Hypoglycaemia in hepatocellular carcinoma: a review

RTT Yeung

Hypoglycaemia in patients with hepatocellular carcinoma is not a particularly important clinical entity, as it usually occurs during the terminal stage of the illness. As many as 13% of patients with hepatocellular carcinoma, however, develop hypoglycaemia early in the course of their illness. This latter group of patients show a distinct pattern in their clinical course and pathology.

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Introduction

In 1929, Nadler and Wolfer first recorded the development of hypoglycaemia in a patient with hepatocellular carcinoma (HCC).[1] One year later, Doege reported the occurrence of hypoglycaemia in a patient with a large fibrosarcoma.[2] In a review of the literature, Kahn found that mesenchymal tumours are responsible for 45% of hypoglycaemia due to non-islet cell tumours (non-islet cell tumour hypoglycaemia [NICTH]) and HCC accounts for 23% of these tumours, which are massive and slow growing.[3]

In 1956, McFadzean and Yeung reported the occurrence of hypoglycaemia in seven patients with HCC.[4] In a study of 142 consecutive HCC patients by the same authors,[5] the majority of patients (87%) were designated Type A, having either no hypoglycaemia or developing hypoglycaemia only within two weeks of their death. In these patients, the tumour was rapid growing and poorly differentiated and there was rapid wasting and profound muscle weakness. It was concluded that in Type A patients, hypoglycaemia occurs solely as a consequence of a progressive increase in demand for glucose by the tumour coupled with a progressive reduction in glucose supply, in part due to progressive encroachment on the residual liver tissue by the tumour and also to undernutrition. The remaining 13%, however, developed hypoglycaemia early in the course of their illness and were designated Type B.

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Clinical manifestations

In Type A patients, the tumour was rapid growing, appetite was impaired, and muscle wasting and weakness were marked. The average survival of these patients was three and a half months. Hypoglycaemia, if present at all, occurred as a terminal event within hours to two weeks of death. In contrast, Type B patients had a slow growing tumour and little or no muscle wasting and weakness. Hypoglycaemia, which was present in all, was frequently the reason for admission and appeared two to 10 months before death.

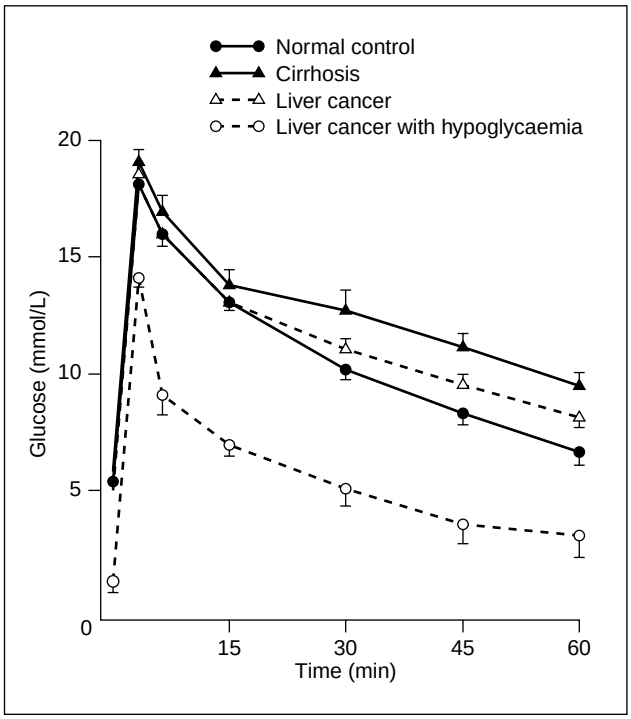

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Fig 1. Glucose responses in intravenous glucose tolerance test

Table. Fasting blood glucose, insulin and C-peptide levels: intravenous glucose tolerance test results in normal controls, cirrhotic patients, patients with hepatocellular carcinoma, and patients with hepatocellular carcinoma and hypoglycaemia

