High density lipoprotein cholesterol in individuals with spinal cord injury: The potential role of physical activity

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Study design/Methods: Literature review. Papers were selected from a literature search of both the Medline and Current Contents data bases and through extensive cross checking of references from the author's personal files.

Objectives: To evaluate the evidence for a reduced level of HDL-C in individuals with spinal cord injury and to discuss physiologic and behavioral factors that may be responsible for the observed reduction, with emphasis on the role of physical activity.

Results/Conclusions: The evidence presented suggests that HDL-C may be lower in persons with SCI; however, the available data should be interpreted cautiously due to lack of control for important confounding factors such as smoking, alcohol consumption and physical activity. Results suggest a potential association between increased physical activity and increased HDL-C in persons with SCI. However, the mode, frequency, intensity and duration of activity and the physiologic mechanism responsible for this association have yet to be clearly elucidated.

Keywords: spinal cord injury; cardiovascular fitness; high density lipoprotein cholesterol; physical activity

Introduction

The life expectancy of persons with spinal cord injury (SCI) has increased dramatically over the past 30 years. For example, the life expectancy for a person injured between 15 and 25 years of age is 54.3 years for persons with tetraplegia and 62.1 years for persons with paraplegia.¹ Similar to the able-bodied population, the longer survival with SCI has been accompanied by a higher prevalence of chronic disease and degenerative conditions in this population.^{2,3} The important causes of death in SCI patients have shifted from infectious diseases, renal failure and pneumonia⁴ to cardiovascular disease and cancer, thus, approximating the causes of death seen in the able-bodied population.^{5,6} Recent studies have shown that cardiovascular diseases were the leading cause of death in persons with longstanding SCI (over 30 years) and among those with SCI age 60 and over.⁷ Adults with SCI are at increased risk for cardiovascular morbidity,^{8,9} and mortality^{5,7,10} compared with able-bodied population. There is also evidence to suggest that the prevalence of undetected asymptomatic coronary heart disease is higher in SCI individuals. Bauman *et al*¹¹ reported a 65% prevalence of silent cardiac ischemia on the basis of an abnormal arm exercise thallium scan

in 20 asymptomatic subjects with paraplegia (mean age 53 years, mean duration of injury 17 years). Interestingly, electrocardiographic evidence of ischemia during arm exercise was present in only 25% of these subjects. Blocker *et al*⁸ have also reported an increased prevalence of electrocardiographic ST-segment depression in 98 long-term survivors compared with the general population.

The increased prevalence of coronary heart disease in individuals with SCI is not explained by higher levels of several established cardiovascular disease risk factors such as blood pressure, cigarette smoking or total serum cholesterol (TC).^{12–14} One potential factor related to the increased risk for coronary heart disease in SCI may be a reduced level of high density lipoprotein cholesterol (HDL-C) in SCI subjects, which may, in part, be associated with a decreased level of physical activity in this group. There is considerable clinical and epidemiologic evidence for an association between the level of HDL-C or the ratio TC/HDL-C and cardiovascular disease risk in able-bodied populations.^{15–19} HDL-C less than 35 mg/dl (0.91 mmol/L) or TC/HDL-C ratio over 4.0 typically define the risk threshold; however, the association between the level of HDL-C and cardiovascular disease risk is continuous, thus these cut points may be considered somewhat arbitrary.²⁰ The purpose of this paper is to evaluate the evidence

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Table 1 High density lipoprotein (HDL-C), total cholesterol (TC) and triglycerides (TG) in spinal cord injured (SCI) subjects and able-bodied controls

