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REVIEW

Coronary heart disease in individuals with spinal cord injury: assessment of risk factors

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Study design: Discussion document.
Objectives/methods: To review the work performed on conditions and disorders that predispose persons with spinal cord injury (SCI) to an increased risk of coronary heart disease (CHD).
Results/discussion: Individuals with SCI have an increased prevalence of abnormalities in carbohydrate and lipid metabolism because of immobilization, muscle atrophy and relative adiposity. In those with SCI, an inverse relationship has been reported between serum high-density lipoprotein (HDL) cholesterol values and abdominal circumference, and a direct relationship between serum triglycerides levels and abdominal circumference. Persons with SCI have lower serum HDL cholesterol levels than able-bodied controls. A higher prevalence of insulin resistance and diabetes mellitus, as well as an earlier occurrence of coronary heart disease (CHD), has been reported in persons with SCI than in the general population. Recently, a higher prevalence and greater degree of coronary artery calcification by electron beam computerized tomography has been demonstrated in persons with SCI, even if matched with the able-bodied population for age, gender, ethnicity and conventional risk factors for CHD. Knowledge of relative risk of CHD in persons with SCI is important for appropriate intervention strategies. The conventional risk factors for CHD were determined in veterans with SCI to assign risk to determine target low-density lipoprotein cholesterol levels for therapeutic intervention. Limitations of conventional guidelines when applied to the SCI population should be appreciated. Conventional risk factors for CHD should be identified and treated in individuals with SCI, according to current standards of care.
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Keywords: paraplegia; tetraplegia; atherosclerosis; carbohydrate metabolism; high-density lipoprotein; body composition

Introduction

Immobilization and paralysis from spinal cord injury (SCI) result in loss of muscle and a relative gain in adiposity. SCI predisposes the individual to medical complications such as lipid abnormalities, carbohydrate intolerance and an atherogenic pattern for coronary heart disease (CHD). One possible etiology for these secondary medical conditions is that they are the result of inactivity in conjunction with adverse body composition changes, which are progressive with advancing age.

A population of veterans with SCI has recently been studied to determine the conventional risk factors for CHD as defined by the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).[1,2] The risk for CHD was determined to be able to set target values for low-density lipoprotein (LDL) cholesterol. Recognizing the potential presence of these metabolic abnormalities and cardiovascular risk in persons with SCI is required for early diagnosis and an improved approach to clinical care. Appropriate interventions are discussed that reduce cardiovascular risk and hold promise to improve longevity and quality of life in persons with SCI.

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Soft tissue body composition changes

Longitudinal studies of body composition after acute SCI are limited, but have shown a brisk, marked loss of lean tissue mass.[3,4] Comparing matched reference populations using

cross-sectional designs in individuals with chronic SCI, investigators have demonstrated lean tissue loss and/or fat tissue gain.[5–7] Rasmann Nuhlicek *et al*.[5] studied subjects with SCI classified into four levels of lesion subgroups and controls; they found reductions in total body water, intracellular water and lean body tissue and increases in fat mass correlating with the level of neurological deficit. In a cross-sectional study, Spungen *et al*.[6] reported significant decreases in percent of regional and total body lean tissue in 132 male subjects equally divided with tetraplegia or paraplegia compared with matched controls. These differences in lean tissue were most pronounced between SCI and control groups in the arms and legs, and less so in the trunk. The subjects with SCI demonstrated a significantly greater reduction of arm percent lean tissue with advancing age than controls (Figure 1a). No difference in the rate of loss was observed between subjects with high or low cord lesions (Figures 1a–d). Compared to able-bodied males who lost about 1% per decade of total body lean tissue, subjects with SCI lost about 3.2% per decade.[6]

Due to the individual variability, the ability to determine the precise amount of lean tissue loss and relative or absolute fat tissue gain attributable to paralysis rather than genetics and/or environmental factors is problematic. Longitudinal studies in those with SCI are difficult to perform—that is, capturing body composition immediately after SCI and then sequentially for decades thereafter. A solution to determining changes in body composition, independent of genetic variability and aging, and somewhat controlling for environment, is the use of a cross-sectional monozygotic twin model. In an identical twin study, with one co-twin in each pair having SCI, Spungen *et al*.[7] reported a loss of total body and extremity muscle mass that was continuous and directly related to the duration of injury. On average, about 4 kg of total body lean tissue was lost with each 5-year period of paralysis.[7]

The losses in lean body tissue, a high-energy body compartment, are directly reflected in the metabolic rate. In 13 subjects with SCI, as well as in the non-SCI twins, a strong relationship was shown between metabolic rate and