	Group 1 normal control (n=14)	Group 2 cirrhosis (n=11)	Group 3 hepatocellular carcinoma (n=29)	Group 4 hepatocellular carcinoma with hypoglycaemia (n=6)
Fasting glucose (mmol/l)	5.3±0.60	5.6±0.61	4.9±0.18	1.16±0.24*
Fasting insulin (μU/ml)	7.1±1.00	16.88±2.82†	6.19±2.91	2.45±1.34*
Fasting C-peptide (pmol/ml)	0.49±0.88	0.85±0.27	0.49±0.07	0.11±0.04*
Intravenous glucose tolerance test	(n=14)	(n=10)	(n=26)	(n=4)
K value (assimilation coefficient)	1.557±0.089	1.145‡±0.071	1.337±0.064	1.943*±0.175
C-peptide AUC (pmol/ml min)	56.8±7.0	98.1±31.4	78.2±13.8	18.9*±10.6

*P<0.05 to 0.001 vs normal control, cirrhosis, HCC
†P<0.01 vs normal control, P<0.05 vs HCC
‡P<0.05 vs normal control and HCC

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Appetite was preserved or even increased. The average survival was seven months. In Type A patients, hypoglycaemia was readily controlled by ensuring a 24-hour intake of approximately 400 gm of carbohydrates, whereas in Type B patients, a carbohydrate intake of 1500 gm or more was commonly required to control the hypoglycaemia.

Biochemical investigations

Intravenous glucose tolerance test

The glucose assimilation coefficient (K) in Type B patients was significantly higher than that of the control group, cirrhotic subjects, and HCC patients without hypoglycaemia (Table, Fig 1).[5,6] Insulin and C peptide responses were suppressed, indicating that the increased glucose assimilation was not due to excessive insulin secretion (Fig 2).[6] These findings are consistent with the hypothesis that hypoglycaemia in these patients might be caused by the tumour producing substances with insulin-like effects.

Glucagon challenge test

Glucagon increases the blood glucose by stimulating glycogenolysis in the liver. The glucose response to glucagon was significantly lower in Type B patients when compared with controls, cirrhotic subjects, and HCC patients without hypoglycaemia (Fig 3).[5-7]

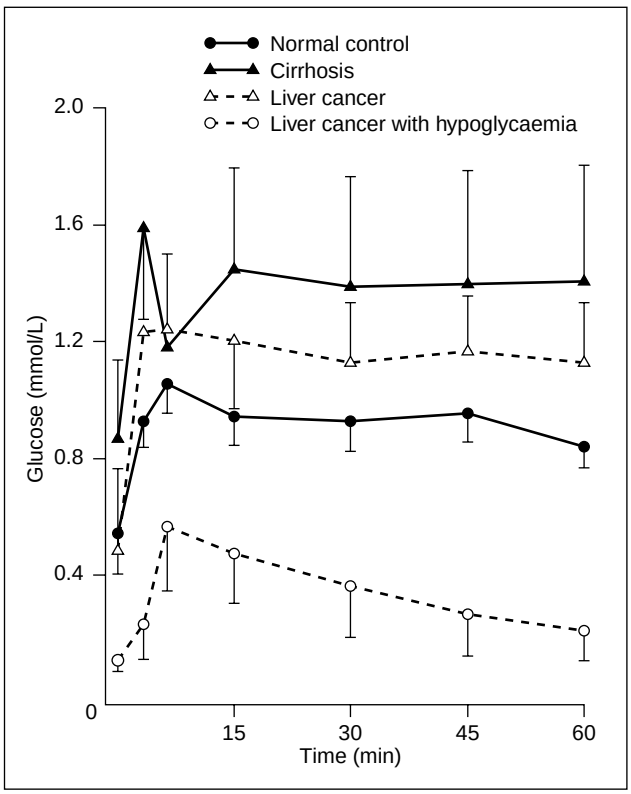

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Fig 2. C-peptide responses in intravenous glucose tolerance test

