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Fasting hypoglycaemia secondary to carnitine deficiency: a late consequence of gastric bypass

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SUMMARY

Twelve years following gastric bypass surgery, a cachectic 69-year-old woman presented with both fasting and postprandial hypoglycaemia. Postprandial symptoms were relieved by dietary modification and acarbose, as is common in such cases. During a supervised fast, symptomatic hypoglycaemia occurred. Concurrent laboratory testing showed suppression of plasma insulin, c-peptide, proinsulin and insulin-like growth factor II. However, beta-hydroxybutyrate was also low, surprising given insulin deficiency. Elevated plasma free fatty acid (FFA) concentrations suggested that lipolysis was not impaired, making cachexia/malnutrition a less likely cause of hypoglycaemia. The apparent diagnosis was failure to counter-regulate—subsequent plasma carnitine measurements showed carnitine deficiency which presumably prevented FFA transport across mitochondrial membranes for ketogenesis. Repletion with high-dose oral carnitine supplements effected resolution of fasting hypoglycaemia.

BACKGROUND

Fasting hypoglycaemia is exceedingly rare following bariatric surgery. Most cases of low blood sugar after gastric bypass are caused by late dumping syndrome or pancreatic islet cell hypertrophy/hyperplasia.[1] Elucidating the cause of fasting hypoglycaemia in association with cachexia requires consideration of insulin action as well as an assessment of counter-regulatory ability.

CASE PRESENTATION

A 69-year-old woman presented with recurrent hypoglycaemia. She had undergone Roux-en-Y gastric bypass for obesity 12 years prior. After surgery she achieved substantial weight loss with a body mass index (BMI) reduction from 45.6 to 16.7 kg/m^2 within several years and maintained the weight loss since that time. Several months before the presentation to us, she developed recurrent episodes of symptomatic hypoglycaemia, with tremors, palpitations, diaphoresis and sometimes lethargy, that responded to intake of carbohydrates. Hypoglycaemic events occurred both postprandially and nocturnally, detected on continuous glucose monitoring, with readings as low as 2.4 mmol/L.

Social history was negative for access to insulin or glucose lowering agents. Family history was negative for metabolic disorders. Review of systems was positive for deconditioning, as well as postprandial abdominal pain and diarrhoea which dated back to her gastric bypass. Physical examination was notable for sarcopenia and cachexia.

INVESTIGATIONS

Postprandial glucose excursions resembled typical postbariatric surgery-induced hypoglycaemia as evident by her continuous glucose monitor tracings of a significant elevation of blood sugars followed by a rapid decline within 1–2 hours of meals (figure 1). In contrast, her nocturnal blood glucose trended down slowly and worsened with persistent fasting (figure 2).

During a supervised fast, blood glucose dropped to 2.8 mmol/L after 11 hours. Glucagon injection induced a glucose increment of 0.8 mmol/L at 30 min, which is less robust than typically seen in insulinoma (increase >1.4 mmol/L). Low proinsulin/insulin/c-peptide levels during the fast also suggested against insulin excess (table 1). Other conditions that could lead to hypoglycaemia by activation of the insulin receptor such as anti-insulin receptor antibodies and insulin-like growth factor II secreting tumour were also investigated and excluded. Oddly, the β-hydroxybutyrate was inappropriately low for the concurrent hypoglycaemia, suggesting absence of counter-regulation, although cortisol concentrations were normal.

Initially, substrate deficiency was the leading diagnosis in view of her malnutrition (as evidenced by temporal wasting, low prealbumin and hypoalbuminaemia). However, appropriately elevated free fatty acid (FFA) concentrations in combination with low β-hydroxybutyrate while fasting, raised suspicion for fatty acid oxidation disorder. Carnitine deficiency was thus suspected given patient's malnutrition status and past gastric bypass. Low plasma carnitine concentration was documented at 24 μmol/L during hospital admission. Additional nutritional workup is shown in table 2; there was no evidence of other micronutrient deficiency.

DIFFERENTIAL DIAGNOSIS

Fasting hypoglycaemia has a wide differential, but the presence of insulin deficiency and low β-hydroxybutyrate narrowed the diagnostic possibilities. Given her extremely low BMI, a diagnosis of malnutrition leading to failure of counter-regulation was initially considered. However, the measured rise in FFA during hypoglycaemia despite absence of ketone production suggested failure to transport FFA into the mitochondria. Carnitine deficiency was confirmed as the likely cause on subsequent blood testing. However, the postprandial hypoglycaemia was due to dietary indiscretion and responded to avoidance of simple carbohydrates.

