The dietary management of hepatic glycogen storage disease

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The dietary management of hepatic glycogen storage disease (GSD) is based on an understanding of the primary biochemical abnormalities.

Plasma glucose levels are maintained by the release of glucose from the liver. The glucose is formed either by the breakdown of glycogen or it is synthesized from substrates such as fructose, galactose, glycerol or amino acids. The final common step in all these pathways is the hydrolysis of glucose-6-phosphate by glucose-6-phosphatase to form glucose (Fig. 1). This enzyme is absent in classical type I GSD.

The other common types of GSD (type III, type VI) are defects in glycogen degradation. The release of glucose from other substrates is not impaired. The α(1–4) bonds in glycogen are hydrolysed by phosphorylase, an enzyme that is activated through a sequence of enzymes. For management purposes abnormalities of this series may be grouped together as type VI GSD. The α(1–6) bonds are hydrolysed by the debrancher, the deficiency of which is also called type III.

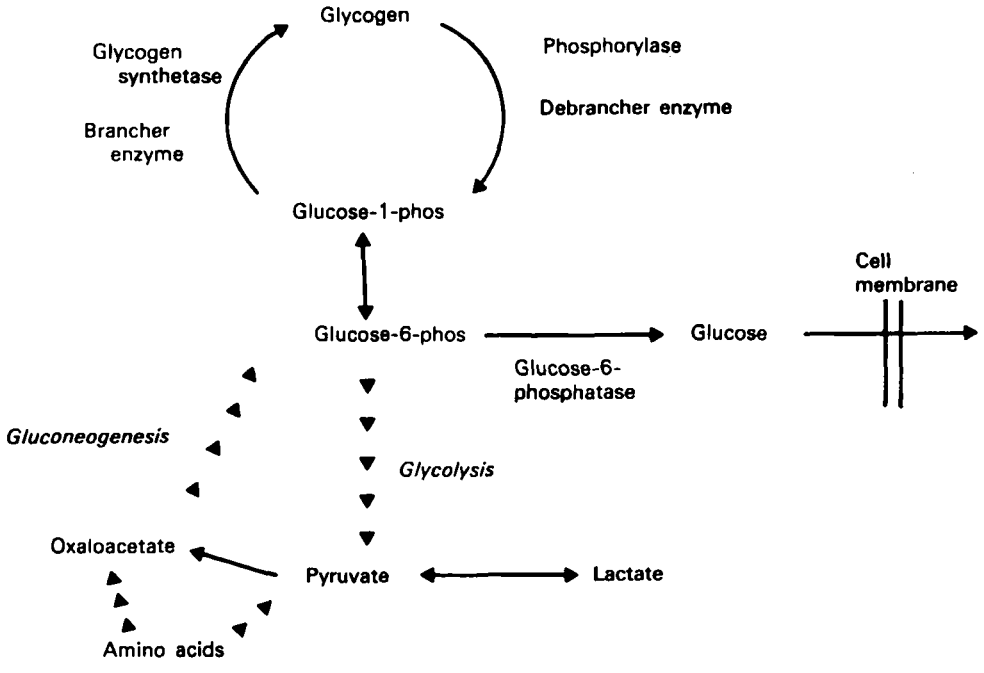

Fig. 1. Glucose and glycogen metabolism in the liver.

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Glycogen is synthesized by glycogen synthetase and the α(1–6) bonds are incorporated into the structure by the brancher enzyme. Abnormalities of glycogen synthesis are rare and have atypical features.

Most children with GSD present during early childhood with hypoglycaemia, lactic acidosis or hepatomegaly. Later in childhood the patients may not thrive and are commonly of short stature with delayed puberty. Secondary abnormalities include a bleeding disorder due to a defect in platelet function (Hutton *et al.* 1976), hyperlipidaemia and hyperuricaemia. The severity of these disorders varies considerably although, in general, patients with type I GSD are more severely affected than those with type III or type VI GSD. An accurate enzyme diagnosis measuring the enzyme activity in liver tissue or in white blood cells is essential for correct management.

In the dietary management of these conditions the regime used in type I GSD (glucose-6-phosphatase deficiency) is distinct from that used in the other forms of hepatic GSD (glycogen synthetase deficiency, type III and type VI GSD). In type I GSD no glucose is released from the liver and the blood glucose must be maintained with exogenous glucose. The aim should be to maintain the blood sugar between 4–6 mmol/l throughout the 24 h period. This may be done by intravenous therapy (Crigler & Folkman, 1978), by frequent oral feeds (Kelsch & Oliver, 1969) or by a combination of frequent oral feeds and nasogastric infusions (Greene *et al.* 1976). Hypoglycaemia is thereby prevented and concurrently the secondary biochemical abnormalities including blood and urinary lactate, lipids and uric acid improve (Fig. 2). Prolonged and continuous intravenous therapy is not feasible and the most satisfactory alternative is a regime using frequent oral feeds by day with a nasogastric infusion at night. Glucose or a short chain polymer is given at a rate of approximately 0·5 g/kg per h. Control may be improved by the use of starch or a more balanced feed (Fernandes *et al.* 1979). The effect of the supplement is monitored by measuring the blood sugar throughout 24 h, with adjustments being made to the regime as necessary.

On such a regime there is often a striking increase in well-being and a marked increase in growth velocity (Greene *et al.* 1976). The patients continue to eat normal meals but galactose and fructose should be restricted. Neither of these monosaccharides can be converted into free glucose and are metabolized to lactate (Fernandes, 1974).

The regimes outlined are not without danger because sensitivity to hypoglycaemia may be restored. If the supply of exogenous glucose is interrupted severe symptomatic hypoglycaemia may develop with potentially fatal consequences (Leonard & Dunger, 1978).

