Serum adipokines in osteoarthritis; comparison with controls and relationship with local parameters of synovial inflammation and cartilage damage

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S U M M A R Y

Objective: Adipose tissue is an endocrine tissue releasing adipokines suggested to be involved in the pathogenesis of osteoarthritis (OA). Nevertheless, their relative contribution and exact mechanisms are still ambiguous. The aim of this study is to compare serum adipokine levels between end-stage knee OA patients and controls and to relate these serum levels to local parameters of cartilage damage and synovial inflammation.

Methods: Serum was collected from 172 severe knee OA patients, shortly before total knee replacement (TKR) surgery and from 132 controls without radiographic knee OA [Kellgren & Lawrence (K&L) = 0]. Serum adiponectin, leptin, and resistin levels were measured by enzyme-linked immunosorbent assay (ELISA). Cartilage and synovial tissue were collected at TKR surgery and assessed for cartilage degeneration and synovial inflammation by histochemistry and biochemical analyses.

Results: The adipokine levels were all distinctly higher in OA patients as compared to controls. Especially adiponectin and leptin were associated with female gender (stand beta = 0.239 and 0.467, respectively, P < 0.001) and body mass index (BMI) (stand beta = 0.189 and 0.396, respectively, P < 0.001). No associations between serum levels of adipokines and cartilage damage (histochemistry, proteoglycan content) were found whereas weak but positive associations with synovial inflammation were found [adiponectin and interleukin-1β (IL-1β), stand beta = 0.172, P = 0.02; resistin and histology, stand beta = 0.183, P = 0.034, adjusted for demographics].

Conclusion: This study suggests an important involvement of adipokines in OA patients considering their high serum levels compared to controls. Associations of systemic adipokines with local synovial tissue inflammation were found, although not represented by similar relations with cartilage damage, suggesting that adipokines are of relevance in the inflammatory component of OA.

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Introduction

Obesity has not only been associated with an increased risk of osteoarthritis (OA) in weight-bearing joints such as hips and knees1,2, but also in non-weight bearing joints such as those of the hand3,4. Therefore, besides biomechanical factors mediating this relationship between OA and obesity2,5, also metabolic factors have been suggested to be involved2,5–10.

White adipose tissue is considered to be a metabolically active endocrine organ that secretes inflammatory cytokines [e.g., interleukin-1β (IL-1β) and tumour necrosis factor-α (TNFα)] and adipokines, such as adiponectin, leptin, and resistin6. Besides their established role in obesity, metabolic disorders, and atherosclerosis, the potential role of adipokines in OA pathogenesis is at present an important subject of study10–12. Based on these studies, OA has been designated by some authors as a metabolic syndrome disorder13. However, the exact role and relevance of adipokines in OA are still unclear12.

Adiponectin is a protein secreted by adipocytes and plays a role in glucose and lipid homeostasis14. Circulating levels of adiponectin are low in obese individuals and increase with weight loss15. The role of adiponectin in OA is controversial: there is conflicting
evidence on whether adiponectin has a protective or rather aggravating role in OA. For example, decreased adiponectin levels in both plasma and synovial fluid have been associated with increased OA severity indicating that it may play a protective role in OA\textsuperscript{16}. Likewise, adiponectin has been shown to up-regulate tissue inhibitor of metalloproteinase (TIMP)-2 and down-regulate IL-1β-induced matrix metalloproteinase (MMP)-13 messenger RNA (mRNA) and protein levels\textsuperscript{17}. Accordingly, higher levels of adiponectin have been associated with lower Kellgren & Lawrence (K&L) grades in knee OA\textsuperscript{16} and a lower risk for progression in hand OA\textsuperscript{18}. In contrast, also proinflammatory tissue destructive effects of adiponectin have been demonstrated on chondrocytes and synovial fibroblasts, inducing key mediators of cartilage degeneration such as nitric oxide (NO), IL-6, IL-8, monocyte chemo-attractant protein (MCP)-1, MMP-3 and MMP-9\textsuperscript{19–21}. Moreover, it has been demonstrated that serum levels of adiponectin were increased in erosive OA as compared to non-erosive OA\textsuperscript{22}.

