PREVALENCE OF HYPERGLYCAEMIA IN PAEDIATRIC PATIENTS ON SYSTEMIC CORTICOSTEROID THERAPY AT THE KENYATTA NATIONAL HOSPITAL

A DISSERTATION SUBMITTED IN PARTIAL FULFILMENT FOR THE DEGREE OF MASTERS OF MEDICINE IN PAEDIATRICS AND CHILD HEALTH.

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JUNE 2012

DECLARATION:

I declare that this dissertation entitled "Prevalence of hyperglycaemia in paediatric patients on systemic corticosteroid therapy at the Kenyatta National Hospital" is the result of my own work and has not been submitted either wholly or partially to this or any other university for the award of any degree or diploma.

Signature..... Date 15/11/12.....

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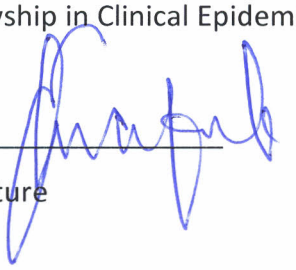

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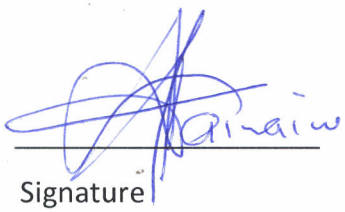

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Acknowledgements:

I wish to express my sincere gratitude:

1. My supervisors Professor Wafula and Dr. L. Wainaina-Mungai, who guided and supported me during this study.
2. The members of the department of Paediatrics and Child Health, university of Nairobi for their collective and individual input into this study.
3. The study assistants Erick and Michael for their time, hardwork and support.
4. Mr. Simiyu for his assistance in the measuring the glucose and packing it ready for use.
5. The staff in the University of Nairobi, department of paediatrics laboratory especially Ms Josephine and Mr.Kibe for the analysis of the blood sugars timely and tirelessly.
6. Statistician Mr. Mutai for his assistance in data management
7. All the parents/guardians and their children who participated in this study.
8. My family and friends for their support.
9. Last but not least my husband Anthony and my son Leon for their support throughout the study.

DEDICATION

Dedicated to my parents for all their effort in bringing me up to who and what I am today. And also dear husband Anthony Muriithi for his constant encouragement and my loving son Leon Muriithi.

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ABBREVIATIONS:

ACTH	Adrenocorticotropic hormone
ALL	Acute Lymphocytic Leukaemia
BMI	Body Metabolic Index
CRH	Corticotrophin-releasing hormone
Dose/kg/d	Dose per kilogram body weight per day
HDL	High Density Lipoprotein
IQR	Inter-Quartile Range
KG	Kilogram
CM	Centimetre
KNH	Kenyatta National Hospital
Mg/dl	Milligram/decilitre
Mmol/l	Micromoles per litre
OGTT	Oral Glucose Tolerance Test
SDM	Steroid induced Diabetes Mellitus
WHO	World Health Organization

1. ABSTRACT

INTRODUCTION

The natural glucocorticoids are steroid molecules produced and released by the adrenal cortex. Synthetic glucocorticoids are widely used in the clinical setting for their immunosuppressive and anti-inflammatory effects. In spite of their useful effects they have been shown to have detrimental effects. Hyperglycaemia is one of them and the interest of this study.

Steroid induced hyperglycaemia is associated with significant morbidity and mortality in the adult population but there is little data available in the paediatrics age group.

OBJECTIVES

The primary objective was to **determine the prevalence of hyperglycaemia in patients aged eighteen years and below on systemic corticosteroid at the Kenyatta National Hospital.**

Secondary objective was to **determine the associated factors associated with development of steroid induced hyperglycaemia**.

This was a hospital based cross-sectional study.

Methods: Once recruited, a researcher developed questionnaire was administered. Height, weight were measured. Two blood samples were collected; a fasting blood sugar and a 2 hour post prandial blood sugar (after an oral glucose load) and thereafter analysed in the laboratory.

RESULTS

Ninety six participants were enrolled into the study. Sixty (62.5%) were male and 36(37.5%) were female. Median age was 8 years. Majority of participants; 85 (88.5%) were on prednisolone for their current treatment. The overall prevalence of hyperglycaemia was 61.5%. The dose per kilogram body weight was found to significantly associated with hyperglycaemia.

Conclusions

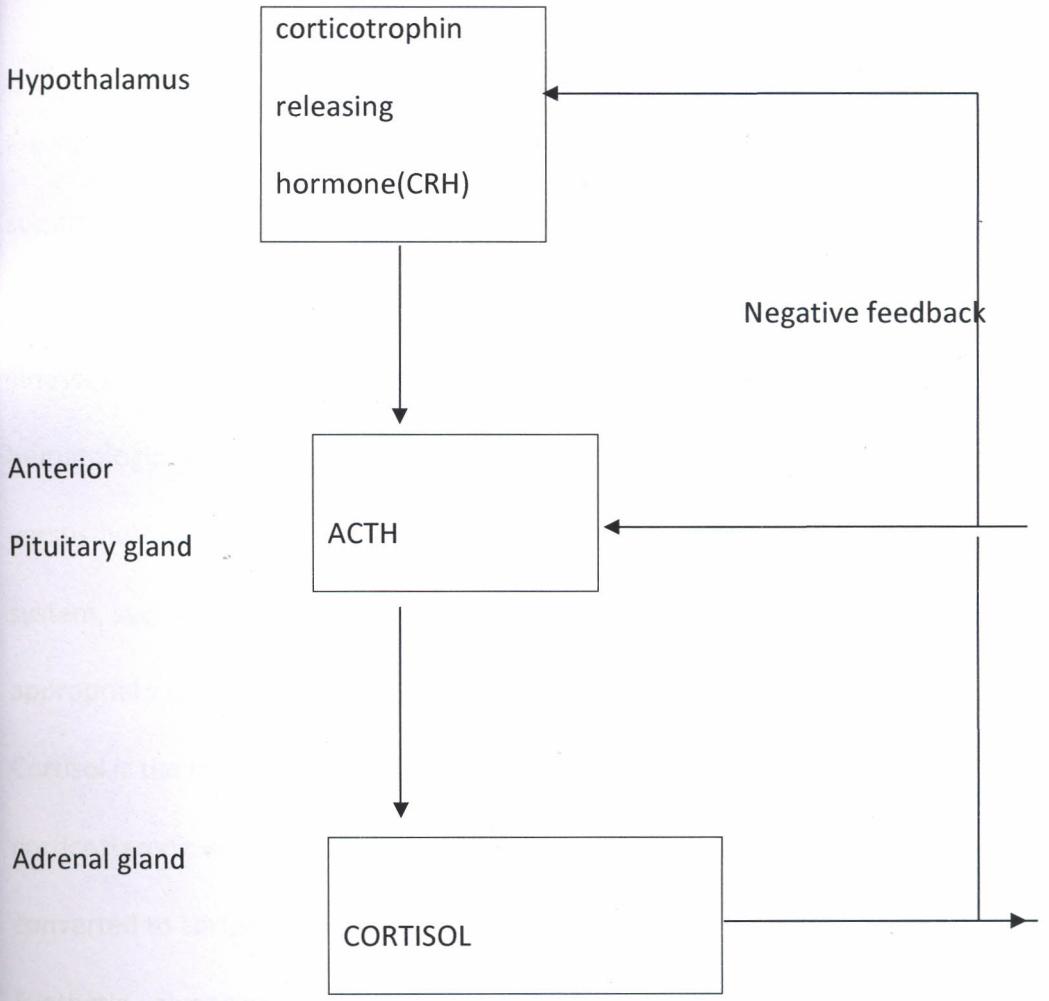
There is a high prevalence of hyperglycaemia in patients on glucocorticoid treatment. There's therefore need to monitor blood sugar of all patients on glucocorticoid therapy.

