The effect of residual neurological deficit on serum lipoproteins in individuals with chronic spinal cord injury

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Subjects with spinal cord injury (SCI) have been shown to have an adverse lipid profile. Prior studies performed with smaller numbers of subjects have not been able to demonstrate any relationship between the level and degree of the neurological deficit and plasma lipid levels. Over a 2 year period we investigated the lipid profiles in 541 subjects from Rancho Los Amigos Medical Center, Downey, California. Subjects were grouped by tetraplegia (Tetra; $n=247$) or paraplegia (Para; $n=294$) and by subgroup for degree of neurological deficit: complete Tetra ($n=156$), incomplete Tetra ($n=91$), complete Para ($n=206$) and incomplete Para ($n=88$). The serum high-density lipoprotein (HDL) cholesterol level was lower in the Tetra than in the Para group (38 ± 0.7 vs 45 ± 0.8 , $P < 0.01$). The group with Tetra had a higher percentage of subjects with serum HDL cholesterol values < 35 mg/dL [an independent risk factor for coronary heart disease (CHD)] than those with Para (38% vs 21%, $P < 0.0001$). A significant inverse relationship was found for degree of neurological deficit and mean serum HDL cholesterol level ($r = 0.19$, $P < 0.001$), with the greater the deficit, the lower the serum HDL cholesterol level. Serum total cholesterol levels were higher in the Para group than in the Tetra group (198 ± 2.6 vs 184 ± 2.6 , $P < 0.01$). However, the ratio of total cholesterol to HDL cholesterol (a discriminator of risk for CHD) was significantly lower in the Para group than the Tetra group (4.8 vs 5.2%, $P < 0.01$). Thus, in persons with SCI a spectrum of depressed serum HDL cholesterol levels and increased cardiovascular risk occur, with the most adverse lipid changes correlating with the severity of neurological deficit.

Keywords: paraplegia; tetraplegia; lipids; coronary heart disease

Introduction

Cardiovascular disease occurs prematurely in persons with spinal cord injury (SCI).^{1–4} The distribution of cholesterol into its fractions has a major impact on atherosclerotic plaque formation. In the general population, a serum lipid profile of depressed serum high-density lipoprotein (HDL) cholesterol levels and elevated low density lipoprotein (LDL) cholesterol levels are appreciated to confer increased risk for coronary heart disease (CHD).^{5–9} Several reports^{10–14} have described lipid levels in persons with SCI. Depressed levels of HDL cholesterol have been repeatedly confirmed in the population of those with SCI, possibly due to the lack of physical activity and the extreme sedentary lifestyles imposed by paralysis.

Abnormalities of carbohydrate metabolism, insulin resistance and hyperinsulinemia have been described in subjects with SCI.¹⁵ In addition, relationships between serum uric acid and plasma insulin levels and serum lipid levels have been described in the general population¹⁶ and in individuals with SCI.¹⁷ These metabolic abnormalities tend to cluster together and comprise a clinical entity, the metabolic Syndrome X, which is appreciated to impart increased risk for CHD.¹⁸

The neurological deficit in persons with SCI is closely related to the degree of immobilization. In prior, smaller studies the effect of completeness and level of lesion has not been noted to have a significant effect on the lipid profile in persons with SCI. The relationship of the lipid profile to the degree of neurological impairment was addressed in a large cohort of subjects with SCI.

Methods

Subjects

Serum lipid profiles were performed during a 24 month period from May 1994 to May 1996, on 541 subjects who were being seen for routine annual physical examination at the Comarr Spinal Injury Clinic at Rancho Los Amigos Medical Center, Downey, CA. The subjects were divided into two groups: tetraplegia (Tetra) and paraplegia (Para). These two groups were further divided into four subgroups of neurological deficit: complete tetraplegia (Com Tetra), incomplete tetraplegia (Incom Tetra), complete paraplegia (Com Para), and incomplete paraplegia (Incom Para). Completeness of lesion was defined according to ASIA standards.¹⁹ Ethnicity was determined by subject's response to the question of race.