Leptin is a protein thought to play a key role in the regulation of body weight by suppressing food intake and stimulating energy expenditure by acting on the hypothalamus\textsuperscript{23,24}. Mice with a mutation in the gene for leptin (ob/ob mice) or the leptin receptor (db/db mice) have an obese phenotype\textsuperscript{25}. Osteophytes, synovium, cartilage, inflammatory cells, and the infrapatellar fat pad can secrete leptin\textsuperscript{26–28}. Leptin is also produced by immune cells upon stimulation with IL-1, IL-6 and lipopolysaccharide (LPS)\textsuperscript{28}. Evidence is increasing that leptin has a proinflammatory role in the pathophysiology of OA\textsuperscript{12}. Higher leptin levels produced by human osteoarthritis cartilage as compared to normal cartilage have been observed\textsuperscript{26,29,30}. Proteolytic enzymes like MMPs and cytokine proteases at both gene and protein level are increased by leptin\textsuperscript{12}. Leptin appears to be involved in the pathologic changes of all tissues involved in the process of OA\textsuperscript{12}. Nevertheless, it is still unclear what the exact mechanism of leptin in the development of OA is as leptin may act dually, inducing both catabolic\textsuperscript{26,31} and anabolic\textsuperscript{effects on articular cartilage.}

Resistin is a dimeric protein produced by adipocytes and macrophages and induces insulin resistance in mice\textsuperscript{28,32}. Levels are (partly) dependent on leptin activity as in leptin activity deficient mouse models (ob/ob and db/db) serum resistin levels are raised\textsuperscript{32}. In humans, resistin appears to have a more important role in inflammatory processes than it has in insulin resistance, as serum levels of resistin correlate better with subclinical inflammation than with insulin resistance\textsuperscript{33}. Expression of resistin mRNA in human peripheral blood mononuclear cells (PBMCs) is increased by the proinflammatory cytokines IL-1, IL-6 and TNF\textsuperscript{34}. Resistin can be detected locally in the synovium of inflamed joints in both rheumatoid arthritis (RA) and OA\textsuperscript{37,33,35}. Nevertheless, the exact role of resistin in OA is unknown. Two studies showed no association between serum resistin levels and progression of hand OA\textsuperscript{18,22}.

The role of adipokines in OA has thus far been investigated in mice models, in \textit{in vitro} studies using human joint tissues and fluids, or systemic levels have been described in relation to joint characteristics by use of indirect markers such as radiographic joint damage. A relation between systemic serum adipokines and actual local joint tissue changes in OA has never been investigated. In the present study, along with serum concentrations of adiponectin, leptin, and resistin, parameters of synovial tissue inflammation and cartilage degeneration were measured in patients with end-stage knee OA undergoing total knee replacement (TKR) surgery. It was anticipated that systemic adipokine levels would be related to synovial inflammation and with that to cartilage damage.

### Material and methods

#### Patient characteristics

Patients at the Sint Franciscus Gasthuis in Rotterdam, The Netherlands, with severe knee OA who were eligible for TKR surgery, were included. At time of TKR surgery, blood, cartilage tissue, and synovial tissue were collected\textsuperscript{46}. Cartilage and synovial tissue were kept in phosphate buffered saline for a maximum of 4 h during transport to the University Medical Centre Utrecht where tissues were further processed under laminar flow conditions. Controls, from whom blood was collected, had recent complaints of pain and/or stiffness of the knee and/or hip related to very early OA, but had no signs of radiological OA as defined by a K&L score of 0 on radiographs of both knees and both hips. These controls were matched for sex.

Demographic characteristics and Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores of the OA patients and controls are shown in Table 1. The study was conducted according to the declaration of Helsinki and received approval from the ethics committee of the hospital. Written informed consent was obtained from all patients before inclusion.

