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ORIGINAL STUDY

Carpal tunnel release surgery at a young age indicates need for diabetes mellitus screening

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Patients with carpal tunnel syndrome (CTS) often suffer from comorbid medical conditions, including diabetes mellitus (DM), hypothyroidism, rheumatoid arthritis, hypertension and hyperlipidemia. There is no conclusive evidence about causation link between these disorders and CTS. It can be proposed that both are caused by a common pathophysiological process, and early CTS diagnosis can be a predictor of future diagnosis of one of the above disorders. A long-term follow-up study was designed to investigate this hypothesis.

This is a retrospective cohort of 90 consecutive patients aged 18-40 years who underwent either carpal tunnel release (CTR, the study cases, n = 36) or ankle fracture repair (the controls, n = 54). The latter were otherwise young and healthy patients, and were considered representative of the general population.

The average postoperative follow-up was 18.75 years (range 16-26) for the CTR group and 19.39 years (16-25) for the control group. DM was diagnosed in 26.5% of the CTR patients compared to 9.3% of the controls (*P* = 0.04). No group differences were detected for the four other investigated chronic disease states.

The findings of this study suggest that CTS may be predictive of DM in young patients, thus calling for screening of CTS patients for DM.

Keywords : carpal tunnel syndrome ; risk factor ; diabetes mellitus.

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INTRODUCTION

Carpal tunnel syndrome (CTS) is the most common non-entrapment neuropathy of the upper extremity whose etiology is unknown. It is associated with female gender and with several

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disease entities, such as autoimmune disorders and metabolic syndrome *(4,7)*. Similarly, many histological and biomechanical studies describe multiple soft tissue pathologic changes in patients with diabetes, that could contribute to development of neuropathy *(11,12)*. However, causal relationship between systemic disorders and CTS has not been proved, and nothing prevents one from hypothesizing that common upstream mechanisms may underlie the pathophysiology of both CTS and those disorders. Most researchers have studied the prevalence of background medical conditions in patients with and without CTS in order to define the risk factors for CTS *(9)*. Conversely, a few authors attempted to investigate a reverse association, i.e., whether CTS itself is a risk factor of other disorders, and they consistently found that CTS may predict other chronic conditions, including diabetes mellitus (DM) and hypothyroidism *(10,13)*. We now add to this growing body of evidence a long retrospective follow-up study of young patients who were operated for CTS. We believe that the need for surgical release as well as the development of CTS prior to the age of 40 years are indicators of the severity of the condition. We considered that if there is a link between CTS and some yet undisclosed morbidity, there would be a greater likelihood of detecting an increased prevalence of chronic disease in the relatively young patients who have the more severe forms of CTS. In addition, the long-term follow-up of our patients made it possible to identify any difference of morbidity in patients who had surgery for CTS and those who did not, given that chronic diseases characteristically develop over a period of time.

MATERIALS AND METHODS

A retrospective cohort design was chosen to compare the risk of developing chronic diseases in a group of patients following carpal tunnel release (CTR) surgery and a control group of patients who underwent ankle fracture repair (ankle open reduction internal fixation [a-ORIF]). All patients were treated at the same tertiary referral hospital. The research was approved by the medical center's institutional review board. The patients were informed that data from the case would be submitted for publication and gave their consent.

It was presumed that young patients undergoing surgery for traumatic injury of the ankle would represent healthy controls who had the same predisposition for developing chronic medical conditions as the general population. However, the comparison between the cases and controls had to be controlled for gender, since male gender is a well-known risk factor for trauma. A list of 161 patients who had either ankle fracture treated operatively by a-ORIF (n = 89, 55%), or CTR (n = 72, 45%) between 1990-2000 was retrieved from the medical center's archives. All the patients were between 18-40 years of age at the time of the surgical intervention. The list contained information on the patient's identity and date and type of surgery.

