Glucocorticoid-induced diabetes among people without diabetes: a literature review

Majid Alabbood\textsuperscript{1}  
MBChB, FICMS, CABMS, DM

Min Ling\textsuperscript{1}  
MBBS, FRACP, PhD

Kenneth Ho\textsuperscript{1}  
MBBS(Hons), FRACP, PhD

\textsuperscript{1}Faculty of Medicine and Health Sciences, Macquarie University, New South Wales, Australia

Correspondence to:  
Dr M Alabbood, MBChB, FICMS, CABMS, DM, Faculty of Medicine and Health Sciences, Ground Floor, 75 Talevera Road, Macquarie University, NSW 2109, Australia; email: dr_majid79@yahoo.com

Received: 28 September 2017  
Accepted in revised form: 8 December 2017

Abstract

The effect of glucocorticoid on glycaemic control in people with diabetes has been studied extensively in the literature. However, data regarding its effect on glucose homeostasis in those without diabetes are sparse. This review aims to investigate the incidence of glucocorticoid-induced diabetes among people without diabetes subjected to high-dose glucocorticoid, to determine its associated risk factors and to examine the effect of high-dose glucocorticoid on glucose homeostasis.

Four databases (Ovid Medline, Scopus, Embase, and PubMed) were searched until August 2017 using the following MeSH terms: ‘glucocorticoid*’, ‘dexamethasone’, ‘diabetes mellitus’ and ‘incidence’. Only studies that included the use of high-dose glucocorticoid (equivalent to 4mg dexamethasone per day) for at least seven days in their methodology were included.

Nine out of 302 identified studies were included in this review. The incidence of glucocorticoid-induced diabetes ranged from 1–50%. Pre-diabetes, age, cumulative dose of glucocorticoid and family history of diabetes were predictors of glucocorticoid-induced diabetes. The use of high-dose glucocorticoid aggravated insulin resistance.

Most of the studies were retrospective, and used low-dose glucocorticoid with a short follow-up period. The incidence of glucocorticoid-induced diabetes reported varies widely depending on the type, dose and duration of glucocorticoid, the underlying condition and the presence of established risk factors for diabetes. Further prospective studies testing the effect of glucocorticoid in those without pre-existing risk factors are required to accurately estimate the incidence of glucocorticoid-induced diabetes. Copyright © 2018 John Wiley & Sons.

Practical Diabetes 2018; 35(2): 63–67

Key words  
glucocorticoid-induced diabetes; glucocorticoid; diabetes; incidence

Introduction

Glucocorticoids (GCs) are used in clinical practice to treat various disorders and have a marked clinical benefit.\textsuperscript{1} However, as with any other medications, serious adverse events may result from their use. An example is hyperglycaemia in people with diabetes, and hyperglycaemia or even new-onset diabetes in those without diabetes.\textsuperscript{2} The latter is frequently termed as glucocorticoid-induced diabetes (GCID). The effect of GCs on glycaemic control in people with diabetes has been studied extensively in the literature. However, data regarding their effect on glucose homeostasis in those without diabetes are sparse.\textsuperscript{3}

Several studies tried to investigate the incidence of GCID. Most of these studies were retrospective and involved the use of a single or small dose of GC with a short period of follow up. Most of these studies have documented an acute rise in blood glucose levels during the period of GC therapy. To investigate the incidence of GCID, a prolonged follow-up period is required to exclude the transient hyperglycaemic effect of GC use. Furthermore, only a few studies examined the effect of GC on glucose homeostasis using homeostatic model assessment (HOMA) and these studies were mostly conducted on non-human subjects.\textsuperscript{4–9} A few other studies tried to determine the risk factors that predict the development of GCID in those exposed to high-dose GC.\textsuperscript{8–11}

This review aims to investigate the incidence of GCID among people without diabetes subjected to high-dose GC. It also aims to determine predictors of GCID and to examine the effect of high-dose GC on glucose homeostasis.

