Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Is there a "burnt-out diabetes" phenomenon in patients on hemodialysis?

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ARTICLE INFO

Article history:
Received 24 March 2017
Received in revised form
21 May 2017
Accepted 6 June 2017
Available online 13 June 2017

Keywords:
Diabetes
Dialysis
Glycemic control
Glycated albumin
Glycated hemoglobin

ABSTRACT

Aims: In patients with diabetes on hemodialysis (HD), glycemic control improves spontaneously, leading to normal glycated hemoglobin (HbA1c) levels; this phenomenon is known as "burnt-out diabetes." However, glycated albumin (GA) might be a better indicator of glycemic control than HbA1c in HD patients. Therefore, the aim of this study was to identify how many patients experience "burnt-out diabetes" using HbA1c and GA levels and to examine the association between cardiovascular comorbidity risk and GA levels.

Methods: Patients with diabetes on HD whose HbA1c levels were measured and whose antidiabetic therapy was recorded were included. First, the "burnt-out diabetes" phenomenon was investigated in patients whose HbA1c levels were measured (HbA1c cohort). Then, it was investigated in patients who were assessed for both HbA1c and GA levels (GA cohort). Risk of cardiovascular comorbidity was assessed using multivariable logistic regression models.

Results: In the HbA1c cohort, 60,019 patients were included. When "burnt-out diabetes" was defined as HbA1c < 6.0% without treatment with antidiabetic medication, it was noted in 11,159 patients (18.6%). In the GA cohort, 23,668 patients were included, and it was found in 4899 patients (20.7%). However, when "burnt-out diabetes" was defined as HbA1c < 6.0% and GA < 16.0% without treatment with antidiabetic medication, it was found in 1286 patients (5.4%). Patients with GA > 18% had a higher risk of cardiovascular comorbidity.

Conclusions: Although the "burnt-out diabetes" phenomenon might be present in 20.7% of patients with diabetes on HD in terms of HbA1c, the rate was significantly decreased to 5.4% in terms of GA.

Conclusions: Clinical Trial Registration number: UMIN000018641

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http://dx.doi.org/10.1016/j.diabres.2017.06.012
0168-8227/

1. Introduction

In patients with diabetes on dialysis with a presumptive diagnosis of diabetic nephropathy, glycemic control improves spontaneously with the progression of chronic kidney disease, loss of residual kidney function, and the initiation of dialysis therapy, leading to normal-to-low levels of glycated hemoglobin (HbA1c) and glucose irrespective of treatment; this phenomenon is commonly observed and is referred to as "burnt-out diabetes" [1–4]. In patients undergoing hemodialysis (HD), the life span of red blood cells is shorter, and blood loss and hemorrhage may occur during HD; thus, by increasing the proportion of young erythrocytes in the blood, both anemia and erythropoiesis-stimulating agents (ESAs) can falsely lower the HbA1c level, which can lead to hyperglycemia being missed. Therefore, patients on HD tend to show low HbA1c levels, which may underestimate glycemic control. Indeed, this phenomenon may be one of the causes of "burnt-out diabetes." In contrast, the glycated albumin (GA) level is not significantly associated with the life span of red blood cells, hemoglobin level, or ESA dose in patients with diabetes undergoing HD [5–7]. Therefore, GA might be a better indicator of glycemic control than HbA1c in diabetic HD patients. However, the optimal target for GA levels in HD patients with diabetes has not been elucidated. We conducted a cohort study of a nationwide registry of HD patients in Japan in order to identify how many patients experience "burnt-out diabetes" by using HbA1c and GA levels; we also examined the association between cardiovascular comorbidity risk and GA levels.

2. Materials and methods

2.1. Database creation

The data were obtained from the annual nationwide surveys of dialysis patients conducted by the Japanese Society for Dialysis Therapy (JSDT). The surveys were conducted by JSDT volunteers, with details described previously [8]. Briefly, data covered 314,438 patients dialyzed at 4268 facilities in the 2013 survey [9]. The study population consisted of patients who received maintenance dialysis therapy in December 2013. We included patients with diabetes and/or diabetic nephropathy whose HbA1c levels were measured and whose antidiabetic therapy was recorded. We excluded patients without a history of diabetes, those who were dialyzed fewer than 3 times a week or fewer than 2 h per treatment, those who had received peritoneal dialysis, and those whose records for date of birth and dialysis initiation were incomplete.

After exclusions, 60,019 patients remained and were included as the HbA1c cohort (Fig. 1). Demographic data and details of medical history were collected, including information on age, sex, dialysis vintage, height, body weight post-dialysis, smoking, history of cardiovascular complications (coronary artery disease, cerebral hemorrhage, cerebral infarction, or limb amputation), type of diabetes, antidiabetic therapy, and antihypertensive drug use.

Antidiabetic therapy was divided into three categories as no medication, insulin therapy, and oral antidiabetic medication only. No medication included patients who were treated with diet modification therapy only or who were not prescribed antidiabetic medication. Insulin therapy included insulin injection therapy only or combination therapy of insulin with any oral antidiabetic medication.

Blood samples were drawn and measured at each dialysis center, typically within 24 h of the sample being taken, and the most recent values at the time of the survey were recorded. Most laboratory values were measured monthly—and at least quarterly—including HbA1c, GA, serum albumin, hemoglobin, calcium, and phosphate. GA was measured using an enzymatic method on a liquid chemistry system on a clinical autoanalyzer. The GA value was calculated as the percentage of GA relative to the total albumin level, which was measured with the new bromocresol purple method using the same serum sample [10].

2.2. Definition of "burnt-out diabetes"

In the HbA1c cohort, "burnt-out diabetes" was defined as follows: (1) patients who had HbA1c level <6.0% and (2) who were not treated with any antidiabetic medication such as insulin and/or oral antidiabetic agents [1–4]. Next, patients in whom both HbA1c and glycated albumin (GA) levels were measured were included in the GA cohort (Fig. 1). After exclusion, 23,668 patients remained and were included in the GA cohort. In the GA cohort, the rate of "burnt-out diabetes" was investigated using HbA1c levels only. Further analysis was performed using HbA1c and GA levels, and "burnt-out diabetes" was defined as follows: (1) patients who had HbA1c level < 6.0%, (2) who had GA level < 16.0%, and (3) who were not treated with any antidiabetic medication. The GA level was set at < 16% because the standard values of GA in the general population are 11.0–16.0% [11]. Similar to the definition for HbA1c levels, we defined GA < 16.0% as burnt-out diabetes priori. The association between cardiovascular comorbidity risk and HbA1c and GA levels were assessed in the GA cohort.

2.3. Statistical methods

Data were summarized using proportions, with means ± standard deviation or median [interquartile range] as appropriate. Categorical variables were analyzed with the chi-square test, and continuous variables were compared using the *t*-test as appropriate. Comparisons of the categorical data between groups were performed by using a repeated-measures analysis of variance (ANOVA) and the Kruskal–Wallis test, as appropriate. Correlations between GA and HbA1c levels were determined by using the Pearson's correlation coefficient. Laboratory data were refined using these limits to exclude outliers: height, 120–200 cm; body weight, 20–150 kg; albumin, 1.0–5.5 g/dL; hemoglobin, 5.0–20.0 g/dL; HbA1c, 4.0–17.0%; and