Serum Lipid Concentrations in Subjects With Phenylketonuria and Their Families

Terry J. DeClue, MD; Jim Davis, MD; Dawn M. Schocken, MPH; Ruth Kangas, RD; Steve A. Benford

- To determine if subjects with phenylketonuria receiving diets significantly lower in cholesterol and saturated fat had serum lipid concentrations different from those of their family members, we measured serum concentrations of total cholesterol, high-density lipoprotein cholesterol, and total triglycerides in the probands with phenylketonuria, their parents, and their siblings. Eleven adults (seven women and four men) and 16 children (eight girls and eight boys) were studied. Ten subjects (four girls and six boys) had phenylketonuria. Subjects with phenylketonuria consumed less cholesterol (0.02 vs 0.41 mmol/d) and fat (median, 21% vs 39.5% of total calories), and their diets had a higher ratio of polyunsaturated to saturated fatty acids (median, 2.0 vs 0.2) than did their siblings without phenylketonuria. The diet of the parents was similar to that of their offspring without phenylketonuria. No differences were noted between the subjects with phenylketonuria consuming a diet lower in saturated fat and cholesterol and their siblings without phenylketonuria in serum concentrations of total cholesterol (median, 3.34 vs 3.07 mmol/L); high-density lipoprotein cholesterol (median, 1.44 vs 1.37 mmol/L); low-density lipoprotein cholesterol (median, 1.44 vs 1.09 mmol/L); or triglycerides (median, 0.89 vs 0.54 mmol/L). We conclude that previously reported lipoprotein abnormalities noted between unrelated subjects with and without phenylketonuria may not be due to differences in dietary intake, but rather due to a (genetic) predisposition of the population with phenylketonuria toward lower serum lipid concentrations.

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Phenylketonuria (PKU) is an inborn error of metabolism secondary to a deficiency of phenylalanine hydroxylase. It is inherited as an autosomal recessive trait, and dietary intervention is the only treatment currently available. The basis of the PKU diet is to restrict phenylalanine intake early in life. To supply the recommended daily allowances of protein, carbohydrates, and fats, special casein hydrolysate formulas are used. As the patient ages, various low-protein solid food exchanges are added to the diet. Because of the reduction of animal protein in the patients' diet, they generally consume a lower percentage of calories from fat and cholesterol than does the general population.\textsuperscript{1,2} It has been suggested that the PKU diet is responsible for the lower values of total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) noted in the subject with PKU.\textsuperscript{3} We evaluated lipoproteins in children with PKU and their families to determine if other (familial) factors might be responsible for these changes in serum total cholesterol.

SUBJECTS AND METHODS

Seven families with at least one child attending the PKU clinic at the University of South Florida were enrolled. Ten children (four girls and six boys) with PKU (median age, 7.3 years; range, 0.75 to 30 years) and six siblings without PKU (two girls and four boys; median age, 7.1 years; range, 5 to 17 years) were evaluated. Two subjects with PKU were older than 25 years (27 and 30 years) and had not been prescribed a phenylalanine-restricted diet at birth. At the time of the study, all subjects with PKU were receiving an appropriate phenylalanine-restricted diet. Eleven parents (seven women and four men) with a median age of 33 years (range, 24 to 48 years) were also studied. All subjects were euthyroid and none was obese. The study was reviewed and approved by the Institutional Review Board of the University of South Florida; informed consent was obtained from each family member before enrollment. Each subject studied completed a 3-day food diary before blood collection. The food diary was analyzed by a registered dietitian using Nutritionist III (N-Squared Computing, Silverton, Ore) for content of protein; carbohydrate; fat; cholesterol; and monounsaturated, polyunsaturated, and saturated fatty acids. The dietary information for each individual was averaged and reported as median and range for a 24-hour period.

On the day of blood collection, following an overnight fast, the subjects' heights and weights were measured and they were allowed to sit for 10 to 15 minutes before blood samples were collected through an antecubital vein. Following collection, the serum was separated immediately. Serum concentrations of total cholesterol, HDL-C, triglycerides, and thyrotropin were measured in all subjects, and phenylalanine levels were determined in the probands with PKU. The serum sample for HDL-C was refrigerated at 4°C until assayed 48 to 72 hours after collection. Serum samples for analysis of total cholesterol, triglycerides, and thyrotropin were frozen at -70°C until assay. Total cholesterol, HDL-C, and triglyceride levels were measured at the University of Miami using nationally standardized methods previously de-
sribed. Thyrotropin level was measured with a standard radioimmunoassay. Serum phenylalanine was measured using ion exchange chromatography with postcolumn triketohydridene hydride (Ninhydrin) detection. Statistical analyses were made using Student's t test.

**RESULTS**

The patients with PKU consumed significantly fewer calories from total fat and protein, but more calories from carbohydrates, than did their family members (Table 1). The subjects with PKU also consumed significantly less cholesterol in their diet, and the ratio of their polyunsaturated to saturated fatty acid intake was much higher. The diet of the parents was similar to that of the siblings without PKU; although the parents consumed more cholesterol, the difference was not statistically significant.

No differences were noted in serum concentrations of total cholesterol, HDL-C, LDL-C, and triglycerides between the subjects with PKU (consuming a diet significantly lower in cholesterol and higher in polyunsaturated fat) and their family members (Table 2). The serum concentrations of total cholesterol, LDL-C, and triglycerides in the parents were higher, but not statistically different, from the offspring with or without PKU. The HDL-C values were similar among all three groups. Thyrotropin levels were normal in all subjects. The mean (±SD) serum phenylalanine concentration in the patients with PKU was 365±242 µmol/L.

