

## **Hypoglycemia in Diabetic - The Role of New Technologies**

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**One common obstacle in the treatment of diabetics is hypoglycemia. Hypoglycemia in diabetic is unpredictable and life threatening. It is a consequence of either treatment or part of the natural history of diabetes. Therefore, many dietary and therapeutic maneuvers have been initiated to tackle such obstacle.**

**Twenty-eight years old Bahraini male known diabetic since birth was suffering from frequent attacks of hypoglycemia mandating visits to the Accident and Emergency Department. His blood biochemistry parameters were normal except for the high HbA1c. His general examination was normal. Several treatment regimens were initiated to combat his hypoglycemia with little success. New insulin analogue was prescribed for the patient to reduce the magnitude and frequency of hypoglycemic attacks and improve the blood sugar control. This method of treatment combined with dietary interventions proved effective in reducing the hypoglycemic attacks in clinical trials.**

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Hypoglycemia is defined as “a low blood glucose level, it is a laboratory finding that may or may not be associated with significant pathology”. Severe Hypoglycemia (SH), is defined by “low blood glucose resulting in stupor, seizure, or unconsciousness that precludes self-treatment”<sup>1</sup>.

Approximately 90% of all patients who receive insulin have experienced hypoglycemic episodes<sup>2</sup>.

In Diabetes Control and Complication Trial (DCCT), it was noted that the incidence of SH in the patients intensively treated with insulin was 6%. The incidence is probably lower in the general population since fewer patients are treated and compliant with the intensive insulin therapy<sup>2</sup>.

The common cause of hypoglycemia in diabetic patients is iatrogenic. Other causes of hypoglycemia should be investigated thoroughly especially in type 1 diabetes<sup>3</sup>. Several studies have emphasized the intensive insulin therapy as a major contributor to normoglycemia and thus reduction of diabetes complication. Severe hypoglycemia however, has made this target difficult to achieve<sup>2</sup>.

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The aim of this report is to present a case with frequent hypoglycemic attacks and new therapy in the management of diabetes.

## **The Case**

Twenty-eight years old Bahraini male known diabetic presented to the clinic for routine periodic follow up. Previously, the patient was under follow up in SMC since birth. He is complaining of frequent attacks of hypoglycemia. Those severe attacks may occur twice monthly mandating hospital management. The attacks resulted in tiredness, agitation and inability to pursue work. The patient had two siblings who died as neonates because of severe hypoglycemia as the patient stated.

There is a strong family history of type 2 diabetes mellitus. He does not smoke cigarettes or consume alcohol. He works as a cleaner in local health vicinity. The patient is on the following medications: Mixtard 40u and 30u twice daily.

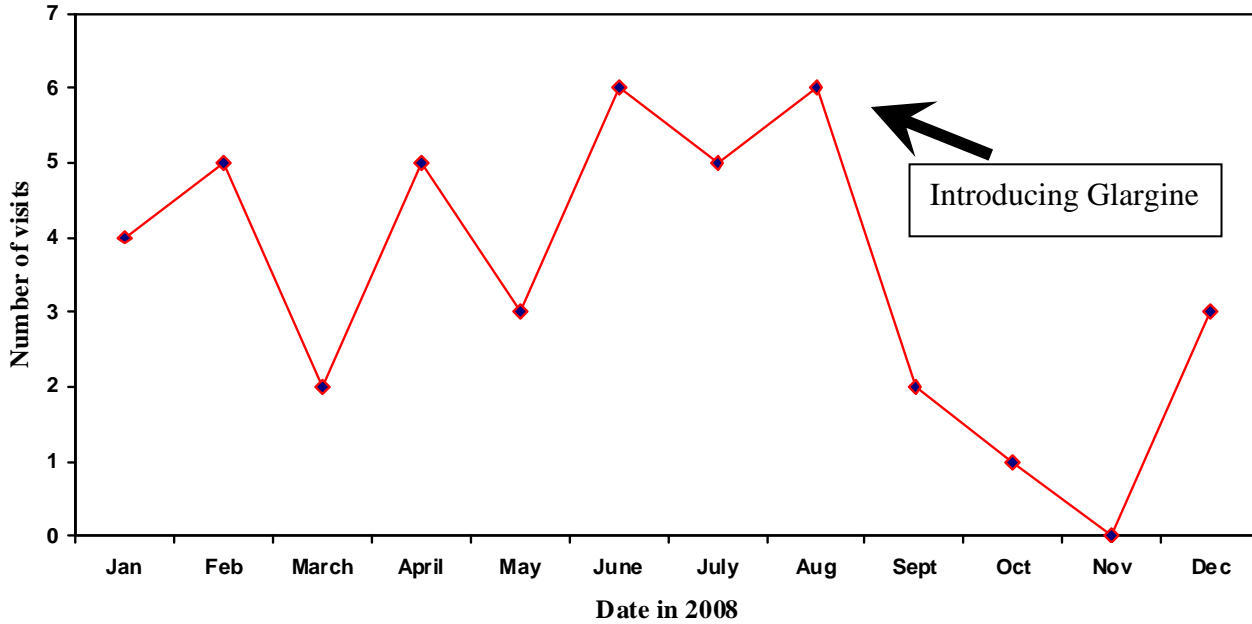
On presentation, the patient was afebrile and had blood pressure 120/80 and BMI 19. He was alert, conscious and oriented. The patient was not jaundiced or dehydrated. The thyroid organ was not palpable. Skin inspection was normal. No tremors were observed and abdominal examination was normal.

