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What is the optimal time for measuring glucose concentration to detect steroid-induced hyperglycemia in patients with rheumatic diseases?

Güven Barış Cansu[a], Döndü Üsküdar Cansu[b,*], Bengür Taşkıran[a], Şule Yaşar Bilge[b], Muzaffer Bilgin[c], Cengiz Korkmaz[b]

[a] Division of Endocrinology, Department of Internal Medicine, Eskişehir City Hospital, Eskişehir, Turkey
[b] Division of Rheumatology, Department of Internal Medicine, Eskişehir Osmangazi University, Eskişehir, Turkey
[c] Department of Biostatistics, Eskişehir Osmangazi University, Eskişehir, Turkey

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ABSTRACT

Objective: Corticosteroids may cause hyperglycemia and diabetes mellitus (DM). Development of DM during long-term steroid use has been well studied; however, data regarding the short-term effects of steroid therapy are scarce. In this study, we aimed to detect the actual time of short-term steroid-induced hyperglycemia in patients without previous impaired glucose metabolism, and the ideal time (which day and in relation to meals) of glucose measurement.

Methods: The 7-point blood glucose (BG) measurements of patients who were commenced moderate to high-dose steroids (≥15 mg/day prednisolone or its equivalent) due to rheumatological diseases during the first 5 days of steroid therapy were recorded. Fasting BG ≥ 7 mmol/L (126 mg/dL) or random BG ≥ 11.1 mmol/L (200 mg/dL) were considered as overt DM in accordance with the 2016 American Diabetes Association guideline, and post-meal BG ≥10 mmol/L (180 mg/dL) was considered as steroid-induced hyperglycemia.

Results: Fifteen males (mean age: 44 ± 16 years) and 35 females (mean age: 41 ± 12 years) were recruited to the study. One thousand seven hundred fifty fasting, pre-meal, and 2-hours post-meal BG concentrations were analyzed. Twenty-one (42%) patients developed steroid-induced DM and 39 (78%) developed steroid-induced hyperglycemia. The highest glucose concentrations were detected on the 3rd day of steroid therapy and 2-h after meals ($p < .0001$).

Conclusion: Intermediate to high-dose steroid therapy causes hyperglycemia after lunch and dinner on the 3rd day of treatment. This time period should be taken into consideration in the detection and treatment of steroid-induced hyperglycemia.

1. Introduction

Glucocorticoids are commonly used in a number of rheumatological, dermatological, neurological, and pulmonary diseases, and certain malignancies and transplant patients with the effect of their anti-inflammatory and immunosuppressive features [1]. Inflammatory status in the course of rheumatic disorders can lead to insulin resistance and hyperglycemia [2]. In addition to inflammation-induced hyperglycemia, prolonged steroid use may cause hyperinsulinemia, insulin resistance, and an inhibitory effect on beta cell functions, which may eventually lead to overt diabetes mellitus (DM). However, these unwanted effects of steroid use can be dose dependent [3]. Despite conflicting studies, insulin resistance is improved with low- dose steroids as inflammation resolves [4–6], whereas moderate to high-dose steroid use leads to hyperglycemia and overt DM [7]. It is well known that hyperglycemia seen in hospitalized patients is a factor that increases mortality and morbidity [8]. There is a close relationship between chronic hyperglycemia and cardiovascular events. Some studies showed that screening individuals at increased risk for diabetes might decrease cardiovascular mortality [9]. Therefore, screening and monitoring hyperglycemia is very important in patients with rheumatic disorders. The European League Against Rheumatism (EULAR) recommended glucose monitoring before starting therapy and during therapy for patients with active disease on low/moderate doses of steroids [10]. However, these recommendations are not clear regarding the screening of hyperglycemia in patients with rheumatic diseases.

Fasting glucose concentrations are commonly normal in patients with steroid-induced hyperglycemia [11,12]. However, it is generally

* Corresponding author at: Department of Rheumatology, School of Medicine, Eskişehir Osmangazi University, Eskisehir 26480, Turkey.
E-mail address: ducansu@hotmail.com (D.Ü. Cansu).

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accepted that steroids cause an increase in postprandial glucose concentrations [11–13]. Another question arises at this point. When does the onset of hyperglycemia occur and what is the best time of day to measure blood glucose concentrations for appropriate early treatment in patients taking moderate or high-dose steroid treatment for the first time? In the literature, there are no studies evaluating the first 5-day course of glucose concentrations after moderate to high-dose steroids in a rheumatological disease.

