RESEARCH REPORT

Insulin resistance increases risk of carpal tunnel syndrome: a case-control study

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Abstract Carpal tunnel syndrome (CTS) is one of the most common upper limb compression neuropathies. In only 50% of cases it is possible to identify a cause. Our objective was to determine the role of glucose metabolism abnormalities in idiopathic CTS. We identified 117 patients with idiopathic moderate or severe CTS and 128 controls. In all we evaluated glucose and insulin levels at fasting and after 2-h oral glucose tolerance test (2h-OGTT). In addition we determined insulin resistance (IR). Following OGTT the prevalence of glucose metabolism abnormalities was significantly higher in the CTS group ($p = 0.001$). IR was documented in 80% of patients, of whom 45% had impaired glucose tolerance, 14% newly diagnosed diabetes mellitus, and 20% IR only. Waist circumference and body mass index were also significantly increased in the CTS group. In this study, we focused on evidence that pre-diabetes may represent a risk factor for CTS. We proposed to determine IR as a rule in all patients with idiopathic CTS.

Key words: 2h-OGTT, carpal tunnel syndrome, diabetes mellitus, diabetic neuropathy, HOMA-index, insulin resistance

Introduction

Carpal tunnel syndrome (CTS) is one of the most common upper limb compression neuropathies *(Katz and Simmons, 2002)*. The incidence and prevalence vary from 0.125% to 1% and 5% to 16%, depending upon the diagnostic criteria *(Atroshi et al., 1999; Bahrami et al., 2005)*. There are two distinct varieties of CTS: acute and chronic. The acute form is relatively uncommon and is most commonly associated with a fracture of the radius *(Melhorn, 1994)*. The chronic form is much more common and symptoms can persist from months to years; however, in only 50% of cases it is possible to identify a cause *(Aroori and Spence, 2008)*. The relationship between CTS and diabetes mellitus (DM) is well documented, with greater incidence multifold than in the general population *(Vinik et al., 2004)*. On the basis of clinical/electrophysiological assessment, one-third of type 2 diabetic patients have CTS, and one-sixth of these report symptoms *(Dyck et al., 1993)*. However, the relationship between CTS and pre-diabetes is controversial *(Gulliford et al., 2006)*.

Pre-diabetes is defined as impaired fasting glucose or impaired glucose tolerance (IGT) following a 2-h oral glucose tolerance test (2h-OGTT). IGT is generally a manifestation of insulin resistance (IR), together with abdominal obesity, hypertension, and

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dyslipidemia. Several studies have demonstrated that IGT is an important contributor to peripheral neuropathy *(Bosco et al., 2009; Summer et al., 2003)*. Besides, also hyperinsulinemia has been reported to cause neuropathological changes in diabetic animals treated with an excess of exogenous insulin *(Dyer and Messing, 1989)*. In this case-control study, we evaluated glucose metabolism in 117 patients with chronic unilateral or bilateral idiopathic CTS and normal fasting glycemia.

Patients and Methods

Patients

Between February 2009 and October 2010, 117 consecutive subjects with chronic idiopathic unilateral or bilateral, moderate or severe CTS confirmed by electrodiagnostic study *(American Association of Electrodiagnostic Medicine et al.,1993)* and 128 healthy controls were evaluated in our laboratory. Exclusion criteria were (1) family history of CTS, (2) electrophysiological findings of peripheral neuropathy, (3) toxic exposure, (4) abnormal results on blood tests including electrolytes, blood glucose, HbA_{1c}, renal function, vitamin B12 level, folic acid, serum protein electrophoresis, (5) DM, (6) connective tissue disease, (7) thyroid disease, (8) radius fracture, (9) pregnancy, and (10) repetitive manual works.

We could not obtain a randomly selected control group, so we recruited normal subjects, coming from the same geographic area, ethnic background, and with similar dietary habits and lifestyle of patients. We selected patient's friends or non-blood relatives, who did not have a known neuropathic disorder or DM.

