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Hyperlipidaemia, diet and simvastatin therapy in steroid-resistant nephrotic syndrome of childhood

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Abstract. In children with steroid-resistant nephrotic syndrome (SRNS) hyperlipidaemia may in the long term be associated with progressive renal insufficiency and increased risk of coronary heart disease. We have assessed the efficacy and tolerability of diet prior to and in combination with a hydroxymethylglutaryl CoA reductase inhibitor, simvastatin, in seven children with SRNS with a mean age of 8 years (range 1.8–16.3 years). Dietary advice to maintain adequate energy and protein intakes with reduced saturated fat and cholesterol intake had little impact on lipid levels pre treatment (mean reduction in cholesterol 1 mmol/l, triglyceride 1.1 mmol/l) but was maintained throughout the study duration. The mean cholesterol and triglyceride concentrations pre treatment were 12.1 ± 2 (SEM) mmol/l and 8 ± 2.1 (SEM) mmol/l, respectively. On a median simvastatin dose of 10 mg/day (range 5–40 mg) there was a 41% reduction in cholesterol to 6.6 ± 0.77 (SEM) mmol/l and a 44% reduction in triglyceride to 3.9 ± 1.38 (SEM) mmol/l at 6 months which was sustained at 12 months in five patients. The drug was well tolerated with no clinical side effects being noted. Over 6 months the mean plasma albumin concentrations increased from 18.2 ± 1.26 (SEM) g/l to 23 ± 2.51 (SEM) g/l, accounted for by three patients (1 complete remission, 1 partial remission, 1 end-stage renal failure). Plasma creatinine concentrations remained stable in five patients with two having progressive chronic renal failure. Growth parameters for both weight and height were maintained. Simvastatin has a beneficial effect on abnormal lipid levels in SRNS but the effectiveness of long-term therapy needs to be evaluated.

Key words: Hyperlipidaemia – Nephrotic syndrome – Steroid resistant – Diet – Drug therapy

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Introduction

Hyperlipidaemia is a well-recognised association of nephrotic syndrome, although the precise disturbances of lipid metabolism which initiate and maintain the hyperlipidaemia are still unclear [1]. Healthy eating dietary advice is advocated in steroid-responsive nephrotic syndrome where the hyperlipidaemia usually resolves as proteinuria abates [2, 3]. However, children with steroid-resistant nephrotic syndrome (SRNS) and persistent hypoalbuminaemia may have hyperlipidaemia for many years. This could contribute to an increased risk of coronary artery disease in adulthood and experimental data suggest it could hasten the progression of renal failure [4, 5].

With the availability of the hydroxymethylglutaryl CoA (HMG CoA) reductase inhibitors there has been a new therapeutic option in the treatment of hyperlipidaemia. Preliminary studies have shown favourable results in the management of children with hypercholesterolaemia [6, 7]. No studies to date have been reported in childhood nephrotic syndrome. We report our findings on dietary therapy followed by the use of the HMG CoA reductase inhibitor, simvastatin, to treat hyperlipidaemia in children with SRNS.

Patients and methods

Between November 1989 and February 1994, seven children (4 female) with SRNS and hyperlipidaemia were studied. Patient details are shown in Table 1. Simvastatin was commenced at a mean age of 8 years (range 1.8–16.3 years). The initial dose in all patients was 5 mg once daily in the evenings, but was increased in most patients in an attempt to reduce cholesterol concentrations to within the normal reference range. Simvastatin was administered on a named patient basis after explanation to and verbal consent from the parents. None of the patients received high-dose methylprednisolone or cyclosporin for treatment of their nephrotic syndrome prior to or during simvastatin therapy.

Patient assessment included 1- to 3-monthly clinic visits with measurements of height, weight, blood pressure and urine protein/creatinine ratios. Fasting cholesterol and triglyceride concentrations

Table 1. Patient details

Patient no.	Sex	Age (years) at start of treatment	Diagnosis	Max. dose of simvastatin (mg)	Duration of treatment (months)	Weight at start (kg)	Height at start (cm)	Nutritional/ micronutrient supplements	Other medications
1	M	1.8	FSGS	10	22	10.0	73.2	K, S, NP	A, Sp
2	M	4.4	HSP	10	31	22.7	108.3	K	P, Sp, N, Fr
3	M	4.7	MCNS	5	6	16.2	103.9	K, S	P, Sp
4	F	5.4	FSGS	40	25	17.6	95.1	K	Sp, E
5	F	11.2	MCGN type I	10	51	33.6	141.3	–	–
6	F	12.3	FSGS	10	35	37.4	151	–	Sp, Fr
7	F	16.3	FSGS	10	7	43.5	153	F	Sp, Fr, E

