行政院國家科學委員會專題研究計劃 成果 報告

糖尿病人之腕隧道症候群發生率（3/3）

The Incidence of Carpal Tunnel Syndrome in Type 2 Diabetes Mellitus

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中文摘要

針對 237 例第二型糖尿病及 440 例正常人我們以電氣生理學方法從事為期兩年觀察腕隧道症候群的發生率，兩組平均年齡分別為 60 ± 13.0 及 58.4 ± 13.4 歲。多變項分析顯示糖尿病人發生腕隧道症候群的相對危險性約為正常人的三倍。又體型較高者較不易發生此症候群。過去工作史、牽動腕部運動的休閒活動及糖尿病控制好壞對腕隧道症候群之發生率的影響正在分析中。

關鍵語：第二型糖尿病、腕隧道症候群、發生率

ABSTRACT

We have conducted a 2-year follow up study of carpal tunnel syndrome (CTS) in 237 type 2 diabetic patients and 440 normal subjects by the electrophysiological methods. Their mean ages were 60 ± 13.0 (mean±SD) and 58.4 ± 13.4, respectively. Mutivariate analysis showed that the relative risk for development of carpal tunnel syndrome in Type 2 diabetes mellitus was approximately 3 times of that of normal subjects. Those with a taller body height was less likely to suffer from carpal tunnel syndrome. The impact of occupational history, recreational activity involving flexion and extension of the wrist and glycemic control to the development of carpal tunnel syndrome is under analyses.

Key words: Type 2 diabetes mellitus, incidence, carpal tunnel syndrome

INTRODUCTION

The peripheral nervous system is frequently affected directly or indirectly in diabetes. In diabetic patients, the stage and severity of diabetes are closely related to the development of various neuropathic complications (1).

The study of carpal tunnel syndrome in diabetes subjects present several inherent difficulties, including the definition of syndrome, staging and severity (with or without neurological symptoms), measurement of progression, and standardization of the tests (2-4). The carpal tunnel space can be reduced because of accumulation of tissue fluids or abnormal depositions. Precipitating conditions causing a reduction in carpal tunnel space include the intake of estrogen, pregnancy, hypothyroidism and amyloidosis. Biomechanical factors, such as repeated flexion and extension of the wrist, are another frequently overlooked cause of carpal tunnel syndrome (5-8). Several studies have described the frequency of carpal tunnel syndrome in diabetes patients and in normal subjects (5, 9-11). Since diabetic patients are at potentially greater risk of developing carpal tunnel syndrome, the understanding of its prevalence in the diabetic population is important not only for clinical management but also for prevention (12).

In the previous study, we confirmed that diabetic patients had a higher prevalence of carpal tunnel syndrome than normal controls. The duration of diabetes and female gender were significantly associated with the presence of carpal tunnel syndrome. So far, there has no study to describe the difference of incidence of carpal tunnel syndrome between normal and diabetic subjects. This study aimed to answer the above mentioned issue.

RESEARCH AND METHODS

Diabetic patients and control subjects

The diagnoses of type 2 diabetes were based on the WHO definition (13). These patients were regularly followed up and had received oral hypoglycemic agents and/or insulin for at least 2 years at the diabetic clinic of National Taiwan University Hospital, Taipei, Taiwan. Those found on clinical and biochemical examinations to have amyloidosis, hypothyroidism, and symptoms of neuropathy, nephropathy, or taking estrogen were excluded. Patients visited the clinic once every 3 months for adjustment of diabetic control by regular measurements of fasting and 2-hour postprandial plasma glucose levels and glycated hemoglobin (HbA_{1C}). Renal and liver function tests were conducted once every 6 months, and ophthalmoscopic examinations and lower extremities circulation examinations once per year. Patients were further examined by a staff neurologist to ensure that there were no coexistent neurological problems, include stroke, Parkinson's disease, or other diseases causing motor or sensory disturbances. Neurological examinations were performed at the beginning, 1 and 2 years after enrollment.

Normal controls were recruited from healthy individuals who visited the hospital for a physical check-up (14). Controls received the same examinations as the diabetic patients, including (1) biochemical tests: fasting plasma glucose (< 6.1 mmol/L), thyroid, renal and liver function tests, and (2) neurological check-up to exclude the above mentioned disorders. Neurological examinations were conducted at the beginning and 2 years after recruitment.

Nerve conduction studies

Nerve conduction studies were performed using a Viking IV electromyograph (Nicolet, Madison, WI) following the established protocol (14,15). Median nerves were stimulated at the wrist and the elbow; ulnar nerves at the wrist, below the elbow,

and above the elbow; peroneal nerves at the ankle and the knee; and tibial nerves at the ankle and the popliteal fossa. Compound muscle action potentials (CMAPs) were recorded with surface electrodes placed on the abductor pollicis brevis (the median nerve), abductor digiti minimi (the ulnar nerve), extensor digitorum brevies (the peroneal nerve), and abductor hallucis longus (the tibial nerve) according to the standard belly-tendon arrangement. Sensory action potentials (SAPs) of the median, ulnar, and sural nerves were recorded by antidromic stimulation. Nerve conduction studies were performed in the limbs of the non-dominant side (15).

