ORIGINAL ARTICLE

Serum leptin, abdominal obesity and the metabolic syndrome in individuals with chronic spinal cord injury

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Study Design: Cross-sectional comparison.

Objective: The mortality rate is higher in individuals with spinal cord injury (SCI), and one major cause is cardiovascular disease (CVD). In the general population, the metabolic syndrome (MetS) is associated with an increased risk of CVD, and abdominal obesity is a major feature. Adipokines, secreted by adipose tissue, contribute to obesity-linked metabolic diseases. The aim of this study is to evaluate the prevalence of MetS, the components of this syndrome, especially body composition, and the relations between adipokines and body composition, in SCI individuals.

Setting: Kanagawa Rehabilitation Hospital, Kanagawa, Japan.

Methods: Forty-four male SCI individuals (57 ± 13 years and 28 paraplegia) and age-matched able-bodied controls were studied. Body composition was assessed by dual-energy X-ray absorptiometry (DXA) and anthropometry (waist circumference). The visceral fat area (VFA) was measured by computed tomography (CT). Plasma adipokine levels, including that of leptin, adiponectin and plasminogen activator inhibitor-1 (PAI-1), were measured.

Results: Overall, 43% of SCI individuals met the criteria for MetS. Total and regional fat mass (FM), as well as VFA, were higher, whereas total and regional lean mass, except for arm, were lower than able-bodied controls. In the SCI, leptin and PAI-1 levels were positively associated and adiponectin levels were negatively associated with waist circumference, VFA and trunk FM. In multiple regression models, only leptin level was independently associated with waist circumference, VFA and trunk FM.

Conclusion: SCI individuals were predisposed to excessive abdominal obesity, and higher leptin levels were strongly associated with higher prevalence of abdominal obesity in this population.

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Keywords: abdominal obesity; adipokine; body composition; leptin; metabolic syndrome; spinal cord injury

Introduction

The longevity of individuals with spinal cord injury (SCI) has improved, but the mortality rate is still higher than that of the general population.[1] The most common underlying and contributing cause of death is cardiovascular disease (CVD),[1] and the SCI population has a higher incidence of ischemic heart disease than able-bodied population.[2] Recently, the presence of metabolic syndrome (MetS) has been used to identify individuals at high risk for CVD in the general population.[3] MetS is characterized by low levels of high-density lipoprotein cholesterol (HDL-C), elevated fasting glucose and triglyceride (TG), abdominal obesity and high blood pressure (BP).[4]

Abdominal obesity is a major characteristic of MetS; it is defined as an excess accumulation of body fat. Since measurement of body fat accurately is not conventional in a clinical setting, body mass index (BMI) has been used as a surrogate marker. Increased BMI is associated with an increased risk of chronic heart disease in the general population.[5] However, BMI measurements of the SCI individuals may not be sensitive indicators, since individuals with chronic SCI have a greater fat mass (FM) and a lower fat-free mass per unit BMI than able-bodied controls.[6]

Fat mass, measured by magnetic resonance imaging (MRI), computed tomography (CT) or dual-energy X-ray absorptiometry (DXA), is more accurate compared with measurement of BMI. Furthermore, simple anthropometric measurements,

such as waist circumference, can also be used. On the basis of these specific markers, several studies have shown that SCI individuals have a lower total body and regional lean mass (LM), especially in lower limb, and a higher FM than controls.[7–9]

Adipose tissue is an important secretory organ that produces various bioactive substances known as adipokines, which include leptin, tumor necrosis factor-α, adiponectin and plasminogen activator inhibitor-1 (PAI-1); they contribute to obesity-linked metabolic and vascular diseases, as well as MetS.[10] In the SCI population, correlation between adipokine levels and body composition is assumed to be different from that in general population because of differences in location of adipose tissue. Additionally, it is still unknown as to which types of the adipokine levels can reflect abdominal obesity in this population.

The primary aims of this study were to evaluate the prevalence of MetS, the components of this syndrome, especially body composition, and the relations between adipokine levels and body composition, in SCI individuals. We hypothesized that the prevalence of MetS, especially abdominal obesity, is high, and the strong relationship between adipokine levels and the markers of abdominal obesity in this population.

