Differences Between Basal and Postprandial Circadian Variation of Insulin Sensitivity in Healthy Subjects and Type 1 Diabetics

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Summary

The circadian variation of basal and postprandial plasma glucose and insulin levels was analyzed in 10 healthy individuals and 10 type-1 diabetic patients treated with a glucose-controlled insulin infusion system. In both groups the postprandial glycemic response to identical low caloric mixed meals ingested at 8 a.m., 1 p.m., and 6 p.m. increased significantly in the course of the day. In contrast to findings in conventional insulin therapy mean postprandial insulin requirements of the diabetic patients increased from 8.5 ± 3.0 IU for breakfast to 9.1 ± 2.0 for lunch and 10.9 ± 3.0 for dinner (p<0.01). Repeated studies with different test meals showed that in the diabetic patients the circadian deterioration of carbohydrate tolerance was reduced after a fiber rich meal with low glycemic effect and insulin requirements. In the healthy subjects basal insulin levels at 8 a.m. were 35% higher than at 1 and 6 p.m. (p<0.01). Basal insulin requirements of the diabetic patients increased significantly from a night value of 0.7 IU/h to 1.18 IU/h during the early morning and remained constant throughout day time.

We conclude that circadian changes in postprandial carbohydrate tolerance are independent from the endogenous rhythmics of basal glucose metabolism. In diabetic patients the circadian pattern of postprandial responses is substantially determined by exogenous factors like diet composition, caloric intake and therapeutic regimen.

Introduction

In non-diabetics glucose tolerance was found to decrease during the course of the day [1–7]. This physiological diurnal fluctuation in glucose tolerance is suggested to be due to enhanced postprandial insulin release in the morning after overnight fasting [3, 2, 5–9] and to reduced peripheral insulin sensitivity in the evening [5, 6, 10, 11].

In contrast to these findings in non diabetic humans the postprandial insulin requirements of insulin dependent diabetic patients observed during intensified conventional insulin therapy and continuous subcutaneous insulin infusion are usually highest after breakfast, and glucose tolerance tends to improve as the day goes on [12–17] This circadian pattern was confirmed by
data resulting from computer assisted insulin dosage adjustment [18]. According to this empirical finding it is a well established rule in insulin therapy to calculate a higher insulin dose per gram carbohydrate for breakfast than for the later meals [19, 20].

Although these diurnal changes in insulin need are generally accepted, only very few studies have been designed to investigate systematically the influence of the time of the day on the postprandial glucose metabolism of diabetic patients. It remains widely unclear which mechanisms are responsible for the observed circadian variation, and why diabetic patients seem to have an inverse diurnal rhythm compared to healthy humans.

Circadian changes in cortisol, growth hormone and catecholamines have been discussed as possible explanations of increased basal insulin requirements during the early morning (dawn phenomenon) [21–25] and could also contribute to a reduced glucose tolerance after breakfast.

It is remarkable, however, that several studies performed in type 1 diabetic patients with strictly standardized test meals and/or intravenous insulin delivery systems failed to confirm highest insulin requirements per gram carbohydrate for breakfast [3, 26, 30]. This finding suggests that in type-1 diabetes factors like the composition of the diet, the size and sequence of the meals and the unphysiological subcutaneous insulin substitution may decisively influence the observed diurnal pattern of insulin requirements and possibly mask an endogenous circadian rhythm of glucose tolerance.

The aim of this study was to analyze the circadian variation of the basal and postprandial insulin requirements of 10 type-l diabetic patients ingesting identical test meals at intervals of five hours, using a glucose controlled insulin infusion system. The influence of the composition of the meal on the diurnal changes in insulin requirements was studied by investigating each subject on three separate days with three different standardized mixed meals. The results of the diabetic patients are compared to the corresponding blood glucose and insulin levels of 10 healthy volunteers.

**Subjects, Materials and Methods**

**Subjects**

10 type-1 (insulin-dependent) diabetic patients and 10 healthy volunteers were studied. The type-1 diabetic patients were 8 males and 2 females aged between 19 and 25 years. Their mean body mass index was 21.6 ± 1.49 kg/m² ranging from 19.3 to 24.3 kg/m². In all patients a relevant endogenous insulin secretion was excluded by radioimmunoassay of C-peptide before and one hour after ingestion of a test meal. Besides diabetes, the subjects suffered from no other organic disease, had no clinical signs of neuropathy and no drugs other than insulin were taken. The duration of diabetes was 2 to 8 years (mean 4.9 ± 2.2 years). The daily insulin dose before the study ranged from 36 to 66 U (mean 51 ± 11 U/day).