Electrophysiological abnormalities were classified as carpal tunnel syndrome only, and combined neuropathy of carpal tunnel syndrome with ulnar nerve entrapment or polyneuropathy. The definition of each entity followed the consensus statements of American Association of Electrodiagnostic Medicine, American Academy of Neurology, and Peripheral Nerve Society (16-19). Polyneuropathy was defined as slowing of nerve conduction velocities and reduction of amplitudes of CMAPs and SAPs beyond 2 standard deviations (2SD) of the limits of norms in more than 2 nerves of the upper and lower extremities (15). Carpal tunnel syndrome was diagnosed if evidence for both of the following criteria were found: (1) the slowing of nerve conduction velocities in the across-carpal tunnel segment of the median nerve and (2) relative prolongation of the sensory latency in the median nerve compared to that in the ulnar nerve (11,18,20,21). Ulnar nerve entrapment at the elbow was defined according to one of the following criteria: (1) an absolute reduction of the nerve conduction velocity in the across-elbow segment of the ulnar nerve, below 45 meters/sec, and (2) a relative reduction of the nerve conduction velocity in the across-elbow segment by 20% compared to that in the forearm segment of the ulnar nerve (16,17,22). In the subsequent discussion, carpal tunnel syndrome means that the patient has no other neurological disorder, and carpal tunnel syndrome complex indicates in addition to carpal tunnel syndrome, the patient also has either one or both

of ulnar nerve entrapment and polyneuropathy.

The questionnaire was derived from previously described method (23).

Statistical significance

Mutivariate analysis by Cox's proportional hazards model was used for estimation of the relative risk. $P<0.05$ was read as having a statistical significance.

RESULT

Table 1 shows the gender, age, body height and body mass index (BMI) distribution of diabetic patients and control subjects. Diabetic subjects showed a higher percentage of male, older in age, taller in height, heavier in weight and BMI.

Compared with normal controls, diabetic subjects revealed a higher incidence of carpal tunnel syndrome (54.6 person/ year vs 25.4 person/year, $p<0.047$) and carpal tunnel syndrome complex (74.0 person/ year vs 28.0 person/year, $p=0.006$). The comparison of other syndrome categories failed to reach a statistical significance (Table 2).

As displayed in Table 2, the univariate analysis of risk factors for newly diagnosed carpal tunnel syndrome were diabetes (relative risk 3.2, 95% CI 1.5-7.0, $p<0.01$) and heavier BMI (relative risk 2.5 for 23.5-25.6 Kg/m^2 group, CI 1.0-6.0, $p<0.05$). Those with a higher body height had a protective effect (relative risk 0.3 for >163.5 cm group, CI 0.1-0.8, $p<0.05$).

The risk factor for newly diagnosed carpal tunnel syndrome complex was diabetes mellitus (relative risk 3.9, CI1.9-7.9, $p<0.01$) and the protective factor was a higher body height (relative risk 0.4 for >163.5cm group, CI 0.2-1.0, $p<0.05$) as clearly shown in Table 4.

Similar to univariate analyses of Tables 3 and 4, model 1V of multivariate

analyses in both Tables 5 and 6 showed that after adjustment of gender, age and weight, diabetes mellitus remained as a risk factor for carpal tunnel syndrome (relative risk 2.9, CI 1.3-6.5, $p<0.05$ in Table 5) and carpal tunnel syndrome complex (relative risk 3.3, CI 1.6-7.0, $p<0.01$ in Table 6); and body height as a protective factor for carpal tunnel syndrome (relative risk 0.1, CI 0.1-0.8, $p<0.05$ in Table 5 and relative risk 0.2, CI 0.1-0.8, $p<0.01$ in Table 6). There were trends that those with female gender, older age and heavier body weight seemed more susceptible to both carpal tunnel syndrome and carpal tunnel syndrome complex.

DISCUSSION

Despite numerous cross-sectional studies of carpal tunnel syndrome, there were very few studies focused on the incidence of this condition (24,25). Furthermore, none of study was ever performed to observe the incidence of carpal tunnel syndrome among diabetic subjects,. The incidence of symptomatic carpal tunnel syndrome (carpal tunnel syndrome plus carpal tunnel syndrome complex) in our normal controls was 10.3 person/year (Table 2), which was approximately 1.5 times of the incidence of the similar age group reported by Nordstorm (25). Our study confirmed that diabetes mellitus was definitely a risk factor leading to carpal tunnel syndrome.