Clinical evaluation

All subjects have been evaluated by a trained endocrinologist and neurologist. Medical records for each group included anamnestic data (dietary habits, life style, drug use), demographic information, body mass index (BMI), waist circumference (WC), glucose and insulin values at fasting and after 2h-OGTT, serum HbA_{1c}, complete blood cell count, renal and hepatic functions, triglycerides, serum lipid, systolic and diastolic pressure, vitamin B12, folic acid, and thyroid function. The clinical diagnosis of CTS was based on the presence of intermittent paresthesia, numbness or hypoesthesia in the median nerve distribution, occurring spontaneously or after repetitive use of the affected hand. Procedure for the 2h-OGTT required fasting after midnight, obtaining a baseline fasting glucose level, and administration of 75 g oral glucose load within a 5-min period. Blood specimens to determine plasma glucose and insulin levels were subsequently drawn at 120 min, timed from the beginning of the glucose load. IR was calculated by the homeostasis model assessment (HOMA) formula *(Matthews et al., 1985)*. Patients and controls were diagnosed for IGT if the 120-min venous plasma glucose value fell between 140 and 200 mg/dl. Criteria for new-onset DM were fasting plasma glucose level higher than 126 mg/dl or 120-min venous plasma glucose level higher than 200 mg/dl on the 2h-OGTT *(Genuth et al., 2003)*.

Electrophysiological evaluation

Motor nerve conduction studies were performed by employing a standard belly-tendon method for recording on the abductor pollicis brevis muscle, with a supramaximal stimulation of the median nerve distally at the wrist and proximally at the elbow. Sensory nerve conduction studies of the median nerve were performed using an antidromic method. An EMG test with a concentric needle was performed in the ABP muscle of each subject. We included only patients with ''moderate'' or ''severe'' CTS for at least 6 months *(Chang et al., 2008)*.

Data analysis

Data were expressed as mean ± SD. Patients were compared to controls with respect to variables representing their current status and, potentially, the etiology of the condition. For categorical variables, this was performed by comparing distributions using chi-square tests and for calculated variables by comparing means using *t* tests with correct test of the normal assumption required. When they were not satisfied due to skewed data distributions, logarithmic transformations were used. Finally, to assess and allow for discrepancies among the clinical characteristics in the group comparisons and to assess the relative significance of potential etiological variables (age, BMI, and WC), logistic regression was used. In all cases, a p value of 0.005 was considered statistically significant.

Results

Demographic features

During a period of 20 months, from February 2009 to October 2010, we recruited prospectively 117 subjects with chronic idiopathic CTS and 128 healthy controls. Gender distribution was similar in both groups. Mean age in the patient group was significantly higher than in control group ($p = 0.002$; Table 1).

Clinical features

The mean duration of symptoms was 28.2 ± 6.9 months. Triglycerides, cholesterol, serum HbA_{1c}, and mean values for blood pressure were similar

Table 1. Demographic and clinical features of 117 patients with ''idiopathic unilateral or bilateral, moderate or severe carpal tunnel syndrome'' and 128 control subjects.

	Patients	Controls	p Value
Demographic features			
Number	117	128	1.81
Age (years)	56.4 (7.1)	50.5 (6.8)	.002
Sex (M/F)	60/57	65/63	1.6
Clinical features			
Fasting glycemia (mg/dl)	81 (9.2)	79 (6.8)	1.2
Fasting insulinemia (UI/ml)	19.8 (2.8)	13.4 (2.9)	0.001
Waist circumference (cm)	81.8 (5.6)	78.8 (5.8)	0.005
BMI	25.6 (5.8)	22 (4.4)	0.005
HOMA-index	3.8 (0.7)	2.4 (0.5)	0.002
Triglycerides (mg/dl)	148.7 (10.6)	143 (9.1)	0.81
Serum lipid (mg/dl)	139 (11.6)	135 (10.1)	0.74
Systolic pressure (mmHg)	120 ± 15.1	119 (9.7)	0.86
Diastolic pressure (mmHg)	73 ± 8.9	69 (9)	0.79
Duration of symptoms (months)	28.2 (6.9)	—	—