Material and methods

Four databases (Ovid Medline, Scopus, Embase, and PubMed) were searched, spanning 1970 until August 2017, using the following
Results

The following data were extracted from the selected articles: authors, year, country, study design, type of GC studied, dose, duration, sample size, and underlying condition (Table 1) and results summary (Table 2). Of the nine included studies, five were RCTs,10,12–14 while the remaining were prospective observational or cross-sectional studies.8,9,11,15 All of the studies examined the effect of prednisolone as GC except one which examined dexamethasone.8 HOMA was included in the methodology of two of the studies.7,8 In addition, two studies used oral glucose tolerance test (OGTT) in their methodology.11,15 With regard to the subjects of the study, three studies were conducted on oncology patients receiving chemotherapy,8,9,14 two on renal transplant patients,10,11 and two on patients with inflammatory rheumatologic diseases.7,15 The incidence rate of GCID ranged from 1–50%,12,14 with a wide range of variation in the reported incidence among different studies. Fasting plasma glucose (FPG),11,15 participants’ age,10,11 family history of diabetes,11 chemotherapeutic protocol8 and GC dose8 were the predictors for the development of GCID. The use of high-dose GC resulted in a significant increase in HOMA-β (from median [IQR] 75 [61–122] to 119 [77–169]; p=0.001) and in HOMA-IR (from median [IQR] 0.8 [0.7–2.5] to 1.5 [1.0–2.8]; p=0.005).7

Incidence of glucocorticoid-induced diabetes

There is a wide variation in the reported incidence of GCID, ranging from 1–50%.12,14 The lower incidence was reported by a multinational RCT conducted on 2267 patients with metastatic castration-resistant prostate cancer who were treated by abiraterone, an androgen biosynthesis blocker, plus 10mg daily prednisolone or prednisolone only and followed up for 30 months.14 Abiraterone is not reported to cause diabetes or hyperglycaemia. The lack of a placebo-only comparator arm and the

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Country</th>
<th>Study design</th>
<th>GC</th>
<th>Dose (mg/day)</th>
<th>Duration</th>
<th>Sample size</th>
<th>Underlying condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abroug, 201412</td>
<td>Tunisia</td>
<td>RCT</td>
<td>PRED</td>
<td>60</td>
<td>10 days</td>
<td>94</td>
<td>COPD</td>
</tr>
<tr>
<td>Alexander, 200913</td>
<td>USA</td>
<td>RCT</td>
<td>PRED</td>
<td>60 then 30</td>
<td>22 weeks</td>
<td>114</td>
<td>Acute inflammatory inner ear disease</td>
</tr>
<tr>
<td>Burt, 201215</td>
<td>Australia</td>
<td>Cross-sectional</td>
<td>PRED</td>
<td>60</td>
<td>6 months</td>
<td>60</td>
<td>Inflammatory rheumatologic disease</td>
</tr>
<tr>
<td>den Uyl, 20122</td>
<td>The Netherlands</td>
<td>RCT</td>
<td>PRED</td>
<td>60</td>
<td>7 days</td>
<td>38</td>
<td>RA</td>
</tr>
<tr>
<td>Fizazi, 201614</td>
<td>Multi-national</td>
<td>RCT</td>
<td>PRED</td>
<td>10</td>
<td>30 months</td>
<td>2267</td>
<td>Prostate cancer</td>
</tr>
<tr>
<td>Gonzalez-Gonzalez, 20139</td>
<td>Mexico</td>
<td>Prospective observational</td>
<td>PRED</td>
<td>100</td>
<td>12 weeks</td>
<td>32</td>
<td>ALL and NHL</td>
</tr>
<tr>
<td>Jeong, 20168</td>
<td>Korea</td>
<td>Prospective observational</td>
<td>DEXA</td>
<td>36 per cycle</td>
<td>6 months</td>
<td>77</td>
<td>GI cancer</td>
</tr>
<tr>
<td>Pirsch, 201510</td>
<td>USA</td>
<td>RCT</td>
<td>PRED</td>
<td>5</td>
<td>5 years</td>
<td>277</td>
<td>Renal transplant</td>
</tr>
<tr>
<td>Yang, 201511</td>
<td>China</td>
<td>Prospective observational</td>
<td>PRED</td>
<td>5</td>
<td>4 months</td>
<td>303</td>
<td>Renal transplant</td>
</tr>
</tbody>
</table>

ALL: acute lymphoblastic leukaemia; COPD: chronic obstructive pulmonary disease; DEXA: dexamethasone; GC: glucocorticoid; GI: gastrointestinal; NHL: non-Hodgkin lymphoma; PRED: prednisolone; RA: rheumatoid arthritis; RCT: randomised controlled trial.

