Optimal Treatments for the Metabolic Syndrome

To the Editor:

We read with interest the review of Blaschke et al1 dealing with obesity and the interrelated disorders of the metabolic syndrome as forerunners of cardiovascular and diabetes and cardiovascular disease. To date, chronic diseases represent a huge proportion of human illness, as cardiovascular diseases, various forms of cancer, and diabetes combine to make up nearly 70% of all deaths in the U.S.2 Obesity is supposed to be one main risk factor underlying these conditions. Lifestyle changes, such as unhealthy diets and a lack of physical activity, have contributed to a worldwide increase in the prevalence of obesity and the metabolic syndrome.3 Accordingly, low consumption of fruit and vegetables, together with physical inactivity, are now among the top 10 causes of mortality in developed countries.4 Abdominal obesity is the body fat parameter most closely associated with the metabolic syndrome and cardiovascular risk.5,6

Lifestyle interventions are the initial therapies recommended for treatment of visceral obesity and the metabolic syndrome.7 This recommendation, however, seems to have been built up exclusively on the assumption that, being key elements in the treatment of all components of the syndrome when they occur in isolation, lifestyle interventions hold the promise to be also an effective treatment for the metabolic syndrome as a whole. The first goal of whatever therapy is the resolution of the disease, where possible. In particular, this may be accomplished by reducing the amount of visceral fat or disconnecting obesity from the metabolic syndrome: in theory, both strategies would lead to a reduced burden of diabetes and cardiovascular disease.

There are some recent studies dealing specifically with the effect of interventions on the resolution of the metabolic syndrome. These studies8–13 were randomized controlled trials with a placebo/control group, a follow-up longer than 6 months, and absence of frank diabetes in participants. Three studies8,10–12 were based on lifestyle interventions and 4 studies11–13 on drugs, with a total of 3369 subjects, 1399 on lifestyle changes and 1970 on drugs. The Diabetes Prevention Program (DPP) addressed the effect of both lifestyle changes and metformin, and therefore the placebo group was counted twice. The follow-up ranged from 6 to 38 months. The results are shown in the Table. The first study was published in 20044:1180 overweight subjects with the metabolic syndrome after a 2-year lifestyle program focusing mainly on a Mediterranean-style diet there was a 48% net reduction in the prevalence of the syndrome. In the participants in the DPP9 who had impaired glucose tolerance at baseline, 18% of the placebo group and 38% of the lifestyle group no longer had the syndrome at 3 years. The Dietary Approach to Stop Hypertension (DASH) diet used in the Iranian study10 is quite similar to a Mediterranean-style diet. Rimonabant is a cannabinoid-1 receptor blocker which has been shown promising in reducing body weight in obesity.11,12 Besides reducing insulin resistance, rosiglitazone improves inflammation and endothelial dysfunction.1 The weighed mean resolution of the syndrome was 24.4% for lifestyle changes and 14.25% for drugs. Excluding the negative results obtained with metformin, the weighed mean resolution for drugs rose to 26.9%, not different from that obtained with lifestyle changes. In most studies, resolution of the syndrome was dependent on reduction in waist circumference and weight loss,9–12 in others it was independent of weight changes.8,13

To date, both intensive lifestyle interventions and some drugs (rimonabant and rosiglitazone) may reduce the prevalence of the metabolic syndrome in about one fourth of patients. However, we agree with Blaschke et al to achieving long-term resolution of the metabolic syndrome is a difficult and weight reduction drugs have not been particularly effective for treatment of obesity. The search for more effective and better-tolerated drugs for the control of obesity and the metabolic syndrome will continue. In the meantime, lifestyle modifications may be a good companion of drugs for reducing the metabolic and cardiovascular burden of visceral obesity and the metabolic syndrome.

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Letter to the Editor

<table>
<thead>
<tr>
<th>Protocol</th>
<th>No.</th>
<th>Follow-Up, Months</th>
<th>Resolution (%) Active/Placebo</th>
<th>Net P Resolution/Value</th>
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</thead>
<tbody>
<tr>
<td>Lifestyle</td>
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<td></td>
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<td></td>
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<tr>
<td>Mediterranean diet</td>
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<td>24</td>
<td>67/19</td>
<td>48/&lt;0.001</td>
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<td>DPP</td>
<td>549/592</td>
<td>38</td>
<td>38/18</td>
<td>20/0.002</td>
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<td>DASH diet</td>
<td>38/40</td>
<td>6</td>
<td>35/20</td>
<td>35/&lt;0.02</td>
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<tr>
<td>Drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Rimonabant</td>
<td>228/108</td>
<td>12</td>
<td>54/21</td>
<td>33/&lt;0.001</td>
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<tr>
<td>Rimonabant</td>
<td>187/185</td>
<td>12</td>
<td>47/25</td>
<td>22/&lt;0.001</td>
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<td>Metformin</td>
<td>570/592</td>
<td>38</td>
<td>23/18</td>
<td>5/NS</td>
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<td>Rosiglitazone</td>
<td>50/50</td>
<td>12</td>
<td>40/10</td>
<td>30/&lt;0.001</td>
</tr>
</tbody>
</table>

DDP indicates Diabetes Prevention Program; DASH, Dietary Approach to Stop Hypertension. P value represents the reported level of significance of active treatment vs placebo.
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