TREATMENT

We started the patient on carnitine supplementation by mouth—levocarnitine 990 mg three times per day. For the postprandial hypoglycaemia, dietary modification

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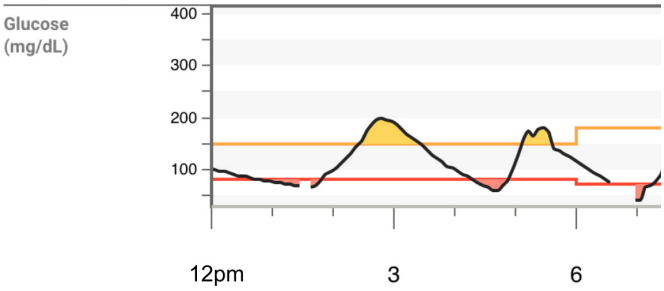

Figure 1 Continuous glucose monitoring showed postprandial hypoglycaemia. The Y-axis shows subcutaneous glucose values in mg/dL (divide by 18 for values in mmol/L).

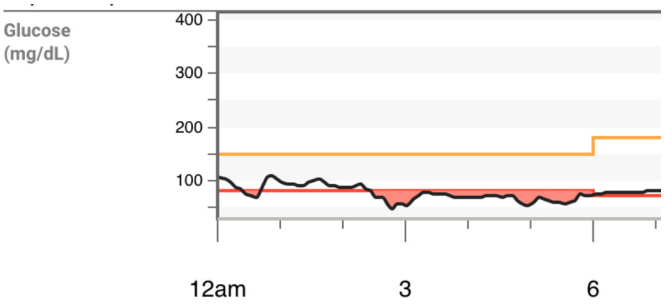

Figure 2 Continuous glucose monitoring showed overnight fasting hypoglycaemia. The Y-axis shows subcutaneous glucose values in mg/dL (divide by 18 for values in mmol/L).

had limited success and thus acarbose 25 mg three times per day with food was started and increased to 50 mg three times per day with moderate relief of symptoms.

OUTCOME AND FOLLOW-UP

Nocturnal hypoglycaemia had resolved at 2-month follow-up, at which point plasma carnitine concentration was 148 μmol/L. Postprandial hypoglycaemia still occurred on occasion when the patient strayed from her recommended diet eliminating simple carbohydrates. No measurable weight change was noted since hospital discharge. We referred the patient back to the bariatric surgery team to address the postprandial abdominal pain, and to a bariatric physician nutrition specialist for weight regain.

Table 1 Concurrent labs were collected during a supervised fast

	Reference range (for hypoglycaemia)	Patient test results
Glucose (mmol/L)	<3.1	2.9
Insulin (uIU/mL)	<3	1
c-peptide (nmol/L)	<0.27	0.17
Proinsulin (pmol/L)	≤8	<1.6
BOHB (mmol/L)	>2.8	0.47
FFA (mmol/L)	>0.78	1.19
IGF-I (ng/mL)	27–228	79
IGF-II (ng/mL)	180–580	244
Anti-insulin receptor Ab	Negative	Negative
Carnitine (µmol/L)	26–66	24.6
8AM cortisol (nmol/L)	>348	627

Normal values quoted are what is expected during fasting, except for IGF-I, IGF-II, anti-insulin Ab, carnitine and 8AM cortisol level, for which reference range is not defined based on glucose level.
BOHB, Beta-hydroxybutyrate; FFA, free fatty acid; IGF, insulin-like growth factor.

Table 2 Serum chemistry results from a thorough nutritional assessment

Micronutrient	Patient value	Normal range
Copper (µmol/L)	20.3	12.6–24.4
Iron (µmol/L)	12.4	6.6–26
Iron binding capacity (µmol/L)	13.4	20–62
Retinol (µmol/L)	1.2	1.05–4.2
Vitamin D, 25 (nmol/L)	92.4	75–200
Alpha tocopherol (IU/L)	15	11.3–27
Zinc (µmol/L)	10.9	9.2–18.4
Vitamin C (µmol/L)	84	23–114
Prealbumin (µmol/L)	2	3.6–7.3
Ceruloplasmin (µmol/L)	18.7	10.7–30
Phosphorus (mmol/L)	1.32	0.9–1.5
Magnesium (mmol/L)	0.8	0.7–1.0
Folic acid (nmol/L)	>45	13.6–34
Vitamin B6 (nmol/L)	80.2	20–125
Copper (µmol/L)	20.3	12.6–24.4

DISCUSSION

Here, we present a case of carnitine deficiency-mediated recurrent hypoglycaemia in a patient who had undergone Roux-en-Y gastric bypass for obesity 12 years prior. Patient is underweight and malnourished and has experienced hypoglycaemic events both postprandially and nocturnally. Postprandial glucose excursions resembled typical postbariatric surgery-induced hypoglycaemia as evident by her continuous glucose monitor tracings of a significant elevation of blood sugars followed by a rapid decline within 1–2 hours of meals; acarbose and dietary modification improved daytime hypoglycaemic frequency, as has been reported many times. In contrast, her nocturnal blood glucose was classified as 'fasting hypoglycaemia'. Whipple's triad for hypoglycaemia was fulfilled.[2] During a supervised fast, labs suggested a non-insulin-mediated process. Appropriate rise in FFA concentrations in combination with low ketones and low plasma carnitine while fasting explained the counter-regulatory failure. Fasting hypoglycaemia was reversed after normalisation of carnitine level.