Serum lipid profile and uric acid determinations

Serum lipid profiles were obtained on the subjects after an overnight fast. Total cholesterol and triglycerides (TG) were assayed on an automated blood analyzer (Hitachi, model 736). High-density lipoprotein (HDL) cholesterol was determined by phosphotungsten precipitation with enzymatic quantification by spectrophotometry. Low-density lipoprotein (LDL) cholesterol was calculated by the equation: total cholesterol-[HDL cholesterol + (TG/50)] = LDL cholesterol. Serum uric acid was measured by automated blood analyzer (Hitachi, model 736). Serum lipid risk factors for CHD were determined using criteria established by the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.²⁰ In addition, the ratio of total cholesterol to HDL cholesterol has been reported as a potent predictor of risk for CHD.^{21,22}

Statistical analyses

The results are reported as mean plus or minus standard error of the mean (mean $\pm$ SEM). All

analyses were performed on a personal computer using the SPSS 4.0 software program. Analysis of variance (ANOVA) applying a Scheffe' post hoc F ratio was used for the continuous variables. Chi-squared analyses were performed to determine differences between the groups and among the subgroups for percent distribution. Multiple regression analysis was used to determine the effect of neurological deficit controlling for ethnicity. Stepwise regression of BMI, HDL, TG, total cholesterol, ethnicity, neurological deficit, DOI, and age were used to predict uric acid.

Results

The total group consisted mostly of men ($n=468$) with a mean age of 36.6 ± 0.49 , (range = 18 to 73) years, and mean duration of injury (DOI) of 11.6 ± 0.38 (range = 1 to 57) years. The 73 women had a mean age of 41.4 ± 1.39 (range = 20 to 72) years, and mean DOI of 15.2 ± 1.31 (range = 1 to 44) years. There were no differences by gender for age or DOI. The distribution by ethnicity for the total group with SCI consisted of 274 (51%) Latino, 135 (25%) non-Latino white, and 132 (24%) African American individuals. The characteristics of the subjects partitioned by groups (Tetra and Para) and subgroups (Com Tetra, Incom Tetra, Com Para, Incom Para) are shown in (Table 1).

When the Tetra group was compared with the Para group, no significant differences were found for age, duration of injury (DOI) or the distribution of gender. Body mass index (BMI kg/m^2) was slightly, but significantly lower in the Tetra group. There were significantly more non-Latino white in the Tetra than in the Para group (Table 1).

The serum lipid profiles of the groups and subgroups were computed (Table 2). In the Tetra group, serum HDL cholesterol, total cholesterol and LDL-cholesterol were significantly lower than in the group with Para ($P < 0.01$; Table 2). Significant differences for mean values of the individual lipid fractions were not found within the Tetra or Para

Table 1 Characteristics of the subjects by group and subgroup

	Tetra ($n=247$)		Para ($n=294$)		Com Tetra ($n=156$)		Incom Tetra ($n=91$)		Com Para ($n=206$)		Incom Para ($n=88$)	
	mean	$\pm$ SEM	mean	$\pm$ SEM	mean	$\pm$ SEM	mean	$\pm$ SEM	mean	$\pm$ SEM	mean	$\pm$ SEM
Age (y)	38	0.67	37	0.65	37	0.77	40	1.21	37	0.8	36	1.11
DOI (y)	13	0.55	12	0.53	13	0.68	13	0.91	12	0.68	10	0.7
BMI (kg/m^2)	24.3	0.31	25.6	0.33*	24.1	0.36	24.8	0.53	25.1	0.39	26.8	0.64
	n		n		n		n		n		n	
Latino	111	45%	163	55%	67	43%	44	48%	111	54%	52	59%
N-L White	86	35%	49	17%*	60	39%	26	29% ^o	37	27%	12	14%*
Afric Amer	50	20%	82	28%	79	19%	21	23%	58	28%	24	27%
Male	221	90%	247	84%	140	90%	81	89%	175	85%	72	82%
Female	26	10%	47	16%	16	10%	10	11%	31	15%	12	18%

Definitions: DOI = duration of injury; BMI = body mass index; N-L White = nonLatino white; Afric Amer = African American; * $P < 0.01$ for Tetra vs Para; ^o $P < 0.05$ for Com Tetra vs Incom Tetra; * $P < 0.05$ for Com Para vs Incom Para