Information on the patients' background and outcome were obtained by a telephone survey conducted by three investigators. Background information included age at surgery, gender, occupation (heavy, light or non-manual labor), marital status, number of children, smoking status, physical activity, height and weight at the time of surgery and current height and weight, medication use, chemotherapy and treatment that included iodine-containing medication. Information on the surgical outcome was collected and transcribed for the purpose of survival analysis. Each subject was asked about the current existence of any chronic medical conditions (hypertension, DM, rheumatoid arthritis, hypothyroidism, and hyperlipidemia) and the time of their diagnoses.

Statistical analysis included the comparison of baseline characteristics of the study and control groups and survival analyses. Categorical variables were compared using the chi-square test, and continuous variables were compared using the t-test. Values of alpha and beta were determined at 0.05 and 0.2, respectively. P values smaller than 0.05 were used as a measure of statistical significance. Survival was defined as living without a diagnosed chronic disease. Patients with a chronic disease at study entry were excluded from survival analysis of that disease. Survival was presented separately for each chronic disease for the cases and the controls by Kaplan-Mayer survival curves. A Cox proportional hazards model was used to compare the hazard of each chronic disease diagnosis between the cases and the controls, and to evaluate contributions of other background variables to the hazard of developing a chronic disease. Next, combinations of variables were systematically incorporated into the model, and the optimal model predictive of each chronic disease diagnosis was selected according to the likelihood ratio test statistic.

RESULTS

One-hundred and sixty-one patients were identified. Ninety (56%) responded and provided complete information, 40 (25%%) refused to participate, no contact information was available for 27 (17%), and four (2%) appeared to have died. The final study cohort included 36 (40%) patients after CTR and 54 (60%) patients after a-ORIF.

The CTR patients were an average of 2.5 years older than the ankle injury patients ($P = 0.05$) at the time of surgery. There was no group difference in the length of follow-up or the patient's age at follow-up between the two groups. The average follow-up time was 18.75 years (range 16-26) for the CTR patients and 19.39 years (range 16-25) for the a-ORIF patients ($P = 0.16$). Of note, the two groups were similar with regard to chronic disease risk factors [Table 1]. The retrieved data revealed a significantly higher percentage of females among the CTR patients than the patients who underwent surgery for ankle fracture (69.4% vs 26.6%, $P <$

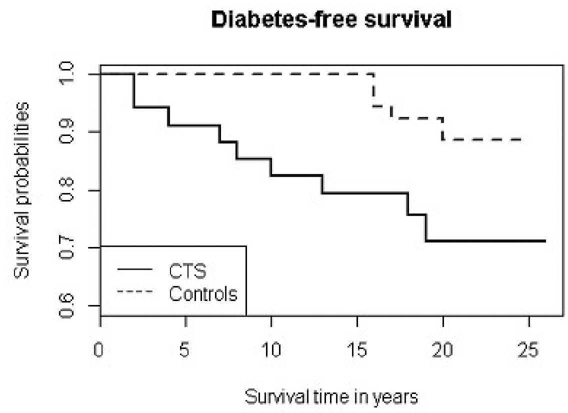

Figure 1. T— ime to development of Diabetes Mellitus following carpal tunnel surgery (CTS = carpal tunnel syndrome) or ankle fracture fixation (a-ORIF).

Table 1. — Study participants' characteristics by surgical procedure

	CTR (n=36)	a-ORIF **(n=54)**	***P* value**
Female (%)	69.4	26.6	0.00*
Average age (yr) at procedure (range)	32.17 (18-39)	29.43 (19-39)	0.05
Average age (yr) at interview (range)	50.92 (38-61)	48.81 (39-62)	0.14
Average follow-up time (yr) (range)	18.75 (16-26)	19.39 (16-25)	0.16
Smokers, n (%)	11 (30.6)	22 (40.7)	0.51
Occupation, n			0.51
Heavy manual labor	4 (11%)	5 (9.3%)	
Light manual labor	20 (50%)	23 (37%)	
Non-manual labor	12 (33%)	25 (46.3%)	
Marital status			0.20
Single, n	11 (30.6%)	25 (46.3%)	
Married, n	25 (69.4%)	29 (53.7%)	
BMI (kg/m^2) (mean ± SD)	26.35±10.41	22.28±2.61	0.04*
Weight gain since surgery, n	18 (53%)	32 (65%)	0.56
Steroids use, n	4 (11%)	4 (7.4%)	0.79
Contraceptives use, n (females)[a]	10 (27.7%)	24.57 (45.5%)	0.70
Physical activity, n[b]	9 (25%)	19 (35%)	0.48

