Decreasing postprandial C-peptide levels over time are not associated with long-term use of sulphonylurea: An observational study

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Abstract

Aim. – The present study aimed to describe changes over 10 years in HbA 1c and beta-cell function, as assessed by postprandial C-peptide (PP-CPT) and C-peptide/glucose (PP-CPT/glucose) ratio, and to investigate whether treatment with sulphonylurea (SU) exerts a deleterious effect on beta-cell function.

Methods. – During 1997–1998, HbA 1c, PP-CPT and PP glucose were measured in 462 patients. Ten years later, 171 of the 341 patients who were still alive were followed-up.

Results. – HbA 1c decreased from 7.41 to 6.96% ($P=0.002$) as treatments were intensified. There was a decrease in both PP-CPT ($P<0.001$) and PP-CPT/glucose ratio ($P=0.063$). A multivariable-regression model was used to evaluate the effects on beta-cell function changes, using the following variables as effect modifiers: gender; age; BMI; diabetes duration; baseline PP-CPT/glucose ratio; HbA 1c; GAD-antibody class; and SU treatment (continuously, periodically, never). Baseline PP-CPT/glucose ratio was the most important variable ($R^2=45\%$, $P<0.001$) for explaining variations in beta-cell function. An increase in HbA 1c was associated with a decrease in beta-cell function, and beta-cell function remained unchanged if glycaemic control was improved. Long-term treatment with SU had no effect on long-term changes in beta-cell function ($R^2=0.1\%$, $P=0.894$).

Conclusion. – Both HbA 1c and beta-cell function decreased over 10 years with SU treatment, but such treatment was not associated with a pronounced decline in beta-cell function. These results, however, need to be interpreted with caution, as this was an observational study. Nevertheless, the present study findings do not support the notion that SU, as used in clinical practice, is harmful to beta-cell function.

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Keywords: Type 2 diabetes; Beta-cell function; Sulphonylurea; C-peptide; Treatment

Résumé

La diminution à long terme du peptide-C postprandial est-elle associée au traitement au long cours par sulfonyleurrées ? Étude observationnelle.

Objectif. – L’objectif de cette étude était de décrire les variations de l’HbA 1c et de la fonction β-insulaire, évaluée par les concentrations de peptide-C postprandial et le rapport peptide-C/glycémie postprandiale après un suivi de dix ans, et de vérifier si le traitement par sulfonyleurrées hypoglycémiantes (SU) exerçait un effet délétère sur la fonction des cellules β.


Résultats. – Les taux de l’HbA 1c, le peptide-C postprandial et le rapport peptide-C/glycémie ont été mesurés chez 462 patients. Dix ans plus tard, 171 des 341 patients encore en vie font l’objet de cette étude.

Conclusion. – La diminution à long terme du peptide-C postprandial est-elle associée au traitement au long cours par sulfonyleurrées ? Étude observationnelle.

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Keywords: Type 2 diabetes; Beta-cell function; Sulphonylurea; C-peptide; Treatment

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1. Introduction

Patients newly diagnosed with type 2 diabetes in the UK Prospective Diabetes Study (UKPDS) showed that the deterioration of glycaemic control observed over time was related to a decline in beta-cell function [1]. Studies have also shown that decreasing levels of C-peptide are associated with increasing diabetes duration [2–5]. However, there appears to be considerable individual variation in the rate of decline of insulin secretory capacity, and the preservation of residual insulin secretion over a long period of time has been reported [6]. Also, when antibody-positive subjects were excluded from a study of patients with newly diagnosed adult-onset diabetes in Sweden, fasting C-peptide levels remained stable over 12 years [7].

The cause of beta-cell dysfunction and the rate of deterioration are both likely to be multifactorial, and genetically and environmentally dependent [8]. In addition to glucose- and lipotoxicity due to hyperglycaemia [9,10], the use of sulphonylurea (SU) therapy has been suspected of being involved in this process via increasing insulin secretory demands, thereby leading to beta-cell exhaustion [11,12]. As SU compounds are widely used and recommended in the current guidelines [13] as a glucose-lowering therapy, it is important to clarify whether or not SU, as used in clinical practice, has any deleterious effects on beta-cell function.

