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The detection of postprandial hypoglycemia with 5-hour oral glucose tolerance test

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ABSTRACT

Introduction

Postprandial hypoglycemia (PH) is a poorly understood phenomenon. Five-hour oral glucose tolerance test (5-OGTT) is often a useful laboratory investigation to understand and establish a diagnosis of PH. The aim of this study is to present the patterns observed during 5-OGTT performed in cases with PH in a tertiary hospital in Nepal.

Methods

5-OGTTs were performed on 52 patients who complained symptomatic postprandial neuroglycopenic symptoms, at the Nepal Medicity hospital during the period of 2 years from 2017 to 2019. The anthropometry, medical history, serum glucose; insulin and cortisol were obtained. The homeostatic model assessment score for insulin resistance (HOMA-IR) based

on fasting glucose and insulin levels were calculated. Data was analyzed using SPSS (Version 20.0).

Results

21 (40.4%) patients out of 52 developed hypoglycemia [blood glucose < 55mg/dl (3.1mmol/L)], among them nine patients developed hypoglycemia at 3 hours, 11 at 4 hours and one at 5 hours post glucose load. The fasting insulin level in patients who developed hypoglycemia was 12.1 ± 5.8 µU/ml compared to the insulin level analyzed at the point of hypoglycemic episode which was 6.4 ± 1.8 µU/ml, P<0.005.

Conclusion

The level of insulin is disproportionately high in the setting of hypoglycemia where it was expected to be nearly absent. The disturbance in physiological mechanism between insulin sensitivity and insulin secretion may be the possible cause of PH.

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INTRODUCTION

The presence of neuroglycopenic symptoms in patients without diabetes is strongly suggestive of a hypoglycemic disorder. There are two types of non-diabetic hypoglycemia where the first one is postprandial hypoglycemia (PH) and the second is fasting hypoglycemia. Reactive or postprandial hypoglycemia causes blood glucose to decrease two to five hours after a diet with high carbohydrate content. Early and late postprandial hypoglycemia occurs in 2-3 hours and 3-5 hours after a meal respectively. (1) Demonstration of hypoglycemia while symptomatic and alleviation of symptoms following normalization of glucose levels is the gold standard test for diagnosing PH. We have previously reported that the PH is the commonest cause of non-diabetic hypoglycemia in a cohort of patients assessed in a tertiary hospital in Nepal. (2) It is our practice in a metabolic clinic to carry out five-hour oral glucose tolerance test (5-OGTT), with insulin measurement at the onset of the symptoms, to diagnose and observe the pattern of PH.