Reference	Sample	Mean age (years)	Duration of injury (years)	HDL-C (mg/dl) ¹ (Mean ± SD)	TC (mg/dl) ¹ (Mean ± SD)	TC/HDL ratio	TG (mg/dl) ² (Mean ± SD)	Control for confounders
Nikkila ²⁸	14 SCI M	Range (17–60)	Acute	31.3 ± 5***	172.2 ± 46.3*	5.5 ^a	127.5 ± 33.6	Body weight
	14 CM			45.5 ± 10.4	235.8 ± 42.5	5.2	104.5 ± 54.6	
	9 SCI W			33.5 ± 8.1***	192.6 ± 45.5*		144.4 ± 49.6*	
Heldenberg <i>et al</i> ²⁷	9 CW	21	0.37	59.4 ± 11.6	236.6 ± 52.9		101.0 ± 56.7	5/10 controls smoked 20 cigarettes/day, diet assessed
	10 TM (Comatose)			40.8 ± 10.5***	205.2 ± 49.1	5.0 ^a	69.7 ± 37.0	
	10 CM			62.1 ± 12.0	205.4 ± 30.2	3.1	69.1 ± 31.3	
Vaziri <i>et al</i> ²⁵	10 PM	59	27	12.0 ± 8.0*	152.0 ± 56.0	12.7 ^a	180.0 ± 96	No
	(Renal Failure)							
	10 PM							
Brenes <i>et al</i> ²⁴	(Healthy)	59	Variable (<6 weeks to over 1 year)	31.0 ± 9.0	142.0 ± 18	4.6	104.0 ± 40*	Body mass index, smoking, Alcohol, anti-spastic medications
	31 PM							
	25 TM							
Bauman <i>et al</i> ²⁹	6 PW	28		34.8 ± 6.8***	172.0 ± 39	4.9 ^a	129 ± 54	No
	4 TW			40.9 ± 6.8***	154.0 ± 28	3.8	90 ± 39	
	126 CM							
Shetty <i>et al</i> ³²	111 CW	29		46.1 ± 15.0	192.0 ± 44	4.2	119 ± 90	Excluded those with chronic disease, alcohol abuse, lipid lowering medication
	50 TM			52.5 ± 13.0	174.0 ± 45	3.3	84 ± 32	
	50 PM			40.0 ± 1.0***	188.0 ± 6.0**	4.9	101 ± 8*	
Krum <i>et al</i> ¹³	50 CM	49	10	37.0 ± 1.0***	191.0 ± 5.0**	5.5	148 ± 15	No
	21 TM			48.0 ± 2.0	210.0 ± 4.0	4.6	134 ± 11	
	21 CM			33.9 ± 1.6***	175.5 ± 5.6**	5.5	144.3 ± 15.3	
Cardus <i>et al</i> ³⁰	102 SCI M	25–63	29% over 10 years	48.3 ± 2.8	213.0 ± 10.5	4.6	125.9 ± 17.8	No
	52 SCI W			43.2 ± 11.6*	207.7	4.8 ^a	NA	
	Control - Age/sex matched data from Australian national sample			52.1 ± 13.5	NA	NA		
Zlotolow <i>et al</i> ³³	46 PM	26	5	43.0 ± 2.1	179.0 ± 6.6	4.6 ^a	179 ± 6.6	No
	50 TM in four subgroups							
	25 young short DOI							
	30 young long DOI	49	19	43.0 ± 2.0	181.0 ± 8.1	4.4	181 ± 8.1	
	29 old short DOI			44.0 ± 2.4	213.0 ± 6.0	4.8	213 ± 6.8	
	12 old long DOI			44.0 ± 3.2	205.0 ± 13.4	4.7	205 ± 13.4	
	Control - US National Data	48	>1.5	NA	NA	NA	NA	Body mass index, diet
	28 PM			35.0 ± 2.0***	195.0 ± 8.0	5.6 ^a	153 ± 14	
	52 CM			49.0 ± 2.0	209.0 ± 6.0	4.3	141 ± 11	

continued

Table 1 continued

Reference	Sample	Mean age (years)	Duration of injury (years)	HDL-C (mg/dl) ¹ (Mean ± SD)	TC (mg/dl) ¹ (Mean ± SD)	TC/ HDL ratio	TG (mg/dl) ² (Mean ± SD)	Control for confounders
Walker and Shephard ¹⁴	48 PT (39 M, 9 W)	33	0.3	35.1 ± 10.4	176.7 ± 29.7	5.5	167.4 ± 77.9	No
Maki <i>et al</i> ²⁶	46 M (23 T/23 P)	50	18	39.0 ± 9.0	186.0 ± 37.0	5.0	136 ± 61	No
Janssen <i>et al</i> ³¹	37 M	37	15					
	8TM			39.7 ± 5.4	188.0 ± 39.4	4.6	124.9 ± 42.5	Assessed smoking, alcohol, body
	5 High PM			40.9 ± 5.4	203.8 ± 31.2	5.1	161.2 ± 76.2	mass index, skinfolds, aerobic
	10 Mid PM			39.4 ± 6.6	206.1 ± 45.9	5.4	163.9 ± 75.3	capacity, physical activity
	14 Low PM			42.5 ± 8.9	198.4 ± 50.6	4.9	138.2 ± 52.3	
	Age/gender matched Dutch National sample							No adjustment for confounders in comparison with control

¹To convert to mmol/L multiply by 0.02586. ²To convert to mmol/L multiply by 0.01129. ³TC/HDL-C ratio calculated from mean data presented in the paper. *P* values for difference between SCI and control. **P* < 0.05, ***P* < 0.01, ****P* < 0.001, *****P* < 0.0001. M = men, W = women, C = control, T = tetraplegic, P = paraplegic, DOI = duration of injury, NA = not available

for a reduced level of HDL-C in individuals with SCI and to discuss the physiologic and behavioral factors that may be responsible for the observed reduction, with emphasis on the role of physical activity and cardiovascular fitness.