In accord with the result of a cross-sectional study, those with a taller body height had a lower incidence of carpal tunnel syndrome .(26)

Diabetes of long duration is associated with advanced glycosylation end products by nonenzymatic reaction of glucose and proteins. The process results in the alterations of extracellular matrix in the nerve sheaths and in the interestitial tissues of the bones and joints. This aggravates the stiffening of connective tissues, and therefore the reduction in the carpal tunnel space. They all contribute to the

increased frequency of carpal tunnel syndrome in diabetes. (27)

Another possibility is that diabetic subjects have an increased susceptibility to focal trauma of diseased nerves, and some have suggested that focal entrapment may be the first manifeastation of diabetic neuropathy (28).

Several investigators found that patients with carpal tunnel syndrome are heavier and shorter than the general population (29-33). Others have identified body mass index as an important cofactor, with obese patients (BMI > 29 kg/m^2) 2.5 times more likely than slender patients (BMI < 20 kg/m^2) to have electrodiagnostic evidence of median nerve neuropathy, although the basis of the association is not understood (34). Our study also showed the similar trends.

CONCLUSIONS

Two-year follow up study showed that type 2 diabetic subjects were more susceptible to carpal tunnel syndrome than normal subjects. More detailed observation will be conducted by putting occupational history, recreational activity and degree of glycemic control into the multivariate analysis.

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Table 1. Gender, age, body height, body weight and body mass index distribution of DM patients and control subjects

Variables		Controls	DM patients	p
Gender				
	Female	255 (58.0)	91 (38.4)	<0.001
	Male	185 (42.1)	146 (61.6)	
Age (year)				
	<=55	205 (46.6)	79 (33.3)	0.002
	55-65	112 (25.5)	85 (35.9)	
	>65	123 (28.0)	73 (30.8)	
	mean±SD	58.4±13.4	60.6±13.0	
Height (cm)				
	<=155	102 (24.8)	59 (25.0)	<0.001
	155-163.5	172 (41.9)	63 (26.7)	
	>163.5	137 (33.3)	114 (48.3)	
Weight (Kg)				
	<=58	186 (47.8)	72 (30.5)	<0.001
	58-67	110 (28.3)	79 (33.5)	
	>67	93 (23.9)	85 (36.0)	
BMI (Kg/m^2)				
	<=23.2	201 (51.9)	86 (36.4)	<0.001
	23.2-25.6	108 (27.9)	80 (33.9)	
	>25.6	78 (20.2)	70 (29.7)	

Table 2. Incidence rate of CTS, CTS complex, symptomatic CTS, asymptomatic CTS, symptomatic CTS complex and asymptomatic CTS complex among DM patients and control subjects.

Events under observation	DM patients			Controls			P value
	Person-years of follow-up	No. of incident cases	Incidence rate (per 1,000)	Person-years of follow-up	No. of incident cases	Incidence rate (per 1,000)	
CTS	329.5	18	54.6	393.0	10	25.4	0.047
CTS complex	324.5	24	74.0	392.5	11	28.0	0.006
Symptomatic CTS	321.5	2	6.2	389.0	2	5.1	0.849
Asymptomatic CTS	325.5	10	30.7	390.5	5	12.8	0.099
Symptomatic CTS complex	314.0	3	9.6	388.0	2	5.2	0.492
Asymptomatic CTS complex	318.0	11	34.6	390.0	6	15.4	0.101

CTS: Carpal tunnel syndrome

CTS complex: Carpal tunnel syndrome complex. Combined either one or both of ulnar nerve entrapment and polyneuropathy.

Asymptomatic: less than one symptom mentioned as items 4, 6, 7, 8, 9 in 1V of the questionnaire.

Symptomatic: having at least 2 of above mentioned symptoms.

Table 3. Univariate analysis of risk factors for newly diagnosed carpal tunnel syndrome of the study subjects

Variables		No. of subjects	No. of incident CTS cases	Relative risk (95% CI)
Diabetic status				
	Controls	440	10	1.0 (Referent)
	DM patients	237	18	3.2‡(1.5-7.0)
Gender				
	Female	346	17	1.0 (Referent)
	Male	331	11	0.7 (0.3-1.4)
Age (year)				
	<=55	284	7	1.0 (Referent)
	55-65	197	9	1.8 (0.7-4.7)
	>65	196	12	2.4 (1.0-6.2)
Height (cm)				
	<=155	161	11	1.0 (Referent)
	155-163.5	235	12	0.7 (0.3-1.7)
	>163.5	251	5	0.3†(0.1-0.8)
Weight (Kg)				
	<=58	258	12	1.0 (Referent)
	58-67	189	7	0.8 (0.3-2.0)
	>67	178	9	1.1 (0.5-2.6)
BMI (Kg/m^2)				
	<=23.2	287	8	1.0 (Referent)
	23.2-25.6	188	13	2.5†(1.0-6.0)
	>25.6	148	7	1.7 (0.6-4.7)

‡ $p<0.01$, † $p<0.05$.

