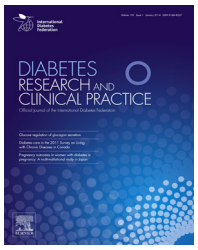
Contents available at ScienceDirect

Diabetes Research and Clinical Practice

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

International Diabetes Federation



Risk factors for the development of glucocorticoid-induced diabetes mellitus

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ARTICLE INFO

Article history:
Received 14 May 2014
Received in revised form
9 October 2014
Accepted 6 February 2015
Available online 21 February 2015

Keywords:
Glucocorticoid-induced diabetes mellitus
Risk factor
Rheumatic disease
Renal disease

ABSTRACT

Aims: To evaluate the incidence of glucocorticoid-induced diabetes mellitus (GC-DM) by repeated measurements of the postprandial glucose and detect predictors for the development of GC-DM.

Methods: Inpatients with rheumatic or renal disease who received glucocorticoid therapy were enrolled in this study. We compared the clinical and laboratory parameters of the GC-DM group with the non-GC-DM group and performed a multivariate analysis to identify risk factors.

Results: During a four-week period, 84 of the 128 patients (65.6%) developed GC-DM. All patients were diagnosed based on the detection of postprandial hyperglycemia. The GC-DM group had an older age (65.2 vs. 50.4 years, $p < 0.0001$), higher levels of fasting plasma glucose (93.3 vs. 89.0 mg/dl, $p = 0.027$) and HbA1c (5.78 vs. 5.50%, 39.7 vs. 36.6 mmol/mol, $p = 0.001$) and lower eGFR values (54.0 vs. 77.1 ml/min/1.73 m^2, $p = 0.0003$) than the non-GC-DM group. According to the multivariate analysis, an older age (more than or equal to 65 years), higher HbA1c level (more than or equal to 6.0%) and lower eGFR (<40 ml/min/1.73 m^2) were identified as independent risk factors for GC-DM (OR 2.95, 95% CI 1.15–7.92, OR: 3.05, 95% CI 1.11–9.21, OR: 3.42, 95% CI: 1.22–10.8, respectively). The risk ratio for the development of GC-DM in the patients with at least one of these three risk factors was 2.28. The dose of glucocorticoids was not statistically related to the development of GC-DM.

Conclusions: Patients with an older age, higher HbA1c level and lower eGFR require close monitoring for the development of GC-DM, regardless of the dose of glucocorticoids being administered.

1. Introduction

Since the efficacy of glucocorticoids for rheumatoid arthritis (RA) was reported, glucocorticoid therapy has been used for the treatment of many inflammatory and autoimmune diseases. Although the introduction of biologic and other immunosuppressive agents has brought about a paradigm shift in the treatment of rheumatic diseases, glucocorticoids remain the major drugs in the treatment of rheumatic diseases, such as systemic vasculitis [1], systemic lupus erythematosus (SLE) [2] and myositis [3]. Glucocorticoids are

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http://dx.doi.org/10.1016/j.diabres.2015.02.010
0168-8227/

also widely used to treat primary nephrotic syndromes, such as membranous nephropathy [4], minimal change nephrotic syndrome (MCNS) [5] and membranoproliferative glomerulonephritis [6].

Various adverse effects of glucocorticoids have been recognized, including infection, osteoporosis, psychiatric disorders, gastrointestinal injury, cataracts, hypertension, arteriosclerosis and so on. Among these side effects, hyperglycemia is a critical systemic effect of glucocorticoid treatment. Glucocorticoids not only aggravate glycemic control in patients with diabetes mellitus (DM), but also cause hyperglycemia in patients without DM prior to the initiation of glucocorticoid therapy. Multiple mechanisms are believed to be involved in the development of glucocorticoid-induced DM (GC-DM), such as increases in hepatic glucose production, the inhibition of glucose uptake into the muscle and adipose tissue and decreases in the β-cell function [7–9]. Persistent and even short-term hyperglycemic conditions impair the immune function and increase the risk of infection and vascular events [10]. It has also been reported that GC-DM is an independent risk factor for vertebral fractures under high-dose glucocorticoid therapy [11].

