DIABETES/METABOLISM RESEARCH AND REVIEWS
*Diabetes Metab Res Rev* 2004; **20**(Suppl 2): S47–S49.
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/dmrr.515

**REVIEW ARTICLE**

# Asymptomatic hypoglycaemia: identification and impact

Ramon Gomis*
Enric Esmatjes

*Endocrinology and Diabetes Service, Hospital Clínic Universitari, IDIBAPS, Faculty of Medicine, University of Barcelona, Barcelona, Spain*

*Correspondence to: Ramon Gomis, Endocrinology and Diabetes Service, Hospital Clínic Villarroel, 170, 08036 Barcelona, Spain.
E-mail: gomis@medicina.ub.es

*Received: 27 May 2004*
*Revised: 27 May 2004*
*Accepted: 19 July 2004*

## Summary

The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive management in people with type 1 diabetes delays the onset and the progression of microvascular complications associated with the disease. However, it is also known that intensive regimens can increase the number of hypoglycaemias and that the perception of symptoms decreases in relation to the statutes of metabolic control [1]. Impairment of hypoglycaemic awareness is reported by up to 50% of patients with type 1 diabetes and it is associated with an increase of severe episodes of hypoglycaemia [2]. Self-monitoring of blood glucose (SMBG) has become a major tool in the management of diabetes. Current recommendations suggest frequent SMBG. The major inconvenience of SMBG is due to the limitations of the glycaemic profile obtained from intermittent finger-sticks. This is an incomplete picture of blood glucose excursions; moreover, the frequent SMBG is not readily accepted by patients suffering from diabetes because it is invasive and painful. 

**Keywords** hypoglycaemia; subcutaneous glucose sensor; pancreas transplantation

## Frequency of severe hypoglycaemia

Most episodes of hypoglycaemia are treated at home or at work by the patient or – when the hypoglycaemia is severe – by relatives or colleagues and do not require the assistance of the emergency medical services. The physical morbidity of an episode of hypoglycaemia ranges from unpleasant symptoms to cognitive dysfunction and coma. Recent studies demonstrated that the burden of severe hypoglycaemia is greater in people suffering from type 1 diabetes, suggesting that the recognized hypoglycaemia represents the tip of the iceberg. On the other hand, in one of these studies, the frequency of severe hypoglycaemia was similar in type 1 and type 2 insulin-treated patients matched for the duration of insulin therapy, indicating that iatrogenic hypoglycaemia becomes a progressively more frequent clinical problem [1,3].

Hypoglycaemia and rapid changes in blood glucose have been shown to increase counter-regulatory hormones such as epinephrine and norepinephrine, which may induce vasoconstriction, platelet aggregation, and consequently ischemia. Several studies have documented electrocardiogram changes, that is, arrhythmias, in acutely induced hypoglycaemia. However, few data were provided about the relationship between cardiac ischemia and spontaneous hypoglycaemia, probably because of the difficulties to obtain one available continuous record of hypoglycaemic episodes [4].

There are other clinical events, such as islet or pancreas transplantation, where hypoglycaemic episodes can result in considerable fear and anxiety.

The pathogenesis of hypoglycaemia in patients with pancreas transplantation remains unclear. In patients with pancreas transplantation with venous drainage, the first pass of insulin and glucagon in the liver is absent as it occurs in other metabolic disturbances such as hepatic failure or cirrhosis of the liver.

Consequently, the hepatic clearance of insulin and glucagon can be altered, resulting in peripheral hyperinsulinaemia and less glucagon inflow to hepatic tissue, probably inducing hypoglycaemia. Another alternative mechanism is a deficit in the counter-regulatory hormone due to other concomitant complications as autonomic neuropathy. The attenuated epinephrine response to hypoglycaemia is a marker of an attenuated autonomic, sympathetic neural as well as adrenomedullary, response that causes the clinical syndrome of hypoglycaemia unawareness – loss of the warning, largely neuropenic symptoms of developing hypoglycaemia. Even in post-transplant diabetic patients, hypoglycaemic unawareness increases the risk of severe hypoglycaemia, so there is a risk of vitreous haemorrhage and blindness [1–3].

## Usefulness of a continuous glucose monitoring system

Recently, we have investigated the risk of hypoglycaemia in diabetic patients treated with pancreas and kidney transplantation (see Table 1). This treatment is indicated in type 1 diabetes suffering end-stage renal disease. We have determined continuous blood glucose using a new subcutaneous glucose sensor monitor (SGSM), Glucoday (A. Menarini Diagnostics), which uses microdialysis of subcutaneous tissue to identify glucose concentrations that mimic blood glucose values. The application of this technology to patients with combined pancreas and renal transplant provides the opportunity to know the real glycaemic profile of the patient throughout the day [5,6].

We analysed 12 patients, consecutively seen in our patient clinic, who fulfilled the criteria of combined pancreas and kidney transplant with normal function of both grafts. The presence of hypoglycaemia was defined when blood glucose levels were lower than 3.3 mmol/L. Moreover, at the end of the study, each patient was evaluated in order to inform us about the discomfort and pain of fibre insertion during the monitoring period.

**Table 1. Frequent factors causing hypoglycaemia in diabetes**

| Patient | Factor |
|---|---|
| Type 1 diabetes | Erroneous administration of dose of insulin |
| Type 2 diabetes | Erroneous dose of sulfonylureas or glinides |
| Type 1 diabetes | Exercise without modification of therapeutic schedule |
| Type 1 diabetes | Skip a meal without modification of therapeutic schedule |
| Type 2 diabetes | Exercise in patients treated by hypoglycaemic sulfonylureas or glinides |
| Type 2 diabetes | Skip a meal without modification of therapeutic schedule |
| Type 1 and 2 | Concomitant medication with hypoglycaemic effects |
| Type 1 diabetes | Brittle diabetes |
| Type 1 diabetes | Kidney and pancreas transplantation |

Asymptomatic episodes of hypoglycaemia during the nocturnal period were observed in three of the twelve patients. Blood glucose levels spontaneously achieved normal values. The subcutaneous glucose sensor monitor was well tolerated and no complications were observed at the site of implantation. On the other hand, subcutaneous glucose concentrations determined by GlucoDay were well correlated with capillary blood glucose determinations ($r$ 0.66, $p \leq 0.01$).

Probably the most interesting finding of the study was the confirmation of the underestimated presence of unrecognized hypoglycaemias in the diabetic population treated by combined pancreas and kidney transplant with normal function of both organs, especially during the nocturnal period [7]. The clinical significance of hypoglycaemia in patients with combined pancreas and kidney transplant is not known. However, the identification of hypoglycaemias is not only an academic entelechy [8–10]. It is also essential to avoid these events in order to maintain a good quality of life. In this sense, the possibility of continuous monitoring of glucose using GlucoDay provides a useful information to identify patients presenting hypoglycaemia and, in addition, to prevent the consequences of this disturbance.

To summarize, the continuous glucose monitoring in routine clinical practice is useful in analysing the glucose profile under real-life conditions, as well as during the nocturnal period to detect unawareness hypoglycaemic episodes, by including groups of patients treated with combined pancreas and kidney transplantation.

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