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Cardiovascular involvement in psoriatic arthritis*

Coinvolgimento cardiovascolare nell'artrite psoriasica

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RIASSUNTO

La psoriasi è una malattia autoimmune infiammatoria cronica della cute geneticamente determinata che coinvolge il 2-3% della popolazione Caucasica. Diversi pazienti sviluppano una forma di artrite infiammatoria nota con il nome di artrite psoriasica (APs), la cui prevalenza non è ben definita. I pazienti affetti da APs hanno un tasso di mortalità superiore rispetto alla popolazione generale, e il rischio di mortalità correla con la severità della malattia al momento dell'esordio. La disfunzione endoteliale e l'aterosclerosi precoce sono state riportate in pazienti affetti da APs che non presentano fattori di rischio per eventi cardiovascolari (CV), tanto che gli Esperti ritengono che gli eventi CV rappresentino una causa di mortalità in questi pazienti così come descritto nei pazienti affetti da artrite reumatoide (AR). Diversi meccanismi correlati alla malattia potrebbero essere coinvolti nello sviluppo del danno vascolare precoce sia nell'APs che nell'AR, quali aumentata sintesi di mediatori dell'infiammazione (quali citochine, chemochine e molecole di adesione), anticorpi contro i componenti delle cellule endoteliali, alterazioni dei subsets dei T linfociti, polimorfismi genetici, iperomocisteinemia, stress ossidativo, riparazione delle alterazioni vascolari, e fattori iatrogeni. In un recente studio che ha coinvolto 22 pazienti affetti da APs senza alcun segno o sintomo di malattia CV, è stato osservato che la concentrazione della dimetil-arginina asimmetrica (ADMA) è significativamente aumentata nei pazienti affetti da APs rispetto ai controlli e che la riserva di flusso coronarica (RFC) è significativamente ridotta. Inoltre, nei pazienti con APs esiste una significativa correlazione tra la RFC e la concentrazione di ADMA nel plasma. La significativa correlazione tra la RFC ridotta e il livello di ADMA aumentato suggerisce che, come nei pazienti affetti da AR all'esordio, i pazienti affetti da APs soffrano di disfunzione endoteliale e di alterazione del microcircolo coronarico. In conclusione, l'APs in fase attiva rappresenta un fattore di rischio per eventi CV, ed è consigliabile che i pazienti affetti da APs siano sottoposti a screening per il coinvolgimento CV subclinico e per i suoi fattori di rischio.

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INTRODUCTION

Psoriatic arthritis (PsA) is usually considered a benign disease, but this idea has been challenged by some recent data. Sheeb et al. (1) found there was no significant difference in survival between patients with PsA and that observed in the general population. However, it has recently been confirmed that PsA is a chronic inflammatory arthritis and that, like rheumatoid arthritis (RA), it is associated with increased cardiovascular mortality (2-4). It has been reported that patients with severe psoriasis requiring hospitalization have a 50% increased risk of cardiovascular (CV) mortality (5), which seems to be associated with markers of disease activity, such as the prior use of medications, a high erythrocyte sedimentation rate (ESR) at presentation, and evidence of radiological alterations (3). Traditional CV risk factors are more com-

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mon in patients with PsA than in controls. A study from the integrated outcomes database, matched 3,066 PsA patients with other subjects in a ratio of 1 to 4 on the basis of age, gender, location and time in the database, and found that the prevalence ratios of peripheral cardiovascular disease (CVD) (1, 6), cardiovascular heart failure (CHF) (1, 5), atherosclerosis (1, 4), ischemic heart disease (1, 3), cerebrovascular disease (1, 3) and hypertension (1, 3) were all higher in the patients with PsA. They also found a higher prevalence of risk factors for coronary artery disease, such as hypertension (1, 3), diabetes (1, 5) and hyperlipidemia (1, 2) than in controls (6). Kimhi et al. (7) found that PsA patients have thicker common carotid arteries than healthy controls. This correlates with the duration of skin and joint disease, spine involvement and fibrinogen levels, as well as with conventional risk factors for atherosclerosis, such as age, body mass index (BMI), blood pressure, and serum glucose levels.

