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ORIGINAL REPORT

ASSOCIATION OF C-REACTIVE PROTEIN AND INSULIN RESISTANCE IN PATIENTS WITH CHRONIC SPINAL CORD INJURY

Chun-Chiang Huang, MD[1], Chin-Wei Liu, MD[2], Ming-Cheng Weng, MD[1], Tien-Wen Chen, MD[1] and Mao-Hsiung Huang, MD, PhD[2,3]

From the [1]Department of Physical Medicine and Rehabilitation, Kaohsiung Municipal Hsiao-Kang Hospital, [2]Department of Physical Medicine and Rehabilitation, Kaohsiung Medical University Hospital and [3]School of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

Objective: **To study the association between C-reactive protein levels and insulin resistance in patients with spinal cord injury.**
Design: **Cross-sectional study.**
Subjects: **Forty-two subjects who had sustained spinal cord injuries at least 6 months before enrolment.**
Methods: **Circulating glucose, insulin and C-reactive protein levels were measured after 12 hours' fasting. The homeostasis model insulin resistance index was used to evaluate insulin resistance. Insulin resistance and C-reactive protein levels were compared between complete/incomplete patients and between paraplegic/tetraplegic patients. The subjects were then divided into 3 groups (C-reactive protein levels <1, 1–3, >3 mg/l) to compare insulin resistance.**
Results: **Eighteen (43%) subjects had C-reactive protein levels > 3 mg/l. The C-reactive protein levels and insulin resistance did not significantly differ between complete/incomplete or between paraplegic/tetraplegic subjects. However, insulin resistance in the high C-reactive protein group (>3 mg/l) differed significantly from that of the other 2 groups, and there was a significant correlation between C-reactive protein and insulin resistance, with $r = 0.7745$.**
Conclusion: **Most young and middle-aged patients with chronic spinal cord injury with high C-reactive protein levels also have high insulin resistance, and their C-reactive protein levels have well correlated with insulin resistance.**

Key words: spinal cord injury, C-reactive protein, insulin resistance, cardiovascular disease.

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Correspondence address: Mao-Hsiung Huang, Department of Physical Medicine and Rehabilitation, Kaohsiung Medical University Hospital, NO.100 Tzyou 1st Road, Kaohsiung 807, Taiwan. E-mail: maohuang@ms24.hinet.net

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INTRODUCTION

As advances in medical management and rehabilitation technology increase the life-span of patients with spinal cord injury (SCI), the incidence of chronic disease in this population has also increased (1). The prevalence of metabolic syndrome, non-insulin-dependent diabetes mellitus (NIDDM) (2, 3) and coronary heart disease (CHD) (4) are reportedly higher in patients with SCI. As traumatic SCI usually occurs in young adults (16–30 years old), CHD and NIDDM occur at younger ages in patients with SCI than in the ambulatory population (5). Insulin resistance is known to be a major cause of metabolic syndrome and NIDDM. Patients with carbohydrate metabolism disorders are predisposed to macrovascular system diseases, which are associated with mortality and further disability in chronic SCI (6).

The aetiology of insulin resistance in SCI is unclear. The resistance may be related to increased adipose tissue (7) and lack of physical activity (8). Obesity is known to be more prevalent in patients with SCI than in the general population (9). Recent, laboratory and experimental evidence indicates that subclinical inflammation plays a central role in cardiovascular complications linked to obesity and insulin resistance (10–12). The inflammation marker C-reactive protein (CRP) is now known to be strongly associated with and independently predictive of CHD and NIDDM (13, 14). Testing for CRP is inexpensive and simple and has been endorsed by the Centers for Disease Control and Prevention (CDC) in the USA as well as the American Heart Association (AHA) (15). However, it is usually considered that CRP data should be used in conjunction with other well-known risk factors, such as cholesterol levels.

Respiratory and renal conditions are the most prevalent comorbidities in the SCI population, and they remain important causes of mortality. However, recent studies suggest that cardiovascular disease (CVD) is now the leading cause of mortality in chronic SCI (16). Therefore, a reliable and accurate tool for identifying the risk of NIDDM, metabolic syndrome and CHD in patients with chronic SCI is vitally needed. However, it remains unclear whether CRP is useful for identifying the risk of developing insulin resistance, NIDDM or cardiovascular disease in patients with SCI. Therefore, the aims of this study are to assess insulin resistance and CRP in different levels and completeness of injury, to clarify the relationship between insulin resistance and CRP as well as the distribution of CRP levels in young and middle-aged SCI populations.