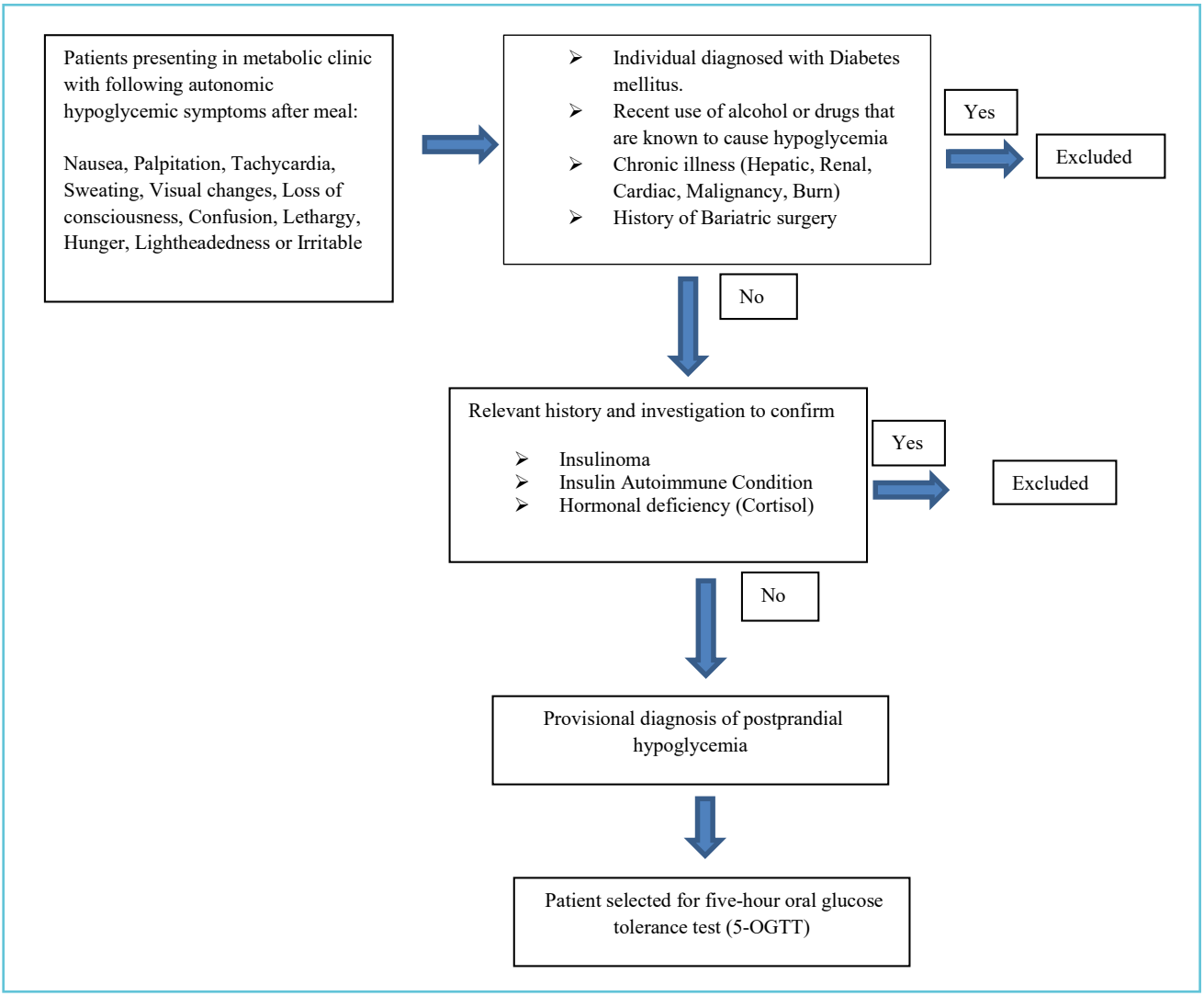
However in clinical practice, the use of 5-OGTT is discredited for the diagnosis of PH as it may show false-positive results. (3) Nevertheless, the 5-OGTT demonstrates the insulin sensitivity of a patient and guides individual therapeutic approach. The aim of this study is to present the patterns observed during 5-OGTT performed in cases with PH in Nepal and discuss the pathophysiological basis behind that pattern. This test is done only in few centers in Nepal.

METHODS

5 hr-OGTT were performed in 52 patients presenting with autonomic hypoglycemic symptoms after meal, at the Nepal Mediciti hospital during the period of 2 years from 2017 to 2019. The sampling scheme is shown in figure 1.

The patients diagnosed with or history of diabetes mellitus, cortisol hormone deficiency, bariatric surgery, drug induced hypoglycemia, Insulinoma and insulin autoimmune syndrome were excluded based on clinical history and relevant investigation. Apart from the antidiabetic medications, the drugs that are known to cause hypoglycemia are quinolones, pentamidine, non selective beta blocker, ACE inhibitors, salicylates, hydroxychloroquine and artemisinins.(4) The adrenal causes of hypoglycemia were ruled out by performing serum cortisol assay in all cases. Insulin glucose ratio (Turners amended ratio) was calculated in each case using [Fasting insulin (µU/ml) × 100 / blood glucose (mg/dl)-30)] formula. (5) The cases with Turners ratio less than 50 were only included in the study to exclude the possible cases of Insulinoma.