Materials and methods

Patients
Forty-four male SCI individuals (an average age of 57 ± 13 years; range, 26–82 years) were studied at the Kanagawa Rehabilitation Hospital (Kanagawa, Japan). The SCI group consisted of 16 tetraplegics and 28 paraplegics with 64% complete and 36% incomplete injury, respectively. SCI was due to traumatic injury in 34 individuals (77%), vascular disease in 3 (7%), infection in 2 (5%), disc disease in 1 (2%), tumor in 1 (2%) and other causes in 3 individuals (7%). Duration of injury was 26 ± 15 years (range, 0.5–57 years). Thirteen (30%) and eight (18%) individuals were on antihypertensive medication and on medication for hypertriglyceridemia, respectively. None of the individuals had signs of acute infection and none were treated with insulin. Two different control groups were enrolled: group A ($n = 125$) served as controls primarily for BP and laboratory data, and group B ($n = 50$) served as controls primarily for body composition. We extracted the data of control individuals from two different health examination databases. The Ethics Committee of Kanagawa Rehabilitation Hospital approved the study protocol, and written informed consent was obtained from all SCI individuals.

Body composition measurements
In the SCI group, body weight, height and waist circumference at the umbilical level were measured in the supine position. For individuals who could not extend all joints fully, the distance from the top of head to the bottom of the heel was measured. In contrast, in the control group, these parameters were measured in the standing position. BMI was defined as the body weight in kilograms divided by the square of the height in meters. Total and regional body composition, including LM and body FM, were evaluated by DXA (DPX-IQ; Lunar Corp., Madison, WI, USA) using Lunar software version 4.6b. Visceral fat area (VFA) was measured by CT at the umbilical level, using a software program (FatScan; N2system, Osaka, Japan). Waist circumference, VFA and trunk FM were used as markers of abdominal obesity.

Blood sampling and laboratory analysis
Blood samples were drawn after an overnight fast. The whole blood samples were centrifuged at $3000\,g$ for 10 min. Levels of TG, HDL-C and fasting plasma glucose (FPG) were measured by an automatic analyzer in a clinical laboratory. Serum insulin was measured using an immunoradiometric assay (SRL Inc., Tokyo, Japan). An estimate of insulin resistance was calculated on the basis of the homeostasis model assessment of insulin resistance using the following formula: FPG (mg dl^{-1}) × fasting serum insulin (μU ml^{-1})/ 405.[11] Plasma leptin levels were measured using a radioimmunoassay kit (Linco Research Inc., St Charles, MO, USA), plasma adiponectin levels were measured using an enzyme-linked immunosorbent assay kit (Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan) and plasma PAI-1 levels were measured using an enzyme-linked immunosorbent assay kit (Sysmex International Reagents Co. Ltd., Hyogo, Japan).

Definition of the MetS
Definition of the MetS was based on the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III),[4] and we modified the definition of visceral fat obesity. The Japanese Society for the Study of Obesity defined visceral fat obesity in Japanese as a VFA $>100\,cm^2$, which corresponds to a waist circumference $>85\,cm$ for men and $>90\,cm$ for women.[12] In this study, MetS was defined as the presence of at least three of the following criteria: VFA $>100\,cm^2$, TG $\geqslant 150\,mg\,dl^{-1}$ or on medication for hypertriglyceridemia; HDL-C $<40\,mg\,dl^{-1}$ in men and 50 mg dl^{-1} in women; BP $\geqslant 130/85\,mm\,Hg$ or on antihypertensive medication and FPG $\geqslant 110\,mg\,dl^{-1}$ or on medication for diabetes. BP was measured in the sitting position.