2. BACKGROUND AND LITERATURE REVIEW

2.1 INTRODUCTION

The natural adrenocortical hormones (corticosteroids) are steroid molecules produced and released by the adrenal cortex. Their secretion is stimulated by the adrenocorticotropic hormone (ACTH); which is regulated by the corticotrophin-releasing hormone (CRH) and circulating cortisol levels through a negative feedback[1]. See figure 1 below.

Figure 1: Hypothalamus-pituitary-adrenal axis



Glucocorticoids are a group of hormonal steroids that have important effects on intermediary metabolism and immune function.

Cortisol (hydrocortisone) is the major natural glucocorticoid. It is released in response to stress, ACTH and low serum cortisol. The amount of cortisol present in the blood undergoes diurnal variation, with the highest levels present in the early morning (approximately 8 am), and the lowest levels present around midnight and four in the morning, or 3–5 hours after the onset of sleep. That is morning level of 4 to 22μg/dl (micrograms/deciliter) and afternoon level of 3.0-17.0 μg/dl (micrograms/deciliter).

The primary functions are to increase blood sugar through gluconeogenesis, suppress the immune system, and aid in fat, protein, and carbohydrate metabolism. The immune-suppressive effect and anti-inflammatory effects of glucocorticoids have lead to the development of many synthetic glucocorticoids which are used in the treatment of different illnesses. These include; autoimmune, collagen, renal, respiratory gastrointestinal, nervous, hematologic, and ophthalmic diseases and in the suppression of the host-versus-graft and graft-versus-host reaction in cases of organ transplantation. Neoplastic disorders of the lymphoid system, such as leukemia and lymphomas, are also treated with glucocorticoids, along with the appropriate chemotherapy[2, 3,4,5,6].

Cortisol is the major glucocorticoid and is the active form in the body, it's followed by corticosterone which is less active and then cortisone which is an inactive compound and its converted to cortisol.

Synthetic glucocorticoids are in most cases rapidly and completely absorbed when administered orally. They are transported and metabolised in a similar fashion as the

endogenous cortisol, but important differences occur due to alteration in the glucocorticoid molecule. An additional double bond between C-1 and C-2, increases the glucocorticoid and decreases mineralocorticoid activity in prednisolone. Methylation at position two or sixteen in methyl prednisone prolongs the half-life by more than 50%, a double bond at C-1 and C-2, a fluoro group at C-9, and an alpha-methyl group at C-16 in dexamethasone increases the glucocorticoid potency by 25 to 50 times and has minimal mineralocorticoid effect[7].

Some of these glucocorticoids are shown in figures 2 to 5 below[8]. The arrows indicate the alterations made on the parent molecule.

Figure 2: Cortisol

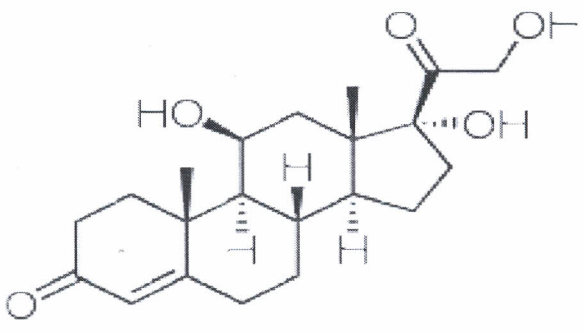


Figure 3: Methylprednisolone

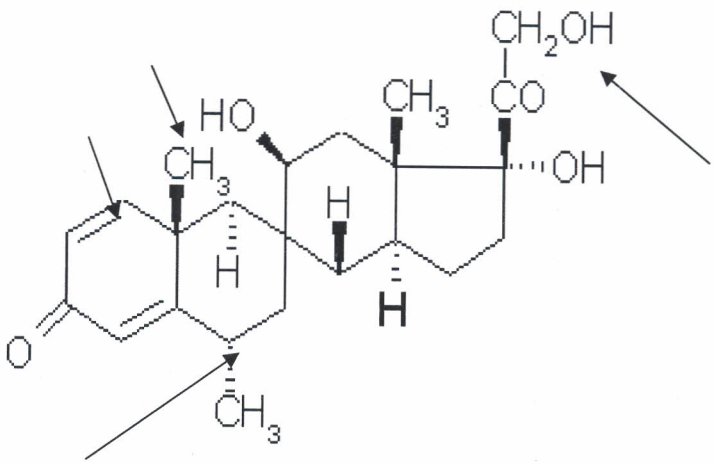


Figure 4: Prednisolone

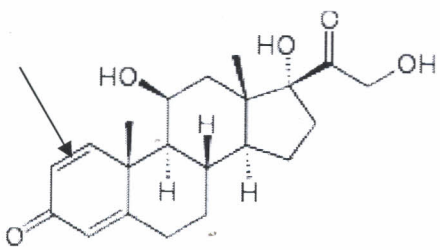
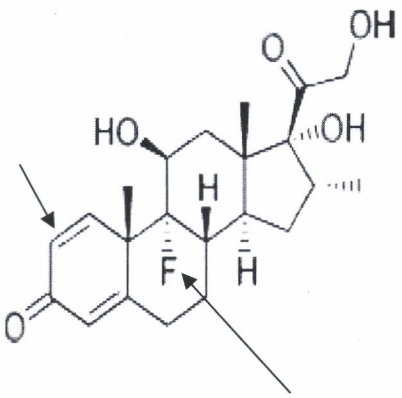


Figure 5: Dexamethasone



2.2 Metabolic effects of steroids

At normal levels, cortisol aids in fat, protein, and carbohydrate metabolism. It increases blood sugar through gluconeogenesis, by stimulating phosphoenolpyruvate carboxykinase and glucose-6-phosphate and inhibiting insulin action (peripheral glucose uptake and glycogenesis). It also stimulates hormone sensitive lipase and thus lipolysis. The resultant insulin resistance stimulates lipogenesis and to a lesser degree inhibits lipolysis leading to a net increase in fat deposition combined with increased release of fatty acids and glycerol into the circulation. These effects are more in the fasted state and aim at maintaining adequate glucose supply to the brain[9].

