells were decreased in

RA (Table 1), negative correlations with STE parameters being disclosed (GCS: r=-0.291, *p*=0.068; GLS: r=-0.301, *p*=0.057).

All these results suggest that vitamin D was independently associated with circulating CD34+ levels in IJD. CD34+ cells paralleled STE parameters in RA, but additional studies are required.

DISCUSSION

Chronic rheumatic conditions, such as RA and PsA, are associated with enhanced atherosclerosis and impaired endothelial function [32]. Since these alterations occur shortly after disease onset and traditional CV risk factors cannot solely account for this increased risk, a role for inflammation has been proposed [33]. In the present report, we have demonstrated an association between the disease activity and biomarkers of endothelial function, atherosclerosis and subclinical myocardial function in PsA and RA during the early phase of the disease. These alterations were linked to the inflammatory burden, disease activity being the main predictor of impaired myocardial dysfunction irrespectively of disease diagnosis. Importantly, altered levels of CD34+ cells and vitamin D were found in both conditions. Overall, our results clearly confirm a role for the inflammatory burden in both subclinical endothelial and myocardial dysfunction in these patients, hence providing a rationale for the utilization of STE assessment for the CV risk assessment in IJD.

The most interesting result from our study was the impaired myocardial functionality in both RA and PsA patients in the very early phase of the disease. This finding suggests that patients with IJD exhibit not only an accelerated atherosclerosis development in the peripheral vasculature but also myocardial dysfunction already at disease onset. Although some authors have previously reported a reduced LV myocardial deformation in RA patients [7,34,35], most of these studies have been focused on patients with long-standing disease and increased prevalence of traditional CV risk factors. Midtbø and colleagues reported an impaired myocardial function in RA patients with respect to controls, but active RA was related to a higher prevalence of hypertension and diabetes as compared with patients in remission and controls [36]. Therefore, it is likely that the impairment in GLS observed in patients with active RA or PsA in that study may be a consequence of accumulated myocardial damage in the context of these risk factors. Therefore, our results expand the current knowledge of myocardial dysfunction in IJD by confirming its very early onset in these conditions, independently of disease duration, traditional CV risk factors and treatment-related effects. Moreover, we observed for the first time that patients with a more pronounced inflammatory status, assessed by CRP, ESR and fibrinogen, and mainly with a more activity status, had a stronger alteration in myocardial function irrespective of their IJD (RA or PsA), suggesting that inflammation could be the principal driver in impairing myocardial function. Interestingly, other studies have found an association between the exposure to different immunomodulatory drugs and improved myocardial LV strain markers [7,34,35].

Disease activity was found to be associated with GLS and GCS in both RA and PsA in univariate and multivariate analysis, therefore confirming a crucial role of the inflammatory burden in the development of such functional alterations. This idea is in line with the protective effect of the low disease activity to reduce CV risk burden in these conditions [5]. In fact, Solomon and colleagues have revealed that an accumulated high disease activity over time was associated with the development of CV disease in RA [37]. Interestingly, despite exhibiting a comparable duration of the symptoms, a stronger impairment of the

endothelial and myocardial function was observed in RA compared to PsA. Moreover, the duration of the symptoms itself was found to be associated with PWV and CD34+ count in RA, but not in PsA. Overall, our findings are in line with an enhanced inflammatory burden in RA compared to PsA. However, the relevance of the inflammatory burden in PsA cannot be underestimated. Although a lower CV risk has been attributed to this condition compared to other IJD [6,38], a substantial increased risk is still found compared to the general population. Actually, PsA patients with high disease activity exhibited impaired PWV and myocardial dysfunction compared to HC in our study. Of note, GLS was found to be a predictor of cIMT in PsA patients, in line with previous studies in psoriasis [39]. Like arterial stiffness, STE parameters are functional surrogate markers of CV risk. As functional measurements, their alteration is likely to be reversible. Taking into account the association between myocardial dysfunction and disease activity, an appropriate control of the inflammatory burden would be advisable in IJD patients. This is especially relevant during the very early stage of the disease, in line with the concept of the therapeutic 'window of opportunity'. Taken together, our results support the need of a prompt and effective control of disease activity for CVD prevention in IJD.