Figure 1 Sampling scheme



Biochemical measurements

The clinically diagnosed cases of PH were subjected to 5-OGTT. Patients were advised for 3 days of normal diet and physical activity followed by 10 hours fasting before the investigation. Serum sample for glucose and insulin was collected before the oral intake of the glucose solution (referred as baseline value). 75 grams of anhydrous glucose in 200 ml of water was provided for oral administration. Serum sample were collected and analyzed for glucose every hour after glucose solution intake and insulin was also analyzed from the same sample if there was any event of hypoglycemia. The cut off glucose value to label hypoglycemia was below 55 mg/dl (3.1mmol/L). (6) The homeostatic model assessment score for insulin resistance (HOMA-IR) based on fasting glucose and insulin levels was calculated for cases who developed hypoglycemia.

Serum glucose and insulin were measured using Vitros “ECiQ immunodiagnostic system” Enhanced Chemiluminescence Immunoassay (ECI) after daily maintenance and running internal control samples, which were found to be within the normal range.

Statistical analysis

All data sets were tested for normality using the Kolmogorov-Smirnov test and are expressed as mean ± standard deviation (SD) if normally distributed, or and as median if not normally distributed. The comparison was evaluated using t-test and the Wilcoxon rank test, as appropriate.

RESULTS

The mean age of 52 patients (16 men and 32 women) was 33.8 ± 11.5 years. 21 patients out of 52 developed hypoglycemia at certain hour during 5-OGTT test. Out of 21 patients, nine patients developed hypoglycemia at 3 hours, 11 at 4 hours and one at 5 hours post glucose load.

The mean ± standard deviation of fasting insulin in patients (n=21) who developed hypoglycemia at a certain hour during 5-OGTT was 12.1 ± 5.8 µU/ml compared to the insulin level analyzed during hypoglycemic episode which was 6.4 ± 1.87 µU/ml and this was significant (P <0.005).

When the insulin concentrations during hypoglycemic episode at 3 hours and 4 hours were compared, it was also significantly lower than at the baseline (5.9 µU/ml and 6.5 µU/ml respectively) as shown in Figure 2.

The homeostatic model assessment score for insulin resistance (HOMA-IR) based on fasting glucose and insulin concentrations was calculated for the cases who developed hypoglycemia at three hours and four hours and the average value was 1.9 and 2.9, respectively.

The average glucose concentration in groups that triggered insulin measurement due to symptomatic hypoglycemia was compared with groups that did not trigger insulin measurement. The average blood glucose within two hours post glucose load was 128.3 mg/dL (7.1 mmol/L) versus 118.6 mg/dL (6.6 mmol/L) in a group that later developed and did not developed hypoglycemia respectively (P <0.005). (Figure 3)

Figure 2 **Average insulin and fasting HOMA-IR in patients developing hypoglycemia at 3 hour (3-hour OGTT) and 4 hour (4 hour OGTT) post glucose load**

