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Hyperlipidemia in childhood nephrotic syndrome

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Abstract. Hyperlipidemia is an important characteristic of nephrotic syndrome (NS). Elevation of plasma total cholesterol, or more specifically low-density lipoprotein cholesterol, is the major lipid abnormality in NS, although hypertriglyceridemia may develop as the disorder progresses. The pathophysiology of nephrotic hyperlipidemia is complex. The prevailing view is that both hepatic synthesis of lipids and of apolipoproteins is increased, and that the clearance of chylomicrons and very low-density lipoproteins is reduced. The precise contribution of increased lipogenesis and decreased lipid catabolism to hyperlipidemia, and their relationship to urinary protein loss, hypoalbuminemia and reduced serum oncotic pressure remain controversial. There are two potential risks of elevated plasma lipids: atherosclerosis and progression of glomerular injury. Although neither of these complications has been proved with certainty, there is growing evidence that both may be long-term consequences of NS. Therefore, the diagnosis and treatment of lipid abnormalities, important aspects of the management of nephrotic children, is summarized here to provide pediatric nephrologists with an informed choice.

Key words: Nephrotic syndrome – Hyperlipidemia – Atherosclerosis – Glomerulosclerosis

Introduction

Hyperlipidemia has been strongly implicated in cardiovascular disease and is now thought to play a role in renal disorders [1]. Whether the lipidemia affects the kidneys directly or indirectly, by causing ischemic heart disease, remains a major question. Berlyne and Mallick [1] demonstrated the increased incidence of ischemic heart disease in nephrotic subjects; however, this increased incidence has been disputed by others [2, 3]. The hyperlipidemia is thought also to be involved in cardiovascular diseases [4, 5] and in progressive glomerular damage leading to renal failure [6]. Both of these complications, and others, yet unknown, may prove to be long-term factors to be considered in childhood nephrotic syndrome (NS) which persists into adulthood.

The most common glomerular disorder in children is associated with NS. NS includes a large number of disorders which have in common the features of massive proteinuria, hypoalbuminemia, edema and hyperlipidemia. Proteinuria greater than 50 mg/kg body weight per day (3 g/1.73 m^2 body surface area per day) is the diagnosing factor.

Although proteinuria, hypoalbuminemia and edema are regularly seen, hyperlipidemia is not universally present, even in adults [7]. It is always present in MCNS, with 95% of children having serum cholesterol greater than 250 mg/dl. In other types, e. g., membranoproliferative glomerulonephritis, only 68% of children had cholesterol at these concentrations [8].

The pathology of nephrotic hyperlipidemia is complex and probably multifactorial. It is believed that increased hepatic synthesis and decreased clearance of circulating lipoproteins contribute to the hyperlipidemia of NS [7, 9]. More work needs to be done, however, to define the cause. Appel et al. [10] consider that the increased hepatic lipogenesis may, in some way, be due to changes in serum albumin concentrations or plasma oncotic pressure; a change in viscosity at the level of the hepatic sinusoids could send a signal. The loss of urinary proteins, including lipoproteins or some other liporegulatory substance, could also trigger the hepatic synthesis of lipids.

Lipid metabolism

A brief description of lipid synthesis and metabolism is presented for background. Plasma cholesterol is derived

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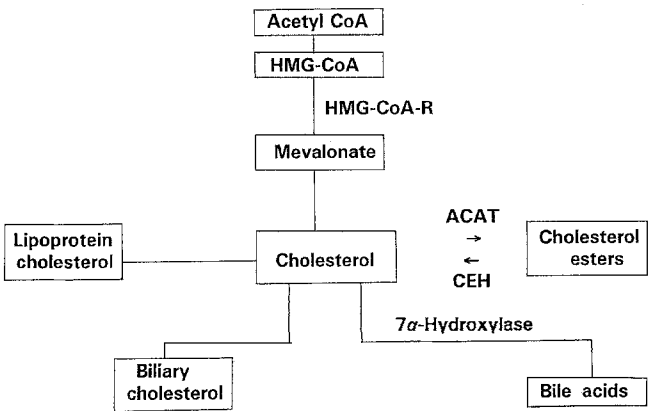