The aim of the present observational study was to describe changes in glycaemic control and beta-cell function over 10 years, and to investigate a possible relationship between changes in beta-cell function and treatment with SU. To assess beta-cell function, we chose to use the C-peptide/glucose ratio, as prevailing blood glucose levels have a major influence on insulin secretion and, thus, on C-peptide levels. We regard this measurement, which is less commonly used, as being more appropriate than C-peptide alone to assess beta-cell secretory capacity when evaluating patients using a variety of glucose-lowering therapies, including insulin [14].

2. Patients and methods

During 1997–1998, 462 patients with type 2 diabetes attended a four-day course at the Diabetes Day Care Centre (DDCC) at Danderyd Hospital in Stockholm. HbA1c, body mass index (BMI) was 28.4 kg/m² (range: 17.8–58.0 kg/m²) and HbA1c was 7.7% (range: 3.8–14.1%). The majority of the patients were referred to the DDCC by general practitioners for reasons that fell into three major groups: for general diabetes education (n = 188), including 137 patients diagnosed with diabetes within 2 years of starting the course; for poor glycaemic control (n = 187); and for other reasons (n = 87), such as the need for adjustment of glucose-lowering treatments or unstable blood glucose, including hypoglycaemia. At baseline, 17% were using dietary treatment alone, 51% were taking oral glucose-lowering drugs (OGLD), 14% were using insulin only, and 18% were taking combined OGLD and insulin. Of the patients treated with OGLD, 56% were taking an SU. Ten years after attending the DDCC course, 121 patients had died: 53% from cardiovascular disease; 17% from cancer; 11% from infections; and 18% from other causes.

The remaining 341 patients thus eligible for the present study were all invited to a follow-up visit at the Clinical Research Centre. Of these, 171 (50%; 106 men, 65 women) agreed to participate. Of the 170 patients not participating in the follow-up, 56% declared that they were not interested, 17% had a severe intercurrent illness rendering them unable to attend and 27% were lost to follow-up.

There were no differences in baseline data between the 171 participants and the 170 non-participants in age, diabetes duration, BMI, PP-CPT and PP-CPT/glucose ratio, and all were equally distributed among the referral categories at baseline. To characterize the non-participants at the time of follow-up, data were collected for recent HbA1c values and weight in 105 (62%) patients. There were no differences between the participants and non-participants in either HbA1c, which was 6.9% (±1.29 SD) vs 6.9% (±1.62 SD), or BMI, which was 29.8 kg/m² (±4.8 SD) vs 29.4 kg/m² (±5.6 SD).

At the follow-up visit, the patients filled out a questionnaire about their medical history and current diabetes treatment. In some cases, a patient’s records were obtained from the patient’s primary healthcare physician to confirm ongoing and/or earlier diabetes treatment. Weight was measured, and blood samples (both fasting and after breakfast) were drawn for HbA1c, glumatic acid decarboxylase (GAD) antibodies, C-peptide and plasma glucose. In the statistical analyses, the C-peptide/glucose ratio was used as the main measurement of beta-cell function, as this ratio corrects for the prevailing glucose level which, in itself, is of importance for endogenous insulin secretion and, thus, for C-peptide levels.

As one aim of the present study was to describe changes in beta-cell function in relation to the use of SU, two subgroups of patients were identified: those treated with SU continuously...
during the 10-year period ($n=43$); and those who had never received treatment with SU ($n=50$).

To evaluate the effects on changes in CPT/glucose ratios between 1997–1998 and 2007, logistic-regression analyses were performed after dividing the patients into three groups, based on exposure to SU: (1) those never treated with SU during the 10-year follow-up; (2) those treated with SU either at the beginning or end of the follow-up period; and (3) those treated with SU during the entire follow-up period.

The present study was approved by the local ethics committee, and all patients provided their written informed consent.

