

Steroid-induced dysglycaemia in patients with haematological disorders a ten-year review in a tertiary hospital in Ghana

Yvonne A. Dei-Adomakoh<sup>1</sup>, Josephine Akpalu<sup>2</sup>, Alfred E. Yawson<sup>3,4</sup>, Ivy Ekem<sup>5</sup>, Margaret Reynolds<sup>6</sup> and Yacoba Atiase<sup>2</sup>

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<sup>1</sup>University of Ghana Medical School, Department of Haematology, Accra, Ghana

<sup>2</sup>Korle Bu teaching hospital, Department of Medicine, Accra, Ghana

<sup>3</sup>University of Ghana Medical School, Department of Community, Accra, Ghana

<sup>4</sup>National AIDS/STI Control Program, Clinical Care Unit, Ghana Health Service, Accra, Ghana

<sup>5</sup>University of Cape Coast, CoHAS, School of Medical Sciences, Department of Haematology, UCC SMS  
University of Cape Coast Cape Coast, Cape Coast

<sup>6</sup>University of Ghana School of Medicine and Dentistry, Accra, Ghana

Corresponding author: Dr Yvonne Akotoa Dei-Adomakoh

E-mail: [deiadom@yahoo.com](mailto:deiadom@yahoo.com)

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## SUMMARY

**Background:** Glucocorticoids (steroids) play a key role in the management of multiple medical conditions including haematological disorders. This study looked at the prevalence of steroid induced dysglycaemia in patients with haematological disorders receiving steroids as part of their treatment with the view of modifying its use and selection of patients where necessary.

**Methods:** A retrospective review of haematology patients on treatment regimens including steroids. Information extracted included, demographic characteristics, clinical information such as age, gender, haematological disorder, type of steroid, daily and cumulative dose of steroid, duration of therapy, family history of diabetes and alcohol use.

**Results:** The case records of 351 haematology patients were reviewed. However, eight patients with dysglycaemia before therapy were excluded. The median age of patients was  $51.0 \pm 26.0$  (IQR: Interquartile Range) years, with an age range of 13 to 87 years, and a female: male ratio of 1.2: 1 ( $p=0.778$ ). The prevalence of Steroid-Induced Dysglycaemia (SID) was 3.79% with a mean diagnosis interval of  $8.8 \pm 2.1$  months. Overall, 245 (71.4%) patients were on continuous steroids. Among the 13 patients who developed SID, 11 (84.6%) were on continuous steroids. In the majority of the patients (97.1%) there was no family history of diabetes in a first degree relative. Significant differences were found between patients with normoglycaemia and those with dysglycaemia with respect to age ( $p=0.049$ ) and duration of steroid therapy ( $p=0.024$ ).

**Conclusion:** The prevalence of steroid-induced dysglycaemia is relatively low among Ghanaian patients with haematological disorders on steroid based chemotherapy.

**Keywords:** steroids, haematological disorders, dysglycaemia, Ghana, risk factors.

**Funding:** None declared

## INTRODUCTION

Glucocorticoids have played a key role in the management of multiple medical conditions including haematological disorders such as non-Hodgkin lymphoma (NHL), multiple myeloma (MM), chronic lymphocytic leukaemia (CLL), Hodgkin lymphoma (HD), acute lymphoblastic leukaemia (ALL), autoimmune haemolytic anaemia (AIHA) and immune thrombocytopenia (ITP) for decades.<sup>1,2</sup> This is due to the fact that they reduce inflammation and tissue damage<sup>1</sup> through their effect on multiple pathways at the cellular and molecular levels.

Glucocorticoids, commonly referred to as steroids, lyse lymphocytes and malignant lymphoid cells, reduce eosinophil numbers, suppress the pathways that result in inflammation and promote those pathways that produce anti-inflammatory effects.<sup>3</sup> The use of steroids however can be associated with a wide variety of adverse effects. This may affect multiple body systems with a significant impact on the patients' physical, social, and psychological functioning resulting in decreased quality of life, reduced treatment adherence with negative impact on survival outcomes.<sup>4,5</sup>

