Advances in Obesity, Endocrinology, and Diabetes

Volume 1 Issue 1 (July-Dec 2024) | **ISSN**: 3049-0715

THE CLINICAL AND THERAPEUTIC ASPECTS OF STEROID-INDUCED DIABETES

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Abstract:

Background and Aims: Glucocorticoid-induced diabetes mellitus (GC-DM)is an underdiagnosed condition that sometimes requires urgent treatment. Indeed, the risk factors of GC-DM as well as its therapeutic management are little known. The aim of this study was to review the characteristics of the population at risk for developing GC-DM as well as its therapeutic modalities.

Methods: A retrospective descriptive study was conducted at Charles Nicolle Hospital in Tunis enrolling 52 patients with GC-DM who were followed up in the Department of Endocrinology and Internal Medicine (1992-2020).

Results: Mean age of patients was 47,8 ± 15,3 years. Eighteen patients (35%) had a family history of diabetes. The median body mass index (BMI) was 25.35 kg/m² [22.04-29.95]. Overweight was found in 25% and obesity in 25%. Twenty-two patients (42%) had hypertension, 21 (40%) had dyslipidaemias and 10 (19%) had IFG. The main underlying diseases requiring steroid therapy included vasculitis in 24 patients (46%) and autoimmune diseases in 15 patients (29%). In 54% of the patients, steroid therapy was administered at a high dose, in 35% at a very high dose, and in 11% at a medium dose. The median fasting blood glucose level at the time of diagnosis of GC-DM was at 14 mmol/L [9-18]. Fifteen patients (29%) developed GC-DM after 1 year. A pharmacological treatment was combined with lifestyle and dietary measures in 50 patients (96%). Oral antidiabetic agents alone were prescribed in 50% of the patients, insulin therapy: alone in 40% and in combination with oral antidiabetic agents in 6%. Methylprednisolone pulse therapy was significantly associated with initiation of insulin.

Conclusion*:* Diabetes should not be neglected during steroid therapy. Strategies for prevention, detection and therapeutic management of GC-DM are the key elements to control the Morbi-mortality related to this condition.

Keywords*:* Diabetes, Secondary diabetes, Glucocorticoid-induced diabetes, Glucocorticoid, Hyperglycaemia, Drug-induced diabetes

1. Introduction

Since their discovery in the mid-20th century, glucocorticoids have been widely used in the treatment of nearly 200 different conditions, primarily of inflammatory and neoplastic origin(1,2). Steroid therapy ranks among the most commonly used treatments in medicine thanks to its anti-inflammatory and immunosuppressive properties(3–5). In a study conducted in the United Kingdom ,the prevalence of long-term steroid therapy in the general population

Volume 1 Issue 1 (July-Dec 2024) | **ISSN**: 3049-0715

was estimated at 0.9%, with a treatment duration exceeding 6 months in a quarter of patients(6).

However, despite the benefits, the administration of glucocorticoids may induce adverse events (AEs) and may increase the level of blood glucose in patients without previously diagnosed glucose intolerance as well as in those who have impaired glucose tolerance or diabetes mellitus (DM)(7,8).

Glucocorticoid-induced diabetes mellitus (GC-DM) is an underdiagnosed condition that may require urgent treatment. Moreover, it is associated with a higher risk of morbi-mortality and represents a risk factor for the development of other complications related to steroid therapy(9–11). However, it remains a poorly documented clinical entity with few studies assessing GC-DM(3,4,11). Most of them focus on the incidence of transient dysglycemia or worsening of hyperglycemia in pre-existing diabetes.

Identifying the at-risk population and understanding the therapeutic characteristics of GC-DM would enhance its prevention, detection, and treatment. Yet, few reports have investigated potential risk factors and therapeutic modalities for GC-DM. We, therefore, conducted this study in order to describe the clinical profile and therapeutic modalities of GC-DM.

2. Materials and Methods

2.1. Patients

We retrospectively reviewed the medical charts of patients with established GC-DM,in the internal medicine and endocrinology department of Charles Nicolle Hospital in Tunis, between 1992 and 2020. We selected patients who met the following four requirements: were older than 15 years at the time of introduction of steroid therapy, received systemic glucocorticoids, had a fasting blood glucose level lower than 126 mg/dl and a HbA1c level lower than 7% less than three months before the introduction of steroid therapy and exhibiteda fasting blood glucose level of 126 mg/dl or highertwice after the introduction of steroid therapy. Patients who had incomplete medical charts or received treatment that might affect blood glucose concentrations (beta-agonist, estrogen, ciclosporin, tacrolimus, lithium, thyroid hormone, L-dopa, phenothiazine, alpha interferon and antiretroviral therapy) were excluded.