Our main aim was to detect the exact day and time of hyperglycemia onset in relation to meals during the early period (1–5 days) of intermediate to high-dosage steroid therapy (≥15 mg/day prednisolone or its equivalent) used for inflammatory rheumatological diseases in patients without any previously established impaired glucose metabolism and to detect the best time for glucose measurement. Our secondary aim was to detect the frequency of steroid-induced DM and probable risk factors.

2. Methods

2.1. Patient selection

Hospitalized patients in the rheumatology unit who were administered intermediate to high-dose steroids for inflammatory rheumatological diseases from January 2015 to January 2017, were retrospectively evaluated. The inclusion criteria were as follows:

1 Candidates for steroid therapy due to rheumatological diseases
2 Age older than 18 years
3 Fasting blood glucose (FBG) concentration < 5.5 mmol/L (100 mg /dL) before steroid commencement
4 Steroid dosage at least 15 mg/day prednisolone or its equivalent (the patients were distributed to 3 groups according to steroid dosage (15–29, 30–59, ≥60 mg/day).
5 Seven-point capillary blood glucose measurement at least for 5 consecutive days

The exclusion criteria were as follows:

1 Previous diagnosis of DM or history of antidiabetic medication
2 FBG over 5.5 mmol/L (100 mg/dL) or random blood glucose over 11.1 mmol/L (200 mg/dL) in electronic data or patients' anamnestic notes.
3 Missing data in 7-point capillary blood glucose measurements
4 Using drugs excluding steroids that may interfere with glucose concentrations
5 Impaired liver and renal function
6 Active infection during steroid therapy and glucose measurements

The demographic data of the study patients and type and duration of primary rheumatological disease, steroid type and dose, family history of DM, and previous history of steroid therapy were recorded.

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) [normal range 0–47.61 nmol/L (0–0.5 mg/dL)] on the 3rd day of steroid therapy were measured.

2.2. Blood glucose measurements and steroid-induced hyperglycemia and DM diagnostic criteria

Seven-point blood glucose measurements were started simultaneously with steroid therapy (day 1). Seven-point capillary blood glucose measurements (fasting, before lunch and dinner, 2 h after each main meal, and bedtime at 11 pm) were performed using a glucometer for at least 5 days. For the 7-point glucose measurements, an Optium H Free Style glucometer was used (Abbott Diabetes Care Roma, Italy). This glucometer uses a GDH-NAD (nicotinamide adenine dinucleotide glucose dehydrogenase) enzymatic reaction to measure glucose in whole blood. The glucometer meets the criteria of the ISO 15197:2013 guidelines.

The patients were stratified into two groups as DM developers and non-DM developers:

1 FBG ≥7 mmol/L (≥126 mg/dL) or random glucose concentration ≥ 11.1 mmol/L (≥200 mg/dL) were defined as DM developers [14].
2 The remaining patients were regarded as non-DM developers. The criteria for non-DM developers were as follows: FBG concentration below 5.5 mmol/L (100 mg/dL) and glucose measurements at any other time points below 11.1 mmol/L (200 mg/dL) were considered normal. Those with FBG 5.6–6.9 mmol/L (100–126 mg/dL) but random values below 11.1 mmol/L (200 mg/dL) were considered as impaired fasting glucose.

Random glucose concentrations between 10.0 and 11.05 mmol/L (180–199 mg/dL) that did not meet the abovementioned criteria were defined as hyperglycemia [15].

Peak glucose concentrations were detected for each patient. The highest glucose concentration was defined as peak glucose and its time point was noted. The study was approved by the local ethics committee of Eskişehir Osmangazi University Medical School (Decision Number: 80558721/G-77).

2.3. Statistical analysis

Continuous variables are given as mean ± standard deviation (SD) or median (Q1-Q3). Categorical variables are given as percentiles (%). The Shapiro-Wilk test was used to determine normal distribution. The Mann-Whitney *U* test was used to compare 2 groups of variables that were non-normally distributed, and the Kruskal-Wallis H test was used for ≥3 groups of non-normally distributed variables. The correlations between non-normally distributed variables were analyzed using Spearman correlation analysis. Cross tables were analyzed using the Pearson Chi-square and Pearson exact-tests. All statistical analyses were performed using IBM SPSS Statistics 21.0 software. $p < .05$ was regarded as statistically significant.

