Risk factors for coronary heart disease in patients with spinal cord injury in Turkey

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Objective: To compare the standard risk factors for coronary heart disease (CHD), defined in National Cholesterol Education Program II (NCEP II) of Turkish spinal cord injury (SCI) patients with healthy controls, discuss the results according to the findings in Turkish population, and SCI patients in the literature.

Design: We assessed 52 age and sex matched healthy control subjects, and 69 SCI patients (16 females, 53 males with the mean age of 33.9 ± 11.37 years) with time since injury of 12.8 ± 13.45 months. The study consisted of 45 paraplegics, and 24 tetraplegics with 54% incomplete, and 46% complete injury.

Results: Risk factors for CHD according to NCEP II were; age and sex in 16%, positive family history in 0%, cigarette smoking in 54%, hypertension (HT) in 0%, high total cholesterol (TC) in 32%, high low-density lipoprotein cholesterol (LDL) in 41%, low high-density lipoprotein cholesterol (HDL) in 52%, and diabetes mellitus (DM) in 7% of our SCI patients, respectively. Compared to controls DM, high TC, LDL, and low HDL were statistically more frequent in SCI patients. We found a negative correlation between serum HDL and time since injury. TC (186 ± 32 vs 205 ± 36 ; $P=0.025$), TC/HDL (5.34 ± 1.17 vs 6.26 ± 1.5 ; $P=0.005$), and LDL/HDL (3.57 ± 0.9 vs 4.16 ± 1.3 ; $P=0.027$) were significantly increased in patients with time since injury of more than 1 year, while HDL levels (35.8 ± 6.36 vs 33.86 ± 6.47 ; $P=0.213$) decreased without reaching statistical significance. The lipid profiles did not show any correlation with the neurological level, and completeness of lesions.

Conclusions: SCI confers additional CHD risk over that present inherently in the parent population due to enforced sedentary lifestyle and this increases with time since injury.

The preliminary study consisting of 26 patients was accepted for poster presentation in Copenhagen, Denmark (18–20 June 1999) at the 38th Annual Scientific Meeting of IMSOP in association with the Nordic Medical Society of Paraplegia.

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Introduction

Previous studies have reported an adverse coronary heart disease (CHD) risk profile in patients with spinal cord injury (SCI).^{1–3} As SCI patients survive longer because of the implementation of modern therapeutic modalities on life threatening complications such as urinary tract infections and pressure sores, the importance of the management of coronary risk factors is likely to increase. Depressed values of high density lipoprotein cholesterol (HDL) have been reported repeatedly in comparison with able bodied subjects^{4–8} which may be due to increased proportion

of adipose tissue,^{8,9} ethnicity,¹⁰ extremely low levels of physical activity,^{4,5,11} time since injury,^{4,12,13} and level and completeness of lesion.¹⁰ Abnormalities of carbohydrate metabolism, insulin resistance, and hyperinsulinemia have also been described in subjects with SCI.¹⁴

The Turkish population has inherent risk factors arising from their genetic make-up aside from the standard risk factors defined in National Cholesterol Education Program II (NCEP II).¹⁵ The purpose of the study was to compare the standard coronary risk factors of the SCI patients with a healthy control group, and discuss the results according to the findings in Turkish population, and SCI patients in the literature.

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Material and methods

We assessed 69 SCI patients during their rehabilitation period in our centre. The time since injury was 12.8 ± 13.45 months (range 2–84 months). Sixteen (23%) females and 53 (77%) males were evaluated. The mean age of the patients was 33.9 ± 11.37 years (range 10–70 years). The mean age of males was 33.7 ± 12.1 , of females 34.6 ± 8.6 years, respectively. Written informed consent was obtained from all patients. The determination of the level of SCI was based on a comprehensive standardized manually performed physical examination.¹⁶ The study consisted of 45 paraplegics (67%) and 24 tetraplegics (33%). ASIA impairment scale indicated 37 incomplete (54%), and 32 complete (46%) injury. In paraplegics 23 complete (52%), and 22 incomplete (48%) injury were investigated. In tetraplegics there were 15 (62%) incomplete and nine (38%) complete injury. Traffic accident (58%) was the most common cause. The other causes were: driving two (3%), infection four (6%), trauma two (3%), vascular two (3%), weapon seven (10%), and fall 12 (17%).

Our control group which consisted of 52 subjects (14 females (27%), 38 males (73%)), mean age 35.5 ± 7.72 years) was selected from young medical staff during their annual check up.