**COMMENT**

Previous investigators have reported that serum or plasma total cholesterol values were significantly lower in subjects with PKU than in unrelated control subjects without PKU. Acosta et al evaluated 93 children with PKU (23 children were not receiving a phenylalanine-restricted diet) and 30 normal control subjects and found that the total and free serum cholesterol values were lower in the children with PKU than in the normal subjects. Galluzzo et al measured plasma levels of total cholesterol and HDL-C in 40 healthy, treated patients with PKU (triglycerides were measured in 30) and 150 sex- and age-matched control subjects. In this study, patients with PKU had significantly lower total cholesterol values than control subjects. There was no difference in HDL-C or triglyceride values, and LDL-C levels were not determined. Similarly, Schulpi and Scarpazou evaluated serum lipid concentrations in 20 Greek children with PKU and compared them with those in 200 matched healthy children. Significant differences were noted in triglyceride, total cholesterol, HDL-C, and very low density lipoprotein cholesterol concentrations, with the subjects with PKU having the more favorable profile. There was no difference in LDL-C levels between the two groups.

Recently, it has been noted that there is genetic heterogeneity in the response of serum lipid concentrations to alterations in the intake of cholesterol and saturated fat. Sensitivity to dietary cholesterol varies among subjects, with the majority effectively compensating for increases in dietary cholesterol by feedback suppression of endogenous cholesterol synthesis, coupled with a reduction in dietary cholesterol fractional absorption. Hypothesizing that familial factors in addition to diet may affect serum lipid concentrations in individuals with PKU, we evaluated subjects with PKU and compared them with their parents and siblings without PKU.

Our study confirms that individuals with PKU receiving an appropriately low-phenylalanine diet consume significantly less cholesterol and a lower percentage of calories from fat in their diet. The majority of the fat consumed by our children with PKU consisted of polyunsaturated fatty acids. Diets high in polyunsaturated fatty acids lower HDL-C in subjects without PKU; however, no differences were noted in our study in HDL-C levels between groups. The small number of patients in this study does not reveal subtle changes that might occur in HDL-C between the various groups.

The greatest differences among the two sibling groups
was between serum concentrations of total cholesterol and HDL-C and total triglycerides. It is interesting that those children (without PKU) who consumed the largest amount of cholesterol and saturated fatty acids in their diet had lower serum total cholesterol and LDL-C concentrations. This is contrary to what one might expect since subjects consuming the highest amounts of dietary cholesterol are expected to have the higher serum total cholesterol concentrations. It is unlikely that age-related differences could account for the differences in serum cholesterol measurements between the siblings with and without PKU, since the subjects with PKU were of similar age. If the two oldest subjects with PKU are excluded in the analysis, the results are essentially the same (serum total cholesterol \( n = 8 \): median, 3.46 mmol/L; range, 2.8 to 4.5 mmol/L). In view of this finding it is possible that the serum total cholesterol changes noted during variations in dietary intake are related to a threshold effect. For example, within genetically similar groups, unless a quantity of cholesterol above a certain threshold is consumed, the serum total cholesterol is unchanged. This would be in agreement with the findings of McNamara et al.\(^5\)

Higher serum triglyceride values in children with PKU have been reported previously and have been suggested to be secondary to the significantly higher percentage of calories from carbohydrates consumed by the subject with PKU.\(^1\) We noted similar findings in our study and agree that increasing the total percentage of calories from fat in the form of monounsaturated fatty acids in the diet (and lowering the polyunsaturated fatty acids and carbohydrates) may have a more favorable effect on serum HDL-C and LDL-C concentrations, as well as on serum triglyceride measurements.\(^6\)

As a group, the families with PKU have favorable lipid profiles (Table 2). Of the seven families studied, one had familial combined hyperlipidemia. The proband with PKU was the only child in this family. Compared with the other siblings (with or without PKU), this child had the highest serum total cholesterol (4.4 mmol/L) and LDL-C (2.8 mmol/L) values. If this family is excluded from the analysis, there is no significant change in the overall results.

Subjects with PKU consume a diet that is less atherogenic than that of the general population. Previous studies have compared lipid profiles in children with PKU (demonstrating lower total cholesterol concentrations) to unrelated normal children without PKU.\(^13\) It is likely that those studies were flawed in their comparisons because they did not control for possible genetic influence in cholesterol metabolism between the two groups. We did not demonstrate any differences in serum total cholesterol levels between children with or without PKU, although the subjects without PKU consumed 10 times more cholesterol and twice the fat in their diet. The highest total cholesterol and LDL-C measurement among the siblings studied was in a child with PKU from a family with familial combined hyperlipidemia. If the serum total cholesterol data from these children with PKU had been compared with data from children from the general population, the wrong conclusion would have been made (ie, that the lower cholesterol and fat in the diet is responsible for the lower serum total cholesterol values in the subjects with PKU). Our study suggests that genetic influences in cholesterol metabolism should be considered an important variable in interpreting total cholesterol data from children. Our data suggest that families with a child with PKU have lower serum total cholesterol values than the general population and that other factors (eg, familial combined hyperlipidemia) have a greater influence on cholesterol metabolism than diet.

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References