Depressed serum high density lipoprotein cholesterol levels in veterans with spinal cord injury

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Cardiovascular diseases are the most frequent cause of death among persons with spinal cord injury (SCI), and these diseases are reported to occur prematurely in the disabled compared to the able bodied population. The mechanism of accelerated coronary heart disease (CHD) in persons with SCI may be partially explicable on the basis of the lipoprotein profile. We performed fasting lipoprotein determinations on 100 veterans with SCI, 50 with paraplegia and 50 with quadriplegia, and 50 veteran controls. The mean age of the subjects with SCI was 47.8 ± 1.4 years with a duration of injury of 16.3 ± 1.2 years. The mean serum high-density lipoprotein (HDL) cholesterol was depressed in subjects with paraplegia or quadriplegia compared to controls (37 ± 1 or 40 ± 1 versus 48 ± 2 mg/dL, $p < 0.0001$). Although serum total cholesterol was lower ($p < 0.01$) in subjects with SCI than in controls, there was no significant difference in mean serum low-density lipoprotein (LDL) cholesterol. Thirty-seven percent of subjects with SCI have serum HDL cholesterol levels less than 35 mg/dL with no significant difference in lipoprotein distribution between high and low cord lesions. Eighteen percent of individuals with SCI have an absolute elevation of LDL cholesterol (greater than 160 mg/dL). About 40% of those with SCI and LDL cholesterol levels between 130 and 160 mg/dL also have serum HDL cholesterol values below 35 mg/dL, all of whom would have their serum HDL cholesterol level undetected if lipoprotein profiles were performed according to present recommendations – that is, only if the serum total cholesterol is elevated. The ratio of serum total cholesterol to HDL cholesterol and serum LDL cholesterol to HDL cholesterol, commonly used ratios for risk of CHD, were calculated and are elevated in groups with SCI. In a subgroup of 12 subjects with paraplegia, a linear correlation is noted between serum HDL cholesterol values and cardiopulmonary fitness by determination of $\dot{V}O_2$ max by upper body ergometry. Also, a linear correlation ($p = 0.02$) is found between serum HDL cholesterol and insulin sensitivity as determined by the minimal-model method.

Keywords: paraplegia; quadriplegia; lipoprotein cholesterol; cardiopulmonary fitness; insulin sensitivity; diabetes mellitus.

Diseases which occur with age are being reported in persons with spinal cord injury (SCI).^{1–5} In one study² cardiovascular diseases were the most frequent cause of death among persons with SCI more than 30 years post injury (46% of all deaths) and among those more than 60 years of age (35% of deaths). Cardiovascular disease mortality has been reported to occur at younger ages

in persons with SCI than in the nondisabled population.² The lipid profile determines a portion of the risk of cardiovascular disease.^{6–10} An increased level of activity is associated with reduced risk of CHD,¹¹ which may be largely due to the direct relationship between activity and high density lipoprotein (HDL) cholesterol. The general recommendation to perform a com-

plete lipoprotein profile in individuals only if the total serum cholesterol is greater than 240 mg/dL may not be appropriate for those who are disabled, since the serum HDL cholesterol has been reported to be markedly reduced in persons with SCI.¹²⁻¹⁴ Thus, we performed a complete lipoprotein profile in 100 subjects with SCI, equally divided between those with paraplegia or quadriplegia, and compared the results to those obtained in 50 able bodied veteran controls. Since both carbohydrate metabolism¹⁵⁻¹⁹ and level of activity^{12,20,21} have each individually been shown to influence the serum HDL cholesterol level, in a subset of 12 subjects with paraplegia cardiovascular fitness and peripheral insulin sensitivity were determined and compared to the level of serum HDL cholesterol.

Methods

Fasting lipoprotein determinations were performed on 50 veterans with paraplegia, 50 with quadriplegia, and 50 veteran controls. The groups were matched for age and body mass index (BMI). Informed consent was obtained from all subjects. The serum total cholesterol and triglycerides were assayed on SMAC (Technion Instruments) using the enzymatic method. The serum HDL cholesterol was determined by the dextran sulfate method (Technicon HDL cholesterol precipitating reagent, Technicon Instruments Corp, Tarrytown, NY) with enzymatic quantification. The serum low density lipoprotein (LDL) cholesterol was calculated from the equation: LDL cholesterol = TC - (HDLc) - (TG/5), where TC is total cholesterol, HDLc is HDL cholesterol, and TG are triglycerides.