Statistical analysis
Data are presented as mean ± s.d. or median and range as appropriate. A P-value of less than 0.05 was considered statistically significant. For continuous variables, the distribution was tested by the Shapiro–Wilk W-test. Then, Student's t-test was used for normally distributed variables, and the Wilcoxon's rank-sum test was used for skewed variables. The Spearman correlation coefficient (ρ) was used to determine the relationships between clinical parameters. Nominal variables were tested using the χ^2-test or Fisher's exact test when appropriate. Multiple regression models, including age, TG, plasma leptin, plasma adiponectin and plasma PAI-1 level, were used to identify the independent predictors of the body composition markers. Statistical analyses were performed using JMP, version 5.1.1 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

The clinical characteristics of the male SCI individuals are shown in Table 1; 43% of SCI individuals met the criteria for MetS. Mean waist circumference, VFA and trunk FM were 88.1 ± 12.1 cm, 191 ± 79 cm^2 and $12\,000 \pm 5200$ g, respectively. Prevalence of MetS, BMI, waist circumference, VFA, total and trunk FM, TG, HDL-C and adipokines level were similar between tetraplegic and paraplegic individuals, whereas tetraplegic individuals had lower systolic BP (107 ± 15 versus 129 ± 16 mm Hg, $P<0.01$) and diastolic BP (67 ± 12 versus 76 ± 9 mm Hg, $P<0.01$) than paraplegic individuals. Furthermore, 12 paraplegics received antihypertensive, whereas only one tetraplegic received antihypertensive.

Table 2 shows comparisons of clinical data between the SCI and able-bodied control individuals. Age was similar between three groups. The SCI individuals had lesser height as compared with individuals in the two different control groups ($P<0.01$). Although body weight tended to be lower and BMI tended to be higher among the SCI, these did not achieve statistical significance ($P=0.06$). The SCI individuals had lower systolic BP ($P=0.02$), diastolic BP ($P<0.01$) and HDL-C ($P<0.01$) as compared with individuals in control group A. TG and FPG were similar between the individuals of the SCI group and control group A. Regarding the other markers of body composition, waist circumference and arm LM were similar between the individuals of the SCI group and control group B. Leg LM ($P<0.01$), trunk LM ($P<0.01$) and total LM ($P<0.01$) were lower, whereas VFA ($P<0.01$), arm FM ($P<0.01$), leg FM ($P<0.01$), trunk FM ($P<0.01$) and total FM ($P<0.01$) were higher in the individuals SCI group than those in control group B.

Table 1 Clinical characteristics of the SCI individuals

Characteristics	Value
n	44
Age (years)	57 ± 13
Duration of SCI (years)	26 (0.5–57)
Tetra/paraplegia	16/28
Complete/incomplete	28/16
Prevalence of MetS	19 (43%)
Systolic BP (mm Hg)	121 ± 18
Diastolic BP (mm Hg)	73 ± 11
Height (cm)	164 ± 11
Body weight (kg)	64.4 ± 13.2
BMI (kg m^{-2})	24.1 ± 4.8
Waist circumference (cm)	88.1 ± 12.1
Visceral fat area (cm^2)	191 ± 79
Trunk FM (g)	$12\,000 \pm 5200$
TG (mg dl^{-1})	124 ± 53
HDL-C (mg dl^{-1})	44 ± 12
FPG (mg dl^{-1})	103 ± 19
Plasma leptin (ng ml^{-1})	5.4 (1.8–16.4)
Plasma adiponectin (µg ml^{-1})	7.24 (2.91–37.2)
Plasma PAI-1 (ng ml^{-1})	20.9 ± 7.4
HOMA-IR	2.49 (0.71–6.71)

Abbreviations: BMI, body mass index; BP, blood pressure; FM, fat mass; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, the homeostasis model assessment of insulin resistance; MetS, metabolic syndrome; PAI-1, plasminogen activator inhibitor-1; SCI, spinal cord injury; TG, triglyceride.
Mean ± s.d. or median (range).