The adverse effects include cataract formation, proximal myopathy, osteoporosis, infections, increased blood pressure, acne and menstrual irregularities in women among others.<sup>4</sup> Endocrine and metabolic effects include, Cushing's Syndrome, adrenal suppression, dyslipidaemia, hyperglycaemia and suppression of gonadotropins, growth hormone and thyrotropin.<sup>5</sup> Steroids could either worsen hyperglycaemia in patients known to have diabetes, or unmask diabetes in patients not previously diagnosed with the condition prior to steroid therapy<sup>6</sup>. Unmasking diabetes in these patients with haematological conditions with suppressed immunity may lead to deterioration of their clinical condition with recurrent infections and a resultant increase in morbidity and mortality. The presence of chronic hyperglycaemia is also associated with increased risk of cardiovascular<sup>7,8</sup> and microvascular complications.<sup>9</sup>

Insulin resistance is the predominant underlying mechanism by which steroids induce the development of diabetes<sup>10</sup>. Steroids decrease hepatic insulin sensitivity resulting in an increase in hepatic glucose production<sup>11</sup>. There is also a reduction of glucose uptake into muscle and adipose tissue by as much as 60% mainly due to a post-receptor effect.<sup>12,13</sup> Steroids have also been shown to induce apoptosis of  $\beta$  cells resulting in impaired  $\beta$  cell function.<sup>14</sup> At the cellular and molecular levels, steroids increase the  $\alpha_2$  adrenoceptor signaling<sup>15</sup>, increase glucose-6-phosphatase activity.<sup>16</sup> and impair glucose metabolism.<sup>17</sup> Steroids have also been found to induce oxidative stress<sup>18</sup> and suppress pro-survival factors such as Nuclear factor  $\kappa$ B.<sup>19</sup> The use of steroids tends to affect post-prandial glucose homeostasis much more, with the fasting plasma glucose level being marginally elevated.<sup>6,20</sup> The glucose excursions induced by steroids are said to be closely similar to their pharmacokinetics, which show a peak effect 4 to 6 hours after administration.<sup>21,22</sup>

This study looked at the prevalence and associated risk factors of steroid induced dysglycaemia (diabetes and pre-diabetes) in patients with haematological disorders receiving steroids as part of their treatment with the view of modifying its use and selection of patients where necessary. The study will also be used as a basis for a prospective study to determine the appropriate timing of screening for SID, the spectrum of dysglycaemia and other associated risk factors for the development of SID among patients with haematological disorders.

## METHODS

### Study Design

This was a hospital-based retrospective review over a ten-year period from January 1, 2003 to December 31, 2013.

### Study Site

The study was conducted at the Haematology unit of the Korle-Bu Teaching Hospital, which is the main referral centre for the southern part of Ghana. The unit renders outpatient (OPD), inpatient and day care services to patients with a wide range of haematological disorders with an average annual OPD attendance of 1200 patients and approximately 60 new cases monthly. New referrals reporting on days outside clinic days, emergency cases and patients requiring chemotherapy and supportive therapy are seen at the haematology day care centre, which has an annual average attendance of 3400 patients.

### Data collection

Patients with haematological disorders such as MM, NHL, HD, ALL, CLL, AIHA, ITP and on a regimen including steroids were included in the study. All patients with confirmed diabetes mellitus and on treatment were excluded from the study. Demographic characteristics including age and sex, clinical information such as type of steroids, daily and cumulative dose of steroids, type of haematological disorders, family history of diabetes and alcohol use were obtained from their case files. Laboratory results especially random and fasting blood glucose prior to the commencement of steroid therapy and after were noted where applicable.

Steroid induced dysglycaemia was defined as patients who developed either diabetes or prediabetes after the initiation of steroid therapy. Steroid-induced diabetes was defined as fasting plasma glucose (FPG)  $\geq 7.0$ mmol/L or random plasma glucose (RPG)  $\geq 11.1$ mmol/L or glycated haemoglobin (HbA1c)  $\geq 6.5\%$  at least on 2 occasions after the initiation of steroid therapy (23). Steroid-induced prediabetes was defined as FPG between 5.7 to  $<7.0$ mmol/L or RPG between 7.8 to  $<11.1$ mmol/L or HbA1c between 5.7 to  $<6.5\%$  on at least 2 occasions after the initiation of steroid therapy. Patients with pre-existing dysglycaemia were excluded from the data collection and analysis.

### Data analysis

The data was captured using Microsoft Excel 2007 Database. Analysis was done with Statistical Package for the Social Sciences (SPSS) software version 20. Data were analysed by simple descriptive statistics (i.e., median and its associated interquartile range, proportions, ratios and percentages) and summarized in tables.