HDL-C

Several cross-sectional studies have compared HDL-C levels in individuals with SCI with able-bodied control groups. Four of the frequently cited papers on this issue^{21–24} report on the same data. Only the original data of Brenes *et al*²⁴ is included in this review.

The major features and results of the available published reports are presented in Table 1. With the exception of the reports by Vaziri *et al*,²⁵ Walker and Shephard¹⁴ and Maki *et al*,²⁶ these studies compared HDL-C, TC, triglycerides (TG) and or TC/HDL-C ratio in samples of SCI individuals with able-bodied control groups. Subjects in these studies were predominantly men (total *n* = 637 men, 71 women). Although the total number of SCI individuals evaluated over all studies is considerable, the sample size of individual studies is generally small and heterogeneous with respect to age, level of lesion, and duration of injury. Over half the reported studies involve less than 50 individuals with SCI. The duration of injury ranges from acute hospitalized patients^{24,27,28} to persons living with SCI for over 18 years.^{13,25,26,29,30} The age range of SCI subjects is also large (approximately 17–71 years).

Despite the heterogeneity in samples both between and within studies, the results across studies are remarkably consistent. With the exception of the reports by Cardus *et al*³⁰ and Janssen *et al*,³¹ results consistently show a significant reduction in HDL-C in SCI individuals compared with able-bodied controls. The mean HDL-C in healthy SCI individuals was 38.6 mg/dl (0.99 mmol/L) [range 31–44 mg/dl (0.8–1.14 mmol/L)] compared to 50.2 mg/dl (1.30 mmol/L) [range 45.5–62 mg/dl (1.18–1.60 mmol/L)] in able-bodied controls. The mean HDL-C in the SCI individuals is also lower than that reported in the National Health and Nutrition Examination Survey [47 mg/dl (1.13 mmol/L)] for 45–54-year-old able-bodied men.¹⁵

Several investigators have reported the percentage of subjects with HDL-C below the risk threshold [35 mg/dl (0.91 mmol/L)] and/or compared this percentage between SCI individuals and able-bodied controls. Shetty *et al*³² reported 57% of men with tetraplegia compared with 10% of able-bodied men had HDL-C less than 35 mg/dl (0.91 mmol/L). Bauman *et al*²⁹ reported that 40% of men with paraplegia and 34% of men with quadriplegia had HDL-C less than 35 mg/dl (0.91 mmol/L). Zoltolow *et al*³³ found that 14 of 28 men with paraplegia had HDL-C less than 35 mg/dl (0.91 mmol/L) while Maki *et al*,²⁶ in a group of 23 men with tetraplegia and 23 men with paraplegia showed 57% had HDL-C less than 40 mg/

dl (1.03 mmol/L). Janssen *et al*³¹ found 17% of 37 men with SCI had HDL-C less than 35 mg/dl (0.91 mmol/L).

The average magnitude of the differences in HDL-C between SCI and able-bodied controls over all studies was 13.4 mg/dl (0.35 mmol/L) [range 8.9–21.3 mg/dl (0.02–0.55 mmol/L)]. This difference in HDL-C represents a large potential increase in risk for cardiovascular disease in the SCI population. Data from the Physicians Health Study of 14 916 men followed for 5 years¹⁷ and the Framingham Heart Study¹⁶ indicate approximately a 3.0–3.5% increase in cardiovascular disease risk for each 1 mg/dl (0.026 mmol/L) decrease in HDL-C. Brenes *et al*,²⁴ using risk estimates developed from the Framingham data, estimated the mean level of HDL-C in their SCI subjects [34.8 mg/dl (0.90 mmol/L)] predicted an excess heart attack risk of 60%. Janssen *et al*,³¹ also using Framingham risk data estimated an increased risk for cardiovascular disease of 18% in SCI subjects based on their level of HDL-C. These risk estimates for level of HDL-C in SCI individuals should be interpreted cautiously, as the importance of low HDL-C or the magnitude of the risk associated with low HDL-C in SCI individuals has not been established.

Total cholesterol

Total cholesterol is generally lower in SCI individuals compared with able-bodied controls. In the seven studies where SCI/able-bodied comparisons are reported, 3/7 (43%) show significantly lower TC in the SCI subjects. In the four studies where nonsignificant differences are reported the TC level of the SCI subjects was consistently lower than that of the able-bodied comparison group. The mean TC level in the studies reviewed was 186.4 mg/dl (4.82 mmol/L) [range 172–206.1 mg/dl (4.45–5.33 mmol/L)] in SCI subjects compared with 210.9 mg/dl (5.45 mmol/L) [range 192–235.8 mg/dl (4.97–6.10 mmol/L)] in able-bodied subjects. Janssen *et al*³¹ reported a lower prevalence of elevated TC in SCI men (14%) compared with able-bodied controls. Shetty *et al*³² reported 81% of 21 men with tetraplegia had TC less than 200 mg/dl (5.17 mmol/L) compared with 50% of able-bodied controls. Among the men with tetraplegia with TC less than 200 mg/dl (5.17 mmol/L), 53% also had HDL-C less than 35 mg/dl (0.91 mmol/L) compared with only 10% of able-bodied controls with both low TC and low HDL-C. Low levels of HDL-C are still a significant risk factor for cardiovascular disease even in the presence of low TC. Data from the Physicians Health Study suggest that higher levels of HDL-C are more strongly associated with protection from cardiovascular disease among those with lower levels of TC.¹⁷ Thus the ratio of TC/HDL-C has been shown to be a powerful predictor of cardiovascular disease risk. It is estimated that a change of 1 unit in this ratio is associated with a 53% increase in risk of myocardial infarction after adjustment for other risk factors.¹⁷