### Serum adipokines in OA and controls

From both cohorts, blood samples were centrifuged, serum was separated, and aliquots stored at \textendash 80 °C. Serum concentrations of adiponectin, leptin, and resistin were measured by enzyme-linked immunosorbent assay (ELISA) (BioVendor, Modrice, Czech Republic). Samples were prepared at appropriate dilutions and all samples were assessed according to the manufacturer’s instructions. Internal control samples were used as supplied by the

#### Table 1

<table>
<thead>
<tr>
<th>Characteristics of subjects</th>
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<tr>
<td><strong>OA</strong> (n = 172)</td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Women/Men</td>
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<tr>
<td>BMI (kg/m\textsuperscript{2})</td>
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<tr>
<td>K&amp;L</td>
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<tr>
<td>WOMAC pain</td>
</tr>
<tr>
<td>WOMAC stiffness</td>
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<tr>
<td>WOMAC function</td>
</tr>
<tr>
<td>Adiponectin (µg/ml)</td>
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<tr>
<td>Leptin (µg/ml)</td>
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<tr>
<td>Resistin (µg/ml)</td>
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Data shown are means (SD) [range].

WOMAC values are on a scale from 0 to 100, 0 meaning no pain, joint stiffness and limitations in function, and 100 meaning maximum pain, joint stiffness and limitations in function.

Significant differences of OA subjects compared to controls are indicated by an asterisk.
manufacturer. Quality controls demonstrated adequate measurements for all patients for all three adipokines. Intra- and inter-plate coefficients of variation [CV%, standard deviation (SD)/mean*100%] as determined from triplicate assessment of a single standard sample in each assay plate were as follows: adiponectin: intra-assay CV = 11.41%, inter-assay CV = 18.44%; leptin: intra-assay CV = 5.0%, inter-assay CV = 37.3%; resistin: intra-assay CV = 17.0%, inter-assay CV = 5.9%.

Parameters of cartilage damage in OA patients

For histochemistry, four cartilage tissue samples (range 5–10 mg, accuracy 0.1 mg) were taken randomly from the cartilage still present on the joint. These samples were fixed in 4% phosphate buffered formalin with 2% sucrose. After embedding in paraffin wax, 5 μm sections were sliced and stained with Safranin-O fast green iron haematoxylin according to standard procedures. Cartilage damage was scored using the modified Mankin score.

For biochemical, 20 randomly taken cartilage samples of each donor were used for biochemical analysis of glycosaminoglycan (GAG) content as a measure of proteoglycan content according to standard procedures. In short, after digestion of the cartilage samples with papain, GAGs were precipitated and stained with Alcian Blue. Blue staining was quantified photometrically by change in absorbance at 620 nm. Chondroitin sulphate (C4383; Sigma) was used as reference. Values for proteoglycan content were normalized to the wet weight of the cartilage sample and expressed as milligrams of GAG per gram wet weight of cartilage tissue (mg/g).

Parameters of OA synovial tissue inflammation

For histochemistry, three synovial tissue samples (range 50–150 mg, accuracy 0.1 mg) obtained at TKR surgery from the suprapatellar region of the knee joint were fixed and embedded and sections stained with haematoxylin-eosin. Synovial tissue inflammation was graded using the modified Goldenberg and Cohen score. In brief, the severity of synovitis was graded from 0 to 10 by adding the scores of three histological criteria, namely synovial lining cell hyperplasia (0–2), villous hyperplasia (0–3), and cellular infiltration by (perivascular) mononuclear and polymorphonuclear leukocytes (0–5). For assessing the overall grade the three specimens of each knee were considered as a unit.

To measure ex vivo proinflammatory cytokine production IL-1β and TNFα production by the OA synovial tissue were determined. Synovial tissue samples obtained from the suprapatellar region of the knee joint each weighing 50–150 mg were cultured individually for 3 days in 4 ml culture medium (Dulbecco’s modified eagle medium (DMEM) supplemented with 2 mM glutamine, 100 IU/ml penicillin, 100 μg/ml streptomycin sulphate, 0.085 mM ascorbic acid and 10% heat inactivated pooled human AB+ serum at 37°C, 5% CO2). In the culture supernatants IL-1β and TNFα were determined by ELISA ( Biosource) according to manufacturer’s instructions and expressed as pg/ml per mg synovial tissue.

