C-peptide and chronic complications in patients with type-2 diabetes and the metabolic syndrome

Thomas Mavrakanas¹,², Claire Frachebois¹, Arezki Soualah¹, Fadhela Aloui¹, Ingrid Julier¹, Dominique Bastide¹

¹. Department of Medicine 1, Hospital of Alès, F-30100 Alès, France
². Laboratory of Pharmacology A, Medical School, Aristotle University, Thessaloniki, Greece

Correspondence:
Thomas Mavrakanas, 61 rue Kifisias, 54248, Thessaloniki, Greece.
thomas_mavrakanas@yahoo.fr

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Summary

Introduction > We investigated the relation between C-peptide levels and the prevalence of diabetic complications in patients with type 2 diabetes and the metabolic syndrome.

Methods > This study includes all patients with diabetes and treated only with oral hypoglycemic agents who were admitted to our department in 2006. The chronic complications of diabetes (vascular disease, retinopathy, nephropathy, neuropathy) were evaluated.

Results > The 77 patients with type 2 diabetes and treated only with oral hypoglycemic agents were divided in two groups, with and without the metabolic syndrome. The two groups did not differ in glycemic control, blood pressure levels, or duration of diabetes. CRP levels were higher in patients with the metabolic syndrome (p = 0.03), and nephropathy was more common (70%, compared with 33%). Similar, C-peptide levels were higher in patients with the metabolic syndrome: 3.12 ± 1.36 compared with 1.82 ± 1.25 (p < 0.001). In patients with the metabolic syndrome, C-peptide levels did not differ in patients with or without diabetic complications (3.01 ± 1.16, compared with 3.96 ± 2.55, p = 0.51). Similarly, C-peptide levels in patients without the metabolic syndrome did not differ according to the presence of complications of diabetes (2.25 ± 1.21 versus 1.36 ± 1.16, p = 0.07). However, C-peptide

Résumé

Le peptide C et les complications chroniques du patient diabétique de type 2 avec syndrome métabolique

Introduction > Nous avons examiné le lien éventuel entre les taux du peptide C et la prévalence des complications chroniques du patient diabétique de type 2 qui est porteur aussi d’un syndrome métabolique.


Résultats > Soixante-dix-sept patients diabétiques de type 2 traités par des antidiabétiques oraux ont été repartis en 2 groupes selon la présence (groupe A) ou l’absence (groupe B) du syndrome métabolique. Il n’existait pas de différence entre les 2 groupes en ce qui concerne l’équilibre glycémique, la pression artérielle ou la durée du diabète. Les taux de la CRP étaient élevés chez les patients avec syndrome métabolique (p = 0.03). La néphropathie était plus fréquente dans le groupe A (70 %) que le groupe B (33 %). Les taux du peptide C étaient élevés dans le groupe A : 3,12 ± 1,36 comparés avec le groupe B : 1,82 ± 1,25 (p < 0,001). Aucune relation n’a été identifiée entre les taux du peptide C dans le groupe...
levels were higher in patients with diabetes and the metabolic syndrome who had either nephropathy or vascular disease, compared with those with those complications but without the metabolic syndrome \((p = 0.01)\). CRP levels did not correlate with C-peptide levels in any patient group.

**Discussion** > Higher C-peptide levels were associated with metabolic syndrome in patients with type 2 diabetes and in diabetes patients who also had nephropathy and vascular disease.

C-peptide, as the peptide connecting the \(\beta\)-chain and the \(\alpha\)-chain in the proinsulin molecule, plays a role in insulin synthesis \([1,2]\). In clinical practice, its concentration provides an indirect measure of the insulin secretory reserve \([3]\). The relation between C-peptide levels and the microvascular and macrovascular complications of type 2 diabetes is unclear. Some studies find that residual insulin secretion has a protective effect against these complications, while others do not. Lower C-peptide levels have been associated with the presence of retinopathy \([4]\), with the progression of diabetic microangiopathies (such as retinopathy and nephropathy) \([5]\), with increasing albuminuria, and with the duration of diabetes \([6]\). On the other hand, higher C-peptide concentrations have been associated with parasympathetic neuropathy \([7]\), coronary artery disease, peripheral vascular disease, and autonomic neuropathy \([8]\). Still other studies report no relation between C-peptide levels and sensorial neuropathy, nephropathy, or retinopathy \([8–10]\).

**What is already known**

The relation between C-peptide levels and the microvascular and macrovascular complications in type 2 diabetes is still unclear: some studies find that residual insulin secretion has a protective effect, whereas others do not. C-peptide levels have been associated with the components of the metabolic syndrome in patients with diabetes.