Fig. 1. The cholesterol biosynthesis pathway, redrawn and modified from Pandak et al. [95]. *HMG-CoA*, 3-Hydroxy-3-methylglutaryl coenzyme A reductase; *ACAT*, acetylco A transferase; *CEH*, cholesterol ester hydrolase

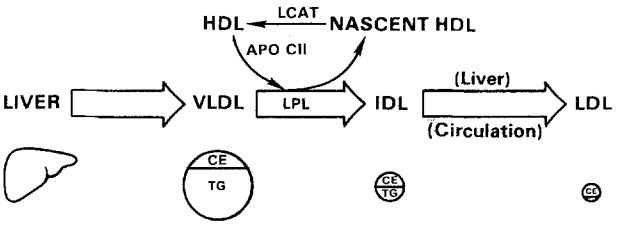

Fig. 2. Metabolic pathway of lipoprotein metabolism. *HDL*, High-density lipoprotein; *LCAT*, lecithin-cholesterol acyltransferase; *APO CII*, apoprotein CII; *VLDL*, very low-density lipoproteins; *LPL*, lipoprotein lipase; *IDL*, intermediate-density lipoproteins; *LDL*, low-density lipoprotein; *CE*, cholesterol esters; *TG*, triglycerides; with permission from Bernard [96]

from three sources: it is synthesized by the liver and the intestinal mucosa and ingested in the diet. The concentration of plasma cholesterol is maintained by a balance of input (as described above) and output, which is achieved by secretion into the bile and further excretion of free biliary cholesterol and bile acids formed from cholesterol into the feces. The liver is the main site of cholesterol synthesis, with the conversion of acetate to mevalonic acid to cholesterol (Fig. 1). The enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase) is the rate-limiting factor [11] which catalyzes production of mevalonic acid, the precursor of cholesterol. Of the cholesterol formed, 70%–80% is quickly converted to cholesterol esters through the action of lecithin-cholesterol acyltransferase (LCAT), and transported to the circulation by the lipoproteins. The remainder is excreted into the bile with subsequent excretion in the feces. Hypercholesterolemia can result from increased synthesis, impaired output or both.

Triglycerides are synthesized by the liver and the intestines from fatty acids and enter the circulation by way of lipoproteins (Fig. 2). At the cellular level, the enzyme lipoprotein lipase (LPL) converts the triglyceride-lipoprotein complex to energy. The free fatty acids produced by hydrolysis of triglycerides are utilized by the body in adipose tissue, muscle cell oxidation or stored. Hypertriglyceridemia can result from overproduction or impaired catabolism.

The major lipoproteins which transport cholesterol esters and triglycerides can be divided into four classes according to their density: chylomicrons, very low-density lipoproteins (VLDL), low-density lipoproteins (LDL) and high-density lipoproteins (HDL). The lipoproteins have a hydrophobic core consisting of triglycerides, cholesterol esters, or both, a surface coat of phospholipids and free cholesterol with specific apoproteins (A, B, C and E) embedded in the coat. These apoproteins target the particle to specific pathways [6, 12].

VLDL are synthesized by the liver and serve primarily to transport triglycerides from the liver to peripheral tissues. However, VLDL are also the major precursor of LDL, being converted to LDL through the enzymatic action of LPL. LDL transport cholesterol from the liver to extrahepatic tissues. High concentrations are associated with an increased risk of cardiovascular disease and death.

HDL are synthesized in the liver and transport primarily free cholesterol, phospholipids and apoproteins. Cholesterol esters are formed from HDL by the action of LCAT. The major function of HDL is thought to be the transporting of cholesterol from peripheral tissues back to the liver. A high concentration of HDL is believed to be protective against atherosclerosis, because it removes the cholesterol from tissues, including arterial walls. The lipoproteins can be removed from the circulation by binding to specific cell surface receptors in the liver.

Lipid abnormalities in NS

Various facets of lipid metabolism may be affected in NS. The severity of the proteinuria and the degree of residual renal function contribute to the hyperlipidemia [8]. In addition to renal pathology, other factors may influence the concentrations of lipoproteins, including age, nutritional status, obesity and treatment with corticosteroids, diuretics or β-blocking drugs.

