Research article

C-reactive protein as an available biomarker determining mental component of health-related quality of life among individuals with spinal cord injury

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Objectives: C-reactive protein (CRP) has been shown to correlate with health-related quality of life (HRQL) in some chronic medical conditions. However, these associations have not yet described in spinal cord injury (SCI). In this study, we tried to identify biomarkers associated with HRQL in SCI.
Design: Cross-sectional.
Setting: Tertiary rehabilitation center.
Participants: Referred patients to Brain and Spinal Cord Injury Research Center between November 2010 and April 2013.
Outcome Measure: Blood samples were taken to measure circulatory CRP, leptin, adiponectin, ferritin, parathyroid hormone, calcitonin, thyroid hormones, fasting plasma glucose and lipid profile. All the analyses were performed with adjustment for injury-related confounders (level of injury, injury completeness and time since injury) and demographic characteristics. HRQL was measured with Short Form health survey (SF-36).
Results: The initial inverse association between CRP and total score of SF-36 (P: 0.006, r = −0.28) was lost after adjustment for confounders. However, the negative correlation between CRP and Mental Component Summary (MCS) remained significant (P: 0.0005, r = −0.38). Leptin level was inversely correlated with Physical Component Summary (PCS) (P: 0.02, r = −0.30).
Conclusion: Although CRP and leptin levels were not related with total scores of SF-36 questionnaire, CRP can be more useful in determining mental component of HRQL whereas leptin can be a determinant of physical component. The combined consideration of these two biomarkers may help to predict HRQL in individuals with SCI.

Keywords: Quality of life, Spinal cord injury, Health survey, Leptin, C reactive protein

Introduction

Previous investigations have tried to determine the association between inflammation and health-related quality of life (HRQL).[1,2] Many evidences support the role of inflammation in predicting poorer HRQL especially among patients suffering from chronic medical conditions such as diabetes,[3] obstructive pulmonary diseases[4] and cancer.[5] Previous researches have tried to determine an inflammatory biomarker for HRQL. In this regard, C-reactive protein (CRP) has been shown to be a suitable determinant of inflammation even among patients with no diagnosis[6] and is also useful for capturing chronicity.[1] High levels of CRP can present generalized inflammation whereas persistent elevated levels can indicate progression of inflammation in chronic diseases.[7] The relationship between inflammation and HRQL in spinal cord injury (SCI) has not yet been described. The presence of a chronic

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inflammatory state in SCI have been demonstrated[8,9] which led us to the hypothesis whether inflammatory biomarkers can predict HRQL among this population as well.

HRQL is a multidimensional construct which is influenced by many factors.[10] The concept of HRQL can be defined as the individual's perception of overall well-being including both psychosocial and physical or health-related domains.[11] Among people with SCI, quality of life (QoL) is affected by burden of disease and disability.[12] It has been shown that sociodemographic characteristics, severity of injury and time since injury are factors that may be independently associated with HRQL.[13] Identification of determinants of HRQL in SCI is clinically essential to detect the potentially modifiable factors. Physical limitations, depressive mood and other problems caused by SCI such as bladder and bowel dysfunctions are among the various factors affecting HRQL.[14] Until now, the influence of inflammation on HRQL among people with SCI remains unknown. Conflicting results exist discussing the role of inflammation in predicting HRQL. Farag *et al.*[15] showed that CRP predicts mental components of Short Form health survey (SF-36), a validated tool to measure self-perceived HRQL,[16] in patients with chronic kidney diseases. According to Farag *et al.*,[15] the significant association between CRP and mental component of HRQL and not the physical component of quality of life supports the multifactorial nature of reduced HRQL among affected individuals. The reasons behind the association between inflammation and mental component of HRQL still remain unknown. Since the physical disability of patients with SCI is permanent, it seems that the physical component of HRQL can hardly be improved by treatment of inflammation whereas the mental component of HRQL can be more vulnerable to inflammations. However, Cummings *et al.*[3] demonstrated that the inverse association between CRP and HRQL is lost in multivariate regression analysis when the effects of confounders are also considered. Since the confounders may vary among different medical conditions, the association between inflammation and HRQL should be assessed in each population with adjustment for confounders for that specific disease.