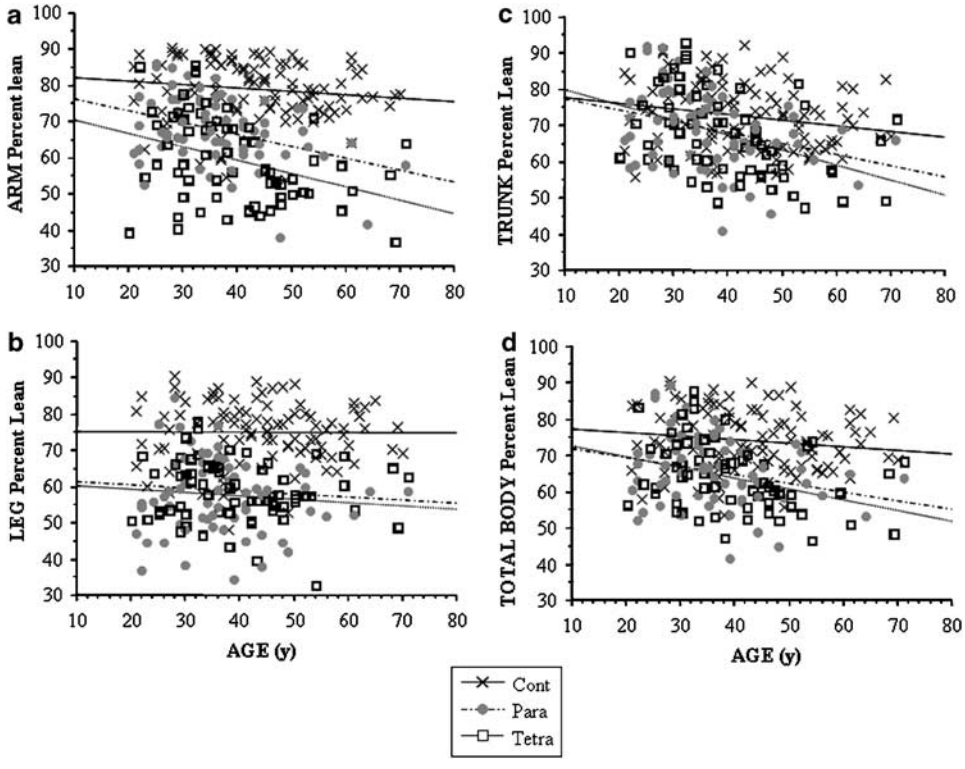

Figure 1 Regional and total body lean tissue percent comparisons among controls and persons with tetraplegia (Tetra) and paraplegia (Para). Data represent cross-sectional differences for age among the groups. Slopes *R*- and *P*-values for each as follows: (**a**) Arm: Cont, control (slope = −0.09; 95% CI, −0.229, 0.049; $R = 0.13$; $P = 0.01$); Para, paraplegia (slope = −0.327; 95% CI, −0.534, −0.120; $R = 0.37$; $P < 0.005$); and Tetra, tetraplegia (slope = −0.373; 95% CI, −0.619, −0.127; $R = 0.36$; $P < 0.005$). (**b**) Leg: Cont (slope = −0.005; 95% CI, −0.146, 0.136; $R = 0.01$; $P =$ NS); Para (slope = −0.093; 95% CI, −0.337, 0.151; $R = 0.09$; $P =$ NS); Tetra (slope = −0.084; 95% CI, −0.265, 0.101; $R = 0.12$; $P =$ NS). (**c**) Trunk: Cont (slope = −0.158; 95% CI, 0.008, 0.333; $R = 0.20$; $P < 0.05$); Para (slope = −0.307; 95% CI, 9.073, 0.549; $R = 0.31$; $P < 0.01$); Tetra (slope = −0.415; 95% CI, 0.189, 0.631; $R = 0.42$; $P < 0.001$). (**d**) Total body: Cont (slope = −0.102; 95% CI, −0.241, 0.038; $R = 0.14$; $P =$ NS); Para (slope = 0.238; 95% CI, −0.456, −0.019; $R = 0.26$; $P < 0.005$); Tetra (slope = −0.296; 95% CI, −0.492, −0.100; $R = 0.36$; $P < 0.005$). There was no overlap in CIs in the panels between the control and the groups with spinal cord injury (SCI; Para and Tetra). A significant difference in the slope of the lines for (**a**) was noted between the control and the SCI groups, but not for the other panels. (reproduced with permission from Spungen, *et al*. Factors influencing body composition in persons with spinal cord injury: a cross-sectional study. *J Appl Physiol* 2003; **95**: 2398–407).

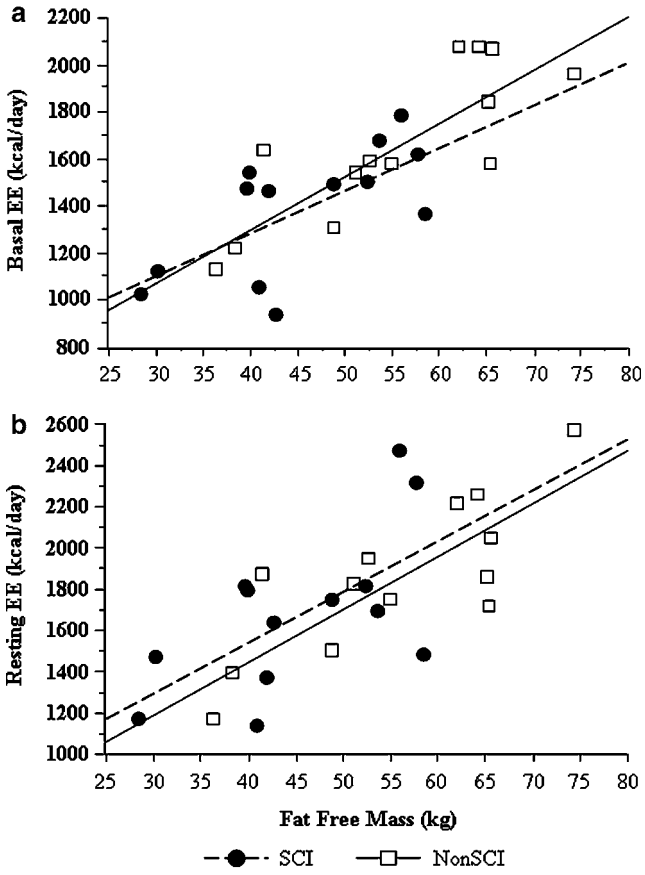

Figure 2 Relationship between energy expenditure and fat-free mass in monozygotic twins discordant for spinal cord injury (SCI). Linear regression analyses between fat-free mass and energy expenditure. (**a**) Basal energy expenditure (EE) (SCI: slope = 17.98; 95% CI, 4.66, 31.304; $R = 0.63$; $P < 0.05$; non-SCI: slope = 22.517; 95% CI, 12.295, 32.740; $R = 0.80$; $P < 0.001$) and (**b**) resting EE (SCI: slope = 24.242; 95% CI, 3.967, 44.517; $R = 0.67$; $P < 0.05$; non-SCI: slope = 25.484; 95% CI, 13.002, 37.965; $R = 0.82$; $P < 0.0005$ reproduced with permission from Bauman *et al.* Relationship between EE and fat-free mass in monozygotic twins discordant for spinal cord injury. *J Rehabil Research Dev* 2004; **4**:1–8).

fat-free mass: the greater reductions in lean body tissue the greater the decreases in resting metabolic rate (Figures 2a and b).[8] This supported earlier work by Mollinger *et al.*[9] who described a 12–29% reduction from predicted values for basal energy by the Harris–Benedick equation for energy expenditure in subjects with SCI: the higher the level of injury (and presumably less lean tissue mass) the greater the reduction in basal energy expenditure.