Statistical analysis

For histochemistry, two observers blinded to the source of the samples scored all samples and the average scores of observers were taken as representative score of each sample. In a few cases consensus was sought when observers scored >1 point difference. The average of all multiple tissue samples (n = 4 for cartilage histology, n = 20 for cartilage GAG content, n = 3 for synovial tissue histology, and n = 3 for cytokine production) of each donor was taken as representative value for each donor. Data are subsequently expressed as the mean (±SD) of donors with n representing the number of donors, unless stated otherwise. Continuous variables were evaluated using Student’s t tests, ordinal variables by Chi-square tests. Linear regression analysis was used to compare adipokine levels between patients and controls, and to study the effect of local joint characteristics on serum adipokine levels. Skewed variables (IL-1β, TNFα, and adipokines) were logarithmically transformed so that normal distribution was obtained. To facilitate direct comparison between regression coefficients of variables and models, coefficients are expressed as standardized betas. Standardized betas represent the number of SDs that the outcome will change as a result of one SD change in the predictor and are therefore independent of the units of measurement of the variables and can vary between −1 and 1. Unadjusted standardized betas are identical to Pearson’s correlation coefficients. In all analyses P < 0.05 was considered statistically significant. All statistical analyses were performed using Statistical package for the social sciences (SPSS) (standard version 15.0, SPSS, Chicago, IL, USA).

Results

Patient characteristics

The characteristics of the 172 OA patients and the 132 controls are shown in Table I. Controls were younger than OA patients (P < 0.001). In addition, the BMI was statistically significantly higher in OA patients than in controls (P < 0.001). By selection, the radiological joint damage (P < 0.001) was higher in the OA patients and gender distribution was similar for both groups. All serum adipokine levels were evidently higher in the OA population compared to the control population, independent of age and BMI differences (Table II).

The joints of the OA patients showed on average the typical characteristics of severe OA. Besides the radiological joint damage, also cartilage histology demonstrated moderate damage with a modified Mankin score of 4.7 ± 1.0 (range 0–11), typical of such an end-stage OA population. This was also reflected in the GAG content of the cartilage (24.4 ± 5.6 mg/g wet weight), clearly lower than that of healthy cartilage. Additionally, a mild inflammatory synovial

| Table II Relationship between serum adipokines and the state of disease, adjusted for demographic variables |
|-----------------|-----------------|-----------------|
|                 | Adiponectin*    | Leptin*         | Resistin*       |
|                 | Linear regression coefficient | P      | Linear regression coefficient | P      | Linear regression coefficient | P      |
| State (OA)      | 0.378           | -0.001          | 0.539           | <0.001          | 0.977           | <0.001          |
| Age (years)     | 0.224           | -0.001          | 0.045           | 0.198           | -0.062          | 0.014           |
| Gender (female) | 0.239           | -0.001          | 0.467           | <0.001          | -0.002          | 0.914           |
| BMI (kg/m²)     | -0.189          | -0.001          | 0.396           | <0.001          | 0.031           | 0.131           |

Bold values represent P < 0.05 that were considered statistically significant.

*Logarithmic transformation was performed to obtain normal distribution.
activity was observed. The synovial tissue was graded as moderately inflamed with a modified Goldenberg and Cohen score of 5.0 ± 1.2 (range 0–10), and IL-1β and TNFα production of 11.7 ± 23.2 pg/ml and 2.3 ± 3.0 pg/ml per mg synovial tissue, respectively.

Relationship between the different adipokine levels and BMI, gender, and age in end-stage knee OA patients

Adiponectin showed a negative correlation with BMI ($R = -0.222$, $P = 0.004$), leptin a positive correlation ($R = 0.599$, $P < 0.001$), and resistin demonstrated no clear BMI dependency. On average, all serum adipokine levels were higher in women than in men ($P < 0.001$ for adiponectin and leptin and no statistical significance, $P = 0.161$, for resistin) [See Fig. 1(A)]. Adiponectin showed an evidently positive correlation with age ($R = 0.276$, $P < 0.001$), leptin levels showed no relation with age, and resistin showed a minor negative relation with age ($R = -0.222$, $P = 0.007$).