2.3 Mechanism of action

The effects of glucocorticoids are mediated by widely distributed cytoplasmic glucocorticoids receptors. These receptors form complexes with the heat shock protein (Hsp) in the absence of the hormonal ligand (glucocorticoids). On entry into the cells the glucocorticoid molecule binds

to the receptor, the glucocorticoid-receptors complex induces conformational changes that allow it to dissociate from the heat shock protein. There is then active translocation of the glucocorticoid- receptor complex to the nucleus where it interacts with the DNA and nuclear proteins. This then binds to the glucocorticoid receptor elements in the promoter region of the glucocorticoid responsive genes[10]. The resultant effect is the activation of protein synthesis among them are phosphoenolpyruvate carboxykinase and glucose-6-phosphatase (which are major enzymes in the gluconeogenesis pathway[11]. The glucocorticoid-receptor complex also forms complexes with and influences the function of other transcription factors which have broad actions on the regulation of growth factors, pro-inflammatory cytokines and chemokines (thus their anti-growth, anti-inflammatory and immunosuppressive effects[12].

In patients with glucocorticoid induced glucose intolerance, insulin levels are usually elevated, but inadequate to control the glucose. In extreme cases the hyperglycaemia may be severe enough to cause non-ketotic hyperosmolar coma. The deterioration of glucose tolerance leads to worsening of morbidity and mortality especially in seriously ill patients. In glucocorticoids induced diabetes mellitus the highest level of glucose are seen in the afternoon, in the evening and post prandially or after a glucose load. Normal levels of glucose maybe seen in the morning.

2.4 Glucocorticoid induced hyperglycaemia

Steroid/ glucocorticoid induced hyperglycaemia is defined as elevated blood sugars occurring in the context of glucocorticoid therapy used for a different disorder. This is an important clinical finding that is usually but not always transient and

if recognized, can effectively be treated. Glucocorticoids antagonize the insulin-mediated inhibition of hepatic glucose release, decreases peripheral glucose uptake by decreasing the translocation of glucose transporters to the cell membrane, especially glucose transporter 4 (GLUT4), and reduce the binding affinity of insulin receptors[11].

The risk of glucocorticoid-induced diabetes increases with the glucocorticoid dosage, duration of therapy, advanced patient age, family history of diabetes mellitus, obesity, certain ethnicity/race, and high blood glucose concentrations before glucocorticoid therapy. The glycemic effect of glucocorticoid use also depends on the route of administration and the type of glucocorticoid used[11]. Longer duration of therapy has also been shown to increase the risk of developing steroid induced hyperglycaemia[13] although its also been shown with short term treatment. It also occurs more with higher dosage of glucocorticoid[14].

2.5 Diagnostic Criteria

The diagnostic criteria for steroid induced diabetes are similar to the diagnosis of diabetes in general only that this occurs in the context of glucocorticoid therapy.

1. Symptoms of diabetes plus casual plasma glucose concentration ≥11.1 mmol/L (200 mg/dl). Casual is defined as any time of day without regard to time since last meal.

Or

2. Fasting plasma glucose ≥7.0 mmol/l (≥126 mg/dl).

Fasting is defined as no caloric intake for at least 8 hours.

Or

3. Two hour post load glucose ≥11.1 mmol/l (≥200 mg/dl) during an OGTT.

The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water or 1.75 g/kg of body weight to a maximum of 75 g. The corresponding categories when the OGTT is used are as follows:

• Two hour post load glucose<7.8 mmol/l (140 mg/dl) =

Normal glucose tolerance

• Two hour post load glucose 7.8—11.1 mmol/l

(140–199 mg/dl) = impaired glucose tolerance (IGT)

• Two hour post load glucose>11.1 mmol/l (200 mg/dl) =

Provisional diagnosis of diabetes[15]

2.6 Review of previous studies

Most of the studies done are in the adult population who were on different doses of glucocorticoids for the management of various primary diseases. The prevalence may varied when the primary lesion was considered.

A survey carried out over a period of 28 years found a prevalence of 9.8% among the patients who had received glucocorticoids for treatment of various diseases. The incidences of steroid induced diabetes varied depending on the primary disease; pemphigus 20%, systemic lupus erythematous 12.5%, chronic nephritis 5% Satisfactory improvement was seen in about 80% of the patients if a strict line of therapy against primary diabetes was oriented. Treatment involved the reduction of steroid or with use of oral hypoglycaemic agents or insulin or both.

Their blood glucose levels returned to normal and urine sugar disappeared rapidly. Four of the five deaths were caused by their primary diseases. One died of pemphigus complicated with infection and shock exhibiting ante-mortem blood glucose level as high as 31.7mmol/L. Obviously hyperosmolar status being the predisposing factor. Due to the fact that most of the patients with steroid induced diabetes were clinically asymptomatic, delayed or misbranded diagnosis was not infrequently seen[16].

The prevalence and risk factors of glucocorticoid-induced diabetes mellitus was shown to be as high as 40.5% in a study on patients with primary renal diseases who were on prednisolone 0.75 +/- 0.10 mg/kg/day. Steroid induced diabetes was diagnosed by measuring 2 hour postprandial blood sugar, although some patients had normal fasting blood glucose level. A high age and high body mass index were independent risk factors for glucocorticoid-induced diabetes[17].

Patients on glucocorticoids therapy for acute exacerbations of Crohn can develop steroid induced diabetes especially when the steroids are used for longer than brief periods even in moderate dosages. These patients were managed by reduction of the steroid dosage. Therefore frequent blood glucose monitoring is recommended in children on prolonged glucocorticoid therapy. Steroid induced diabetes experienced by the reported cases may be a marker for the onset of diabetes in their adulthood and hence the need for follow-up [18].