Total cholesterol/HDL-C

Five of the 12 studies reviewed provided data on TC/HDL-C ratio. The mean TC/HDL-C ratio across the five studies in healthy SCI subjects was 5.11 (range 4.6–5.5). Only two studies presented TC/HDL-C ratios for both SCI subjects and able-bodied controls.^{29,32} Both reports found no significant differences between SCI and able-bodied controls, although the TC/HDL-C ratio was consistently higher in the SCI subjects. The results were similar for the remaining seven studies where the TC/HDL-C ratio could be calculated from the reported levels of TC and HDL-C (TC/HDL-C ratio mean = 4.8, range 4.4–5.5). In the studies reviewed the TC/HDL-C ratio in SCI individuals generally exceeded the risk level of 4.0, with the exception of a TC/HDL-C ratio (3.8) in six women with tetraplegia.²⁴

Triglycerides

Six of the 12 studies included in Table 1 provided data on serum TG. Serum TG were significantly higher in SCI compared with controls in two of the reports.^{25,28} In the four other studies TG tended to be higher in SCI than in controls, however the differences were not statistically significant. The mean TG level over the six studies included in Table 1 was 133 mg/dl (1.50 mmol/L) in SCI compared with 111.4 mg/dl (1.26 mmol/L) in able-bodied controls. As will be discussed in more detail in a following section, elevated TG are often associated with reduced levels of HDL-C, both of which are associated with increased coronary heart disease risk.^{34,35}

Limitations of available data

The available literature suggests decreased HDL-C, normal or low TC, and higher TG and high TC/HDL-C ratios in SCI individuals compared with able-bodied controls. However, these results need to be interpreted cautiously. The majority of the available evidence is for men. The data for women are based on three studies with a total *n* of 71. The reason for the observed differences in HDL-C between able-bodied and individuals with SCI are unclear. There are a number of factors that significantly effect HDL-C. For example, cigarette smoking,^{36,37} beta blockers or diuretics,^{38,39} anti-spastic medication³⁸ decrease HDL-C, whereas moderate alcohol intake,^{40,41} and physical activity⁴² increase HDL-C. Diet may also effect HDL-C level although published results are inconsistent.^{43–46} Bauman *et al*⁴⁷ have recently reported significantly higher HDL-C in African-American compared with white or Latino men with chronic SCI. The studies presented in Table 1 have not adequately controlled for these potentially important confounders. Several studies have measured confounding factors; however, they have not used this information to adjust lipid values for comparisons between SCI and able-bodied

samples.^{13,27,31} Confounders need to be considered in future studies comparing SCI individuals with able-bodied controls to determine the magnitude of the difference, if any, in HDL-C between these groups and to determine what factors may be associated with reduced HDL-C in this population. The next section describes a hypothetical model that offers a potential explanation for the reduced level of HDL-C in SCI and discusses the empirical evidence to support several of the hypothesized associations.

Biologic plausibility for lower HDL-C in SCI

SCI results in a constellation of changes including decreased physical activity, decreased lean and increased fat mass, and increased paralyzed muscle mass that individually, or in concert, may increase the probability for insulin resistance and hyperinsulinemia, which in turn may be associated with increased plasma triglycerides and decreased HDL-C. A model depicting these associations is presented in Figure 1. There is empirical evidence to support several important aspects of these hypothesized associations.

Decreased physical activity

Although limited, the data on the physical activity level of individuals with SCI suggests they lead a sedentary lifestyle and avoid participation in vigorous physical activity to a greater extent than their able-bodied counterparts. Coyle and Kinney⁴⁸ in a survey of 790 adults with physical disabilities (23% SCI) showed that sedentary pursuits (reading, TV viewing, socializing,

and art and music appreciation) comprised their favorite leisure time activities. Only 11% of the sample listed non-competitive sport as their favored leisure time pursuit. Dearwater *et al*⁴⁹ using an electronic motion sensor to monitor physical activity, found the level of activity in a sample of 28 men with SCI to be 30-fold lower than in similar aged, able-bodied college students.