In persons with SCI, the usual clinical measures of total body fat (for example, weight or body mass index (BMI)) underestimate the degree of adiposity.[6,10] Body fat topography in able-bodied individuals is clearly an important factor associated with metabolic disorders, and it probably is as well in persons with SCI.[11,12] Related to these adverse body compositional changes and reduced levels of activity, individuals with SCI have a pattern of metabolic alteration that would be considered to be atherogenic.[1,2,12]

Carbohydrate metabolism in SCI

Impaired glucose tolerance (IGT) and diabetes mellitus (DM) occur more frequently in persons with SCI than in the able-bodied population.[13–16] Peripheral resistance of insulin to mediate glucose uptake may be demonstrated in most individuals with SCI who have a disorder in glucose tolerance. Mild deteriorations in oral glucose tolerance are associated with insulin resistance and hyperinsulinemia, and this metabolic milieu is recognized as atherogenic.[17] Worsening of carbohydrate tolerance will ensue if the pancreas' compensatory response is insufficient, as may be expected to occur with advancing age.

Bauman *et al.*[13] performed a standard oral glucose tolerance test in 100 subjects with all levels of SCI and in 50 able-bodied controls.[13] In subjects with SCI, 22% were diabetic by criteria established by the World Health Organization, whereas only 6% of the control group were diabetic.[13,18] A total of 82% of the controls had normal oral glucose tolerance, compared with 38% of those with quadriplegia and 50% of those with paraplegia. Subjects with SCI had significantly higher mean plasma glucose and insulin values at the later time points during the oral glucose tolerance test when compared with controls. The group with SCI had significantly higher sum plasma glucose values at younger ages after an oral glucose load. Values for insulin sensitivity were significantly related to level of fitness, and directly correlated with lean body mass and indirectly correlated with adiposity, although failing to reach significance for the body composition changes.[13] Tharion *et al.*[16] performed oral glucose tolerance testing in persons with SCI as part of their annual medical care in South India. Fasting hyperglycemia was present in 19 and 23% had elevated values at 2 h after a glucose load.[16]

The relationship between oral carbohydrate tolerance and several variables, including level and completeness of lesion, gender, ethnicity, age, duration of injury and calculated percent body fat, was studied.[14] Subjects with complete tetraplegia had significantly worse carbohydrate tolerance with greater peak and sum plasma insulin concentrations and were more frequently classified with a disorder in carbohydrate tolerance than the other neurological deficit subgroups (Figure 3). The glucose curves were not significantly different between men and women, but the plasma insulin levels at the intermediate time points were significantly higher for men than women, suggesting a state of relative insulin resistance in men. Stepwise regression analyses demonstrated that peak serum glucose was significantly associated with increased total body percent fat, complete tetraplegia, older age and male gender; the peak plasma insulin was associated with increased total body percent fat and male gender. In this study, glucose tolerance appeared to be independent of the effects of ethnicity, and glucose abnormalities generally increased with advancing age.[14]

Studies in able-bodied individuals have established associations between hypertension, hyperinsulinemia, obesity and disorders of glucose tolerance, and these associations are being reported in persons with SCI.[12,14,19–22] The fasting plasma glucose has been shown to highly correlate with

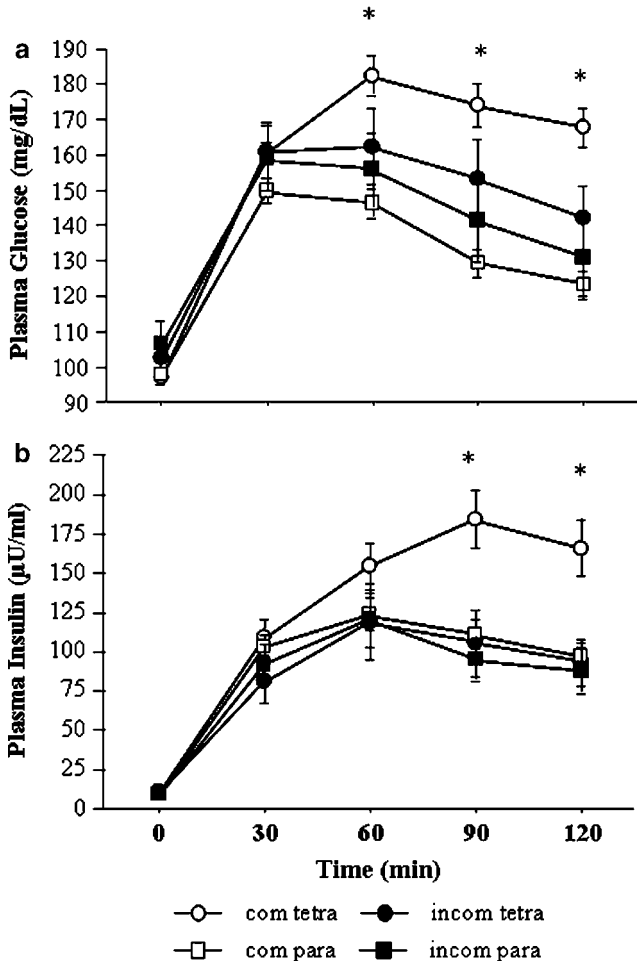

Figure 3 Comparison of oral glucose tolerance by neurological deficit. Shown is the serum glucose concentration vs time after a 2 h oral glucose tolerance test (**a**) and the plasma insulin levels vs time after a 2 h oral glucose tolerance test (**b**). An asterisk (*) above the time point represents significant differences ($P<0.05$) between the motor complete tetraplegia group and the three other neurological deficit groups, performed by ANOVA applying a Scheffe's *post hoc* F ratio (incomplete tetraplegia, complete paraplegia, incomplete paraplegia reproduced with permission from Bauman WA, Adkins RH, Spungen AM, *et al*. The effect of residual neurological deficit on oral glucose tolerance in persons with chronic spinal cord injury. *Spinal Cord* 1999; **37**: 765–771).

basal rates of hepatic glucose output.[22] Because the average fasting plasma glucose is generally within the normal range or only mildly elevated in subjects with SCI, peripheral insulin resistance is the major factor responsible for glucose intolerance. Possibly reflecting a state of insulin resistance, an increased prevalence of hypertension has been reported in persons with chronic paraplegia.[23] Insulin resistance is also prominent in those with chronic tetraplegia, but because of overriding vasomotor factors that lower blood pressure (for example, attenuated sympathetic nervous system regulation), chronic hypertension is infrequently observed. In a subset of subjects with SCI, hyperuricemia has been reported, another finding related to hyperinsulinemia.[24]