Patients receiving higher average daily prednisone dosage after renal transplant were more likely to develop hyperglycaemia, prevalence of 8.8%. The diabetes has been shown to be

transient and easily controlled but complication like cerebral vascular accidents (CVA) and aspergillosis in a native kidney may also occur. It was therefore recommended that steroid-induced diabetes following kidney transplantation may constitute a group at greater risk for complications thus the need to monitor the blood sugar in this group of patients[19].

The odds ratio for new-onset diabetes mellitus in patients treated with glucocorticoids ranged from approximately 1.5 to 2.5. Total glucocorticoid dose and duration of therapy were seen to be strong predictors of diabetes induction. Other risk factors included age and body mass index. Failure to treat glucocorticoid-induced hyperglycaemia is related to the presumed short duration of administration of glucocorticoid treatment and the emphasis on fasting plasma glucose only[13].

In patient on prednisolone for treatment of pemphigus vulgaris the prevalence was shown to be 27.9% and there were no differences between those who developed diabetes and those who did not in respect of age, positive family history, blood pressure, BMI, HDL[20]. The cumulated prednisone dose of steroid was shown to be the most significant factor significantly associated with the development of steroid induced diabetes, Odds ratio of 6.35 ($p< 0.02$)[21]. Longer duration of therapy and higher dosage are other significant factors associated with development of steroid induced hyperglycaemia necessitating treatment. Hyperglycaemia is also associated with higher risk of rejection in post renal transplant patients the diagnosis was made within three months after transplantation[22].

At puberty, patients on steroid have a higher risk of developing hyperglycemia this is due to the transient insulin resistance that occurs during puberty. During the transition from Tanner stage I

to Tanner stage III, insulin sensitivity decreases by approximately 30% in both boys and girls. This reduction is accompanied by increases in fasting glucose and insulin, and insulin increment in response to glucose. The decrease in insulin sensitivity is not statistically associated with changes in body fat, visceral fat, or levels of androgens or estradiol [23]

The diagnosis of steroid induced hyperglycaemia can be made as early as 48 hours[14] or 4.5days[24] of starting therapy by measuring blood sugar and checking urine for glycosuria but if diagnosis is dependent on symptoms then its delayed up to 26 days from the initiation of therapy. The treatment includes insulin without stopping the steroids[25].

The treatment involves a reduction in the glucocorticoid dose, and if the glucocorticoid is stopped, hyperglycaemia may fully reverse over weeks or months. When hyperglycaemia is persistent (mostly during the day, with normal to minimally elevated fasting glucose levels), the addition of insulin-sensitizing drugs (thiazolidindiones, metformin) and/or insulin secretagogue would be enough in patients with blood glucose levels less than 250 mg/dL. If blood glucose levels are higher than 250 mg/dL, especially if the patient is symptomatic, then insulin therapy should be considered Response to treatment is good but frank diabetes has been shown to occur especially in older patients[26].

3. JUSTIFICATION AND UTILITY

Steroid induced hyperglycaemia is a known adverse effect of glucocorticoid therapy and has been documented in various studies mainly in the adult population but the magnitude or prevalence in the paediatric population is not known. This study aimed at determining the prevalence of hyperglycemia in paediatric population at KNH.

This study aimed at determining the prevalence of steroid induced hyperglycaemia in the paediatric age group and also assess the associated risk factors. This knowledge will assist the health care professional to evaluate the patients on corticosteroids appropriately.

The timely detection of steroid induced hyperglycaemia and the administration of appropriate treatment help reduce the morbidity associated with it without necessarily stopping the treatment of the primary disease.

4. RESEARCH SCOPE

4.1 Primary Objective

To determine the prevalence of hyperglycaemia in patients aged eighteen years and below on systemic corticosteroid therapy for treatment of various conditions at the Kenyatta National Hospital.

4.2 Secondary Objective

To determine the risk factors associated with development of hyperglycaemia. The risk factors of interest in my study include age, dose, duration and preparation of steroid used, body mass index and family history of diabetes.

4.3 Hypothesis

There is a high prevalence of hyperglycaemia in patients on glucocorticoid therapy at the Kenyatta National Hospital.

5. STUDY METHODOLOGY

5.1 Study Design

A hospital based cross-sectional study.

5.2 Study Population

Patients aged eighteen years and below who were on glucocorticoids for treatment of various conditions who fulfilled the inclusion criteria.

5.3 Inclusion Criteria

- Patients aged eighteen years and below who were on systemic glucocorticoids therapy for at least 3 days.
- Patients whose parents gave consent.

5.4 Exclusion Criteria

- Those whose parents declined to give consent
- Patients known to have diabetes

5.5 Study Area

The study was carried out at the Kenyatta National Hospital, in the renal outpatient clinic, paediatrics outpatient clinic and hemato-oncology clinic and in the paediatrics wards, dermatology ward.

5.6 Study Period

The study was carried out over a period of 6 months.

5.7 Sampling and sample size

Patients were recruited consecutively in the wards and in the clinics at the time that we were able to be at the site.

Fisher's formula[27]