Cardiopulmonary fitness and insulin sensitivity were determined in a subset of 12 subjects with paraplegia. Fitness was determined by an upper body ergometry metabolic stress test. Determination of fitness was accomplished by measurement of oxygen uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), minute ventilation (VE), heart rate (HR), and work (watts).^{22,23} A metabolic cart (system 2900, SensorMedics Corp, Yorba Linda, CA) was used to measure $\dot{V}O_2$, $\dot{V}CO_2$, and VE. A heart rate

telemeter (Polar Pacer, Computer Instruments Corp) was used to measure HR. Work was measured by use of a Fleisch Universal Ergostat upper extremity ergometer. A 12 watt incremental protocol²⁴ using one minute stages was employed until the subject reached maximum effort, as determined by the following criteria: R ($\dot{V}CO_2/\dot{V}O_2$) > 1.10, HR $\geq$ 85% maximum predicted heart rate (MPHR = 220-age), subjective exhaustion or other limiting symptoms.

An intravenous glucose tolerance test with tolbutamide was performed according to the modified minimal-model method of Bergman²⁵. After placement of 2 intracatheters, 4 basal samples were collected over 20 min, after which glucose (0.3 g/kg) was injected over one min. An additional injection of tolbutamide (Orinase i.v., Upjohn, Kalamazoo, MI) was given over 20 sec, 20 min after glucose. Subjects with BMI < 30 kg/m² were given 300 mg tolbutamide; subjects with BMI > 30 kg/m² were given 500 mg. Blood samples were collected at the following times after glucose injection: at t = 0:2, 4, 8, 19, 22, 30, 40, 50, 60, 70, 90, 120, and 180 min. The insulin sensitivity index was calculated from the fast sampling intravenous glucose tolerance (FSIGT) test results using the program MINMOD which was run on the VAX-750 at the USC Physiology and Biophysics Department. This program accepts as input the temporal pattern of plasma insulin during the FSIGT, and must fit a simple (minimal) model of insulin-dependent glucose utilization to the measured glucose pattern.

Diagnostic classification from a standard 75 g oral glucose tolerance test, which was administered as part of an annual physical examination, was taken from the hospital record of each subject.

All calculations and statistical analyses were performed using the STATVIEW software program. Results are expressed as the mean value plus or minus standard error of the mean (SEM). ANOVA was used to determine the significance of differences in lipid levels among the groups. The unpaired Student's t-test was used to assess the significance of differences in lipid values

between subjects with paraplegia or quadriplegia. Linear regression analyses were performed to determine the correlation between HDL cholesterol and triglycerides, cardiopulmonary fitness ($\dot{V}O_2$ max), or insulin sensitivity (S_i).

Results

The characteristics of the study and control groups are shown (Table I). The subjects with paraplegia and quadriplegia have a marked depression in mean serum HDL cholesterol when compared to controls (Table II). Except for serum triglycerides, which were noted to be lower in those with quadriplegia, there is no significant difference in any serum lipoprotein values between those with paraplegia or quadriplegia. The mean serum total cholesterol is significantly lower in the subjects with SCI compared to controls, due in part to the depressed mean serum HDL cholesterol level (Table II). The mean serum LDL cholesterol is not significantly different between those with paraplegia or quadriplegia or between either group with SCI and the control group.

Table I Characteristics of study group

	Paraplegia	Quadriplegia	Control
Age	49.5 $\pm$ 1.9	46.2 $\pm$ 2.0	48.8 $\pm$ 1.8
BMI	26.0 $\pm$ 0.5	24.0 $\pm$ 0.8	26.8 $\pm$ 0.7
DOI	17.6 $\pm$ 1.7	15.0 $\pm$ 1.7	

BMI = body mass index (kg/m^2); DOI = duration of injury (yrs). Results are expressed as mean $\pm$ SEM.