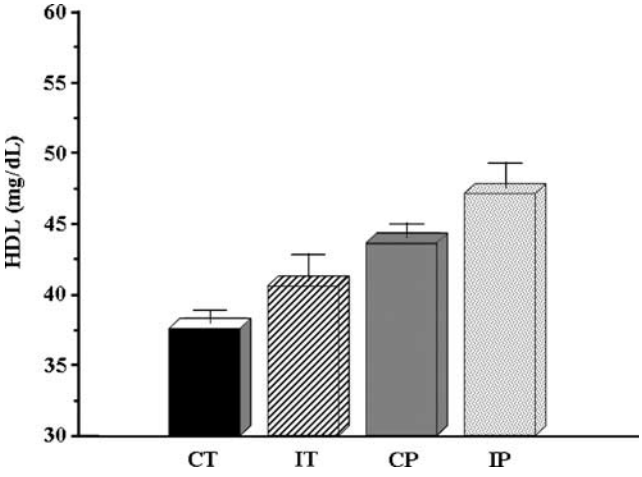

Figure 4 Serum high-density lipoprotein (HDL) cholesterol levels by neurological deficit. Tetra, tetraplegia; Para, paraplegia. Values are expressed in mean ± s.e.m. (reproduced with permission from Bauman *et al*. The effect of residual neurological deficit on serum lipoproteins in individuals with chronic spinal cord injury. *Spinal Cord* 1998; **36**: 13–17).

Lipid metabolism and cardiovascular disease

Elevation in LDL cholesterol and depression of high-density lipoprotein (HDL) cholesterol are two important risk factors for CHD.[25,26] Individuals with SCI are believed to have premature CHD. Approximately 10% of the US population has HDL cholesterol values <35 mg per 100 ml, whereas about 24–40% of those with chronic SCI have levels below this value for HDL cholesterol.[22,26–29] Although the mechanism by which low levels of HDL cholesterol predispose to CHD is uncertain, it has been postulated that HDL cholesterol is vital for reverse cholesterol transport, which mobilizes cholesterol from the arterial wall, as well as antioxidant, antiinflammatory, antiplatelet and anticoagulant effects.[30] In subjects with chronic SCI and in controls, an inverse correlation has been demonstrated between serum triglycerides (TGs) and HDL cholesterol, a relationship that may reflect the effects of elevated plasma insulin.[22,31–33] Maki *et al*.[12] found a significant indirect correlation between abdominal circumference and serum HDL cholesterol and a direct correlation with serum TG values, as well as for the ratio of total to HDL cholesterol. Indeed, in persons with SCI, a significant relationship was shown between serum HDL cholesterol and insulin sensitivity, as determined by the minimal-model method.[13] Subjects with chronic tetraplegia had lower levels of serum HDL cholesterol than those with paraplegia (38 ± 0.7 vs 45 ± 0.8 mg per 100 ml, $P<0.1$).[20] Subjects with motor complete injury tend to have lower values of serum HDL cholesterol than those with motor incomplete within the subgroups of tetraplegia and paraplegia (Figure 4); a significant, albeit weak, inverse relationship was found for degree of neurological deficit and serum HDL level ($R=0.19$, $P<0.0001$); however, no significant difference was noted between complete and incomplete lesions for those with paraplegia or tetraplegia.[20] Men with SCI had lower HDL cholesterol than control men, but there

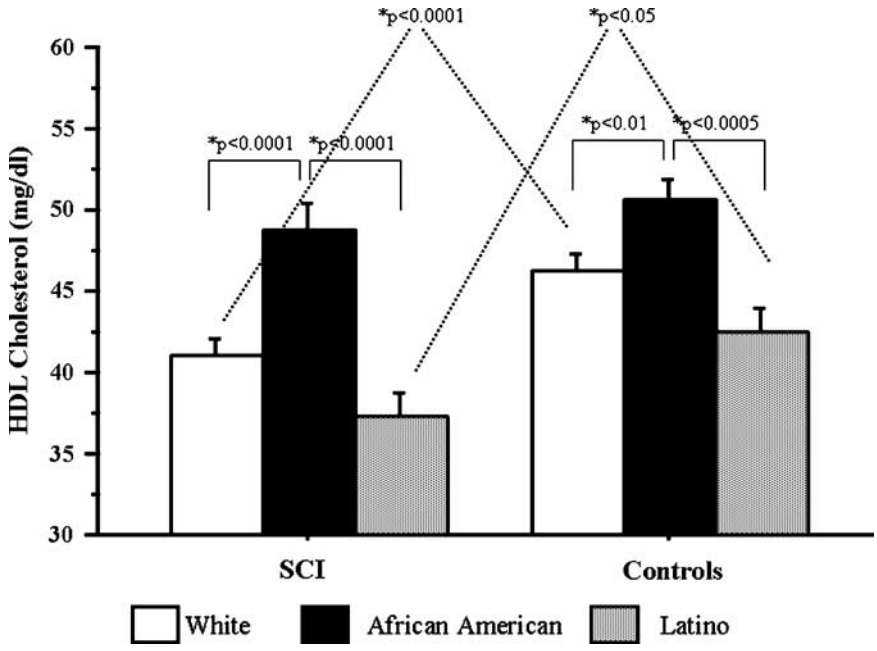

Figure 5 Comparison of serum high-density lipoprotein (HDL) cholesterol among ethnic subgroups. The bar graphs display mean ± s.e.m. serum HDL cholesterol levels in the groups with spinal cord injury (SCI) and controls stratified by ethnicity. Within (solid lines) and between (dashed lines) group differences are shown (reproduced with permission from Bauman, *et al.* Carbohydrate and lipid metabolism in chronic spinal cord injury. *J Spinal Cord Med* 2001; **24**:266–277).

was no significant difference found for predominantly premenopausal females with or without SCI.[29] Caucasians and Latinos with SCI had lower serum HDL cholesterol levels than the ethnic-matched able-bodied group (Figure 5).[34] African Americans with SCI had significantly higher serum HDL cholesterol values and a lower ratio of serum total to HDL cholesterol than Caucasians or Latinos with SCI, as well as lower serum TGs (Figure 5); of note, and without a known explanation, African Americans with SCI had serum HDL cholesterol values that were not significantly different from African Americans without injury.[34]