Table 2 Lipid profile by group and subgroup

	<i>Tetra</i> (<i>n</i> = 247)		<i>Para</i> (<i>n</i> = 294)		<i>Com Tetra</i> (<i>n</i> = 156)		<i>Incom Tetra</i> (<i>n</i> = 91)		<i>Com Para</i> (<i>n</i> = 206)		<i>Incom Para</i> (<i>n</i> = 88)	
	mean	±SEM	mean	±SEM	mean	±SEM	mean	±SEM	mean	±SEM	mean	±SEM
TC (mg/dL)	184	2.6	198	2.6*	181	3.1	190	4.5	196	2.4	205	5.3
TG (mg/dL)	122	5.5	122	5.5	122	7.3	121	8.2	119	6.2	129	11.6
HDL (mg/dL)	39	0.7	45	0.8*	38	0.9	40	1.2	44	0.9	47	1.4
LDL (mg/dL)	121	2.4	129	2.3*	118	2.8	125	4.4	128	2.6	132	4.6

Definitions: TC = total cholesterol; TG = triglyceride cholesterol; HDL = high density lipoprotein cholesterol; LDL = low density lipoprotein cholesterol; * $P \leq 0.01$ for Tetra vs Para

subgroups for completeness of lesion. However, a significant inverse relationship was found for degree of neurological deficit and serum HDL level ($r = 0.19$, $P < 0.001$). The subgroup with the most impairment had the lowest mean serum HDL cholesterol value, and the subgroup with the least impairment had the highest mean level of serum HDL cholesterol; appropriate for degree of neurological deficit, the other two subgroups had values for HDL cholesterol which were intermediate (Table 2). The serum triglyceride level was not statistically different between the two groups. However, there was a significant inverse correlation between serum triglycerides and HDL cholesterol values ($r = -0.32$, $P < 0.0001$).

Serum HDL cholesterol levels < 35 mg/dL are recognized as an independent risk factor for CHD. A greater fraction of subjects in the Tetra group had HDL cholesterol less than 35 mg/dL than those in the Para group (38 vs 21%; $P < 0.001$). A significant inverse relationship was found for degree of neurological deficit and percentage of subjects within each subgroup for serum LDL cholesterol values ≥ 130 mg/dL, (Comp Tetra 51%, Incom Tetra 42%, Com Para 49%, and Incom Para 32%) ($\chi^2_{(3)} = 12.6$, $P < 0.005$). The ratio of total cholesterol to HDL cholesterol was significantly lower in the Para group than the Tetra group (4.8 vs 5.2%, $P < 0.01$). The distribution of subjects within a total to HDL cholesterol ratio of greater than or equal to 5.0 was found to be slightly higher in the Tetra group compared with the Para group (43 vs 38%, respectively). No significant differences were found among the four subgroups for the total cholesterol to HDL cholesterol ratio greater than or equal to 5.0. No other significant differences were found between the Tetra and Para groups for the distribution of cardiovascular lipid risk factors.

Ethnicity was found to have a significant effect on HDL cholesterol. Subjects in the Latino and non-Latino white groups had significantly lower serum HDL cholesterol than those in the African American group (40.5 ± 1.09 and 40.8 ± 1.17 vs 47.3 ± 0.70 , respectively, $P < 0.0001$). Using a multiple regression model to test the effect of the degree of neurological deficit (Com Tetra, Incom Tetra, Com Para, Incom Para) over and above the effect of ethnicity on HDL

cholesterol, the level of impairment was found to be significant ($r = 0.26$, $P < 0.0001$). The greater the neurological deficit, the lower the mean HDL-cholesterol value. African American had a lower total to HDL cholesterol ratio than non-Latino whites or Latinos (4.40 ± 0.15 vs. 5.17 ± 0.18 and 5.18 ± 0.12 , $P < 0.005$).

BMI was found to correlate with triglycerides ($r = 0.33$, $P < 0.0001$) and HDL cholesterol ($r = -0.23$, $P < 0.0001$). In addition, uric acid correlated with BMI ($r = 0.36$, $P < 0.0001$), triglycerides ($r = 0.30$, $P < 0.0001$) and HDL cholesterol ($r = -0.22$, $P < 0.0001$).

Discussion

The serum lipid profile has been shown to be a potent predictor of CHD.⁵⁻⁹ In a report by LaPorte,¹¹ serum HDL cholesterol appeared to be related to level of activity, with marathon runners having the highest values and those with acute spinal cord injury, the lowest. However, within the lowest end of the activity spectrum, it has been unclear as to whether the level of mobility has a beneficial effect upon serum HDL cholesterol. Until this present study, the numbers of patients studied were relatively small, and lacking the power to determine if the reduced activities of daily living of a severely impaired person had an effect on the lipid profile.