Inflammation may also reveal the existence of active infections especially among people with SCI who are known to be at greater risk for urinary tract[17] and pulmonary infections.[18] Therefore, we hypothesized whether inflammatory biomarkers can predict HRQL in subjects with SCI. Among individuals with SCI, injury-related variables play the most important role in determining quality of life.[19] HRQL is dependent to many factors including marital status,[20] post injury duration[21] and injury level.[22] However, it has been shown that the influence of other demographic characteristics including age[23,24] and sex[20,25] on HRQL is weaker. Altogether, the influence of these variables should be considered while identifying the role of circulatory biomarkers in determining HRQL.

Along with CRP, there are other biomarkers that have been shown to have altered circulatory concentrations after SCI including leptin,[26] adiponectine and thyroid hormones.[27] In this study, the relationships between some biomarkers including CRP, leptin (a hormone made by adipose cells that regulates energy balance by inhibiting hunger), adiponectin (hormones derived from fat tissue), thyroid hormones, serum ferritin (a protein in the body that binds to iron), calcitonin (a 32-amino acid linear polypeptide hormone that is produced in humans primarily by the parafollicular cells) fasting plasma glucose and plasma lipid profile and HRQL have been assessed after adjustment for injury-related variables. To our knowledge, this is the first study trying to identify a determinant biomarker of HRQL among people with SCI.

Methodology

Study design and participants

Referred individuals with SCI to Brain and Spinal Cord Injury Research Center have been invited to participate in this investigation. Exclusion criteria were: pregnancy, lactation, amputation, and non-traumatic SCI etiology, history of diabetes, cancer, endocrinology disease, acute infection, and consumption of special medications such as glucocorticoid, hormones, thyroid hormones, anticonvulsive agents, heparin, aluminum-containing antacids, lithium, omega-3 fatty acids or other nutrients supplements. Those with history of smoking and substance abuse were excluded as well. Data was collected between November 2010 and April 2013. Written consent was obtained from each participant before enrollment. The study was approved by the ethics committee of Tehran University of Medical Sciences.

Clinical measurements

Patients' age, sex and time since injury were asked directly during interviews and were indexed in pre-prepared forms. Completeness of injury was defined as either complete either complete (no preserved sensory or motor function) or incomplete (variable motor function preserved below the neurological level of injury). Level of injury was assessed with clinical examinations and magnetic resonance Images and was confirmed by

a neurologist. Classification of participants according to American Spinal Cord Injury Association (ASIA) Impairment Scale was as follows: ASIA-A indicates complete injury with no preserved motor or sensory function below the neurological level. ASIA-B describes incomplete injury in which only sensory function is preserved below the neurological level. ASIA-C illustrates preserved motor function in which more than half of key muscles below the neurological level have a muscle grade <3. ASIA-D indicates preserved motor function in which at least half of key muscles below the neurological level have a muscle grade of 3 or more. Only ASIA-A represents complete injury.[28,29] Body weight was measured using a digital wheelchair scale, and body height was obtained measuring the supine length. Body mass index (BMI) was calculated as body weight (in kilograms) divided by height (in meters) squared.

Assessment of health-related quality of life (HRQL)

HRQL was assessed using SF-36 questionnaire. This instrument is a standard measurement tool for assessment of quality of life (QoL) and has been used for a long time among people with SCI. The psychometric properties of the Iranian version of SF-36 questionnaire along with its validity and reliability are well documented.16 Iranian version of the SF-36 is the identical version of the SF-36 offered in Farsi. This measurement tool includes 36 items which assess QoL in eight domains: physical functioning (PF), role limitation due to physical problems (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitation due to emotional problems (RE) and mental health (MH). These scales provide two component summary scores: physical component summary (PCS) and mental component summary (MCS). Scores range from 0 to 100 and higher scores are representative of better QoL. PCS includes domains of physical functioning, role limitation due to physical problems, bodily pain and general health. MCS includes domains of vitality, social functioning, role limitation due to emotional problems and mental health.[30]

