

# Recurrent Hypoglycaemia in a Diabetic Patient: The Unexpected Diagnosis

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## ABSTRACT

Hypoglycaemia is a common complication seen in diabetic patients receiving insulin. However, insulin is not the risk factor for hypoglycaemia attack as patient with underlying liver problem is also at risk. Thus, as an attending physician, a high index of suspicion is required in dealing with hypoglycaemia patient. We report a 60-year-old woman with underlying diabetes mellitus who presented with recurrent hypoglycaemic episodes and noted to have multiple benign liver cysts that progressed into hepatic failure secondary to hepatocellular carcinoma.

## INTRODUCTION

Hypoglycaemia is a common complaint by diabetic patients during clinic consultation. Hypoglycaemia is well recognized as a problem in management of diabetes in which the insulin is the major contributing factor. However, causes of hypoglycaemia may be multifactorial. Thus a thorough assessment is required to identify other factors than insulin as the cause of hypoglycaemia. All clinician should be familiar with their patients' medical history and able to properly assess the situation to provide optimal care. We presented a case of a type 2 diabetes mellitus patient treated with insulin who presented with recurrent hypoglycaemic and noted to have undiagnosed liver carcinoma.

## CASE REPORT

A 60-year-old woman presented with multiple episodes of hypoglycaemia over a period of four months since her last clinic visit. Her comorbidities include hypertension, dyslipidaemia and type 2 diabetes mellitus that requiring high-dose insulin premix in three divided doses (50 units, 10 units, 50 units).

Daily capillary blood sugar (CBS) control was satisfactory, with her latest HbA1c improving from 11% to 8.9%. The patient began to have hypoglycaemic episodes since she started reducing her carbohydrate intake. She also experienced abdominal discomfort, early satiety, and loss of appetite. She had lost 5 kg in four months. During these episodes, her CBS reading fluctuated between 2.9 and 4.0 mmol/L. She proceeded to initially halve her insulin doses and later completely stopped taking the insulin injections. Her CBS readings improved, with no further episodes of hypoglycaemia.

She had a history of multiple benign liver cysts diagnosed in 2014 via CT scan after persistently having raised liver enzymes. Her serial liver function test results are shown in Table 1. Her viral hepatitis screening was non-reactive. A repeated multiphase CT scan of the liver in 2016 was reported as having multiple liver lesions, with no significant change in size or characteristic of the lesions over time (as compared to 2014), i.e. the features represent stable disease. She was then discharged from the surgical specialist clinic follow-up.

**Table 1:** Serial liver function test results

|                           | 2014 | 2015 | 2016 | 2017 | 2018 | 2019  | 2020<br>inward | Normal<br>range |
|---------------------------|------|------|------|------|------|-------|----------------|-----------------|
| Alpha-fetoprotein (IU/mL) | 7.4  | 7.7  | 8.3  | 9.9  | 9.4  | 4,880 |                | <7.4            |
| Total bilirubin (µmol/L)  | 9.9  | 9.6  | 11.9 | -    | 11.6 | 20.4  | 277            | <17.1           |
| ALP (U/L)                 | 92   | 129  | 104  | -    | 113  | 192   | 330            | 50–136          |
| ALT (U/L)                 | 103  | 140  | 77   | 95   | 97   | 81    | 83             | 30–65           |
| AST (U/L)                 | 51   | 106  | 46   | 69   | 61   | 80    | 285            | 15–37           |
| Albumin (G/L)             | 33   | 30   | 31   | -    | 35   | 32    | 24             | 34–50           |

On examination, her vital signs were stable. Her capillary blood sugar was 8.0 mmol/L. There was a firm mass over the right upper quadrant of the abdomen, measuring 15 cm below the right costal margin. The mass was smooth and non-tender, and there was also no splenomegaly or ascites. Inguinal lymph nodes were not palpable. Examination of other systems was unremarkable. Bedside abdominal ultrasound revealed an enlarged liver with multiple liver lesions of varying sizes and echogenicity. The initial impression was that there was a progression of the liver lesions, complicated with recurrent hypoglycaemia. The patient was advised for admission; however, she declined.

Further blood investigations including full blood count, liver and renal function and alpha-fetoprotein were immediately obtained. Significant laboratory findings include a raised level of total bilirubin at 20.4 µmol/L, alkaline phosphatase (ALP) at 192 U/L, alanine aminotransferase (ALT) at 81 U/L, aspartate transaminase (AST) at 80 U/L and alpha-fetoprotein at 4,880 IU/mL. An abdominal ultrasound performed 1 week later was suggestive of multicentric hepatoma, and the patient was admitted for further management.