$$N = \frac{Z^2 p (1-p)}{D^2}$$

N=minimum sample size

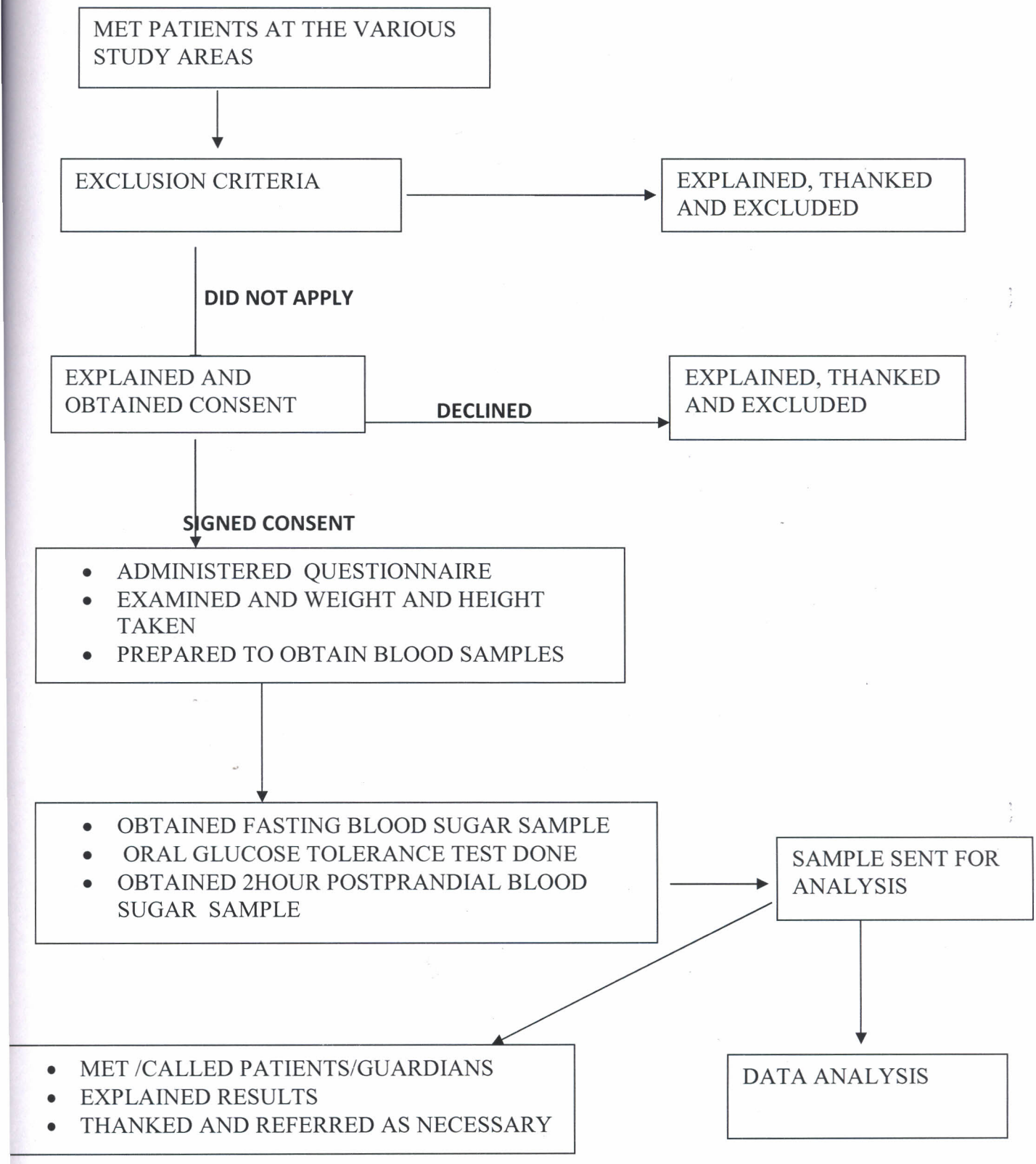
Z=standard normal deviate for 95% C.I=1.96

P=estimated prevalence of glucocorticoid induced diabetes (50%)

D=precision (0.1)

N= 96

5.8 Recruitment of study subjects



5.10 Methods

Patients were recruited in the ward and in the various specialised clinics on the basis of meeting the inclusion criteria. The study purpose and method were explained to them and assured that treatment will continue whether or not they participated in the study. After obtaining an informed consent (Appendix 1), a researcher developed questionnaire (appendix 2) was administered to the patient that included bio data (age, sex,), treatment history, and family history of diabetes. A physical examination was carried out. Patients and/or guardian were instructed on the time of collection of samples; those in the wards the primary nurse was be involved in ensuring the patient is fasted for at least six hours before the fasting blood sugar sample was taken after which the oral glucose tolerance test was done and second sample taken 2 hour post challenge after an oral glucose challenge of 1.75mg/kg(maximum 75grams) of anhydrous glucose mixed in a glass of water[28]; the samples were analysed using a Haemostat blood biochemistry machine at the department of paediatrics University of Nairobi. For the patients coming through the clinic the recruitment was also on the basis of fulfilling the inclusion criteria. The procedure was explained to the guardian and/or the patient and the samples collected (as for the in patients) on a specific day that was agreed upon by the guardian and primary investigator or the study assistant. Their cell phone number was also taken so as to confirm the appointment and also to clarify the instructions. Results were disclosed to the guardian and/or patient and those with hyperglycaemia referred to the paediatric endocrinology clinic for further management.

5.10 Case definition

Hyperglycaemia was defined as a fasting blood sugar >7mmol/l (126mg/dl) or 2 hour post-glucose challenge >200mg/dl (11.1mmol/l).

5.11 Data Analysis

Data was cleaned and processed using SPSS® (Version 8.0). The t-test was used to compare continuous variables between patients with and without steroid induced hyperglycaemia. The variables to be analyzed included age, body mass index (BMI), type of steroid used, daily and cumulative dose of steroid, and duration of treatment, fasting blood sugar and post glucose load blood sugar and family history of diabetes.

6. ETHICAL CONSIDERATIONS

- Written informed consent was sought from the guardian/ parent and assent was sought from the patients. This was done after a detailed explanation of the study. (Appendix 1).
- It was explained that participation in the study was voluntary and that the information collected was to be used for the purpose of the study and that there will be no material gain from the study.
- Medical advice and treatment was offered to all subjects whether or not they participated in the study and their treatment was continued whether or not they participated in the study.
- Those found to have hyperglycaemia were referred to the endocrinology clinic for treatment.
- Safety precautions were taken into consideration. Blood was drawn under aseptic technique and all measures were taken to ensure patients and staff safety.
- Study subjects were assured that confidentiality was observed, their names were not used in the study documents but a serial number was assigned instead. The hospital number was solely for the purpose of identification and facilitation of any necessary referrals.

- Approval to carry out the study was sought from the department of paediatrics and child health, University of Nairobi and clearance obtained from the Ethics and Research committee at Kenyatta National Hospital.

7. RESULTS

Table 1: Demographic characteristics

Variable	Frequency (%)
Age in years	
Median (IQR)	8.0(4.0-10.0)
Min-Max	0.5-16.0
Age group	
0.5-4	28 (29.2)
5-9	36 (37.5)
10-14	31 (32.3)
15-16	1 (1.0)
Sex	
Male	60 (62.5)
Female	36 (37.5)
Family history of diabetes	
Yes	10 (10.4)
No	86 (89.6)
Weight in kg, median (IQR)	22.8 (15-30)
Height in cm, mean (SD)	113.7 (26.3)
BMI, mean (SD)	17.1(3.6)

The study enrolled 96 participants who were either admitted in the paediatrics ward or attending various out-patient clinics at the KNH. Males consisted of 60 (62.5%) and 36 (37.5%) were female. The ages ranged between 6 months and 16 years old. Median age was 8 years with an IQR of 4-10. Family history of diabetes was positive in 10 (10.4%) of the participants. The median weight of the participants was 22.8kg. The mean height was 113.7cm and the mean BMI was 17.1. as shown in table 1 above.