Values are expressed as mean (SD) unless otherwise indicated. p *value* was evaluated after adjustment for age.
BMI, body mass index; HOMA, homeostasis model assessment.
BMI: [Weight (kg)/height^2 (h)^2]; HOMA-index: basal glucose plasma (mg/dl) × basal insulin plasma (UI/ml)/405; The differences between the proportions with insulin resistance ≥2.7 on the HOMA formula.

between the two groups. BMI and WC were significantly higher in patients than in controls ($p = 0.005$; Table 1).

Electrophysiological features

Electrophysiological study was normal in all controls. Bilateral CTS was present in 41 (35%) cases: in 65 (56%) patients CTS was categorized as ''moderate'' and in 44% as ''severe''. Nerve conduction study of the ulnar and the sural nerves was normal in all subjects (Table 2).

Impaired glucose tolerance and insulin resistance

The mean fasting glucose was 81 ± 9.2 mg/dl in patients group and 79 ± 6.8 mg/dl in control group, respectively, while the mean fasting insulin was significantly higher in the patient group ($p = 0.001$). Following 2h-OGTT, we found a high prevalence of glucose metabolism abnormalities in 70 (60%) patients and in 28 (22%) subjects of the control group. After adjusting for age, WC, and BMI the difference between patients and controls was significant ($p = 0.001$). The IR calculated with HOMA formula was present in 94 patients (80%), of whom 53 (45%) had also IGT (IGT_p+IR), 17 (14%) newly diagnosed DM ($NDDM_p$+IR), and 24 (20%) IR only. Twenty-three (19.6%) patients in the CTS group had normal glucose metabolism (NGM) condition and were not IR (Fig. 1). In the control group IR was present in 42 (33%) subjects, of whom 21 (16%) had IGT (IGTc+IR), 7 (5%) had newly diagnosed DM (NDDMc+IR) and 14 (11%) subjects had IR only (NGMc+IR). Eighty-six (67%) in the control group were NGM without IR (NGMc-IR). After similar adjustments for age, BMI, and circumference, however, HOMA-index was significantly higher in patients with only IR ($p = 0.005$) in IGT subgroups ($p = 0.005$) and mainly in DM subgroup than in the control subgroups, respectively ($p = 0.001$; Table 3).

Discussion

In this case-control study, we investigated the prevalence of abnormal glucose metabolism by 2h-OGTT and IR-index in subjects with idiopathic CTS. Eighty percent of our patients had IR, of whom, after a 2h-OGTT, 45% had IGT, 14% DM, and 20% IR only. These percentages were significantly higher than those reported in our control subjects. IR is a form of glucose dysmetabolism that precedes type-2 DM and patients with IR are at high risk for DM *(Storgaard et al., 2003)*. Substantial experimental evidence suggests that both diabetes and IR cause endothelial dysfunctions *(Cersosimo and De Fronzo, 2006)*. Several works report long-lasting hyperglycemia in subjects who developed subsequent neuropathy *(Singleton et al., 2003)*. Most of the epidemiological

Table 2. Electrophysiological features of 117 patients with ''idiopathic carpal tunnel syndrome (CTS)''.

		Electrophysiological features			
	No, (%)	DML Median nerve (ms)	SNCV Median nerve (m/s)	SNAP Median amplitude (μV)	Fibrillation/PSW ABP sites
No	117				
CTS severity, no (%)					
Moderate	65 (56)	4.1 ± 0.2	35.4 ± 2.4	6.3 ± 2.9	≤1
Severe	52 (44)	6.3 ± 0.7	Not assessed	Absent	≥2

Values are expressed as mean (SD) unless otherwise indicated.
ABP, abductor pollicis brevis; DML, distal motor latency; ms, millisecond; m/s, meter per second; SNAP, sensory nerve action potential; SNCV, sensory nerve conduction velocity; μV, micronVolts.