At the present time, there are several strategies for raising serum HDL cholesterol. Increasing level of activity, smoking cessation and pharmacological treatment all have been shown to be effective. In persons with or without SCI, increased cardiopulmonary fitness has been demonstrated to raise the serum HDL cholesterol level.[22,28,29,35–37] In a prior report by our group, persons with paraplegia had significantly higher serum HDL cholesterol values for relatively small increases in maximum oxygen uptake determined by arm ergometry stress testing.[13] Hooker *et al*.[28] demonstrated that moderate-intensity wheelchair ergometry for 20 min, three times per week for 8 weeks, significantly increased HDL cholesterol from 39 ± 11 to 47 ± 8 mg per 100 ml, and decreased the ratio of total to HDL cholesterol from 5.0 ± 0.9 to 4.0 ± 0.5. Circuit resistance training in five men with complete SCI was found to improve peak oxygen consumption by 30% with an associated 9.8% increase in HDL cholesterol (41 ± 5 to 45 ± 12 mg per 100 ml) and a reduction in the ratio of total to HDL cholesterol of about 1 unit (5 ± 1 to 4 ± 1).[37] In the general population, an increase of 1 unit in the ratio of serum total to HDL cholesterol has been found to be associated with a mean increase of 53% in risk of a coronary event.[38] Thus, a modest upper exercise regimen that improves cardiovascular fitness may be expected to increase serum HDL cholesterol and reduce CHD risk, although the latter has not been specifically studied in persons with SCI. Inactivity, independent of lipid values or other risk factors for CHD, may be an independent risk factor for CHD.[39] Persons with SCI should be strongly encouraged to reach and maintain the highest level of daily activity, compatible with their neurological levels of injury.

A Model System Collaborative Study showed that Niaspan 2 g per day in persons with SCI raised serum HDL cholesterol from 32 ± 3 to 40 ± 7 mg per 100 ml, an average increase of 25%, associated with a reduction in serum LDL cholesterol and a significant improvement in TC to HDL ratio from 5.4 to 4.2 (MS Nash, personal communication). In addition to immobilization, high calorie or fat diets may increase plasma TGs and depress serum HDL cholesterol.[40] In a cross-sectional study of outpatients with SCI, persons with shorter duration of injury tended to have higher saturated fat intakes and higher serum TG values than those with longer duration of injury.[41] Mild-to-moderate alcohol consumption has been reported to increase serum HDL cholesterol levels.[42] Cigarette smoking has also been shown to be associated with insulin resistance and lower serum HDL cholesterol levels.[43] In the general population, cigarette smoking has been shown to reduce HDL cholesterol by about 7 mg per 100 ml.[44] A similar reduction in serum HDL cholesterol may be expected in those with SCI, although it has not been reported. Serum HDL cholesterol levels have been reported

to increase between 11 and 15% after smoking cessation.[45] Current cigarette smoking is an independent risk factor for CHD and, when reduced or eliminated decreases the risk for CHD.[1,2]

CHD in persons with SCI

In the able-bodied population, symptoms of CHD are commonly precipitated by activity, often strenuous. It should be appreciated that the risk of a cardiac event is related to the severity of CHD, not symptoms of CHD.[46] The ability of a person with SCI, especially those with higher, more complete lesions, to engage in significant physical activity is often difficult, and, if at all possible, limited. In addition, if an individual with SCI has an ischemic cardiac event, because of nervous interruption of sensory pathways, it may pass unnoticed. Although peripheral vascular disease would be expected to be present because of multiple metabolic cardiovascular disease risk factors, a cigarette smoking prevalence comparable to the able-bodied population and age, it may be undiagnosed in a nonambulatory, older SCI population. Thus, the identification of CHD risk or other macrovascular disease risk equivalents for CHD may be grossly underestimated in those with SCI, requiring a more aggressive approach to determine the presence of atherosclerotic occlusive vascular disease.

Whiteneck *et al*.[47] reported that cardiovascular diseases were the most frequent cause of death among persons with SCI more than 30 years after injury (46% of all deaths) and among those more than 60 years of age (35% of all deaths). Using thallium scintillation stress testing, Bauman *et al*.[48,49] found that asymptomatic CHD determined by upper body exercise stress testing was present in 13 of 20 subjects with paraplegia (mean age, 52 years) and by dipyridamole infusion in 4 of 6 subjects with tetraplegia (mean age, 47 years). Lee *et al*.[50] determined the prevalence of CHD by thallium^{201} myocardial perfusion single photon computed tomography in 47 asymptomatic patients with SCI, segregated into four groups dependent upon the level (tetraplegia vs paraplegia) and completeness of injury (complete vs incomplete); those with complete tetraplegia had the greatest and those with incomplete paraplegia had the least prevalence of heart disease. Budoff *et al*.[51] studied coronary artery calcification (CAC) by electron beam computerized tomography in a group of 91 subjects with SCI who were matched 3:1 with non-SCI controls for age, gender, ethnicity and individual risk factors. In the group with SCI, the investigators found that the mean coronary artery calcium score was significantly greater (75 ± 218 vs 28 ± 104), the prevalence of any CAC was higher (51 vs 39%), and those with high scores (>100) was greater (16% vs 7%); these findings were not explained by the clustering of traditional risk factors; persons with tetraplegia had a greater prevalence of severe CAC scores than did persons with paraplegia (6.8 vs 2.1%; $P<0.05$).[51] Because these studies were of a relatively small sample size, a larger cohort is needed to more accurately determine the prevalence of CHD in the population of persons with SCI.[48–51]

