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Association of Severity of Osteoarthritis and Carotid Atherosclerosis in Patients with Metabolic Syndrome

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Abstract

Study Background: Increasing evidence in the literature suggests a link between osteoarthritis and atherosclerosis represented by the pro-inflammatory state, independently by concurrent factors such as the joint overload caused by obesity.

In this study we examined the role of metabolic syndrome, a cluster of cardiovascular risk factors with a significant pro-inflammatory background, on the severity of both carotid atherosclerosis and osteoarthritis.

Methods: We evaluated 68 patients (14 males, 54 females) with (mean±standard error) age and body mass index of 76.99±1.01 years and 27.63±0.62, respectively. The subjects were divided in two groups by the presence of metabolic syndrome (according to Adult Treatment Panel III criteria). Each patient received a score of severity for carotid atherosclerosis (by echo-doppler examination of supra-aortic arteries) and for osteoarthritis (by standard X-ray). The sites of osteoarthritis was divided in related or not related to weight overload.

Results: The body mass index of patients with (n.42) or without metabolic syndrome (n.26) were 28.94±0.84 and 25.87±0.77, respectively ($p<0.025$). The severity of carotid atherosclerosis were 1.59±0.17 and 0.82±0.18 in the patients with or without metabolic syndrome ($p<0.01$). The severity of osteoarthritis were 2.59±0.15 and 2.04±0.27 in the patients with or without metabolic syndrome ($p=0.06$). Metabolic syndrome was significantly related to severity score of carotid atherosclerosis and osteoarthritis ($r=0.932$ $p<0.01$ and $r=0.936$ $p<0.01$, respectively). Severity score of carotid atherosclerosis and osteoarthritis were significantly related ($r=0.895$ $p<0.05$).

Conclusion: In this preliminary study, we showed a link between severity of osteoarthritis and atherosclerosis in metabolic syndrome, pointing out the possibility of a common background belonging to the degenerative and inflammatory reactions involving both the cardiovascular and articular system.

Keywords: Atherosclerosis; Osteoarthritis; Metabolic syndrome

Abbreviations: ADAMTS: A Disintegrin and Metalloproteinase with Thrombospondin Motifs; ATPIII: Adult Treatment Panel III; BMI: Body Mass Index; CV Risk: Cardiovascular; CA: Carotid Atherosclerosis; FGF: Fibroblast Growth Factor; HDL: High Density Lipoprotein; IL: Interleukin; IMT: Intima-Media Thickness; M: Mean; MMP: Metalloproteinases; ANOVA: One-Way Analysis of Variance; OA: Osteoarthritis; A-OA: Associated Osteoarthritis; RANKL: Receptor Activator of Nuclear Factor Kappa-B Ligand; RA: Rheumatoid Arthritis; SE: Standard Error; TNF: Tumour Necrosis Factor

Introduction

It is well known that cardiovascular (CV) risk is significantly increased in patients with inflammatory rheumatic diseases. In fact, the incidence of myocardial infarction and CV pathologies is almost twice in rheumatoid arthritis (RA) than in controls [1]. In a recent large database in the United Kingdom (1.11 million of males and 1.26 million of females), the age and gender adjusted incidence of all-cause mortality and of major vascular events during almost 5 years of follow-up were high in patients with RA [2]. Both CV risk factors and inflammation markers are significantly associated with carotid intima-media thickness (IMT) and plaque in RA [3].

Recently, it has been pointed out that osteoarthritis (OA) is not a mere degenerative joint disease but a complex pathology that, beside the cartilage, involves the synovial membrane and the subchondral bone with a significant local inflammatory reaction [4]. Local pro-inflammatory cytokines (interleukin, IL-1 beta, IL-17, IL-18 and tumour necrosis factor, TNF-alpha) induce the cartilage damage, activating the catabolic mediators of cartilage degeneration by chondrocytes and macrophages, such as the metalloproteinases (in particular MMP-13) and aggrecanases ("a disintegrin and metalloproteinase with thrombospondin motifs" ADAMTS-4 and -5) [4].

The level of systemic inflammation in OA is lower than the level observed in the classical inflammatory arthritis (such as in RA), but, however, the local immune system activity is always higher than the activity observed in normal subjects.

Increasing evidence in the literature suggests that there is a link between OA and atherosclerosis represented by the pro-inflammatory state, independently by concurrent factors such as the joint overload caused by obesity.

In this study we examined the role of the metabolic syndrome, a cluster of CV risk factors with a significant pro-inflammatory background, on the severity of both carotid atherosclerosis and OA.

It is well known that the adipose tissue is not a passive energy-saving depot, but in particular the visceral adipose tissue in metabolic

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syndrome is a key pathogenic fat that releases substances acting on metabolism and inflammation (adipokines and cytokines). Examples of adipokines include adiponectin, leptin, and resistin and of inflammatory cytokines include the same TNF-alpha and IL-6 involved both in plaque formation (and resolution) and cartilage damage (and healing).