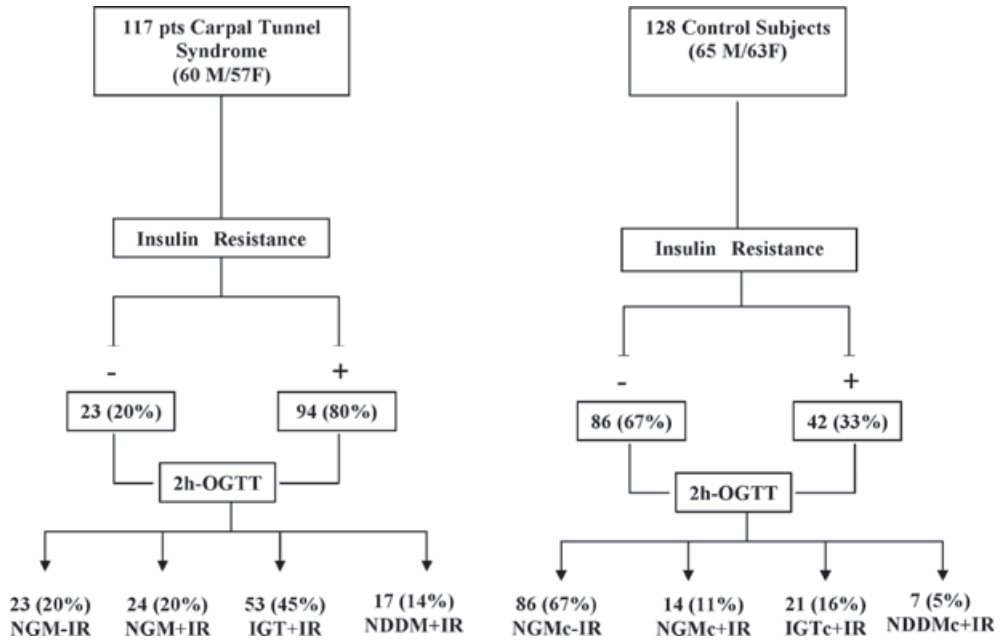

Figure 1. Flowchart comparing insulin resistance between carpal tunnel syndrome (CTS) and control subjects.

Table 3. Glucose metabolism assessment in 117 patients with ''idiopathic unilateral or bilateral, moderate or severe carpal tunnel syndrome'' and 128 control subjects (NGM-IR, NGM+IR, IGT+IR and NDDM+IR) according to 2h-OGTT and HOMA formula.

	NGM-IR		NGM+IR		IGT+IR		NDDM+IR	
	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls
Adjusted for age, BMI, and waist circumference								
No. (%)	23 (20)	86 (67)*	24 (20)	14 (11)*	53 (45)	21 (16)*	17 (14)	7 (5)*
Fasting glycemia	64.6 (4.2)	70 (6.6)	82 (8.6)	76.6 (9)	88.4 (7.3)	86 (9.4)	89 (15.4)	83 (9.3)
Fasting insulinemia	10 (1.2)	8.9 (1.7)	19 (3.3)	15 (3.1)	23.5 (7.2)	14.6 (2.8)§	26 (6.8)	15 (2)§
Glycemia 2h-OGTT	80 (7.4)	86 (9.1)	81 (9.3)	74 (14.8)§	189 (20.4)	164 (19)§	242 (20.6)	221 (16)*
Insulinemia 2h-OGTT	17 (2.3)	15 (3.1)	44 (5.4)	31(6.3)*	50 (7.5)	32 (3.9)*	52 (9.3)	35 (6.3)*
HOMA-index	1.6 (0.1)	1.4 (0.2)	3.8 (1.2)	2.8 (0.4)§	5.1 (2.8)	3 (0.6)§	5.7 (2.3)	3.1 (0.3)*