Table 4. Univariate analysis of risk factors for newly diagnosed carpal tunnel syndrome complex of the study subjects

Variables		No. of subjects	No. of incident CTS complex cases	Relative risk (95% CI)
Diabetic status				
	Controls	440	11	1.0 (Referent)
	DM patients	237	24	3.9‡(1.9-7.9)
Gender				
	Female	346	19	1.0 (Referent)
	Male	331	16	0.9 (0.5-1.7)
Age (year)				
	<=55	284	9	1.0 (Referent)
	55-65	197	12	1.8 (0.8-4.3)
	>65	196	14	2.2 (0.9-5.1)
Height (cm)				
	<=155	161	13	1.0 (Referent)
	155-163.5	235	14	0.7 (0.3-1.5)
	>163.5	251	8	0.4†(0.2-1.0)
Weight (Kg)				
	<=58	258	14	1.0 (Referent)
	58-67	189	10	1.0 (0.4-2.1)
	>67	178	11	1.1 (0.5-2.5)
BMI (Kg/m^2)				
	<=23.2	287	12	1.0 (Referent)
	23.2-25.6	188	15	1.9 (0.9-4.1)
	>25.6	148	8	1.3 (0.5-3.2)

‡ $p<0.01$, † $p<0.05$.

Table 5. Multivariate analysis of risk factors for newly diagnosed carpal tunnel syndrome of the study subjects

Variables	Model I RR (95% CI)	Model II RR (95% CI)	Model III RR (95% CI)	Model IV RR (95% CI)
Diabetic status				
Controls	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
DM patients	2.7†(1.2-6.1)	3.2‡(1.4-7.2)	2.9‡(1.3-6.5)	2.9†(1.3-6.5)
Gender				
Female	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Male	0.5 (0.2-1.1)	1.0 (0.4-3.0)	0.4 (0.2-1.1)	1.0 (0.3-3.1)
Age (year)				
<=55	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
55-65	1.4 (0.5-3.8)	1.3 (0.5-3.6)	1.5 (0.5-4.1)	1.2 (0.4-3.4)
>65	2.4 (0.9-6.2)	1.9 (0.7-5.2)	2.5 (1.0-6.5)	1.9 (0.7-5.1)
Height (cm)				
<=155		1.0 (Referent)		1.0 (Referent)
155-163.5		0.9 (0.3-2.4)		0.7 (0.3-2.1)
>163.5		0.3 (0.1-1.2)		0.1†(0.1-0.8)
Weight (Kg)				
<=58			1.0 (Referent)	1.0 (Referent)
58-67			0.9 (0.4-2.5)	1.0 (0.4-2.8)
>67			1.6 (0.6-4.6)	2.8 (0.9-8.1)
BMI (Kg/m^2)				
<=23.2	1.0 (Referent)			
23.2-25.6	2.3 (1.0-5.7)			
>25.6	1.6 (0.6-4.5)			

‡ $p<0.01$, † $p<0.05$.

Table 6. Multivariate analysis of risk factors for newly diagnosed carpal tunnel syndrome complex of the study subjects

Variables	Model I RR (95% CI)	Model II RR (95% CI)	Model III RR (95% CI)	Model IV RR (95% CI)
Diabetic status				
Controls	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
DM patients	3.3‡(1.6-6.9)	3.7‡(1.8-7.7)	3.4‡(1.6-7.1)	3.3‡(1.6-7.0)
Gender				
Female	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Male	0.6 (0.3-1.3)	1.4 (0.5-3.7)	0.6 (0.3-1.3)	1.3 (0.5-3.7)
Age (year)				
<=55	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
55-65	1.4 (0.6-3.5)	1.3 (0.5-3.2)	1.5 (0.6-3.6)	1.3 (0.5-3.1)
>65	2.1 (0.9-4.9)	1.7 (0.7-4.0)	2.2 (0.9-5.1)	1.7 (0.7-4.0)
Height (cm)				
<=155		1.0 (Referent)		1.0 (Referent)
155-163.5		0.7 (0.3-1.9)		0.7 (0.2-1.7)
>163.5		0.3 (0.1-1.0)		0.2‡(0.1-0.8)
Weight (Kg)				
<=58			1.0 (Referent)	1.0 (Referent)
58-67			1.0 (0.4-2.4)	1.1 (0.5-2.7)
>67			1.3 (0.5-3.4)	2.2 (0.8-6.0)
BMI (Kg/m^2)				
<=23.2	1.0 (Referent)			
23.2-25.6	1.7 (0.8-3.7)			
>25.6	1.2 (0.5-2.9)			

‡ $p<0.01$, † $p<0.05$.