Table 2 Comparisons of clinical data

	SCI	Control A	Control B	P^a
n	44	125	50	
Age (y)	57 ± 13	57 ± 9	57 ± 17	0.99
Height (cm)	164 ± 11	168 ± 6	168 ± 7	<0.01
Body Weight (kg)	64.4 ± 13.2	65.0 ± 9.6	68.9 ± 10.2	0.06
BMI (kg m^{-2})	24.1 ± 4.8	23.1 ± 3.0	24.3 ± 3.2	0.06
Systolic BP (mm Hg)	121 ± 18	127 ± 14	NA	0.02
Diastolic BP (mm Hg)	73 ± 11	78 ± 8	NA	<0.01
TG (mg dl^{-1})	124 ± 53	138 ± 116	NA	0.29
HDL-C (mg dl^{-1})	44 ± 12	59 ± 16	NA	<0.01
FPG (mg dl^{-1})	103 ± 19	102 ± 18	NA	0.81
Waist circumference (cm)	88.1 ± 12.1	NA	85.7 ± 7.8	0.33
VFA (cm^2)	191 ± 79	NA	135 ± 70	<0.01
Arm FM (g)	1940 ± 850	NA	1370 ± 507	<0.01
Arm LM (g)	5030 ± 1450	NA	5420 ± 663	0.11
Leg FM (g)	6350 ± 2600	NA	4650 ± 1810	<0.01
Leg LM (g)	9530 ± 2750	NA	$16\,900 \pm 2870$	<0.01
Trunk FM (g)	$12\,000 \pm 5200$	NA	9120 ± 3960	<0.01
Trunk LM (g)	$20\,700 \pm 3330$	NA	$23\,500 \pm 2580$	<0.01
Total FM (g)	$22\,200 \pm 8890$	NA	$16\,000 \pm 5910$	<0.01
Total LM (g)	$38\,500 \pm 6380$	NA	$49\,600 \pm 5420$	<0.01

Abbreviations: BMI, body mass index; BP, blood pressure; FM, fat mass; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LM, lean mass; NA, not applicable; SCI, spinal cord injury; TG, triglyceride; VFA, visceral fat area.
Mean ± s.d. or median (range).
^{a}Comparison between SCI and control group individuals.

Figure 1 shows comparisons of the markers of abdominal obesity. The individuals with SCI had higher VFA (191 ± 79 versus 135 ± 70 cm^2, $P<0.01$) and higher trunk FM ($12\,000 \pm 5200$ versus 9120 ± 3960 g, $P<0.01$). However, there was no significant difference in waist circumference (88.1 ± 12.1 versus 85.7 ± 7.8 cm, $P=0.33$) between the two groups.

The results of the Spearman correlation tests are summarized in Table 3. All markers of body composition, including BMI, waist circumference, VFA and trunk FM, were closely interrelated ($P<0.01$). Plasma leptin levels, plasma PAI-1 levels and homeostasis model assessment of insulin resistance were positively associated with these parameters of body composition ($P<0.05$). In contrast, plasma adiponectin levels were associated only with VFA ($\rho = -0.38$, $P<0.01$). TG levels were positively associated with all of these markers, except for VFA, whereas HDL-C levels were not associated with any marker.

Table 4 shows the results of the multiple regression models that included age, TG, plasma leptin, plasma adiponectin and plasma PAI-1. Most of these variables showed relationship to the markers of abdominal obesity in univariate analyses. Only plasma leptin levels were independently associated with waist circumference (total adjusted $R^2 = 0.475$, $P<0.01$), VFA (total adjusted $R^2 = 0.379$, $P<0.01$) and trunk FM (total adjusted $R^2 = 0.554$, $P<0.01$).

Discussion

One of the chief purposes of this study is to evaluate the prevalence of MetS and the components of this syndrome,
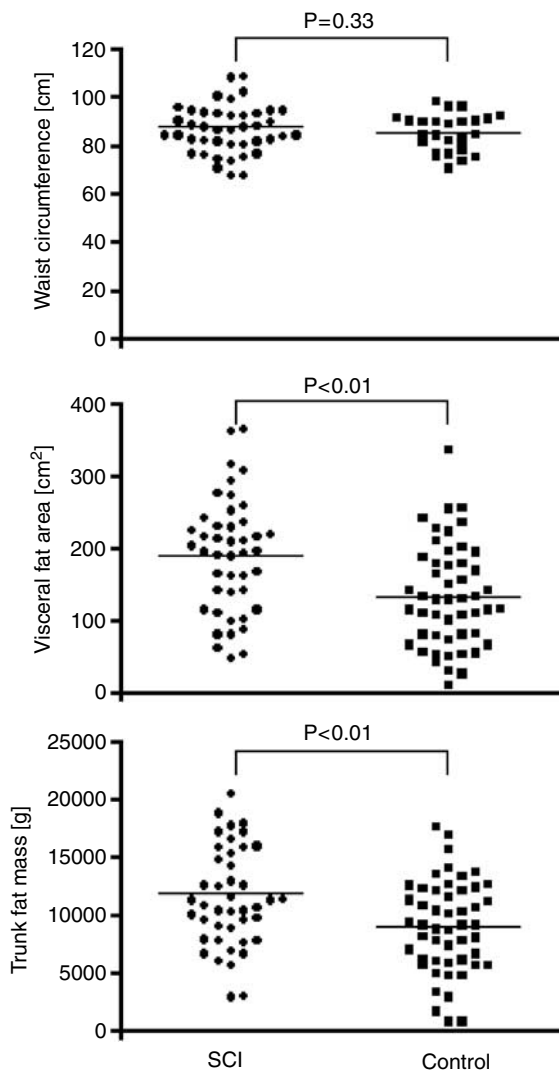
Figure 1 Comparisons of the markers of abdominal obesity, including waist circumference, VFA and higher trunk FM, between the SCI and control groups. FM, fat mass; SCI, spinal cord injury; VFA, visceral fat area.

