

Review Article

# Awareness of Iatrogenic Hypoglycemia Secondary to Anti-Diabetic Agents in Diabetic Nephropathy: A Case Report and Review of Literature

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## ABSTRACT

Diabetes mellitus is now a major cause of chronic kidney disease with a prevalence of 11% to 83.7% in Africa. The presence of drug-induced hypoglycemia further increases the risk of death by 2-3 folds; a risk that is further heightened by the presence of nephropathy of which many diabetics are unaware due to poor screening practice by health workers in diabetes clinics. Sufficient data also exist to show that many diabetics have poor knowledge about harmful effects of anti-diabetic agents.

We conducted electronic search of literature using various search engines such as MEDLINE, pub med, research gate, google scholar, cross-ref etc using keywords such as ‘nephropathy, diabetes, hypoglycemia, renal failure, iatrogenic, anti-diabetic agents’. We then identified the case of a 60 year old diabetic with subclinical undiagnosed severe chronic kidney disease (NKF-KDOQI stage 5) who presented to our Emergency Unit with hypoglycemic coma after he self-medicated on 5mg glibenclamide daily over 72 hours. Our review relates poor knowledge of diabetes and renal failure among diabetics and physicians to the danger of recurrent of hypoglycemia and increased risks of mortality.

We conclude that diabetes clinics need to be properly structured to include special rooms for practice-oriented interactive sessions and audio-visual presentations; we suggest running multiple diabetes clinics in settings where the patient load is enormous; dieticians and trained Diabetes Health Educators should be integrated into the diabetes out-patient clinics.

**Keywords:** hypoglycemia, iatrogenic, anti-diabetic agent, nephropathy

## INTRODUCTION

The World Health Organization projects that diabetes mellitus will be the seventh leading cause of death by 2030. [1] Almost parallel to this is the rise in the prevalence of diabetic nephropathy; its prevalence is reported to be as high as 40% to 48.1%; in the United States,

approximately 3% of persons with newly diagnosed type 2 diabetes have overt nephropathy. [2-4] A recent review of 32 studies in Africa showed prevalence rates of between 11% and 83.7% for diabetic nephropathy. [5] There are evidences to prove that diabetic patients have insufficient education about their disease, complications

and treatment. [6] This may not be unconnected to the exponential rise of diabetes globally which has placed a distracting burden on diabetes clinic staff who have to contend not only with the disease but its attendant multi-systemic complications, each of which demands specialist care. This deficiency is further heightened in developing countries where the patient-doctor ratio is abysmal. For instance, one study showed that only 33% of diabetic patients received adequate health education in a primary health care Centre in the Asir region of Saudi Arabia which serves about 15,000 inhabitants. [7] In that study, it was found that their educational programme excluded topics focusing on need for early detection of diabetic kidney disease and drug choices. The Centre also lacked trained diabetic health educators and specialized room for such exercise. [7] This is typical of most diabetes clinics in our environment and most other developing economies where poor attention is paid to standard health infrastructure.

The National Kidney Foundation-Clinical Practice Guidelines on diabetes care recommends screening of types 1 and 2 diabetics for kidney disease after five years of onset and at diagnosis respectively. [8] However, most Centers are far from reaching this ideal. A recent report by Okafor *et al* showed a poor screening practice in a teaching hospital in South-eastern Nigeria, a pattern which seems to have persisted over the last decade in Nigeria. [9-10] As far back as 2006, Bosan reported that primary care physicians tested less than 10% of their patients for proteinuria while only 30% of them tested for proteinuria in 39% of those they were treating for diabetes mellitus even though this observation is not limited to Nigeria. [10-13] This can further increase the risk of morbidity and mortality among diabetic patients as they tend to be unaware of their renal status thereby resulting in susceptibility to drug-induced hypoglycemia's highlighted in this report on a 60 year old man with undiagnosed

diabetic nephropathy who developed hypoglycemic coma after he self-medicated on 5mg glibenclamide daily over 72 hours.