Table 2: Diagnosis

Diagnosis	Frequency (%)
Malignancies	24 (25.0)
Renal disease	33 (34.4)
Infectious disease	13 (13.5)
Neurological disorders	3 (3.1)
Connective tissue disorder	2 (2.1)
Hematological disorder	6 (6.3)
Skin disorder	1 (1.0)
Others	14 (14.6)

The participants were on treatment for different medical conditions. About one third of the patients were on treatment for renal disease 33 (34.4%), 24 (25%) were on treatment for malignancies, 13(13.5%) infectious diseases, 3 (3.1%) neurological disorders, 2 (2.1%) connective tissue disorder, 6 (6.3%) haematological disorder, 1 (1.0%) skin disorder and 14 (14.6%) for other conditions.

Table 3: Steroid treatment

Variables	Previous corticosteroid treatment	Current corticosteroid treatment
Drugs		
Prednisolone	28 (29.2)	85 (88.5)
Dexamethasone	1 (1.0)	9 (9.4)
Methylprednisolone	1 (1.0)	2 (2.1)
None	66 (68.8)	0
Duration of treatment in days Median (IQR)	28 (10-60)	14 (7-24)
Dosage/day Median (IQR)	50 (22.5-60)	27.5 (15-40)
Dose/kg/day Median (IQR)	1.8 (0.9-2.2)	1.3 (0.8-1.8)

The participants were on different types of glucocorticoids for previous and current treatment, 28(29.2%) were on prednisolone, 1 (1.0%) on dexamethasone and 1 (1.0%) on methylprednisolone for their previous treatment. For current treatment; 85 (88.5%) were on prednisolone, 9 (9.4%) on dexamethasone and 2(2.1%) methylprednisolone. All participants were on treatment at recruitment into the study and were on corticosteroids throughout. The duration of treatment ranged between 1 and 1095 days with a median of 28 days with an interquontile range of 10-60 days for their previous treatment and 2 and 180 days with a median of 14 days with an IQR of 7-24 days for the current treatment. The median dose was

1.8mg/kg/day and 1.3mg/kg/d for previous and current treatment respectively, this is for prednisolone which was the glucocorticoid that most patient were on.

Table 4: Use of other concurrent medication

Variable	Frequency (%)
Other concurrent medication	
Yes	17 (17.7)
None	79 (82.3)

The majority of participants 79 (82.3%) were not on other medication that could induce hyperglycaemia compared to 17(17.7%) who were.

Table 5: Overall prevalence

Hyperglycaemia	Frequency (%)
Yes	59 (61.5)
No	37(38.5%)
Fasting blood sugar, mean (SD)	5.8 (1.3)
2hr-post prandial, mean (SD)	7.0 (1.8)

Hyperglycaemia was found in 59 (61.5%)participants, whereas 37 (38.5%) had normal blood sugar. The mean fasting blood sugar was 5.8 (1.3SD) as in table 5 above.

Table 6: Prevalence of hyperglycaemia

variables	Frequency (%)
Normal	37 (38.5)
Impaired fasting glucose	24 (25.0)
Impaired glucose tolerance	18 (18.8)
Diabetes	17 (17.7)

Thirty seven (38.5%) had normal blood sugar, 24 (25%) had impaired fasting blood sugar, 18 (18.8%) had impaired blood tolerance and 17(17.7%) had diabetes as in table 6 above.

Table 7: Factors associated with hyperglycaemia

Variable	Hyperglycaemia		OR (95% CI)	P Valu
	Yes	No		
Age in years, median (IQR)	8.0 (4.0-10.0)	8.0 (3.5-11.0)	-	0.483
Drug previously used				
Prednisolone	11 (39.3%)	17 (60.7%)	-	0.179
Current drug				
Prednisolone	52 (61.2%)	33 (38.8%)	1.6 (0.1-26.1)	0.751
Duration of treatment in days , median (IQR)				
Previous	28 (3-60)	30 (14-60)	-	0.394
Current	13 (7-23)	14 (7-28)		0.872
Cumulative	14 (7-33)	21 (7-62)		0.327
Dosage/day, median (IQR)				
Previous	60 (30-200)	50 (22.5-60)	-	0.197
Current	22.5 (15-40)	30 (14-45)		0.664
Dose/kg/day, median (IQR)				
Previous	2.0 (1.2-9.7)	1.4 (0.8-1.9)	-	**0.036**
Current	1.3 (0.8-1.9)	1.3 (0.9-1.7)		0.982
Cumulative dose, median (IQR)				
Previous	1200 (800-2700)	1680 (900-1800)	-	0.801
Current	300 (140-630)	300 (150-700)		0.708
Previous + current	420 (175-1200)	450 (200-1890)		0.254
BMI, mean (SD)	16.8 (3.2)	17.6 (4.2)	-	0.296
Family history of diabetes				
Yes	4 (40.0%)	6 (60.0%)	0.4 (0.1-1.7)	0.309
No	44 (60.3%)	29 (39.7%)	1.0	
Other concurrent medication				
Yes	11 (64.7%)	6 (35.3%)	1.2 (0.4-3.5)	0.762
No	48 (60.8%)	31 (39.2%)	1.0	

The various associated factors were assessed in this study are as shown in the table 7 above. The analysis done was for prednisolone since the other glucocorticoids (dexamethasone and methylprednisolone) had few numbers for valid statistics. The dose/kg/day for previous treatment was the only factor that was found to be statistically significant.

8. DISCUSSION

The participants of the study consisted of males 60 (62.5%) and 36(37.5%) were females. The age varied between 6months and 16 years , with a median age was 8 years with an IQR of 4-10.

The participants were on treatment for different medical problems. About one third of the patients were for renal disease 33 (34%), 24 (25%) were on treatment for malignancies. This may correlate well with the age of the study population and the peak age of the common diagnosis which were renal disease which was mainly nephrotic syndrome and ALL in the malignancy group.

The majority of the participants were on prednisolone 28 (29.2%) for previous treatment and; 85 (88.5%) for current treatment. Prednisolone is most commonly used glucocorticoid in most of the conditions where the treatment is indicated. This compares well with other studies done[16,18,19,21] where prednisolone was the commonly used glucocorticoid. Prednisolone is preferred in most regimens due to the ease of administration which is oral and the dosage is not large compared to the others like methylprednisolone which is administered intravenously.

The prevalence of hyperglycaemia in this study was found to be 61.5%. This is different for other studies done [17, 19]which showed a prevalence of 40.5% and 8.8% respectively. The prevalence of steroid induced diabetes was significantly higher in this study and also the pre-diabetic states of impaired glucose tolerance and impaired fasting glucose.