Body weight was measured on a balance beam scale designed to accommodate wheelchairs. Body length was measured to the nearest centimeter in a supine position using a plastic measuring tape. Measurements for the abdominal circumference (AC) were made at umbilicus after a normal expiration with subjects supine. Body mass index (BMI) was calculated as the weight in kg divided by the squared height in meters, and $>27 \text{ kg/m}^2$ is a contributing risk factor.¹⁷

Conicity index (CI), an index of abdominal adiposity was measured as described by Valdez *et al.*¹⁸ CI is equal the abdominal circumference in m/0.109 square-root weight/height in kg and m, respectively.

A diastolic blood pressure above 90 mmHg and a systolic blood pressure above 140 mmHg or being on antihypertensive treatment were considered as diagnostic for hypertension (HT).¹⁹ Diabetes mellitus (DM) and impaired fasting glucose (IFG) were defined according to the report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.²⁰ A questionnaire was used to assess alcohol consumption (number of glasses per week), smoking behavior (number of cigarettes per day) and family history of CHD. Blood samples were obtained after an overnight fast. Total cholesterol (TC) and triglycerid (TG) concentrations were measured using enzymatic tests on the Olympus Au-560 automated analyzer (Japan). HDL was determined after selective precipitation of the very low density lipoprotein-cholesterol (VLDL) and low density lipoprotein-cholesterol (LDL). LDL in mg/dl was calculated according to the Friedewald equation as follows: $\text{LDL} = \text{TC} - (\text{HDL} + \text{TG}/5)$.²¹ Serum uric acid

(SUA) and plasma glucose were measured by automated blood analyzer.

The results are reported as mean $\pm$ standard deviation. The limits of statistical significance was $P < 0.05$. Correlation between two groups were carried out with Pearson bivariate correlation tests. Numerical variables were compared with Student's *t*-test. Non numerical values were compared with χ^2 test. In 2×2 contingency tables Yates correction was done. When assumptions were violated in 2×2 tables Fischer's exact test was used. The statistical analysis was done by using Statistical Package for Social Sciences (SPSS) for Windows 10.0.

Results

Demographic parameters of our SCI patients and controls are shown in Table 1. Means and standard deviations for biochemical and demographic parameters as well as the proportion of subjects falling outside the 'normal range' are shown in Table 1 and 2. Impaired fasting glucose, DM, hyperuricemia, high TC, LDL, low HDL, high TC/HDL, LDL/HDL ratios were statistically more common in the SCI group, while positive family history was statistically more common in the control group (Table 2). Age, sex, HT, obesity, high TG, and smoking were not statistically different between the groups. Time since injury was correlated directly with TC/HDL and LDL/HDL ratios, inversely with HDL ($P < 0.01$, $r = 0.36$; $P < 0.05$, $r = 0.27$; $P < 0.05$, $r = -0.26$, respectively). TC (186 ± 32 vs 205 ± 36 ; $P = 0.025$), TC/HDL (5.34 ± 1.17 vs 6.26 ± 1.5 ; $P = 0.005$), and LDL/HDL (3.57 ± 0.9 vs 4.16 ± 1.3 ; $P = 0.027$) were increased significantly with time since injury more than one year while HDL levels (35.8 ± 6.36 vs 33.86 ± 6.47 ; $P = 0.213$) decreased without reaching statistical significance. HDL showed inverse correlations with time since injury, TG, TC/HDL, and LDL/HDL ratios ($P < 0.05$, $r = -0.24$; $P < 0.001$; $r = -0.71$; $P < 0.001$, $r = -0.57$, respectively). The lipid profiles did not show any correlation with the neurological level, and completeness of lesions. There was no statistically significant difference for CHD risk factors in tetraplegics and paraplegics or for complete and incomplete lesions. SUA levels were directly correlated with TC ($P < 0.01$; $r = 0.36$), TG ($P < 0.001$; $r = 0.46$), and TC/HDL ratio ($P = 0.01$; $r = 0.30$). No patient or control had a history of alcohol consumption, and drug use affecting CHD risk factors.

Discussion

We found, that the SCI group had more risk factors for CHD compared to the age and sex matched control group. Obesity, high TG, and smoking were more common in the SCI group without reaching statistical significance. The adverse risk profile of increased TC and ratios TC/HDL, LDL/HDL were more common with time since injury greater than 12 months.