2.1. Laboratory methods

Serum C-peptide concentrations were analyzed immunologically using a commercial kit (AutoDELFIA, PerkinElmer), with a reference value of 0.25–1.0 mmol/L and a coefficient of variation of 8%. HbA1c was measured using high-performance liquid chromatography (Variant II, Bio-Rad Laboratories) and the Mono-S standard, with a coefficient of variation of 2.6%. Plasma glucose was analyzed using the glucose-oxidase method (Beckman Instruments). Antibodies against GAD were analyzed using enzyme immunoassay (Medizym®, Medipan GmbH) with a negative value ≤ 5 IE/mL.

2.2. Statistical methods

The statistical analyses were performed using STATISTICA software, version 8 (StatSoft® Inc., Tulsa, OK, USA). A multivariable-regression model was used to evaluate the effects on changes (differences) in CPT/glucose ratio between 1997–1998 and 2007. The variables used in the model were gender, baseline age, BMI, diabetes duration, baseline PP-CPT/glucose ratio, HbA1c, GAD-antibody class, use of metformin at follow-up and SU treatment group. GAD was categorized into two groups: ≥ 200; and < 200. Change in HbA1c was categorized into three groups: < − 0.2; > 0.2; and − 0.2 to 0.2. Backward selection (exclusion criterion: $P > 0.05$) was used to decide which variables to include in the final model, although variables of clinical importance were included regardless of $P$ value. To evaluate the effect of a single predictor on regression, the difference in $R^2$ (coefficient of determination) between the final model and a reduced model was calculated. Regression results are presented together with unadjusted means.

Because of confounding factors, simple regression analysis is not optimal for analyzing data in an observational study of this type. However, simple regression analysis was used here to obtain descriptive statistics to evaluate whether or not the association between PP-CPT/glucose and diabetes duration or HbA1c at follow-up was positive or negative, although caution is advisable when interpreting the results.

3. Results

3.1. Unadjusted results

Patients’ characteristics, and measurements at baseline and follow-up, are shown in Table 1. Over the 10-year study period, glucose-lowering treatments had been intensified so that the use of insulin had increased from 32 to 74%, and combined OGLD and insulin treatment rose from 18 to 52%, whereas the use of insulin secretagogues remained similar at 56% vs 48%. The types of SU treatment being used at follow-up were glibenclamide (68%), glimepiride (25%) and glipizide (7%). After 10 years, there was a decrease in HbA1c from 7.41 to 6.96% (mean difference: $− 0.45$; 95% CI: $− 0.73$, $− 0.16$; $P = 0.002$), while PP-CPT decreased from 2.09 to 1.53 mmol/L ($− 0.56$; 95% CI: $− 0.70$, $− 0.42$; $P < 0.001$) and the PP–CPT/glucose ratio changed from 0.176 to 0.158 ($− 0.018$; 95% CI: $− 0.038$, 0.001; $P = 0.063$).

A positive titre (> 200 IE/mL) of GAD antibodies was found in 12 patients (7%). These patients differed from the GAD-negative patients in BMI, PP-CPT and PP-CPT/glucose ratio, with the latter decreasing from 0.137 to 0.081 (mean difference: $− 0.056$; 95% CI: $− 0.11$, 0.002; $P = 0.056$). When excluding the 12 GAD-positive patients from the analyses, the decrease in ratio was less ($P = 0.139$), while the other parameters analyzed remained unaffected.

A simple linear-regression model showed a negative relationship between the PP-CPT/glucose ratio and diabetes duration ($r = − 0.339$; $P < 0.001$). There was also a negative correlation between PP-CPT/glucose ratio and HbA1c at follow-up ($r = − 0.52$; $P < 0.001$).

