REDUCED CHOLESTEROL LEVELS IN AFRICAN-AMERICAN ADULTS WITH SICKLE CELL DISEASE

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In a recent study of boys and girls with sickle cell disease (SCD) in Nigeria, a common finding with this genetic hematologic disorder was a marked reduction in total cholesterol. Epidemiologic studies have identified a relation between low serum levels of total cholesterol (<130 mg/dL) and increased mortality from all causes. We were interested in knowing if hypocholesterolemia was present in African-American adults with SCD. We therefore compared the plasma lipid profiles of the 16 men and 20 women with SCD who received care at the University of Texas Medical Branch at Galveston between 1996 and 2001 with those of 2,415 gender-matched African Americans who were seen at the same hospital but who did not have SCD. The age-adjusted mean total cholesterol concentrations of the SCD males and females were 147 ± 42 mg/dL and 179 ± 36 mg/dL, compared to male and female control values of 200 ± 75 mg/dL and 216 ± 61 mg/dL, respectively. These differences between SCD subjects and controls were statistically significant ($p<0.001$). The LDL-cholesterol levels of the men and women with SCD (68 ± 28 mg/dl and 95 ± 33 mg/dl, respectively) were also significantly reduced relative to the controls (121 ± 58 mg/dl and 128 ± 54 mg/dl, respectively, $p=0.001$). The triglyceride levels of the men with SCD were much reduced relative to the male controls (102 ± 34 mg/dL versus 194 ± 215 mg/dL, $p=0.02$), but were not different between the SCD females and their control group. The HDL-cholesterol levels of the SCD subjects and the controls were not different. These results indicate that total cholesterol and LDL-cholesterol concentrations are significantly reduced in adult men and women with SCD in the United States, and should heighten interest in the implication that low levels of cholesterol might exacerbate the medical problems inherent in this genetic disease. (*J Natl Med Assoc.* 2003;95:813–817.)

Key words: hypocholesterolemia ♦ sickle cell disease ♦ African-American ♦ cholesterol ♦ LDL ♦ low-density lipoprotein ♦ lipids

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INTRODUCTION

Although advances in supportive therapies have greatly increased the life expectancy of individuals with sickle cell disease (SCD) in the U.S. and other technologically advanced countries, the morbidity and mortality of this genetic/hematologic disorder remain high. In recent years, in children and adolescents with SCD in northern Nigeria, we have documented various biochemical and nutritional abnormalities—increased urinary excretion of essential amino acids[1], decreased proportions of polyunsaturated n-3 fatty acids in serum phospholipids[2], decreased fat-free mass in males[3], a marked reduction in bone density[4], and decreased serum

concentrations of total cholesterol, LDL (low-density lipoprotein)-cholesterol, and HDL (high-density lipoprotein)-cholesterol[5].

The finding of very low levels of total cholesterol (100–102 mg/dL) in the circulation of Nigerian boys and girls with SCD[5] should be cause for concern, since there is epidemiologic evidence that hypocholesterolemia—defined as a serum or plasma cholesterol concentration below 135 mg/dL—is associated with an increase in mortality from all causes[6,7]. We were interested in the question of cholesterol levels in the blood of adults in the U.S. with SCD. However, the literature contains few reports that address this issue.

We therefore sought to determine if hypocholesterolemia was present in African-American adults with SCD by comparing the total, LDL- and HDL-cholesterol levels of adults who, over the past five years, were admitted to the hospital at the University of Texas Medical Branch at Galveston with the corresponding values for age-adjusted African Americans at the same hospital—but who did not have SCD. The present report compares these data for a total of 36 men and women with SCD, versus 2,415 controls who did not have SCD.

METHODS

Subjects. This study was a hospital-based cross-sectional study of adults with sickle cell disease. The University of Texas Medical Branch (UTMB) at Galveston has developed a clinical laboratory data repository that contains the clinical chemistry, hematology, and serology results for all hospital patients between 1996 and 2001, and is linked to diagnosis (ICD-9) codes. The Oracle (version 8.0 Oracle Corp., Redwood Shores, CA) database permits one to pose questions to search for all hospital patients who had a diagnosis of sickle cell anemia, were black, and who had laboratory results for total cholesterol. All of the SCD subjects were confirmed as HbSS by electrophoresis, with the exception of one subject who was HbSC. In order to limit the number of cholesterol values, only the value obtained when the patient first presented at the hospital was used. Over the five-year time period, we found 36 patients who met these criteria (of the 36 subjects, nine males and 16 females also had HDL and triglyceride values allowing calculation of the LDL concentration).