especially body composition in SCI. In the present study, 43% of male SCI individuals met the criteria for MetS as defined by the modified NCEP definition. The original NCEP ATP III definition includes a cut-off for abdominal obesity (waist circumference, >102 cm for men and >89 cm for women) that has been shown to be inappropriate for Asian populations;[13] therefore, Japanese Society for the Study of Obesity defined the cut-off point of visceral fat obesity in Japanese as a VFA >100 cm^2, which corresponds to a waist circumference >85 cm for men and >90 cm for women.[12] Although we did not have age-matched controls who met the criteria for MetS in the control group, the prevalence of MetS, especially in SCI men, appeared to be higher than that

Table 4 Multiple regression model for each marker of body composition

Independent variable	Regression coefficient	95% confidence interval	P
Dependent variable: waist circumference (total adjusted $R^2 = 0.475$, n = 42, P < 0.01)			
Age	−0.087	−0.321–0.146	0.45
TG	0.013	−0.047–0.074	0.66
Leptin	2.03	1.31–2.75	<0.01
Adiponectin	−0.350	−0.779–0.080	0.11
PAI-1	−0.038	−0.470–0.395	0.86
Dependent variable: visceral fat area (total adjusted $R^2 = 0.379$, n = 43, P < 0.01)			
Age	−0.644	−2.29–1.01	0.43
TG	−0.160	−0.603–0.283	0.47
Leptin	9.01	3.77–14.2	<0.01
Adiponectin	−3.15	−6.29–0.015	0.05
PAI-1	2.86	−0.294–6.02	0.07
Dependent variable: trunk fat mass (total adjusted $R^2 = 0.554$, n = 43, P < 0.01)			
Age	−43.5	−134–47.3	0.33
TG	11.5	−12.9–35.9	0.35
Leptin	885	596–1170	<0.01
Adiponectin	−62.6	−235–110	0.47
PAI-1	45.3	−129–219	0.60

Abbreviations: PAI-1, plasminogen activator inhibitor-1; TG, triglyceride.

Table 3 Spearman correlation coefficient (ρ) between each clinical parameter in SCI individuals

	BMI	Waist	VFA	Trunk FM	TG	HDL-C	Leptin	Adiponectin	PAI-1	HOMA-IR
BMI	1									
Waist	0.71[††]	1								
VFA	0.49[††]	0.64[††]	1							
Trunk FM	0.79[††]	0.90[††]	0.66[††]	1						
TG	0.36[†]	0.38[†]	0.20	0.45[††]	1					
HDL-C	−0.12	−0.23	−0.14	−0.11	−0.27	1				
Leptin	0.62[††]	0.67[††]	0.59[††]	0.80[††]	0.28	−0.08	1			
Adiponectin	−0.19	−0.30	−0.38[†]	−0.27	−0.41[††]	0.35[†]	−0.07	1		
PAI-1	0.32[†]	0.39[†]	0.44[††]	0.50[††]	0.52[††]	−0.16	0.34[†]	−0.48[††]	1	
HOMA-IR	0.41[††]	0.49[††]	0.36[†]	0.57[††]	0.40[†]	−0.31	0.42[††]	−0.40[††]	0.38[†]	1

Abbreviations: BMI, body mass index; FM, fat mass; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, the homeostasis model assessment of insulin resistance; PAI-1, plasminogen activator inhibitor-1; SCI, spinal cord injury; TG, triglyceride; VFA, visceral fat area; waist, waist circumference.
[†]P<0.05.
[††]P<0.01.

reported in general Japanese workers (19.5% in men and 7.9% in women).[14] Further studies with a greater number of individuals are needed to confirm the higher prevalence of MetS in SCI individuals.