## CASE REPORT

Patient is a 60 year old recently diagnosed type 2 diabetic-hypertensive male who had been using oral nifedipine 20mg and glibenclamide 5mg daily for three days which were passed on to him by a friend who is incidentally also hypertensive and diabetic. After the third dose, he lapsed into sudden unconsciousness.

At presentation, he was in coma (Glasgow Coma Score, 3/15) with a blood sugar of 1.3mmol/L at 04:30 hours. Temperature was 37.2°C, blood pressure was 200/80mmHg, pulse rate was 76bpm and respiratory was 16cpm. He had locomotor brachialis and thickened arterial wall. The pupils were normal, round and equally responsive to light. There was no nuchal rigidity. Kernig's sign was negative.

He regained consciousness with a blood sugar of 9.5mmol/L after correction of hypoglycemia with 50ml of 50% dextrose. Interestingly, 5 hours later, the blood sugar fell back to 1.6mmol/L despite continuous infusion of 5% dextrose. Laboratory findings showed serum creatinine of 2,274µmol/L, urea of 56.1mmol/L, hyperkalaemia (5.7mmol/L) and acidosis (17.1mmol/L). The total white cell count was  $6.9 \times 10^9$  cells/cmm and his haemoglobin concentration was 4mg/dl. Serology screening was negative for HIV 1 and 2 viruses, and hepatitis B and C viruses. The serum uric acid was elevated (0.46mmol/l). The fluid was replaced with 10% dextrose and patient was reviewed by the dietitian and placed on standard dietary therapy. The fasting blood glucose stabilized to between 5.2 and 5.9mmol/l after 72 hours.

Patient was assessed to have knowledge deficit of diabetes, dietary modifications, lifestyle adjustments and drugs for diabetes care. He has been placed into our chronic kidney disease treatment program which includes counseling on the

disease (via interactions with our health team of Nephrologists, dieticians, Clinical Psychologists, dialysis nurses and medical

social workers), insulin therapy, blood pressure control, dialysis, nutritional rehabilitation and psycho-social support.

**Table 1: Dosing Adjustments by CKD Stage for Drugs Used to Treat Hyperglycemia** [8,26]

Class	Drug	Half-life (hours)	Primary route of excretion	Hypoglycaemic effect in renal disease	Dosing Recommendation CKD Stages 3, 4, or Kidney Transplant	Dosing Recommendation Dialysis
First generation sulphonylureas	Acetohexamide	4-8	Kidney	Very high	Avoid	Avoid
	Chlorpropamide	36	Kidney	High	Reduce dose by 50% when GFR <70 and ≥50 mL/min/1.73 m <sup>2</sup> Avoid when GFR <50 mL/min/1.73 m <sup>2</sup>	Avoid
	Tolazamide	4-8	Kidney	Very high	Avoid	Avoid
	Tolbutamide	4-8	Kidney	Very high	Avoid	Avoid
Second generation sulphonylureas	Glipizide	2-4	Kidney	Unlikely	Preferred sulphonylurea No dose adjustment necessary	Preferred sulphonylurea No dose adjustment necessary
	Gliclazide			Unlikely	Preferred sulphonylurea No dose adjustment necessary Not available in United States	Preferred sulphonylurea No dose adjustment necessary Not available in United States
	Glyburide	10	50% kidney, 50% gut	High	Avoid	Avoid
	Glimepiride	9	50% kidney, 50% gut	Moderate	Initiate at low dose, 1 mg daily	Avoid
Alpha-glucosidase inhibitors	Acarbose	Approx. 2	Kidney		Not recommended in patients with SCr >2 mg/dL	Avoid
	Miglitol	Approx. 2	Kidney		Not recommended in patients with SCr >2 mg/dL	Avoid
Biguanides	Metformin	2-6	Kidney	Unlikely. High risk of lactic acidosis	Contraindicated with kidney dysfunction defined as SCr ≥1.5 mg/dL in men or ≥1.4 mg/dL in women	Avoid
Megitinides	Repaglinide	0.6-1.8	Bile, minimally via kidney	Low	No dose adjustment necessary	No dose adjustment necessary
	Nateglinide	1.5		Moderate	Initiate at low dose, 60 mg before each meal	Avoid
Thiazolidinediones	Pioglitazone	3-7	Gut, minimally via kidney		No dose adjustment necessary	No dose adjustment necessary
	Rosiglitazone	3-7	Gut, minimally via kidney		No dose adjustment necessary	No dose adjustment necessary
Incretin mimetics	Exanatide	2.4	proteolysis	Unlikely	No dose adjustment necessary	No dose adjustment necessary
Amylin analogues	Pramlintide	48 minutes	Kidney	Moderate	No dose adjustment necessary for GFR 20-50 mL/min/1.73 m <sup>2</sup>	No data available
Di-peptidyl peptidase inhibitors	Sitagliptin	8-14	87% kidney, 13% gut	Moderate	Reduce dose by 50% (50mg/day) when GFR < 50 and ≥ 30 mL/min/1.73 m <sup>2</sup> and by 75% (25 mg/day) when GFR < 30 mL/min/1.73 m <sup>2</sup>	Reduce dose by 75% (25 mg/day)