3.2. Regression analysis (adjusted results)

In the multiple-regression analysis (Table 2), the baseline PP-CPT/glucose ratio was the most important independent variable ($R^2 = 45%$; $P < 0.001$) for explaining the variation in long-term changes in CPT/glucose ratio. The second most important variable was insulin therapy ($R^2 = 7%$; $P < 0.001$), while change in HbA1c from baseline to follow-up was the third most important variable ($R^2 = 5%$; $P < 0.001$). An increase in HbA1c between 1997–1998 and 2007 was asso-

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patients’ characteristics and metabolic status at baseline and at follow-up.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1997–1998 ($n=171$)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.8 (9.0)</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>5 (0–38)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.99 (4.45)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.40 (1.77)</td>
</tr>
<tr>
<td>PP-CPT (mmol/L)</td>
<td>2.10 (0.99)</td>
</tr>
<tr>
<td>PP-CPT/glucose ratio</td>
<td>0.149 (0.021–0.867)</td>
</tr>
<tr>
<td>PP-plasma glucose (mmol/L)</td>
<td>14.4 (5.92)</td>
</tr>
</tbody>
</table>

Data are expressed as means (SD) for normally distributed variables unless otherwise indicated.

* Variables expressed as medians (range); PP: postprandial; CPT: C-peptide.
Table 2

<table>
<thead>
<tr>
<th>Factor/covariable</th>
<th>Group</th>
<th>Change in ratio</th>
<th>Group</th>
<th>Change in ratio</th>
<th>Effect</th>
<th>95% CI</th>
<th>R2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>Treatment with sulphonylurea</td>
<td>Never</td>
<td>-0.010</td>
<td>Always</td>
<td>-0.016</td>
<td>0.006</td>
<td>-0.034</td>
<td>0.045</td>
</tr>
<tr>
<td></td>
<td>Never</td>
<td>-0.010</td>
<td>At some point</td>
<td>-0.018</td>
<td>0.008</td>
<td>-0.025</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>At some point</td>
<td>-0.018</td>
<td>Always</td>
<td>-0.016</td>
<td>-0.002</td>
<td>-0.032</td>
<td>0.036</td>
</tr>
<tr>
<td>HbA1c (± 0.2%)</td>
<td>Unchanged</td>
<td>0.013</td>
<td>Decrease</td>
<td>0.000</td>
<td>0.013</td>
<td>-0.039</td>
<td>0.065</td>
</tr>
<tr>
<td></td>
<td>Increase</td>
<td>-0.056</td>
<td>Decrease</td>
<td>0.000</td>
<td>-0.056</td>
<td>-0.088</td>
<td>-0.024</td>
</tr>
<tr>
<td></td>
<td>Increase</td>
<td>-0.056</td>
<td>Unchanged</td>
<td>0.013</td>
<td>-0.069</td>
<td>-0.119</td>
<td>-0.02</td>
</tr>
<tr>
<td>GAD</td>
<td>Negative</td>
<td>0.009</td>
<td>Positive</td>
<td>-0.038</td>
<td>0.047</td>
<td>-0.005</td>
<td>0.1</td>
</tr>
<tr>
<td>Insulin at follow-up</td>
<td>Yes</td>
<td>0.056</td>
<td>No</td>
<td>0.027</td>
<td>-0.083</td>
<td>-0.117</td>
<td>-0.05</td>
</tr>
<tr>
<td>Duration at baselinea</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–0.003</td>
<td>-0.005</td>
<td>-0.001</td>
</tr>
<tr>
<td>BMI at baselinea</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.001</td>
<td>-0.002</td>
<td>0.005</td>
</tr>
<tr>
<td>PP-CPT/glucose ratio at baselinea</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>-0.730</td>
<td>-0.86</td>
<td>-0.62</td>
</tr>
</tbody>
</table>

a Change in long-term CPT/glucose per unit of independent variable; GAD: glutamic acid decarboxylase; BMI: body mass index; PP-CPT: postprandial C-peptide.

ciated with a decrease (mean change: -0.056) in long-term PP-CPT/glucose ratio, although the ratio remained essentially unchanged when HbA1c was decreased (mean change: 0.0003). SU treatment had no substantial effect on long-term CPT/glucose (R2 = 0.1%; P = 0.894), nor did gender and use of metformin at follow-up show any effects on the PP-CPT/glucose ratio (R2 = 0.29%; P = 0.329 and R2 = 0.34%; P = 0.288, respectively). The model explained 61% of the variance in long-term CPT/glucose. The heterogeneity of changes in beta-cell function among patients is illustrated in Fig. 1, which shows the PP-CPT/glucose ratios in 1997–1998 and in 2007 for each patient plotted against diabetes duration in the two subgroups of patients [continuous SU treatment (n=43) vs no exposure to SU (n=50)] over the 10-year period.