A mail survey of 229 college graduates with locomotor disabilities (59 semi-ambulatory, 115 paraplegics, 55 tetraplegics) assessed physical activity on a 5-point scale in response to the question 'When compared to other persons of your age your physical activity level is (1) much less than others to (5) much greater than others. Approximately 55% of the sample rated their current physical activity level as less or much less than their peers.⁵⁰

Decreased physical fitness

The negative effect of inactivity on cardiovascular fitness is well documented in both able-bodied and SCI populations.^{51,52} Both cross sectional and longitudinal studies in individuals with SCI have demonstrated that peak oxygen uptake is higher in active compared to inactive groups and that peak oxygen uptake can be increased significantly as result of endurance exercise training.^{53,54–57} It is estimated that approximately 25% of individuals with paraplegia, despite a relatively young age, show a peak oxygen uptake less than or equal to 15 ml/kg/min.⁵² This level of cardiovascular fitness is inadequate for a young adult and barely sufficient to meet the demands of independent living. Low levels of cardiovascular fitness are associated with increased risk for cardiovascular disease and total mortality in able-bodied individuals.^{58–60}

Changes in body composition

Increased body fat is not only a risk factor for coronary heart disease through increased insulin resistance and hyperinsulinemia leading to non-insulin dependent diabetes mellitus (NIDDM),^{61,62} but is also associated with other chronic diseases such as cancer,⁶³ and hypertension.⁶⁴ Denervation and sedentary lifestyle associated with SCI result in increased fat and decreased lean tissue. Bauman *et al*¹¹ reported lean tissue to be 33% lower in a sample with SCI compared to ambulatory controls matched for age, gender, height and weight. They hypothesized that decreased lean tissue may be responsible for the increased insulin resistance often associated with SCI. Maki *et al*²⁶ reported significant associations between central obesity, measured by abdominal circumference, and serum TG ($r=0.59$, $P<0.001$), HDL-C ($r=-0.42$, $P<0.01$) and TC/HDL-C ratio ($r=0.48$, $P<0.01$) in 43 men with SCI. Individuals with SCI are prone to the development of obesity. Resting metabolic rate is 10–30% lower in SCI compared with able-bodied persons of comparable age⁶⁵ with metabolic rate inversely

Figure 1 Hypothetical model: The effect of spinal cord injury on physical activity, high density lipoprotein cholesterol and cardiovascular disease risk

associated with level of lesion.⁶⁶ The lower resting metabolic rate and the limited muscle mass available to increase metabolism during exercise make it difficult for individuals with SCI to control weight.

Insulin resistance and hyperinsulinemia

Several investigators have reported a high prevalence of impaired glucose tolerance among individuals with long-standing SCI.^{11,67–69} For example, Bauman and Spungen¹¹ found 22% of 100 SCI men (50 paraplegic, 50 tetraplegic) were diabetic based on results of an oral glucose tolerance test, compared with only 6% of age-matched, able-bodied controls. They noted that the results of glucose tolerance tests were normal in 82% of control subjects compared with 38% of subjects with tetraplegia and 50% of subjects with paraplegia. Bauman⁷⁰ provides an excellent review on carbohydrate and lipid metabolism in individuals after SCI.

Poor glucose tolerance in SCI is characterized by elevated levels of plasma insulin, suggesting an increase in insulin resistance.^{11,68} Both poor glucose tolerance and high insulin levels have been associated with increased cardiovascular disease risk.^{71–73} High levels of plasma insulin have been associated with decreased HDL-C, possibly through an increase in plasma TG.^{29,69,74–76} An association between elevated insulin and elevated TG has been demonstrated in individuals with SCI. For example, Zhong *et al*⁶⁹ have shown significantly higher TG in a subgroup of 197 SCI individuals, mean age 50 years, mean duration of injury 18 years, who were hyperinsulinemic compared with a subgroup with normal insulin levels. Increased levels of TG have also been associated with reduced HDL-C in both SCI and able-bodied samples. Bauman *et al*²⁹ showed a significant inverse association between serum TG and HDL-C in SCI individuals (50 paraplegic, 50 tetraplegic) and in able-bodied controls. In a subgroup of 12 paraplegics, Bauman *et al*²⁹ also reported a significant positive correlation between insulin sensitivity and HDL-C. Laakso *et al*⁷⁴ reported that able-bodied subjects who were insulin resistant had higher TG and lower HDL-C than subjects with normal glucose tolerance. Significant inverse correlations between serum TG and HDL-C in both SCI and able-bodied subjects ($r = -0.41$ – $r = -0.67$) have also been reported by several other investigators.^{31,33,41} However, Bauman *et al*²⁹ failed to detect significant differences in HDL-C in SCI subjects who were classified as normal, impaired, or diabetic based on an oral glucose tolerance test.

