diet alone [1]. In patients in remission, progressive hyperglycaemia precedes, and is a strong risk factor for subsequent relapse [2]. More recently, short-term studies have shown that glucotoxicity, but not lipotoxicity, is involved in the occurrence of β-cell dysfunction and abnormal muscle insulin signalling [3]. Thus, both insulin secretion defect and insulin resistance may be involved in relapse.

The case we have described shows that the insulin resistance normally associated with pregnancy was not sufficient to trigger metabolic decompensation in our patient. This suggests that, despite the severe initial presentation, recovery of β-cell function was near-normal, or at least able to counteract insulin resistance. Since glucotoxicity is a major determinant of the insulin secretion defect observed in ketosis-prone type 2 diabetes, maintenance of normal glucose control is crucial to avoid relapse of metabolic decompensation. In this respect, monotherapy with metformin, which is not associated with the risk of hyperglycaemia, should be used during the remission phase in patients who have ketosis-prone type 2 diabetes.

Inclusion of C-reactive protein in the identification of metabolically healthy but obese (MHO) individuals

**Prise en compte de la CRP pour identifier les sujets obèses dépourvus d’anomalie métabolique**

**To the Editor:**

There has been considerable interest recently in the establishment of clinical criteria to identify individuals who are potentially at risk for metabolic and cardiovascular complications. For example, much attention has been paid to the establishment of criteria to identify individuals who have the metabolic syndrome [1]. This clustering of the risky phenotypes (such as central body fat, hyperglycaemia and dyslipidaemia) in which insulin resistance may play a central role could predispose individuals to an increased risk of cardiovascular disease and type 2 diabetes [1].

Interestingly, a unique subset of obese individuals has been described in the literature that appears to be ‘protected’ from the development of metabolic disturbances associated with obesity [2]. These individuals—termed ‘metabolically healthy, but obese’ (MHO)—despite having large quantities of fat mass exhibit a healthy metabolic profile, including remarkably high levels of insulin sensitivity, a favourable lipid and inflammatory profile, and no signs of hypertension. Evidence suggests that MHO individuals may account for as much as 20–30% of the obese population [2]. This is a striking finding that underscores the need to identify these individuals using simple clinical markers.

Recognition of MHO patients is important because the absence of metabolic complications could influence their prognosis and treatment. We recently proposed simple clinical markers that could identify MHO individuals [3]. It should be noted that these criteria have recently been duplicated by an independent research team, thereby confirming that they are appropriate for identifying a specific subgroup of the obese population [4]. In that study, the authors showed that these individuals displayed a more favourable metabolic and inflammatory state than ‘at-risk’ individuals.

In addition, C-reactive protein (CRP) has been suggested for the identification of the metabolic syndrome [5]. The findings of Cook et al. [6] further showed that CRP may be an important marker for clinical use. Moreover, we reported that MHO individuals (identified using the hyperinsulinaemic–euglycaemic clamp) have 92% lower CRP levels than those ‘at risk’ [2]. Therefore, we considered it timely to attempt to redefine the simple clinical metabolic criteria that identify MHO individuals.

The proposed selection of MHO clinical markers is based on those previously described [3], except that CRP is included as a clinical marker for the identification of MHO individuals, and total cholesterol is excluded as it is highly correlated with LDL cholesterol. Based on the review by Bassuk et al. [7], which showed that CRP levels above 3 mg/L significantly increased the risk of cardiovascular disease, we suggest that the cut-off point for this new marker be less than or equal to 3 mg/L. Furthermore, based on the recent study by Karelis et al. [2], we now suggest the new defining level for homoeostasis model assessment (HOMA)
of less than or equal to 2.7. Pooling criteria from these studies adds scientific rigour and clinical relevance to our attempt to establish criteria for the identification of MHO individuals. The previous suggestion that four out of the five criteria need to be met to make a diagnosis of an MHO individual remains the same (Table 1). This is similar to the characterization of the metabolic syndrome used by the Adult Treatment Panel (ATP) III, in which three out of five criteria had to be met to make the diagnosis of the metabolic syndrome [1]. We realize that the presentation of a redefining set of criteria is open to criticism, given that even the metabolic syndrome criteria proposed more than 20 years ago are still widely debated.

Our laboratory results in obese postmenopausal women identified 32 MHO individuals out of a possible 139 subjects (23%) who met the criteria for these metabolic markers. Those 32 MHO women have an average age of 57.1 ± 4.5 years, a body mass index score of 31.5 ± 4.4 and percentage body fat of 46.6 ± 4.5. Patients meeting this profile could have a lower risk for cardiovascular disease and type 2 diabetes. In support of this hypothesis, a recent longitudinal study reported that the protective metabolic profile observed in MHO subjects persisted over time, and translated into lower incidences of type 2 diabetes and cardiovascular disease [8]. It should be noted that LDL-cholesterol values in the MHO group (2.9 ± 0.8 mmol/L) were higher than the proposed defining level (less than or equal to 2.6 mmol/L). This is explained by the fact that we opted to have four out of the five criteria met for a diagnosis of MHO individuals, and several MHO subjects met the other criteria, but not the one for LDL cholesterol.

We believe these markers may be clinically useful. It is important to educate healthcare professionals and physicians regarding the different needs of subsets of obese individuals. The identification of the MHO individual in a clinical setting could have important implications for therapeutic medical decision-making. The tendency to treat obese individuals with a ‘one-size-fits-all’ approach may be counterproductive in the MHO individual.

### Table 1

<table>
<thead>
<tr>
<th>Metabolic markers</th>
<th>Defining level</th>
<th>MHO (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOMA index</td>
<td>≤ 2.7</td>
<td>2.5 ± 1.0</td>
</tr>
<tr>
<td>hs-C-reactive protein (mg/L)</td>
<td>≤ 3.0</td>
<td>1.6 ± 1.0</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>≤ 1.7</td>
<td>1.2 ± 0.4</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>≤ 2.6</td>
<td>2.9 ± 0.8</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>≥ 1.3</td>
<td>1.6 ± 0.3</td>
</tr>
</tbody>
</table>

Values are expressed as means ± S.D. When four out of the five criteria are met, a diagnosis of the MHO individual may be made.

### Acknowledgments

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### References