Dramatic recovery of counter-regulatory hormone response to hypoglycaemia after intensive insulin therapy in poorly controlled Type I diabetes mellitus

Dear Sir,

The Diabetes Control and Complications Trial Research Group has demonstrated that strict glycaemic control delays the development and progression of diabetic complications (retinopathy, nephropathy, and neuropathy) in patients with Type I (insulin-dependent) diabetes mellitus [1]. When, however, the glucose level is kept, with insulin therapy, close to the normal range in Type I patients, iatrogenic hypoglycaemia often occurs [2]. Recurrent hypoglycaemia can lead to impairment of the counter-regulatory hormone response and awareness of hypoglycaemia [3–7]. Therefore it is important for us to make therapeutic efforts not only to maintain the glucose level as close as possible to the normal range but also to prevent hypoglycaemia.

A 27-year-old woman (160 cm, 54 kg) with Type I diabetes was admitted to our hospital for glycaemic control. She had been diagnosed 2 years before admission, and insulin therapy had been begun at another hospital. Her glycaemia was poorly controlled with intermediate-acting insulin (injected once at breakfast) without self-monitoring of blood glucose. At the time of admission, HbA_{1c} was 10.9% and she had no diabetic complications (retinopathy, nephropathy, and neuropathy). Since her admission to our hospital, she has been self-monitoring her blood glucose level 7 times a day, and asymptomatic hypoglycaemia was often detected (at least once a day). No symptoms of hypoglycaemia appeared even when the blood glucose level had dropped below 2.2 mmol/l. Although patients with neuropathy are often not aware of hypoglycaemia, she had no clinical signs of diabetic neuropathy. To examine whether unawareness of hypoglycaemia is related to impairment of the counter-regulatory hormone response to hypoglycaemia, we performed a stepped hypoglycaemic clamp. Additional insulin was given on the day before the clamp test and her fasting blood glucose levels before the test were stable and kept under 7.8 mmol/l. Insulin was infused (2.57 mU/kg/min) to keep the plasma insulin level at 200 μU/ml and then plasma glucose was clamped by varying glucose infusions at sequential target glucose concentrations of 4.4, 3.9, 3.3, 2.8, and 2.2 mmol/l. Each of these steps lasted 30 min. The first 15-min period was allowed for the desired plateau plasma glucose concentration to be reached and the last 15 min to maintain it at a steady state. The average of glucose infusion rate was 8.72 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ and the total amount of glucose infusion was 70.6 mmol. Venous blood samples were drawn every 30 min to determine the levels of plasma counter-regulatory hormones (epinephrine, norepinephrine, growth hormone (GH), adrenocorticotropic hormone (ACTH), cortisol, and glucagon). None of the counter-regulatory hormones we examined increased even after the blood glucose level had decreased to 2.2 mmol/l (Fig. 1). There were no symptoms of hypoglycaemia during the overall experiment period. After 3 months of intensive therapy (regular insulin at each meal and intermediate-acting insulin at bedtime), the HbA_{1c} level decreased to 7.4% without the glucose level falling below 2.8 mmol/l and then the stepped hypoglycaemic clamp was performed again. The insulin was given until the day before the test and we performed the clamp early in the morning in the same way as the first test. At that time her body weight was almost the same as 3 months before (54 kg) and her fasting blood glucose levels before the test were stable and kept under 7.8 mmol/l. The counter-regulatory hormone response to hypoglycaemia had improved remarkably (Fig. 1) and symptoms of hypoglycaemia (palpitation and perspiration) appeared when the blood glucose level fell to 2.8 mmol/l. The only exception for this phenomenon was the response of GH secretion. Previously it has been reported that GH response was not easily blunted by frequent hypoglycaemia [6], however GH response of this subject was already blunted in the first test. Although the reason for this is not known, it is possible that GH response mechanism was irreversibly damaged for some reason and therefore had not recovered at all even after 3 months of intensive therapy. The average glucose infusion rate was 0.50 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ (the total amount of glucose infusion was 4.2 mmol) which was very low compared with that in the first clamp test. The decrease of glucose infusion rate is likely to be a result of recovered responses of counter-regulatory hormones and an associated increase of endogenous glucose production as well as decrease of the use of glucose by the whole body.