Nephrotic subjects regularly have elevated total and LDL cholesterol (Fig. 3). Patients with severe proteinuria or hypoalbuminemia will have increased triglycerides with VLDL cholesterol [13, 14]. Quantitative differences in the lipoprotein fractions of nephrotic patients may vary [15]. Cholesterol/triglyceride ratios and cholesterol, cholesterol esters and phospholipids/protein ratios are increased in each lipoprotein fraction [15]. Plasma apoprotein abnormalities are present: apo B (the VLDL and LDL component) is elevated [8]. Apo C11 is elevated in the plasma [16], even though there is renal loss. This co-factor is necessary for the activity of LPL (Fig. 2). Serum apo CIII, the competitive inhibitor of apo CII, is increased in nephrotic patients. LPL activity is inhibited by an increase in the apo CIII/apo CII ratio [9].

HDL, shown to be cardioprotective, have been reported as high [17, 18], normal [16, 19, 20] or low [13, 15, 21]. Sokolovskaya and Nikiforova [22] clarified the picture to some degree by showing the HDL cholesterol concentrations were low in untreated nephrotics, normal in patients treated with non-steroidal drugs and high in patients treated with steroids. The distribution of HDL subtypes was ab-

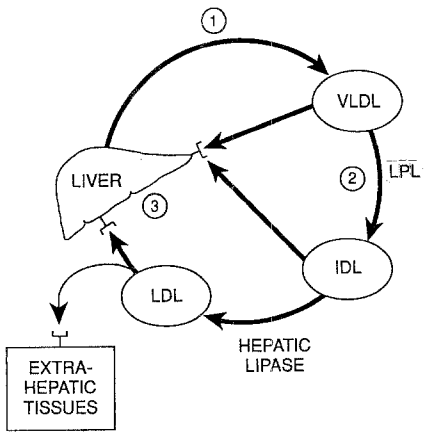

Fig. 3. Mechanisms of hyperlipidemia in nephrotic syndrome. 1. Overproduction of VLDL. 2. Defective lipolysis. 3. Decreased LDL receptor activity. Redrawn with modifications from Wheeler et al. [7]

normal, with subtype HDL3 slightly elevated and HDL2 very low. This latter subtype aids in preventing atherosclerosis. An abnormal distribution of omega-6 fatty acids has also been seen in some nephrotic children [8]. The arachidonic acid in plasma phospholipids and the linoleic acid in triglycerides of subcutaneous adipose tissue were elevated compared with an age-matched group of healthy children [8].

Hyperlipidemia does not always persist in the NS. Sometimes it is transient and can be correlated with the disease activity; other times, it persists indefinitely [8]. Even if the patient enters remission, the elevated lipids may persist. Zilleruelo et al. [23] showed that 24 of 51 children with MCNS in remission continued to have elevated cholesterol, triglycerides, LDL and VLDL. However, high total cholesterol concentrations were also seen in patients with longer and more frequent relapses.

Pathophysiology

Three causes of hyperlipidemia in nephrosis have been postulated (Fig. 3): (1) increased hepatic synthesis of cholesterol, triglycerides and lipoproteins; (2) decreased post-hepatic LPL activity leading to diminished conversion of LDL to HDL; (3) decreased LDL receptor activity and increased urinary loss of HDL causing disturbed lipoprotein metabolism. Each of these will be considered in detail.

Increased cholesterol synthesis has been shown in nephrosis in man and in rats [24, 28]. The hypoalbuminemia common to both species in nephrosis may explain the increased synthesis of lipoproteins, but cannot account for increased synthesis of cholesterol. Both liver and intestinal (from diet) synthesis of cholesterol depends on the HMG-CoA reductase activity for the conversion of acetyl CoA to cholesterol. This is a rate-limiting step. Gopler et al. [26] suggested that impaired mevalonate metabolism by the kidney could enhance cholesterol by increasing available mevalonate, the precursor to cholesterol. Experimental nephrosis produced by puromycin aminonucleoside [26], a nephrotoxin [29], has been shown to increase HMG-CoA reductase activity in the liver. We, however, have noted that at late stages of severe experimental nephrosis, there is decreased activity of HMG-CoA reductase measured at the apex of its diurnal cycle [30]. There was no increase in serum cholesterol, which may be due to a marked elevation of cholesterol ester hydrolase [31] with consequent excretion in the bile. Marsh and Drabkin [27] further showed an increase in in vivo and in vitro hepatic cholesterol synthesis 48 h after nephrosis was induced, but decreased hepatic synthesis 5–7 days later. The issue of increased hepatic synthesis of cholesterol in nephrosis has not been resolved.