3. Results

3.1. Patient characteristics and distribution of steroid doses used

In our study, 15 male (mean age: 44 ± 16 years) and 35 female (mean age 41 ± 12 years) patients were analyzed. The distribution of rheumatological diseases and their brief features are shown in Table 1. Seven (14%) patients were on 15–29 mg/day and 20 (40%) were on 30–59 mg/day prednisolone or its equivalent therapy, and 23 (46%) were using more than ≥60 mg/day prednisolone or its equivalent. The mean daily steroid dosage was 47.3 ± 18.5 mg. Twenty-three (46%) patients had used steroids for at least 6 months prior to the study. Eight (16%) patients had a family history of DM.

3.2. The rate of abnormal BG and mean hemoglobin A1c (HbA1c) concentrations

FBG ≥7 mmol/L (126 mg/dL) was detected in 15 (30%) patients, random glucose ≥11.1 mmol/L (200 mg/dL) was detected in 20 (40%), and random glucose ≥10 mmol/L (180 mg/dL) was detected in 39 (78%) patients. Twenty-one (42%) patients, who had either capillary FBG ≥7 mmol/L (126 mg/dL) and/or random glucose ≥11.1 mmol/L (200 mg/dL), were diagnosed as having steroid-induced DM. The mean HbA1c prior to the study was approximately 36 mmol/mol (5.46 ± 0.36%), and the mean fasting venous blood glucose was 4.8 ± 0.5 mmol/L (88.0 ± 9.9 mg/dL). All laboratory and demographic data and clinical features are shown in Table 1.

Table 1
Demographic and clinical features and laboratory data of the whole study group, and DM developers and non-DM developers.

Variable	Study group	DM developers	Non-DM developers	*p* value
n	50	21	29	–
Gender, Female/Male	35/15	16/5	19/10	0.167
Age, years	44.6 ± 13.5 (20–74)	41.9 ± 12.4	48.4 ± 14.4	0.067*
BMI, kg/m^2	25.1 ± 3.7	25.2 ± 4.01	24.8 ± 3.5	0.672*
Disease group, n, (%)				0.201
SLE, n, (%)	13 (26)	6 (28.5)	7 (24.1)	
Vasculitis, n, (%)	8 (16)	6 (28.5)	2 (9.5)	
Sjögren's syndrome, n, (%)	2 (4)	1 (4.7)	1 (3.4)	
PMR, n, (%)	1 (2)	0 (0)	1 (3.4)	
RA, n, (%)	5 (10)	1 (4.7)	4 (13.7)	
Inflammatory myositis, n, (%)	4 (8)	3 (14.2)	1 (3.4)	
Scleroderma, n, (%)	4 (8)	1 (4.7)	3 (10.3)	
Behçet's disease, n, (%)	13 (26)	3 (14.2)	10 (34.4)	
Disease duration, years	4.23 ± 5.45	4.61 ± 6	3.9 ± 5	0.689**
Median	2.0 (0.0–6.25)	1.0 (0.25–9.5)	2.0 (0.0–6.5)	
Family history of DM, n, (%)	8 (16)	4 (13.8)	4 (13.8)	0.706
ESR, mm/h	48.9 ± 29.1	56.8 ± 27.1	43.2 ± 29.7	0.073**
Median	43 (24–63.5)	51 (33–80)	35 (23.5–61)	
CRP, nmol/L (mg/dL)	250.4 ± 371.4 (2.63 ± 3.90)	266.6 ± 266.6 (2.8 ± 2.8)	228.5 ± 428.5 (2.4 ± 4.5)	0.085**
Median	1.16 (0.34–2.65)	2.44 (0.34–4.02)	0.80 (0.34–1.53)	
Previous history of steroid use, n, (%)	23 (46)	11 (52.4)	12 (41.4)	0.609
Mean steroid dose, mg/day	47.39 ± 18.5	52.3 ± 15.7	43.8 ± 19.7	0.206**
Median	53 (30–64)	64 (40–64)	48 (30–64)	
Steroid dose, n				0.206
15–29 mg/day	7	1	6	
30–59 mg/day	20	8	12	
≥60 mg/day	23	12	11	
Fasting blood glucose, mmol/L, (mg/dL)	4.88 ± 0.54 (88.04 ± 9.9)	4.94 ± 0.67 (89.1 ± 12.2)	4.83 ± 0.43 (87.2 ± 7.9)	0.522*
HbA1c (mmol/mol) (%)	36 (5.46 ± 0.36)	37 (5.58 ± 0.4)	35 (5.37 ± 0.3)	**0.015****
Median	5.45 (5.22–5.77)	5.70 (5.31–5.85)	5.42 (5.19–5.51)	
Peak glucose, mmol/L, (mg/dL)	11.26 ± 1.94 (203 ± 35)	12.98 ± 1.60 (234 ± 29)	9.99 ± 0.99 (180 ± 18)	< **0.001****
Median	196 (185–222)	230 (209–257)	188 (173–195)	
Capillary FBG ≥ 7 mmol/L (126 mg/dL), n, %	15 (30)	–	–	
Random capillary BG ≥ 11.1 mmol/L (200 mg/dL), n, %	20 (40)	–	–	
Random capillary BG 9.99–11.04 mmol/L (180-199 mg/dL), n, %	39 (78)	–	–	
DM developers, n, (%)	21 (42)			