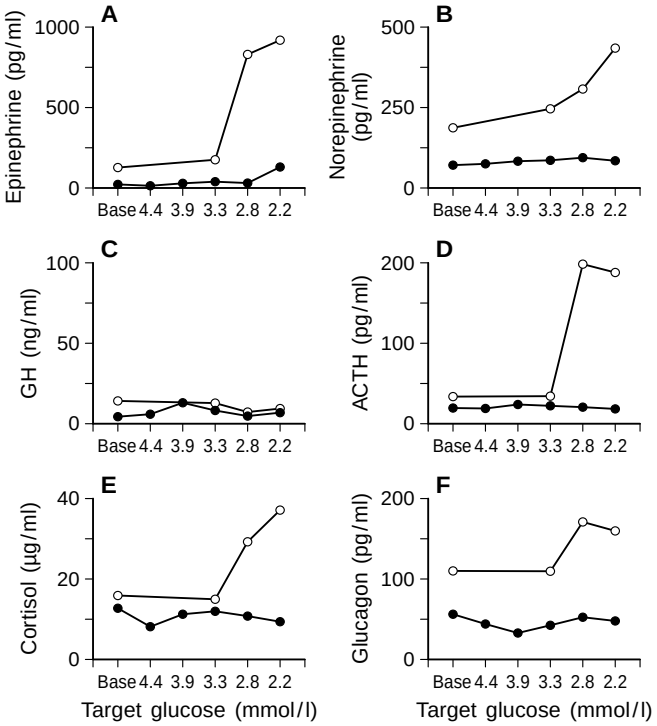

Fig. 1 A, B, C, D, E, F. Levels of counter-regulatory hormones (epinephrine, norepinephrine, GH, ACTH, cortisol, and glucagon) during stepped hypoglycaemic clamp studies before (●) and after (○) 3 months of intensive insulin therapy. **A** epinephrine. **B** norepinephrine. **C** GH. **D** ACTH. **E** cortisol. **F** glucagon

Intensive insulin therapy is often associated with an increase in the frequency and severity of hypoglycaemia [2], and recurrent hypoglycaemia is known to impair counter-regulatory hormones to hypoglycaemia [3–6]. Attention has been called to the need for therapeutic efforts not only to maintain the glucose level close to the normal range ($HbA_{1c} \leq 7\%$), but also to prevent iatrogenic hypoglycaemia by maintaining

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HbA_{1c} 6% or more [7]. We therefore tried to lower the HbA_{1c} level of the patient with intensive insulin therapy, and after 3 months of treatment, good glycaemic control was obtained without lowering the glucose level below 2.8 mmol/l and the HbA_{1c} level was decreased from 10.9% to 7.4%. Previous studies have shown that the counter-regulatory hormone response to hypoglycaemia could be improved after meticulous prevention of hypoglycaemia [8–10], but in these patients, HbA_{1c} levels increased in order to avoid hypoglycaemia with intensive insulin therapy [8, 9]. Our results show that intensive therapy with regular insulin improved not only the glycaemic control but also the counter-regulatory hormone response to hypoglycaemia in a young patient with Type I diabetes. We agree with previous reports [8, 9] that meticulous prevention of hypoglycaemia is important for maintaining and improving the counter-regulatory hormone response.

In conclusion, at least when the HbA_{1c} level is high even after treatment with intermediate-acting insulin, intensive therapy with regular insulin is likely to be very useful for improvement of the counter-regulatory hormone response to hypoglycaemia as well as of the glycaemic control. Although strict glycaemic control is often accompanied by hypoglycaemia, intensive insulin therapy enables us to avoid hypoglycaemia and improve control in poorly controlled Type I diabetes patients, both of which seem to improve the counter-regulatory hormone response to hypoglycaemia and awareness of it.

Yours sincerely,
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Hereditary haemochromatosis mutations (HFE) in patients with Type II diabetes mellitus

Dear Sir,

Recently the gene and its mutations responsible for hereditary haemochromatosis, a well-established, albeit rare, cause of diabetes mellitus, were identified on the short arm of chromosome 6 [1, 2]. Hereditary haemochromatosis is one of the most common genetic disorders and predominantly affects Caucasians, with a prevalence of between 1 in 200 and 1 in 400 for homozygotes [3, 4]. More than 83% of patients studied who had hereditary haemochromatosis were found to be homozygous for a mutation of the *HFE* gene resulting in a Cys282Tyr amino acid exchange, 5% were heterozygous [1]. A second mutation (His63Asp) that is not linked to the Cys282Tyr polymorphism occurred on the remaining allele in 8 of 9 heterozygotes. Recent studies showed that this variant is also associated with the development of hereditary haemochromatosis but with lower penetrance [1, 5]. In total, 87% of patients with haemochromatosis were reported to be homozygous for *C282Y* or compound heterozygotes *C282Y/H63D* [1]. Iron overload such as in idiopathic haemochromatosis can cause diabetes and therapy with an iron-chelating agent improved glycaemic control in a group of patients with Type 2 diabetes [6]. Type 2 diabetes is typically, however, not associated with subclinical iron overload [2]. Since heterozygosity for clinical haemochromatosis was associated not only with an increased risk for colorectal neoplasia but also for diabetes mellitus [7], we hypothesised whether heterozygosity for hereditary haemochromatosis causing mutations could be a risk factor for diabetes mellitus. Accordingly we screened patients with Type 2 diabetes for the two identified *HFE* mutations. The Cys282Tyr mutation was analysed in 206 patients and 175 control subjects, the His63Asp mutation in 195 patients and 180 control subjects. Patients with Type 2 diabetes had been treated for at least 3 years from diagnosis by diet or oral antihyperglycaemic agents. Healthy control subjects had no family history of diabetes. Oligonucleotides for poly-

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