



# Aetiology of Spontaneous Hypoglycaemia in a South African Hospital

## Bir Güney Afrika Hastanesinde Spontan Hipogliseminin Etiyolojisi

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### Abstract

**Purpose:** To determine the etiology of spontaneous hypoglycaemia at admissions in Nelson Mandela Central Hospital, Mthatha, Eastern Cape, South Africa.

**Material and Method:** A retrospective review of medical records for the patients admitted with spontaneous hypoglycaemia from January 2008 till December 2015 was carried out. The medical records of patients with blood glucose levels <2.5 mmol/L were reviewed for age, gender, relevant medications, alcohol history, retroviral status, blood glucose, plasma insulin, C-peptide, ketone, cortisol, IGF-1 level, liver and kidney function, and documented etiology of hypoglycaemia.

**Results:** There were 26 patients (65.4% females) with the mean age of 39.6±22.3 years (range 13–95 years). The mean blood glucose levels during hypoglycemic episodes were 1.6±0.6 mmol/L (range 0.5–2.9 mmol/L). Half of the patients (n=13/26) were retroviral positive. Hypoglycemia was associated with the elevated or inappropriately normal plasma insulin levels in 35.3% subjects and with the suppressed plasma insulin levels in 64.7% of cases. Eight cases of spontaneous hypoglycemia were pregnancy related. All pregnancy related cases of hypoglycemia were noted in retroviral positive subjects. The main cause for hypoglycemia was hypocortisolism.

**Discussion:** The admissions in the case of spontaneous hypoglycemia were mainly due to hypocortisolism. All pregnant and postpartum patients with spontaneous hypoglycemia were retroviral positive.

**Keywords:** Hypoglycemia; hypocortisolism; retroviral disease; pregnancy

### Özet

**Amaç:** Nelson Mandela Merkez Hastanesine, Mthatha, Doğu Cape, Güney Afrika, spontan hipoglisemi müracaatlarının etiyojisini belirlemektir.

**Gereç ve Yöntem:** Ocak 2008'den Aralık 2015'e kadar spontan hipoglisemi nedeniyle müracaat eden hastaların medikal kayıtlarının retrospektif gözden geçirilmesidir. Kan glukozu <2,5 mmol/L altında olan hastaların medikal kayıtları yaş, cinsiyet, ilgili ilaçlar, alkol hikâyesi, retroviral durumu, kan glukozu, plazma insülin, C-peptit, keton, kortizol, IGF-1 düzeyi, karaciğer ve böbrek fonksiyonları ve belgelenmiş hipoglisemi etiyojisi yönünden gözden geçirilmiştir.

**Bulgular:** Toplam 26 hastanın (%65,4 kadın) ortalama yaşı 39,6±22,3 yıl ve yaş aralığı 13 ile 95 arasındadır. Ortalama kan glukoz düzeyleri hipoglisemi atakları esnasında 1,6±0,6 mmol/L ve 0,5-2,9 mmol/L aralığındadır. Hastaların yarısı (n=13/26) retroviral pozitifdir. Hipoglisemi, hastaların %35,3'ünde yükselmiş veya uygunsuz olarak normal plazma insülin düzeyleriyle ve %64,7'sinde baskılanmış plazma insülin düzeyleriyle ilişkilidir. Sekiz spontan hipoglisemi olgusu gebelikle ilişkilidir. Tüm gebelikle ilişkili hipoglisemi olguları retroviral pozitif hastalardadır. Hipogliseminin esas nedeni hipokortizolizmdir.

**Tartışma:** Spontan hipoglisemi müracaatları esas olarak hipokortizolizme bağlıdır. Hipoglisemili tüm gebe ve postpartum hastalar retroviral pozitifdir.

**Anahtar kelimeler:** Hipoglisemi; hipokortizolizm; retroviral hastalık; gebelik

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## Introduction

Spontaneous hypoglycaemia is a term used for low blood glucose unrelated to therapy for diabetes. Hypoglycaemia is classically diagnosed based on the Whipples triad of documented low blood glucose level, symptoms and signs of hypoglycaemia with relief after normalization of blood glucose (1). Diabetes related treatment is the commonest reason for hypoglycaemia admissions (2-4). Diabetes related hypoglycaemia is usually due to the use of medications that raise plasma insulin levels and is more common with Type 1 than Type 2 diabetes (5,6).