Table 1. Baseline characteristics of the 9 studies included for final review: authors, year, country, study design, type of glucocorticoid studied, dose, duration, sample size, and underlying condition.

Box 1. Medline search strategy

1. ‘glucocorticoid’/
2. ‘dexamethasone’/
3. 1 or 2 (above)
4. ‘diabetes mellitus’/
5. 3 and 4 (above)
6. ‘incidence’/
7. 5 and 6 (above)
8. limit 7 (above) to human
9. limit 8 (above) to English language

McSH terms: ‘glucocorticoid*’, ‘dexamethasone’, ‘diabetes mellitus’ and ‘incidence’. A detailed search strategy of Ovid Medline is shown in Box 1. Moreover, a hand search of key journals and reference lists was performed. Duplicates were removed.

Inclusion criteria were: English language full-text randomised controlled trials (RCTs) and prospective observational studies that included the use of high-dose GC (equivalent to 4mg dexamethasone per day) for at least seven days in their methodology. In addition, studies that included the use of smaller doses of GC but for a longer time (at least a month) in their methodology were included. Exclusion criteria were: meta-analyses, reviews, retrospective studies, conference abstracts, case studies and studies that included pregnant women. Accordingly, 302 studies were identified but nine were included for final review (Tables 1 and 2). Only data from people without diabetes were extracted from studies that included both people with and without diabetes.
absence of clear definition criteria for new-onset diabetes were among the major limitations of this study. The investigators utilised both FPG and random plasma glucose (RPG) for the diagnosis of GCID without clearly stating the criteria for diagnosis. However, the large sample size (n=2267), long follow-up period (30 months) and the study design contributed to the strength of this study.

Similarly, a relatively low incidence (9%) was reported in a prospective cohort study conducted on 303 renal transplant patients without prior diabetes receiving prednisolone 5mg daily, as an immune-suppressor, for four months.11 OGTT was done under test conditions before the study and every three months thereafter for 12 months. Diabetes was defined according to American Diabetes Association (ADA) criteria.16 Approximately 9% of the participants developed new-onset diabetes after transplantation compared to a similar proportion who developed impaired glucose tolerance. The large sample size, study design and the use of OGTT, a highly sensitive test for early detection of new-onset diabetes, are among the strengths of this study. However, it was limited by generalisability and the fact that it was conducted in a single centre.11

In contrast to the two aforementioned studies, the remaining seven studies reported a high incidence of GCID. Two studies were conducted on patients with rheumatologic disorders receiving prednisolone as an anti-inflammatory.7,15 Both of them investigated the use of a considerably high-dose prednisolone (60mg/day) and reported an incidence of GCID of 15%15 and 24%,7 respectively.

The first study, performed by Burt et al.,15 was a cross-sectional one with a long follow-up period of six months and utilised OGTT under test conditions for detection of diabetes depending on the World Health Organization (WHO) criteria.17 This study reported a prevalence of GCID of 15% compared to 10% of the control group (no prednisolone) which was non-significant (p=0.45). An important finding of the Burt et al. study is that FPG was significantly lower in the prednisolone group (5.0±0.1 vs 5.3±0.1mmol/L, p=0.001) which led them to recommend the use of OGTT rather than FPG for screening of GCID. Nevertheless, this study was biased by the fact that the control group was heavier than the treatment one (BMI 28.9 vs 26.5kg/m² respectively, p=0.02).15

The second study was an RCT conducted by den Uyl et al.7 on 38 rheumatology patients and used OGTT and ADA criteria for the diagnosis.16 A major bias of the study was its design. The researchers randomised participants into two arms: one received 60mg/day and the other 30mg/day of prednisolone instead of placebo.7 Having rheumatoid arthritis, a chronic inflammatory process, per se is well documented as a risk factor for the development of diabetes as shown in the Burt et al. study.15