Laboratory measurements

Blood samples were taken under antiseptic conditions from antecubital vein (a superficial vein of the upper limb). CRP was measured with ELISA kit with detection limit of 47 pg/ml. Enzyme-linked Immunosorbent Assay Kit was used to measure thyroid stimulating hormone (TSH), thyroxine (T4) (the main hormone secreted by thyroid gland which is the inactive form) and triiodothyronine (T3). T3 is a thyroid hormone which is the more metabolically active hormone produced from T4. The levels of leptin, adiponectin were measured as well. Blood samples were collected and centrifuged at 3000 rpm for 10 minutes at 4°C. Samples were sent to the Endocrinology and Metabolism Research Institute laboratory for analysis and were frozen immediately. Parathyroid hormone levels were measured by using radioimmunoassay (Wallac Gamma Counter; Perkin Elmer, Waltham, MA, USA). Normal level of PTH was considered between 10 and 55 pg/mL. Plasma concentrations of total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL-C), high density lipoprotein (HDL-C) and fasting blood glucose (FBG) were measured by enzymatic procedures using Pars Azmon Kits (Tehran, Iran). ELISA kits were also used to measure serum ferritin and calcitonin.

Statistical analysis

Baseline values of categorical variables are presented with percentages and values of continuous variables are presented with mean ± standard deviation. Since elevated levels of CRP have been reported to be associated with older ages,[31] age was considered as a confounder. Partial correlation with adjustment for injury-related confounders (level of injury, completeness, ASIA score, type of plegia, i.e. tetraplegia vs. paraplegia, and time since injury) and demographic confounders (age, sex and BMI) was performed to assess the association between continuous variables including CRP, ferritin, calcitonin, PTH, leptin, adiponectin, FBG, thyroid hormones and lipid profile with scores of SF-36 questionnaire. Moderated Multiple Regression analysis was used to examine whether the effect of sex, plegia type and injury completeness (dichotomous variables) were significant on the association between CRP and leptin, and HRQL. Comparison of means was performed using One-Way Analysis of Variance (ANOVA). The relationship between categorical values was assessed using Pearson χ^2 test. $P < 0.05$ was considered statistically significant. All analysis was performed using SPSS software version 21 (IBM Corp, Armonk, NY, USA).

Results

Eighty five men (81.7%) with mean age of 51.80 ± 13.44 years and 19 women (18.3%) with mean age of 56.05 ± 7.89 years participated in this investigation. The mean time since injury was 9.31 ± 6.71 years among men and 9.68 ± 5.99 years among women. Age and time since injury did not differ between two sexes (P: 18 and 0.82, respectively). The most common injury level

Table 1 Injury-related characteristics and laboratory measurements in participants with spinal cord injury

Category		Men (n: 85)		Women (n: 19)		P-value
		Number (Percentage)	Mean (SD)	Number (Percentage)	Mean (SD)	
Age (year)			51.80 (13.44)		56.05 (7.89)	0.18
Time since injury (year)			9.31 (6.71)		9.68 (5.99)	0.82
Level of Injury	Cervical	18 (21.2%)	-	3 (15.8%)	-	0.46
	Thoracic	50 (58.8%)	-	14 (73.7%)	-	
	Lumbar	17 (20.0%)	-	2 (10.5%)	-	
Completeness of Injury	Complete	66 (77.6%)	-	15 (78.9%)	-	0.58
	Incomplete	19 (22.4%)	-	4 (21.1%)	-	
ASIA score	A	63 (74.1%)	-	15 (78.9%)	-	0.80
	B	10 (11.8%)	-	2 (10.5%)	-	
	C	4 (4.7%)	-	0 (0%)	-	
	D	8 (9.4%)	-	2 (10.5%)	-	
Plegia type	Tetraplegia	11 (12.9%)	-	2 (10.5%)	-	0.56
	Paraplegia	74 (87.1%)	-	17 (89.5%)	-	
Ferritin (ng/ml)		-	182.31 (68.16)	-	36.01 (30.39)	<0.0001**
Calcitonin (pg/ml)		-	11.25 (10.50)	-	4.55 (2.66)	0.009**
triiodothyronine (T3) (pg/ml)		-	1.11 (0.32)	-	1.08 (0.26)	0.78
thyroxine(T4) (μg/dl)		-	8.97 (2.73)	-	9.02 (2.27)	0.94
Thyroid Stimulating Hormone (TSH) (μIU/ml)		-	1.97 (1.31)	-	2.08 (1.36)	0.74
Parathyroid Hormone (PTH) (pmol/l)		-	3.44 (2.82)	-	2.41 (1.01)	0.58
C-Reactive Protein (mg/l)		-	6.85 (5.21)	-	2.72 (2.14)	0.19
Leptin (ng/dl)		-	11.66 (10.87)	-	31.32 (33.85)	<0.0001**
Adiponectin (ng/dl)		-	5.65 (2.87)	-	7.23 (3.35)	0.08
Triglyceride (mg/d)		-	152.54 (64.06)	-	105.0 (45.09)	0.003**
Total Cholesterol (mg/dl)		-	175.69 (34.38)	-	185.9 (32.48)	0.23
HDL-C (mg/dl)		-	41.31 (8.94)	-	53.21 (12.53)	<0.0001**
LDL-C (mg/dl)		-	100.49 (24.97)	-	106.1 (24.17)	0.37
Fasting Plasma Glucose (mg/dl)		-	91.31 (24.05)	-	79.94 (8.06)	0.04*
Body Mass Index (kg/m^2)		-	23.62 (4.05)	-	25.06 (5.61)	0.19