A key unanswered question is why does insulin resistance develop in individuals with SCI? As mentioned previously, denervation of skeletal muscle, changes in body composition (decreased lean and increased fat mass), and reductions in physical activity associated with SCI may all play a role in increasing insulin resistance. Duckworth *et al*⁶⁷ have shown that an insulin resistant group of SCI patients was significantly heavier than SCI patients with normal

insulin sensitivity even though their level of body mass index was not such to be classified as obese. Bauman and Spungen¹¹ using body composition measured by dual energy X-ray absorptiometry (DEXA), found the average per cent fat in SCI subjects to be approximately 30%; however, unlike reports in able-bodied subjects, adiposity was not a significant determinant of insulin sensitivity.⁷⁷ Additional reports have shown decreased insulin sensitivity associated with increased body fat in healthy able-bodied subjects^{78–80} and able-bodied subjects with NIDDM.⁸¹ It is possible that factors other than increased body fat are important determinants of insulin sensitivity in SCI, or perhaps the currently available measures of body composition do not provide accurate estimates of body fat in individuals with SCI.⁸²

Decreased muscle mass associated with SCI may play a role in the insulin resistance observed in this group^{83,84} considering that skeletal muscle is a major site of glucose uptake. In addition, paralyzed muscle associated with SCI may also affect insulin resistance. Both *in vivo* and *in vitro* animal studies have suggested impaired glucose uptake and insulin resistance in denervated muscle.^{85,86}

Reduced physical activity also plays an important role in impaired glucose tolerance and hyperinsulinemia.^{87,88} Minimal amounts of physical activity have been shown to improve glucose tolerance.⁸⁹ Exercise training decreases insulin secretion in both the basal state and in response to a carbohydrate load.^{90–92} However, Duckworth *et al*⁶⁷ did not find an association between level of physical activity and insulin sensitivity in SCI subjects. Increased cardiovascular fitness has also been associated with increased insulin sensitivity.⁹³ Bauman and Spungen¹¹ reported that peak oxygen uptake measured during arm ergometry was the strongest determinant of peripheral insulin sensitivity in 12 individuals with paraplegia.

It appears that a reduction in physical activity in SCI, which favors decreased cardiovascular fitness, increased fat mass and decreased lean mass may play a pivotal role in the apparent reduction in HDL-C observed in this group. However, the data on the association between either physical activity or cardiovascular fitness and HDL-C in individuals with SCI is limited. In the following section we review the literature regarding the association of both physical activity and cardiovascular fitness and HDL-C in individuals with SCI.

Physical activity and HDL

Numerous cross-sectional and longitudinal studies in able-bodied individuals have reported a favorable effect of increased physical activity on HDL-C.⁴² However, there is considerable controversy regarding the amount and intensity of physical activity required to elicit this effect.⁹⁴ Several studies have suggested that vigorous exercise training programs, ie, running, stair climbing etc. greater than 75% maximal heart

rate or greater than 7 kcal/min are necessary to elicit significant increases in HDL-C^{45,95-97} while other reports suggest that HDL-C can be significantly increased by low to moderate intensity exercise training.⁹⁸⁻¹⁰¹ A recent report by Crouse *et al*¹⁰² suggests that changes in blood lipids in hypercholesterolemic men are not influenced by exercise intensity when the caloric expenditure of the exercise programs are held constant.

In contrast to an extensive literature on HDL-C and physical activity in able-bodied samples the literature regarding the effect of physical activity on HDL-C in SCI subjects is limited to four cross-sectional studies of physical activity and HDL-C,^{13,24,31,103} three reports on the cross-sectional association between cardiovascular fitness and HDL-C^{29,31,104} and one exercise training study.¹⁰⁵

Cross-sectional studies of physical activity

Results from two studies which report SCI athlete/non-athletes comparisons for HDL-C, TC and TG are presented in Table 2.^{24,103}

In the Brenes *et al*²⁴ report athletes were involved in an aerobic exercise program a minimum of 3 days per week and participated in the following sports: 12 track and field, five swimming, three weight training, and two road racing. Dallmeijer *et al*¹⁰³ defined active participants as those who had engaged in regular sport activities for at least 6 months. Results of both studies showed significantly higher HDL-C in active compared with sedentary men. Triglyceride levels did not differ significantly between male athletes and sedentary controls in either study. Brenes *et al*²⁴ reported significantly lower TC in

athletes compared with controls, while no significant differences in TC were noted between activity groups by Dallmeijer *et al*.¹⁰³ The differences in TC and HDL-C between male SCI athletes and SCI controls reported by Brenes *et al*²⁴ persisted after control for body mass index, cigarette smoking and alcohol consumption. It is interesting to note that the mean HDL-C in the male SCI athletes [42.7 mg/dl (1.10 mmol/L)] in the Brenes study, while higher than sedentary SCI controls, was still lower than that reported for the sedentary able-bodied control group [46 mg/dl (1.19 mmol/L)], although the difference was not statistically significant.²⁴ This suggests that in some individuals the amount of training associated with participation in wheelchair sports may not be of sufficient intensity or duration to increase HDL-C in persons with SCI to the levels typically observed in able-bodied samples. Multiple regression analysis reported by Dallmeijer *et al*¹⁰³ indicated that sport participation was the only significant independent predictor of HDL-C while both age and time since injury were significant predictors of TG.

