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Baseline red blood cell distribution width predicts long-term glycemic remission in patients with type 2 diabetes

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ABSTRACT

Aims: We explored whether red blood cell distribution width (RDW), a routinely checked item of complete blood cell counts, was an indicator of long-term euglycemia remission in patients with type 2 diabetes after short-term continuous subcutaneous insulin infusion (CSII).

Methods: We analyzed the original data of patients enrolled in three randomized control trials from 2002 to 2014. CSII was administered to drug-naïve patients with newly diagnosed type 2 diabetes to achieve and maintain euglycemia for 2 weeks.

Results: A total of 185 patients were involved and 98 patients (52.97%) who achieved and maintained euglycemia for at least 12 months were classified as the remission group, and the others as the non-remission group. Patients in remission group had a relatively lower value for baseline RDW (38.82 ± 2.76 vs 39.89 ± 2.78 fL, $p = 0.017$) compared with those in non-remission group. A graded decrease of remission rate (67.50%, 55.00%, 53.66% and 30.77% for Quartile 1 to Quartile 4 respectively, $P < 0.05$) was observed with the increasing of RDWs. The risk of hyperglycemic relapse was significantly increased for those in the highest quartile compared with the lowest (hazard ratio = 2.68; 95% CI, 1.38–5.22). Those who achieved euglycemia within 7 days or obtained a better fasting glucose after therapy had preferable remission rates.

Conclusions: Patients with lower baseline RDWs are more likely to maintain a one-year euglycemia remission after short-term CSII. A faster normalization of glucose during treatment and a lower fasting glucose after therapy are correlated with a long-term glucose control.

1. Introduction

The number of patients with diabetes is dramatically increasing due to the population boom, aging, urbanization, obesity and sedentary lifestyles, resulting in a heavy burden on family and society [1]. The natural course of diabetes is characterized by the progressive deterioration of β-cell function over time, irrespective of lifestyle changes and pharmacological inter-

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ventions [2]. New therapies, such as glucagon-like peptide-1 (GLP-1), can ameliorate β-cell dysfunction in animal or in vitro experiments [3–5], yet have no effect on human β-cell regeneration [6]. Our previous studies have demonstrated that early short-term subcutaneous insulin infusion (CSII) can restore some β-cell function, improve the acute insulin response (AIR), induce a long-term drug-free euglycemic remission and thus make itself a promising method. However, nearly half of the patients experienced hyperglycemic relapses during the one-year follow-up [7–9]. Therefore, determining potentially influential factors of euglycemic remission is necessary.

It is well-known that diabetes is a complex metabolic disorder, the development and progression of which and its complications are potentially driven by oxidative stress and inflammation. Recent studies have shown that the red blood cell distribution width (RDW), which is related to impaired erythrocyte generation and degradation, reflecting a high level of oxidative stress and chronic inflammation, is a novel prognostic marker in patients with diabetes or cardiovascular diseases [10]. A growing number of studies have implied that the values of RDW are associated with glucose levels [11]. A larger RDW, even within the normal range, is correlated with an increased risk of developing complications in patients with type 2 diabetes [12]. As a measurement of the variability in size of circulating red blood cells, RDW can be conveniently determined by using complete blood cell counts (CBCs) without any additional costs. It might be an economical marker that provides information independent of traditional risk factors for the progression and treatment of diabetes.

So in this study, we examined the influence factors of long-term euglycemic remission after 2–3 weeks of intensive insulin therapy and explored whether RDW played a role in glycemic remission.

2. Subjects and methods

2.1. Subjects

We analyzed the original data from the drug-naive patients with newly diagnosed type 2 diabetes who were enrolled in three randomized controlled trials from 2002 to 2014 with similar inclusion and exclusion criteria (NCT00147836, NCT00948324 and NCT01471808). Patients aged 25–70 years were diagnosed type 2 diabetes mellitus based on 1999 World Health Organization diagnostic criteria, with a fasting plasma glucose (FPG) ranging from 7.0 to 16.7 mmol/L and a body mass index (BMI) 21–35 kg/m^2. To avoid interference from the disparity of therapies, only those who received CSII therapy alone were included in our study. Patients who used multiple daily insulin injections, oral antidiabetic drugs, or combinational therapy of CSII and other agents were uninvolved. Patients with anemia, infections, stroke, heart attack, acute complications or chronic complications of diabetes such as diabetic nephropathy and retinopathy, which indicated that the disease was not of recent onset, were excluded from the study. Those who had suffered severe concomitant diseases or who had any conditions that would greatly influence glycemic levels were also excluded.

2.2. Study design

Following a 2–3-day run-in period before hospitalization, patients underwent baseline evaluations and an intravenous glucose tolerance test (IVGTT). CSII was implemented to achieve and maintain glycemic targets (FPG 4.4–6.0 mmol/L and 2-h PG 4.4–8.0 mmol/L) as soon as possible by using insulin lispro (Humalog, Eli Lilly Inc., USA) or insulin aspart (NovoRapid, Novo Nordisk, Denmark). The initial dosage was 0.4–0.8 IU/kg/day based on glucose levels, 50% of which was assigned as a basal dosage and the remainder as a bolus divided equally into three pre-meal infusions. Capillary blood glucose was monitored 8 times per day (before and 2 h after each meal, bedtime and 3 AM) during CSII therapy. Insulin doses were titrated daily according to the results of the capillary glucose measurements to achieve euglycemia. After glycemic targets were achieved and maintained for 14 days, CSII was suspended and IVGTT was repeated on the following day. Patients were then discharged from hospital and followed up every 3 months until hyperglycemia relapsed.

The patients were educated on diet, physical exercise, lifestyle improvements, and self-management during hospitalization. They were instructed to incorporate lifestyle modifications regardless of whether they were in the hospital or discharged. All patients were evaluated every 3 months. Glycemic remission was defined as FPG < 7.0 mmol/L and 2-h PG < 10.0 mmol/L in patients without any hypoglycemic agents. If the glucose level exceeded this range, it was defined as a hyperglycemic relapse. Appropriate antidiabetic drugs or insulin would then be supplied based on the American Diabetes Association (ADA) guideline of the year to those patients with hyperglycemic relapse. Patients whose glucose met the criteria of glycemic remission during one-year follow-up were classified as the remission group, otherwise as the non-remission group.

2.3. Measurements

Anthropometric indices such as age, gender, smoking habits, and BMI were recorded, and laboratory data including CBCs, FPG, 2 h PG, glycated hemoglobin (HbA1c), and lipid profiles were assessed. Insulin secretion was estimated by assessing the acute insulin response (AIR) during an IVGTT before and after CSII suspension. AIR was calculated as the incremental trapezoidal area during the first 10 min after infusion of 25 g glucose.

2.4. Statistical analysis

All statistical analyses were performed using the SPSS15.0 statistical software package. Normally distributed data, expressed as the means ± standard deviations (SDs), were analyzed using the *t* test (two groups) or single-factor analysis of variance (multiple groups). Non-normally distributed variables that could not transformed into normally distributed data were presented as medians (interquartile ranges) and analyzed using the rank-sum test to identify significance differences between groups. The chi-square test was used to analyze frequencies. And 95% confidence intervals (95% CI)