Two-sample Wilcoxon Rank-Sum (Mann-Whitney) test was used to examine whether there is a statistical difference in the median of the continuous variables (age, cumulative dose and duration of steroid therapy) by steroid-induced dysglycaemia status (normoglycaemia/dysglycaemia).

This test is appropriate because the continuous variables were not normally distributed to allow for independent T-test. Also, Fisher's exact tests was used to test the association between exposure categorical variables and the steroid-induced dysglycaemia status. Statistical significance was set at  $p < 0.05$  (two-sided).

**Ethical issues**

Ethical Approval was obtained from the Ethical and Protocol Review Committee of University of Ghana Medical School (Protocol identification number- MS-Et/M.2-P 4.5 /2014-2015). Clearance was also received from the Head of the Haematology Unit where the review was conducted.

**RESULTS**

Overall the data were collected from the medical records of 351 patients. However, eight patients had dysglycemia before therapy and were excluded from the analysis. The median age of patients was  $51.0 \pm 26.0$  (IQR: Interquartile Range) years, minimum age was 13 years and maximum age was 87 years. Overall 184 (53.4%) patients were female with a female: male ratio of 1.2: 1 ( $p=0.778$ ). Majority (97.1%) of the patients did not have a family history of diabetes in any first degree relative. Forty-four 44 (12.8%) patients had coexisting hypertension (Table 1).

The common haematological disorders managed during the period under review were NHL, MM, CLL, HD, ALL, AIHA and ITP which were documented in 100

(29.2%), 62 (18.1%), 60 (17.5%), 13 (3.8%), 16 (4.7%), 26 ( 7.6%) and 24 (7%) patients respectively (Table 2). Thirteen patients (3.79%) on steroid-based therapy developed dysglycaemia with a mean interval from onset of therapy of  $8.8 \pm 2.1$  months. Both fasting and random plasma glucose were used for the diagnosis of dysglycaemia. Patients who developed dysglycaemia had a median age of  $61.0 +15.0$  (IQR) years compared to  $51.0+27.0$ (SD) years for those who had normoglycaemia ( $p=0.049$ ) (Table 1). An equal proportion (38.5%) of patients in the 50-59years and 60-69years age groups developed dysglycaemia (Figure 1).

The most commonly used steroid among the patients was prednisolone with the usual starting dose being 1mg/kg/day. Overall, 245 (71.4%) patients were on a continuous steroid-based treatment regimen. Among the 13 patients who developed SID, 11 (84.6%) were on continuous steroid-based treatment regimens. Patients who developed dysglycaemia had a median duration of exposure to steroids of  $103.0 \pm 94.0$ (IQR) days compared with  $49.5 \pm 60.0$ (IQR) days for those with normoglycaemia ( $p=0.024$ ). The median cumulative dose of steroids was higher among patients with dysglycaemia compared to those with normoglycaemia ( $p= 0.129$ ) (Table 3).

There was no significant difference between the two groups with respect to alcohol intake, family history of diabetes, hypertension, haematological diagnosis or cumulative dose of steroids.

**Table 1** Demographic and risk factors of patients with normoglycaemia and dysglycaemia

VARIABLE	Normoglycaemia N (%)	Dysglycaemia (%)	N All Patients N (%)	p-value
Age (median ± iqr)	51 ± 27.0	61 ± 15.0	51.0 ± 26.0	0.049 <sup>A</sup>
Sex				
Male	154 (46.7)	5 (38.5)	159 (46.4)	0.778 <sup>B</sup>
Female	176 (53.3)	8 (61.5)	184 (53.6)	
First degree relative with dm				
No	321 (97.3)	12 (92.3)	333(97.1)	0.324 <sup>B</sup>
Yes	9 (2.7)	1 (7.7)	10 (2.9)	
Alcohol intake				
No	276 (83.6)	11 (84.6)	287 (83.7)	0.341 <sup>B</sup>
Yes	47 (14.2)	1 (7.7)	48 (14.0)	
Not stated	7 (2.1)	1(7.7)	8 (2.3)	
Hypertension				
No	290 (87.9)	9 (69.2)	299 (87.2)	0.071 <sup>B</sup>
Yes	40 (12.1)	4 (30.8)	44 (12.8)	
Steroid therapy				
Duration (days)	49.5 ± 60.0	103.0 ± 94.0	51.0 ± 63	0.024 <sup>A</sup>
Cumulative dose (mg)	2640.0 ± 2745.0	3,960.0 ± 3335.0	2720.0 ± 2715.0	0.129 <sup>A</sup>