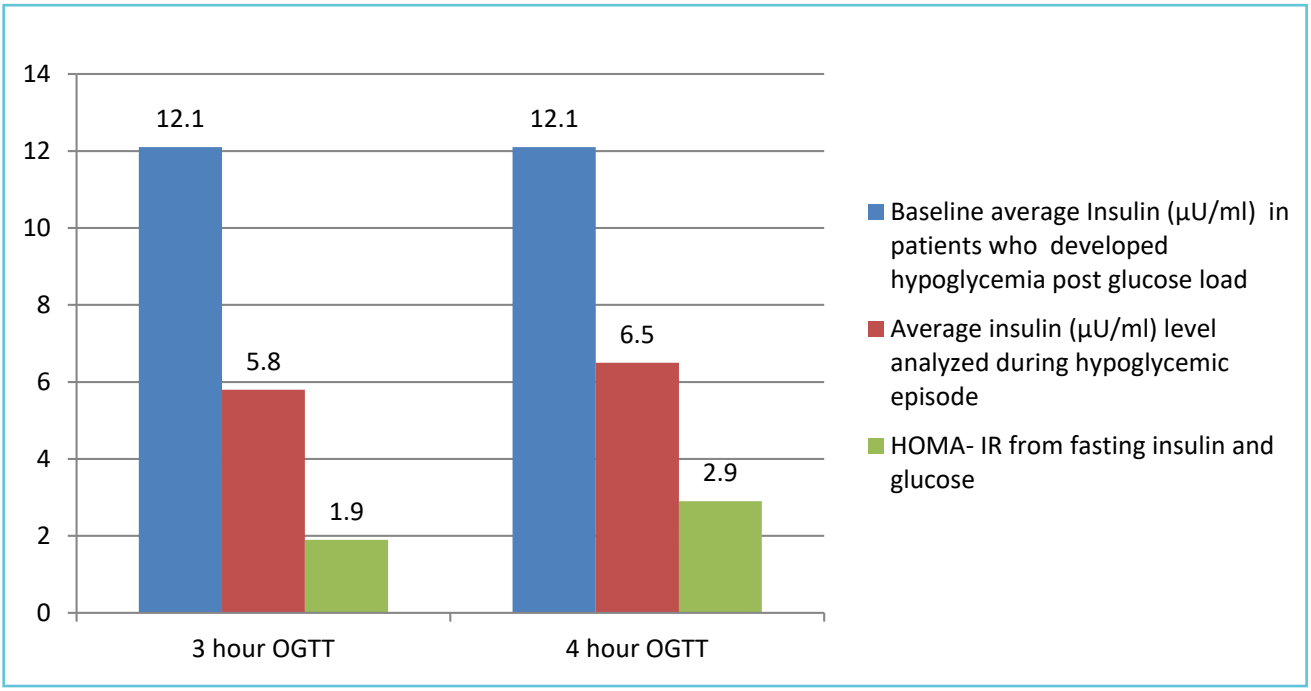
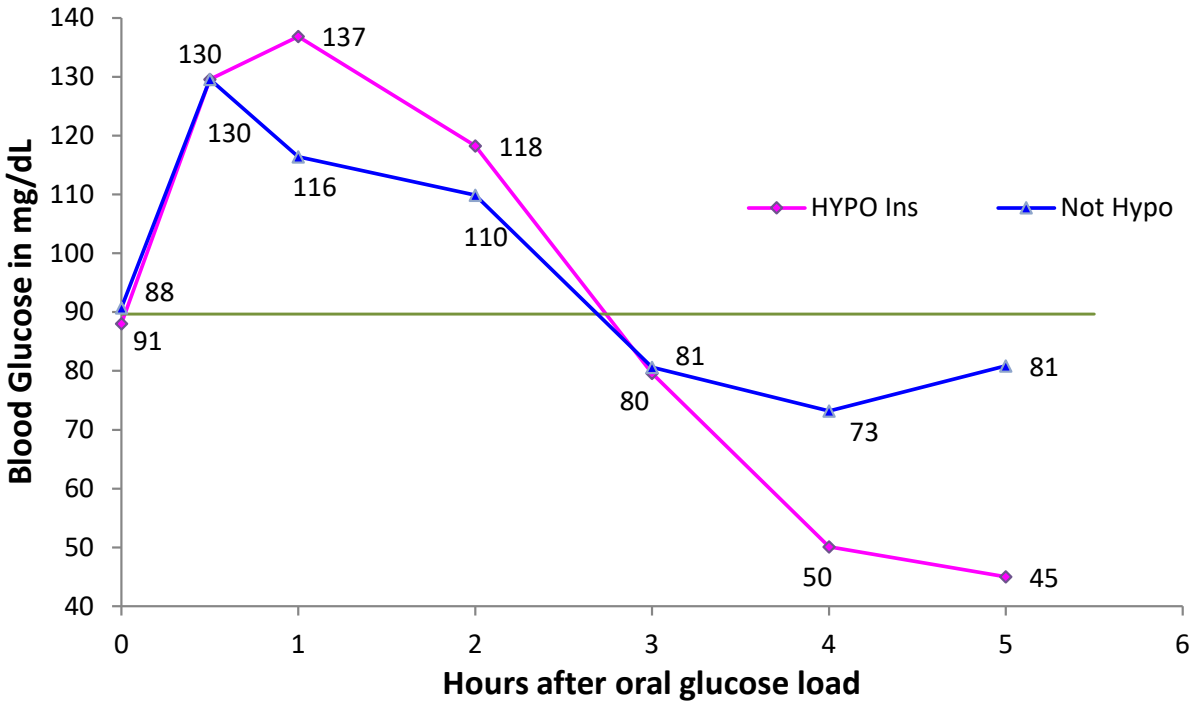