Additional evidence for an association between physical activity and HDL-C in SCI is available in the reports of Krum *et al*¹³ and Janssen *et al*.³¹ Krum *et al*¹³ assessed physical activity on an ordinal 5-point scale (0=no exercise to 4=wheelchair athlete) in 102 SCI patients, ages 25-64 years. Results showed a non-significant positive association between HDL-C and reported exercise ($r=0.54$, $P=0.086$). Janssen *et al*³¹ also reported no significant association between the frequency of physical activity (number of hours per week of active sport participation) and HDL-C.

Table 2 High density lipoprotein cholesterol (HDL-C), total cholesterol (TC) and triglycerides (TG) in active and sedentary individuals with spinal cord injury

Reference	Sample	Age (years) (Mean $\pm$ SD)	HDL-C (mg/dl) ¹ (Mean $\pm$ SD)	TC (mg/dl) ¹ (Mean $\pm$ SD)	TG (mg/dl) ² (Mean $\pm$ SD)
Brenes <i>et al</i> ²⁴	17 M SCI Athletes (8 T, 7 P, 2 ?)	28	42.7 $\pm$ 6.9**	151 $\pm$ 27*	115 $\pm$ 84
	56 M SCI Sedentary (31 T, 25 P)	29	34.8 $\pm$ 6.8	172 $\pm$ 39	129 $\pm$ 54
	5 W SCI Athletes (1 T, 4 P)	28	50.8 $\pm$ 4.0	145 $\pm$ 23	72 $\pm$ 30
	10 W SCI Sedentary (6 T, 4 P)	29	40.9 $\pm$ 6.8	154 $\pm$ 29	90 $\pm$ 39
Dallmeijer <i>et al</i> ¹⁰³	11 TM Active	29	43.7 $\pm$ 8.1*	177.9 $\pm$ 42.5	118.7 $\pm$ 59
	13 TM Sedentary	36	36.7 $\pm$ 7.7	189.5 $\pm$ 50.3	173.6 $\pm$ 89

¹To convert to mmol/L multiply by 0.02586. ²To convert to mmol/L multiply by 0.01129. * $P<0.05$, ** $P<0.01$. M=men, W=women, T=tetraplegic, P=paraplegic

Cross-sectional studies – cardiovascular fitness

Bostom¹⁰⁴ assessed the association between cardiovascular fitness assessed by maximal arm ergometry and HDL-C in nine men with SCI (T5–T12), mean age 31 years, at least 4 years post-injury (average injury duration = 13.7 years) who lived independently in the community. The mean HDL-C in this sample, 46 ± 8 mg/dl (1.19 ± 0.21 mmol/L), is higher than that reported in any group of SCI men included in Table 1. The authors speculate that the higher level of HDL-C in this sample may be due to a higher level of physical activity. This speculation is supported by their finding of a peak oxygen uptake of 29.1 ± 3.6 ml/kg/min which is higher than that reported for sedentary subjects with paraplegia^{31,106} but less than that reported in wheelchair racers.¹⁰⁷ The arm ergometry peak oxygen uptake was not significantly associated with either HDL-C ($r=0.47$) or TC ($r=-0.51$), but was significantly associated with a reduced TC/HDL-C ratio ($r=-0.86$, $P<0.01$) and TG ($r=-0.73$, $P<0.05$). Inadequate statistical power most likely explains the lack of statistical significance in the association of HDL-C and TC with cardiovascular fitness. Janssen *et al*³¹ found no significant association between peak oxygen uptake, assessed by wheelchair ergometry, and HDL-C ($r=0.16$) or TG ($r=-0.10$) in 37 SCI men. However, peak oxygen uptake was significantly associated with TC/HDL-C ratio ($r=-0.35$, $P<0.05$). Bauman *et al*²⁹ in a subgroup of 12 subjects with paraplegia (total $n=50$) reported a nonsignificant direct association between HDL-C and cardiovascular fitness determined by arm crank ergometry; however, the magnitude of the correlation was not provided.

