

EFFECT OF HAEMODIALYSIS ON INSULIN REQUIREMENTS IN URAEMIC DIABETIC PATIENTS. STUDIES WITH THE ARTIFICIAL BETA-CELL

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Summary

This study investigates the effect of dialysis on the 24-hour insulin requirements in uraemic insulin dependent diabetic patients maintained at normoglycaemia using an artificial beta-cell. Five patients were studied twice, namely before initiation of dialysis treatment (mean 14 days) and after a mean of 46 days on chronic dialysis. The mean total diurnal insulin consumption was reduced significantly from $44.7 \pm 2.9\text{U}$ (mean \pm SEM) before dialysis to $35.0 \pm 2.3\text{U}$ after dialysis therapy ($p < 0.01$). The reduction included the prandial as well as the basal insulin requirements ($p < 0.02$). It is most likely that an insulin receptor or a post-receptor defect account for the insulin insensitivity present in uraemia. Our study demonstrates that this defect is at least partly reversible after dialysis treatment.

Introduction

Abnormal glucose tolerance is present in the majority of uraemic patients [1, 2]. The pathophysiologic mechanisms responsible for the carbohydrate intolerance associated with renal failure are not known in detail. Although several factors seem to contribute much evidence points to increased tissue insensitivity to insulin as a key factor [2, 3].

The present study was performed in order to determine the effect of dialysis treatment on the diurnal insulin requirements assessed by a glucose controlled insulin infusion system in uraemic patients with insulin dependent diabetes mellitus.

Materials and methods

Patients

Five non-obese insulin dependent diabetics with severe renal failure participated in the study. Mean age was 38 years. No medication known to interfere with

insulin requirements was given. The patients had been on protein-fixed (60g/day) and carbohydrate-fixed diet for at least six weeks before the studies. All the participants had given informed consent.

Apparatus

A glucose controlled insulin infusion system (Biostator GCIIS, Life Science Instruments, Ulm, FRG) was used. The constants selected for the algorithms were: KR = 70, KF = 67, BI = 80, RI = 0.20/kg body weight, QI = 40, FI \approx 400, BD = 55, RD = 25, QD = 20 and FD \approx 400. The operation mode was 3:0. These constants result in minimum insulin requirements with near normal blood glucose variations [4].

Experimental design

All subjects were investigated twice, namely before initiation of dialysis treatment (mean 14 days) and after a mean of 46 days on chronic dialysis. The patients were admitted to hospital at least 48 hours before initiation of the 24-hour study, intermediate acting insulin was withdrawn and the patients were treated with soluble insulin intramuscularly only. The last soluble insulin dose was given at least nine hours before the patients were connected to the artificial pancreas and this occurred at least four hours before start of the study in order to achieve normoglycaemic equilibrium. The examinations started at 8.00 hours, 12.00 hours and 17.00 hours. No snacks were allowed. The daily caloric intake was 5600KJ. The patients stayed in bed during the experiments. Lights were off from 23.00 hours to 7.00 hours. Blood samples were drawn hourly for determination of plasma growth hormone, pancreatic glucagon and blood intermediary metabolites through a cannula placed in the shunt vein.

Statistics

Student's t-test for paired data was used for statistical analysis.

Results

The mean total diurnal insulin consumption was reduced significantly from 44.7 ± 2.9 U (mean \pm SEM) before dialysis to 35.0 ± 2.3 U after dialysis therapy ($p < 0.001$). The average pre-dialysis insulin requirements were thus 25 per cent higher than those found post-dialysis. The reduction included the prandial as well as the basal insulin requirements ($p < 0.02$). Figure 1 shows the 24-hour insulin infusion rate and blood glucose concentrations in one patient. In this patient, the diurnal insulin requirements were 42.9U before commencement of dialysis treatment versus 31.4U after five weeks on haemodialysis for five hours three times a week, a reduction in insulin consumption of 29 per cent. The total requirements during the three meals (0–180min) were 22.0U versus 16.1U and the basal requirements (01–05h) were 5.2U versus 4.2U in the two situations.