It is noteworthy that among STE parameters, GLS was impaired in both PsA and RA, whereas GCS was only altered in RA. Interestingly, GLS was reported to be a more sensitive marker than circumferential or radial strains [12]. Upon pathological traits, subendocardial myocardial fibers (longitudinally orientated and thus responsible of the longitudinal contraction) are affected earlier than subepicardial fibers (hence accounting for unchanged circumferential and radial strains). Then, a more pronounced systemic inflammation in RA patients can explain the impairment of both STE parameters compared to their PsA counterparts. Equivalent results were observed when PsA patients were classified by disease activity. These results reinforce our previous findings on inflammatory burden and myocardial dysfunction. The elucidation of the best LV myocardial strain marker according to IJD progression warrant further studies.

Our findings stress the need of an appropriate monitoring of disease activity-mediated myocardial dysfunction in IJD and, presumably, other inflammatory conditions. Recently, other authors have reported that subclinical alterations in the myocardium can be present in other autoimmune rheumatic diseases, such as sarcoidosis [40,41]. Although a number of techniques for CV risk assessment and management have been proposed [32,42,43], most of them are focused on endothelial dysfunction and atherosclerosis, whereas myocardial functionality has not received enough attention. Despite the recent advances in the CV risk management, there is still a considerable room for improvement, hence supporting the need for additional tools. Actually, the research agenda of latest EULAR recommendations for CV risk management in IJD proposes the study of cardiac abnormalities as well as the inclusion of additional CV risk biomarkers to assist in the clinical setting [5]. Taking into account all these ideas, strain imaging by STE can be proposed as a promising tool to address this clinical unmet need. Strain imaging has proved to be a valuable non-invasive opportunity for identifying subclinical CVD [8,44,45], being able to detect subtle LV myocardial dysfunction in an objective and angle-independent fashion. In fact, we have

previously reported that STE was able to identify very early mechanical changes in hypertensive patients prior to the occurrence of LV hypertrophy [46], thereby reinforcing its applicability for early assessment and patient stratification.

Finally, the role of CD34+ cells and vitamin D as biomarkers was analyzed. Interestingly, vitamin D was a predictor of circulating CD34+ cells levels in IJD, even after adjusting for disease activity, hence suggesting that vitamin D levels can be a surrogate marker of impaired CD34+ levels. Our findings pose the question as whether vitamin D supplementation could counteract the disease activity-mediated detrimental effects on CD34+ cells and myocardial dysfunction. Chronic inflammation leads to oxidative stress, myocyte dysfunction and increased fibroblast activity causing myocardial collagen deposition and interstitial fibrosis [47–49], hence hampering myocardial contraction [50]. Furthermore, vitamin D deficiency has been related to cardiac tissue remodeling [51] and LV hypertrophy [52]. Since inflammatory pathways and oxidative stress seems to underlie the myocardial dysfunction, and taken into account the effects of vitamin D on tissue remodeling [52] and on anti-inflammatory and anti-oxidative pathways [53,54], the potential beneficial effects of vitamin D on myocardial dysfunction warrants future studies.

