# Letters to the Editors

## Lack of association between adipokines and ghrelin and carotid intima-media thickness in patients with severe rheumatoid arthritis

Sirs,
Accelerated atherosclerosis and increased incidence of cardiovascular (CV) events are implicated in the elevated mortality observed in patients with rheumatoid arthritis (RA) (1). Besides classic CV risk factors (2) and the genetic component (3-5), chronic inflammation plays a pivotal role in the development of atherosclerosis in RA (2, 3). Intima-media thickness (IMT) of the common carotid artery, determined by high resolution B-mode ultrasound, is a useful non-invasive surrogate marker of macrovascular atherosclerosis disease in RA (6). The presence of subclinical atherosclerosis, manifested by increased values of the carotid IMT in RA patients without clinically evident CV disease at the time of the carotid ultrasonography study is consistent with the high rate of silent ischaemic heart disease and sudden cardiac death observed in RA patients (6). In this regard, we have recently reported that carotid IMT is a good predictor of CV events in the extended follow-up of patients with RA (6).
The adipose tissue has a major endocrine function secreting several hormones (7, 8). These various protein signals have been given the collective name of adipokines. These bioactive molecules influence metabolic processes like insulin resistance, glucose and lipid metabolism (7). They also have immunologic and inflammatory actions and seem to be involved in the pathogenesis of autoimmune and rheumatic diseases (7, 8). We previously investigated whether inflammation, adiposity, insulin resistance or some other characteristics associated with the development of metabolic syndrome were potential determinants of circulating adipokines resistin, adiponectin, leptin, and visfatin concentrations in a group of RA patients on periodical treatment with the TNF-α blocker-infliximab due to severe disease (9-12). We also found that TNF-α blockade in patients with severe RA resulted in increased circulating ghrelin concentrations and that the latter was associated with decreased endothelial activation (13).
Briefly, patients included in these studies met the 1987 American College of Rheumatology criteria for RA and were recruited from Hospital Xeral-Calde, Lugo, Northwest Spain (9-13). In this regard, information on the characteristics of this Caucasian population was previously reported (3). They formed part of an ongoing study on CV disease in RA (14). Each of the RA patients had been switched from traditional disease modifying antirheumatic drugs (DMARDs) to anti-TNF-α-infliximab treatment because

**Table I.** Correlation of variables with carotid artery intima-media thickness in a series of patients with rheumatoid arthritis. All the patients had severe disease, refractory to conventional disease modifying anti-rheumatic drugs, undergoing periodical treatment with infliximab therapy.

| Variable | Total correlation (p-value)* | Partial correlation (p-value)** |
|---|---|---|
| Adiponectin, n = 29 | 0.3946 (0.04) | 0.0249 (0.91) |
| Resistin, n = 29 | -0.3509 (0.07) | -0.2371 (0.29) |
| Leptin, n = 29 | 0.1859 (0.35) | -0.0923 (0.68) |
| Ghrelin, n = 29 | -0.1808 (0.37) | -0.2690 (0.23) |
| Visfatin, n = 14 | 0.1280 (0.66) | 0.3390 (0.41) |

*Pearson correlation coefficient; Spearman correlation coefficient for visfatin.
**Partial correlation and p-values adjusting for gender, age at study, disease duration, rheumatoid factor, and classic cardiovascular risk factors.

of severe and active disease (Disease Activity Score-28 [DAS28] >5.1) (15, 16). In all patients, treatment with a DMARD had been initiated when a diagnosis of RA was made. Prior to anti-TNF-α therapy, patients were required to have been treated with at least two DMARDs including chloroquine or hydroxychloroquine, sulphasalazine, gold, methotrexate (at least 15 mg/week), leflunomide, and cyclosporine A (3 mg/kg/day). Infliximab therapy (initial dose of 3 mg/kg) was administered intravenously at 0, 2, 6 weeks and subsequently every 8 weeks. However, in some patients, because of disease severity, the dose was increased to 5 mg/kg and, if deemed necessary, the interval between infliximab infusions was shortened to 6 weeks.
All patients had received treatment with both non-steroidal antiinflammatory agents and low doses of prednisone (generally 5 mg bid) immediately after disease diagnosis. At the time of the study, each patient was on infliximab 3 or 5 mg/kg given at 6 or 8 weekly intervals and methotrexate 15–25 mg weekly with or without chloroquine 250 mg day or hydroxychloroquine 200 mg/day, prednisone 2.5–7.5 mg daily and a non-steroidal antiinflammatory agent (naproxen 500–1000 mg or diclofenac 50-100 mg daily). The blood pressure was below 140/90 mmHg in each patient at the time of the study. However, some patients were required to be on treatment with antihypertensive agents or statins. Patients with diabetes were excluded.
In the present study we aimed to determine whether serum levels of resistin, adiponectin, leptin, visfatin and ghrelin might influence the degree of severity of carotid artery IMT in patients with severe RA, refractory to conventional DMARDs, undergoing periodical treatment with infliximab following the traditional treatment schedule described above.
Carotid IMT was determined by ultrasonography as previously reported (6). Determination of adipokines and ghrelin (performed in the fasting state) was reported elsewhere (9-13).
Correlation analyses are shown in Table I. Although the overall (total) correlation between adiponectin and resistin and carotid