The overproduction of hepatic lipoproteins may also play a role [24]. Marsh and Drabkin [24] suggested that increased lipoprotein production results from hypoalbuminemia which acts as a signal to increase synthesis. The mechanism for this is not yet understood. A fall in plasma oncotic pressure has also been implicated. Kaysen et al. [32], however, believe that plasma cholesterol concentrations are independent of albumin synthesis but depend on the renal clearance of this protein. Since increased plasma concentration depends not only on production but also on excretion, it has been hypothesized by several investigators [33–35] that there is a reduction in excretion due to the large size of the lipoprotein molecule, leading to increased plasma concentration of the lipoprotein.

Regardless of the cause of increased hepatic synthesis, the net result is an increased influx of VLDL into the circulation [24, 33, 36]. The triglycerides of VLDL are quickly hydrolyzed by LPL and hepatic triglyceride lipase with the increased formation of LDL [6]. With progression of nephrosis, some patients develop hypertriglyceridemia, possibly because of increased synthesis of VLDL triglycerides with defective lipolysis of this protein. Increased LDL might result from decreased catabolism, possibly due to reduced LDL receptor activity with a defective ligand receptor interaction [37, 38].

If there is decreased post-hepatic LPL activity, there is decreased conversion of VLDL to LDL. It has been shown that there is defective catabolism of lipoproteins in NS, with a reduction in clearance of chylomicrons and VLDL triglycerides [39, 40]. Garber et al. [39] postulated a decrease in LPL activity. This has been shown by two groups [41, 42]; however, other investigators [43, 44] have failed to show this reduction in activity.

An enzyme important in maturation of the HDL particle, LCAT, is reduced in nephrosis [21]. This reduction could result in reduced HDL3 to HDL2 conversion. The latter is necessary for transport and recycling of the LPL co-factor, apo CII to chylomicrons and VLDL triglyceride. Furukawa et al. [45] suggested the defect in lipoprotein catabolism is a direct result of abnormal lipoprotein composition. Thus, the resistance of VLDL to lipolysis may be due to its abnormal composition rather than decreased activity of LPL.

Decreased LDL receptor activity and urinary loss of HDL has been suggested as a cause of defective metabolism of lipoproteins leading to increased serum concentrations. Studies investigating the urinary loss of possible liporegulatory substances, e.g., apo CII, HDL, LCAT or heparan sulfate [9, 32, 46, 48], isolated from urine of