*Significance set at $P < 0.05$. [a]Refers to the current or past regular use of birth control pills. [b]Refers to current or past involvement in any amount of recreational physical activity. CTR = carpal tunnel release. a-ORIF = ankle open reduction internal fixation. BMI = body mass index. SD = standard deviation.

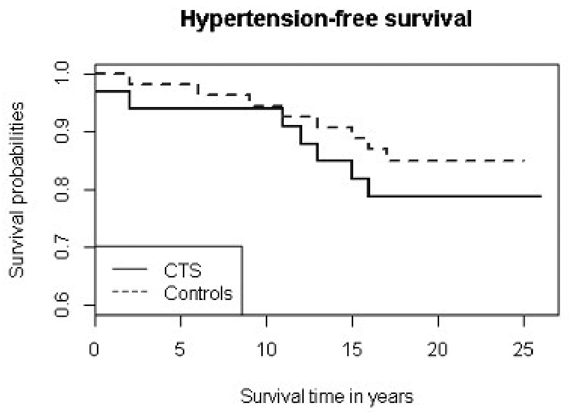

Figure 2. — Time to development of Hypertension following carpal tunnel surgery (CTS = carpal tunnel syndrome) or ankle fracture fixation (a-ORIF).

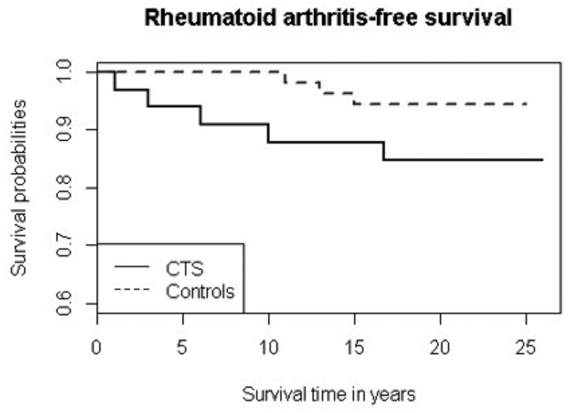

Figure 4. T— ime to development of Rheumatoid Arthritis following carpal tunnel surgery (CTS = carpal tunnel syndrome) or ankle fracture fixation (a-ORIF).

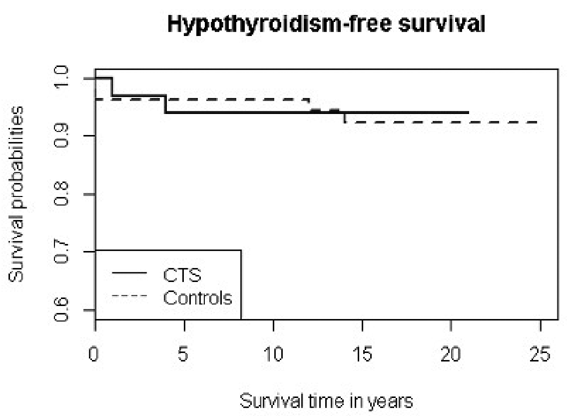

Figure 3. — Time to development of Hypothyroidism following carpal tunnel surgery (CTS = carpal tunnel syndrome) or ankle fracture fixation (a-ORIF).