A control group included those who were black, hospitalized, similar in age to the SCSD subjects, HbAA, and who had laboratory results for total cholesterol. As with the study group, only the first total cholesterol result obtained when the patient initially presented at the hospital was used. This gave a control group that consisted of a total of 2,415 male and female patients. No information on diet or smoking history was available.

Biochemical analyses. Total cholesterol, triglycerides, and HDL concentrations were obtained using a Vitros 950 analyzer. LDL-cholesterol was calculated using the following equation: LDL-cho-

Table 1. Concentrations of Lipids in the Serum of Men and Women with Sickle Cell Disease (SCD) and Controls

	Males					Females				
Parameter	**SCD**	**n**	**Controls**	**n**	**p-value**	**SCD**	**n**	**Controls**	**n**	**p-value**
Age (years)	36 (11)*	16	43 (8)	736	0.001	43 (15)	20	48 (13)	1679	NS
Total cholesterol (mg/dL)	147 (42)	16	200 (75)	736	<0.001	179 (36)	20	216 (61)	1679	0.002
HDL-cholesterol (mg/dL)	42 (16)	9	45 (16)	453	NS	48 (16)	16	57 (23)	976	NS
LDL-cholesterol (mg/dL)	68 (28)	9	121 (58)	443	0.001	95 (33)	16	128 (54)	976	<0.001
Triglycerides (mg/dL)	102 (34)	12	194 (215)	645	0.02	154 (134)	17	177 (158)	1294	NS

* Mean (SD); NS, Not significant (p>0.05).

lesterol = total cholesterol – (HDL-cholesterol + Triglycerides / 5).

Statistical analysis. Descriptive statistics, group comparisons, and correlations were made using the Number Cruncher Statistical Software (NCSS, version 6, Kaysville, UT). Results are expressed as mean ± standard deviation. The least-square age-adjusted means were calculated using analysis of variance. A two-sample t-test was used to determine the statistical significance of a parameter between the different groups. A p-value of 0.05 or less was considered statistically significant.

RESULTS

Comments on the study population. As shown in Table 1, the men with SCD ranged in age from

Figure 1. (A) Total cholesterol concentrations in serum of male patients with SCD versus age (•). The solid line represents the 50th percentile for the male controls; the dashed lines represent the 5th and 95th percentiles for the male controls. **(B)** Total cholesterol in the serum of female patients with SCD (•). The solid lines represent the 50th percentile for the female controls; the dashed lines represent the 5th and 95th percentiles for the female controls.