METHODS

Subjects

Participants with SCI of more than 6 months duration caused by trauma episodes were recruited between April 2006 and September 2007 at our rehabilitation departments. Informed consent was obtained from

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all subjects. All subjects were assessed during their annual medical follow-up. Data for medications and medical history were gathered by questionnaires and from medical records. Exclusion criteria were: any symptomatic infection within the 4 weeks before enrolment, presence of NIDDM or cardiovascular disease, current use of anti-hyperlipidaemic, anti-inflammatory or glucose-regulating drugs.

Measurement of CRP levels

Blood samples were taken after participants had fasted for 12 h. Lipid profile, CRP, plasma glucose and insulin values were also recorded. Plasma concentrations of glucose were determined by the glucose oxidase method. The CRP concentrations were measured by Behring nephelometry using an N Latex CRP mono reagent (Behring Diagnostics, Marburg, Germany). CRP measurements were obtained only if the CRP level was < 10 mg/l, as values > 10 mg/l indicate an acute infection (17).

Assessment of insulin resistance

Plasma insulin concentrations were measured by immunoradiometric assay (insulin-RIA bead II, Abbott, Japan). Insulin resistance was evaluated by the homeostasis model assessment insulin resistance index (HOMA-IR) calculated as fasting plasma insulin (μU/ml) × fasting plasma glucose (mmol/l)/22.5 (18).

CRP risk categories

In accordance with Centers for Disease Control (CDC) and the American Heart Association (AHA) recommendations (15), the subjects were categorized into the following 3 groups for comparison of HOMA-IR: group I (low risk) with CRP level < 1 mg/l, group II (medium risk) with CRP 1–3 mg/l and group III (high risk) with CRP > 3 mg/l.

Neurological examination

Examination of the completeness and level of injury were performed by physiatrists at the beginning of the rehabilitation period. Patients were classified according to the American Spinal Injury Association (ASIA) impairment scale (19).

Statistical analysis

The statistical results were presented as number, percentage, mean and standard deviation (SD). SPSS Version 12.0 (SPSS Inc, Chicago, IL, USA) software was used for statistical analysis. Student's *t*-test was used for group comparisons. Linear regression analysis was performed to determine the relationship between CRP and HOMA-IR. Multiple group comparisons were performed using analysis of variance (ANOVA) with *post-hoc* analysis. A p-value of < 0.05 was considered statistically significant.

RESULTS

A total of 42 subjects (age range 23–50 years) with traumatic SCI were analysed. Table I shows the demographic characteristics of the study population. Two subjects had indwelling urinary catheters for neurogenic bladder dysfunction and 28 had intermittent urinary catheters. Twenty-seven subjects had a history of smoking and 3 were current smokers.

Table I. *Demographic characteristics of study patients.*

Characteristics	
Number	42
Age, years, mean (SD)	38.10 (8.57)
Male/female, *n*	38/4
Duration of injury, months, mean (SD)	44.12 (30.44)
Completeness (ASIA), *n* (%)	
A	22 (52.4)
B	3 (7.1)
C	11 (26.2)
D	6 (14.3)
Level, *n* (%)	
Paraplegia	22 (52.4)
Tetraplegia	20 (47.6)
Current smoker, *n*	3
CRP, mg/l, mean (SD)	2.65 (1.63)
HOMA-IR, mean (SD)	1.34 (1.09)
LDL, mg/dl, mean (SD)	131.4 (32.03)
HDL, mg/dl, mean (SD)	33.42 (5.90)
Chol/HDL, mean (SD)	5.68 (1.35)

ASIA: American Spinal Injury Association classification; CRP: C-reactive protein; HOMA-IR: Homeostasis model assessment insulin resistance; LDL: low denisty lipids; HDL: high density lipids; ChoL: cholesterol; SD: standard deviation.