Exercise training studies

Hooker and Wells¹⁰⁵ reported on eight SCI individuals (four men, four women) who participated in two different supervised 8-week wheelchair ergometer exercise training programs, 20 min per session, three times per week. The training programs differed by intensity: low (50% to 60% heart rate reserve) and moderate (70% to 80% heart rate reserve). Results showed no difference in peak aerobic capacity or peak power output as a result of training. There were no significant changes in TC, TG or HDL-C in the low intensity group. In the moderate intensity group HDL-C increased from 39–47 mg/dl [1.0 – 1.22 mmol/L] ($P<0.10$), TC/HDL-C ratio decreased from 5 to 4 ($P<0.10$) and TG decreased from 96 to 78 mg/dl [1.08 to 0.88 mmol/L] ($P<0.01$). These results are suggestive of a favorable effect of supervised wheelchair ergometer training on HDL-C in SCI individuals, however, this study involved a very small number of subjects who were not randomly assigned to treatment and involved no control group. In addition, the study sample was heterogeneous regarding level of lesion, duration of injury and gender and there was no control for diet, cigarette smoking, or alcohol consumption.

Other evidence for a physical activity/HDL-C association

The level of lesion may serve as a surrogate measure for participation in physical activity. A higher level of physical activity and higher HDL-C might be expected in subjects with paraplegia compared to those with tetraplegia. However, the results of several studies that have evaluated HDL-C in both these groups have not supported this hypothesis.^{13,24,29–31} The finding of no difference in HDL-C by lesion level may be associated with both behavioral and physiologic differences between the groups. This is exemplified in the report of Maki *et al*²⁶ who compared HDL-C in 23 subjects with paraplegia and 23 subjects with tetraplegia approximately 50 years of age. The unadjusted data showed no difference in HDL-C by level of lesion. However, after adjustment for differences in abdominal circumference the level of injury explained an additional 10% of the variance in HDL-C. Adjustment for differences in abdominal circumference revealed an HDL-C 6 mg/dl (0.16 mmol/L) lower in tetraplegics compared with paraplegics. In contrast, Bauman *et al*¹⁰⁸ have shown significantly lower HDL-C ($P<0.01$) in 247 individuals with tetraplegia [39 mg/dl (1.0 mmol/L)] compared with 294 individuals with paraplegia [45 mg/dl (1.16 mmol/L)].

The duration of injury may also be associated with changes in activity level and potential alteration in the level of HDL-C. There does not appear to be a consistent pattern of results among the few studies included in this review where information on the duration of injury and HDL-C is available. Krum *et al*¹³ compared HDL-C in SCI individuals with durations of injury greater than 10 years (29% of the sample) with those with injury for less than 10 years. HDL-C was lower in those with longer [39 mg/dl (1.0 mmol/L)] compared with shorter duration of injury [43 mg/dl (1.11 mmol/L)]. This is in contrast to the results of Brenes *et al*²⁴ who reported a significant positive correlation between the length of the convalescent period and HDL-C ($r=0.36$, $P<0.01$). HDL-C level were 30.5 mg/dl (0.79 mmol/L) in 12 subjects less than 6 weeks post-injury, 32.6 mg/dl (0.84 mmol/L) in 14 subjects 7–52 weeks post-injury, and 37.5 mg/dl (0.97 mmol/L) in 30 cases greater than 52 weeks post-injury.

Summary and recommendations

The limited available data suggest a potential important role for physical activity to increase the level of HDL-C in SCI subjects, possibly as a result of decreased body fat, increased insulin sensitivity or increased cardiovascular fitness and associated metabolic changes, any and all of which may be associated with decreased cardiovascular disease risk. The available information on physical activity and HDL-C in SCI subjects comes from studies that have used imprecise measures of physical activity

including athlete/non-athlete comparisons,²⁴ semi-quantitative rating scales¹³ or reported hours per week of active sport participation.³¹ Additional studies using more precise physical activity measures that are developed and validated in SCI subjects are needed to provide further insight into exercise parameters associated with HDL-C in this population. The effect of physical activity on HDL-C in SCI should be further investigated with both cross-sectional studies of SCI subjects over a complete range of physical activity levels and with longitudinal training studies of variable frequency, intensity, duration and mode. In both cross-sectional and longitudinal studies it will be important to assess and adequately control for important confounders and obtain samples of sufficient size to minimize the heterogeneity inherent in samples with SCI. It will be important to determine if individuals with SCI, given the reduction in active muscle mass, can exercise at an intensity and duration sufficient to increase HDL-C. From a practical perspective it would be useful to know if individuals with SCI are capable of increasing their daily physical activity, apart from structured exercise programs, to a level that will significantly affect HDL-C.

Finally, studies should be undertaken to further elucidate the mechanism of altered lipid metabolism in SCI. Do the observed alterations in HDL-C result from metabolic dysregulation inherent in SCI or are they more strongly associated with behavioral factors such as smoking, alcohol consumption, diet or physical inactivity? Knowledge of the mechanism for any reduction in HDL-C in individuals with SCI may provide insight into the design of behavioral interventions to decrease cardiovascular disease risk in this group.

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