

CLINICAL CASE SEMINAR

Prevention of Recurrent Pancreatitis in Familial Lipoprotein Lipase Deficiency with High-Dose Antioxidant Therapy

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ABSTRACT

We describe a dramatic response to antioxidant therapy in three patients with familial lipoprotein lipase deficiency complicated by frequent severe episodes of pancreatitis who had failed to respond to

other dietary and pharmacological measures. Antioxidant therapy may be an important advance in the management of this type of patient. (*J Clin Endocrinol Metab* 84: 1203–1205, 1999)

Lipoprotein lipase removes triglycerides from the circulating triglyceride-rich lipoproteins (chylomicrons and very-low-density lipoproteins) and is located on the capillary endothelium of tissues such as adipose tissue and skeletal and cardiac muscle. Familial lipoprotein lipase deficiency (FLLD) (1, 2) is an autosomal recessive disorder caused by mutation of the gene for lipoprotein lipase (3). Frequently, the disorder is associated with grossly elevated serum triglyceride levels, sometimes as high as 100 mmol/L. It is refractory to lipid-lowering drug therapy; and often, the only long-term means of treatment is the adoption of a diet that is low in all types of fat. Unfortunately, even with extremely restrictive diets (intended to contain as little as 10 g of fat each day), serum triglyceride levels are rarely maintained at values less than 20 mmol/L (2). Many patients with the disorder are prone to attacks of pancreatitis, and these are the source of considerable morbidity and premature mortality. We describe a novel approach to the prevention of pancreatitis using high-dose antioxidant therapy, which was highly effective in three patients with FLLD in whom attacks of pancreatitis were particularly frequent before the introduction of the new treatment.

Case Reports

In none of the three patients with FLLD, in this report, was lipoprotein lipase activity detectable in postheparin plasma, despite the demonstration of apolipoprotein CII (the circulating activator of lipoprotein lipase) in all three. The patients all had FLLD, complicated by pancreatic disease, and are a consecutive series treated with oral antioxidant therapy

(AOT), initially as selenium- β -carotene-C-E, two tablets three times daily (Wassen, Mole Park, UK), which provided α -tocopherol (270 IU/day), β -carotene (9000 IU/day), vitamin C (540 mg/day), and organic selenium (600 μ g/day), and a separate tablet of methionine (0.5 g qds; Evans, Chessington, UK) (4, 5). More recently Antox (Pharmanord, Morpeth, UK) has replaced this combination of supplements in similar doses (6). These maintain blood glutathione, plasma vitamin C and serum selenium levels towards the upper end of the reference range (4–6) and are pharmacological with respect to vitamin E and β -carotene (Table 1).

In none of the patients was there any discernible diminution in serum lipid levels after treatment (Table 2). None of the patients had diabetes mellitus, as defined by the World Health Organization, and none had an excessive alcohol intake.

Patient TS had been always ill as a child. Lipoprotein lipase deficiency was diagnosed when she was 6 yr old. At the age of 18, after diagnostic laparotomy for severe abdominal pain, pancreatitis was diagnosed, and she required intensive care support, followed by surgical drainage of a pseudocyst. She experienced a total of 93 attacks of pancreatitis in the next 10 yr (Fig. 1), such that she used opiate analgesia daily. Diet and bezafibrate were unsuccessful in controlling her hypertriglyceridemia. Small-duct diffuse noncalcific pancreatitis was diagnosed. Further surgery included cholecystectomy, partial pancreatectomy with splenectomy, and gastroenterostomy; and finally, total pancreatectomy was attempted but abandoned after 9 h. A percutaneous transhepatic cholangiogram showed intrahepatic duct dilatation, caused by biliary stricture. Other measures for pain control were tried without success (including high doses of pancreatic extracts, two celiac plexus blocks, and splanchnicectomy). No further surgery was possible; and at this stage, in 1995, she was referred to Manchester Royal Infirmary. Transjugular liver