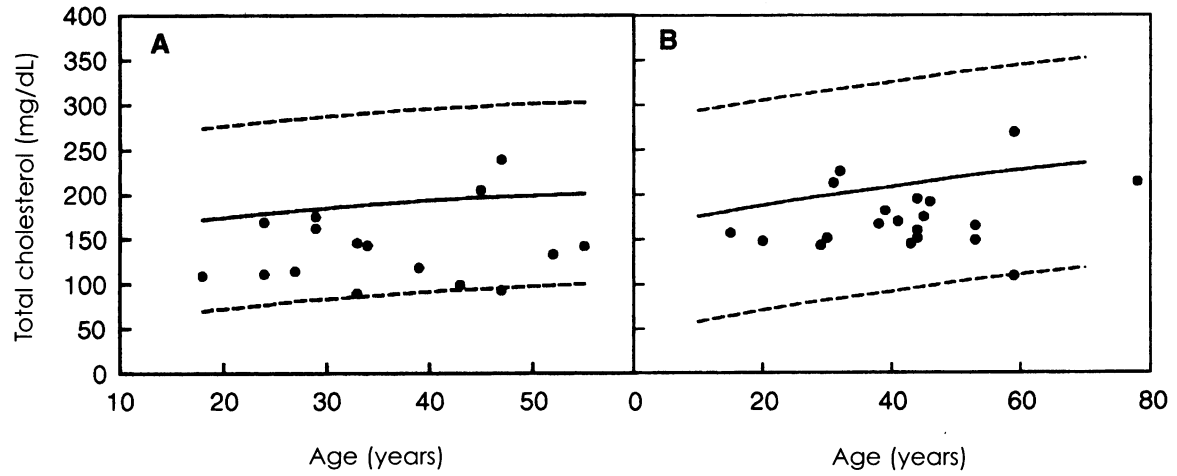
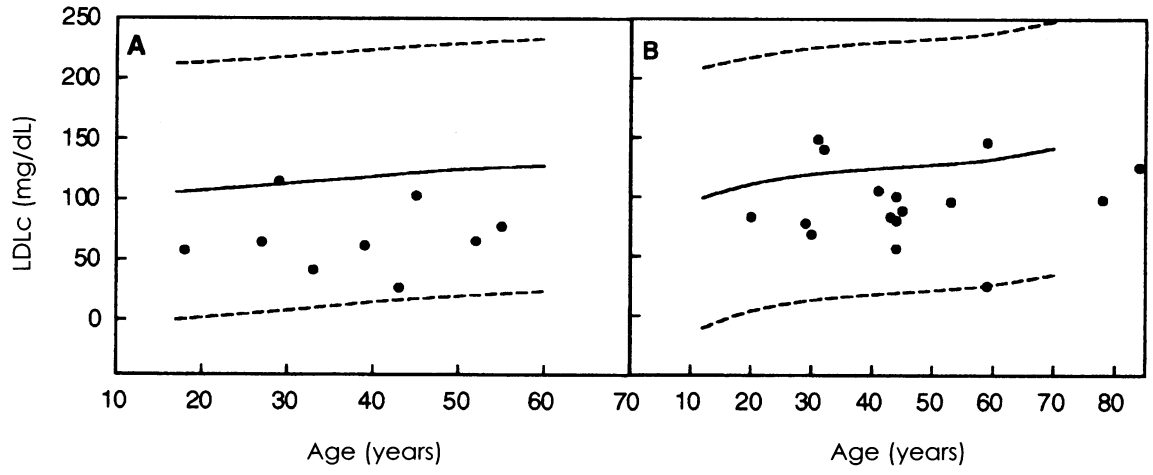


Figure 2. (A) LDL- cholesterol concentrations in serum of male patients with SCD versus age (•). The solid line represents the 50th percentile for the male controls; the dashed lines represent the 5th and 95th percentiles for the male controls. **(B)** LDL-cholesterol in the serum of female patients with SCD (•). The solid lines represent the 50th percentile for the female controls; the dashed lines represent the 5th and 95th percentiles for the female controls.



18–55 years, with the average age of the group being 36 years. The mean age of the women with SCD was 44 years, and the age range of this population was 16–84 years. Although the mean age of the female controls was not significantly different from the SCD subjects, the mean age of the male controls was significantly higher than the mean age of the male SCD subjects (p=0.001).

Serum lipid concentrations in adult males and females with sickle cell disease. Table 1 compares the average plasma levels of total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides between men and women with SCD and their gender-matched controls. Although the male SCD subjects and controls were not strictly age-matched, the age-adjusted least-square means for total cholesterol were significantly different. The mean total cholesterol levels of the male SCD subjects (147 mg/dL) and females with SCD (179 mg/dL) were much lower than those of their respective control groups (male controls: 200 mg/dL, female controls: 216 mg/dL). In both cases, these differences were highly significant ($p \leq 0.002$). On an individual basis, 14 of 16 (88%) males with SCD had a total cholesterol concentration that fell below the 50th percentile of the male controls (Figure 1A). For the female SCD patients, 17 of 20 (85%) had total cholesterol levels that fell below the 50th percentile of the female controls (Figure 1B).

The mean HDL-cholesterol levels of the males and females with SCD were only slightly lower than those of their respective controls, and these differences were not statistically significant. However, the mean LDL-cholesterol concentrations of the SCD males and females were only 56% and 73% those of the mean values of the controls. On an individual basis, eight of nine (89%) males (Figure 2A) and 13 of 16 (81%) females (Figure 2B) with SCD had an LDL-cholesterol level that was between the 50th and fifth percentiles of their respective control groups.