FSGS, Focal segmental glomerulosclerosis; HSP, Henoch-Schonlein purpura nephritis; MCGN, mesangiocapillary glomerulonephritis; MCNS, minimal change nephrotic syndrome; K, Ketovite (tablets); S, Sytron; F, Forceval (adult capsule); NP, Nutrison Paediatric; P, prednisolone; S, spironolactone; N, nifedipine; F, frusemide; A, atenolol; E, enalapril

were determined by standard enzymatic methods along with renal and liver function tests and creatinine phosphokinase (CPK) activity.

Dietary modification was commenced at a median time of 8 months (range 2–38 months) prior to simvastatin therapy. Each patient received an individual dietary prescription to ensure a nutritionally adequate and balanced diet [8] prior to and throughout treatment, with a recommended intake for energy, vitamins and minerals in accordance with Dietary Reference Values for food, energy and nutrients (DRV, 1991) [9] for chronological age. Protein intake was prescribed between 1 and 2 g/kg body weight per day (10%–15% of total energy). Dietary fat was modified to decrease the intake of saturated fatty acids and cholesterol and was replaced with mono- or polyunsaturated fats and oils where practical. Total fat intake was reduced when necessary to achieve approximately 35% of the total energy intake or what was considered realistic for each child and family. Three patients (patients 1, 6 and 7) were vegetarian. Complex carbohydrates including non-starch polysaccharides (NSP, dietary fibre) to maintain an energy of 45%–50% of the total energy intake were encouraged, with advice to reduce refined carbohydrate (non-milk extrinsic sugars) intake where possible, but not so to compromise on overall energy intake. A "no added salt" diet was recommended, ensuring that the diet was also adequate in all micronutrients. Nutritional and micronutrient supplements were prescribed as detailed in Table 1.

Dietary analysis. Three-day dietary records (including 1 weekend day) were completed by the parents during the study period. Analysis of the diets was carried out using standard food composition tables [10] with the aid of a computer-based programme (Microdiet, Universityof Salford, UK).

Statistical analysis. Differences in the serum lipid and albumin concentrations measured at baseline, on diet alone and on simvastatin at 2-, 6- and 12-monthly intervals were analysed with Friedman's chi-squared and Wilcoxon signed rank tests for individual group comparisons (with Bonferroni correction).

Results

No clinical side effects were noted while on simvastatin therapy. The median dose of simvastatin used in the seven patients was 10 mg/day, with one patient (patient 4) showing no response to 40 mg/day despite checks on compliance. Two children had transient increases in CPK levels above the normal range, but therapy was not altered and CPK levels returned to normal.

The mean serum cholesterol concentration at baseline was 12.1±2 (SEM) mmol/l (normal range 3.6–6.7 mmol/l). Dietary modification reduced serum cholesterol concentrations by a mean of 1 mmol/l (8.3%). Following simvastatin therapy there was a 30% (3.3 mmol/l) fall in cholesterol concentrations ($P < 0.05$) within the first 2 months of treatment (Fig. 1). The total decrease in cholesterol at 6 months on simvastatin therapy was 41% ($P < 0.05$), with the mean cholesterol concentrations after 12 months of treatment in five patients being 6.8±1.22 (SEM) mmol/l.

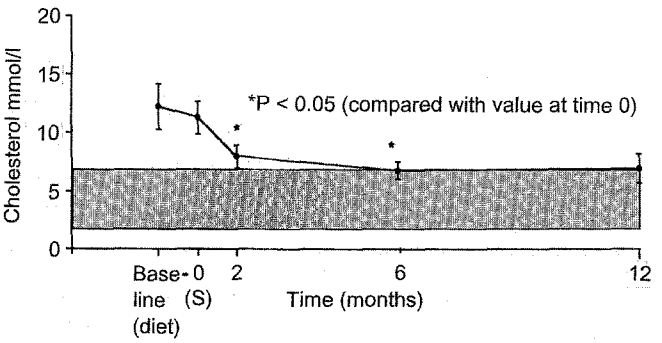

Fig. 1. Mean serum cholesterol concentration following simvastatin (*S*) treatment. ▒, Normal reference range