Spontaneous hypoglycaemia, not related to diabetes may be categorized as fasting or post-prandial. Reported causes of fasting hypoglycaemia include endogenous hyperinsulinaemic states such as insulinoma, insulin antibody and insulin receptor antibody (7-10). Non-hyperinsulinaemia associated causes of hypoglycaemia include septicaemia, alcohol ingestion, renal failure, liver failure and malignancies secreting IGF-2 (11-14). A rare but familial cause of hypoglycaemia is Type B insulin resistance which is due to the binding of antibodies to the insulin receptor (15). Post prandial hypoglycaemia typically occurs within 1-3 hours of meal ingestion as a result of rapid intestinal transport of glucose (16). Drug induced causes of hypoglycaemia include deliberate or accidental administration of insulin or insulin secretagogues such as sulphonylureas and meglitinides, quinolones such as gatifloxacin and ciprofloxacin, quinine, pentamidine, betablockers, angiotensin converting enzyme inhibitors and venlafaxine (17-20). The mechanisms of drug induced hypoglycaemia range from increased stimulation of insulin secretion, decreased clearance of insulin and interference of glucose metabolism (17). Endocrinopathies that can cause or contribute to hypoglycaemia include hypoadrenalism, growth hormone deficiency and hypothyroidism (21-23).

While hypoglycaemia can be immediately corrected by administering glucose to the patient, definitive therapy can only be ensured by ascertaining the underlying aetiology.

There is no published report on the aetiology of patients who present with spontaneous hypoglycaemic episodes in our environment. This study aims to report the aetiology of patients admitted with spontaneous hypoglycaemia in our hospital.

**Methods:** This is a retrospective review of hospital records over the 7-year period from January 2008 till December 2015. Subjects are all adult patients admitted into Nelson Mandela Academic hospital for non-diabetes related hypoglycaemia from 2008 to 2015 for whom records are available. Patients' medical records were reviewed for age, gender, relevant drugs and alcohol history, retroviral status, laboratory parameters (blood glucose, liver function, kidney function, plasma insulin, C-peptide, ketone, cortisol, IGF-1 level and documented cause of hypoglycaemia).

**Ethical considerations:** Ethical approval for the study was obtained from the Ethics committee, Faculty of Health Sciences, Walter Sisulu University, Mthatha.

**Routine Practice:** Patients presenting with spontaneous hypoglycaemia are admitted for evaluation. Where the glucometer capillary blood glucose is  $\leq 3$  mmol/L, venous blood is taken for

laboratory glucose, insulin, C-peptide, ketone, cortisol, IGF-1, liver and renal function. Correction of hypoglycaemia with a 20mls bolus of 50% glucose is then effected. Where hypoglycaemia had been corrected at the referring hospital or in our emergency unit before taking bloods that will enable the ascertainment of aetiology, the patient is fasted while on admission for a maximum of 48 hours. Fasting involves depriving the patient of all calories including oral feeds and glucose containing intravenous fluids. Patient is however allowed water orally or non-glucose containing intravenous fluids like normal saline. Patient is questioned and examined hourly for symptoms and signs of hypoglycaemia with glucometer testing for glucose obtained by a finger prick. This is continued until the glucometer glucose is  $\leq 3$  mmol/L when venous blood is drawn for laboratory blood glucose, liver function, kidney function, plasma insulin, C-peptide, ketone, cortisol and IGF-1 level. Fasting is stopped before 48 hours once venous plasma samples have been collected following a glucometer reading of  $\leq 3$  mmol/L or at 48 hours where the glucometer reading remains persistently above 3 mmol/L. Patients presenting with alcohol induced hypoglycaemia who were treated in the emergency department and discharged home without admission into the medical wards were excluded.

The 26 patients herein reported on comprise of 19 patients that were referred from other hospitals and admitted via the medical emergency department of Nelson Mandela Central Hospital Mthatha and 8 patients admitted in the Obstetrics department of Nelson Mandela Central Hospital [5 during labour and 3 in the post-partum period].

**Interpretation of Results:** Hypoglycaemia is confirmed by a laboratory blood glucose  $< 2.5$  mmol/L. Hyperinsulinaemia and elevated plasma C-peptide are respectively defined as plasma insulin  $\geq 2$   $\mu$ U/L and plasma C-Peptide  $\geq 1$  mcg/L in response to plasma glucose  $< 2.5$  mmol/L. Hypocortisolism is defined as plasma cortisol  $< 500$  nmol/L in response to plasma glucose  $< 2.5$  mmol/L. Insulinoma was diagnosed based on non-suppressed plasma insulin and C-peptide of  $\geq 2$   $\mu$ U/L and 1 mcg/L respectively in the presence of adequate hypoglycaemia of  $< 2.5$  mmol/L in addition to radiologic evidence of pancreatic tumour.