In conclusion, the results herein presented expand the current knowledge about the subclinical CV alterations in IJD. To the best of our knowledge, this is the first study where myocardial alterations are analyzed in patients with very early IJD, which represents a major strength of our study. Although a number of previous studies have described an increased prevalence of atherosclerosis and endothelial dysfunction, our results went further by reporting the LV myocardial strain alterations in IJD patients, regardless of disease diagnosis. Additionally, these pathological findings were found in middle-aged patients already at disease onset with preserved LVEF, in the absence of traditional CV risk factors and related to disease activity. Being our patients not exposed to any DMARD at recruitment allowed us to rule out a potential medication-related confounding effect in our findings. A number of limitations of the present study must also be remarked. First, although stringent criteria were used to control for traditional CV risk factors, lifestyle factors such as diet [55] or physical activity were not appraised. However, there is not a strong evidence pointing to these factors as potential bias for STE in the current literature. Second, because of the cross-sectional design of our study, our findings require confirmation in prospective follow-up studies to evaluate the clinical relevance of the subclinical myocardial impairment in IJD patients. Third, although our data support a good reliability and reproducibility of the STE assessments, certain variability may be expected for multi-centric comparisons [56]. Then, standardization of the image processing and analysis algorithms as well as the validation of appropriate cut-off values are required to guide its routine clinical utilization in the future.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Author contributions

ALG, JRC and GM conceived the study, analyzed and interpreted the data and drafted the manuscript. COA, GD, CZ, SL and MA were in charge of patient recruitment, clinical data collection and clinical data analyses. AS (Ana Suárez) and AS (Antonino Saitta) participated in the conception, design and critical revision of the results. All the authors participated in the discussion of the results and literature search. All authors approved the final version of the manuscript.

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TABLES

Table 1: Characteristics of the subjects recruited in the present study.

	HC (n=58)	PsA (n=35)	RA (n=41)	*p*#	*p* (Dunn-Bonferroni)		
					C *vs.* PsA	C *vs.* RA	PsA *vs.* RA
Age, median (range)	45 (24 – 66)	45 (23 – 59)	46 (32 – 62)	ns			
Gender, f/m	35/23	26/9	32/9	ns			
CV risk-related parameters							
BMI, kg/m^2	24.79±2.73	24.70±2.61	25.15±3.71	ns			
Total cholesterol, mg/dl	181.84±20.88	185.00±22.84	198.05±36.43	ns			
HDL-cholesterol, mg/dl	50.41±9.91	58.00±19.81	58.00±12.87	0.020	0.070	0.021	1.000
LDL-cholesterol, mg/dl	114.00±20.88	106.29±34.94	116.56±35.53	ns			
Total/HDL-cholesterol ratio	3.73±0.80	3.12±0.89	3.62±0.85	ns			
Glucose, mg/dl	88.00±7.04	89.50±10.76	89.00±14.09	ns			
Creatinine, mg/dl	0.66±0.14	0.71±0.16	0.65±0.16	ns			
SBP, mm	122.09±8.85	120.50±11.34	124.27±10.03	ns			
DBP, mm	70.06±6.29	72.00±8.64	74.15±10.94	ns			
CD34+ cell count, cell/μl	2.35±1.14	2.12±0.80	1.58±0.58	<0.001	0.380	0.002	0.024
Clinical features							
DAS28		3.33±0.55	3.61±0.88	ns			
Duration of the symptoms, months		9.37±7.75	6.43±6.00	ns			
Fibrinogen, mg/dl	264.56±50.88	297.26±72.61	321.76±58.91	<0.001	0.068	<0.001	0.343
Vitamin D, ng/ml	31.75±5.05	23.53±4.84	23.68±6.42	<0.001	<0.001	<0.001	0.699
CRP, mg/dl	0.34±0.16	0.50±0.50	0.95±1.18	0.049	1.000	0.011	0.167
ESR, mm		25.06±10.60	27.02±20.40	ns			
HAQ (0-3)		0.52±0.61	1.15±0.64	<0.001			
VAS (0-100)		48.82±15.12	59.42±18.01	0.034			
RF, UI/ml		7.6±2.9	100±100.4	<0.001			
ACPA, n (%)			20 (49.0)				
BASDAI		1.76±2.14					