The mean serum triglyceride concentration at baseline was 8±2.1 (SEM) mmol/l (normal range 0.3–2.1 mmol/l). Dietary therapy reduced serum triglyceride concentrations by a mean of 1.1 mmol/l (13.8%). Following simvastain therapy the mean serum triglyceride concentrations decreased by 2.5 mmol/l (36%, P = NS) within the first 2 months, with a total decrease of 44% at 6 months. By 12 months the mean serum triglyceride concentration in five patients was 4.4±1.23 (SEM) mmol/l (Fig. 2).

Figure 3 shows an increase in mean serum albumin concentrations from 18.2±1.26 (SEM) g/l at baseline to 23±2.51 g/l at 6 months. This increase was accounted for by a rise in serum albumin concentration in patient 3 who developed delayed complete remission, patient 6 who showed partial remission of her nephrotic state and patient 2 who developed end-stage renal failure. The mean creatinine concentration for the seven children was 63 μmol/l (range 21–114 μmol/l) at baseline and 81 μmol/l (range 21–154 μmol/l) at 6 months post treatment. Patient 2 with Henoch-Schönlein purpura nephritis developed end-stage renal disease at 12 months. The mean early morning urine protein/creatinine ratio at baseline was 2,095 mg/mmol (range 710–4,750 mg/mmol) and 2,160 mg/mmol (range 284–4,121 mg/mmol) in five patients at 12 months (excluding patients 2 and 3).

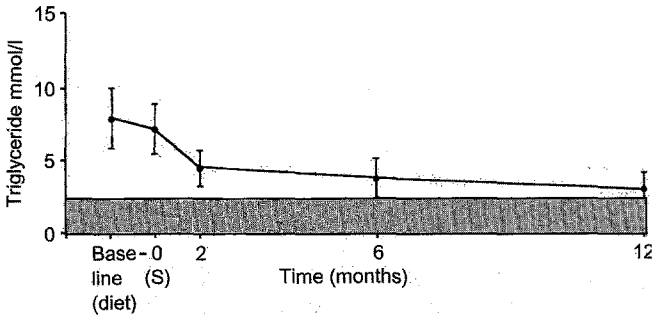

Fig. 2. Mean serum triglyceride concentration following S treatment. ▒, Normal reference range

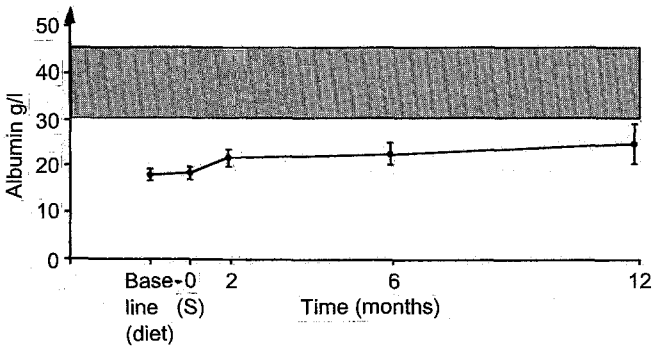

Fig. 3. Mean serum albumin concentration following S treatment. ▒, Normal reference range

The mean energy intake of the seven patients was 95% (range 73%–131%), as compared with DRV, 1991 [9], and the mean protein intake was 1.9 g/kg body weight per day (range 0.8–2.7 g); 13% (range 7.4%–16%) of the total energy intake was from protein. The mean percentage energy intake derived from carbohydrate was 49% (range 38%–55%) of which 20% was from extrinsic sugars. The mean percentage energy intake derived from fat was 39% (range 33%–46%), of which 11.6% was from saturated, 9.6% from monounsaturated and 17.8% from polyunsaturated fatty acids, respectively. The mean dietary fibre (NSP) intake was 18 g/day (range 8.1–25.8 g) and the mean sodium intake was 5.1 mmol/kg body weight per day (range 2.1–6.0 mmol).

The mean height and weight standard deviation scores were -1.16 ± 0.48 (SEM) and -0.35 ± 0.54 (SEM) respectively at the start of simvastatin therapy and -1.07 ± 0.50 (SEM) and -0.39 ± 0.51 (SEM) respectively at 12 months.