Table 1 Demographic parameters of SCI patients and controls

	Controls (n = 52)	SCI patients (n = 69)	P value
Age (years)	35.5 ± 8	34 ± 11	N.S
Sex			
Males	38 (73%)	53 (77%)	N.S.
Females	14 (27%)	16 (23%)	
Height (m)	1.68 ± 8.7	1.7 ± 8.2	N.S.
Weight (kg)	70.2 ± 9.9	73.6 ± 12	N.S.
Abdominal circumference (cm)	85.7 ± 11	84.8 ± 10	N.S.
Conicity index	1.21 ± 0.15	1.18 ± 0.09	N.S.
BMI (kg/m ²)	24.97 ± 3.3	25.5 ± 4	N.S.
Duration of SCI (months)		12.8 ± 14	N.S.
Biochemistry			
Glucose (mg/dl)	82 ± 9	92 ± 18	P < 0.001
Uric acid (mg/dl)	3.8 ± 1	5.8 ± 2	P < 0.001
Total cholesterol (mg/dl)	166 ± 22	194 ± 35	P < 0.001
Triglycerides (mg/dl)	130 ± 50	138 ± 63	N.S.
HDL cholesterol (mg/dl)	42 ± 8	35 ± 7	P < 0.001
LDL cholesterol (mg/dl)	98 ± 16	130 ± 32	P < 0.001
VLDL cholesterol (mg/dl)	26 ± 10	28 ± 13	N.S.
Total cholesterol/HDL-cholesterol	4.1 ± 0.8	5.73 ± 1.39	P < 0.001
LDL-cholesterol/HDL-cholesterol	2.45 ± 1.11	3.82 ± 1.11	P < 0.001

Table 2 Cardiovascular risk and contributing factors

	Controls (n = 52)	SCI patients (n = 69)	P value
Age >45 years for males	6 (11%)	11 (16%)	0.54
Age >55 years for females or premature menopause	0 (0%)	0 (0%)	–
Hypertension (>140 mmHg for systolic >90 mmHg for diastolic)	0 (0%)	0 (0%)	–
Impaired fasting glucose (Glucose <126 and >110 mg/dl)	0 (0%)	8 (12%)	0.01
Diabetes mellitus (Glucose >126 mg/dl)	0 (0%)	5 (7%)	0.04
Obesity (BMI >30 kg/m ²)	2 (4%)	7 (10%)	0.19
Smoking	22 (42%)	37 (54%)	0.21
Hyperuricemia (>7.5 mg/dl)	0 (0%)	12 (17%)	0.001
High total cholesterol (>200 mg/dl)	0 (0%)	22 (32%)	<0.001
Low HDL cholesterol (<35 mg/dl)	13 (25%)	36 (52%)	0.002
High LDL cholesterol (>130 mg/dl)	0 (0%)	28 (41%)	<0.001
High triglyceride (>200 mg/dl)	1 (2%)	7 (10%)	0.07
Total cholesterol/HDL (>4.5)	17 (32%)	55 (80%)	<0.001
LDL/HDL (>30)	10 (19%)	56 (81%)	<0.001
Positive family history*	8 (15%)	0 (0%)	<0.001

*Myocardial infarction or sudden death in first degree consanguinity in men before 55, in women before 65 years of age

In the literature on CHD risk factors in SCI, the patient populations have different age, time since injury, and different risk factors inherent from their population of origin. The results from these studies are difficult to compare if the population of origin is not taken into account. Therefore we analyzed our results first by comparing them with our controls, then with two big Turkish population studies, and finally with the SCI population elsewhere.

TC and LDL levels were significantly increased in 32% and 41% of the SCI patients compared to controls. In the 1990 results of the prospective TEKHARF study on CHD risk factors in Turkey,

25% of the cohort had TC > 200 mg/dl.²² In the Turkish Heart Study Mahley have reported similar prevalence rates; for high TC 32% in men, 22% in women, and for high LDL (>130 mg/dl) 37% in men, 28% in women, respectively.²³ These results indicate that the study controls were clearly different from the representative Turkish populations of the TEKHARF and the Turkish Heart Study cohort. However, while the study controls were chosen from young and healthy population, these cohorts included healthy and diseased people randomly sampled from Turkey which explains the difference. The increased lipid levels seen in SCI patients may be due to the influence of enforced

sedentary lifestyle of our SCI patients acting over the standard factors of diet and level of physical activity in the Turkish population. TC and LDL levels of our SCI patients seemed higher than seen in other studies (Maki with 26%, 33%, Tharion with 8%, 10%)^{8,24} with exception of nearly similar values of LDL (44%) reported in the study of Bauman.⁷ This observed difference may be due to longer time since injury in the aforementioned studies which may select surviving patients with good lipoprotein profile and differences in basic risk factors of their parent population.