4. Discussion

The main findings of the present observational study were that beta-cell function, assessed as the ratio of postprandial C-peptide and glucose, deteriorated over 10 years in the study participants as a whole, and that there was considerable variation between patients in loss of beta-cell function. In GAD-positive patients, the loss of beta-cell function appeared to be somewhat more pronounced. However, long-term treatment with SU was not associated with acceleration of the degenerative process.

Fig. 1. Individual values (PP-CPT/glucose ratio) in 1997/1998 and in 2007 for each patient plotted against diabetes duration: (left) patients treated with sulphonylurea (SU) continuously (n = 43) during the 10-year period; (right) patients never exposed to SU during the 10 years (n = 50). Note: the data are not corrected for changes in HbA1c and other confounding factors.
The UKPDS had demonstrated progressive deterioration in glucose control over time [1]. In addition to that landmark study, an increase in HbA1c levels has, more recently, been associated with longer diabetes duration in some studies [15,16]. In contrast, glycaemic control improved in the present study despite deterioration of beta-cell function, most likely as a reflection of more intensive glucose-lowering therapies targeted at the stricter glycaemic goals currently being advocated [13]. Notably, this is in accordance with data from the recently published results from the UKPDS post-trial, where a decrease in HbA1c was seen in both the intensively treated and conventionally treated groups of patients after the primary study had ended [17].

Chronic hyperglycaemia (or glucotoxicity) contributes to progressive impairment of insulin secretion and lowers insulin sensitivity and, thus, has been postulated to harm beta cells [18]. In short-term studies, near-normalization of glycaemia through intensified treatment has partially restored beta-cell function and insulin secretion [19–21]. In the present study population, beta-cell function remained unchanged when glycaemic control was improved. We also observed that higher HbA1c levels were associated with lower levels of both PP-CPT and PP-CPT/glucose ratio. However, in our observational study, whether this finding reflects a primary loss of beta-cell function or an effect of prevailing glucotoxicity blunting insulin secretion cannot be determined.

There appears to be considerable individual variation in the rate of decline of insulin-secretion capacity. Although a decline in the present study participants was observed as a whole, the changes in PP-CPT and PP-CPT/glucose ratio over 10 years varied considerably among individuals. In approximately half the group, there was a decrease over time but, among the remainder, the ratio remained essentially unchanged or even increased after 10 years. This finding is consistent with that of a previous study by Zangeneh et al. [6], which demonstrated a similar pattern of changes in insulin secretion, as assessed by fasting and stimulated C-peptide in 89 GAD-antibody-negative patients followed for 12 years. In the present study, 7% (n = 12) were GAD-antibody-positive at follow-up, but no baseline data are available, which means that the number of GAD-positive patients in 1997–1998 is unknown. However, the prevalence in the present study is in line with data for older patients reported in the study by Tuomi et al. [22]. We also observed that GAD positivity was clearly associated with lower PP-CPT/glucose ratios at follow-up and, in the regression model, GAD positivity was one of the variables tested to correct for a possible effect on decreased beta-cell function.

In the present study, C-peptide was measured 1.5 h after breakfast. The standard breakfast test is believed to be a valid alternative to the glucagon-stimulation test, as it is easy to perform and there is good correlation between C-peptide increments in these two tests [23].