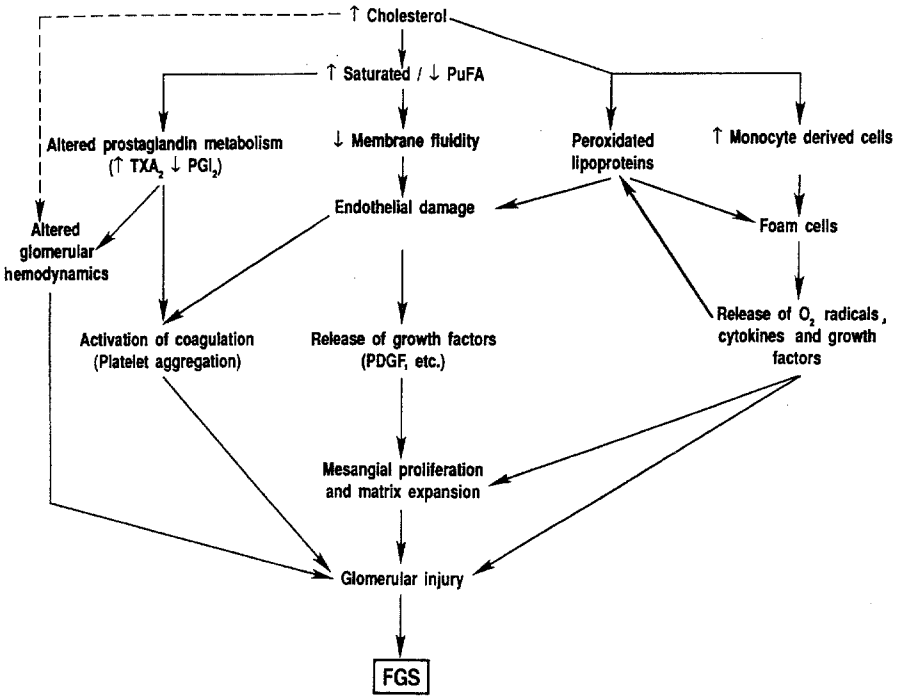

Fig. 4. Diagram of events thought to play a role in cholesterol-induced glomerular injury. *PuFA*, Polyunsaturated fatty acids; *TXA_2*, thromboxane A_2; *PGI_2*, prostaglandin I_2; *PDGF*, platelet-derived growth factor; *FGS*, focal gomerulosclerosis. With permission from Schmitz et al. [56]

nephrotic patients or animals with experimentally induced nephrosis, failed to show a causal relationship with hyperlipidemia.

Complications of hyperlipidemia

Although hyperlipidemia in nephrotic disease has been reported over many years, its clinical significance has not been defined [31, 49]. High plasma lipids confer at least two potential risks. First, elevated plasma cholesterol concentrations are causally associated with atherosclerosis, which in many cases leads to cardiovascular disease. Secondly, there is a strong possibility that lipid deposits could form in the renal glomerulus and ultimately cause renal failure. The data to support both possibilities are being accumulated but, so far, do not prove the hypotheses [31, 50].

Nephrotic hyperlipidemia and cardiovascular disease

Atherosclerosis in the general population is usually associated with increases in total and LDL cholesterol with low concentrations of HDL. High concentrations of HDL are considered cardioprotective. The cardiovascular disease in NS is believed to be the result of the hyperlipidemia. These patients, however, also have hypertension, hypercoagulability and other risk factors which could contribute to the development of the cardiovascular disease.

Atherosclerosis usually develops over a life-time (30–50 years); few nephrotic patients have been followed for that long. The duration of the hyperlipidemia could be a contributing factor. Many patients go into remission and the elevated plasma lipid concentrations decline. Few well-executed clinical studies on atherosclerotic risk factors have been reported [1–3]. Some studies are primarily an accumulation of case histories and anecdotal records [50–52] with no control of the known atherosclerotic risk factors such as hypertension, smoking, steroid therapy, etc. Some include a range of renal etiologies with a preponderance of patients with MCNS who respond readily to treatment.

In 1979 Wass et al. [3] reported a large study of 159 adult patients with NS followed over a period of 5 years; a control group was studied simultaneously. They concluded that there was no increased risk of ischemic heart disease, angina or other arteriosclerotic complications in this population. Renal failure was the stated cause of death of the nephrotic patients. Consequently, the cardiovascular state was not evaluated as the renal disease was predominant.

Hyperlipidemic glomerular injury

Recent studies have suggested that hyperlipidemia is a factor contributing to the progression of the initial glomerular injury in NS (Fig. 4) [53–59]. Increased cholesterolemia could lead to focal glomerulosclerosis through several pathways: (1) altered prostaglandin metabolism (with increased thromboxanes and decreased prostacyclin) could alter the viscosity of the blood which in turn could produce altered glomerular hemodynamics with increased platelet activation leading to glomerular injury; (2) an increased ratio of saturated fatty acids to unsaturated fatty acids would decrease membrane fluidity causing endothelial damage with release of platelet-derived growth factors leading to mesangial proliferation and matrix expansion; (3) the increase in peroxidated lipoproteins causes

release of free radicals, cytokines and growth factors which could result in glomerular injury. Most of the data come from animal studies where the pathology is easily examined.

The pathology includes increased mesangial matrix and cellularity, lipid-laden "foam cells" and infiltration of the glomerulus by macrophages and monocytes, a condition closely resembling arteriosclerosis. Certain studies [56, 60, 61] suggest that the glomerulus is subjected to high concentrations of atherogenic lipids. Large LDL particles are not totally filtered where small HDL particles are readily excreted in the urine [62, 63]. High concentrations of LDL have been shown to be toxic to mesangial cells [64]. In addition, since lipid-lowering agents [65–68] show beneficial effects on the glomerular injuries in experimental rats, a causal effect of the hyperlipidemia is implicated. Further studies are needed to define the roles of the atherogenic agents in causing glomerular damage.