Materials and Methods

We evaluated 68 patients (14 males, 54 females) consequentially coming from our outpatients. The mean±standard error (m±SE) age and body mass index (BMI) were 76.99±1.01 years and 27.63±0.62, respectively.

The subjects were divided in two groups on the basis of the presence of the metabolic syndrome, evaluating abdominal circumference (in cm), systolic and diastolic blood pressure (mmHg), high density lipoprotein (HDL) cholesterol (mg/dl), triglycerides (mg/dl), glycaemia (mg/dl) (according to the diagnostic criteria of ATPIII, Adult Treatment Panel III) [5].

The carotid atherosclerosis (CA) was measured by echo-doppler examination of supra-aortic arteries, considering bilaterally three sites (the common carotid, the bifurcation and the internal carotid). A score of atherosclerosis (number of sites with presence of plaques) was assigned, ranging from 0 (no plaque) to 6 (three plaques bilaterally); a score of 0.5 was assigned when IMT was above the normal level, in absence of plaques [6].

The presence of OA was evaluated by standard X-ray. A score of severity of OA was assigned, using the Greenfield's Individual Disease Severity Index-IDS) [7]. The index grades each condition on a 0 to 4 scale on the basis of the following framework: 0=absence of disease; 1=asymptomatic disease; 2=symptomatic disease controlled by therapy; 3=symptomatic disease uncontrolled by therapy; 4=the worst possible severity of the disease.

We considered sites of OA related to weight overload: thoracic-lumbar-sacral vertebrae, hips, knees, ankles and feet. Sites of OA not related to weight overload were considered: cervical vertebrae, shoulders, elbows and hands. Associated OA was considered the OA with involvment of both sites (related and not related to weight overload).

The difference between the parameters in patients with or without metabolic syndrome were evaluated by the one-way analysis of variance (ANOVA). The relationship between the score of metabolic syndrome and the severity of OA and atherosclerosis was examined by the linear regression analysis. A $p<0.05$ was considered as significant.

Results

The patients with metabolic syndrome (n=42, 8 males and 34 females, age 76.6±1.3 years) presented a percentage of CA and OA of 61.9% and 83.7%, respectively. The patients without metabolic syndrome (n=26, 6 males and 20 females, age 77.6±1.7 years) showed a percentage of CA and OA of 46.1% and 73.1%, respectively (the differences of percentages between the two groups were not significant, n.s.).

The BMI of the patients with or without metabolic syndrome were 28.94±0.84 and 25.87±0.77, respectively ($p<0.025$). On the basis of the categorical scales, the severity of CA in the patients with or without metabolic syndrome were 1.59±0.17 and 0.82±0.18 ($p<0.01$). The severity of OA in the patients with or without metabolic syndrome were 2.59±0.15 and 2.04±0.27 ($p=0.06$).

In the patients with metabolic syndrome, the distribution of OA was the following: weight related=20%, not weight related=4%, associated OA=76%. In the patients without metabolic syndrome the distribution of OA was the following: weight related=44%, not weight related=6%, associated OA=50% (differences between distribution of OA was not significant). Even if the difference of BMI between the patients with or without metabolic syndrome was significant, the distribution of weight related OA was not increased in the patients with metabolic syndrome. It is noteworthy that these patients presented a trend towards a more diffuse (associated) OA than the patients without metabolic syndrome ($z=1.937$ $p=0.053$).

Metabolic syndrome was significantly related to the severity scores of CA and OA ($r=0.932$ $p<0.01$ and $r=0.936$ $p<0.01$, respectively) (Figure 1 and Figure 2). The severity scores of CA and OA were significantly related ($r=0.895$ $p<0.05$) (Figure 3).

There was a trend to increase the number of OA-affected sites (diffuse, associated OA) when the abdominal circumference raised ($r=0.152$ $p=0.06$).

No association was found between systolic and diastolic blood pressure, high density lipoprotein cholesterol, triglycerides or glycaemia and OA.

The age and gender distribution was not statistically different between the two groups and the results was not influenced by them or by any potential confounder.

Discussion

In the present preliminary study, we showed a link between severity of osteoarthritis and atherosclerosis in metabolic syndrome, pointing out the possibility of a common background belonging to the degenerative and inflammatory reactions involving both the cardiovascular and articular system.

In fact, the pro-inflammatory milieu and the oxidative stress are mechanisms involved in both (atherosclerotic and articular) lesions [4].