The patient's serum test results were as follows: fasting glucose, 10.7 mmol/L; sodium 141mmol/L; potassium, 3.97 mmol/L; creatinine, 85  $\mu$ mol/L; urine ketones were negative; and hemoglobin A1c 6.9%. His serum lipids values were within normal levels. Thyroid function tests were normal. Liver enzymes were normal.

The patient was given Insulin Glargine 26-30 units per day as a basal treatment. The bolus doses were provided by the short acting insulin Aspart and the doses were titrated through carbohydrate counting and under the guide of meticulous blood sugar monitoring.

The regimen has reduced the frequency and severity of the patient's hypoglycemic attacks and he felt less tired and less agitated. The patient's mood and productivity were improved.

Figure 1 depicts the pattern of patient's visits to SMC from January 2008 till December 2008 before and after initiating the new regimen.



**Figure 1: The Number of Patient's Visits to SMC in 2008 before and after Introducing Glargine**

The sudden surge of the patient's hospital visits in December 2008 cannot be attributed to failure of treatment but might be explained by the infrequent visit to the hospital. It is the trend of visits to the hospital that really measures the improvement in patient status along with the general well being and severity of hypoglycemic attacks. The patient has experienced an improvement in his general status and decrease in the number of severe hypoglycemic attacks.

## DISCUSSION

Hypoglycemia could lead to Neurogenic and Neuroglycopenia symptoms; it may result into coma and death if untreated<sup>4</sup>.

The patient's HbA1c, on the other hand, is 6.9% which is in the fair control zone, which is not acceptable in Bahrain practice, according to the International Federation of Clinical Chemistry (IFCC), which is adopted by the Bahrain Ministry of Health<sup>5</sup>. It is equivalent to 8.5% by the National Glycohemoglobin Standardized Program (NGSP), which is used by the American Diabetes Association (ADA) (Table 1)<sup>6</sup>. IFCC figure of 6.9% may give a false assurance about blood sugar control. Alternating severe hypoglycemia and hyperglycemia may yield a near normal HbA1c which may obscure the fact that blood sugar is not controlled.

**Table 1: HbA1c Levels of Control by (IFCC) Figures<sup>5</sup>**

<b>HbA1c level in %</b>	<b>Level of control</b>
2.4-4.3	Within reference range
4.4-<5.3	Excellent
5.3-5.9	Good
6-7	Fair
>7	Poor

The patient suffered hypoglycemic attacks since birth. He was admitted in SMC 22 times because of hypoglycemia in the period between 1990 and 2001; no earlier record could be traced. The patient visited the emergency room more than 10 times for hypoglycemic attacks in 2007.

The patient was on a combination of intermediate-acting and short-acting insulin since birth.

Traditionally, intermediate-acting insulins are known to induce severe hypoglycemic attacks because of their variability in absorption, delays in action, and prolonged insulin activity. NPH insulin was the only insulin used to provide basal insulin supply. This intermediate-acting insulin sometimes causes nocturnal hypoglycemia due to its erratic plasma insulin peaks, particularly during the night<sup>7</sup>.

Recently, the patient was on a fixed combination insulin therapy twice daily. Fixed combination insulin therapy adds further to the incidence of nocturnal hypoglycemia and early morning hyperglycemia<sup>7</sup>.