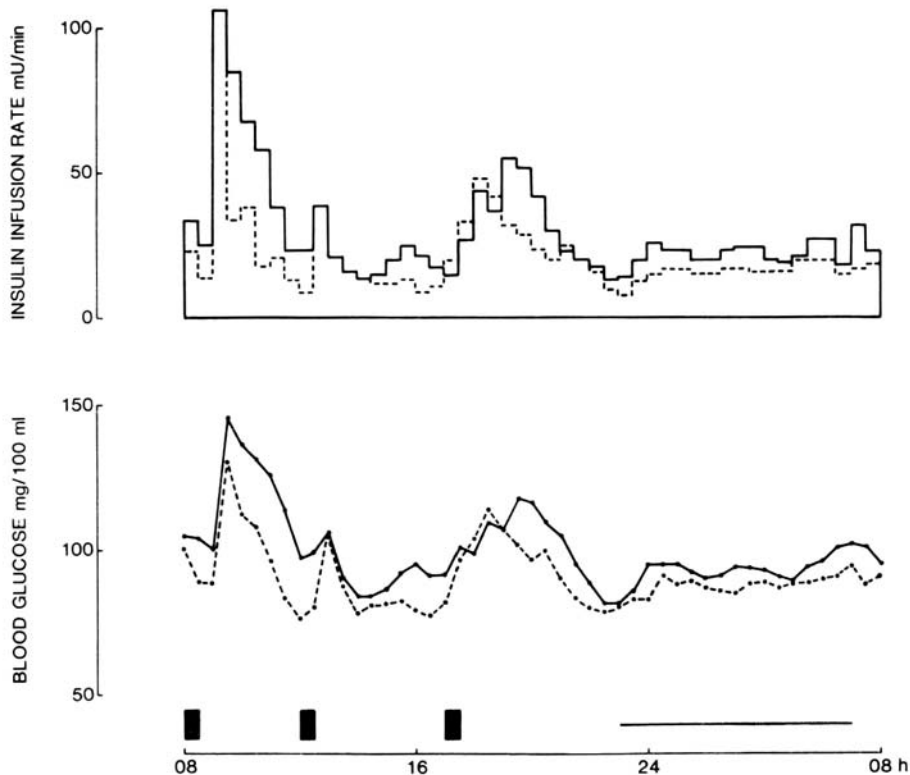


Figure 1. 24-hour insulin infusion rate and blood glucose concentrations in one uraemic insulin dependent diabetic patient studied 21 days before (closed lines) and 34 days after (open lines) initiation of haemodialysis. The bars indicate meals

No correlation between insulin requirements and the degree of azotaemia was found. In spite of the insulin consumption being decreased after starting dialysis, mean diurnal blood glucose was significantly lower post-dialysis compared to the pre-dialysis values ($91.0 \pm 1.6\text{mg}/100\text{ml}$ versus $99.6 \pm 2.0\text{mg}/100\text{ml}$, $p < 0.001$). The plasma concentrations of the counter-regulatory hormones, growth hormone and pancreatic glucagon as well as the intermediary metabolites did not differ in the two situations.

Discussion

Our study demonstrates a significant reduction of the diurnal insulin requirements in uraemic insulin dependent diabetics after commencement of dialysis treatment as compared to pre-dialysis requirements. The insulin consumption did not correlate with the degree of azotaemia. Neither did the plasma levels of the counter-regulatory hormones in the two situations apparently account for the

altered insulin consumption.

More than a decade ago Westervelt [3] in elegant forearm infusion experiments gave evidence for a decreased insulin responsiveness of the skeletal muscles in uraemia. In addition, DeFronzo et al [5] demonstrated a correction of the insulin resistance after ten weeks on haemodialysis by employing an insulin clamp technique in non-diabetic uraemic patients. In order to pursue the nature of the defective glucose homeostasis DeFronzo [6] also measured the insulin binding capacity of monocytes from uraemic patients. However, no relationship between sensitivity to insulin and insulin receptors was found, suggesting that a post-receptor defect i.e. an impaired intracellular glucose metabolism or a defective glucose transport system may be responsible. It is however indisputable that other factors contribute to the glucose intolerance present in a large number of non-diabetic uraemic patients. Recently, an increased hepatic glucose production has been reported [7], probably partly due to hepatic insensitivity to insulin and partly to increased sensitivity to glucagon [8]. The response to glucagon has been shown to be reversible after dialysis.

The striking reduction in insulin requirements after dialysis in the uraemic diabetics joining our study strongly indicates an increase in insulin sensitivity, peripheral as well as hepatic, analogous with the insulin clamp studies in non-diabetic patients. The clinical importance of the present data for optimisation of carbohydrate and metabolic status of uraemic diabetic patients is obvious. The mechanisms responsible for the tissue insensitivity to insulin in uraemic patients and the correction after dialysis are under current investigation.

References

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