Hypoglycaemia is initially categorized as hyperinsulinaemic or non-hyperinsulinaemic. Hyperinsulinaemic causes include insulinoma, insulin antibodies, insulin receptor antibodies, accidental or surreptitious administration of insulin, sulfonylureas, quinine etc. Non-hyperinsulinaemic causes include alcohol ingestion, hypocortisolism, renal failure, hepatic failure and tumors that produce IGF2.

**Data processing and analysis**

Data was entered into an excel spread sheet and analyzed using SPSS version 21, Chicago Illinois. Continuous variables are expressed as mean  $\pm$  standard deviation while categorical variables are expressed as percentages or proportions. Means of continuous variables were compared using the student's t test while categorical variables were assessed with Chi square test. Statistical significance was taken as  $P \leq 0.05$ .

## Results

Complete results for plasma insulin, C-peptide and cortisol levels were available for 17 patients. Three patients had results for plasma C-peptide and cortisol levels but not plasma insulin levels. These 3 patients were a 59-year-old female, retroviral negative with plasma C-peptide of 0.1 mcg/L and plasma cortisol of 892 nmol/L. A second patient was a 57-year-old female, retroviral negative with plasma C-peptide of 1.8 mcg/L and plasma cortisol of 964 nmol/L while the 3<sup>rd</sup> patient was a 55-year-old male with plasma C-peptide of 1.3 mcg/L and plasma cortisol of 1464 nmol/L. This latter patient had renal failure manifested by serum creatinine of 811 mmol/L.

Six patients had no documented results for insulin, C-peptide and cortisol. They comprised of 3 males and 2 females with an age range of 13-62 years. One of these patients is a 29-year-old female on anti-retrovirals with hypoglycaemia of 1.9mmol/L and in labour at the 24<sup>th</sup> week of gestation.

The mean age of the 26 patients is 39.6±22.3 years with an age range of 13 to 95 years. Females represented 65.4% (n=17/26) of all patients. The mean blood glucose level during the hypoglycaemic episodes was 1.6±0.6 mmol/l (0.5-2.9). Half of the pa-

tients (n=13/26) were retroviral positive. Hypoglycaemia was associated with elevated or inappropriately normal plasma insulin levels in 35.3% and suppressed plasma insulin levels in 64.7% of cases. Eight cases of spontaneous hypoglycaemia were pregnancy related (5 occurred during labour, while 3 happened post-delivery).

Table 1 shows the profiles of hyperinsulinaemic patients (n=6). All except one patient were female. Three of the patients were retroviral positive, two of whom were on anti-retrovirals. These two patients on anti-retrovirals experienced hypoglycaemic episodes post-delivery. All hyperinsulinaemic patients had elevated plasma levels of C-peptide except one patient with low plasma C-peptide of 0.3 despite raised plasma insulin of 2.1 miu/L. Three of the hyperinsulinaemic patients had optimal serum cortisol levels during the hypoglycaemic episode. In one of these patients, computerized tomogram scan revealed malrotation of the gut and in another patient, insulinoma was diagnosed following computerized tomogram scan of the abdomen and biopsy of metastatic nodules to the liver which was histologically confirmed as insulinoma.

Table 2 shows the profiles of eleven non-hyperinsulinaemic patients, comprising of eight females and three males. The majority,

**Table 1. Demographic and retroviral status and laboratory profiles of hyperinsulinemic patients**

Patient	Sex	Age in years	BG mmol/L	RVD status	Cyesis	Plasma Insulin miu/L	Plasma C-peptide mcg/L	Plasma Cortisol nmol/L	Diagnosis
1	F	95	1.1	Neg	Neg	11.5	2.3	321	Hypocortisolism
2	F	39	1.8	Pos on ARV	Post del	2.1	0.3	332	Hypocortisolism
3	F	21	2.1	Pos on ARV	Post del	7.1	1.4	403	Hypocortisolism
4	F	48	0.5	Neg	Neg	19.8	6.7	559	Malrotation of gut
5	F	27	1.6	Pos	Neg	4.7	1.1	762	Insulinoma
6	M	15	1.7	Neg	NA	5.3	2.8	-	-

BG: Blood glucose, RVD: Retroviral disease, Neg: Negative, Pos: Positive, Del: Delivery; NA: Not applicable, -: Not available.