Serum HDL cholesterol generally has been reported to be depressed in individuals with SCI.¹⁰⁻¹⁴ In the subjects with SCI and in the controls, strong inverse correlations have been demonstrated between serum triglycerides and HDL cholesterol.¹⁰ Although plasma insulin levels were not determined in our study, 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,²³ which tends to lower serum HDL cholesterol, possibly by enhancing clearance mechanisms.²⁴ In the report herein, the degree of neurological impairment has been demonstrated to correlate with the serum level of HDL cholesterol. In general, the individuals with more restricted mobility had lower HDL cholesterol levels, although the level of physical activity was not specifically addressed.

Of note, a fairly large percentage of the population studied had an absolute or a relative elevation in the serum LDL cholesterol level. For unclear reasons, there appeared to be a correlation between the percentage of subjects with LDL cholesterol values ≥ 130 mg/dL and degree of neurological impairment, with more complete and higher lesions associated with higher percentages for this degree of LDL cholesterol elevation. It may be speculated that dietary factors may have played a role in this observation.

The ratio of serum total to HDL cholesterol has been reported by Stampfer *et al*²² to be a particularly strong discriminator for risk of myocardial infarction; a one unit increase in this ratio was associated with a mean increase of 53% in the risk of myocardial infarction. Despite significantly higher LDL cholesterol values in the Para group, the ratio of serum total cholesterol to HDL cholesterol was significantly higher by about half of one percent in the Tetra group compared with the Para group, demonstrating the predominant effect on the lipid profile of the depressed HDL cholesterol values in those with higher spinal cord lesions. Approximately 40% of the total population had a ratio of serum total cholesterol to HDL cholesterol greater than 5.0. Recent studies have clearly demonstrated that a reduction in serum LDL cholesterol level, as well as the ratio of serum total cholesterol to HDL cholesterol, is associated with reduction in events of CHD.^{25–28}

Factors other than immobilization may play a role in determining the serum triglyceride and/or HDL cholesterol level. High calorie and high fat diets have been shown to increase serum triglycerides and depress serum HDL cholesterol levels,²⁹ whereas only increasing dietary fat content while maintaining calories constant may result in elevating this lipid fraction. Although moderate alcohol consumption has been demonstrated to elevate HDL cholesterol levels,³⁰ excessive alcohol intake may also depress serum HDL cholesterol levels.³¹ Cigarette smoking has also been demonstrated to be associated with lower serum HDL cholesterol levels.³² As in the general population, a genetic predisposition to low values may occur in patients with SCI.

The serum HDL cholesterol level has been found in several population-based studies to be higher in African Americans than in other races.^{33–37} In the study herein, our findings demonstrate that in individuals with SCI, African Americans tend to have higher HDL cholesterol values than non-Latino whites or Latinos. However, controlling for ethnicity, level and completeness of lesion played an even stronger role in determining the serum HDL cholesterol concentration. Of note, African Americans had a significantly lower total cholesterol to HDL ratio than the other ethnic groups studied.

In a prior report by Zhong *et al*¹⁷ in 197 subjects with chronic spinal cord injury, the levels of serum uric acid and serum triglycerides in the subgroup with hyperinsulinemia were significantly higher than in

subjects with normal plasma insulin levels. By linear regression analysis, the serum uric acid concentration was positively associated with peak plasma insulin level and BMI.¹⁷ In the study herein, serum uric acid was directly correlated to BMI and serum triglycerides and inversely related to serum HDL cholesterol, which may reflect the metabolic consequences of insulin resistance and hyperinsulinemia. It should be mentioned that BMI is a surrogate measure for obesity and may be somewhat more unreliable as a predictor of adiposity in persons in whom lean tissue is lost, as occurs with the loss of muscle and bone in those with SCI.

Our findings suggest that level of mobility, and thus postulated level of physical activity, has an effect on the serum HDL cholesterol concentration in persons with SCI, even in the most severely impaired. African Americans tend to have higher levels of serum HDL cholesterol than non-Latino whites or Latinos. However, independent of the effects of ethnicity, level and completeness of lesion exerts a predominant effect on serum HDL cholesterol values, possibly due to differences in level of activity among the subgroups. The associations demonstrated among serum lipid values, serum uric acid and BMI suggest that individuals with spinal cord injury have several of the features of the metabolic constellation of Syndrome X^{18,35} and thus are at increased risk for CHD.

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