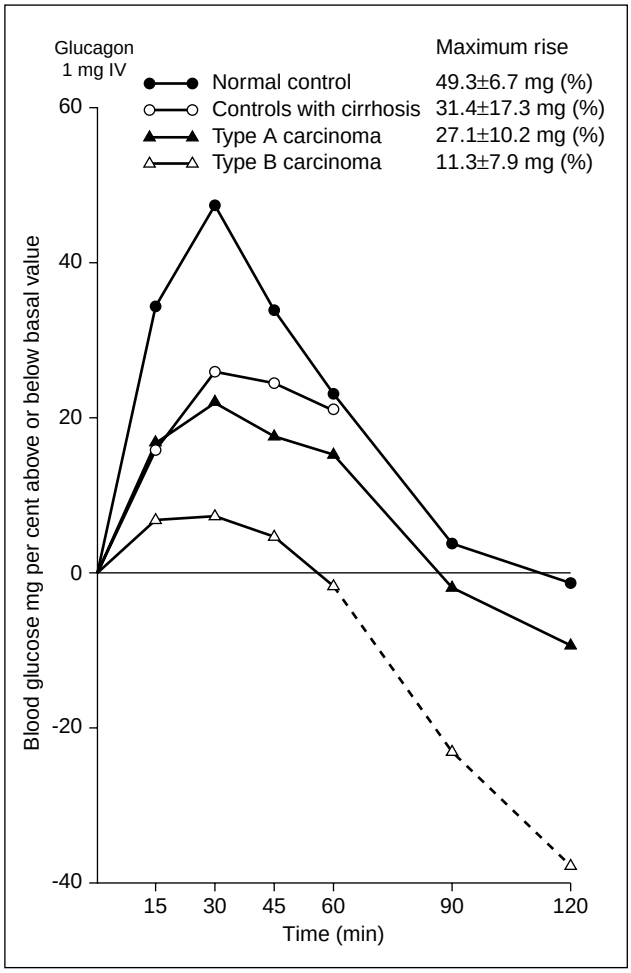

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Fig 3. The response to glucagon in normal controls, controls with cirrhosis, Type A carcinoma and Type B carcinoma

Furthermore, there was a progressive reduction in the response to glucagon until it was no more than a transient slowing of a precipitous fall in blood glucose level. This impaired glucose response to glucagon in Type B patients was not due to damaged glucagon receptors since the plasma cyclic AMP response to glucagon was increased in these patients when compared with that in the other groups (Fig 4).[7]

Liver and tumour glycogen

In Type B patients, the tumour was well differentiated and the glycogen contents of the tumour and residual liver were higher than the corresponding values found in Type A patients and were the same, or in some cases, higher than those found in the livers of control patients (Fig 5, Fig 6).[5]

Liver enzymes

Glucose-6-phosphatase activity was completely

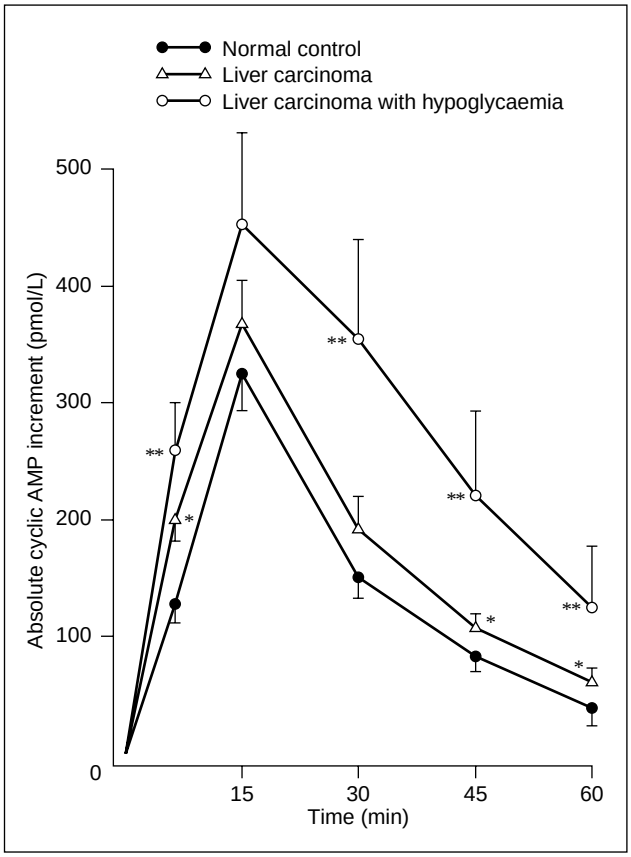

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Fig 4. Absolute cyclic AMP increments after glucagon challenge. The fasting 0 min cAMP level is taken as baseline.