The control population showed comparable relations with BMI, gender, and age [see Fig. 1(B)] but clearly less profound, probably due to the limited variation in adipokine levels (limited window; see Table I). For leptin, the positive correlation with BMI was statistically significant ($R = 0.555$, $P < 0.001$) and the higher levels in women compared to men was statistically significant ($P < 0.001$). Resistin showed borderline significantly higher levels in women than in men ($P = 0.072$). All other relations were not statistically significant.

Relationship between serum adipokines and local parameters of cartilage tissue degeneration

Unsurprisingly, linear regression analysis showed no association between any parameter of cartilage degeneration and serum adipokine levels. Separate analysis of men and women as well as adjustment for age, gender and BMI did also not demonstrate any statistically significant association (all $P > 0.1$, data not shown).

Relationship between serum adipokines and local parameters of synovial tissue inflammation

In contrast with the aforementioned absence of associations between adipokines and cartilage damage, local synovial tissue inflammation was (marginally) related to serum adipokine levels (Table III). Resistin levels were statistically significantly associated with histologically determined grade of synovial tissue inflammation ($P = 0.026$, $R^2 = 0.038$). After adjustment for age, gender, and BMI, an association between IL-1β production and adiponectin became apparent ($P = 0.020$, $R^2 = 0.285$). Resistin levels remained statistically significantly associated with histological grade of synovial tissue inflammation ($P = 0.034$, $R^2 = 0.101$).

Discussion

Clearly higher serum levels of all three adipokines in end-stage knee OA patients were found compared to controls without any radiographic sign of cartilage damage, independent of BMI, age, and gender. In the OA population clear relations with age were found for adiponectin and resistin and with BMI for adiponectin and leptin. No associations were found between serum adipokine levels and cartilage damage whereas a marginally positive association with synovial inflammation was found.

Large studies on multiple simultaneously assessed serum adipokine levels in knee OA patients as compared to controls are scarce. Most studies are only small, focus on single adipokines, and/or focus on hand OA or cardiovascular/metabolic disease. Therefore our study provides new data on many aspects of serum adipokine levels and demographics in knee OA patients. Potential differences between female and male knee OA patients for serum adipokine levels have not been described thus far, except for one study in 30 knee OA patients demonstrating statistically significantly different plasma leptin levels between female and male patients in univariate correlation analysis, without specifying which gender showed the highest levels, while adiponectin levels were similar between both genders. Our study demonstrates higher adiponectin and leptin levels in female compared to male knee OA patients, not attributable to differences in BMI and age. Also in healthy subjects, adiponectin and leptin levels have been reported to be higher in women than in men. These differences could not be completely explained by antropomorphometric differences of body fat distribution between genders.

The influence of BMI on serum adipokine levels observed in our end-stage OA cohort is conform literature, adiponectin negatively correlating with BMI, and leptin positively correlating with BMI in healthy subjects. Apparently, these relations persist in end-stage knee OA. Most studies show either no or a positive correlation between resistin and BMI in various patient categories. To the best of our knowledge, this has never been demonstrated in knee OA subjects as ours, which shows no correlation between resistin and BMI.

Our study with exclusively end-stage OA patients demonstrates evidently increased serum adipokine levels in knee OA patients compared to controls. A small study by Honsawek et al. showed increased plasma adiponectin levels in K&L grade 2 OA subjects compared to controls, but decreased levels in K&L grade 4 OA subjects. Choe et al. showed increased serum resistin levels in radiographic hand OA patients compared to non-radiographic hand OA patients and controls. To the best of our knowledge, our study is the first one that demonstrates increased serum leptin and resistin levels in knee OA patients compared to controls.

The control subjects in our study had pain and/or stiffness of knee(s) and/or hip(s), but did not have grossly visible radiographic knee OA (i.e., K&L grade 0). Nevertheless, more subtle individual radiographic OA features as determined by Knee Image Digital Analysis could be observed in these subjects. Irrespective, using these subjects as (disease) controls might have led to underestimation, but never overestimation, of the difference between adipokine levels of end-stage knee OA patients and controls.