Table II Characteristics of study group

Serum lipoproteins	Paraplegia	Quadriplegia	Control
HDL cholesterol	37 $\pm$ 1 [■]	40 $\pm$ 1 [■]	48 $\pm$ 2
Total cholesterol	191 $\pm$ 5*	188 $\pm$ 6*	210 $\pm$ 4
LDL cholesterol	124 $\pm$ 5	128 $\pm$ 6	136 $\pm$ 4
Triglycerides	148 $\pm$ 15	101 $\pm$ 8 [•]	134 $\pm$ 11

Serum lipoproteins levels expressed as mean $\pm$ SEM in mg/dL. ANOVA was used to determine statistically significant changes among groups.

[■] $p < 0.0001$, * $p < 0.01$, [•] $p < 0.05$.

Since the ratio of total serum cholesterol to HDL cholesterol, as well as the ratio of serum LDL cholesterol to HDL cholesterol, has been found to be strongly correlated with the risk of CHD,^{26,27} these ratios have been determined in our subjects (Table III). In the group with paraplegia compared to the control group, a significant difference is noted between the ratio of total cholesterol to HDL cholesterol and the ratio of LDL cholesterol to HDL cholesterol. An additional significant difference is noted in the group comprising all subjects with SCI compared to the control group for the ratio of LDL cholesterol to HDL cholesterol.

An inverse correlation is noted between serum HDL cholesterol and triglyceride values in subjects with paraplegia ($p < 0.0001$) and quadriplegia ($p < 0.005$), and in controls ($p < 0.005$) (Fig 1). A direct correlation is noted between the serum HDL cholesterol values and $\dot{V}O_2$ max, $p = 0.10$. In a subgroup of 12 subjects with paraplegia, there is a significant linear correlation ($p = 0.02$) between serum HDL cholesterol and insulin sensitivity (Fig 2).

Table III Ratio of total cholesterol or LDL cholesterol to HDL cholesterol

Groups	TC/HDLc	LDLc/HDLc
SCI	5.1 $\pm$ 0.1	3.5 $\pm$ 0.1*
Paraplegia	5.5 $\pm$ 0.3*	3.5 $\pm$ 0.2*
Quadriplegia	4.9 $\pm$ 0.2	3.4 $\pm$ 0.2
Control	4.6 $\pm$ 0.2	3.0 $\pm$ 0.1

TC = total cholesterol, HDLc = HDL cholesterol, LDLc = LDL cholesterol.

ANOVA was used to determine statistically significant changes among groups.

* $p < 0.05$.

Figure 1 Correlations between triglycerides and HDL cholesterol in veterans with paraplegia (top, triangles), and quadriplegia (middle, squares), and control subjects (bottom, circles).

The serum HDL cholesterol levels were divided into 3 groups: less than 30, 30–34, and levels equal to or greater than 35 mg/dL (Table IV). There is no significant difference in the serum HDL cholesterol distribution between subjects with paraplegia and those with quadriplegia. Forty percent of subjects with paraplegia and 34% of those with quadriplegia have serum HDL cholesterol levels less than 35 mg/dL.

Similarly, serum LDL cholesterol values were divided into 3 groups: less than 130, 130 to 160, and greater than 160 mg/dL (Table V). There is no significant difference in levels of LDL cholesterol distribution between subjects with paraplegia and those with quadriplegia. Eighteen percent of indi-

Figure 2 Correlation between HDL cholesterol and insulin sensitivity as determined by the minimal-model method.²⁵ Insulin sensitivity is expressed in units $10^{-4} \text{ min}^{-1} \text{ per } \mu\text{u/ml}$.

Table IV Serum HDL cholesterol levels (mg/dL)

Group	HDL-C	# of subjects	Percent
SCI	<30	13	13
	30–34	24	24
	≥35	63	63
Paraplegia	<30	9	18
	30–34	11	22
	≥35	30	60
Quadriplegia	<30	4	8
	30–34	13	26
	≥35	33	66

Table V Serum LDL cholesterol levels (mg/dL)

Group	LDL-C	# of subjects	Percent
SCI	<130	56	56
	130–160	26	26
	>160	18	18
Paraplegia	<130	29	58
	130–160	14	28
	>160	7	14
Quadriplegia	<130	27	54
	130–160	12	24
	>160	11	22

viduals with SCI have an absolute elevation of LDL cholesterol, ie greater than 160 mg/dL; 7 of these 18 subjects also have a serum HDL cholesterol less than 35 mg/dL, thus having 2 independent risk factors of

CHD. Of the 26 subjects with SCI and serum LDL cholesterol values between 130 and 160 mg/dL, 11 have depressed serum HDL cholesterol levels, thus having one relative and one absolute risk factor of CHD.