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TABLE 1. Serum concentrations of vitamin C, selenium, vitamin E, and β -carotene and whole-blood concentration of glutathione of three patients (TS, BS and CW) with familial lipoprotein lipase deficiency before and after administration of antioxidant vitamins (Antox, 1 tablet four times daily) for 10 weeks

| | Units | Reference range | Patients before and after antioxidant therapy | | | | | |
|-------------------------|--------------------------------|-----------------|---|-------|--------|-------|--------|-------|
| | | | TS | | BS | | CW | |
| | | | Before | After | Before | After | Before | After |
| Serum vitamin C | $\mu\text{g/mL}$ | 4–20 | 14.5 | 18.3 | 14.6 | 19.7 | 10.4 | 20.4 |
| Serum selenium | $\mu\text{g/mL}$ | 83–152 | 47 | 161 | 66 | 127 | 80 | 142 |
| Whole blood glutathione | $\mu\text{mol/g Hb}$ | 7.5–12.2 | 7.2 | 12.4 | 5.7 | 8.6 | 7.5 | 8.5 |
| Serum vitamin E | mg/L | 5.7–14.9 | 43 | 256 | 70 | 134 | 28 | 141 |
| | $\text{mmol/mmol cholesterol}$ | 3.5–6.2 | 19.2 | 31.3 | 10.7 | 22.8 | 8.6 | 24.3 |
| Serum β -carotene | $\mu\text{g/L}$ | 19–254 | 53 | 1504 | 60 | 306 | 67 | 151 |

TABLE 2. Range and median values for serum triglycerides and cholesterol, before and after AOT, in three patients (TS, BS, CW) with familial lipoprotein lipase deficiency

| | TS | | BS | | CW | |
|-----------------------|----------------------------------|--------------------------------|----------------------------------|--------------------------------|----------------------------------|--------------------------------|
| | Triglycerides mmol/L | Cholesterol mmol/L | Triglycerides mmol/L | Cholesterol mmol/L | Triglycerides mmol/L | Cholesterol mmol/L |
| Range pre-AOT | 14.2–51.8 | 9.4–15.2 | 9.3–57 | 8.5–12.9 | 6.2–31 | 8–20 |
| Median value pre-AOT | 23.6 | 10.3 | 25.8 | 10.1 | 11.5 | 12.5 |
| Range post-AOT | 19.2–62 | 6–18.4 | 15–40.2 | 6.8–12.9 | 6.2–74.8 | 6.9–17.4 |
| Median value post-AOT | 27 | 10 | 23.6 | 10.1 | 19.4 | 13.5 |

All measurements were made every 3–4 months at outpatient visits, and samples taken during episodes of acute pancreatitis were excluded. For each patient, at least eight values were available before and after commencement of AOT. Reference range for serum triglycerides, 0.4–2.2 mmol/L; and for serum cholesterol, 3.0–6.5 mmol/L.

biopsy showed histological features of suppurative cholangitis, and paraaminobenzoic acid excretion index was reduced, at 0.78 (normal, >0.84), in keeping with moderately impaired pancreatic exocrine function. AOT was commenced in 1995 when she was 27 yr old. Since then, she has had only two mild episodes of pancreatitis, associated with acknowledged temporary noncompliance with AOT, and her liver alkaline phosphatase has decreased to 250 IU/L (upper limit of normal, 330 IU/L), from a pretreatment value of 2000–4000 IU/L (probably as the result of decreased inflammation of the head of her pancreas, previously causing biliary obstruction).

The initial diagnosis of FLLD was made in patient BS, after biopsy of eruptive xanthomata, at the age of 7 yr. She spent a significant part of her adolescent years in the hospital, with abdominal pain, despite a low-fat diet and inappropriate therapy with cholestyramine and later, more appropriately, with clofibrate. Laparotomy was subsequently carried out on two occasions. The second occasion was after severe abdominal pain and shock, after spontaneous vaginal delivery of a stillborn infant. Abruptio placenta and acute pancreatitis were confirmed, and acute renal failure complicated her recovery. She was referred to the Manchester Royal Infirmary in 1989. Despite intensification of diet and attempts at treatment with fibric acid derivatives and fish oil, she continued to have recurrent episodes of pancreatitis. AOT was commenced in 1993, when she was 41 yr old, and no further episodes of pancreatitis have occurred (Fig. 1).