Temporary hyperglycaemia is often benign and asymptomatic. Blood glucose levels can rise well above normal for significant periods without producing any permanent effects or symptoms. However, chronic hyperglycaemia at levels more than slightly above normal can

produce a very wide variety of serious complications over a period of years, including kidney damage, neurological damage, cardiovascular damage, retinopathy and neuropathy. Other complications that can occur include diabetes ketoacidosis and hyperosmolar non-ketotic coma both which are associated with significant morbidity and mortality[25].

Impaired fasting glucose and impaired glucose tolerance are thought to be pre-diabetic states and hence close monitoring is recommended especially if the steroid therapy cannot be discontinued. Steroid induced diabetes requires necessary treatment to be administered.

The median duration of treatment was 28 days and 14 days for previous and current treatment respectively and the dose per kg per day was between 0.9-2-2 with a median of 1.8mg/kg/d. This is within the recommended duration and dosages of treatment although some of the patients had been the treatment for longer than recommended duration especially so for the renal disease. The cumulative doses were quite high as shown in table 7. The dose/kg /day were found to be significantly related to development of hyperglycaemia. However there was no statistical significance found between the glucocorticoid used and duration of treatment in this study. This is different from other studies because the longer duration of treatment and higher cumulative dose tended to be associated with hyperglycaemia[21, 22].

The use of concurrent medication was not associated with a statistically significant risk of hyperglycaemia. And so did the family history of diabetes. This correlates well with another study[24].

The BMI of the study population had a normal distribution is different from the other studies and there was no statistically significance as a risk of hyperglycaemia.

Management involves the discontinuation or reduction of dose of the glucocorticoid where feasible and the administration of insulin[26].

Steroid sparing regimen of treatment can be used where possible but the cost of these agents may be a limiting factor. Their use also is associated with other adverse effects and may require parenteral administration hence their use is limited.

Limitations

1. The cost of doing the blood sugars limited the number of participants recruited; this may have an impact on assessing the associated factors for hyperglycaemia.
2. There was an increased number of participants who declined to participate, especially in the out-patient clinic due to the fact that they had to wait for two hours for the sampling to be done.
3. There was also a high drop out rate especially the participants who were recruited in the outpatient setting.

There was a higher number of patients in the wards this could affect the results because they were on treatment for a relatively shorter time. It was generally easier to recruit in patients and there was lower drop out rate with this cohort. The exact numbers of in- versus out-patients and the drop out rate is not available because the data analysed was only for the patients that the blood sugar was measured.

The power of the study is low due to the small sample size and the secondary objective may not be fully fulfilled in this study. The cost of the blood sugar analysis was the main limitation as far as recruiting a bigger sample size was concerned.

Conclusions

1. There is a high prevalence of hyperglycaemia (61.5%) in patients on glucocorticoid treatment.
2. The only risk factor that was significantly associated with hyperglycaemia was the dose of corticosteroid used.

Recommendations

1. All patients on glucocorticoid therapy should have their blood sugar monitored, preferably before starting therapy and also during treatment.

2. There is need for a prospective study to be carried out to be able to assess the risk factors.

9. REFERENCES

1. Turk Rhen and John A. Cidlowski. Anti-inflammatory Action of Glucocorticoids. New Mechanisms for Old Drugs. *New England Journal of Medicine. 2005; 353:1711-1723.*

2. Dimitrios T. Boumpas, George P. Chrousos, Ronald L. Wilder, Thomas R. Cupps and James E. Balow. Glucocorticoid Therapy for Immune-mediated Diseases: Basic and Clinical Correlates. *Annals of internal medicine. 1993; 119:* 1198-1208.

3. Harter JG. Corticosteroids: their physiologic use in allergic disease. *New Yolk State Journal of Medicine. 1966; 66: 827-840.*

4. Jeanette I. Webster, Leonardo Tonelli and Esther M. Sternberg. Neuroendocrine regulation of immunity. *Annual Review of Immunology. 2002; 20:125-163.*

5. Castilla C, Perez-Simon JA, Sanchez-Guijo FM, et al. Oral beclomethasone dipropionate for the treatment of gastrointestinal acute graft-versus-host disease (GVHD). *Biology of Blood and Marrow Transplant. 2006; 12:936-41.*

6. Rix M, Birkebaek NH, Rosthoj S, Clausen N. Clinical impact of corticosteroid-induced adrenal suppression during treatment for acute lymphoblastic leukemia in children: A prospective observational study using the low-dose adrenocorticotropin test. *Journal of Pediatrics. 2005; 147:645-650.*

7. Magiakou M.A, Chrousos GP. Corticosteroid therapy and withdrawal. *Current Therapy in Endocrinology and Metabolism.1994; 120-124.*

8. Liddle GW. Studies of structure-function relationships of steroids. *Metabolism. 1958; 7: 405-407.*

9. Tayek JA and Katz J. Glucose production, recycling, Cori cycle, and gluconeogenesis in humans: relationship to serum Cortisol *America Journal of Physiology Endocrinology and metabolism.1997; 272:E476-E484.*

10. Hanson R.W and Reshef L. Regulation of phosphoenolpyruvate carboxykinase (GTP) gene expression. *Annual review of biochemistry1997; 66:581-611.*

11. Robert C.A and Brian R.W. Glucocorticoids and insulin resistance: old hormones, new targets. *Clinical Science 1999; 96:513–523.*

12. Rhen T, Cidlowski J.A. Anti-inflammatory action of glucocorticoids--new mechanisms for old drugs. *New England Journal of Medicine 2005;* 353: *1711–23*

13. Clore JN, Thurby-Hay L. Glucocorticoid-induced hyperglycemia. Endocrine Practice. *2009; 15(5):469-74.*

14. Dohini AC, Raval D, Saul M, Korytkowski MT, Devita MA: Retrospective chart review-Prevalence and predictors of corticosteroid-related hyperglycemia in hospitalized patients. *Endocrine Practice 2006; 12:358-62.*

15. Craig ME, Hattersley A, Donaghue KC. Definition, epidemiology and classification of diabetes in children and adolescents. *Pediatric Diabetes 2009; 10: 3–12.*

16. Shi MZ and Zhang SF. Steroid diabetes: an analysis of 28 cases. *Chinese journal of internal medicine 1989; 28:139-41,185.*

17. Uzu T, Harada T, Sakaguchi M, Kanasaki M, Isshiki K, Araki S, Sugiomoto T, Koya D, Haneda M, Kashiwagi A, Yamauchi A. Glucocorticoid-induced diabetes mellitus: prevalence and risk factors in primary renal disease. *Nephron Clinical Practice. 2007; 105:54-7.*

18. Srdan Banac; Mladen Persić; Katarina Cvijović, case report on steroid induced diabetes in children with Crohn disease. *Acta medica croatica 2002; 56:35-8.*