**What this article adds**

Higher C-peptide levels are associated with nephropathy and with vascular disease in patients with diabetes and the metabolic syndrome. C-peptide levels have been associated with the individual components of the metabolic syndrome in diabetic patients. In patients with type-2 diabetes mellitus, elevated serum levels of C-peptide are associated with body mass index (BMI), elevated serum triglycerides, low levels of high density lipoprotein cholesterol (HDL-C), and hypertension \([5,11,12]\). Elevated serum C-peptide levels are also reported to be a clinically important marker of the cardiovascular risk associated with the metabolic syndrome \([13]\). However, the relation between C-peptide levels, the prevalence of diabetic complications in patients with type 2 diabetes, and the metabolic syndrome has not yet been investigated. The aim of our study was to investigate these potential relations.

**Methods**

This study included all patients with diabetes admitted in our unit in 2006, but excluded patients treated with insulin, because it interferes with the endogenous insulin secretion in patients with type 2 diabetes \([14]\).

The same nurse measured height and weight of all patients, who wore light clothing and no shoes. Blood pressure was measured in the right arm with an electronic device, while the patient was in sitting position after 10 minutes of rest. Fasting total cholesterol, HDL-C, and triglycerides were measured for all patients by enzymatic assay, glycosylated hemoglobin (HbA1c) by immunochemistry, microalbuminuria by nephelometry, C-peptide by chemiluminescence, and high-sensitivity C-reactive protein (hsCRP) by turbidimetry. The automated analyzers Immulite 2000 (Siemens Healthcare Diagnostics Inc.) and Dimension RxL (Dade Behring Inc.) were used to perform those measurements.

Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Blood pressure was reported as the average of two consecutive determinations. Hypertension was defined as a systolic/diastolic blood pressure of 140/90 mmHg or higher or current antihypertensive
C-peptide and chronic complications in patients with type-2 diabetes and the metabolic syndrome

Patients were systematically screened for the chronic complications of diabetes. An ophthalmologist examined patients for funduscopy through dilated pupils to diagnose retinopathy. Nephropathy was defined by the presence of an albumin excretion rate (AER) higher than 30 mg/24 h (microalbuminuria). Vascular disease was defined by a diagnosis of either coronary or peripheral artery disease, and coronary artery disease by a history of myocardial infarction, angina pectoris, coronary artery bypass surgery, or coronary angioplasty, or by electrocardiographic modifications typical of ischemia. Peripheral artery disease was defined by ischemic foot ulcers, gangrene or amputation for ischemic gangrene, vascular surgery, transient ischemic attacks, stroke, intermittent claudication, absent foot pulse, or abnormal brachial and posterior tibial blood pressure, measured by Doppler techniques. Neuropathy was defined by at least two abnormalities among signs, symptoms, and clinical examination (including a monofilament sensory test).

The metabolic syndrome was defined by at least two of the following conditions: elevated blood pressure (>130/85) or current antihypertensive treatment, elevated plasma triglycerides (>1.5 g/L); low HDL-C (<0.4 g/L for men and <0.5 g/L for women), and BMI >30 kg/m² or waist circumference >102 cm for men and >88 cm for women.

Patients were divided in two groups, according to whether or not they had the metabolic syndrome. Informed consent was obtained from all subjects.

Results are reported as means ± standard deviations or percentages. The Shapiro-Wilk and Kolmogorov-Smirnov tests were used to assess normality. Confidence intervals (95%) were calculated for C-peptide with the t-distribution. The two-sample t test was used to compare the C-peptide levels of both groups and to obtain their p-values. The normal distribution was used to approximate the binomial distribution to calculate 95% confidence intervals (95% CI) for the prevalence of the chronic diabetic complications. Pearson’s correlation coefficient r was used to measure the association between C-peptide and CRP levels, and the p value was calculated. Statistical significance was defined by a p value of 0.05 [15].

Results

During 2006, our unit admitted 114 patients with diabetes, 106 of whom had type 2 diabetes, 77 of them treated only with oral hypoglycemic agents, and 29 with insulin alone or insulin and oral agents. Of the 77 patients with type 2 diabetes and treated with oral hypoglycemic agents, 47 (61%) were diagnosed with the metabolic syndrome. Table I reports the characteristics of the 77 specifically studied here, overall and divided into two groups according to the presence of metabolic syndrome. The two groups did not differ in glycemic control, blood pressure levels, or duration of diabetes. CRP levels were higher (and elevated) in the group with metabolic syndrome.

The prevalence of chronic complications of diabetes according to whether patients have (group A) or do not have (group B) the metabolic syndrome is shown in Table II. Nephropathy was more common in patients with metabolic syndrome but there is no difference between the two groups for other complications. Table III reports the C-peptide levels overall, according to metabolic syndrome, and according to the presence of each complication. C-peptide levels were higher overall in the patients with the metabolic syndrome and in those with metabolic syndrome and without vascular disease, or retinopathy or neuropathy. Finally, C-peptide levels were also elevated in patients with the metabolic syndrome who had nephropathy or vascular disease compared to those without the metabolic syndrome and with those complications. C-reactive protein levels did not correlate with those of C-peptide in the group with (r = 0.15, p = 0.50) or without (r = 0.13, p = 0.63) metabolic syndrome.
C-peptide levels in patients with (group A) or without (group B) the metabolic syndrome. The 95% CI in parentheses