Simultaneous determination of C-peptide and glucose minimizes the influence of blood glucose levels and glucose-lowering therapies on insulin secretion [14]. Treatment with exogenous insulin is associated with a decrease in C-peptide concentrations, a finding that may reflect the reduction in glucose levels during insulin therapy [24]. Albareda et al. [14] also showed that C-peptide levels decreased during insulin treatment although, in that study, the C-peptide/glucose ratio remained unchanged. In the present study, we noted a slight decrease in C-peptide/glucose ratio in patients with ongoing insulin therapy. This may reflect the fact that patients with low endogenous insulin production are more likely to be treated with insulin. For this reason, when evaluating beta-cell function in patients treated with insulin as well as OGLD, we believe that the C-peptide/glucose ratio offers more useful information on beta-cell function than does a single C-peptide value and, consequently, this ratio was used to assess beta-cell function.

In the UKPDS, beta-cell function was assessed using homeostatic model assessment (HOMA), but this model is not applicable to insulin-treated patients and, thus, could not be used in the present study. The UKPDS showed that the progressive loss in beta-cell function occurred at the same rate, regardless of the type of oral pharmacological treatment used [1]. Despite this observation, there has been considerable concern that treatment with SU drugs stress beta cells by increasing insulin-secretion demand, thereby hastening the progressive deterioration of beta-cell function. Islet amyloidosis in patients with type 2 diabetes is caused primarily by deposition of islet amyloid polypeptide (IAPP), and IAPP has been proposed to be involved in the development of beta-cell dysfunction and type 2 diabetes [25]. In addition, experimental evidence of an association between elevated IAPP secretion, SU treatment and islet amyloidosis has been put forward [26]. Another hypothesis is that increased secretion of proinsulin, induced by SU, could be a sign of increased beta-cell stress [27]. However, such a hypothesis is not supported by other investigators [28]. Furthermore, SU drugs, especially glibenclamide, can induce beta-cell apoptosis in vitro [12], although there may be some differences between different SU drugs in terms of function and survival of cultured human islets. Indeed, del Guerra et al. [29] have recently shown that gliclazide protects human beta cells against apoptosis.

Few long-term clinical studies have considered whether SU compounds exert a negative effect on beta-cell function. In the study by Alvarsson et al. [11] of newly diagnosed type 2 diabetic patients, early insulin treatment compared with SU therapy resulted in preservation of beta-cell function, as documented by a more pronounced C-peptide response to glucagon after 1 and 2 years. In the ADOPT trial [30], SU derivatives were associated with earlier beta-cell failure than either metformin or rosiglitazone when followed-up four years later.

The present 10-year, longitudinal follow-up study included patients who were using all kinds of treatments. To assess a possible effect of SU treatment on beta-cell function, we classified patients by SU exposure during follow-up, and used these groups in the multiple-regression analysis. Treatment with SU (continuously for 10 years, periodically or never) explained none of the observed variable changes in PP-CPT/glucose ratios.

Our observational study has several limitations. First, of the original 462 patients, only 37% were reinvestigated, as 26% had died by the time of follow-up and 37% did not attend the follow-up. However, those that were followed-up did not differ significantly from the non-participants and, hence, we believe that the investigated group is representative of beta-cell func-
tion over time. Second, there was considerable heterogeneity in diabetes duration, glucose levels and glycaemic control, as well as in treatment modalities, including different combinations of OGLD and insulin regimens. Such heterogeneity is problematic when attempting to evaluate beta-cell function with a simple test such as postprandial C-peptide and glucose. This may also be seen as a study strength, however, as it reflects a representative sample of a population of patients with type 2 diabetes. Third, using postprandial C-peptide only, and not fasting or incremental C-peptide, may be considered a flaw. However, at baseline, the standard test only measured postprandial C-peptide and, therefore, no data for fasting C-peptide were available for analyses.

In conclusion, both HbA1c and beta-cell function, assessed as the ratio of PP-CPT to glucose, decreased over 10 years, but long-term treatment with SU drugs was not associated with a more pronounced decline in beta-cell function. However, considering the observational nature of the present study as well as its limitations, these results need to be interpreted with caution. Nevertheless, they do not support the notion that SU therapy as used in clinical practice is harmful to beta-cell function.

Declaration of competing interest

Nothing to declare.

References