19. Fennell RS, Van Deusen J, Riley W.J. Steroid-induced diabetes in paediatric renal transplant recipients. *The International journal of pediatric nephrology.1983; 4:103-7.*

20. Mahin Valikhani, Mohsen Khoshniat, Ali Naser Tork. Risk factors and frequency of steroid-induced diabetes in pemphigus vulgaris patients during a one year study. *Tehran University of medical sciences e-journal. 2007; 6: 301-307.*

21. Raúl Ariza-Andraca C, Barile-Fabris LA, Frati-Munari AC, Baltazár-Montufar P. Risk factors for steroid diabetes in rheumatic patients. *Archives of medical research. 1998; 29:259-62.*

22. Gunnarsson R, Arner P, Lundgren G, Magnusson G, Ostman J, Groth CG. Steroid diabetes after renal transplantation--a preliminary report. *Scandinavian journal of urology and nephrology supplementum.1977; 42:191-4.*

23. Michael I.Goran and Barbara A. Gower. Longitudinal Study on Pubertal Insulin Resistance. *Diabetes.2001; 50: 2444-2450.*

24. Perlman K and Ehrlich RM. A retrospective study on the prevalence of hyperglycemic episodes on children on corticosteroids. *American Journal of Diseases of children.1982; 136:64-8.*

25. Yang JY, Cui XL and He XJ. Case reports: Non-ketotic hyperosmolar coma complicating steroid treatment in childhood nephrosis. *Paediatrics nephrology journal.1995:9621-2.*

26. Levetan CS, Magee MF. Hospital management of diabetes. *Endocrinology and Metabolism Clinics of North America. 2000; 29:745-770.*

27. Daniel WW. Biostatistics: A Foundation for Analysis in the Health Sciences. 1999; 7: 180-185.

28. Performance of oral glucose tolerance test. Diabetes Care 2006; 29: s43-s48.

10. APPENDICES

APPENDIX 1

i. INFORMED CONSENT

To be read and questions answered in a language which the subject understands.

I, Dr. Cecilia G. Maina wishes to carry out a study entitled Prevalence of Hyperglycaemia in Patients on Systemic Glucocorticoids at the Kenyatta National Hospital. The purpose of the study is to establish the proportion of patients with elevated blood sugar while on glucocorticoid therapy, under the supervision of Professor E. Wafula and Dr Lucy Wainaina-Mungai who are both lecturers at the Department of Paediatrics at the University of Nairobi.

This is a medical research study and you are required to understand the following general principles:

i. Your agreement is entirely voluntary
ii. You may withdraw from the study at any time
iii. Refusal to participate will not lead to any penalty or loss of benefit to which you are otherwise entitled
iv. After reading the explanation, please feel free to ask any questions that will allow you to understand clearly the nature of the study.

The procedure will involve asking you questions concerning your age, diagnosis, the treatment you are on any family history of diabetes. Physical examination will be done to determine the weight, height and assessment of pubertal development. Invasive procedure of drawing of

blood will be done under sterile conditions. This will be done twice. The first before any food has been taken and the second after taking a sugar solution. Results will be confidential and will be disclosed and explained to you and guardian.

Benefits of the study include the evaluation of the blood sugar and diagnosing of high blood sugar which is one of the adverse effects of steroid therapy. If blood sugar is found to be elevated, referral will be done to the endocrinology clinic for standard management.

Risk of participating in the study is pain on the drawing of blood, infection during the procedure will be minimised by observing standard infection control measures (use of gloves, cleaning and disinfecting the skin, proper disposal of materials used). They'll also be required to fast for at least 6hours before the test which; delays will be avoided to prevent the patients waiting for longer than necessary.

The participant should feel free to contact the following people for any clarifications on the study:

- Dr. Cecilia Maina; phone number 0721415756 (primary investigator).
- Professor Ezekiel M. Wafula and Dr. Lucy Wainaina-Mungai lecturers in the department of Paediatrics University of Nairobi (the supervisors).
- Kenyatta national hospital-ethics and research committee phone number 020-726300-9.

ii. **CONSENT FORM**

I, undersigned do hereby volunteer to participate in this study. The nature and purpose of the study have been explained to me by Dr. Cecilia G. Maina. I understand that all information gathered will be for the purposes of this study only.

Signed _____ date _____

Serial number _____

Signed _____ date _____

(Dr. Cecilia G. Maina)

APPENDIX 2

QUESTIONNAIRE SERIAL NO: _____

QUESTIONNAIRE FOR THE STUDY ON PREVALENCE OF HYPERGLYCAEMIA IN PATIENTS ON SYSTEMIC GLUCOCORTICOIDS THERAPY AT THE KENYATTA NATIONAL HOSPITAL

A. Sociodemographic data

1. Patient hospital Number _____

2. Age (years)_____

3. Sex male ☐ female ☐

4. Family history of diabetes YES ☐ NO ☐

B. Treatment history

1. Diagnosis_____

2. Type of steroid used previously and dosages

   a) Name of drug _____

   b) Duration of treatment _____

c) Dosage/day _____

Dose/kg/day _____

3. Current type of steroid and dosage

   a) Name of drug _____

   b) Duration of treatment _____

   c) Dosage/day _____

4. Other concurrent medication _____

   Drugs of interest are those that can cause hyperglycaemia.

C. Physical examination

1. Weight (kg)_____
2. Height (cm)_____
3. BMI (weight/height^2) _____

D. Blood sugar measurement

Time	Blood sugar in mmol/l
FBS	
2-HR POST PRANDIAL	

APPENDIX 3

Study instruments:

A researcher developed questionnaire (see appendix 1)

Weighing scale; for the measurement of weight.

Stadiometer/ infantometer for the height /length determination.

Fluoride bottles, needles, syringes, gloves and surgical spirit and swabs for the purposes of collection of samples.

Anhydrous glucose, measuring scale, clean cups and water for preparation of the glucose solution for the Oral glucose tolerance test.

Humastat 600 blood biochemistry machine, for the measurement of the blood sugars. The machine is at the Department of Paediatrics laboratory in the University of Nairobi. It analyses serum sugars and gives results in millimoles per litre. The machine is calibrated every morning and they also run internal controls every morning. The laboratory participates in international external quality controls every three months.

Appendix 4:

BUDGET IN KENYA SHILLINGS

Stationary, printing and photocopies.....10,000.00

Laboratory charges and sampling.....32,000.00

Materials (Gloves, needles syringes, etc) 5,000.00

Data analysis.....20,000.00

Miscellaneous.....5,000.00

Study assistant.....25,000.00

Total.....97, 000.00

Funding was sourced from personal savings

Time spent cannot be quantified.