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Results summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abroug, 201412</td>
<td>49.5% (p=0.015)</td>
</tr>
<tr>
<td>Alexander, 200913</td>
<td>17%</td>
</tr>
<tr>
<td>Burt, 201215</td>
<td>15%</td>
</tr>
<tr>
<td>den Uyl, 20122</td>
<td>24%</td>
</tr>
<tr>
<td>Fizazi, 201614</td>
<td>1%</td>
</tr>
<tr>
<td>Gonzalez-Gonzalez, 20139</td>
<td>34%</td>
</tr>
<tr>
<td>Jeong, 20168</td>
<td>16%</td>
</tr>
<tr>
<td>Pirsch, 201510</td>
<td>37%</td>
</tr>
<tr>
<td>Yang, 201511</td>
<td>9%</td>
</tr>
</tbody>
</table>

BMI: body mass index; CI: confidence interval; CT: chemotherapy; DEXA: dexamethasone; FPG: fasting plasma glucose; GCID: glucocorticoid-induced diabetes; HOMA: homeostatic model assessment; IQR: interquartile range; IR: insulin resistance; NA: not available; OGTT: oral glucose tolerance test.

Table 2. Results summary of the 9 studies included for final review
On the other hand, the higher incidence of GCID was reported by an RCT conducted by Abroug et al.,12 on 94 patients with chronic obstructive pulmonary disease receiving high-dose prednisolone (60mg/day) for 10 days. The over-estimated incidence in this study is explained by two factors: first, the lower level used for defining hyperglycaemia (10mmol/L instead of 11.1mmol/L which is the lower threshold to diagnose diabetes depending on RPG according to ADA and WHO criteria); and, second, the use of RPG during therapy instead of at the end of the follow-up period.12 Other studies reported an incidence of GCID of 16%,8 17%,13 34%9 and 37%.10

In general, the incidence of GCID is widely variable according to the type of GC, dose, duration, presence of risk factors and underlying disease. Most of the studies were conducted on patients with pre-existing inflammatory conditions such as oncology and rheumatology diseases which are considered as risk factors for diabetes themselves.

Predictors of glucocorticoid induced diabetes
There are several established risk factors that can predict the development of type 2 diabetes. Among these factors are high BMI, family history of diabetes, sedentary lifestyle, chronic inflammatory processes and pre-diabetes.17 Of the nine studies included, five examined these predictors.8-11,15 Fasting plasma glucose was the predictor in the Yang et al. and Burt et al. studies (p=0.001 in both).11,15 Furthermore, half of the participants in the den Uyl et al. study had pre-diabetes.7 This implies that people with impaired fasting glucose or pre-diabetes are at higher risk of developing GCID. Meanwhile, participants’ age was the predictor in the Yang et al. and Pirsch et al. studies (p=0.001 in both).10,11 In other words, the older the patient, the more likely they are to develop GCID. In the same way, the chemo-therapeutic protocol that was used (continuous GC more than cyclical; p=0.002), the cumulative dose of GC (p=0.04) and a family history of diabetes (p=0.01) were the predictors in the Gonzalez-Gonzalez et al., Jeong et al. and Yang et al. studies, respectively.5,9,11 Therefore, those with established risk factors for diabetes need to be monitored closely when subjected to high-dose GC. Similarly, those with pre-diabetes, a family history of diabetes and those receiving higher doses need close monitoring.