Values are expressed as mean (SD) unless otherwise indicated.
2h-OGTT, 2-h oral glucose tolerance test; BMI, body mass index; HOMA, homeostasis model assessment; NDDM+IR, newly diagnosed diabetes mellitus with IR; NGM-IR, normal glucose metabolism (NGM) without insulin resistance (IR); NGM+IR, NGM with IR; NGM+IGT, NGM with impaired glucose tolerance.
BMI: [Weight (kg)/height^2 (h)^2]; HOMA-index: basal glucose plasma (mg/dl) $\times$ basal insulin plasma (UI/ml)/405.
p Value evaluated after adjustment for age, BMI, and waist circumference:
*$<$0.001; §$<$0.005.

studies clearly showed that early hyperglycemia *(Summer et al., 2003; Smith and Singleton, 2008)* is sufficient to damage distal peripheral nerves. In a recent case-control study performed in 162 subjects we found that pre-diabetes may represent a risk factor for third cranial nerve palsy *(Bosco et al., 2009)*. The relationship between CTS and DM is frequently reported, while the association with pre-diabetes is controversial. Gulliford *et al*. documented that the incidence of CTS, Bell's palsy, and other peripheral nerve disorders are increased before diagnosis of diabetes *(Gulliford et al., 2006)*. Nevertheless, in this study the authors defined ''pre-diabetes'' as the time preceding the onset of diabetes and not a condition made evident through the OGTT *(Genuth et al., 2003)*. Our data documented a strong linkage between CTS and glucose metabolism abnormalities. IGT is generally a manifestation of IR; together with abdominal obesity, hypertension, and dyslipidemia, it is a component of the metabolic syndrome (MS), which predicts for diabetic complications *(Bosco et al., 2009)*. We suggest that ''idiopathic CTS'' may be frequently associated with IR in the form of ''pre-diabetes''. Moreover, we found a close association between WC and BMI in patients with CTS ($p = 0.005$). Central adiposity is closely associated with the development of IR *(Fujioka et al., 1987)* and obesity is associated with increased risk of CTS *(Bland, 2005)*. Our data reinforce the linkage between CTS and IR

and highlight IR as an independent risk factor for neuropathic injury. In our patients with CTS, IR was present in 80%, while 2h-OGTT resulted impaired in only 60%. These values were significantly higher than the control group. HOMA-index value allowed more identification in a subgroup of patients (20%) with IR and NGM than in controls. In these patients plasma glucose levels following the 2h-OGTT were within the normal range, whereas plasma insulin levels and HOMA-index values were markedly elevated. A methodological limitation to our study was the control group: we recruited subjects similar to our patients for sex, geographic areas, ethnic background, dietary habits and life style; they differ for age, WC, and BMI. Nevertheless, after adjustment for these variables the association between abnormal glucose metabolism and CTS remained strongly significant in the patient group. However, if IR leads to compensatory hyperinsulinism and subsequent development of CTS, this could be related to the effects of IR on endothelial function; in fact, insulin has both vasodilatatory effect, which is largely endothelium dependent and a vasoconstrictor effect through the stimulation of the sympathetic nervous system. Moreover, the microvascular dysfunction may be an important shared mechanism: vascular damage, which results from lipid deposition and oxidative stress to the vessel wall, triggers an inflammatory reaction, and the release of chemoattractants and cytokines worsens the IR and endothelial dysfunction *(Boyanovsky et al., 2003)*. Our findings suggest that neuropathic injury is an early event in patients with glucose metabolism imbalance still not clinically manifested and that principally HOMA-IR can be identified in non-diabetic subjects with high risk of CTS. Finally, we propose that a 2h-OGTT and mainly IR should be performed as a rule in all patients with idiopathic CTS and normal fasting glycemia. Based on the results of this study, additional studies with age-matched case-control subjects are needed before definite causal relationships between CTS and pre-diabetes markers.

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