In type III, type VI GSD, and glycogen synthetase deficiency glucose cannot be released by the breakdown of glycogen but plasma glucose levels may be maintained by utilizing alternative pathways. Both fructose and galactose can be converted to glucose and need not be excluded from the diet. Glucose can also be formed from amino acids by gluconeogenesis so that frequent small feeds high in protein are indicated. (Fernandes & Van der Kamer, 1968; Aynsley-Green *et al.*

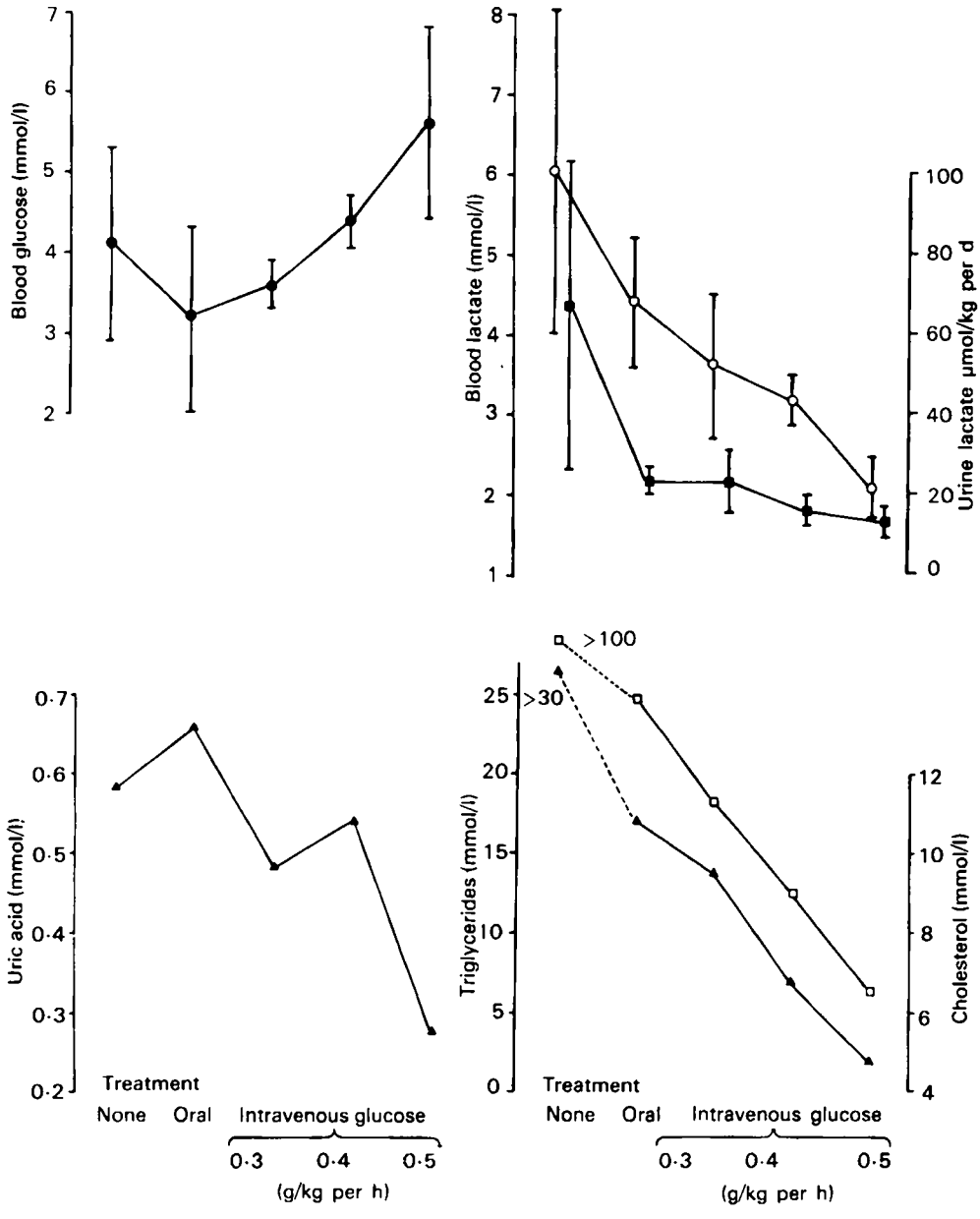

Fig. 2. The effect of oral and intravenous glucose therapy on blood glucose, lactate uric acid, total cholesterol and total triglycerides and on urinary lactate excretion in a patient with type I glycogen storage disease. Each graph represents five consecutive weekly periods; week no. 1, no treatment; 2, oral treatment with glucose drinks 2 hourly by day and 3 hourly by night giving glucose 0·5 g/kg per h; 3, 4, 5, intravenous treatment with glucose 0·3, 0·4 and 0·5 g/kg per h respectively.

Blood glucose (●) and lactate (○) levels represent the mean and one standard deviation (SD; represented by vertical bars) of six values taken at 4 h intervals for 24 h. Urine lactate (■) values are the mean and one SD of seven 24 h specimens. Uric acid (▲), cholesterol (▲) and triglyceride (□) are single values taken at the end of the treatment period.

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1977). The effect of the diet on the blood sugar and secondary metabolic abnormalities should be monitored and the diet adjusted appropriately. The protein intake may need to be increased up to twice the normal intake for age.

With careful dietary management the outlook for physical and mental development in the early years of life for all forms of hepatic GSD has now improved. However, there are now several reports of hepatic adenomas and hepatic carcinomas developing in patients with type I GSD in their second or third decades (Howell *et al.* 1976; Miller *et al.* 1978). Treatment may cause pre-existing lesions to regress and prevent new tumours developing (Roe *et al.* 1979). Long-term dietary control of the metabolic abnormalities of GSD may be essential to prevent this and other complications.

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