The incidence of GC-DM ranges widely in previous reports, and several risk factors for the development of GC-DM have been identified [12–18]. The differences in findings depend on variability in the underlying diseases, dose of glucocorticoids, observation period and definition of GC-DM evaluated in each study. In addition, the frequency of measurement of the daily blood glucose profile also influences the incidence of GC-DM. Although glucocorticoids are known to induce postprandial hyperglycemia, few reports have evaluated this issue based on sufficient postprandial glucose measurements. Therefore, we evaluated the incidence of GC-DM among inpatients with rheumatic and renal diseases, whose glucose levels were measured frequently and explored predictors for the development of GC-DM within a short period after the initiation of glucocorticoid therapy.

2. Patients and methods

2.1. Patient population

We retrospectively reviewed the medical charts of inpatients with rheumatic or renal disease who started glucocorticoid therapy in the nephrology or rheumatology unit of Okayama University Hospital between April 2006 and December 2013. Patients in whom postprandial glucose was measured at least three times for during the four-week observation period were enrolled in this study. The exclusion criteria were as follows: a previous diagnosis of DM; either a high hemoglobin A1c (HbA1c) value (6.5% or greater, NGSP) or a high serum fasting plasma glucose level (126 mg/dl or greater) prior to the initiation of glucocorticoid therapy; a past history of receiving glucocorticoid therapy.

2.2. Diagnosis of glucocorticoid-induced DM

Following the initiation of glucocorticoid therapy, the blood glucose levels were assessed using glucose meters; in most cases, the Medisafe® device was used.

Patients exhibiting either a fasting glucose level of 126 mg/dl or higher, or a postprandial glucose level of 200 mg/dl or more twice after the initiation of glucocorticoid therapy were diagnosed with GC-DM.

2.3. Laboratory analysis

The following clinical and laboratory parameters obtained before the initiation of treatment with glucocorticoids were extracted from the patients' medical records: age, gender, body mass index (BMI), family history of DM, presence of hypertension, fasting plasma glucose, HbA1c, white blood cell (WBC) count, red blood cell (RBC) count, estimated glomerular filtration rate (eGFR), serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), low-density lipoprotein (LDL)-cholesterol and triglycerides and treatments (use of methylprednisolone pulse therapy, maximum dose of glucocorticoids, total dose of glucocorticoids and dose of glucocorticoids at the 28th day).

2.4. Statistical analysis

The paired *t*-test and Chi-square test were performed to analyze differences between the GC-DM group and the non-GC-DM group. Subsequently, we performed a logistic regression analysis to identify independent risk factors. In a multivariate analysis, continuous variables, except for age, were changed to categorical variables using quartiles. Age was divided into two categories (>65 years or less than or equal to 65 years). Candidate risk factors were selected according to the results of the univariate analysis and the findings of previous reports. A p value of less than 0.05 was considered to indicate a statistically significant difference. All statistical analyses were performed using the JMP 9.0 software package (SAS Institute Inc., Cary, NC, USA). The patient background data are presented as the mean ± SD, and the data in the table comparing the characteristics of the groups are given as the mean ± SE.

2.5. Ethical considerations

The study protocol was compliant with the Helsinki Declaration and was approved by the Ethics Committee of the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences (authorization number: No. 1916). Informed consent to participate in the study and to have their data published was obtained from each patient.

3. Results

3.1. Patient background characteristics

We recruited 184 inpatients treated with glucocorticoid therapy. Of these patients, 56 were excluded because their postprandial glucose measurements were taken less than three times. Therefore, 128 patients were enrolled in this study. The mean frequency of postprandial glucose measurements during the first two weeks after the initiation of glucocorticoid therapy was 10.6 ± 8.0 times. The patient population comprised 79 (61.7%) females and 49 (38.3%)