BG: blood glucose, BMI: body mass index, CRP: C-reactive protein, DM: diabetes mellitus, ESR: erythrocyte sedimentation rate, FBG: fasting blood glucose, PMR:polymyalgia rheumatica, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus. Data in means ± SD and/or in medians (interquartile ranges).

* Independent Sample *t*-test.

** Mann Whitney *U* test.

3.3. Distribution of abnormal BG according to days

The number of blood glucose measurements (excluding fasting glucose values) exceeding 11.1 mmol/L (≥200 mg/dL) was highest on the 3rd day of steroid therapy (in 28 over 300 measurements); 300 denotes the glucose measurements excluding fasting glucose of 50 patients (50 patients × 6-point glucose measurements = 300 measurements). The value of 28 pertains to the number of glucose measurements exceeding 11.1 mmol/L on the 3rd day (Fig. 1).

3.4. The number of patients with abnormal BG

FBG ≥7 mmol/L (126 mg/dL) was detected in one patient on day 1, 9 patients on day 2, 12 patients on day 3, and 4 patients on day 4, and 5 patients on day 5. The number of patients with FBG ≥7 mmol/L (126 mg/dL) was also highest on the 3rd day of steroid therapy ($p = .005$).

3.5. The role of other confounding factors on abnormal BG

DM developers ($n = 21$) and non-DM developers ($n = 29$) were not different in terms of steroid dose, age, body mass index (BMI), previous steroid history, underlying rheumatological disease, and family history of DM. Baseline HbA1c concentrations were significantly higher in DM developers [37 vs. 35 mmol/mol (5.58% vs. 5.37%), $p = .015$] (Table 1). The mean blood glucose measurements according to the day of measurement and the relation to meals are given in Table 2.

3.6. Changes in CRP and BGs on the 3rd day of steroid therapy

The mean baseline concentration of CRP dropped from 231.4 nmol/L (2.43 mg/dL) to 88.5 nmol/L (0.93 mg/dL) on the 3rd day of steroid therapy ($p < .001$). However, the mean day 1 concentration of glucose increased from 7.47 mmol/L (134.6 mg/dL) to 7.78 mmol/L (140.1 mg/dL) on the 3rd day of steroid therapy ($p = .040$). The changes in CRP and glucose concentrations are depicted in Fig. 2.

4. Discussion

In this study, we found peak glucose concentrations at 2 h after lunch and dinner on the 3rd day of intermediate to high-dose steroid therapy given for inflammatory rheumatological diseases. The estimated incidence rate of steroid-induced DM was 42%. These results provide the best time to measure blood glucose concentrations, which will lead to effective hyperglycemia treatment.