***On comparison with normal controls, patients with HCC had significantly higher cAMP responses (P<0.05).**

****On comparison with the other two groups, patients with HCC and hypoglycemia had significantly higher cAMP responses (P<0.05).**

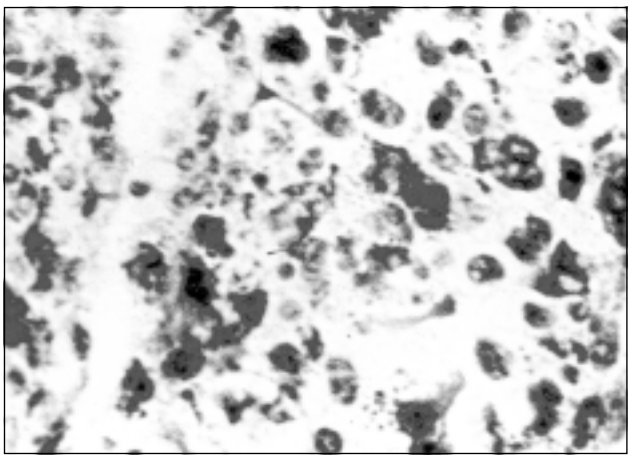

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Fig 5. Type A anaplastic hepatocellular carcinoma stained for glycogen (7 mg glycogen per g)

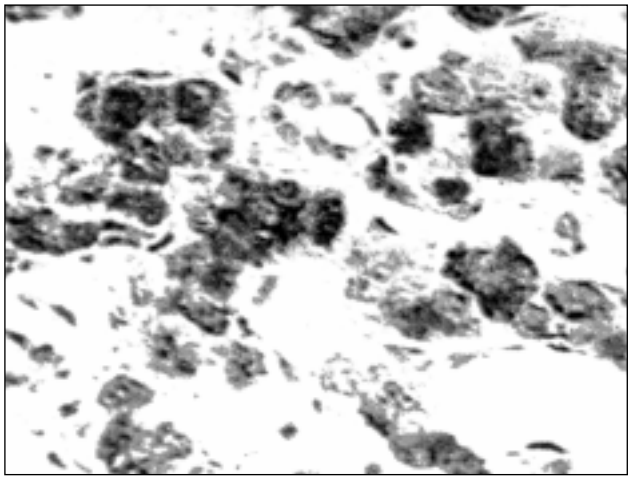

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Fig 6. Type B well differentiated hepatocellular carcinoma stained for glycogen (31 mg glycogen per g)

absent in the Type B tumours and reduced in the Type A tumours and in the residual liver tissues of both types. Phosphorylase activity was abnormal in both types. In contrast, glucose-6-phosphate dehydrogenase and lactate dehydrogenase were increased in the tumours and residual tissue of both types.[5]

In 1973, Yeung et al rezported an unusual patient with HCC and early hypoglycaemia who had a normal glucose response to glucagon.[8] His clinical manifestations were otherwise indistinguishable from those of Type B. Histologically, the well differentiated malignant cells were loaded with