Direct comparison between the patient and control population was hampered by differences in age and BMI between them, since age and BMI were associated with serum adipokine levels. However, the observed differences persisted after adjustment for these differences in multiple linear regression analysis.

This study is the first to relate serum adipokine levels directly to local synovial tissue inflammation of the OA joint albeit marginally. Although the three adipokines generally showed positive correlations with synovial inflammation, relations were not very robust. Adiponectin showed a statistically significant positive correlation with synovial IL-1β production, thereby suggesting a relation with proinflammatory features in OA. Resistin was also positively associated with parameters of synovial inflammation. Accordingly, resistin levels have been shown to be elevated in RA patients and show a correlation with inflammation and joint destruction in RA. It has been stated that the infrapatellar fat pad shows an inflammatory phenotype with its cytokine and adipokine production, and therefore contributes to the pathophysiological changes in OA. In general it is to be considered that systemic (serum) and local adipokine levels are involved in local synovial tissue inflammation in OA although relations are not strong.

Based on available literature on the involvement of adipokines in OA pathogenesis, it was anticipated that (part of the) adipokines would (also) relate to cartilage damage in the OA joints. However, in
Fig. 1. Relationship between serum adipokine levels and BMI, gender and age in end-stage OA patients (A) and controls (B). Statistics are as obtained from Pearson’s correlation analysis.
this cohort no association with actual cartilage damage, quantified by histology and proteoglycan levels of the cartilage, was observed. This apparently contrasts with findings of others. For example, leptin levels were shown to be positively correlated with hip joint space narrowing grade in randomly selected subjects aged 52–78 years. Pathogenetic differences between knee and hip OA as well as differences in OA severity, end-stage compared to mild to moderate disease, might be explanatory for the discrepancy with our results. In knee OA patients, plasma and synovial fluid adiponectin levels showed negative correlations with knee OA K&L grade. This relation only persisted for synovial fluid levels after adjusting for demographic variables. The latter fits the absence of a correlation between serum adipokine levels and actual cartilage damage in the present study.

A major difference between all previously performed studies and our study is that most of them quantify cartilage damage radiographically, while we quantified cartilage damage histologically and biochemically. Although the evaluation of the cartilage itself instead of surrogate markers is more direct, it might also be more sensitive to the noise that results from all complex dynamics that continuously take place within the joint. On the other hand, recent observations suggested a clear relation between actual cartilage damage and features of radiographic joint damage including K&L grading. Furthermore, our local cartilage parameters might be biased because evaluation of articular cartilage did not take into account denuded bone areas. Reassuring in this respect is that also macroscopically, while we quantified cartilage damage histologically and proteoglycan levels of the cartilage, was observed. This apparently contrasts with findings of others. For example, leptin levels were shown to be positively correlated with hip joint space narrowing grade in randomly selected subjects aged 52–78 years. Pathogenetic differences between knee and hip OA as well as differences in OA severity, end-stage compared to mild to moderate disease, might be explanatory for the discrepancy with our results. In knee OA patients, plasma and synovial fluid adiponectin levels showed negative correlations with knee OA K&L grade. This relation only persisted for synovial fluid levels after adjusting for demographic variables. The latter fits the absence of a correlation between serum adipokine levels and actual cartilage damage in the present study.

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In conclusion this study supports involvement of adipokines in knee OA. Serum adipokine concentrations were evidently increased in knee OA patients as compared to controls, independent of age and BMI. Some relations between systemic adipokines and local synovial tissue inflammation were found although not represented by similar relations with actual cartilage damage, implying adipokines are especially of relevance in the inflammatory component of the disease, and cartilage degeneration to be dominated by other, presumably intrinsic, processes.

Author contributions

All authors contributed to the conception and design of the study, the drafting and revision of the manuscript. And all authors approved the final submission.

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Conflict of interest

JWJ Bijlsma received a consultancy fee from Pfizer Inc (<10,000 US$). All other authors have no conflicts of interest to declare.

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References


53. Pepene CE. Evidence for serum visfatin but not adiponectin or resistin as an independent predictor of endothelial dysfunction in polycystic ovary syndrome. Clin Endocrinol (Oxf) 2011.