## DISCUSSION AND REVIEW

Our index case highlights the pertinent issue of inadequate knowledge of diabetes among its sufferers and the unfavourable consequences, need for primary physicians to screen all type 2 diabetics at first contact for renal impairment among other complications of diabetes in order to offer counseling on disease retardation, risk of hypoglycemia and appropriate choice of anti-diabetic agents among other necessary steps. Our index patient and his friend demonstrated a typically poor knowledge of the disease and factors that should determine choice of anti-diabetic agents. Their attitude to self-care and practice were evidently poor.

### Diabetic nephropathy and iatrogenic hypoglycemia

Iatrogenic hypoglycemia (plasma glucose  $<3.9\text{mmol/l}$  following use of one or more anti-diabetic agents) has become a formidable barrier to achieving glycaemic control thus leading to significant morbidity and mortality among diabetics. [14] It is described as “severe” when the patient becomes symptomatic (usually neuroglycopenic) or requires the assistance of another individual. The prevalence of iatrogenic hypoglycemia among diabetics vary with the type of anti-diabetic agent, the type of diabetes, presence of neuropathies and target HbA1C. [15] For instance, it is known to occur at a lower frequency among type 2 diabetics than in type 1. [16] According to the United Kingdom Prospective Diabetes Study (UKPDS), the proportion of patients who suffered a major hypoglycemic event annually over the first decade showed a higher rate among those on insulin; 0.4% for chlorpropamide, 0.6% for glibenclamide and 2.3% for insulin at HbA1c levels comparable to the Diabetes Control and Complications Trial. [16-17]

In one Nigerian study, hypoglycemia was found to be the most frequently documented side effects of prescribed oral hypoglycemic agents. In that study, the glibenclamide-metformin

combination was used in 95.8% of these subjects. [18]

It has since become established that the degree of renal impairment and decreased renal gluconeogenesis are among the established risk factors for hypoglycemia; these are linked to delayed clearance of insulin and other hypoglycemic agents and a low plasma glucose load. [19] For type 2 diabetics who have renal impairment, the risk of severe hypoglycemia may be raised by as much as 2 to 3 times in those with an estimated glomerular filtration rate (eGFR) less than  $60\text{ mL/min/1.73m}^2$ . [20]

### Pathophysiology of hypoglycemia in diabetic nephropathy

Renal impairment is considered an independent risk factor for severe hypoglycemia. Normally, the kidney plays an important role in metabolizing circulating insulin, reabsorbing filtered glucose, contributing to gluconeogenesis, and excreting drugs and their metabolites with blood glucose lowering agents. [21] More than 90% of insulin is excreted by the kidneys and quite a number of oral hypoglycemic agents such as the first generation sulphonylureas, glibenclamide, metformin, dipeptidyl peptidase inhibitors, glucagon-like peptide inhibitors and amylin analogues. [8]

