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Influence of exogenous insulin on C-peptide levels in subjects with type 2 diabetes

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Abstract

Aim: The aim of this study was to determine whether the influence of insulin therapy on fasting and stimulated C-peptide levels in type 2 diabetic subjects is due to plasma glucose reduction or a direct effect of exogenous insulin.
Methods: Plasma glucose and serum C-peptide levels were determined before and after IV injection of 1 mg glucagon on three separate days in 21 type 2 diabetic subjects. Day 1: without pharmacological treatment and fasting plasma glucose >11.1 mmol/L; day 2: fasting plasma glucose 4.4–7.8 mmol/L, 1 h after withdrawing intravenous regular insulin infusion; day 3: fasting plasma glucose 4.4–7.8 mmol/L with bed-time NPH insulin.
Results: Fasting and glucagon stimulated C-peptide levels were higher on day 1 than days 2 and 3. Fasting, but not stimulated C-peptide levels, were lower on day 3 than day 2. These differences were not appeared when the percentage of C-peptide increment or the C-peptide/glucose ratio were compared in the three days.
Conclusions: Blood glucose reduction instead of exogenous insulin is responsible for the C-peptide decrease during insulin therapy in type 2 diabetic subjects.

Keywords: C-peptide; Insulin treatment; Type 2 diabetes mellitus; Glucagon

1. Introduction

Our previous decades, interest in the measurement of fasting and glucagon stimulated C-peptide levels has increased, as it may be of clinical benefit. In patients with diabetes, C-peptide concentration can help to differentiate type 1 and type 2 diabetes, to select the best treatment in patients with type 2 diabetes (insulin versus oral agents or insulin-sensitizing versus insulin-secretagogue agents) and in the decision to discontinue insulin therapy, especially in obese subjects [1–4].

However, although C-peptide response to glucagon is one of the most reliable insulin secretion

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indicators because it is simple, safe and reproducible [5,6], its interpretation is difficult because of the lack of standardization and the influence of factors such as blood glucose levels and treatment with hypoglycemic drugs. Acute and chronic elevations of the pre-stimulatory blood glucose level potentiate the insulin response to glucagon [7,8], while acute and chronic reduction of blood glucose levels results in a decreased insulin response [7–9] and a blood glucose concentration below 3.5 mmol/L results in an almost total suppression of the stimulating glucagon action [10]. Furthermore, whether or not the decreased serum C-peptide concentration observed with insulin therapy is due to a blood glucose reduction or direct suppressive effect of exogenous insulin is not clear [9,11].

Thus, the aim of the present study was to clarify whether the effect of insulin therapy on fasting and glucagon stimulated C-peptide in type 2 diabetes is due to glycemic improvement or a direct effect of exogenous insulin.

2. Patients and methods

Twenty-one subjects with type 2 diabetes with a mean age of 63.3 ± 8.5 years, mean body mass index (BMI) of 26.9 ± 5 kg/m^2 and diabetes duration of 7.7 ± 5 years participated in this study. Fifteen had previously been treated with oral anti-diabetic agents, four only with diet and two had been recently diagnosed (Table 1). All had normal values of plasma creatinine. No patient had an intercurrent illness and liver and thyroid function were normal. No subject was taking any medication, which altered glucose metabolism at the time of study. All patients had stopped oral anti-diabetic agents at least 48 h prior to hospitalization. The study was approved by the Local Ethics Board and informed consent was obtained from all patients.

Table 1
Clinical characteristics of the 21 type 2 diabetic patients

Patients	21
Age (years)	63.3 ± 8.5
Sex (male/female)	7/14
BMI (kg/m^2)	26.9 ± 5
Diabetes duration (years)	7.7 ± 5
Creatinine concentration (μmol/L)	82 ± 10
HbA1c (%)	10.7 ± 3
Previous treatment	
Diet only	4
Oral anti-diabetic agents	15
No treatment	2

2.1. Study design

After admission to hospital, all patients were studied after a 12-h overnight fast on three separate days. Day 1 (hyperglycemia): patients were studied with a fasting plasma glucose concentration >11.1 mmol/L after at least 48 h without any hypoglycemic treatment except diet. Day 2 (near-normoglycemia—iv regular insulin): the study was performed with fasting plasma glucose between 4.4 and 7.8 mmol/L, which was obtained with an overnight intravenous infusion of regular insulin. Based on a previous report of Gjessing et al. [12], insulin infusion was stopped 1 h before blood samples were obtained, in order to restore insulin levels. Day 3: (near-normoglycemia—NPH insulin): this study was also performed at levels of fasting plasma glucose between 4.4 and 7.8 mmol/L, which was maintained with bed-time NPH insulin. On each occasion, after placement of a cannula in an ante-cubital vein, blood specimens for plasma glucose and serum C-peptide determinations were obtained before and 6 min after an intravenous bolus of 1 mg of glucagon (Glucagon Gen Hypokit®, Novo Nordisk).

Plasma glucose was determined by an oxidase method (Technicon RA-XT analyzer, Technicon Instruments, Tanytown, NT, USA). Serum C-peptide concentrations were measured by radioimmunoassay (RIA-Coat® C-Peptide, Byk-Sangtec Diagnostica GmbH & Co-KG, RFA) with a limit of detection of 99 pmol/L. Intra- and inter-assay variability were <5 and <10%, respectively and cross-reactivity with proinsulin 25%.

2.2. Statistical analysis

Data are shown as mean ± S.D. Differences in glucose and C-peptide concentrations between study days were assessed by two-way Anova and Student's paired *t*-tests. A *p*-value of <0.05 was considered statistically significant.