Secondary Metabolic Changes in Von Gierke’s Disease
(Type I Glycogen Storage Disease)

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ABSTRACT

Deficiency of glucose-6-phosphatase in Type I glycogen storage disease (GSD) results in hypoglycemia and excessive accumulation of glucose-6-phosphate. As a result, lactic acid, uric acid, and lipids are formed as end-products. The formation of these metabolites are discussed with an emphasis on monitoring therapeutic progress. In addition, hyperlipidemia and associated changes in apolipoproteins are considered as indices of the clinical course.

Introduction

Increased storage of glycogen occurs in the liver, intestine, and kidney secondary to a deficiency of glucose-6-phosphatase, the recessively inherited defect in von Gierke’s disease. Symptoms owing to hypoglycemia present early in the neonatal period which results from an inability to break down hepatic glycogen, normally a major source of glucose for the fasting infant. Nocturnal intragastric feeding of a high carbohydrate formula will effectively prevent hypoglycemia as well as dramatically reduce urate, lactate, triglyceride, and cholesterol levels. Thus, prevention of hypoglycemia and its ensuing counter-hormonal response has merited attention. What had been a serious disease without any effective medical treatment, now is amenable to effective therapeutic regimens involving nocturnal infusions of high carbohydrate formulae such as Vivonex* (90.5 percent carbohydrate). It is, therefore, advisable to monitor progress and to consider the levels of lactate, urate, lipids and lipoproteins as indices of the primary glycolytic process. In this review, these metabolites will be viewed in terms of their mechanism of formation following a discussion of the hypoglycemia.

Hypoglycemia

In spite of the complete absence of hepatic glucose-6-phosphatase activity in almost all cases of Type I GSD, the glucose levels are sustained at an acceptable level without significant symptomatology. The blood sugar will decrease to below 70 mg per dl after a short fast of two to four hours and as low as 20 mg per dl after six to eight hours. Nevertheless, glucose-6-phosphate may undergo hydrolysis by re-

* Norwich-Eaton Pharmaceuticals.
sidual glucose-6-phosphatase activity or by non-specific phosphatases to sustain the blood sugar and prevent even more severe falls. Also, glucose may be released from the liver by the action of amylo-1,6-glucosidase, but only if constant resynthesis of glycogen occurs to provide regeneration of the branch points. The relative absence of symptoms may also be accounted for by a sparing effect owing to the metabolism of alternate substrate such as ketones and lactate.

In addition to hypoglycemia, basal plasma insulin levels are 50 to 60 percent of normal and urinary C-peptide, a good index of endogenous insulin secretion, is found to be decreased. Both glucose and arginine cause an attenuated insulin response and the hypoinsulinemia results in lowered glucose tolerance when the patient is challenged with a glucose load. The hypoinsulinemia probably results from chronically low glycemic stimuli with the result that these patients are less likely to have rapid falls in blood sugar due to insulin secretion. Therefore, during therapy, there should be an awareness of offsetting the hypoinsulinemia with prolonged stimulation of insulin secretion as is provided during continuous feeding regimes. For example, intragastric infusion of glucose significantly increased the insulin secretory response during the first month of treatment. Subsequent cessation of the continuous supplies of high dietary carbohydrate could result in severe hypoglycemia owing to a continued insulin secretory response in the face of low glucose levels.

Lactate

When galactose is given to the patient, it forms glucose-6-phosphate which is then diverted to form excess lactate, a diagnostic test virtually to confirm GSD Type I prior to a liver biopsy (table I). Also, exogenous glucagon or epinephrine will enhance the formation of glucose-6-phosphate from glycogen and induce lactate formation. Hypoglycemia will induce secretion of these counter-hormones and cause subsequent lactate formation indicating that the lactate levels will tend to rise during hypoglycemic episodes and revert to normal during continuous nocturnal intragastric feeding. In addition, excess lactate may enhance further storage of hepatic glycogen. Using a constant infusion of 14C lactate to investigate lactate production and incorporation into glucose, Sadeghi-nejad concluded that lactate becomes recycled to form hepatic glycogen which in turn will undergo repeated glycogenolysis and glycolysis.