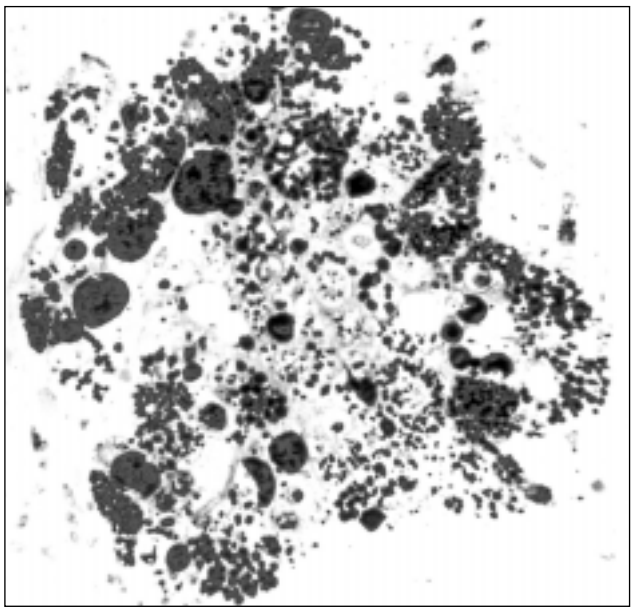

Fig 7. Patient's tumour stained for neutral fat (475 mg fat per g)

fat and on chemical analysis, the lipid content was found to be 475 mg/g of tumour tissue (Fig 7). The glycogen content was not increased. Enzyme studies of the tumour showed reduced activities of the rate-limiting enzymes for glycogenolysis and gluconeogenesis, viz. glucose-6-phosphatase, fructose-1,6-diphosphatase, pyruvate carboxylase, and phosphoenolpyruvate carboxykinase.

Pathogenesis

The clinical manifestations of NICTH are indistinguishable from those produced by an insulinoma. These patients are usually older, however, their hypoglycaemia is severe, and tumours are readily found on physical examination or by imaging. In addition to persistent hypoglycaemia, the characteristic biochemical findings include hypoketonaemia, suppressed insulin, proinsulin, C peptide levels, and lack of response of growth hormone and glucagon to hypoglycaemia. The glucose response to glucagon, however, is often normal in NICTH other than HCC.

In 1974, Megyesi et al[9] reported elevated plasma non-suppressible insulin-like activity (NSILA) in three of seven patients with NICTH, raising the possibility of insulin-like growth factors (IGF) being the responsible agent. However, his results could not be confirmed by others using different techniques to extract and assay IGFII from the serum. More recently, using molecular biology techniques, Daughaday and co-workers[10] produced convincing evidence that IGFII was responsible. They found high concentrations of mRNA for IGFII and IGFII immunoreactive peptide in a leiomyosarcoma and elevated levels of plasma IGFII in the patients' serum before tumour removal and a fall to normal levels with the disappearance of hypoglycaemia after operation. Furthermore, most of the IGFII exists in the serum as Big IGFII and this Big IGFII has reduced affinity for IGF binding protein, making it more available for receptor interaction. Big IGFII also suppresses growth hormone and glucagon secretion, further aggravating the hypoglycaemia. Recently, Zapf published a brief but comprehensive review of the pathogenesis of hypoglycaemia in NICTH.[11]

In HCC patients, there are additional factors such as a progressive reduction in hepatic glucose output due to tumour involvement and poor nutrition. The autocrine/paracrine effect of Big IGFII produced by the tumour may also account for the reduced activities of rate-limiting enzymes for glycogenolysis and

gluconeogenesis in the tumour and residual liver. In a study of patients with HCC and other tumours with or without hypoglycaemia and patients with hepatitis B virus (HBV) antibody positivity, Daughaday et al[12] found an increase of Big IGFII in six of 11 asymptomatic patients with HBV antibodies suggesting that the disordered processing of Pro-IGFII occurs in some patients at this stage of hepatitis B infection. Increased proportions of Big IGFII have also been found in the sera of some patients with large tumours who are not hypoglycaemic.

Treatment

When hypoglycaemia occurs in patients with HCC, the tumour is usually already massive and not amenable to surgery. Nevertheless, the relatively small proportion of patients who are Type B may be maintained relatively symptom-free for many months if their hypoglycaemia is controlled by frequent feeding or parenteral infusion. Large doses of corticosteroid or frequent administration of growth hormone can also give temporary relief, although these are both associated with adverse side-effects.

Acknowledgements

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