IMT seemed to be significant or marginally significant (p=0.04 and p=0.07 respectively), such a correlation remained out of the range of significance when partial correlation was adjusted for gender, age at the time of study, disease duration, rheumatoid factor status, and classic CV risk factors (Table I).
Although adipocytokines have been demonstrated to exert a key role in the interface between obesity, inflammation, insulin resistance, and atherosclerosis in the general population, little is known about their contribution in RA. In this regard, adipocytokines have not been demonstrated to represent a significant risk factor for indirect measures of organic arterial wall atherosclerotic damage, as assessed by carotid IMT in the present cohort of long-standing active RA patients on infliximab treatment, or by coronary artery calcification evaluation, as shown in a recent work by Rho et al. (17).
As shown in the present study, single determinations of adipokines or ghrelin levels in long-standing RA patients with severe disease showed no significant correlation with the carotid artery IMT. Therefore, a determination of these bioactive molecules cannot replace the use of the ultrasonography evaluation of the carotid IMT as predictor of CV events in patients with RA without clinically evident CV disease.
In conclusion, our present data do not support a role of serum levels of adipokines or ghrelin as predictors of subclinical atherosclerosis. They seem to confirm the marginal role played by these molecules in the pathogenesis of subclinical atherosclerosis in RA.
Additional studies to further determine the mechanisms involved in inflammation and accelerated atherosclerosis in RA are warranted.

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*Competing interests: none declared.*

## References

1. GONZALEZ-GAY MA, GONZALEZ-JUANATEY C, MARTIN J: Rheumatoid arthritis: a disease associated with accelerated atherogenesis. *Semin Arthritis Rheum* 2005; 35: 8-17.
2. DESSEIN PH, JOFFE BI, VELLER MG *et al.*: Traditional and nontraditional cardiovascular risk factors are associated with atherosclerosis in rheumatoid arthritis. *J Rheumatol* 2005; 32: 435-42.
3. GONZALEZ-GAY MA, GONZALEZ-JUANATEY C, LOPEZ-DIAZ MJ *et al.*: HLA-DRB1 and persistent chronic inflammation contribute to cardiovascular events and cardiovascular mortality in patients with rheumatoid arthritis. *Arthritis Rheum* 2007; 57: 125-32.
4. GONZALEZ-GAY MA, LLORCA J, PALOMINO-MORALES R, GOMEZ-ACEBO I, GONZALEZ-JUANATEY C, MARTIN J: Influence of nitric oxide synthase gene polymorphisms on the risk of cardiovascular events in rheumatoid arthritis. *Clin Exp Rheumatol* 2009; 27: 116-9.
5. PALOMINO-MORALES R, GONZALEZ-JUANATEY C, VAZQUEZ-RODRIGUEZ TR *et al.*: Interleukin-6 gene -174 promoter polymorphism is associated with endothelial dysfunction but not with disease susceptibility in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2009; 27: 964-70.
6. GONZALEZ-JUANATEY C, LLORCA J, MARTIN J, GONZALEZ-GAY MA: Carotid intima-media thickness predicts the development of cardiovascular events in patients with rheumatoid arthritis. *Semin Arthritis Rheum* 2009; 38: 366-71.
7. LAGO F, DIEGUEZ C, GOMEZ-REINO J, GUALILLO O: The emerging role of adipokines as mediators of inflammation and immune responses. *Cytokine Growth Factor Rev* 2007; 18: 313-25.
8. HÄRLE P, SARZI-PUTTINI P, CUTOLO M, STRAUB RH: No change of serum levels of leptin and adiponectin during anti-tumour necrosis factor antibody treatment with adalimumab in patients with rheumatoid arthritis. *Ann Rheum Dis* 2006; 65: 970-1.
9. GONZALEZ-GAY MA, GARCIA-UNZUETA MT, GONZALEZ-JUANATEY C *et al.*: Anti-TNF-alpha therapy modulates resistin in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2008; 26: 311-6.
10. GONZALEZ-GAY MA, LLORCA J, GARCIA-UNZUETA MT *et al.*: High-grade inflammation, circulating adiponectin concentrations and cardiovascular risk factors in severe rheumatoid arthritis. *Clin Exp Rheumatol* 2008; 26: 596-603.
11. GONZALEZ-GAY MA, GARCIA-UNZUETA MT, BERJA A *et al.*: Anti-TNF-alpha therapy does not modulate leptin in patients with severe rheumatoid arthritis. *Clin Exp Rheumatol* 2009; 27: 222-8.
12. GONZALEZ-GAY MA, VAZQUEZ-RODRIGUEZ TR, GARCIA-UNZUETA MT *et al.*: Visfatin is not associated with inflammation or metabolic syndrome in patients with severe rheumatoid arthritis undergoing anti-TNF-alpha therapy. *Clin Exp Rheumatol* 2010; 28: 56-62.
13. GONZALEZ-GAY MA, GARCIA-UNZUETA MT, BERJA A *et al.*: Anti-tumour necrosis factor alpha therapy modulates ghrelin in patients with severe rheumatoid arthritis. *Ann Rheum Dis* 2008; 67: 1644-6.
14. GONZALEZ-JUANATEY C, LLORCA J, GARCIA-PORRUA C, MARTIN J, GONZALEZ-GAY MA: Effect of anti-tumor necrosis factor alpha therapy on the progression of subclinical atherosclerosis in severe rheumatoid arthritis. *Arthritis Rheum* 2006; 55: 150-3.
15. GONZALEZ-GAY MA, GARCIA-UNZUETA MT, DE MATIAS JM *et al.*: Influence of anti-TNF-alpha infliximab therapy on adhesion molecules associated with atherogenesis in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2006; 24: 373-9.
16. VAN GESTEL AM, STUCKI G: Evaluation of established rheumatoid arthritis. *Baillieres Best Pract Res Clin Rheumatol* 1999; 13: 629-44.
17. RHO YH, CHUNG CP, SOLUS JF *et al.*: Adipocytokines, insulin resistance, and coronary atherosclerosis in rheumatoid arthritis. *Arthritis Rheum* 2010; 62: 1259-64.