2.2. Diagnosis of glucocorticoid -induced diabetes mellitus

Any blood glucosemeasurements carried out whilst on glucocorticoids were reviewed. Patients exhibiting a fasting blood glucose level of 126 mg/dl or higher at leasttwice after the initiation of steroid therapy werediagnosed with GC-DM.

2.3. Demographics, clinical characteristics, and laboratory findings

The information obtained included age, gender,family history of DM (DM in first-degree relatives),hypertension, dyslipidemia, body weight and height. Body massindex (BMI) was also calculated.Since data for waistcircumference and lipid profile (particularly high-density lipoprotein (HDL) cholesterol) waslacking in most patients, the presence of metabolicsyndrome was not determined.Patients exhibiting a fasting blood glucose level before steroid therapy of 100 mg/dl or higher and less than 126 mg/dl were diagnosed with impaired fasting glucose(IFG).Clinical data included diseases for which steroids were

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prescribed, charecteristics of steroid therapy (molecule, administration route, maximum daily prednisoloneequivalent dosage, duration, concurrent steroid pulse therapy), characteristics of GC-DM (onset time of GC-DM after the initiation of steroid therapy, prednisoloneequivalent dosage at the time of diagnosis, blood glucose level at the time of diagnosis), therapeutic modalities used for managing GC-DM and other adverse events (AEs) related to steroid therapy.

We adopted the following terminology:

- Low dose <7.5 mg prednisone equivalent aday
- Medium dose >7.5 mg, but <30 mg prednisone equivalentaday
- High dose >30 mg, but <100 mg prednisone equivalent aday
- Very high dose >100 mg prednisone equivalent a day
- Pulse therapy >250 mg prednisone equivalent a day for one or a few days(12).

2.4. Statistical analysis

All statistical analysis were performed using SPSS software, version 22.0.
The results were expressed as mean ± standarddeviation (SD) or median and interquartile range.We determined the significance of differences between independent groups using a Chi-square test or Fisher's exacttest for categorical variables. Correlations between quantitative variables were made with Pearson's correlation coefficient. A p value ofless than 0.05 was considered to be significant.

2.5. Ethics statement

We have ensured the confidentiality of the information during the data collection for this study. We have no conflicts of interest to declare.

3. Results

3.1. Patient characteristics

We recruited 80inpatients diagnosed with GC-DM. Among these patients, 15 were excluded due to incomplete medical charts, while 13 were excluded because they were concurrently undergoing potentially diabetogenic treatments.Therefore, 52 patients were enrolled in thisstudy.

The study population comprised 27 (52%) males and 25 (48%) females.The clinical and laboratory characteristics of thepatients are summarized in Table 1.

Table1–Baselinecharacteristicsofthepatients.

Patients(no)	52(Male27, female25)
Age(years)	47.8 ± 15.3
FamilyhistoryofDM	18(35%)
BMI (Kg/m²)	25.35 [22.04-29.95]
Hypertension	22(42%)
Dyslipidemia	21 (40%)
Totalcholesterol (mmol/L)	4.23 [3.7-6.41]
Triglyceride(mmol/L)	1.76 [1.16-2.45]
IFG	10(19%)

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DM: diabetes mellitus, BMI: body mass index, IFG: impaired fasting glucose

The mean age of thepatients was 47.8 ± 15.3 years, with 60% of them being older than 45 years.Eighteen patients (35%) had a family history of DM. The median body mass index (BMI) was 25.35 kg/m² [22.04-29.95].BMI in 50% of the patients was in normal range, overweight was found in 25% and obesity in 25%. Twenty-two patients (42%) had hypertension, 21 (40%) had dyslipidemia and 10 (19%) had IFG. The main underlying diseases requiring steroid therapy included vasculitis in 24 patients (46%) and autoimmune diseases in 15 patients (29%) (Table 2).

Table2–Underlyingdiseases.

Underlyingdiseases	Vasculitis	Auto-immune diseases	Granulomatosis	Hemopathies	Others
Patientsnumber (%)	24 (46%)	15 (29%)	2 (4%)	2 (4%)	9 (17%)

3.2. Steroid therapy characteristics

The most frequently prescribed molecules were prednisone in 49 patients (94%) and methylprednisolone in 25 patients (48%). All patients received oral steroid therapy and 18 patients (35%) also received intravenous steroid therapy (steroid pulse therapy). The median maximum daily dose was 65.25 mg prednisone equivalent [55-78.75].In 54% of the patients, steroid therapy was administered at a high dose, in 35% at a very high dose, and in 11% at a medium dose.The median duration of steroid therapy was 12 months [4-64].