Ketones

Ketone formation may be enhanced by the excess supply of peripherally mobilized fatty acids available for hepatic β-oxidation. However, relatively low ketone levels are observed in GSD Type I because high pyruvate levels will provide a supply of oxaloacetate and prevent formation of acetyl Co A and subsequent generation of ketones. Also, when insulin secretion is enhanced and glucagon suppressed during high carbohydrate therapy, there are less ketones available as an energy source.

It is of interest to note that Petterson et al find that urinary dicarboxylic acid excretion parallels the degree of ketosis in glycogen storage disease as well as in starvation and diabetic ketoacidosis. Formation of this group of compounds (adipic acid, suberic acid) may represent a mechanism whereby ketosis is spared because when succinyl Co A is produced from fatty acids by cooxidation, the dicarboxylic acids thus formed undergo β-oxidation.

Uric Acid

Clinical manifestations of gout in GSD Type I, such as arthropathy, chronic tophaceous gout, and nephropathy, may ap-
pear in adolescence\textsuperscript{19,28} and worsen with age, although uric acid formation has been regarded by some as a relatively minor event.\textsuperscript{91}

Elevation of uric acid levels partly reflect increased purine synthesis as indicated by the finding of increased \textsuperscript{14}C-1-glycine into urate.\textsuperscript{2,33} This would suggest that increased glycolysis is the source of purine synthesis but increased availability of ribose-5-phosphate from glycolysis does not increase phosphoribosyl pyrophosphate so that an alternate mechanism may be involved. Depletion of adenosine triphosphate during hypoglycemia promotes degradation of preformed adenosine monophosphate to inosine monophosphate and urate\textsuperscript{23} and is enhanced by glucagon secretion.\textsuperscript{22} An additional mechanism by which uric acid becomes elevated is a reduction in urate clearance owing to competition for tubular reabsorption by lactate\textsuperscript{29}; however, since Jeune et al observed that several patients had a normal or increased urate clearance, urate production may predominate.\textsuperscript{34}

\textbf{Platelets}

Corby et al\textsuperscript{9} found that the abnormality in platelet aggregation in GSD Type I is associated with impaired release of adenosine diphosphate (ADP) from platelets in response to added collagen and epinephrine. The same defect is associated with an increase in platelet cholesterol suggesting that the elevated serum cholesterol in GSD Type I may transfer to platelets causing increased cell membrane fluidity.\textsuperscript{8}

The generalized elevation in phospholipids described by Jakovčić et al\textsuperscript{32} is unlikely to contribute to a platelet defect since patients with primary defects in platelet function may have a relative decrease in phosphatidyl ethanolamine and an increase in phosphatidyl choline.\textsuperscript{58} However, abnormal proportions of platelet factor 3 phospholipids may be significant.\textsuperscript{94}

\textbf{Lipids}

Hyperlipidemia is a consistent feature of GSD Type I.\textsuperscript{22} Furthermore, Rosenfeld et al\textsuperscript{55} have recently described Type IIb and Type IV hyperlipidemia in Type I GSD patients and also indicated that the samples contained chylomicrons as well as abundant very low density lipoprotein (VLDL). In contrast, Type III GSD patients tended to have a Type IIb hyperlipidemia whereas Type VI and IX GSD patients have a Type IIa profile. In 1974,
Alaupovic et al reported high levels of apolipoprotein B in Type III compared with Type I patients in association with their hyperlipidemia. Also, elevated apolipoprotein C-III levels were consistent with hypertriglyceridemia which appeared to be prominent in Type I GSD. Low levels of apolipoproteins A-I and A-II were found in Type I GSD reflecting low high density lipoprotein (HDL) cholesterol levels. The combination of hypertriglyceridemia with low HDL cholesterol is indicative of a block in catabolism of triglyceride-rich VLDL as is found characteristically in Type V hyperlipidemia and would indicate that a defect in peripheral degradation of triglyceride-rich particles may exist.