New insulin analogues and new modalities in insulin delivery especially in type 1 diabetic have made blood sugar control achievable.

One of the new insulin analogues is Glargine. It is produced by recombinant DNA technology. The change of Amino acid in Glargine stabilizes the hexamer. Consequently, it has delayed and prolonged absorption after subcutaneous administration. This renders the analogues peak less with steady and predicted absorption over the 24 hours<sup>8</sup>.

Short-term studies in type 1 or type 2 diabetes have shown that once daily insulin Glargine reduces fasting plasma glucose (FPG) levels to a comparable or to a

significantly greater extent than once or twice-daily NPH insulin with a significant reduction of nocturnal hypoglycemia<sup>9</sup>.

In a long term study published in diabetes care, it was found that lower fasting blood sugar levels with fewer episodes of hypoglycemia were achieved with insulin Glargine compared with conventional daily NPH insulin in patients with type 1 diabetes<sup>10</sup>.

A Meta analysis review compared the incidence of hypoglycemia in patients treated with Aspart to those treated with regular insulin, observed 25% decreased incidence of hypoglycemia in the Aspart-treated group<sup>10</sup>. Therefore, it is quite possible to eliminate or reduce the incidence of SH with new insulin analogues.

Anticipation of hypoglycemia is important to prevent its occurrence and its sequelae. This anticipation mandates the patient should be aware of symptoms and signs of hypoglycemia prior to its occurrence and should take effective measures to prevent it<sup>8</sup>.

Hypoglycemia is preceded by cyclic hypoglycemic episodes. Recurrent hypoglycemia may lead to hypoglycemia-associated autonomic failure causing defective counter regulation and hypoglycemic unawareness<sup>8</sup>.

The prediction of hypoglycemia is done classically by a structural equation model history of SH, A1C, hypoglycemia awareness, and autonomic score. Some reports have studied a certain blood sugar pattern suggestive of imminent SH<sup>9</sup>.

Clinically, certain risk factors may be implicated in the evolvement of hypoglycemia. Patients must be warned against these risk factors in order to reduce the incidence of hypoglycemia<sup>9</sup>.

#### Hypoglycemia Risk Factors<sup>9</sup>

- Missed or delayed meals
- Eating less food at a meal than planned
- Vigorous exercise without carbohydrate compensation
- Taking too much diabetes medicine (e.g., insulin, insulin secretagogues, and meglitinides)
- Drinking alcohol

Continuous subcutaneous insulin infusion (CSII) using short acting or rapid acting insulin is an increasingly suggested mode of hypoglycemia reduction especially in older type 1 diabetics<sup>10</sup>.

Mode of delivery of the CSII is variable. The most popular, easy to use, cheap and simple is multiple injections or the more sophisticated and expensive insulin pump can be used<sup>11</sup>. Pump therapy is not advocated by some studies for the treatment of hypoglycemia in childhood; however, recent reports, have recommended its usage in any age if the technical problems are avoided<sup>11</sup>.

Whatever the method of insulin delivery used, conjunct nutritional advices and regular blood sugar monitoring must accompany such regimen.

The patient could be classified as "permanent neonatal diabetes" which is a rare inborn error of metabolism. The patient was investigated thoroughly abroad and in SMC by an endocrinologist, but his records could not be traced to confirm or exclude "permanent neonatal diabetes". Neonatal diabetes is a rare entity that describes hyperglycemia in the first month of life. Hyperglycemia could be transient with possible recurrence at a later stage or permanent. The presence of HLA-DR3 and DR4 increases the likelihood of permanent diabetes. Permanent neonatal diabetes is a syndrome, which includes hyperglycemia that may require insulin therapy; other features of the syndrome are renal impairment, mental subnormality and celiac disease. The diagnosis of the syndrome is based on genetic studies, rather than clinical impression<sup>12</sup>.

## CONCLUSION

**Hypoglycemia, with its various degrees, in diabetic patients using insulin therapy is a common phenomenon, which mandates comprehensive analysis. The causes of hypoglycemia are diverse but iatrogenic and dietary causes are the commonest. New insulin analogues and technologies have contributed to lessening the problem but with the continuous recommendations of strict sugar control, this problem still exists requiring more aggressive therapy.**

**The case presented illustrates diabetic patient with hypoglycemia that was successfully controlled by combined insulin analogue and effective dietary therapy. It gives further hope about the role of new insulin analogues in controlling blood sugar without causing significant hypoglycemia.**

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