PASI		0.91±1.31					
	Subclinical CVD and myocardial dysfunction parameters						
cIMT, mm	0.79±0.18	0.82±0.19	0.98±0.16	<0.001	1.000	<0.001	<0.001
PWV, m/s	5.11±0.83	6.42±1.39	7.91±1.93	<0.001	<0.001	<0.001	0.009
GLS, %	-23.25±1.80	-21.57±2.59	-18.13±1.36	<0.001	0.020	<0.001	<0.001
GCS, %	-24.50±.70	-24.97±2.50	-20.15±1.34	<0.001	1.000	<0.001	<0.001
	Echocardiographic assessment						
Septum, mm	10.20±1.00	10.20±1.76	11.20±1.90	ns			
LV mass index	77.40±12.00	77.80±15.50	82.90±10.70	ns			
Posterior wall thickness, mm	9.00±1.20	8.90±1.70	8.70±1.50	ns			
LV DD, mm	50±6.75	52.71±3.5	50.6±2.8	ns			
LV ESD, mm	36.20±2.20	37.00±5.24	35.6±3.90	ns			
E/A	1.10±0.34	1.25±0.10	1.20±0.29	ns			
EF, %	62.88±3.30	61.9±4.79	60.0±4.47	ns			

Variables are summarized as mean ± standard deviation or n (%) unless otherwise stated. Differences were assessed by Kruskal-Wallis tests (with Dunn's Bonferroni correction for multiple comparisons' tests), $\chi 2$ or Mann-Withney U tests, as appropriate.

[#]*p*-values: *p*-values obtained in Kruskall-Wallis, $\chi 2$ or Mann-Withney tests, depending on the distribution of the variables and the groups included in the analyses. When Kruskal-Wallis tests achieved a *p*-value<0.050, multiple comparisons' tests were performed and p-values are indicated in the last columns.

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; HDL: high density lipoprotein-cholesterol; LDL: low density lipoprotein cholesterol; CRP: C-reactive protein.; GLS: global longitudinal strain; GCS: global circumferential strain; PWV: pulse wave velocity; cIMT: carotid intima-media thickness; DAS 28: Disease Activity Score; HAQ: Health assessment questionnaire; VAS: visal analogic scale; PASI: Psoriasis Area Severity Index. LV: left ventricular; EDD: end diastolic diameter; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; ns: non-significant

Table 2: Characteristics of PsA patients classified according to disease activity.

	DAS28 ≤ 2.9	DAS28 > 2.9	*p*
Age	45.91±7.13	42.71±9.84	0.409
Gender, f/m	8/3	18/6	0.636
CV risk-related parameters			
BMI	24.58±1.68	24.61±2.98	0.875
Total cholesterol	178.00±25.71	180.76±22.35	0.804
HDL-cholesterol	55.14±8.05	59.00±22.63	0.455
LDL-cholesterol	104.00±33.55	93.27±3.95	0.423
Total/HDL-cholesterol ratio	3.32±0.84	3.04±0.92	0.494
Glucose	91.00±12.11	86.00±10.14	0.336
Creatinine	0.68±0.18	0.72±0.16	0.451
SBP	112.00±10.36	123.33±10.46	0.066
DBP	69.00±11.42	73.00±7.74	0.497
Clinical features			
Duration of symptoms	6.90±3.08	9.00±8.9	0.174
Fibrinogen	252.00±43.90	318.00±74.37	**0.008**
CRP	0.21±0.14	0.45±0.56	**0.016**
ESR	17.91±6.48	28.33±10.60	**0.002**
HAQ	0.22±0.37	0.66±0.61	0.038
BASDAI	0.79±1.76	2.19±2.17	0.098
PASI	1.49±1.53	0.72±1.14	0.123
Subclinical CVD parameters			
cIMT	0.80±0.14	0.84±0.34	0.612
PWV	5.50±1.24	6.85±1.27	**0.005**
GLS	-22.35±1.98	-21.04±2.85	0.066
GCS	-27.00±15.74	-24.30±2.37	**0.007**

Differences between PsA patients with low and high disease activity were evaluated by Mann-Withney U tests or $\chi 2$ tests, as appropriate. Variables with significant differences are highlighted in bold.

Table 3: Multivariate regression analysis of myocardial dysfunction parameters in RA.