Eruptive xanthomata in childhood were also an early feature of FLLD in patient CW. Dietary fat restriction and clofibrate were instituted at the age of 15 yr. Episodes of pancreatitis began in his late teenage years; and on average, he had 4–5 admissions per year (Fig. 1). A variety of lipid-lowering agents were tried (including fish-oil; bezafibrate;

and later, simvastatin), but his symptoms failed to abate, and he commenced AOT in 1991 at the age of 42 yr. He has had only three episodes of minor abdominal pain since commencing AOT.

Discussion

The reason for the susceptibility to acute pancreatitis in some patients with FLLD, and indeed in severe hypertriglyceridemia from other causes, is (at present) not adequately explained. There is no doubt, however, that patients of the type described here all too often succumb to complications of their pancreatitis, and this represents an enormous therapeutic challenge (2). Our treatment with AOT seemed to have a dramatic effect on the course of the disease in the patients reported in whom all other attempts at treatment by dietary restriction, drug therapy, or surgery had failed. Furthermore, the abolition of pancreatitis attacks after AOT, in the three patients in this report, occurred without any change in serum triglyceride concentration. Occasionally, in chronic pancreatitis, the frequency and severity of attacks can tail off as the result of bout after bout of inflammation, causing effacement of acinar tissue. However, the sudden and sustained reduction in attacks in all three patients argues against the disease naturally burning itself out in such a way in any of them.

The dose of antioxidants chosen was the result of earlier studies in recurrent pancreatitis from other causes and in animal models of acute pancreatitis (4–6). The rationale for this approach is supported by recent experimental studies suggesting that disruption of glutathione homeostasis, associated with a burst of free-radical activity, in pancreatic acinar cells, may be an initiating event in acute pancreatitis (7–9). Although the precise sequence of events leading to

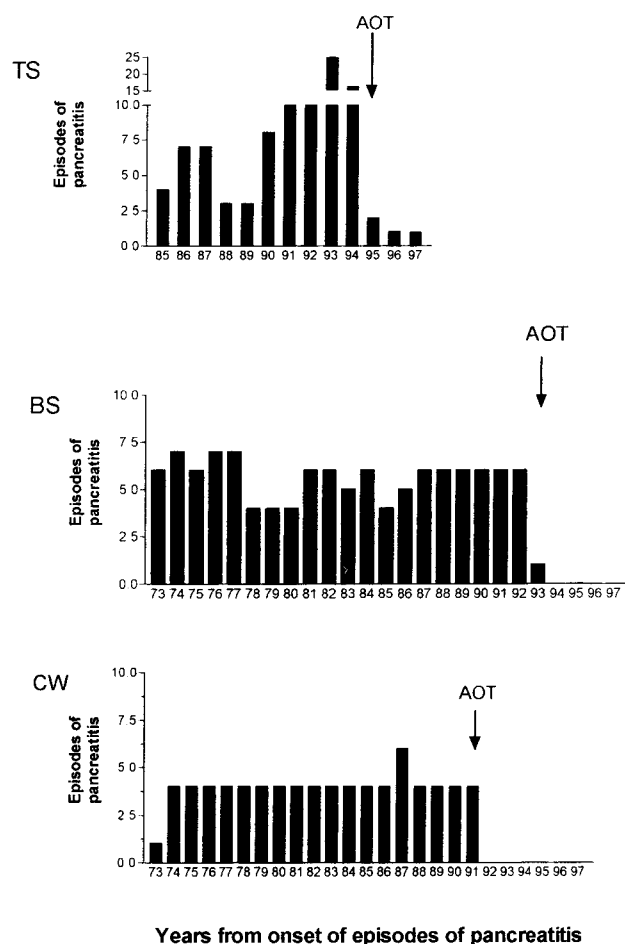


FIG. 1. The number of episodes of pancreatitis documented by hospital admissions each year in three patients before and after the introduction of antioxidant therapy (AOT).