Our studies on a child with Type I GSD treated with nocturnal intragastric infusion of Vivonex indicates that both apo C-III and triglyceride undergo parallel fluctuations over a six month observation period. During the same period increases in apo A-I and apo B corresponded with peak insulin responses. The data would suggest that apo C-III is being cosecreted with similar proportions of triglyceride and cholesterol which are assembled as lipoproteins in the Golgi apparatus, and that insulin regulates apo B and apo A-I secretion. (Apolipoproteins A-I, B and C-III were measured by electroimmunoassay, using methodology developed by Curry et al in our laboratory.)

Further information on hyperlipidemia in the glycogenoses is provided by Jako­vic et al. They studied eight cases with Type I and two cases with Type III GSD. Neutral lipid and phospholipid distribution in the density classes were assessed, and it was observed that in Type I GSD, all the lipids were increased in the density classes less than 1.019. Sphingomyelin remained normal in contrast to other phospholipids which were elevated in density classes less than 1.019. On the other hand, lysolecithin was increased mainly in the fraction greater than 1.063. The two Type III GSD patients were characterized by an elevation of the phospholipids in the 1.019 to 1.063 fraction. No specific conclusions were made other than the hyperlipidemia could arise from increased production of lipids. This may be accounted for by the increase of reduced nicotinamide-adenine dinucleotide (NADH) and nicotinamide-adenine dinucleotide phosphate hydrogenase (NADPH) as well as acetyl Co A owing to excessive glycolysis. An increased availability of glycerol, in addition to a fatty acid supply derived either from endogenous synthesis or peripheral mobilization, would both contribute to triglyceride synthesis. For example, the fatty acids would increase when hypoglycemia results in hormonal mobilization of stored fatty acids which is probably brought about mainly by norepinephrine, as in hypoglycemic diabetic subjects.

In contrast to Type I GSD, Clark et al observed that an inbred strain of rats with a deficiency of phosphorylase kinase have a low level of glucose-6-phosphate and low blood glucose. Fatty acid and cholesterol synthesis are consequently limited and VLDL, which arise mainly from the esterification of fatty acids, are low. Also, patients with phosphorylase or phosphorylase kinase deficiency have less profound hypoglycemia than Type I or III GSD. Therefore, lower lipid levels can be accounted for by less glucose being available for the glycolytic pathway and consequently less lipid production. There will be less peripheral fatty acid mobilization and also less secondary hypoinsulinemia which occurs when the blood sugar is chronically low.

Forget et al, based on previous work done by their group, postulated that decreased lipid clearance may account for the hyperlipidemia. They observed diminished triglyceride elimination rates and diminished post-heparin lipoprotein lipase activity five minutes after heparin indicating that low lipoprotein lipase ac-
tivity may account for the hyperlipidemia and this, in turn, may result from low insulin levels. After treatment of GSD Type I with nocturnal gastric drip feeding, Fernandes et al. reported that cholesterol levels tended to normalize but that triglyceride tended to remain elevated in six patients. In the same study, they found that lipoprotein lipase activity, although increased after therapy had commenced, remained low. This would concur with our experience after two months of therapy, which failed to reduce the triglyceride level and also with the study done by Lowe et al. This suggests that the defect in lipoprotein lipase activity may be transiently corrected but that an inherent defect remains, a phenomenon which could be due to prolonged hypoinsulinemia dating from birth.

Thus, more attention needs to be given to the hyperlipidemia of Type I and III GSD with a view to long term therapy directed more specifically to lipid lowering. More information on the relative importance of enhanced lipid production and decreased clearance could be gained by utilizing apolipoproteins as indices during therapy. The remaining secondary metabolic sequelae in GSD Type I, with the possible exception of hyperuricemia, are virtually normalized by continuous high carbohydrate feeding regimens and, therefore, assume less long-term significance.

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References