The serum lipoprotein profile was divided by the carbohydrate tolerance of the subjects with SCI (Table VI). No significant difference in lipoprotein profile is demonstrated between groups with normal, impaired or diabetic oral glucose tolerance.

Discussion

Several reports have revealed lower HDL cholesterol levels in persons with SCI.¹²⁻¹⁴ The Framingham Study^{6,7} and other epidemiological studies^{10,11} have reported an inverse relationship between the HDL cholesterol level and CHD. In this report, we noted a depressed mean serum HDL cholesterol level in subjects with paraplegia and quadriplegia compared to mean values in able bodied controls. Almost 40% of the subjects with SCI had serum HDL cholesterol levels below 35 mg/dL, an independent risk factor of CHD. In the subjects with SCI and in the controls, strong inverse correlations were demonstrated between serum triglycerides and HDL cholesterol. This inverse relationship may reflect the effects of plasma insulin, elevated as a consequence of reduced peripheral insulin sensitivity, on lipid metabolism. Hyperinsulinemia may cause increased hepatic triglyceride production,¹⁹ which, in turn, tends to lower serum HDL cholesterol, perhaps by enhancing clearance mechanisms.¹⁶

Brenes *et al*¹³ reported that in relatively

young and inactive men with SCI the mean serum HDL cholesterol level was depressed, whereas in highly trained wheelchair athletes the mean value for serum HDL cholesterol was closer to normal levels. No significant difference was noted between mean serum HDL cholesterol levels in inactive subjects with paraplegia or quadriplegia.¹³ Dearwater *et al*¹⁴ noted that in untrained men with SCI, the mean serum HDL cholesterol level was depressed compared to the mean value in wheelchair athletes. In a small number of subjects Hooker and Wells²⁸ addressed the effects of low intensity and moderate intensity wheelchair ergometry exercise on lipids. Only in the moderate intensity exercise group was a significant increase in serum mean HDL cholesterol level demonstrated. It should be noted, however, that the mean serum HDL cholesterol value before exercise training in the low intensity group was higher than the mean value after exercise training in the moderate exercise group.

There are additional lipoprotein measurements or mathematical expressions that have been associated with risk of CHD. In a recent study,²⁶ the ratio of serum total cholesterol to HDL cholesterol was a particularly strong discriminator of risk of myocardial infarction. An increase of one unit was associated with a mean increase of 53% in the risk of myocardial infarction.²⁶ Subjects with paraplegia in our report had about a one unit increment in this ratio compared with the control group. The inverse relationship between serum HDL cholesterol and risk of myocardial infarction appeared stronger for men with lower levels of total cholesterol,²⁶ such as those with SCI in this report. This ratio was a stronger predictor of risk than was total cholesterol, total HDL cholesterol, subfractions of HDL cholesterol, or levels of apolipoproteins.²⁶ The ratio of LDL cholesterol to HDL cholesterol may be a better indicator of risk of CHD in individuals with SCI since a depressed HDL cholesterol lowers total cholesterol but does not affect LDL cholesterol. Hence, the additional significant difference between the control group and the subjects with SCI was present when this latter ratio was used rather than the ratio of

Table VI Serum lipoprotein profile in SCI when divided by carbohydrate tolerance

Lipoprotein	NL	IGT	DM
HDL cholesterol	39 ± 1	38 ± 2	39 ± 2
total cholesterol	189 ± 6	199 ± 8	186 ± 7
LDL cholesterol	125 ± 5	134 ± 8	124 ± 7
triglycerides	124 ± 17	130 ± 14	123 ± 15

Results are expressed as mean ± SEM

total cholesterol to HDL cholesterol. Other measurements, such as alipoprotein B-100 (the main apoprotein in the LDL particle) and alipoprotein A-I (one of the apoproteins in the HDL particle), as well as other lipid and/or apoprotein ratios (B-100 to HDL cholesterol or B-100 to A-I), may also be significant predictors of risk of CHD in the person with SCI. A properly controlled, long term prospective study of CHD morbidity and mortality in relationship to lipoprotein and apoprotein values in per-

sons with SCI will provide us with this information.

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