Discussion

Our experience confirms that dietary manipulation alone has little impact on the hyperlipidaemia of children with a persistent nephrotic state, whereas simvastatin produced a significant and sustained reduction in lipid levels. Although each child was not subjected to a prolonged period of dietary modification prior to commencing simvastatin, the modest reduction of 8.3% in cholesterol levels was in keeping with the 5% reduction achieved in adults in a controlled trial of simvastatin usage [11]. However, consistent and frequent dietary advice to this heterogeneous group of patients and their families is advocated. The mean percentage energy intake achieved from fat, of 39%, was considered practical for this group of patients to maintain adequate energy intakes while also allowing for food preferences; 11% of the total fat was derived from saturated fatty acids which would appear satisfactory as dietary recommendations for children (>5 years) and adults state that the saturated fat intake should provide an average of 10% of the total dietary energy intake [9, 12]. The mean intake of monounsaturated fatty acids for our patient group was 9.6% of the total fat intake and is in keeping with current recommendations that such fat should comprise no greater than 10%–15% of the total energy intake. The mean polyunsaturated fat intake of 17.8% of the total energy was high if based on recommendations that such an intake should not exceed 10% of the energy intake [9].

The mean dietary fibre intake (NSP) of 18 g/day was exceptionally good within the group of children and was in part contributed by those children who were vegetarian and the consumption of wholemeal bread generally consumed within the group. The mean sodium intake of 5.1 mmol/kg body weight per day was higher than predicted when following a "no added salt" diet. However, this does reflect the reality of children's diets with respect to sodium content, with the consumption of manufactured products within the context of a mixed diet. Growth parameters for both weight and height of the seven patients were maintained during the study period.

The interest in the treatment of hyperlipidaemic proteinuric patients with lipid-lowering therapy has arisen from the suggestion that hyperlipidaemia may itself accelerate the progression of chronic renal failure [4, 5]. A recent double-blind placebo-controlled trial of simvastatin in adult patients with the nephrotic syndrome or significant proteinuria and hypercholesterolaemia failed to show significant differences in urine protein levels or decline in plasma inulin clearance over 6 months of treatment [11]. However, larger more prolonged trials will be required. We cannot comment upon the effect of simvastatin on the progression of renal disease in our group of patients because any change in mean albumin levels and urine protein/creatinine ratios during the study period could be accounted for by the changing clinical status of some patients.

Simvastatin was effective at lowering lipid levels and no major side effects were noted in our study population. Two patients had transient rises in CPK levels but therapy was not altered and levels returned to normal limits with continuous treatment. Myopathy is one of the rare side effects reported with HMG CoA reductase inhibitors and careful monitoring of clinical symptoms, such as muscle pain or weakness, with CPK levels is important. The risk of myopathy may be increased with the concomitant use of immunosuppressive therapy such as cyclosporin. Minor asymptomatic transient increases in serum transaminases may occur after initiation of therapy, and rarely an apparent hypersensitivity syndrome has been reported.

The long-term safety and effectiveness of simvastatin in children has not been established but two previous studies in adult patients with nephrotic syndrome reported no side

effects [13, 14]. However, in the more recent controlled trial, 4 of 15 adult patients did not complete the simvastatin treatment, due to adverse clinical effects in 3 (gout, diarrhoea and atypical chest pain) and 1 had elevated baseline aspartate transaminase and creatinine kinase values [11]. Only one of our patients did not respond to 10 mg simvastatin daily and little response was achieved by increasing the dose stepwise to 40 mg (2.3 mg/kg body weight) daily despite checks on compliance. Recent evidence in adults suggests that most of the cholesterol-lowering effect is achieved with 10 mg simvastatin daily, with the majority of the reduction in lipid levels being achieved in the first 4 weeks of treatment [11].

Simvastatin has been reported to be effective in lowering lipid levels in children with hypercholesterolaemia not due to nephrotic syndrome [6, 7]. The relationship of the nephrotic syndrome to coronary heart disease is controversial [15, 16], and lipid-lowering therapy may never be shown to reduce coronary heart disease mortality because of the large trial size required. However, recent reports [17, 18] suggesting a beneficial effect of lowering cholesterol with an HMG CoA reductase inhibitor on coronary angiographic appearances and a reduction in cardiac mortality in the general population suggest that our patients with a persistently nephrotic state should have the benefit of this therapy.

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