Steroid-induced DM is defined as an abnormal increase in blood glucose concentrations in a patient with no established diagnosis of DM, whereas steroid-induced hyperglycemia is defined as abnormally increased blood glucose concentrations regardless of DM diagnosis [12]. There are no established diagnostic criteria specifically designed for steroid-induced DM, so specialized committees have set up certain recommendations [12,16]. It is generally assumed that the best predictive criterion for steroid-induced DM is a random glucose concentration exceeding 11.1 mmol/L (200 mg/dL) [17]. Consequently, the answer to the question, which patients using steroids should be monitored for

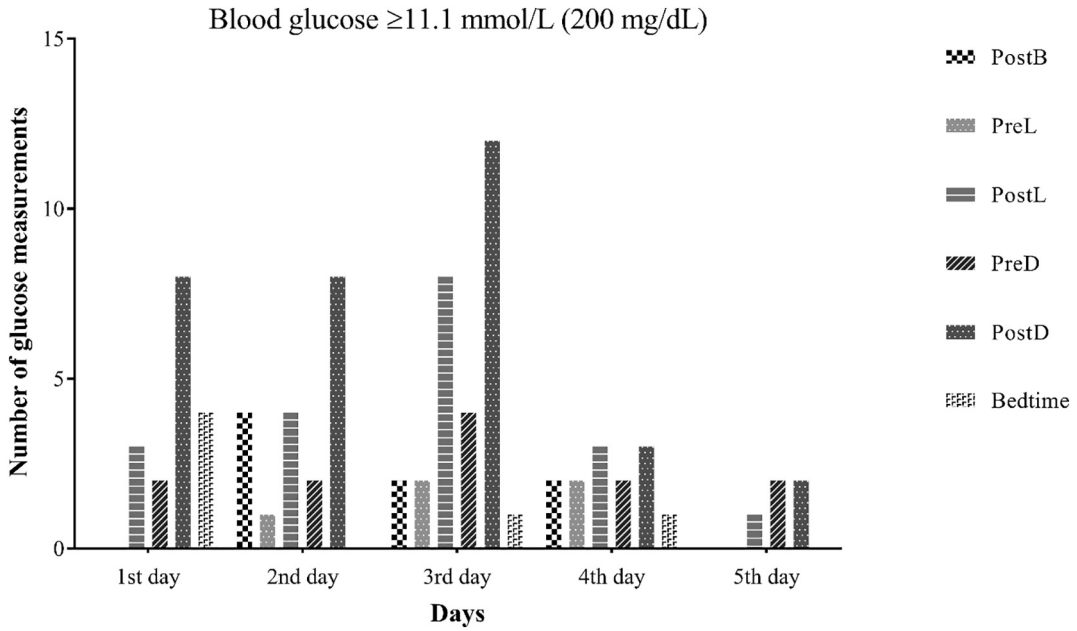

Fig. 1. Distribution of patients with blood glucose concentrations ≥200 mg/dL according to days and meals. The total number of glucose measurements (excluding fasting) exceeding 11.1 mmol/L according to days (1st day: 17, 2nd day: 19, 3rd day: 28, 4th day:12, 5th day: 5 measurements). (B: breakfast, D: dinner L: lunch).

Table 2
Means of glucose measurements according to days and meals (mmol/L).

Day	Fasting	Post breakfast	Pre-lunch	Post-lunch	Pre-dinner	Post-dinner	Bedtime
1st	6.60 ± 0.77	7.75 ± 1.77	6.32 ± 1.34	8.48 ± 1.87	7.38 ± 1.89	8.88 ± 2.09	8.50 ± 2.11
2nd	6.31 ± 1.15	7.98 ± 1.99	6.61 ± 1.71	8.16 ± 1.75	7.78 ± 2.11	8.83 ± 1.80	7.20 ± 1.43
3rd	6.46 ± 1.48	7.40 ± 1.71	6.91 ± 1.63	8.66 ± 2.34	8.13 ± 2.22	9.28 ± 2.17	7.66 ± 1.49
4th	6.24 ± 0.78	7.57 ± 1.61	6.68 ± 2.02	8.51 ± 1.77	7.82 ± 1.73	9.16 ± 1.68	7.43 ± 1.65
5th	6.05 ± 0.72	7.08 ± 1.59	5.81 ± 1.26	8.06 ± 1.52	8.02 ± 1.88	8.71 ± 1.67	7.10 ± 1.09