Assessment of risk for CHD

In the general population, about 25% of individuals have an elevation of the serum LDL cholesterol level (>130 mg per 100 ml). The level of serum LDL cholesterol in individuals with SCI has been reported to be similar to that of able-bodied persons. The recommendations of the NCEP for therapy are based upon the level of serum LDL cholesterol in association with the presence or absence of CHD or risk factors for CHD.[1,2] A population of 222 male veterans with SCI (Table 1) was studied to determine the conventional risk factors for CHD as defined by the ATP III guidelines, to calculate the risk for CHD, and to determine the target LDL cholesterol levels for treatment.[1,2,52] The values for serum total cholesterol, LDL cholesterol and TGs are similar to those in the general population. Of note, the values for HDL cholesterol in those with SCI was shifted to the left (Figure 6d), with mean value of 38 ± 12 mg per 100 ml in the group with SCI compared with 51 ± 13 mg per 100 ml in the group of able-bodied controls. The serum TG values for subjects with tetraplegia were significantly lower than those for controls (116 ± 76 vs 148 ± 86 mg per 100 ml; $P<0.0001$), whereas no significant difference was found between those with paraplegia and controls; a possible, but unproven, explanation for the depressed TGs in persons with higher cord lesions may be that they were in negative calorie balance, having lost the ability to feed themselves. An inverse relationship was present between BMI and serum HDL cholesterol values (Figure 7a). A direct relationship was noted between BMI and serum TGs (Figure 7b). An inverse relationship was found between serum HDL cholesterol and plasma TGs (Figure 7c). DM was diagnosed on the fasting serum glucose in 5% of patients, whereas DM was diagnosed in 17% of subjects on the 2 h serum glucose value. Hyperinsulinemia was present in 34% of patients (31% with tetraplegia vs 18% with paraplegia). Significant linear relationships were evident for BMI vs fasting or 2 h plasma insulin levels for those with SCI, with higher BMI values correlating with higher plasma insulin concentrations.[52]

Hypertension was present in 23% of the entire veteran group; in the subgroups by level of lesion, hypertension was more frequent in those with paraplegia than tetraplegia (32 vs 10%; Table 2).[52] A total of 34% of the patients were current cigarette smokers. A positive family history for CHD was noted in 33% of the patients (Table 2).[52] CHD was reported to be present in only 8% of patients (Table 3). Two or more CHD-risk factors were present in the majority of patients (Table 3). By the Framingham scoring system to

Table 1 Characteristics of the study groups

	Tetra (n = *103*)	*Para* (n = *119*)	
	n *(%)*	n *(%)*	P-*value*
Age (year)	46 ± 14	52 ± 14	0.0027
DOI (year)	16 ± 12	19 ± 13	0.0687
BMI (kg m^{-2})	24.3 ± 5.2	25.5 ± 4.4	0.076

Abbreviations: BMI, body mass index; DOI, duration of injury; Tetra, tetraplegia; para, paraplegia.

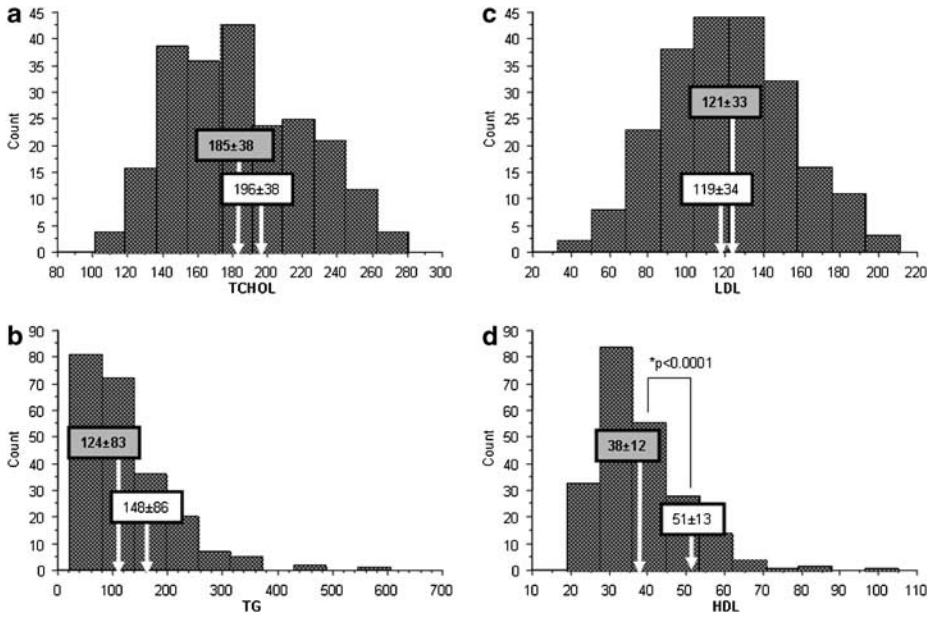

Figure 6 Histogram distribution of serum lipid fractions: Count or number of subjects is represented on the y axis for values of total cholesterol (**a**), triglycerides (TGs) (**b**), LDL, low-density lipoprotein cholesterol (**c**) and HDL, high-density lipoprotein cholesterol (**d**). The shaded boxes present the mean ± s.d. for the spinal cord injury (SCI) veteran population; the unshaded boxes present the mean ± s.d. for the able-bodied veteran population. Note the leftward shift of HDL cholesterol in the veterans with SCI (**d**) (reproduced with permission from Bauman, *et al*. Risk assessment for coronary heart disease in a veteran population with spinal cord injury. *Top Spinal Cord Inj Rehab* 2007; **12**: 35–53).

determine short-term risk, 54% of patients with SCI had 10-year risk of between 10 and 20%, with only 8 of these patients (4%) having a 10-year risk of >20% (Table 3). The increased risk of CHD by NCEP criteria in those with paraplegia was due almost exclusively to the increased prevalence of hypertension in this group compared with those with tetraplegia. It should be appreciated that the NCEP classification does not take into account the greater depression in level of HDL cholesterol in persons with values <40 mg per 100 ml in those with tetraplegia compared to those with paraplegia; a greater percent of individuals with tetraplegia than those with paraplegia had HDL cholesterol values <35 mg per 100 ml (51 vs 38%; $P=0.05$), and for values <30 mg per 100 ml (25 vs 14%; $P=0.05$).

Considerations for treatment of LDL cholesterol

The major CHD risk factors and the stratification of CHD risk with target values for LDL cholesterol have been described for a group of veterans with SCI (Tables 2 and 3).[52] Twenty-nine percent of the total group is at high risk of CHD (for example, 35 subjects with CHD or risk equivalents plus an additional three subjects with a 10-year risk >20%), with 22% (28/129) requiring intervention to lower LDL cholesterol to <100 mg per 100 ml; 45% (58 subjects) of the total group is at moderate risk of CHD (those with two or more risk factors, a 10-year risk ⩾10%, and without CHD or risk equivalents for CHD), with 19% (24 of 129 subjects) requiring intervention to lower LDL cholesterol to <130 mg per 100 ml (Table 4).