pancreatitis in FLLD is not established, studies in the isolated perfused pancreas (10) lead us to speculate that heightened free-radical activity in patients with FLLD may relate to periods of pancreatic ischemia, resulting from a sluggish pancreatic microcirculation caused by high concentrations of chylomicrons. Under normal conditions, there is some leakage of lipase into the pancreatic microcirculation, but this is heightened by free-radical damage to acinar cells (8–10). Once lipase is present in the capillaries in FLLD, the abundant triglyceride substrate there will be rapidly hydrolyzed, and the resultant nonesterified fatty acids are intensely in-

flammatory. Chylomicrons and very-low-density lipoproteins are the source not only of proinflammatory nonesterified fatty acids from triglycerides (11) but also of polyunsaturated fatty acyl groups from triglycerides and phospholipids. These are, themselves, highly susceptible to free-radical attack, leading to lipid peroxidation with subsequent breakdown, to form cytotoxic lysolipids, aldehydes, and ketones (12). These will further intensify the inflammatory process, and their formation may be an additional stage in the process against which antioxidants can provide protection.

The safety profile of AOT is high, but caution is needed in patients with renal impairment (selenium is renally excreted) or a family history of organic psychoses (which may be precipitated by methionine) and in the presence of an iron storage disease [in which retention of iron in its ferrous (Fe^{II}) form could favor its participation in Fenton and other free-radical-generating reactions (13)]. We recommend interval monitoring of blood levels of glutathione, vitamin C, and selenium to ensure that optimal levels are obtained.

References

1. Brunzell JD. 1995 Familial lipoprotein lipase deficiency and other causes of the chylomicronemia syndrome. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *Metabolic and molecular basis of inherited disease*. 7th ed. New York: McGraw-Hill; 1913–1932.
2. Durrington PN. 1995 *Hyperlipidaemia. Diagnosis, management*. 2nd ed. Oxford: Butterworth Heinemann.
3. Lalonel J-H, Wilson DE, Luerius P-H. 1992 Lipoprotein lipase and hepatic triglyceride lipase: molecular and genetic aspects. *Curr Opin Lipidol*. 3:86–95.
4. Uden S, Bilton D, Nathan L, Hunt LP, Main C, Braganza JM. 1990 Antioxidant therapy for recurrent pancreatitis: placebo-controlled trial. *Aliment Pharmacol Ther* 4:357–371.
5. Uden S, Schofield D, Mitter PF, Day JP, Bothiglieri T, Braganza JM. 1992 Antioxidant therapy for recurrent pancreatitis: biochemical profiles in a placebo-controlled trial. *Aliment Pharmacol Ther* 6:229–240.
6. Schofield D, Rameh B, Leach FN, Braganza JM. 1997 Antioxidant profiles after three antioxidant regimens for ten weeks: implication for clinical trial design. *Digestion*. [Suppl 2] 58:26 (Abstract).
7. Guyan PM, Uden S, Braganza JM. 1990 Heightened free radical activity in pancreatitis. *Free Radic Biol Med* 8:347–354.
8. Braganza JM. 1996 The pathogenesis of chronic pancreatitis. *Q J Med*. 89:243–250.
9. Braganza JM, Chaloner C. 1995 Acute pancreatitis. *Curr Opin Anaesthesiol*. 8:126–131.
10. Sanfey H, Buckley GB, Cameron JC. 1984 The role of oxygen derived free radicals in the pathogenesis of acute pancreatitis. *Ann Surg*. 200:405–413.
11. Havel RJ. 1969 Pathogenesis, differentiation, and management of hypertriglyceridaemia. *Adv Intern Med*. 15:117–154.
12. Esterbauer H. 1995 The chemistry of oxidation of lipoproteins. Chapter 3. In: Rice-Evans C, Bruckdorfer KR, eds. *Oxidative stress, lipoproteins and cardiovascular dysfunction*. London: Portland Press; 55–79.
13. Sharer N, Taylor PM, Linnker BD, Gutteridge JMC, Braganza JM. 1995 Safe and successful use of vitamin C to treat painful calcific chronic pancreatitis despite iron overload from primary haemochromatosis. *Clin Drug Invest*. 10:310–315.