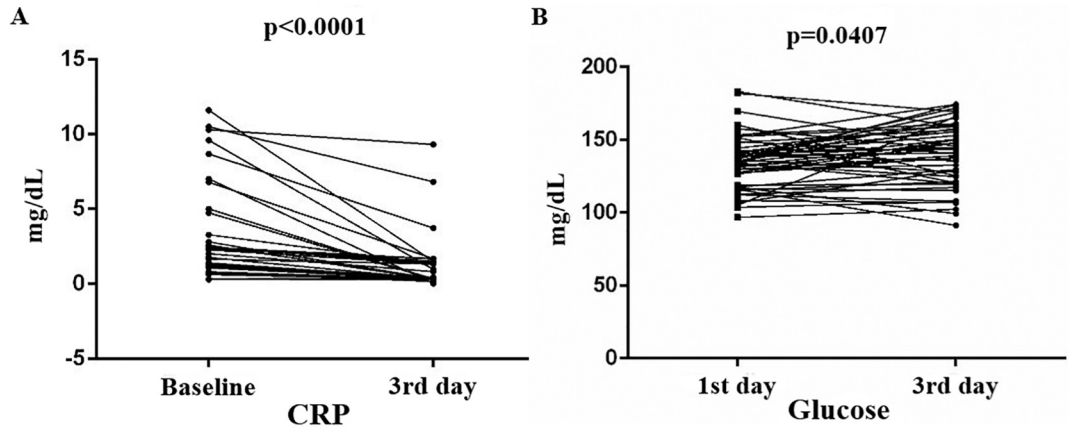

Fig. 2. A - Change in CRP concentration baseline and on the 3rd day of steroid therapy. B - Change in mean daily glucose concentration on 1st and on 3rd day of steroid therapy for each patient. The change was evaluated using paired sample *t*-test.

glucose concentrations, is every patient. Although studies that evaluated the incidence of steroid-induced DM in various patient groups varied according to the diagnostic criteria used, the prevalence of new-onset DM covers between 5 and 45%, mostly 10–20% [15,18–21]. A similar rate was found in studies investigating the metabolic effects of steroids and resultant hyperglycemia and DM in rheumatological diseases (Table 3) [22–31]. Low-dose steroids were used in most of these studies and the development of DM in long term was evaluated.

The short-term effects of intermediate to high-dose steroids on blood glucose concentrations have not been well studied. The first study was conducted by Svenson et al. in 1987, and a recent study was performed in 2012 by den Uyl et al. in drug-naive patients with RA [5,23]. The investigators evaluated glucose tolerance through an oral glucose tolerance test (OGTT), beta cell function, and insulin sensitivity in patients with RA after 1 weeks' treatment of 30 and 60 mg prednisolone. At the end of the study, the incidence of type 2 DM increased from 7% to 24%, especially in the 60-mg prednisolone group. However, the authors observed no DM after 1 week of 30-mg prednisolone therapy. This study is the most comprehensive study regarding inflammation, steroid therapy, and glucose tolerance [23]. In another study performed

Table 3
Studies dealing with development of DM during short term intermediate-high dose and long-term steroid use in rheumatological diseases and our results.

Author	Rheumatological disease	Steroid dose	Duration of follow-up	Number of patients	DM frequency	Diagnostic criteria of DM	Duration of steroid use	Study design
Short term high dose steroid studies								
den Uyl D 2012 [23]	RA	30 mg/60 mg	1 week	41 (21/20)	Baseline 0/3 (0/7%) 1st week 0/10 (0/24%)	OGTT (start of study and in the first week)	1 week	Prospective
Katsuyama T 2014 [24]	Rheumatological or renal disease	Mean 38.5 mg/day	4 weeks	128	n = 84 (65.6%)	BG ≥ 11.1 mmol/L (200 mg/dL), at least 3 postprandial measurements per week for 4 weeks	4 weeks	Retrospective
Our study	Inflammatory rheumatological diseases	15–29 mg, 30–59 mg, ≥60 mg	5 days	50	DM n = 21 (42%) Hyperglycemia n = 39 (78%)	FBG ≥7 mmol/L (126 mg/dL) PPG ≥ 11.1 mmol/L (200 mg/dL) Hyperglycemia ≥10 mmol/L (180 mg/dL)	5 days	Cross-sectional
Long term steroid studies								
van Everdingen AA 2002 [25]	RA	10 mg/day	6 months	40	2/40 (5%)	Need for OAD according to PPG and FBG measurements was assumed DM	6 months	Prospective
Panthakalam S 2004 [26]	RA	Oral 5–15 mg Parenteral 120 mg every 4–6 weeks	Steroid use for a mean of 24 months (6–60) 12 months	102	9/102 (8.8%)	FBG PPG	24 months	Prospective
Ha Y 2011 [27]	SLE	≥1 mg/kg/day	Steroid use at least for 4 weeks	127	16/127 (12.6%)	FBG PPG HbA1c	4 weeks 1 mg/kg/day 6 months in total	Prospective
Hoes JN 2011 [28]	RA	6.3 mg/day mean dose (5–10 mg)	Steroid use at least for 3 months	58	DM 11% IGT 35%	OGTT	≥3 months	Prospective
Burt MG 2011 [22]	Inflammatory rheumatological disease	4–10 mg/day	≥ 6 months	60	DM 15% IGT or DM 43%	OGTT	4–10 mg/day stable dose at least for 6 months	Prospective
Movahedi M 2016 [29]	RA	Database	1998–2013	12,657 9002 (Not yet used GC) 5999 (Ever used GC)	Incidence per 1000-person year 12 16.9	DM diagnosis according to ICD codes and taking antidiabetic medicine	The last 6 months	Retrospective
Ito S 2014 [30]	RA and collagen tissue disease	Mean 15.6 mg	3 months	78	27/78 (43.5%)	FBG PPG	3 months	Prospective
Solomon DH 2010 [31]	RA PsA/Psoriasis	17% of study group using steroids 5% of study group using steroids		48,718 40,346	8.6 per/1000 person-years 8.2 per/1000	DM diagnosis according to ICD and prescription for DM	Cox regression including risk factors For OC: HR:1.3 For TC: HR:1.3	Prospective