Effect of glucocorticoids on glucose homeostasis
Insulin resistance and β-cell function can be assessed indirectly by utilising HOMA which can be calculated from FPG and fasting plasma insulin (FPI).18 HOMA-IR and HOMA-β are surrogate markers for insulin resistance and β-cell function, respectively. By studying HOMA changes, glucose homeostasis can be assessed. Three studies examined the effect of high-dose GC on HOMA.7-9

The first study was a prospective observational one conducted on 32 patients with haematologic malignancies receiving extremely high-dose prednisolone (100mg/day) for 12 weeks as adjuvant to chemotheraphy.9 This study demonstrated a decrease in HOMA-IR (from mean ± SD 2.2±0.79 to 2.2±0.74) for those who developed diabetes, and an increase (from 2.2±0.79 to 2.2±0.74) in those who did not. On the other hand, HOMA-β decreased (from 112.8±47.8 to 98.8±21.9) in those who developed diabetes, and increased (from 112.8±47.8 to 132±68.9) in those who did not. Accordingly, the researchers suggested that the primary mechanism involved in the onset of GCID is most likely increased insulin resistance (despite the fact that they reported a decrease in HOMA-IR), associated with a limited compensatory ability of the pancreas.9 Unfortunately, the investigators did not compare the changes in HOMA before and after GC treatment for significance. Instead, they compared those who developed diabetes against those who did not.

In contrast to the first study, den Uyl et al. demonstrated a significant increase in HOMA-IR and HOMA-β from 0.8 (0.7–2.5) to 1.5 (1.0–2.8), p=0.005, and from 75 (61–122) to 119 (77–169), p=0.001, respectively.7 Hence, these findings represent a robust evidence of the effect of GCs at tissue level. High-dose GC therapy results in an increase in insulin resistance associated with a compensatory raise in β-cell function to overcome this stress.

The third study was a prospective observational study conducted on 77 patients with gastrointestinal cancer receiving high-dose dexamethasone as adjuvant to chemotheraphy. This study demonstrated a significant increase in HOMA-IR (from 3.44±5.52 to 6.04±6.37, p=0.001) and in C-peptide (from 1.86±1.38ng/ml to 4.91±3.88ng/ml, p=0.021) after six months of follow up.3 However, this study was limited by generalisability and the lack of HOMA-β analysis which limited the ability of accurate interpretation of HOMA.19

In brief, two studies revealed that the use of high-dose GC aggravated insulin resistance yet its effect on β-cell function was a matter of conflict.

Discussion
The strengths of this review include the incorporation of RCTs and prospective studies only that involve the use of high-dose GC in their methodology, and the exclusion of retrospective studies. However, there are two main limitations of this review: the inclusion of studies on different types of GCs and of studies using different doses and duration of GC therapy.

In conclusion, there is a dearth of data on the incidence of GCID among people without diabetes. Most of the studies were retrospective and used low-dose GC with a short follow-up period. The incidence of GCID reported varies widely depending on the type, dose and duration of GC therapy, the underlying condition and the presence of established risk factors for diabetes. Studies conducted on people with a pre-existing inflammatory condition such as rheumatoid arthritis or cancer would result in the over-estimation of the real incidence. To accurately estimate the incidence of GCID among people without diabetes, there should be RCTs or case-control studies testing the effect of GCs in healthy people or at least in those
without pre-existing risk factors. Patients with risk factors such as old age, pre-diabetes, obesity, family history of diabetes and using high-dose GC need close monitoring of their blood glucose, preferably using OGTT, to early detect new-onset diabetes while on high-dose GC therapy. Undertaking an assessment of pre-existing risk factors before commencing GC therapy could help in deciding on the type of steroid, dose and dose form to be used in order to decrease the risk of developing diabetes.

Furthermore, noting the pattern of plasma glucose profile changes while on GC therapy could help to choose the most suitable glucose-lowering agent to be used. The lowest effective dose of GC must be used for the shortest possible duration to lower the incidence of GCID.

More studies are required in order to examine the effect of GC on glucose homeostasis via utilisation of the hyperglycaemic clamp and the hyperinsulinaemic-euglycaemic clamp procedures which are the ‘gold standards’ for measurement of β-cell function and insulin resistance, respectively. However, as these tests are rather laborious and demanding, an accepted alternative method would be to compute the value of HOMA which can be simply done by entering data regarding FPG and FPI into a calculator or equation.

Lastly, the most likely mechanism of GCID is an increase in insulin resistance accompanied by failure of the pancreas to compensate by secreting more insulin.

Declarations of interests

There are no conflicts of interest declared.

References