Abdominal obesity *per se* is a risk factor for CVD. In the general population, as reflected in the 5881 participants of the Framingham Heart Study, Kenchaiah et al.[5] reported that the risk of heart failure increased by 5% in men and 7% in women for each unit increment in the BMI. Since body weight does not distinguish between FM and fat-free mass, the BMI would appear to be a poor surrogate marker of obesity in SCI individuals. Buchholz et al.[15] found that the $30 \, kg \, m^{-2}$ BMI cut-off level had a 100% specificity and only a 20% sensitivity in distinguishing obese from non-obese individuals with paraplegia. Indeed, in the present study, the BMI was not significantly different between the SCI group and able-bodied controls.

Thus, more accurate ways to measure visceral fat in the SCI population are needed. In this study, waist circumference, VFA determined by CT and trunk FM determined by DXA were used as markers of abdominal obesity. As expected, these three parameters were closely interrelated. Leg LM, trunk LM and total LM were lower, whereas arm FM, leg FM, trunk FM and total FM, as well as VFA and waist circumference, were higher in the SCI group. These results are consistent with previous reports. Spungen et al.[7] reported that total body and regional LM were lower and FM was higher in male SCI individuals using DXA. Modlesky et al.[8] reported that the skeletal muscle mass of the mid-thigh determined by MRI and the fat-free soft tissue mass of the mid-thigh determined by DXA were lower in the male SCI population. However, to the best of our knowledge, this is the first report to demonstrate abdominal obesity in the SCI population based on the VFA on CT.

The other chief finding of the present study was that, on multiple regression analyses, plasma leptin level was an independent determinant of the markers of abdominal obesity, including waist circumference, VFA and trunk FM. A range of soluble products, the so-called adipokines, secreted by adipose tissue, which is a highly active endocrine organ, plays an important role in the creation of abdominal fat. Leptin, the product of the adipose-specific *ob* gene, regulates food intake and energy expenditure. Furthermore, leptin induces high BP and tachycardia via increased adrenergic activity; this suggests that leptin may be an important link between obesity, increased sympathetic activity and hypertension.[16] Among SCI individuals, several univariate analyses have shown that leptin levels are positively associated with BMI and FM.[17] Additionally, Mamoun et al.[17] reported that the leptin levels increased gradually from week 24 after injury. Although in the present study, plasma adiponectin, plasma PAI-1 and homeostasis model assessment of insulin resistance were related to abdominal obesity, only the plasma leptin level was an independent determinant of abdominal obesity in multiple regression models.

There are several limitations of this study. First, the number of the SCI individuals was relatively small. Additionally, we used two separate control groups for different comparisons. We obtained the data of control individuals from two different health examination databases; one was mainly for laboratory data and the other was mainly for body composition, including CT, DXA and anthropometry. Hence, we could not compare all measures against the same control group, and could not assess the prevalence of MetS among able-bodied controls. Second, selection bias was inevitable. All SCI individuals were hospital-based, while most of the laboratory data of the able-bodied controls were obtained during routine physical examination. Third, we did not monitor physical activity, which was reported to attribute an increased FM in the SCI.[18] Fourth, we used the same criteria of MetS as for general population. The criteria of abdominal obesity might be different, because of differences in location of adipose tissue in the SCI.

In conclusion, SCI individuals were predisposed to excessive abdominal obesity represented by waist circumference, VFA and trunk FM. The strong relationship between serum leptin and abdominal obesity suggests that this hormone can be used as a surrogate marker of the MetS in SCI individuals. Since the effects of the MetS on CVD in SCI are still unknown, further studies, particularly longitudinal studies with more individuals, are needed.

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