HDL levels were significantly depressed in 52% of our SCI patients compared to controls (25%). HDL showed inverse correlations with the time since injury, TG, TC/HDL, and LDL/HDL ratios. High TG levels described as level >200 mg/dl were present in 10% of the SCI patients and in 2% of the controls. In the Turkish Heart Study 53% of Turkish men and 26% of Turkish women had HDL levels <35 mg/dl.²³ The same prevalences were 15%, and 5% for American men and women, respectively. The difference may be genetically determined; probably due to increase of hepatic lipase activity in the Turkish population. In the TEKHARF study high TG was found in 15% of males, and in 10% of females which were comparable to our SCI patients.²² The prevalence of low HDL (<35 mg/dl, 52%) and high TG (>150 mg/dl, 26%) in our SCI patients were comparable to prevalence reported by Tharion *et al* (58% and 21%) and Maki *et al* (41% and 32%).^{8,24} However, the ratios TC/HDL and LDL/HDL, a stronger predictor of CHD risk²⁵ were numerically and percentage-wise higher than observed in other studies (5.73 ± 1.39 , 3.82 ± 1.11 vs Baumann with 5.1 ± 0.1 ; 80%, 81% vs Maki with 57%, 56%) in SCI.^{7,8} They were also higher than controls (32% and 19%), and in those observed in the Turkish Heart Study cohort (TC/HDL >4.5 in 64% of men, in 38% of women).²³ Maki *et al* and other authors have suggested that the high prevalence of these ratios in their SCI patients was primarily due to a high prevalence of reduced HDL. But the higher ratios seen in our study may be due to other factors that may influence HDL levels, like smoking, genetic factors mentioned above, and lower levels of physical activity. This may be ascertained by the finding of increased adverse risk profile for CHD in our SCI patients with time since injury more than 12 months and the negative correlation of HDL with time since injury. We found no relation of low HDL levels with other putative factors like level of injury, completeness of lesion, obesity, alcohol consumption, and medications like beta blockers, diuretics etc. The lack of the association between HDL and level or completeness of lesion may be due to the relatively small sample size of our study group.

Our SCI patients had a significantly increased DM (7%), and IFG (12%) prevalence compared to

controls. The calculated prevalence of DM was 6.3% for females, and 4.6% for males in the TEKHARF cohort in 1990, comparable to our SCI patient group.²⁶ In the TEKHARF study subjects were diagnosed as diabetic if their fasting plasma glucose (FPG) were >130 mg/dl or if they gave a history of diabetes. Slightly fewer people will be diagnosed with diabetes if the new FPG criteria is used alone than if either the FPG or the oral glucose tolerance test (OGTT) is used and interpreted by the previous World Health Organization (WHO) and National Diabetes Data Group (NDDG) criteria.^{20,27,28} Although the OGTT and FPG are both suitable tests, in epidemiological studies, the FPG is strongly recommended because it is easier and faster to perform, more convenient and acceptable to patients and controls, more reproducible, and less expensive. Tharion *et al*²⁴ and Duckworth *et al*²⁹ have reported higher prevalence of DM and impaired glucose tolerance (19% and 23%; 23% and 40%, respectively), may be due to different cutpoint values or to different methodology used. Our SCI patients had a prevalence of 10%, our controls of 4% for obesity. The prevalence of obesity described as BMI >30 kg/m² was present in 9% of males and in 28.5% of females in the TEKHARF cohort in 1990,³⁰ comparable to Western males, and our SCI patients which were mostly males. In other SCI studies^{7,8} BMI were in the range of 25.5–26.0 comparable to our SCI patients and to the TEKHARF cohort for men (25.4 for men, 27.7 for women). The differences between our SCI patients and other SCI populations may be due to shorter duration since injury and younger age of our SCI patients. Our SCI patients had a significantly increased hyperuricemia prevalence (17%) compared to controls. SUA levels were correlated with TC, TG, and TC/HDL ratio which may imply that our SCI patients have some features of the metabolic syndrome (also known as syndrome X or the insulin resistance syndrome) and thus are at increased risk for CHD.³¹ However, prevalences of obesity, HT, and IFG of our SCI patients were not high. In addition, whatever the cause, increased SUA levels were accepted as an independent cardiovascular risk factor.^{32,33} The results of these two studies both demonstrated that a single, baseline SUA predicted cardiovascular disease mortality over the ensuing 20 years.

We concluded, that compared to other SCI populations, our SCI patients were younger, smoked more, had higher TC, LDL levels, and TC/HDL, LDL/HDL ratios, but lower prevalence of HT and DM. SCI seems to confer additional CHD risk factors due to sedentary lifestyle over the preexisting risk profile of the parent population which increases with time since injury.

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