Postgastric surgery carnitine deficiency has been described in several case reports, although such diagnoses were mostly made after patients presented with hyperammonaemic encephalopathy.[3] Carnitine deficiency presenting as fasting hypoglycaemia is rarely reported.[4] Malnutrition is likely a risk factor for acquired carnitine

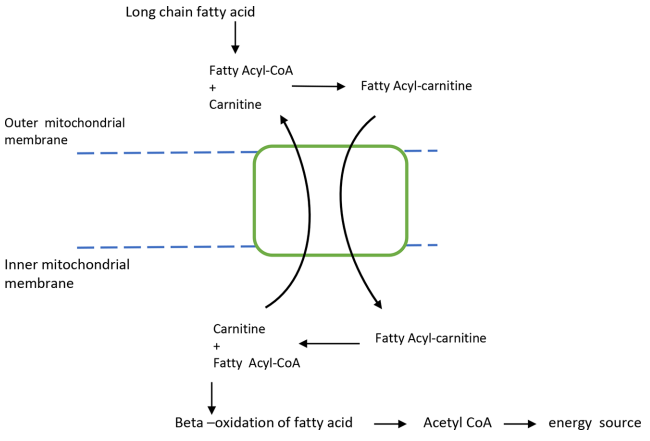

Figure 3 Carnitine plays a crucial role in the transport of long-chain fatty acids across the mitochondrial membrane for β-oxidation and energy generation during fasting.

deficiency,[4] as seen in our patient. Carnitine plays a crucial role in the transport of long-chain fatty acids across the mitochondrial membrane for β-oxidation during fasting, as demonstrated in figure 3. Inhibition of fatty acid oxidation can also increase organ glucose consumption (glucose-fatty acid cycle). Carnitine deficiency-induced orexin deficiency that results in anorexia is another possible mechanism being proposed in an animal model,[5] although our patient's appetite has not increased with carnitine repletion. Carnitine supplementation results in improvement of hypoglycaemia[6] and should be considered in workup of bariatric surgery patients who present discordance between FFA and serum ketones during fasting hypoglycaemia. There is a paucity of literature on carnitine deficiency in adult populations, as it appears to be rare. Primary carnitine deficiency is an autosomal recessive disorder of the carnitine transporter system that results in urinary carnitine wasting. It is possible that our patient is a heterozygote, where doubling of urinary carnitine has been described.[7] In combination with poor absorption due to her gastrointestinal surgeries, this might have precipitated her severe deficiency. Future studies are needed to investigate the prevalence of carnitine deficiency as well as fasting hypoglycaemia attributed to carnitine deficiency in patients with a history of gastric bypass.

Patient's perspective

Here's my input re levo carnitine (LC)

I spent a year suffering with hypoglicemia (HG), going thru two 24-hour fasting exams as well as other hit and miss testing. Luckily for me, my doctors and the medical staff did not give up on me. As I went thru various treatments, I continued to suffer with sharp glucose swings from 6.7 to 2.2 or less. This didn't only affect me but it put a lot of stress on my husband as well.

When I began taking LC, I slowly started to improve. Due to chronic pneumonia, I was in the hospital every 4–6 weeks which ended up with changes to my LC dosing and resultant HG instability.

It is not easy living with HG but LC has improved it. On behalf of those with this disease, I thank those who came up with LC and I thank my doctors for not throwing in the towel but instead spending hours researching the best treatment.

Learning points

- Accurate history taking is crucial to determining the cause of hypoglycaemia following bariatric surgery. Almost all hypoglycaemia is postprandial and mostly responds to diet manipulation and avoidance of simple carbohydrates.
- Fasting hypoglycaemia requires assessment of plasma insulin, c-peptide and β-hydroxybutyrate at the time of hypoglycaemia to determine whether the aetiology is mediated via the insulin receptor or not.
- Substrate deficiency should be included in the differential diagnosis of non-insulin mediated hypoglycaemia in a patient with cachexia and malabsorption. Following bariatric surgery, deficiency of carnitine—while rarely described—can contribute to failure of counter-regulation and result in hypoglycaemia.

Contributors There are three endocrinology trainees (XC, BK and JN) and one consultant endocrinologist (KCM) as authors. We all four wrote the manuscript together. BK and KCM met the patient during her second hospitalisation and worked her up. JN took over inpatient management and got the carnitine started. XC met the patient during a subsequent hospitalisation and together with KCM, has been regularly seeing the patient as an outpatient to help supervise her glucose levels and carnitine and overall care.

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