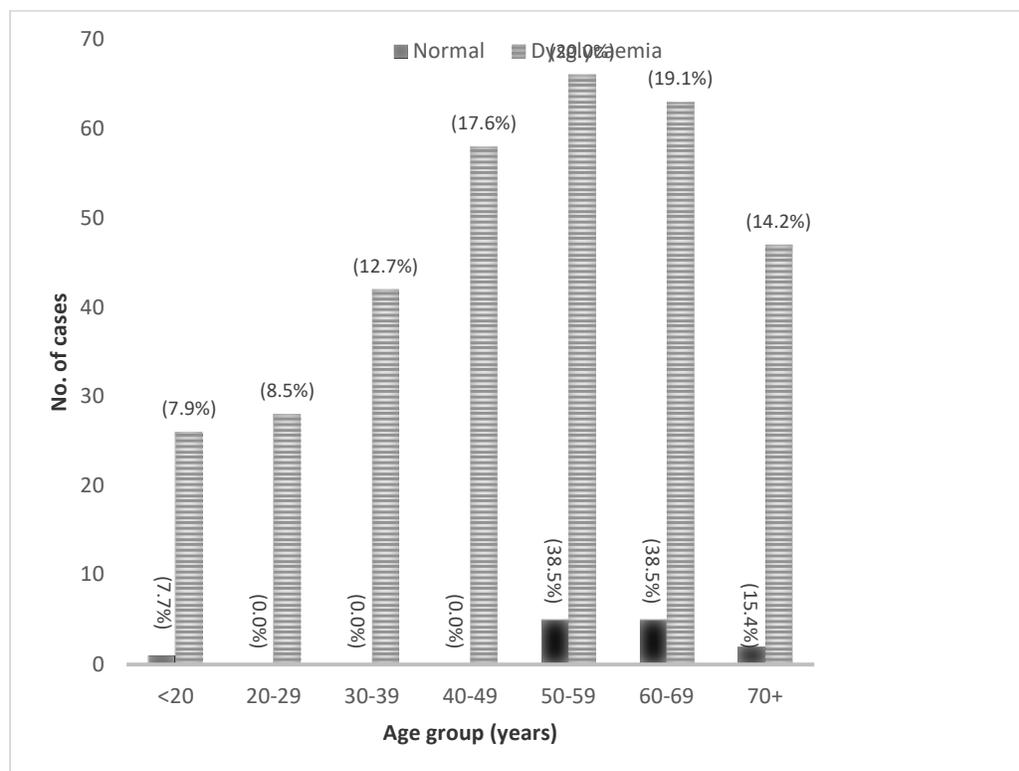
IQR: Interquartile Range; DM: Diabetes Mellitus; A: p-value From Two-Sample Wilcoxon Rank-Sum Tests; B: p-Value From Fisher's Exact Test.

**Table 2** Distribution of haematological disorders in normoglycaemia and dysglycaemia patients in the Korle Bu Teaching Hospital

Haematological Diagnosis	Normoglycaemia n (%)	Dysglycaemia n (%)	All Patients n (%)	Fisher's Test p-value
NHL	98 (29.7)	2 (15.4)	100 (29.2)	0.609
HD	13 (3.9)	0	13 (3.8)	
MM	57 (17.3)	5 (38.5)	62 (18.1)	
ALL	16 (4.9)	0	16 (4.7)	
CLL	57 (17.3)	3 (23.1)	60 (17.5)	
AIHA	25 (7.6)	1 (7.7)	26 (7.6)	
ITP	24 (7.3)	0	24 (7.0)	
Others (> one disorder)	40 (12.1)	2 (15.3)	42 (12.2)	
<b>Total</b>	<b>330 (100.0)</b>	<b>13 (100.0)</b>	<b>343(100.0)</b>	

**Table 3** Duration of steroid treatment and development of dysglycaemia

Treatment regimen	Normoglycaemia n (%)	Dysglycaemia n (%)	All Patients n (%)	p- value
<1week	37 (11.2)	0	37 (10.8)	0.593
1-3weeks	59 (17.9)	2 (15.4)	61 (17.8)	
Continuous	234 (70.9)	11 (84.6)	245 (71.4)	
<b>Total</b>	<b>330 (96.2)</b>	<b>13 (3.8)</b>	<b>343 (100)</b>	