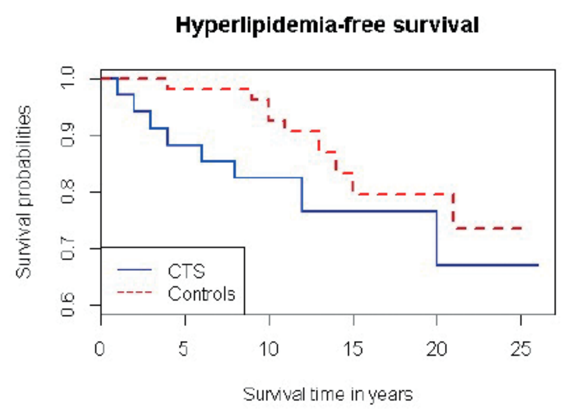

Figure 5. — Time to development of Hyperlipidemia following carpal tunnel surgery (CTS = carpal tunnel syndrome) or ankle fracture fixation (a-ORIF).

0.001). This difference, however, was unlikely to affect the comparison of DM rates between genders : analysis of the female population alone revealed that the rate of DM was 30.4% in the CTR patients and 12.5% in the a-ORIF patients (OR=2.98, $P = 0.26$).

The development of five chronic conditions (reported as percent of new cases) among the patients in the CTS and control groups were investigated : DM (26.5% vs 9.3%, respectively) [Fig. 1], hypertension (21% vs 15%)[Fig. 2], hypothyroidism (6% vs 7.5%)[Fig. 3], rheumatoid arthritis (15% vs 5%)[Fig. 4] and hyperlipidemia (26.5% vs 22.2%)[Fig. 5]. There was a significantly higher rate of DM diagnosis among the CTR patients compared to controls (26.5% vs. 9.3%, respectively, $P = 0.04$). No significant differences were identified in the rates of diagnosis of any of the other chronic conditions [Table 2]. The Cox proportional hazards model showed that even after controlling for gender, CTR was still associated with an increased risk of subsequent DM diagnosis (OR=2.7, $P = 0.09$).

Separate Cox models assessed the proportional hazard of the background factors for the development of DM. It emerged that non-manual labor was negatively associated with DM (HR=0.22, P = 0.043), while older age at the time of either surgery

Table 2. — Selected chronic conditions diagnosed among all the study participants

	CTS (n=36)	Ankle fracture (n=54)	*P* value
Diabetes mellitus	26.5%	9.3%	0.04*
Hypertension	21%	15%	0.56
Hyperlipidemia	26.5%	22.2%	0.84
Rheumatoid arthritis	15%	5%	0.25
Hypothyroidism	6%	7.5%	1

* Significance set at $P < 0.05$. CTS = carpal tunnel syndrome

was positively associated with DM (HR=1.11, $P = 0.048$) [Table 3].

DISCUSSION

We conducted this retrospective cohort study to investigate whether severe CTS requiring surgery among relatively young patients is associated with the subsequent diagnosis of a chronic systemic disease during a long postoperative follow-up. A control group of patients who underwent a-ORIF during the study period and who were presumably representative of the healthy general population, was also followed-up for comparison. The five selected chronic conditions that developed among the subjects in both groups were DM, hypertension, rheumatoid arthritis, hyperlipidemia, and hypothyroidism. More CTS patients developed each of these conditions, with the exception of hyperthyroidism, and more CTS patients gained weight since surgery. Only the difference in DM rates between the groups, however, reached a level of significance ($P = 0.04$).

Previous studies on the association between DM and CTS yielded mixed results *(2,5,8)*. One recent meta-analysis showed a definite positive association between them after controlling for age, gender and body mass index *(9)*. While the hypothesis of CTS causation by DM was investigated in most of the reported cases, the exact mechanism by which DM causes nerve damage remains unknown. The possibility of CTS being a predictor of DM was investigated by several cross-sectional studies. De Rijk et al *(10)* evaluated the yield of screening for underlying DM, hypothyroidism and connective tissue diseases among 516 patients with CTS. The patients underwent three blood tests (glucose, thyroid-stimulating hormone and erythrocyte sedimentation rate), and those with abnormal results were retrospectively followed for the final diagnosis of an underlying disease. Only two patients were diagnosed with new DM, and another two were diagnosed with new hypothyroidism *(10)*. In another cross-sectional study, the investigators reviewed the medical records of 297 patients who filed work compensation claim for CTS and were then referred to additional screening. One new case of DM and 13 new cases of hypothyroidism were identified by screening *(1)*. Another study reported on the yield of preoperative DM and hypothyroidism screening in 109 patients who underwent CTR : two patients were subsequently diagnosed with hypothyroidism and one with DM. Those authors found the results supportive of the recommendation of the British Society for Surgery of the Hand to screen for these disorders before CTR surgery *(4)*.