<table>
<thead>
<tr>
<th>C-peptide</th>
<th>All Patients</th>
<th>A</th>
<th>B</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>2.59 ± 1.45</td>
<td>3.12 ± 1.36</td>
<td>1.82 ± 1.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(2.66–3.58)</td>
<td>(1.31–2.34)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≥1 complication</td>
<td>2.79 ± 1.21</td>
<td>3.01 ± 1.16</td>
<td>2.25 ± 1.21</td>
<td>0.056</td>
</tr>
<tr>
<td>(2.43–3.16)</td>
<td>(2.59–3.43)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No complications</td>
<td>2.01 ± 1.91</td>
<td>3.96 ± 2.55</td>
<td>1.36 ± 1.16</td>
<td>0.132</td>
</tr>
<tr>
<td>(0.99–3.03)</td>
<td>(0.62–2.09)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disease</td>
<td>2.89 ± 1.23</td>
<td>3.39 ± 1.25</td>
<td>2.05 ± 0.61</td>
<td>0.012</td>
</tr>
<tr>
<td>(2.23–3.54)</td>
<td>(2.50–4.28)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No vascular disease</td>
<td>2.56 ± 1.56</td>
<td>3.05 ± 1.43</td>
<td>1.71 ± 1.46</td>
<td>0.008</td>
</tr>
<tr>
<td>(2.06–3.07)</td>
<td>(2.46–3.63)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Retinopathy</td>
<td>2.22 ± 1.34</td>
<td>2.66 ± 1.13</td>
<td>1.06 ± 1.29</td>
<td>0.074</td>
</tr>
<tr>
<td>(1.33–3.12)</td>
<td>(1.72–2.61)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No retinopathy</td>
<td>2.90 ± 1.49</td>
<td>3.48 ± 1.47</td>
<td>1.99 ± 1.01</td>
<td>0.005</td>
</tr>
<tr>
<td>(2.36–3.45)</td>
<td>(2.77–4.19)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Nephropathy</td>
<td>2.89 ± 1.28</td>
<td>3.20 ± 1.13</td>
<td>1.90 ± 1.27</td>
<td>0.010</td>
</tr>
<tr>
<td>(2.45–3.34)</td>
<td>(2.74–3.66)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No nephropathy</td>
<td>2.23 ± 1.28</td>
<td>2.51 ± 1.20</td>
<td>2.08 ± 1.36</td>
<td>0.522</td>
</tr>
<tr>
<td>(1.57–2.89)</td>
<td>(1.25–3.78)</td>
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<tr>
<td>Neuropathy</td>
<td>2.89 ± 0.87</td>
<td>2.78 ± 0.89</td>
<td>3.15 ± 0.81</td>
<td>0.393</td>
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<tr>
<td>(2.49–3.30)</td>
<td>(2.26–3.30)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No neuropathy</td>
<td>2.86 ± 1.62</td>
<td>3.51 ± 1.59</td>
<td>1.83 ± 1.09</td>
<td>0.008</td>
</tr>
<tr>
<td>(2.21–3.52)</td>
<td>(2.66–4.36)</td>
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</table>

The p-values correspond to the difference between groups A and B.

Discussion

In our study, C-peptide levels were elevated in patients with diabetes who also had the metabolic syndrome. We also found that C-peptide levels were higher in diabetic patients with the metabolic syndrome and concomitant nephropathy or vascular disease than in patients with those complications but without the metabolic syndrome. However, when complications were examined as a whole, their presence was not correlated with C-peptide levels in patients with diabetes or in those with diabetes and the metabolic syndrome. CRP levels were also found to be elevated in diabetes patients with the metabolic syndrome. Moreover, no correlation was found between C-peptide and CRP levels.

It must be noted that C-peptide is thought to be only a marker of chronic complications of diabetes, and there is no known pathophysiological relation between C-peptide itself and these complications. The cross sectional nature of our study may be responsible for a selection bias, since patients with severe complications who might have higher or lower C-peptide levels may have died prematurely.

We confirmed the previously reported relation between C-peptide levels and the presence of metabolic syndrome in diabetics [5,11,12]. It seems that major insulin resistance, a common feature in patients with the metabolic syndrome, is responsible for increased insulin secretion and the resultant elevation in C-peptide levels. Different studies have reported both positive and negative relations between C-peptide levels and complications of diabetes [4–8], while still other studies have failed to identify any correlation [9,10]. Our data show a positive relation among patients with diabetes and the metabolic syndrome between higher C-peptide levels and the presence of nephropathy or vascular disease. CRP levels are known to be associated with cardiovascular risk [16] and to predict development of the metabolic syndrome [17]. Our data also confirm that CRP levels are higher in patients with diabetes who have the metabolic syndrome compared with those who do not.

Conflicts of interest: none.

References