BG: blood glucose, DM: diabetes mellitus, IGT; impaired glucose tolerance; FBG: fasting blood glucose, GC: glucocorticoids, HR: hazard ratio, ICD: international classification of diseases, OAD: oral antidiabetic drug, OC: oral corticosteroids, OGTT: oral glucose tolerance test, PPG: postprandial blood glucose, PsA: psoriatic arthritis, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, TC: topical corticosteroids.

on 128 patients receiving a mean dose of 38.5 mg/day prednisolone for both rheumatological and renal diseases, a high frequency of DM (65.6%) was found according to the criteria as set out by the authors: PBG ≥11.1 mmol/L (200 mg/dL) at least thrice a week for 4 consecutive weeks [24]. In another study, impaired glucose tolerance was observed in 17–32% of transplant patients receiving high-dose steroids [13]. The frequency of hyperglycemia [> 9.91 mmol/L (178.3 mg/dL)] was estimated as 39% in 168 patients receiving intermediate to high-dose steroid therapy for the short-intermediate term (2 months) in 2017 [15]. In our study, the incidence of steroid-induced DM was 42% according to the American Diabetes Association (ADA) criteria, steroid-induced hyperglycemia was 78% if the glucose measurement at any time of day was ≥180 mg/dL, and 40% if random blood glucose was ≥11.1 mmol/L (200 mg/dL). The rate of new-onset steroid-induced DM was similar to the data in long-term steroid use. However, the rate was higher in comparison with the 24% in den Uyl et al.'s study performed with patients using short-term intermediate to high-dose steroid, in which the diagnosis of DM was established according to an OGTT, and lower than in Katsuyama et al.'s study, which evaluated DM in the 4th week of therapy [23,24]. These discrepancies may arise from using only fasting [≥7 mmol/L (126 mg/dL)] and random glucose concentrations [≥11.1 mmol/L (200 mg/dL)] instead of an OGTT to define steroid-induced DM, and using a random glucose concentration [≥10 mmol/L (180 mg/dL)] to define steroid-induced hyperglycemia. The frequency of DM increased along with steroid dosage (15–29 mg/day, 30–59 mg/day, and ≥ 60 mg/day; 14%, 40%, and 46%, respectively). The reason for the higher incidence of intermediate to high-dose steroid-induced hyperglycemia in our study may be due our diagnostic criteria [≥10 mmol/L (180 mg/dL)] in comparison with the 39% in the abovementioned study executed in a hematology department [15].

In general, it is believed that steroids cause hyperglycemia after meals. There is no consensus regarding the optimal screening time for steroid-induced hyperglycemia. We found no studies in the literature with which to compare our findings regarding the short-term (1–5 days) glycemic effects of intermediate to high-dose steroids by measuring glucose concentrations at 7 time points for 5 consecutive days. In a cohort study performed on patients using prednisolone for chronic obstructive pulmonary disease (COPD), post meal glucose concentrations after lunch and dinner measured using a continuous blood glucose monitoring system best predicted hyperglycemia [22]. Only measuring FBG for the diagnosis of DM may fall short of detecting steroid-induced hyperglycemia and steroid-induced DM. On the contrary, post meal hyperglycemia after lunch provides the best diagnostic accuracy. Preprandial glucose before dinner has the lowest sensitivity despite its convenience [12,13]. In patients at high risk for DM without established diagnoses, some authors advocate measurement of post meal capillary blood glucose concentrations 2 h after lunch, once or twice a week [11].