**Table 2. Demographic and retroviral status and laboratory profiles of non hyperinsulinemic patients**

Patient	Sex	Age in years	BG mmol/L	RVD status	Cyesis	Plasma Insulin miu/L	Plasma C-peptide mcg/L	Plasma Cortisol nmol/L	Diagnosis
1	M	21	1.8	Neg	NA	<2	<0.1	155	Hypocortisolism
2	F	31	0.9	Pos	Pos	<2	0.8	431	Hypocortisolism
3	M	77	2.3	Neg	NA	<2	1.9	447	Hypocortisolism
4	F	20	0.9	Pos on ARV	30 wks	1	0.9	467	hypocortisolism
5	M	28	0.8	Pos	NA	0.5	0.1	472	Military TB and hypocortisolism
6	F	78	1.6	Neg	Neg	<2	0.8	490	Hypocortisolism
7	F	23	1.6	Pos on ARV	12 wks	0.5	0.1	836	PTB on therapy
8	F	22	1.7	Pos on ARV	31 wks	1.3	1.3	840	Cmv IgM pos
9	F	26	1.6	Pos on ARV	Post del	1.5	3	871	Disseminated TB
10	F	21	2.1	Neg	Neg	<2	0.8	>2069	Exfoliative Dermatitis
11	F	32	2.9	Pos	neg	<2	0.8	>2069	-

BG: Blood glucose, RVD: Retroviral disease, Neg: Negative, Pos: Positive, Del: Delivery, PTB: pulmonary tuberculosis; Cmv: Cytomegalovirus, IgM: Immunoglobulin M, NA: Not applicable, -: Not available

**Table 3. Demographic and retroviral status and laboratory profiles of pregnancy-related patients**

Patient	Age in years	BG mmol/L	RVD status	Cyesis	Plasma Insulin miu/L	Plasma C-peptide mcg/L	Plasma Cortisol nmol/L	Diagnosis
1	39	1.8	Pos on ARV	Postpartum	2.1	0.3	332	Puerperal sepsis, Hypocortisolism
2	21	2.1	Pos on ARV	Postpartum	7.1	1.4	403	Hypocortisolism
3	31	0.9	Pos	Pos	<2	0.8	431	Hypocortisolism
4	20	0.9	Pos on ARV	30 wks	1	0.9	467	Hypocortisolism
5	23	1.2	Pos on ARV	12 wks	0.5	0.1	836	PTB on therapy
6	22	1.7	Pos on ARV	31 wks	1.3	1.3	840	Cmv IgM positive
7	26	1.6	Pos on ARV	Postpartum	1.5	3	871	Disseminated TB
8	29	1.9	Pos on ARV	24 wks	-	1.3	-	-

BG: Blood glucose, RVD: Retroviral disease, Neg: Negative, Pos: Positive, Del: Delivery, NA: Not applicable, - : Not available

(n=7/11) were retroviral positive, of which in five patients, it was pregnancy related. Nine of the eleven patients with low to suppressed plasma insulin levels also had low plasma C peptide levels. However, 2 patients had elevated plasma C peptide levels despite low plasma insulin levels. Six patients had sub-optimal plasma cortisol levels and were subsequently managed as hypoadrenalism. Five patients had optimal plasma cortisol levels despite the presence of risk factors for hypoadrenalism such as tuberculosis and cytomegalovirus infection.

Table 3 shows the profiles of all 8 pregnancy related cases of spontaneous hypoglycaemia, all of who were retroviral positive. All but one of the pregnancy related cases of hypoglycaemia were already on treatment with anti-retrovirals. In one patient, result for plasma insulin was not available, though the plasma C-peptide was elevated. Two patients were hyperinsulinaemic while 5 were non-hyperinsulinaemic. Four patients had sub-optimal plasma cortisol responses to hypoglycaemia while three patients had optimal plasma cortisol responses despite presence of risk factors for hypoadrenalism such as tuberculosis and cytomegalovirus infection. Three of these pregnancy related cases of hypoglycaemia occurred in the post-partum period of which two of these patients were acutely ill; one with puerperal sepsis and the other with disseminated tuberculosis. One patient was in a relatively stable condition.

## Discussion

The majority of our patients with spontaneous hypoglycaemia were non-hyperinsulinaemic with sub-optimal plasma cortisol response that is consistent with hypocortisolism. We defined hypocortisolism as plasma cortisol < 500 nmol/L in response to hypoglycaemia of < 2.5 mmol/L. Indeed, in the majority of these patients, hypoglycaemia resolved with glucocorticoid therapy.