The subjects were classified by ASIA impairment scale and injury level as complete/incomplete and paraplegic/tetraplegic SCI patient groups. The CRP and HOMA-IR did not significantly differ between complete/incomplete or between paraplegic/tetraplegic SCI patients (Table II).

As Fig. 1 shows, CRP correlated positively with insulin resistance (HOMA-IR) in the study population ($r = 0.7745$; $p < 0.0001$). There was a progressive increase in HOMA-IR medium values with higher CRP levels in the overall population and the largest increase in the subgroup with CRP levels > 3 mg/l, as shown in Fig. 2.

Classification according to CDC/AHA-recommended CRP cut-off points revealed 8 (19%) subjects in group I, 16 (38%) in group II, and 18 (43%) in group III, as shown in Table III. The HOMA-IR in group III was significantly ($p < 0.0001$) higher than that of groups I and II (Table III).

Table II. *C-reactive protein (CRP) and homeostasis model assessment insulin resistance (HOMA-IR) in complete/incomplete and paraplegic/tetraplegic patients with spinal cord injury. Classification according to American Spinal Injury Association (ASIA) criteria.*

	Completeness		Level	
	Complete	Incomplete	Paraplegic	Tetraplegic
Number	22	20	22	20
Age, years, mean (SD)	37.4 (8.12)	38.8 (7.34)	37.8 (5.21)	38.3 (4.30)
Duration, months, mean (SD)	44.0 (35.44)	44.2 (30.77)	48.5 (31.11)	39.2 (34.17)
CRP, mg/l, mean (SD)	2.71 (1.82)	2.59 (1.46)	2.52 (1.35)	2.79 (1.90)
HOMA-IR, mean (SD)	1.70 (1.06)	1.41 (0.96)	1.51 (0.86)	1.62 (1.17)

All p-values were > 0.005.
SD: standard deviation; CRP: C-reactive protein; HOMA-IR: Homeostasis model assessment insulin resistance.

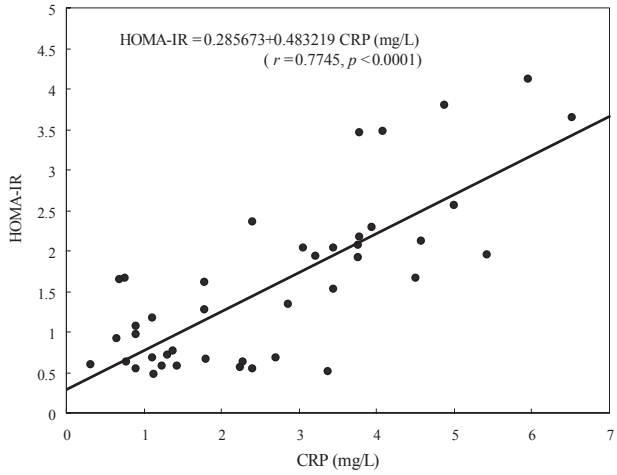

Fig.1. Relationship between C-reactive protein (CRP) and homeostasis model assessment insulin resistance index (HOMA-IR) in the study population.

DISCUSSION

Few studies have examined the relationship between CRP values and insulin resistance in a chronic SCI population. Lee et al. (20) demonstrated elevated CRP levels in individuals with SCI (mean age 50.2 years; SD 13) who are insulin resistant and/or display components of metabolic syndrome, which suggests a clinically significant association with cardiovascular risk in this population. Moreover, some subjects in that study had taken cholesterol-lowering, anti-inflammatory or glucose-regulating drugs. To control for possible confounding factors, the present study analysed only patients with traumatic SCI and excluded subjects who had taken drugs that might have affected CRP levels (17), as well as those with history of cardiovascular disease and diabetes. Furthermore, as traumatic SCI occurs primarily in young adults, and diagnoses of CHD and diabetes occur in SCI populations at younger ages than in the general population, this study analysed a population younger than that of other studies in order to evaluate the value of early screening.

