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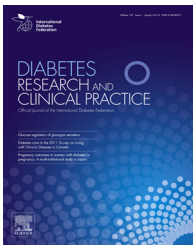

Insulin requirement profiles of short-term intensive insulin therapy in patients with newly diagnosed type 2 diabetes and its association with long-term glycemic remission

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ABSTRACT

Aims: To investigate the insulin requirement profiles during short-term intensive continuous subcutaneous insulin infusion (CSII) in patients with newly diagnosed type 2 diabetes and its relationship with long-term glycemic remission.

Methods: CSII was applied in 104 patients with newly diagnosed type 2 diabetes. Daily insulin doses were titrated and recorded to achieve and maintain euglycemia for 2 weeks. Measurements of blood glucose, lipid profiles as well as intravenous glucose tolerance tests were performed before and after the therapy. Afterwards, patients were followed up for 1 year.

Results: Total daily insulin dose (TDD) was 56.6 ± 16.1 IU at the first day when euglycemia was achieved (TDD-1). Thereafter, TDD progressively decreased at a rate of 1.4 ± 1.0 IU/day to 36.2 ± 16.5 IU at the end of the therapy. TDD-1 could be estimated with body weight, FPG, triglyceride and waist circumference in a multiple linear regression model. Decrement of TDD after euglycemia was achieved (ΔTDD) was associated with reduction of HOMA-IR ($r = 0.27$, $P = 0.008$) but not with improvement in β cell function. Patients in the lower tertile of ΔTDD had a significantly higher risk of hyperglycemia relapse than those in the upper tertile within 1 year (HR 3.4, 95%CI [1.4, 8.4], $P = 0.008$).

Conclusions: There is a steady decline of TDD after euglycemia is achieved in patients with newly diagnosed type 2 diabetes treated with CSII, and ΔTDD is associated with a better long-term glycemic outcome.

1. Introduction

High prevalence of type 2 diabetes has become a major public health concern all over the world. In China, it's estimated that 11.6% of Chinese adult have diabetes, while only less than 40% achieving the glycated hemoglobin A1c (HbA1c) target of 7% [1]. Prospective research has shown that early intensive glycemic control could result in long-term micro-vascular and possible macro-vascular benefits in type 2 diabetes [2,3].

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However, persistent maintenance of optimal glycemic control is one of the major challenges in the management of type 2 diabetes. As decline of β cell function is irreversible to date, the effects of anti-hyperglycemic agents may fade over time, leading to deterioration of glycemic control [4]. Elevation of blood glucose in turn accelerates the process of β cell failure via glucotoxicity. New therapeutic strategies are required to stop the vicious cycle.

Short-term intensive insulin therapy has been employed in the management of newly diagnosed type 2 diabetes in recent years. In previous studies, short-term intensive insulin therapy ameliorated β cell dysfunction, especially acute insulin response (AIR) [5–7], as well as insulin resistance measured by HOMA-IR [7,8], thereby inducing a prolonged glycemic remission of over 1 year without anti-hyperglycemic agents in more than 50% of patients [7,9]. Based on these benefits, short-term intensive insulin therapy was recommended for selective patients with newly diagnosed type 2 diabetes in Chinese guidelines [10].

However, relatively long hospitalization periods for titrating insulin dosage and frequent monitoring of blood glucose limit the application of the therapy. As the decision and subsequent titration of insulin dosage is highly reliant on the experience of the physicians, 4–6 days was usually required for achieving glycemic targets. Lack of knowledge about the insulin requirement profiles during the therapy may delay the achievement of euglycemia and, what is worse, increase the risk of hypoglycemia. Another question that remains unanswered is which factors predict glycemic remission. Several post-therapy indicators such as increment of AIR, reduction of HOMA-IR, 1,5-anhydroglucitol, fasting plasma glucose (FPG) and 2-h post-prandial blood glucose (2hPG) [7,8,11–13], have been suggested as possible indicators of remission. However, earlier and more potent predictors are still of interest. Therefore, we performed this retrospective study investigating the insulin requirement characteristics during short-term continuous subcutaneous insulin infusion (CSII) therapy in patients with newly diagnosed type 2 diabetes in order to refine the insulin titration procedure. In addition, we also examined the relationship between long-term glycemic remission and change of insulin requirement during the therapy.

2. Subjects

One hundred and four drug naïve patients with newly diagnosed type 2 diabetes were included from the CSII treated alone group in two independent randomized control trials (NCT00948324 and NCT01471808, ClinicalTrials.gov) performed in the Endocrinology department of The First Affiliated Hospital of Sun Yat-sen University from June 2007 to May 2013. Both studies shared similar recruitment criteria which have been described elsewhere [14]. Briefly, patients were diagnosed according to the World Health Organization 1999 diagnostic criteria [15]. The included patients were between 25 and 70 years old, with body mass index (BMI) between 21 and 35 kg/m^2 and fasting plasma glucose (FPG) between 7.0 and 16.7 mmol/L. Patients with acute or severe chronic complications of diabetes, severe concomitant diseases, use of medication which vastly influence glycemic levels, and positive for glutamic acid decarboxylase antibody were excluded. This research was approved by the research ethics board of Sun Yat-Sen University. Signed informed consent was obtained from each participant.

3. Materials and methods

3.1. Study design

All patients were admitted to hospital. Before treatment, there was a 2–3 day run-in period during which baseline evaluations were carried out. CSII was implemented to achieve glycemic targets (FPG between 4.4 mmol/L and 6.0 mmol/L and 2hPG between 4.4 mmol/L and 7.8 mmol/L) using insulin lispro (Humalog, Eli Lilly and Company, USA) or insulin aspart (Novo Nordisk, Bagsværd, Denmark). The initial insulin dose was delivered with a total daily dose (TDD) of 0.4–0.5 IU/kg, 50% of which was assigned as total basal dose and 50% as total pre-meal dose. Initial total basal dose was administered evenly throughout 24 h, and total pre-meal dose was divided equally before each meal. Insulin doses were adjusted according to the results of capillary blood glucose measurements, which were carried out eight times daily (before and 2 h after breakfast, lunch and supper, 11 pm, and 3 am). Everyday insulin requirement profiles were recorded. After glycemic targets were maintained for 14 days, CSII was withdrawn and baseline assessments were repeated the next day (at least 15 h after the cessation of insulin therapy). No medicine for hyperlipidemia was given during the therapy.

During hospitalization, all patients received an education program concerning diabetes self-management, which included sports advice, life style modification, and food intake guidance. Calories were calculated by a nutritionist to ensure that carbohydrates, protein and fat accounted for 50–60%, 10–15% and 20–30% of total calories, respectively, as recommended by current Chinese guideline [10]. Patients were encouraged to take a 1-h post-meal walk after each dinner. After withdrawal of CSII, all patients were followed monthly for 3 months and every 3 month thereafter with FPG and 2hPG monitored. Glycemic remission was defined as FPG < 7.0 mmol/L and 2hPG < 10.0 mmol/L without any anti-hyperglycemic agents [5,7,14]. Life-style modifications were recommended to be maintained after hospital discharge. Patients who had hyperglycemia relapse were reassessed a week later. If hyperglycemia was reconfirmed, anti-hyperglycemic agents were initiated according to current guidelines for diabetes.

3.2. Blood sampling and measurements

At baseline, demographic and anthropometric data, such as body weight, height, and waist circumference, were recorded. Venous blood was drawn for measurements of FPG, 2hPG (after breakfast), and lipid profiles. An intravenous glucose tolerance test (IVGTT) was performed on the subsequent morning in the fasting state using 50 mL of 50% glucose solution as previously described [7]. Blood samples were