Three patients [patients numbered 1,2,3 in Table 1] with sub-optimal cortisol response to hypoglycaemia were however, hyperinsulinaemic. This may suggest the possibility of both hypoadrenalism and hyperinsulinaemia as operative mechanisms for hypoglycaemia in these patients. There were no records of exposure to medications that may be associated with hyperinsulinism. Repeated episodes of hypoglycaemia can blunt the plasma cortisol response to hypoglycaemia, but there were no

documented records of previous hypoglycaemic episodes in these patients. As this is a retrospective study, it is possible that these patients may very well have a purely hyperinsulinaemic hypoglycaemia with a low cortisol resulting from non-documented unrecorded hypoglycaemic episodes. In one of these patients, hyperinsulinism was accompanied by a low C-Peptide level as may be expected with exogenous insulin administration. There was however, no record of exogenous insulin administration in this patient.

Two patients [numbered 10 and 11 in Table 2] had marked hypercortisolism with suppressed plasma insulin response to hypoglycaemia. Patient numbered 10 was cachectic with exfoliative dermatitis and retroviral negative. He had a suppressed level of plasma IGF-1 at < 20 ug/L with elevated plasma CA-125 level and the possibility of tumour associated hypoglycaemia was considered. We are unable to measure IGF-2 in our laboratory. The low IGF-1 in this patient may be a result of raised IGF-2 with binding of IGF-2 to IGF-1 receptor causing a suppression of IGF-1 secretion via a negative feedback mechanism. The low IGF-1 in patient numbered 10 may also result from possible malnutrition. Computerized scans of the chest, abdomen and pelvis and subsequent Gastro-intestinal endoscopy did not reveal any tumour. This patient had a normal liver function tests result which will argue against chronic liver disease as the cause of very low IGF-1. The episodes of hypoglycaemia in this patient however, abated with subcutaneous octreotide at 100 mcg three times daily. Patient numbered 11 unlike patient numbered 10 (Table 2) was retroviral positive with markedly elevated serum cortisol and suppressed plasma insulin level. It is notable that three non-hyperinsulinaemic patients had adequate plasma cortisol responses despite the presence of tuberculosis and cytomegalovirus infection which are risk factors for hypocortisolism (24,25). Possible explanations include the existence of subclinical hypoadrenalism or cortisol resistance. Four of five patients with satisfactory plasma cortisol response to hypoglycaemia were retroviral positive. Indeed cortisol resistance has been found to be associated with the retroviral infection (26).

It is notable that all the cases of hypoglycaemia that occurred during pregnancy and postpartum were in retroviral positive patients. South Africa has the most number of persons living with retroviral disease, with retroviral disease prevalence of 11.4% (27). Furthermore, 90% of

recent retroviral infections occur in women aged 15-24 years with current pregnancy associated with the highest retroviral disease rates (28). Retroviral positivity is a major risk factor for hypocortisolism from factors such as cytomegalovirus adrenalitis, tuberculous adrenalitis and ketoconazole therapy for opportunistic infections (24,25,29). However, in only four of these pregnancies were plasma cortisol levels below 500 nmol/L that is diagnostic of hypoadrenalism. In the other 3 cases, the plasma cortisol levels were above 500 nmol/L suggestive of cortisol resistance, subclinical hypoadrenalism or another unidentified aetiology for hypoglycaemia.

The limitations of this study include not measuring plasma levels of ACTH which will assist in the diagnosis of cortisol resistance and sub-clinical hypoadrenalism. The aetiology of hyperinsulinaemic hypoglycaemia could have been further interrogated if plasma levels of sulphonylureas and insulin antibodies were assessed. Plasma IGF-2 assay is not available in our laboratory. Thyroid function was not measured in our patients, neither was growth hormone assessed during 48 hour fast, therefore the contributory effects of hypothyroidism or growth hormone deficiency in our patients cannot be assessed. However, we have not reported hypoglycaemia in our patients with isolated hypothyroidism.

## Conclusions

Majority of our patients admitted with hypoglycaemia were non-hyperinsulinaemic with hypocortisolism as the predominant cause for hypoglycaemia. All pregnancy and post-partum related cases occurred in retroviral positive patients.

## Ethics

It was obtained from Ethics Committee Walter Sisulu University.

## Authorship Contributions

Concept: Chukwuma Ekpebegh, Dizayn: Chukwuma Ekpebegh  
Data Collection or Processing: Chukwuma Ekpebegh, Analysis or Interpretation: Chukwuma Ekpebegh, Literature Search: Chukwuma Ekpebegh, Writing: Chukwuma Ekpebegh.

Conflict of Interest: No conflict of interest was declared by the authors.

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