3.3. GC-DM characteristics

The median onset time of GC-DM after the initiation of steroid therapy was 3 months [0.7-12.5]; 25 patients (48%) were diagnosed in the first 3 months, and 15 patients (29%) after 1 year. At the time of diagnosis, the median dose of glucocorticoids was 50 mg prednisone equivalent[30-69], with 37 patients (71%) undergoing high-dose steroid therapy.The median fasting blood glucose level at the time of diagnosis of GC-DM was at 14 mmol/L [9-18].There wasn't a positive correlation between fasting blood glucose level at the time of diagnosis of GC-DM and the daily dose of glucocorticoids ($r=0.107$, $p=0.53$).

3.4. Management of GC-DM

A pharmacological treatment was combined with lifestyle and dietary measures in 50 patients (96%). Only two patients (4%) received solely lifestyle and dietary measures with fasting blood glucose levels of 10 mmol/L (181 mg/dL) and 7.93 mmol/L (143 mg/dL), respectively.Oral antidiabetic agents alone were prescribed in 50% of the patients, insulin therapy alone in 40%, and a combination of insulin therapy and oral antidiabetic agents in 6%.The most frequently prescribed oral antidiabetic agents were sulfonylureas in18 patients (35%) and metformin in 14 patients (27%). Meglitinides and α-glucosidase inhibitors were prescribed in only one patient each (2%). No patient was prescribed incretin mimetics or thiazolidinediones.Insulin therapy was prescribed in 24 patients (46%), using human insulin in all cases: long-acting (46%) or rapid-acting (2%).

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3.5. Other adverse events of steroid therapy

In our study, 14 patients (27%)had one or more additional adverse events associated with long-term steroid therapy (Table 3).

Table1–Summary of other corticosteroid-related adverse events (AEs)

Outcome/AE	Patients number (%)
Infection	8 (16%)
Aseptic osteonecrosis	2(4%)
Osteoporosis	2 (4%)
Central obesity (cushingoid facies)	2(4%)
Gastro intestinal ulcer	1 (2%)
Hypertension	1(2%)
Cataract	1(2%)

3.6. Associated factors with onset time of GC-DM

Table4–Associated factors with onset time of GC-DM.

	Onset time of GC-DM before 12 months	Onset time of GC-DM after 12 months	*p*Value
Patients(no)	37	15	
Age> 45 years*	(71%)	(29%)	**0.01**
FamilyhistoryofDM	23	4 (8%)	0.45
BMI (overweight/obesity)	(44%)	3 (6%)	1
Hypertension	13	7	1
Dyslipidemia	(25%)	(13%)	0.67
IFG	17	5	0.73
	(33%)	(10%)	0.6
High-dose steroid therapy	12	4 (8%)	0.32
mPSL pulse therapy	(23%)	0 (0%)	
	14	10	
	(27%)	(19%)	
	9	6 (12%)	
	(17%)		
	29		
	(56%)		
	9 (17%)		

GC-DM: glucocorticoid-induced diabetes mellitus, DM : diabetes mellitus, BMI: body mass index, mPSL: methylprednisolone

* Significantlydifferentbetweenthetwogroups.

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Table 4 shows that except for age over 45 years(p=0.01), the onset of GC-DM before 12 monthswas not significantly associated with any risk factors for type 2 diabetes.Moreover, no significant differences were found between the twogroups in the modalities of prescription of steroid therapy (dose, methylprednisolone pulse therapy).

3.7. Associated factors with insulin therapyin GC-DM

Table5–Associated factors with insulin therapy in GC-DM.

	Use of insulin therapy	Use of oral antidiabetic agents alone	*p*Value
Patients(no)	24(46 %)	26 (50%)	
Age> 45 years	14 (27%)	17 (33%)	0.86
FamilyhistoryofDM	11 (21%)	7 (13%)	0.14
BMI (overweight/obesity)	14 (27%)	12 (23%)	0.13
Hypertension	12 (23%)	10 (19%)	0.4
Dyslipidemia	10 (19%)	11 (21%)	1
IFG	3 (6%)	7 (13%)	0.7
High-dose steroid therapy	20 (38%)	23 (44%)	0.36
mPSL pulse therapy*	12 (23%)	6 (12%)	**0.04**

GC-DM: glucocorticoid-induced diabetes mellitus, DM : diabetes mellitus, BMI: body mass index, mPSL: methylprednisolone

* Significantlydifferentbetweenthetwogroups.

Patients requiring insulin therapy did not have more type 2 diabetes risk factors than those prescribed solely oral antidiabetic agents.Moreover, there was no significant association between insulin therapy and high-dose steroid therapy. Methylprednisolone pulse therapy was significantly associated with insulin use (0.04).