In patients with renal disease, basal insulin levels become elevated for a number of reasons depending on the stage of the renal disease. In early stages, it is due to reduction in the blood flow. In more severe cases, the process of degradation of insulin by the kidney is hampered due to loss of renal mass. In the most severe case (those with  $\text{GFR} < 20\text{ ml/min/1.73m}^2$ ), the reduced clearance is in addition due to a decrease in the filtration. Such altered metabolism of insulin in diabetic patients with renal disease makes them particularly vulnerable to the hypoglycemic effects of exogenously administered insulin and other insulin secretagogues. [22]

In the Action to Control Cardiovascular Risk in Diabetes

(ACCORD) trial, an albumin-creatinine ratio greater than 300 mg/g or a serum creatinine greater than 1.3 mg/dl was associated with a significantly increased risk of severe hypoglycemia. [23] This observation is supported by findings from the Action in Diabetes and Vascular Disease: PreterAx and Diamicon MR Controlled Evaluation (ADVANCE) trial, which showed an increase in the risk of severe hypoglycemic episode by 1% for each  $\mu\text{mol/l}$  rise in serum creatinine. [24] Davis et al suggested that patients with  $\text{eGFR} < 60 \text{ ml/min/1.73m}^2$  had a 3 fold increase of severe hypoglycemia. [20] Also patients who had a macroalbuminuria level (urinary albumin excretion  $\geq 300 \text{ mg/day}$ ) even with a normal eGFR level had an independently increased risk of severe hypoglycemia with type 2 diabetes. [25]

#### **Oral anti-diabetic agents and nephropathy**

According to the 2007 National Kidney Foundation-Kidney Disease Outcome Quality Initiative (NKF-K/DOQI) guidelines, oral hypoglycemic agents should be avoided in dialysis patients. [8] This is due to the lack of adequate data concerning the use of oral agents in dialysis patients and their inability to adequately excrete these agents.

First generation sulphonylureas are notorious for causing iatrogenic hypoglycemia and are therefore no longer recommended for diabetics. [8] For several decades, concerted efforts have resulted in the emergence of some newer anti-diabetic agents that do not predispose to hypoglycemia even among those with renal impairment. Anti-diabetic agents that are generally safe in diabetic nephropathy include repaglinide, thiazolidinediones, pramlintide, and sitagliptin; those requiring dose adjustments include the second generation sulphonyl ureas and metformin because of risk of lactic acidosis; those that are not recommended include glyburide, alpha-glucosidase inhibitors (acarbose and miglitol), exenatide. A comprehensive table

of OHA adjustment is provided in table 1. [8,26]

#### **Morbidity and mortality**

Iatrogenic hypoglycemia often causes recurrent physical morbidity, recurrent or persistent psychosocial morbidity, or both and sometimes causes death. [27] Diabetic patients need to be aware that anti-diabetic agents are capable of causing hypoglycemia aside insulin. About 25% of diabetic patients with hypoglycemia are known to present with coma. [28]

Our patient presented with coma after accumulated doses of glibenclamide. Obviously, he was not aware of the profound hypoglycemic effect of this second generation sulphonylurea thereby suggesting a lack of or, inadequate education by the primary physician. Even though nearly all patients will recover from hypoglycemia after treatment with 50% dextrose, one must be acutely aware that every episode of hypoglycemic coma predisposes the patient to epileptiform seizure-induced cardiac arrhythmia and risk of sudden-cardiac death. [29] Other morbidities known to have resulted from hypoglycemia-induced coma include fractures and dislocations from accidental falls, brain injury and the 'dead in bed syndrome'. [30-31]