The plasma triglyceride levels were also reduced in the SCD patients, while the mean triglyceride concentration in the SCD males was only 53% of control ($p<0.001$). The mean triglyceride values of the females with SCD, and the female controls were not significantly different. The triglyceride concentrations of all the male SCD subjects were below the 50th percentile for their control group; however, only one-third of the female SCD patients had a triglyceride value below the 50th percentile (data not shown).

DISCUSSION

The finding of reduced serum cholesterol concentrations in the serum of African-American adults with SCD is consistent with our recently reported finding of extraordinarily low total serum cholesterol levels in Nigerian children with this same hematologic disorder[5]. The mean total cholesterol levels of our male and female SCD subjects in Texas were only 50% and 60% as high as those of the corresponding age-adjusted controls, and at 130–150 mg/dL were in the lower half of the UTMB hospital's reference range for total cholesterol (120–200 mg/dL). There were commensurate reductions in the levels of LDL-cholesterol in the adult SCD subjects in the present study: the mean LDL-cholesterol levels of the men and women with SCD were 44% and 26% less than the means of the control males and females, respectively.

Such low levels of cholesterol in two such different populations of SCD subjects—one set, Nigerian children, the other African-American adults in Texas—indicate to us that reduced cholesterol levels are intrinsic to the disease, and not something that is idiosyncratic to a particular diet or lifestyle. Others have reported low serum or plasma cholesterol concentrations in patients with SCD[8-10].

Our findings prompt at least two questions: what is the basis of the reduced serum cholesterol in SCD, and what might the implications be of their having low circulating levels of cholesterol? With regard to the first question, the lower cholesterol levels may be due partly to the decreased red-cell volume that occurs in SCD, resulting in an increased plasma volume, and having a dilution effect on plasma constituents. In addition, the pathway of cholesterol biosynthesis is subject to strong down-regulation in SCD patients relative to non-SCD individuals; that is, the LDL-cholesterol: LDL receptor pathway by which the expression of β-hydroxymethyl-glutaryl-CoA reductase (the enzyme that catalyzes the rate-limiting step in the cholesterol biosynthesis pathway) is regulated is exceptionally active or efficient[11]. Another possibility—but one that seems less likely—is that the dietary intake of cholesterol is low in children and adults with SCD. A third reason for the low cholesterol levels in SCD may relate to the activity of lecithin:cholesterol acyltransferase (LCAT), the enzyme in blood which is responsible for the removal of cholesterol from tissue membranes. LCAT catalyzes the transfer of a fatty acid from the

sn-2 position of lecithin to the 3-hydroxyl group of cholesterol[12,13]. It is this acylation reaction which allows for the transfer of cholesterol (as cholesterol ester) from membranes to very low-density lipoprotein (VLDL) in the circulation[14]. LCAT is activated by HDL and prefers lecithin molecules that contain polyunsaturated fatty acids. Since, at least in the Nigerian children we have studied, the sera of SCD patients have significantly reduced levels of HDL, as well as serum phospholipids that are deficient in n-3 polyunsaturated fatty acids[2], it is conceivable that these circumstances act to reduce the activity of LCAT and hence the rate of transfer of cholesterol from tissue membranes into VLDL in the circulation[13].

In the present and previous studies we conducted, the other question the data with SCD presented is, What, if any, are the health-related implications of markedly low cholesterol levels? Several epidemiological studies have shown that the graph of mortality from all causes versus plasma cholesterol concentration is U-shaped—such that below a level of 135 mg/dL total cholesterol, the probability of mortality is increased relative to what it is between 135- and 200 mg/dL[6,7,15]. Hypocholesterolemia has also been shown to be a risk factor for various affective disorders, including depression. Furthermore, marked hypocholesterolemia has been linked to suicide[16].

There were several significant limitations of the present study. First, since the controls were hospitalized patients there was a possibility of selection bias which could have resulted result in lipid values for the control group that were not representative of a healthy, non-hospitalized population. Second, the number of subjects with SCD was relatively small.

Future studies should be aimed at investigating the cholesterol content of the tissue membranes of children and adults with SCD, and at assessing the regulation of cholesterol synthesis in these populations.

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