Treatment of nephrotic hyperlipidemia

In general, the adverse effects can be altered when the hyperlipidemia is corrected, either by diet, lipid-lowering drugs or a combination of both. In experimental NS, animal models [69–71] show that diet and drugs can slow the development of glomerulosclerosis. In patients with coronary heart disease, the correction of the hyperlipidemia frequently leads to a decreased incidence of the progression and severity of atherosclerotic diseases [72, 73].

Dietary therapy

Dietary therapy should be instigated early in the event of hyperlipidemia. The total nutritional needs of the patient must be evaluated and corrected as necessary. The nutritionist must consider the ability of the patient to be taught and to comply with the required diet. Under optimal circumstances, dietary therapy is the most physiological approach and is necessary even if lipid-lowering agents are to be added. In the cases of severe hypercholesterolemia with NS, dietary therapy alone may not be effective [74]. There are few studies using diet alone which have tested the effect on the hyperlipidemia of NS [74, 75].

Extremely low fact diets can accentuate hypertriglyceridemia while lowering the serum cholesterol [6]. Therefore, fat intakes of 30% of total calories, with a lowering of saturated fatty acids to 10% and dietary cholesterol to less than 300 mg/day is recommended [6, 74]. Omega 3-fatty acids from cold water fish [76] lower lipids in serum but there is not sufficient evidence to prescribe them clinically.

Pharmacological treatment

While nephrologists treat the hyperlipidemia of NS pharmacologically, there have been few studies to systemically test the efficacy of this treatment. The medications used are: bile acid-binding resins, probucol, fibric acids, HMG-CoA reductase inhibition and nicotinic acid. They work by different mechanisms.

Bile acid sequestrants. Bile acid sequestrants (cholestyramine and colestipol) are non-absorbable resins with quarternary amine groups that bind bile acids. By sequestering bile acids in the intestine, they interfere with enterohepatic circulation [77], which enhances conversion of cholesterol to bile acids, reduces hepatic cholesterol content and enhances synthesis of LDL receptors [78] with a fall in plasma LDL cholesterol. According to Valeri et al. [79], 15–25 g/day of colestipol produced a 32% decrease in LDL cholesterol in seven patients with hypercholesterolemia of NS. Rabelink et al. [80] showed a lowering of LDL cholesterol in NS by 19% with 8 g of cholestyramine taken twice daily. Because LDL cholesterol concentration remained rather high in both studies, the bile acid sequestrants are not recommended when used alone.

Probucol is an antioxidant which inhibits the oxidation of LDL and thus promotes the clearance of LDL from the circulation. While it causes a moderate reduction of LDL cholesterol [81], it also reduces HDL cholesterol concentrations [82]. A recent theory of atherogenesis implicates oxidized LDL in the uptake of LDL cholesterol by arterial wall cells [83]. Probucol may protect against atherosclerosis by inhibiting the oxidation of LDL. Nephrotic patients with hypercholesterolemia have been treated effectively by this agent without serious side effects [84]. However, its use in children has yet to be studied.

Fibric acids. Clofibrate is the most common fibric acid used to treat hyperlipidemia. It acts by inhibiting secretion of and promoting metabolism of VLDL triglycerides with an increase in HDL cholesterol concentration. The fibric acids have many adverse side effects such as myopathy, gallstones and gastrointestinal distress. They are not recommended in treating the hyperlipidemic nephrotic patient [6, 85].

HMG-CoA reductase inhibitors act by inhibiting the rate-limiting enzyme in cholesterol biosynthesis with enhanced formation of LDL receptors [86–88]. The receptors recognize all apo B-containing lipoproteins, thereby promoting direct hepatic clearance of VLDL and LDL with a lowering of plasma LDL cholesterol and VLDL triglycerides. Both lovastating and simvastating reduce total and LDL cholesterol (27%–45%), but do not affect HDL cholesterol. Although the lipid concentrations are lowered, they are not normalized [89, 74, 76].

