LETTER TO THE EDITORS

OBESITY, INFLAMMATION, VASCULAR REACTIVITY, AND CARDIOCIRCULATORY EVENTS

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INTRODUCTION

In the interesting clinical article by Bahia et al., obese subjects with metabolic syndrome are prospectively compared with lean controls. The addressed question is highly relevant and up-to-date, namely, the relationship between obesity with metabolic syndrome, inflammation, and secretion of adipokines on one hand, and insulin resistance, endothelial function, and vascular reactivity on the other.

They found out that the obese population displayed impaired vascular reactivity, and the 2 measured adipokines, adiponectin and resistin, correlated with 1 vascular reactivity variable each. Inflammation was prominent in this cohort (elevated C-reactive protein/CRP), but comparatively few correlations were assigned to this measurement; just 1 adipokine (resistin) and 1 component of the coagulation cascade, plasminogen activator inhibitor-1 (PAI-1), seemed to be involved.

One may thus speculate that if a link exists between CRP and vascular reactivity, it is an indirect one, via resistin, but as no such result is shown, statistical significance was probably weak or absent. But why should one insist on this detail?

Inflammation, insulin resistance, hyperlipidemia, and hypercoagulability surely bring to mind advanced obesity with metabolic syndrome. Deranged endothelium-dependent and independent vasodilation, along with an increased risk for future cardiocirculatory events, fit very well in this picture. Within this context, the authors feel confident in attributing much prognostic importance to insulin resistance and to abnormal resistin levels.

It is known, however, that chronic microinflammation, not necessarily associated with insulin resistance and all severe neuroendocrine and metabolic dysfunctions typical of advanced obesity, is a much larger problem involved in a vast array of diseases, from renal failure to rheumatoid arthritis and other autoimmune diseases, and from chronic obstructive pulmonary disease and hypopituitary adults to the elderly in general. Although inappropriate adipokine expression may not be a prominent feature in these circumstances, cardiovascular death is more probable all the same. Is there a chance that inflammation is a more important culprit?

CLINICAL EXPERIENCE

In a prospective, placebo-controlled double-blind investigation with 40 morbidly obese subjects, of which 13 were preliminarily evaluated and 24 have completed the protocol, either suffering or not from comorbidities, we were recently able to demonstrate that CRP, along with serum amyloid A (SAA), another acute phase protein, directly correlated with initial blood glucose, serum lipids, and white blood cell count (Table 1). All of these markers have been associated with increased mortality in different population groups.

<table>
<thead>
<tr>
<th>Initial variable</th>
<th>CRP</th>
<th>SAA</th>
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<tr>
<td>Blood glucose</td>
<td>r= 0.889 ***</td>
<td>r= 0.889 ***</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>r= 0.422 **</td>
<td>r= 0.316 *</td>
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<tr>
<td>Triglycerides</td>
<td>r= 0.466 **</td>
<td>r= 0.871 ***</td>
</tr>
<tr>
<td>HDL</td>
<td>r= - 0.375 *</td>
<td></td>
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<tr>
<td>LDL</td>
<td>r= 0.502 **</td>
<td></td>
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<tr>
<td>White blood cell count</td>
<td>r= 0.612 ***</td>
<td>r= 0.428 **</td>
</tr>
</tbody>
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(*) p<0.05; (**) p<0.02; (***) p<0.01.

Another point that deserves to be raised is treatment and its impact on the reported aberrations. What are the therapeutic priorities, and which derangement is more amenable to control?

Weight loss is not only imperative, it is theoretically the best prescription. If excess adipose tissue is eliminated, adipokines, including leptin, TNF-alpha, and IL-6, will not be overexpressed; therefore, alleviation of
sulphur resistance and dyslipidemia will follow, and inflammation and hypercoagulability should regress, all at the same time. Nevertheless, this is easier said than done, and tangible results are not achieved in the short term, but only after substantial time and effort. Furthermore, not all physiological disturbances and comorbidities fully respond to weight reduction. That is why secondary prevention of cardiovascular events often comprises pharmacologic intervention.

Aiming to get a better insight into the pathophysiology of microinflammation, and to test the hypothesis that nutrients may be safe, inexpensive, and effective, in the same protocol we introduced flaxseed flour (Farinha de linhaça dourada, Linolive, CISBRA, São Paulo) into the diet. This is a rich source of the vegetable omega-3 fatty acid alpha-linolenic acid (ALA) (30 g of supplement/day corresponded to 5 g of ALA), which is subsequently converted by the liver into eicosapentanoic acid (EPA), and it is recommended by the American Heart Association for patients without coronary disease. Within 2 weeks, alleviation of inflammation according to both markers, CRP and SAA, was clearly achieved.

It is worth mentioning that although resistin was not monitored in the study, no change in body weight or tests for glucose, insulin, leptin, or lipids were detected. It is therefore unlikely that insulin resistance influenced any results.

REFERENCES


FINAL CONSIDERATIONS

Reduced long-term morbidity and mortality would be the final proof that one is following the correct pathophysiological path. Experience with ALA is relatively recent, but marine omega-3 fatty acids, which were introduced decades ago, fulfill this requirement. They diminish coronary artery disease, fatal and nonfatal myocardial infarction, sudden cardiac death, and all-cause mortality. Indeed, protection against sudden death after myocardial infarction can be achieved with supplementation for as little as 3 months.

Of course, causes of cardiovascular morbidity and mortality can hardly be encompassed by a single trigger or key mechanism. Antiplatelet action, angiotensin inhibition, and lipid lowering may be advantageous, and it is recognized that intake of ALA by itself, besides being anti-inflammatory, shifts the polyunsaturated fatty acid metabolic pathway to EPA, thus favoring the formation of products with a predominant anti-aggregating and vasorelaxing action. The importance of stabilization of vulnerable atherosclerotic plaques, progression of atherosclerosis, hemostatic activity, and vascular inflammation as well as the potential influence of omega-3 fatty acids have been recently debated as well.

Still, there are reasons to believe that the role of inflammation in cardiovascular morbidity and mortality should be more emphasized, both in obesity/metabolic syndrome and in multiple other illnesses. By the same token, anti-inflammatory maneuvers should be attempted in this setting.