#### **Monitoring glycaemic control in diabetic nephropathy**

One important challenge with glycaemic control and reduction of mortality is ensuring euglycemia without life threatening spikes or troughs. This has been achieved with reliable success using HbA1c. However, for patients with nephropathy who are prone to anaemia from a complexity of causes such as increased red cell fragility, dialysis-associated blood-letting and extracorporeal clots, recent transfusion, iron deficiency, accelerated erythropoiesis due to administration of erythropoietin, and metabolic acidosis. This may pose a challenge as HbA1c is dependent on normal red cell mass for reliability. Recent reports indicate that glycated albumin may be employed as a



more reliable measure of control than HbA1c in diabetic nephropathy. [32] However, it is not without its own shortcomings as it can only indicate glycaemic control over 1 to 2 weeks unlike 60 to 120 days for HbA1c. It is also affected by presence of proteinuria in the patient and use of peritoneal dialysis modality. Problems with its availability in our environment may be another drawback leading most Centres to fall back to HbA1c.

### **Knowledge of anti-diabetic agents among diabetics**

Diabetes education is the cornerstone of diabetes management because diabetes requires day to day knowledge of nutrition, exercise, monitoring and medication. [33] There is a general conclusion from various studies that the knowledge of diabetes and self-care among the sufferers of this disease is poor. [34-38] For instance, among 100 type 2 diabetics in Mangalore, India, 66% were aware of nephropathy though only 13% considered it as a serious complication of diabetes while parallel works by Okoro et al and Kyriazis et al revealed that low percentages (43.1% vs 51.7%) of subjects did not know the name of the anti-diabetic medications they were taking and (69.4% vs 60.5%) did not know the side effects. [35,36,38] Okoro et al showed a corresponding low level of counseling of patients on their anti-diabetic medications by pharmacists in the study area. [36] Browne et al in a study done in the UK found that out of 261 patients only 15% knew the correct mechanism of action of their medication and 62% took tablets correctly in relation to food. Moreover only 10% of those taking a sulphonylurea knew it may cause hypoglycemia and 20% of those taking metformin were aware of its gastrointestinal side effects. [39] Vivian and Leung established that during treatment some patients in the study group adjusted the dosage of their medications according to the severity of their hyperglycaemic symptoms without due consultation with their physicians. [40] Some patients did not even know the purpose of the drugs.

In the United Kingdom, according to the Diabetes Information Jigsaw Survey, only 17% of the diabetics received information about their diabetes treatment every time they were given a prescription and 8% received none [41] while Browne et al found out that out of 261 patients only 35% of patients recalled receiving advice about their medication with only 1% receiving written advice. [39]

### **CONCLUSIONS AND RECOMMENDATIONS**

There is a need to create appropriate settings that will translate to easy acquisition of knowledge about diabetes by the patients, their relatives and the general public. Atmosphere for peer group learning may be beneficial. For instance, a higher knowledge of diabetes and hypoglycemia was found among members of Diabetes Association of Nigeria who received special attention from visiting physicians and nurses during their regular meetings than controls. [42] Diabetes clinics need to be properly structured to include special rooms for counseling and practice-oriented interactive sessions, media rooms fitted with facilities for audio-visual presentations in easy-to-understand language(s), information storage and retrieval system, food models and manikins for demonstrations. In order to fully achieve these, it may be necessary to run multiple diabetes clinics in settings where the patient load is enormous. On the other hand, where possible, the staff strength of the diabetes staff should be increased.

In resource-poor settings where there is inadequacy of personnel, nurses (and other staff) in diabetes clinics should be given special training on diabetes care as they form majority of the healthcare professionals that educate these patients. In one study, the knowledge of general nurses on diabetes was found to be poor. [43] We concur with the recommendations of Al-Khaldi and Khan that dieticians and trained Diabetes Health Educators should be invited to participate in health education of

diabetics at primary care settings. [7] Better still, we suggest efforts should be made to employ these professionals into the health system at all levels of care.

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