The ATP III treatment recommendations are guidelines to 'inform, not replace' the physician's clinical judgment, which must ultimately determine the appropriate treatment for each individual. Thus, the intensity of risk-reduction therapy should be adjusted to an individual's risk of having an occlusive myocardial event, and special considerations should be operative in different population groups. Men with SCI may have a greater risk because their HDL cholesterol levels are generally lower, with the percentage of those with extremely low serum values being quite remarkable (44% of the total group having HDL cholesterol values <35 mg per 100 ml, and 19%, <30 mg per 100 ml). Because the magnitude of the HDL cholesterol depression is often more marked in those with SCI than in the general population, the risk of having a coronary event would be expected to rise along a continuum of risk. For each 1 mg per 100 ml decrement in serum HDL cholesterol, the risk of a coronary event increases 2% in men.[53] If the serum HDL cholesterol is ⩽30 mg per 100 ml, the risk of having a coronary event would be estimated to increase to about ⩾20%, independent of other risk factor assessment. A total of 19% of the study cohort had serum HDL cholesterol values depressed of this magnitude.[52] Therefore, a single risk factor may elevate an individual's risk of CHD to a level requiring the practitioner to set a more stringent target criterion for the cut-off value for serum LDL cholesterol than advised in the Framingham scoring system. In contrast to the heightened risk of CHD in men with SCI, premenopausal women with SCI may have a risk of CHD more comparable to that of the general female population because their HDL cholesterol levels were found to be similar.[21,29]

The objective of the treatment of hyperlipidemia is to prevent or reduce the morbidity and mortality associated with CHD. To this end, several treatment programs in the

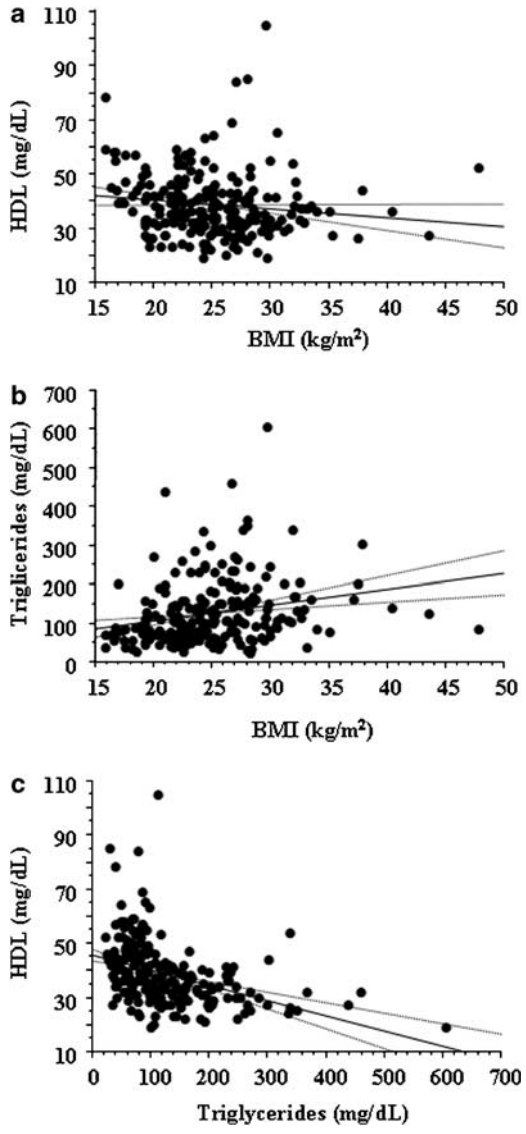

Figure 7 Relationships among high-density lipoprotein (HDL), triglyceride (TG) and body mass index (BMI) in persons with spinal cord injury (SCI). (**a**) HDL cholesterol with BMI ($R=-0.127$, slope $=-0.315$; 95% CI, -0.639, 0.012; $P=0.05$); (**b**) TG with BMI ($R=0.24$, slope $=4.098$; 95% CI, 1.875, 6.321; $P<0.005$); (**c**) HDL cholesterol and TG ($R=-0.394$, slope $=-0.056$; 95% CI, -0.073, -0.039; $P<0.0001$). The CI has been provided for each line (reproduced with permission from Bauman, *et al*. Risk assessment for coronary heart disease in a veteran population with spinal cord injury. *Top Spinal Cord Inj Rehab* 2007; **12**: 35–53).

general population have been reported to be successful. Low-fat and -cholesterol diets may be expected to reduce levels of serum LDL cholesterol between 10 and 20%. To maintain a therapeutic benefit, the patient must remain on diet therapy indefinitely. There are two classes of pharmacological agents that are generally used to lower serum LDL cholesterol: hydroxymethylglutaryl-coenzyme A (HMG CoA) reductase inhibitors (statins) and bile acid-binding resins. The bile acid-binding resins may be less desirable in persons with SCI because they have a tendency to cause increased constipation, abdominal flatulence and interfere with the absorption

Table 2 Major risk factors for CHD

	Tetra (n = *103*)	*Para* (n = *119*)	
Major risk factors	n *(%)*	n *(%)*	P-*value*
Cigarette smoker	33 (31)	41 (34)	NS
HTN (⩾140/90 mm Hg)	10 (10)	36 (32)	0.0002
Low HDL (<40 mg/dl)	67 (64)	77 (60)	NS
Family Hx CHD	32/94 (34%)	36/110 (33%)	NS
Men ⩾45 year	54 (50)	82 (69)	0.005

Abbreviations: Cigarette smoker, current smoker having smoked greater than 100 cigarettes in lifetime; CHD, coronary heart disease; HDL, high-density lipoprotein; HTN, hypertension.
Bauman *et al. Top Spinal Cord Inj Rehab* 2007; **12**: 35–53.