Table 3. — Estimated hazard ratios for diagnosis of diabetes mellitus

	Hazard ratio	95%Confidence interval	*P* value
Procedure (CTS)	3.34	1.17-9.99	0.03*
Male gender	0.4	0.13-1.19	0.1
Older age at surgery	1.11	1.003-1.23	0.04*
Current/past smoking	0.9689	0.3-2.9	0.9
Occupation (office vs others)	0.22	0.049-0.989	0.048*
Marital status (married vs other)	1.82	0.172-1.751	0.3
Body mass index at surgery	1.009	0.944-1.077	0.8
Weight gain since surgery	1.012	0.96- 1.057	0.6

*Significance set at $P < 0.05$. CTS = carpal tunnel syndrome.

In one large epidemiologic case-control study, the investigators retrospectively assessed the risk of CTS diagnosis in the 10 years preceding the diagnosis of DM. That investigation included 2655 patients newly diagnosed with DM during a period of one year and two matched control groups selected out of about 654,000 patients. There was a relative risk of 1.36 (95% confidence interval (95%CI) 1.26-2.11) for a CTS diagnosis among the patients who were subsequently diagnosed with DM *(4)*. Those authors related that finding to abnormal glucose metabolism in pre-diabetic patients that could lead to hyperglycemic neuropathy. Another large case-control study included 33,571 patients newly diagnosed with DM over a period of five years and a group of 167,777 matched controls. The odds ratio for a previous diagnosis of CTS was 1.31 (95%CI 1.22-1.4) *(6)*.

The current study has a few advantages over the earlier ones. One of the strengths is that we used a retrospective cohort design, which is considered a higher level of evidence than the previously performed case-control studies. In addition, we compared the cases to a healthy control group and assessed for many relevant confounders. The choice of a control group of patients who underwent surgery for traumatic injury in the same medical department had the advantage of selecting a healthy population matched for area of residence and most of the risk factors for DM. The only differences between the groups were age at surgery and percent of females, both of which were higher among the study patients. Although the age difference reached a level of statistical significance, it was only about 2.5 years. Yurdakul et al. *(3)* also noted that CTR is associated with female gender. Female gender could theoretically serve as a confounder, although it is not known to be associated with DM. However, there was a higher prevalence of subsequent DM when only the females of the two groups were compared (30.4% DM in the CTR group and 12.5% DM in the a-ORIF group), and the COX model showed increased odds for DM for the CTR group after controlling for gender ($P = 0.09$). One of the limitations of this study is that we managed to contact only 56% of the patients, raising the possibility of a selection bias, although it could be expected that the less healthy and socially disadvantaged patients to be lost from follow-up, and that a selection bias would equally affect both the study and control groups. Use of the patient's self-reporting to determine surgical outcome could also introduce some bias, but we think that a telephone survey with questions formulated specifically to address the research question of interest is more informative than a medical chart review for long-term outcome assessment. Lastly, the study sample was small, and it could be that the low statistical power prevented identification of significance of CTS as a predictor of DM after adjustment for occupation and age at surgery. Nevertheless, the COX model for prediction of DM that included the type of surgical procedure was a better fit than the one without it.

We conclude that this study supports the growing evidence that severe CTS at a relatively young age is predictive of a DM diagnosis. Despite some limitations, the study used a retrospective cohort design with long follow-up duration and robust data assessment methodology. We hope that it adds some quality evidence to support a policy of screening of CTS patients for DM.

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