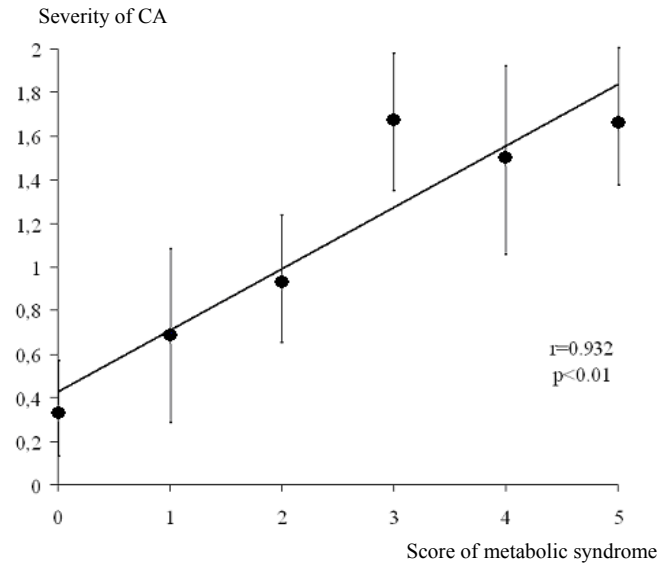

Figure 1: Relationship between the score of metabolic syndrome and the severity of carotid atherosclerosis (CA) (n=68).

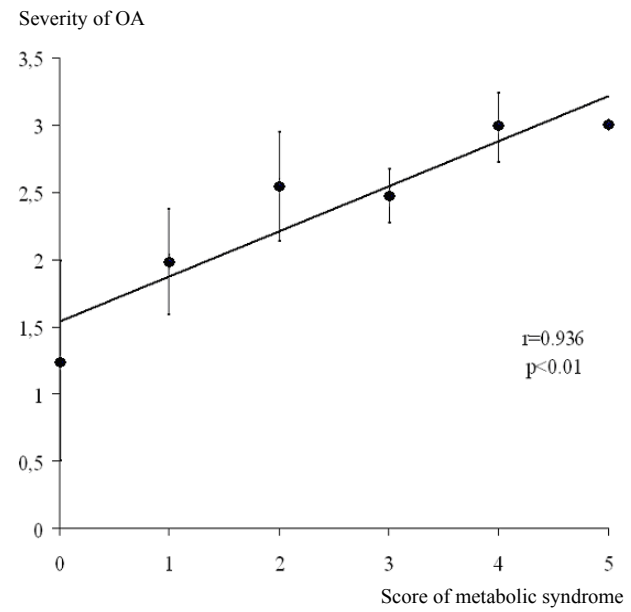

Figure 2: Relationship between the score of metabolic syndrome and the severity of osteoarthritis (OA) (n=68).

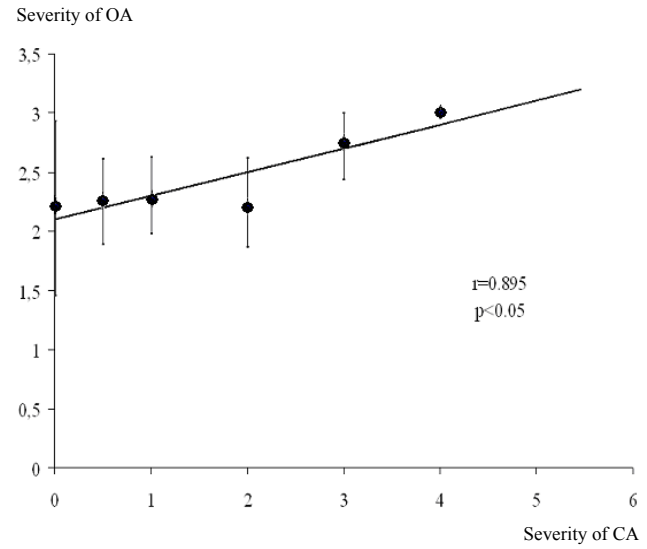

Figure 3: Relationship between the severity of carotid atherosclerosis (CA) and of osteoarthritis (OA) (n=68).

In a population study in Iceland (The AGES Reykjavik Study), the severity of the atherosclerosis carotid plaques and of the coronary calcifications resulted significantly associated in females with hand OA (a site not related to weight overload), with an odds ratio of 1.25 for the plaques and 1.42 for the calcifications [8]. The severity of atherosclerosis and osteoarthritis were significantly related.

Looking for a common factor in both pathologies, it has been pointed out that the metabolic syndrome, in its wider role of cluster of CV risk factors, can increase the pro-inflammatory state, influencing the severity of articular pathology.

In this context, the presence of abdominal visceral adipose tissue can induce a modulation of mediators with significant actions on skeleton (leptin, resistin, visfatin, vitamin D, RANKL/RANK, Wnt, Dickkopf, FGF-18 and low-density lipoprotein receptor-related protein, IL-6, TNF-alpha) [4].

Our results suggest that, with increasing abdominal circumference and the appearance of the metabolic syndrome, the patients showed a trend towards a more diffuse kind of OA, with an associated involvement of weight related and not related sites.

The articular lesions may therefore share a similar pattern of biochemical and inflammatory mechanisms with the atherosclerotic lesions, induced by the metabolic syndrome.

From a unifying point of view for these two pathologies, the metabolic syndrome (and its pro-inflammatory state) is assuming an increasing role, that has to be evaluated in order to put in evidence the patients with an increased risk of developing both CV diseases and inflammatory-mediated pathologies such as OA. Further observations are necessary in order to describe how the severity of the atherosclerotic disease may contribute to the progression of OA, or vice-versa, in a bidirectional relationship.

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