Increased incidences of diabetes mellitus and obesity have been reported in psoriatic patients (8). PsA and psoriasis patients have an altered atherogenic lipid profile (9, 10) mainly consisting of increased LDL sub-fractions and decreased HDL levels. Gonzalez-Gay et al. (11) found that there is a correlation between serum uric acid concentrations and subclinical atherosclerosis in PsA patients without any clinically evident CVD.

Gonzalez-Juanatey et al. (12, 13) found that patients with PsA without CV risk factors or clinically evident CVD show endothelial dysfunction and a high prevalence of macrovascular disease in the form of increased carotid artery intima media thickness (IMT) in comparison with ethnically matched controls.

Metabolic syndrome (MS) is made up of a group of traditional risk factors that includes abdominal obesity, atherogenic dyslipidemia, hypertension, and insulin resistance (14). The presence of MS is a strong predictor for type 2 diabetes mellitus, stroke, and CV, although controversy remains over whether metabolic syndrome is a distinct entity and whether the predictive value of the metabolic syndrome for CV risk is higher than that expected from individual risk factors alone (15).

Recently, a cross-sectional study (16) indicated that MS occurs more frequently in patients with PsA than in the general population. Among patients with RA, AS (ankylosing spondylitis), and PsA, PsA patients show the highest risk for the presence of atherosclerotic risk factors, in particular of obesity, impaired glucose tolerance, and hypertriglyceridemia, and hence of metabolic syndrome. Moreover, the use of anti-TNFα treatment was associated with a trend towards a lower prevalence of metabolic syndrome supporting the idea that persistent inflammation is an aggravating factor for atherosclerotic risk (16).

In conclusion, all of these findings demonstrate the potential association between PsA and atherosclerotic disease.

CYTOKINES AND PSORIATIC ARTHRITIS

Various disease-related mechanisms may be involved in the development of premature vascular damage in patients with PsA or RA, including an increased synthesis of pro-inflammatory mediators (such as cytokines, chemokines and adhesion molecules), autoantibodies against endothelial cell components, perturbations in T-cell subsets, genetic polymorphisms, hyperhomocysteinemia, oxidative stress, abnormal vascular repair, and iatrogenic factors (17-21).

Pro-inflammatory cytokines are important mediators of systemic and local inflammation, and the abundant expression of interleukin-1 (IL-1) and tumor necrosis factor-α (TNFα) has been found in psoriatic skin lesions and in the synovial tissue of patients with RA or PsA (22). The synovial infiltrate in both groups of patients is comparable in terms of the number of fibroblast-like synoviocytes and macrophages, but the number of T cells is considerably lower in the synovium of patients with PsA, and the number of their plasma cells also tends to be lower. TNFα, IL-1β, IL-6 and IL-18 expression is high in both cases (23, 24).

TNF is an inflammatory cytokine released by activated monocytes, macrophages and T lymphocytes that promotes the inflammatory responses involved in the pathogenesis of both RA and PsA (25). It also promotes dyslipidemia and insulin resistance, both of which are traditional risk factors for atherosclerosis; it up-regulates adhesion molecules, leading to the formation of fatty streaks and the start of atherosclerosis; and it is involved in inflammation leading to plaque rupture (26-28). It may also promote thrombophilia, thus encouraging thrombotic events.

In fact, Ingegnoli et al. (29, 30) showed increased levels of prothrombin fragment 1+2 (F1+2) and D-dimer, plasminogen activator inhibitor (PAI-1) antigen, PAI-1 activity and tissue-type plasminogen activator (t-PA) antigen in patients with RA compared to controls. Moreover, the same authors reported a reduction in fibrinolysis inhibition and coagulation biomarkers in RA patients after infliximab treatment, supporting the hypothesis that anti-TNF agents reduce the whole thrombotic risk in these patients not only due to cytokine inhibition but also due to its effects on coagulation (29, 30).