4. Discussion

Steroid therapyis burdened of several adverse events, particularly metabolic impairments(4,13). Hyperglycemia is a known and frequent adverse event(6,13) that can occur in both known diabetic patients aggravating glycemic controlof their diabetes, or in thosewithout previously diagnosed glucose intoleranceconstituting GC-DM(7,8,14).The diabetogenic effect of glucocorticoids is not constant and does not have the same intensity in all patients undergoing steroid therapy. Indeed, some patients are at a higher risk of

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developGC-DM than others. Several factors involved in the occurrence of GC-DMwere identified(8,11,15).

With aging, insulin sensitivity progressively declines(16) as well as beta-cell function, and basal insulin secretion level decreases(15). Several studies have shown that the risk of GC-DM increases with age(7,8,15,17–23). Considering the association of GC-DM and age, a mean age of47.8 ± 15.3years in the present study can be understood. In addition, 35% of patients who developed GC-DM had a family history of DM.It was noted that family history of DM was associated with a higher risk of developing GC-DM(7,24,25). In a study by Fajans et al., conducted on non-diabetic patients, the prevalence of diabetes after the administration of 45 mg of prednisone was 24% and 2.7% in patients with and without a family history of DM, respectively(26).

Glucocorticoids induce insulin resistance at both hepatic and peripheral levels, resulting in dysglycemia(3). This insulin resistance is dose-dependent and also related to the duration of steroid therapy(27,28). In addition, a decrease in insulin secretion capacity was noted at higher doses of glucocorticoids(29,30). Thus, both the dose and duration of steroid therapy were identified as risk factors for GC-DM(3,4,6,11,14,18,21,24,31–36). In the present study, the median maximum daily dose was 65.25 mg prednisone equivalent [55-78.75] and the median duration of steroid therapy was 12 months [4-64]. Given the underlying diseases requiring high-dose and long-term steroid therapy in internal medicine, these results can be understood. In our study, there wasn't a positive correlation between fasting blood glucose level at the time of diagnosis of GC-DM and the daily dose of glucocorticoids. However, Pilkey et al. reported that afternoon blood glucose levels were positively correlated with the dose of dexamethasone received(37). This can be related to the stronger hyperglycemic effect of glucocorticoids postprandially than in the fasting state(30,38).In the present study, 30% of the patients developed GC-DM after one year of steroid therapy. In the studies conducted by Gabbouj et al. and Kim et al., GC-DM occurred after more than a year in 43% and 14.5% of cases, respectively(15,39). Additionally, in Uzan's study, 33.3% of patients developedGC-DM beyond 24 months of steroid therapy(24). This underlines the importance of ongoing glycemic monitoring in patients undergoing steroid therapy.

Despite the existence of varying recommendations published by different international organizations, consensus therapeutic guidelines for GC-DM are not yet established(4,6,8,11,40). Therefore, the therapeutic management of GC-DM follows the same principles used in the treatment of type 2 DM. It involves a progressive and additive approach(11). The therapeutic means available for the treatment of GC-DM are also the same(40). Metformin, combined with lifestyle and dietary measures, is recommended as the first-line approach in cases of intermediate-acting steroid therapy prescribed at low doses and administered in the morning(32). In the present study, metformin was prescribed in 14 patients (27%). This may be understood by its low cost, the absence of risk of hypoglycemia, and its insulin-sensitizing effect, thereby limiting the metabolic adverse effects of steroid therapy(41,42). In our study, sulfonylureas were the primary oral antidiabetic agents prescribed in 18 patients (35%). In Vidler's study, 7 out of 8 patients with GC-DM (87%) were also treated with sulfonylureas without any reported incidents of hypoglycemia(10). Additionally, their effectiveness in GC-DM was studied by Kasayama et al., and the results were satisfying, showing adecrease in the mean fasting blood glucose level from 227mg/dL

down to 126mg/dL(43). According to several authors, insulin therapy is often the treatment of choice in GC-DM, especially during the initial phase of steroid therapy, thanks to its potent effect and its safety(3,8,11,44).In contrast to the findings reported in the study by Li et al.(45), the prescription of methylprednisolone pulse therapy in our patients was significantly associated with the initiation of insulin therapy (p=0,04). This discrepancy in results may be explained by the variability in doses, duration, and frequency of methylprednisolone pulse therapy.

5. Conclusion

Although, retrospective in analysis, and based on a modest sample size, our study confirmed that GC-DM occurs more frequently in a high-risk population and requires specific therapeutic management. Therefore, we recommend early screening, through close monitoring of postprandial blood glucose in patients at risk of developing GC-DM, in order to adopt an adequate therapeutic strategy. Prospective studies are needed to establish standard protocols for the prevention, detection, and therapeutic management of GC-DM.

Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication.

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