**Figure 1** Age distribution of patients with steroid induced dysglycaemia

## DISCUSSION

Steroids are known to impair glucose metabolism and the resulting dysglycaemia may have a varied clinical presentation. This can range from a transient hyperglycaemia in most patients to the development of life-

threatening acute complications of hyperglycaemic hyperosmolar state and diabetic ketoacidosis.<sup>24-26</sup>

There is a wide variation in the reported prevalence of Steroid-induced dysglycaemia (SID) due to differences in the study populations, steroid doses, duration of follow-up and the diagnostic criteria used.<sup>24</sup>

Among post-transplant, connective tissue disease, respiratory disease, neurological and primary renal disease patients, the prevalence of SID ranges from 0.4% to 54%.<sup>24,27,30</sup> This study has shown the prevalence of steroid-induced dysglycaemia to be 3.79% among patients with haematological disorders in Ghana. This result falls within the range reported among various groups of individuals on long-term steroid therapy.<sup>24,27-30</sup>

The development of dysglycaemia in this study was found to be significantly associated with an older age and a longer duration of steroid therapy. Increasing age, high BMI, impaired glucose tolerance prior to therapy, cumulative dose of steroids, a long duration of steroid therapy, the relative potency of the glucocorticoid and the absolute and cumulative dose of steroids are all identified risk factors for the occurrence of SID.<sup>29-32</sup>

In a study among non-diabetic patients diagnosed with primary renal disease and treated with prednisolone at 0.75 mg/kg/day, 42% were found to have 2-hour post-lunch plasma glucose concentrations higher than 200 mg/dL (11.1mmol/L) although fasting plasma glucose remained normal.<sup>29</sup> Although in our study prednisolone was administered at a dose of 1mg/kg/day, the prevalence of dysglycaemia was relatively low. The use of FPG to screen for hyperglycaemia in some of our patients could have contributed to the low prevalence rate because it is well known that steroids commonly cause post-prandial hyperglycaemia rather than fasting hyperglycaemia.<sup>6,20,29</sup> In another retrospective study, the odds ratio for starting pharmacological therapy for diabetes was 1.77, 3.02, 5.82, and 10.34 for patients receiving a hydrocortisone-equivalent dose of less than 39mg/day, 40 to 79 mg/day, 80 to 119mg/day, 120 mg/day or more respectively.<sup>33</sup> It does appear, that the higher the dose, the higher the chances are, of developing dysglycaemia. In our study however, although majority of our patients who developed dysglycaemia were on a continuous steroid-based therapy regimen and also received a higher cumulative dose of steroids compared with our normoglycaemic patients, these were not statistically significant.

With increasing age, glucose tolerance progressively declines<sup>34</sup> due to the decline of  $\beta$ cell function and reduction in basal insulin secretion<sup>35</sup>. Data on other factors such as obesity, reduced physical activity and gestational diabetes<sup>36</sup> which also confer an increased risk of dysglycaemia were not captured in this study.

Haematological malignancies in coexistence with diabetes could be overwhelming for both patients and clinicians.<sup>37</sup> Additionally, the treatment of diabetes in the presence of cancer could pose a major challenge for physicians<sup>37</sup>.

The presence of chronic hyperglycaemia is associated with increased risk of cardiovascular morbidity and mortality.<sup>8,38</sup> Therefore early detection of SID and the institution of appropriate therapeutic interventions is essential to reduce the associated health burden.

This study could serve as a baseline for a future prospective study with the view of adequately identifying risk factors associated with the development of dysglycaemia in this group of patients. It would facilitate the formulation of local guidelines for the screening and management of SID among them.

The study had some limitations, it was a retrospective study and thus other important risk factors like increased waist circumference, previous history of gestational diabetes was not captured.

## CONCLUSION

The prevalence of steroid-induced dysglycaemia is relatively low among Ghanaian patients with haematological disorders and on steroid-based regimens. Older age and longer duration of steroid therapy were significantly associated with dysglycaemia. Early identification of patients at high risk of dysglycaemia will further enable a reduction in morbidity associated with this complication. Overall, the review provided justification to modify the use of steroids in patients with haematological disorders.

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