IL-6 is a pro-inflammatory cytokine that stimulates hepatocytes to synthesize acute phase response proteins, such as C-reactive protein (CRP) and fibrinogen (30). It may also contribute to atherosclerosis and arterial thrombosis by enhancing endothelial cell adhesiveness, activating the production of tissue factor, fibrinogen and factor VIII, by increasing platelet production and aggregation, and decreasing endogenous anticoagulant levels (31).

BIOLOGICAL THERAPY: PSORIATIC ARTHRITIS AND CV INVOLVEMENT

The introduction of the anti-TNFα agents infliximab, etanercept and adalimumab has dramatically improved the outcome of severe RA and also reduced the burden of CVD (32). There is compelling evidence that TNFα antagonists improve both axial and peripheral psoriatic arthropathies (33), and significantly inhibit radiological progression in a sustained manner. They also seem to reduce disease-related mortality (20).

Angel et al. (34) showed that anti-TNF agents reduce inflammatory activity and improve aortic stiffness in patients with inflammatory arthritis, thus supporting the hypothesis of a favorable anti-inflammatory effect on CV risk in PsA patients.

A double-blind, placebo-controlled study involving 127 patients with PsA showed that anti-TNF agents induce a significant reduction in concentrations of CRP, lipoprotein(a), and homocysteine, and an increase in the serum sex hormone-binding globulin, apolipoprotein (Apo) AI, Apo B, and triglycerides; however, the study did not confirm the cardioprotective effect of anti-TNF agents in this cohort of patients (35).

Tocilizumab is a recombinant humanized anti-IL6 receptor mAb that prevents interactions between IL-6 and the membrane-expressed receptor or its soluble counterpart, thus inhibiting IL-6 signal transduction (32). Its clinical efficacy has been assessed in adult patients with active moderate-to-severe RA, including those with an inadequate response to TNF antagonists, and the current data suggest that its tolerability profile is acceptable, infections being the most frequently reported adverse events. Although RA and PsA are clinically separate diseases of a different etiology, the similarities in the synovial infiltrate and increased pro-inflammatory cytokine production in PsA support the view that, in addition to TNFα blockade, targeted treatments against other pro-inflammatory cytokines such as IL-6 might be effective in PsA and co-morbidities such as CVD (36).

PLASMA ASYMMETRIC DIMETHYLARGININE (ADMA) CONCENTRATIONS AND CORONARY FLOW RESERVE

Plasma asymmetric dimethylarginine (ADMA), a major endogenous inhibitor

of nitric oxide synthase, is a newly discovered risk factor for endothelial dysfunction associated with enhanced atherosclerosis (37, 38).

It has been reported that ADMA is a predictor of cardiovascular risk (39), and increased plasma ADMA levels have been observed in patients with diseases associated with atherosclerosis, (40) such as hypercholesterolemia (41), hypertriglyceridemia (42), peripheral arterial disease (43), hypertension (44), type 2 diabetes mellitus (45), acute coronary syndromes (46, 47) and end-stage renal failure (48). We have recently found that plasma ADMA levels are significantly higher in patients with early rheumatoid arthritis (ERA), and that this has a statistically significant negative effect on coronary flow reserve (CFR), which is significantly reduced in ERA patients without any signs or symptoms of coronary artery disease (CAD) (49).

We previously showed that CFR is reduced early in patients with long-standing RA without any clinical evidence of heart disease, (50) and in a recent study of 22 PsA patients and 35 healthy controls with no history or current signs of CVD, we found that ADMA levels were significantly higher in the PsA patients (0.71±0.07 *vs* 0.48±0.07; p=0.00) who also had a significantly reduced CFR (2.86±0.70 *vs* 3.3±0.43; p<0.01) (51). Common carotid IMT was greater in the PsA patients, but the difference was not significant (0.64± 0.26 *vs* 0.62 ± 0.5 mm). There was a significant correlation between CFR and plasma ADMA levels in the PsA group (R=0.28; p<0.01), but no correlation between plasma ADMA levels and IMT (R=0.02; p=0.32), the Disease Activity Score 28 (DAS-28) (p=0.52) or the Psoriasis Area and Severity Index (p=0.98).