Duration of steroid treatment is as important as steroid dose in the development of steroid- induced DM. It is well known that the longer duration of steroid therapy is, the greater the chances of developing DM. Hyperglycemia due to short-term steroid use may also contribute to a longer duration of hospitalization, higher incidence of infections, and increased rates of morbidity and mortality. Some patients without an established diagnosis of DM continue to have an increased risk of DM, despite the expectations of normalization of glycemia after completion of steroid therapy [11]. Despite the fact that steroids are widely used, even in high doses, steroid-induced hyperglycemia and steroid-induced DM are often neglected. This may arise from the lack of sufficient prospective studies about the diagnosis and treatment and settled recommendations. Nevertheless, there are some recommendations and guidelines regarding steroid-induced hyperglycemia and steroid-induced DM published by certain associations [14,18].

The most prominent risk factors for steroid-induced DM are steroid dose (> 20 mg prednisolone), duration of steroid therapy, advanced age, high BMI, high HbA1c concentration, and a previous history of impaired glucose tolerance [11,12]. In addition, personal history of gestational DM or family history of DM are linked to a tendency for hyperglycemia [17]. In contrast to previous studies, we observed no differences between DM developers and non-DM developers in terms of steroid dose, age, BMI, history of previous steroid use, underlying rheumatological disease, and family history of DM. The two groups differed only in baseline HbA1c concentrations. Burt et al. also found no differences between DM developers and non-DM developers in terms of the abovementioned parameters in patients with COPD receiving steroids [22].

Increased glucose production in the liver induced by steroids is the main cause of postprandial glucose increase [32]. Van Raalte et al. proposed that the diabetogenic effects of steroids were more pronounced in diseases such as COPD, which were characterized by low-grade inflammation, whereas anti-inflammatory effects dominated in diseases with high-grade inflammation such as RA [33]. We evaluated this proposal via baseline and 3rd day concentrations of CRP as an inflammatory marker in patients receiving intermediate to high- dose steroids for rheumatological diseases. All patients showed a significant decrease in CRP on the 3rd day ($p < .001$). The greatest excursion in glucose was detected before dinner and at bedtime on 3rd day (the comparison of CRP and glucose concentrations on the 1st day and 3rd day are shown in Fig. 2). Our results support the hypothesis that because inflammation is suppressed by steroids, their hyperglycemic effect dominates the picture. In a study it was shown that steroid-induced insulin resistance contributed to postprandial hyperglycemia for 4 h following steroid intake [34]. The peak effect of intermediate-acting steroids prednisone and methylprednisone are observed 4–6 h after ingestion and lasts for 14–16 h [35]. The hyperglycemic effects of once daily administration of these steroids will ensue in the afternoon and evening (especially after lunch) and will not sustain until the fasting glucose concentration in the next morning [36].

A limitation of this study is the lack of an OGTT before the study. However, it would be injudicious to delay steroid therapy until an OGTT because many of the patients had involvement of the vital organs. Therefore, we did not perform an OGTT before steroid therapy in order to exclude DM. Secondly, 3 patients were excluded from the study due to high glucose concentrations and the need for intervention. However, these patients' data did not affect the results even when included in the statistical analysis. Another potential limitation is that the diseases included in the study are not homogeneous. We could not exclude the possibility that different inflammatory severities of the diseases might have influenced the results. However, CRP concentrations were not different between the DM developers and non-DM developers. Finally, although our small sample size limits the value of the study, the 7-point BG analysis from each patient provided crucial information about the time of steroid-induced hyperglycemia.

In conclusion, we detected steroid-induced hyperglycemia and/or DM more commonly according to postprandial glucose measurements on the 3rd day of short-term intermediate to high-dose steroid therapy in patients with rheumatological diseases. During the management of intermediate to high-dose steroid therapy in rheumatological diseases, glucose monitoring should be performed postprandially during the first 3 days and whenever 7-point measurements are available.

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