		B	95% CI	*p*
GLS	Age	0.033	-0.006, 0.071	0.091
	BMI	0.021	-0.069, 0.112	0.631
	CRP	0.142	-0.095, 0.379	0.229
	ESR	0.005	-0.013, 0.022	0.580
	DAS28	8.075	4.439, 11.710	**<0.0001**
	SBP	0.011	-0.035, 0.057	0.628
	DBP	0.008	-0.031, 0.048	0.672
	Vitamin D	-0.711	-3.150, 1.727	0.554
	CD34+ cells	0.425	-1.298, 2.148	0.617
	Duration of the symptoms	-0.138	-0.965, 0.689	0.735
GCS	Age	0.015	-0.029, 0.060	0.486
	BMI	-0.007	-0.112, 0.097	0.889
	CRP	0.105	-0.169, 0.379	0.440
	ESR	0.015	-0.005, 0.036	0.131
	DAS28	7.214	3.013, 11.415	**0.002**
	SBP	0.030	-0.023, 0.083	0.260
	DBP	-0.019	-0.064, 0.027	0.409
	Vitamin D	-1.860	4.678, 0.959	0.187
	CD34+ cells	0.742	-1.249, 2.733	0.451

Duration of symptoms	0.072	-0.883, 1.028	0.878

Multiple linear regression analyses of GLS or GCS as dependent variable in RA patients. Variables found to be significant predictors are highlighted in bold.

Table 4: Multivariate regression analysis of PCA components on GLS and GCS in RA

		B	95% CI	*p*
GLS	Component 1	0.989	0.713, 1.265	**<0.0001**
	Component 2	-0.021	-0.304, 0.261	0.878
	Component 3	-0.262	-0.560, 0.036	0.083
	Component 4	0.118	-0.190, 0.426	0.442
GCS	Component 1	1.067	0.812, 1.323	**<0.0001**
	Component 2	-0.002	-0.263, 0.260	0.988
	Component 3	-0.175	-0.451, 0.100	0.205
	Component 4	0.160	-0.125, 0.445	0.261

Multiple linear regression analyses of GLS or GCS as dependent variable in RA patients. Variables found to be significant predictors are highlighted in bold.

Table 5: Multivariate regression analysis of CD34+ frequency in PsA and RA.

		B	95% CI	*p*
PsA	Age	-0.002	-0.010, 0.006	0.613
	BMI	0.009	-0.017, 0.035	0.491
	CRP	0.154	-0.045, 0.352	0.124
	ESR	-0.001	-0.010, 0.009	0.905
	DAS28	-0.152	-0.307, -0.001	**0.050**
	cIMT	-0.079	-0.674, 0.517	0.788
	PWV	0.002	-0.043, 0.048	0.920
	Vitamin D	0.019	0.005, 0.033	**0.009**
	Duration of symptoms	-0.003	-0.011, 0.006	0.512
RA	Age	0.001	-0.007, 0.008	0.911
	BMI	-0.003	-0.022, 0.016	0.734
	CRP	-0.015	-0.064, 0.033	0.520
	ESR	-0.001	-0.004, 0.003	0.520
	DAS28	0.011	-0.075, 0.097	0.792
	cIMT	-0.258	-0.983, 0.467	0.472
	PWV	-0.029	-0.065, 0.007	0.105
	Vitamin D	0.010	0.001, 0.019	**0.028**
	Duration of the symptoms	0.016	0.004, 0.028	**0.010**

Multiple linear regression analysis including CD34+ frequency as dependent variable. Variables found to be significant predictors are highlighted in bold.

HIGHLIGHTS

- Subclinical myocardial dysfunction is found in very early rheumatoid arthritis (RA) and psoriatic arthritis (PsA) with normal ejection fraction (EF)
- Inflammatory burden is associated with altered myocardial functionality in inflammatory joint diseases (IJD)
- Speckle-tracking echocardiography may be useful for CV risk stratification in IJD