## DISCUSSION

Hypoglycaemic symptoms are a common complaint among patients with type 2 diabetes mellitus who are on insulin. However, there could be several explanations for the frequent hypoglycaemic episodes seen in this case. A suggested approach for managing individuals with hypoglycaemia is to first classify them according to their clinical characteristics such as in ill patients or healthy patients.<sup>1</sup> Those who are ill, tend to have different underlying causes for the hypoglycaemic episodes than

those who are healthy. Our patient might not be healthy as per appearance with the evidence of weight loss and enlarging liver mass upon examination. With underlying liver disease, it is always important to explore this as a possible cause of hypoglycaemia. A worsening hepatic condition might contribute to this as the liver plays a dominant role in regulating glucose homeostasis via numerous pathways, including gluconeogenesis, glycogenesis, glycogenolysis and glycolysis.<sup>2</sup> Patients with hepatic failure have an elevated risk of hypoglycaemia due to depleted glycogen stores and defective gluconeogenesis. This condition, also known as hyperinsulinaemic hypoglycaemia, has been reported in non-diabetics with concomitant liver failure.<sup>3</sup>

Other common causes of hypoglycaemia in diabetes patients were also due to chronic kidney disease (CKD), high insulin doses and oral antidiabetic agents such as sulfonylurea group. In patients with CKD, hypoglycaemia occurs due to altered clearance of glucose-lowering medications, decreased kidney gluconeogenesis process and blunted counter-regulatory response.<sup>4</sup> However, the patient's renal profile was reported to be in the normal range. High insulin doses also can lead to hypoglycaemia. In this patient, he was on 110 units of insulin per day, which is a high dose, despite her body weight being just 80 kg. Insulin promoted the uptake of glucose into the muscle. Thus, higher insulin doses lead to reduce glucose levels in the blood circulation. Fortunately, our patient did her self-monitoring blood sugar (SMBG) regularly, until she was completely off her insulin injection by herself.

Oral anti-diabetic agents also can lead to hypoglycaemia, especially in the sulphonylurea group. However, our patient was not on any sulphonylurea medications. The reason for the worsening of the liver function is likely due to the transformation of her benign liver cysts into multicentric hepatoma as supported by the raised alpha-fetoprotein level and the ultrasound findings. A population-based prospective cohort reported that patients with a history of diabetes mellitus did have an increased risk of developing non-viral hepatocellular carcinoma, which is about twofold higher.<sup>5</sup> The persistence of high blood sugar might also accelerate tumorigenesis in hepatocellular carcinoma formation.<sup>6</sup> The clinical presentation of

hepatocellular carcinoma varies from asymptomatic, paraneoplastic syndromes to life-threatening conditions. It is possible that this patient presented with paraneoplastic syndrome from a non-islet cell tumour; less than 5% of these types of tumours secrete insulin-like growth factor II which causes hypoglycaemia.<sup>7</sup> In the case of incidentally identified asymptomatic simple hepatic cysts, follow-up or treatment is not needed.<sup>8</sup> Meanwhile, hepatocellular carcinoma surveillance is recommended for those with cirrhosis and chronic hepatitis B infection.<sup>9</sup> Since there are no indications that subjected her to routine surveillance of hepatocellular carcinoma, the early diagnosis was missed in this case. The hepatomegaly causes compression of nearby structures including the stomach, which leads to early satiety and a reduced appetite. Also, insulin sensitivity improves after weight loss.<sup>1</sup> With these, the risk of hypoglycaemia would be increased if high doses of insulin were continuously given.

The United Kingdom Prospective Diabetes Study (UKPDS) showed that total exogenous insulin dose was associated with total weight gain<sup>10</sup> and with the high doses of insulin, weight gain should be anticipated instead of weight loss. This should always raise suspicion when the opposite happens, warranting further investigation. Hypoglycaemia among patients with diabetes should not be taken lightly as it is related to a decreased quality of life and work productivity; it may also increase the risk of having accidents and even result in mortality.<sup>11</sup> As primary care physicians, we play a crucial role in identifying those patients at risk of hypoglycaemia and properly managing them, especially in those with underlying liver diseases. A high index of suspicion for other causes of hypoglycaemia should be maintained. In this case, hepatic failure secondary to hepatocellular carcinoma is one of the most possible causes.

#### Conflict of Interest

The authors have no conflict of interest

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