It has recently been demonstrated that CFR is a highly sensitive (>90%) diagnostic marker of CAD, and that a CFR of less than 2 accurately predicts the presence of severe (i.e. >70%) coronary stenosis (52). The significant correlation between the reduced CFR and increased ADMA levels in PsA patients may indicate endothelial dysfunction and impaired coronary microcirculation, as found in patients with early RA (49). Kimhi et al. (7) found that PsA patients have higher common carotid artery IMT values than healthy controls and the same results were also reported from a larger study (53). We also found this in our experience, although the difference was not statistically significant. This may have been due to the relatively small number of patients, but it could also indicate that CFR (a functional parameter) is a more sensitive marker of subclinical atherosclerosis than IMT. In a study of 20 patients treated for 18 months with DMARDs (10 with methotrexate and 10 with adalimumab), we found that both drugs significantly reduced DAS-28 (6.0±0.8 *vs* 2.0±0.7; p<0.0001) and improved CFR (2.4±0.2 *vs* 2.7±0.5; p<0.01), whereas the changes in common carotid IMT and plasma ADMA levels were not significant (54). In addition to their well-known anti-phlogistic effects, DMARDs improve coronary microcirculation without having any direct effect on IMT or ADMA, clinical markers of atherosclerosis in patients with RA and possibly in those with PsA (55, 56).

However, Tam et al. (57) in a pilot study showed that treatment with anti-TNF agents may determine a reduction in IMT in PsA patients, associated with improvement in inflammatory markers, but independent of changes in lipid profiles. Moreover, Mazlan (58) et al. reported a significant association between CV risk and positive IMT in PsA patients, although there was no association with disease activity, disease severity or DMARD therapy.

Finally, Di Minno, (59) in a study involving 224 patients with PsA (120 on TNF-α blockers and 104 on DMARDs), reported that IMT in PsA patients without CV risk was higher than in controls. Furthermore, they showed that treatment duration inversely predicted IMT in PsA patients on TNF blockers but not in those on DMARDs.

In conclusion, all these data indicate that active PsA is a risk factor for CVD. PsA patients should, therefore, be screened for subclinical forms of the disease and its risk factors, and an early treatment approach should be adopted.

RIASSUNTO

Psoriasis is a chronic, genetically determined and immunomediated inflammatory skin disease that affects 2-3% of the Caucasian population. A considerable proportion of these patients develop a form of inflammatory arthritis known as psoriatic arthritis (PsA), although the prevalence of this has not been well defined. Patients with PsA have a higher mortality rate than the general population and the risk of mortality is related to disease severity at the time of presentation. Endothelial dysfunction and early atherosclerosis have been found in patients with PsA without any cardiovascular disease (CVD) risk factors, and experts believe that CVD is one of the leading causes of death, as it is in patients with rheumatoid arthritis (RA). Various disease-related mechanisms may be involved in the development of premature vascular damage in both cases, including an increased synthesis of proinflammatory mediators (such as cytokines, chemokines and adhesion molecules), autoantibodies against endothelial cell components, perturbations in T-cell subsets, genetic polymorphisms, hyperhomocysteinemia, oxidative stress, abnormal vascular repair, and iatrogenic factors. In a recent study of 22 patients with PsA without any signs of CVD, we found that the plasma concentration of asymmetric dimethylarginine (ADMA) levels were significantly high and coronary flow reserve (CFR) was significantly reduced. Moreover, there was a significant correlation between CFR and plasma ADMA levels in the PsA group. The significant correlation between the reduced CRF and increased ADMA levels suggests that, like patients with early RA, PsA patients suffer from endothelial dysfunction and impaired coronary microcirculation. Active PsA is a risk factor for CVD, and so PsA patients should be screened for subclinical forms of the disease and its risk factors, and an early treatment approach should be adopted.

Parole chiave: artrite psoriasica; coinvolgimento cardiovascolare; dimetil-arginina asimmetrica; fattori di rischio.
Key words: *psoriatic arthritis; cardiovascular involvement; asymmetric dimethylarginine; risk factors.*

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