The analytical results revealed a positive correlation between CRP and insulin resistance. Inflammation may be associated

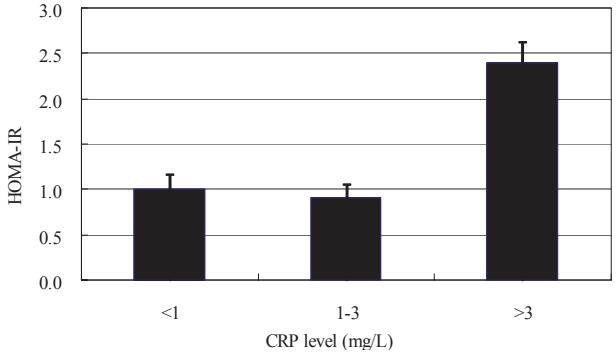

Fig. 2. Homeostasis model assessment insulin resistance index (HOMA-IR) values in spinal cord injury patient subgroups defined by C-reactive protein (CRP) risk category.

Table III. *Comparison of homeostasis model assessment insulin resistance index (HOMA-IR) in various C-reactive protein (CRP) risk categories*

CRP level	*n* (%)	HOMA-IR mean (SD)	*p*-value*
I	8 (19)	1.00 (0.44)	<0.0001
II	16 (38)	0.91 (0.51)	
III	18 (43)	2.40 (0.93)	
Total	42 (100)		

**p*-value: Group III in comparison with groups I and II.
SD: standard deviation.

with development of insulin resistance in patients with chronic SCI. Obesity is more prevalent in SCI patients than in able-bodied subjects, and even non-obese SCI subjects have a higher than average fat content (9, 21). Adipose tissue is now known to participate actively in regulating physiological and pathological processes, such as the secretion of adipokine, including cytokines (such as interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α) and leptin), and is involved in the inflammation process (10). The CRP is an acute phase protein synthesized in the liver by hepatocytes. Production of CRP is stimulated by pro-inflammatory cytokines, particularly IL-6 and TNF-α (22). The release of adipokines by either adipocytes or adipose tissue-infiltrated macrophages causes chronic inflammation, which may play a central role in cardiovascular complications linked to obesity and insulin resistance, which are risk factor for diabetes and CHD (11). In addition, recent data indicating that CRP within atheromatous plaque (23) is a correlate of endothelial dysfunction (24) and has a direct role in cell adhesion molecular expression (25) suggest that CRP may play a direct role in the atherosclerosis process. Therefore, persistently elevated CRP may increase the risk of NIDDM or CHD in patients with chronic SCI.

The CRP levels in almost half (43%) of the subjects exceeded 3 mg/l, and these subjects were significantly more resistant to insulin than those with CRP levels lower than 3 mg/l. Bo et al. (26) documented significantly higher median insulin and HOMA-IR values in healthy subjects (aged 45–64 years) with CRP levels >3 mg/l. Ridker et al. (27), in a cohort study of 22,000 middle-aged ambulatory males, demonstrated that those with baseline CRP levels in the highest quartile had a 2-fold and 3-fold increased risk of stroke and myocardial infarction, respectively. These effects were independent of all other lipid and non-lipid risk factors and were noted in both smokers and non-smokers. Therefore, patients with SCI with CRP levels above 3 mg/l have a higher risk for cardiovascular disease than those with lower CRP levels and should be carefully monitored. Additionally, most of the patients with chronic SCI in the examined population (mean age 38.1 years, SD 8.57) had high CRP. Therefore, early screening and management of these modifiable risk factors are recommended to reduce cardiovascular disease in this population.

Groah et al. (28) have shown that risk of cardiovascular disease increases with rostral level of SCI and severity of SCI. Neither SCI level nor SCI severity were associated with CRP or insulin resistance in our population. Rebhun

et al. (29) reported that CRP became elevated but below the levels normally manifested in acute and chronic SCI, which may be related to some underlying disease state rather than to a urinary tract infection or the injury itself. In our study, CRP was found to be positively correlated with insulin resistance. However, this cross-sectional study did not determine whether the correlation between CRP and insulin resistance is temporal. Therefore, further studies of a larger population and with longer follow-up are needed in order to evaluate CRP as an indicator for indentifying patients with chronic SCI who are at risk of insulin resistance syndrome, diabetes and even cardiovascular disease.

In conclusion, most young and middle-aged patients with chronic SCI also have high CRP levels and high insulin resistance, and their CRP levels have well correlated with insulin resistance.

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