Table 3 Ten-year risk assessment

Risk category	*Tetra*	*Para*	*LDL Goal*
CHD	5/94 (5%)	13/111 (12%)	<100
DM by FPG	4 (4)	7 (6)	<100
DM by OGTT 2 h Glu	18 (17)	20 (17)	<100
10-Year Risk >20%	2 (2)	6 (5)	<100
⩾2 Risk factors	64 (66)	92 (79)*	<130
10-Year risk 10–20%	42 (39)	68 (57)**	<130
0–1 Risk factor	33 (34)	24 (21)*	<160
10-Year risk <10%	63 (59)	45 (38)**	<160

CHD, coronary heart disease; DM, diabetes mellitus; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test.
Bauman *et al. Top Spinal Cord Inj Rehab* 2007; **12**:35–53.
*$P<0.05$; **$P<0.005$.

Table 4 Assessment of risk for coronary heart disease

Risk	*Subjects*[a] *(%)*	*Target value (mg/dl)*
CHD or risk equivalents ($n=35$)	74	<100
⩾2 Risk factors (n = *61*)		
10-Year risk >20%	3	<100
10-Year risk 10–20%	34	<130
10-Year risk <10%	5	<130
0–1 Risk factor ($n=33$)	9	<160

Abbreviation: CHD, coronary heart disease.
[a]Percent of subjects in each group who qualify for intervention based on the ATP III guidelines.

of nutrients and medications, as well as being less potent in their lipid-lowering potential.

Approximately 17–20% of veterans with SCI were classified as having DM.[13,14,52] The determinants of insulin resistance are level of cardiovascular fitness, muscle mass and fat mass.[54] Obesity, physical inactivity and a high-fat diet are recognized risk factors for diabetes, all of which can be modified. DM is a CHD risk equivalent, and, therefore, the target value for LDL cholesterol is <100 mg per 100 ml. In one report, 87% patients with classifiable DM would have been missed if relying on only the fasting plasma glucose value rather than the 2-h time point in an oral glucose tolerance test, underscoring the need to perform provocative testing.[52]

Persons with paraplegia have been reported to have an increased prevalence of hypertension.[23] If one assumes an

increased frequency of hypertension in the individuals with paraplegia, then an increase in those with pre-hypertensive values is also likely. Indeed, reduced baroreceptor sensitivity has been shown in this population, which is appreciated to be an antecedent condition to the development of hypertension.[55] In a recent report, there appears to be an increased risk of developing cardiovascular disease, predominantly CHD, in persons with pre-hypertension (blood pressure 120/80 to 139/89) compared with those with optimal blood pressure levels.[56] Compensatory increased activity of the renin–angiotensin system to maintain hemodynamic stability by vasoconstriction and increased cardiac contractility is present in those with higher cord lesions (for example, above thoracic level-6). Elevated levels of angiotensin II may also increase collagen and myocyte growth, oxidative stress, inflammation and coagulability, which may be associated with the development and progression of cardiovascular disease, a consideration not captured by the conventional assignment of risk for CHD.

Potential problems with the criteria for metabolic syndrome in persons with SCI

The ATP III guidelines specifically identified the metabolic syndrome as a multiplex risk factor of cardiovascular disease and established criteria to better define it.[1,2] Persons with SCI may not be easily categorized by the ATP III criteria for the metabolic syndrome, or by criteria of other organizations.[2,57,58] Because the ATP III criteria for the metabolic syndrome are the most commonly used in the United States, this discussion focuses on its definition, although a similar line of reasoning may be applied to the other classifications.

To satisfy the ATP III criteria, three of five risk factor criteria must be present (abdominal obesity by waist circumference, blood pressure and levels of TGs, HDL cholesterol, and fasting glucose).[1,2] Those with SCI may be relatively obese because of the loss of muscle mass, but this may not be quantifiable by performing a waist circumference measurement. Blood pressure values are generally lower in persons with higher cord lesions than those in the general population. In those with SCI, the fasting serum glucose is usually within the normal range, despite frequently significant insulin resistance and hyperinsulinemia. If an oral glucose tolerance test is performed, the persons with SCI may be classified as having IGT or DM (performing this provocative study is not a criterion for diagnosis of the syndrome by the ATP III guidelines). Despite an inverse relationship demonstrated between TG and HDL cholesterol, patients with SCI often have fasting TG levels <150 mg per 100 ml. Thus, individuals with SCI may not satisfy criteria for the metabolic syndrome, as defined by ATP III, or, for that matter, other classifications.

Finally, in the general population the determination of the presence or absence of the metabolic syndrome does not appear to confer additive risk over and above that of the conventional risk factors for CHD.[59] Because of the aforementioned considerations, it is crucial to be knowledgeable of the underlying metabolic pathophysiology of those with SCI.

Conclusion

Adverse changes in body composition and inactivity predispose persons with SCI to metabolic abnormalities that tend to accelerate the development and appearance of CHD. Atrophy of muscle and absolute and/or relative increases in body fat occur shortly after injury, continuing at an increased rate in persons with SCI with advancing age. Insulin resistance and hyperinsulinemia develop with associated disorders in carbohydrate and lipid metabolism. The ability of the pancreas to compensate for these changes may diminish with duration of injury and advancing age.

Conventional risk factors for CHD were identified in a population of veteran outpatients with SCI. After persons with known DM were excluded, approximately 17% were classified as having DM on oral glucose tolerance testing and 39% had two or more risk factors for CHD. Compared with the general population, in subjects with SCI serum HDL cholesterol values were shifted to the left with several patients having extremely low levels, highlighting the need that HDL cholesterol be recognized as a risk factor requiring special consideration with regard to therapeutic intervention. Persons with paraplegia may have increased hypertension and pre-hypertension, increasing CHD risk. Individuals with tetraplegia may have relatively low blood pressure values but compensatory elevated levels of angiotensin II to maintain blood pressure during upright posture; elevated levels of angiotensin II are appreciated to have a myriad of deleterious effects on the vasculature. The absence of activity and symptoms of cardiovascular disease in this population may reduce identification of macrovascular disease and may hinder the correct stratification of CHD risk for the cut-off values for serum LDL cholesterol by the ATP III guidelines. From various noninvasive imaging approaches, CHD appears to occur prematurely in those with SCI, and, of interest, may not be as closely related to traditional risk factors as has been demonstrated in the able-bodied population. Because of idiosyncrasies of the population, persons with SCI may not be classified by the established criteria as having the 'metabolic syndrome', despite being inactive and relative obesity with associated metabolic disorders that predispose them to an increased risk of CHD. The conventional risk factors in individuals with SCI should be identified and aggressively treated according to current standards of care.

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