There are occasionally side effects, including gastrointestinal complaints, an increase in liver enzymes and insomnia. Myopathy is also an uncommon complication. The long-term safety of these agents is not documented for nephrotic patients.

Nicotinic acid. The mechanism of action of nicotinic acid in lowering lipids is not known. However, it is an effective LDL-lowering drug [90]. It also reduces VLDL triglycerides, increases HDL cholesterol and inhibits the secretion

of apo B-containing lipoproteins by the liver. The side effects include gastrointestinal distress, hepatic dysfunction increase in uric acid concentration and glucose intolerance. There are no reports in the literature for its use in NS.

Conclusions

Although combinations of agents have been tried for lowering lipids in primary dyslipidemia, with success, the dual approach has not been tried in NS hyperlipidemia. Fibric acids and nicotinic acid are not recommended in NS. The combination of bile acid sequestrants and HMG-CoA reductase inhibitors has been successful [91, 92]. Probucol can be used, together with reductase inhibitors, and may be particularly useful in nephrotic patients where LDL concentrations cannot be normalized with other agents. The majority of these medications are inadequate for use in childhood NS. Even in adults, these medications would be initiated only with caution, because the lipoprotein pattern in NS usually does not constitute a major risk factor for coronary heart disease and especially in view of the rapid reversal of hyperlipidemia with remission of the NS [93]. The recognition of the association of atherosclerosis with NS in adult patients [94] is leading to more advocates for treatment.

The problem of treating the hyperlipidemia of the nephrotic child still remains unsolved. Frequently, as in adult patients, the hyperlipidemia disappears with remission of the childhood nephrosis. Those, however, who have persistent hyperlipidemia should be educated to maintain an adequate weight for their height and age with regular aerobic exercise [8] and diet. Diet should contain less than 250 mg/day of total cholesterol, no more than 30% of fat and a ratio of 1:1 of polyunsaturated to saturated fatty acids. It is premature to recommend fish oil supplementations because the beneficial effects of omega-3 fatty acids are still being evaluated [8, 76]. Any medication that increases lipids should be discontinued. In rare instances, a bile acid sequestrant, such as cholestyramine, could be given in doses modified for standard body weight and surface area.

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Literature abstracts

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Creatinine related reference ranges for urinary homovanillic acid and vanillylmandelic acid at 6 months of age

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The relationship between homovanillic acid (HVA), vanillylmandelic acid (VMA), and creatinine in the urine of 6 month old babies has been studied and reference ranges in the form of centiles constructed for HVA and VMA against creatinine. Over 10000 urine samples were collected from babies in four health districts in the north of England. HVA and VMA concentration, either independently or when divided by creatinine concentration, were dependent upon the absolute concentration of creatinine in the sample. After adjustment for creatinine significant differences in the mean concentration of HVA were found between sexes. No such differences were found for VMA. HVA and VMA were also found to be age dependent.

Centiles were constructed using a procedure which makes no distributional assumptions about the data. The net effect of utilising these centiles was to increase the predictive value of a positive screening test from 20% to 40% without any increase in the false negative rate.

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Fetal vesicoureteral reflux: outcome following conservative postnatal management

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Of 222 infants with a urinary tract abnormality detected antenatally 30 male and 9 female patients (64 renal units) were found to have primary vesicoureteral reflux. Grade of reflux was predominantly severe, with grade III or higher noted in 83% of the patients. Prenatal and postnatal ultrasound failed to detect any abnormality in 29 refluxing units (45%) discovered contralateral to the known abnormal system, although 19 had grade III or higher reflux. Of the 64 refluxing units 8 underwent primary ureteral reimplantation, 12 were lost to follow-up and 44 were managed conservatively for a mean of 3.3 years. Reflux ceased in 61% of the cases, improved in 14% and remained unchanged in 23%. In only 1 unit did the grade of reflux increase. Documented urinary tract infection occurred in 6 of the 39 reflux patiens. Dimercaptosuccinic acid renography performed in 21 infection-free patients demonstrated global reduction in renal parenchyma in 4 units, focal parenchymal defects in 3 and normal function in 14. Conservative postnatal management of fetal vesicoureteral reflux is justified. Global and focal parenchymal changes can occur in the kidneys of infants with reflux despite the absence of urinary tract infection.