Figure 3 Average glucose concentration in groups triggering (HYPO Ins) and not triggering (Not Hypo) insulin measurement



DISCUSSION

The results of the 5-OGTT carried out at our metabolic clinic have shown various biochemical patterns. The relationship between blood glucose and factors influencing it such as insulin sensitivity, insulin resistance, and counter regulatory hormones has role in this differing pattern. It was proposed back in 1996 by Leonetti F et al that PH may arise from an increased insulin response, which might be related either to insulin resistance or to increased glucagon like peptide-1 (GLP-1), renal glycosuria, defects in glucagon response and high insulin sensitivity. (7)

We have observed symptomatic hypoglycemia both at early (within three hours after the glucose load) and late phase of the 5-OGTT (after three hours). In our study, nine cases (42.9%) developed reactive hypoglycemia at three hours post glucose load. The mean value of HOMA-IR for these nine cases was 1.9 suggestive of mild insulin resistance. Similarly, it is evident from our study that the cases who developed PH at four hours post glucose load, but not at three hours post glucose load, had higher HOMA-IR (2.9 versus 1.9). Similar finding has been reported earlier. (8, 9) The mild form of insulin resistance, observed in cases with PH at 3 hours post glucose load, does not explain the hypoglycemic episode. Tamburrano *et al* reported that this type of idiopathic PH is due to the increased insulin sensitivity. (10)

In our study, baseline insulin level in patients who developed hypoglycemia was significantly higher compared to insulin level during of hypoglycemic episode. It is interesting to note that the insulin level during hypoglycemic episode at 3 hours and 4 hours was not clinically significant

though it was statistically (5.9 µU/ml versus 6.5 µU/ml). The level of insulin is disproportionately high in the setting of hypoglycemia where it was expected to be nearly absent. The insulin half-life is reported to be only 4-5 minutes. This phenomenon could be linked to the abnormal delayed insulin secretion. The delayed insertion of insulin mediated glucose transporter (GLUT-4) has been suggested as a possible cause for this phenomenon. (11, 12) The delayed insertion of GLUT-4 results in very less amount of glucose to be handled by it, as the glucose entry through insulin independent transporters (GLUT 1-3) increases. The continued hyperinsulinemia recruits greater number of GLUT-4 inappropriately at a late stage where hyperglycemia is already approaching normoglycemia and causes rapid entry of glucose into cells resulting in hypoglycemia.

Abnormalities in circulating insulin do not explain all cases of reactive hypoglycemia, since there have been reports of many patients with normal insulin response. (13) Defects in counter regulatory response of glucagon (14), exaggerated response of GLP-1 (15), renal glycosuria (16), defect in hepatic glucose-6-phosphate enzyme system (17) and accelerated stomach emptying (18) are among the commonest causes described in literature. However, in our study, we did not measure the glucagon and GLP-1 level.

A complete work-up including measurement of glucose, insulin, C-peptide, proinsulin, oral hypoglycemic agent screen, and insulin antibodies should be performed at the onset of any hypoglycemic event. Insulin and C-peptide are co-products of proinsulin, and therefore released in the bloodstream at equimolar amounts, with insulin metabolized in the liver, and C-peptide excreted by the kidneys. When the C-peptide concentration is low or undetectable but the insulin concentration is high, then inappropriate insulin administration is a possible cause of hypoglycemia. In our study we measured the insulin level but not the C-peptide, to study the patterns of PH, since the cases with inappropriate insulin administration were already ruled out.

In our study, the pattern of the individual patients reveals a considerable "between individual" variation, which is not surprising but requires some more observations for lasting conclusions. While this disease is often ignored by many physicians and the 5-hour oral glucose tolerance test is often disregarded, it may add therapeutic benefit to the individual patient.

CONCLUSION

Postprandial hypoglycemia represents disturbances of balance between glucose utilization and glucose supply. The disturbed homeostatic loop between insulin sensitivity and insulin secretion may be the characteristic aspect of PH. The pathophysiology varies between individual, and 5-OGTT may be useful to understand this.

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Conflict of interest:

The authors declare that there is no conflict of interest in the publication of this manuscript.

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