ASIA: American Spinal Cord Injury Association, HDL-C: High Density Lipoprotein, LDL-C: Low Density Lipoprotein.
* Significance at level of $P < 0.05$.
**Significance at level of $P < 0.01$.
P-values stand for Pearson χ^2 test between categorical variables and one-way analysis of variance (ANOVA) for comparison of means between groups.

was at thoracic sections (58.8% and 73.7% among men and women, respectively). The majority of patients had complete injury with ASIA score A (Table 1). There was no significant difference in the injury-related characteristics between men and women. Serum concentrations of ferritin and calcitonin were significantly lower in women ($P < 0.0001$ and 0.009, respectively). HDL-C was significantly higher among women ($P < 0.0001$) whereas TG was higher among men (P: 0.003). Although BMI was not significantly different between two sexes, leptin, a hormone derived from adipose tissues,[32] was significantly higher among women ($P < 0.0001$) due to higher amount of fat tissue in female body composition. By considering these differences among men and women, sex was considered as a confounder and further analysis to detect the biomarkers associated with HRQL was performed with controlling for sex as well. Table 1 illustrates the baseline injury-related characteristics and laboratory measurements in participants with SCI.

Although partial correlation analysis was performed with controlling for dichotomous variables including sex, injury completeness and plegia type, the effect of these dichotomous variables as the moderators on the association between CRP and total score of SF-36 questionnaire was insignificant (P: 0.83, 0.28 and 0.81, respectively). Similarly, the moderation influence of sex, injury completeness and plegia type on the relationship between leptin and HRQL was not statistically significant (P: 0.70, 0.52 and 0.60, respectively) (Table 2).

The obtained scores in domains of SF-36 questionnaire are shown in Table 3. Men had significantly higher scores in domains of bodily pain and social functioning (P: 0.018 and 0.046, respectively) however the total score and scores of physical and mental component summary did not differ between two sexes.

Before adjustments for injury-related confounders (time since injury, level of injury, completeness, ASIA score and plegia type) and demographic characteristics (age, sex and BMI), the correlation analysis showed a

Table 2 Moderated multiple regression analysis to assess the moderating effect of dichotomous variables on the association between C-reactive protein (CRP) and health-related quality of life

Independent Variable	Dichotomous moderator		R	R^2	Adjusted R^2	R^2 Change	F Change	P-value
CRP	Sex	Model 1	0.301	0.091	0.068	0.091	4.048	0.021
		Model 2	0.302	0.091	0.057	0.001	0.045	**0.832**
	Injury completeness	Model 1	.318	.101	0.079	0.101	4.541	0.014
		Model 2	0.337	0.114	0.080	0.013	1.159	**0.285**
	Plegia type	Model 1	0.298	0.089	0.066	0.089	3.956	0.023
		Model 2	0.299	0.090	0.055	0.001	0.054	**0.817**
Leptin	Sex	Model 1	0.103	0.011	-0.024	0.011	0.306	0.738
		Model 2	0.115	0.013	-0.040	0.003	0.144	**0.706**
	Injury completeness	Model 1	0.248	0.062	0.029	0.062	1.872	0.163
		Model 2	0.262	0.069	0.019	0.007	0.416	**0.522**
	Plegia type	Model 1	0.102	0.010	-0.024	0.010	0.297	0.744
		Model 2	0.123	0.015	-0.038	0.005	0.276	**0.601**

Dependent variable was set as total score of SF-36 questionnaire and the interaction item was calculated by multiplying independent variable and dichotomous moderator each time.

Table 3 Values of Short Form health survey (SF-36) domains among men and women with spinal cord injury

Domain	Men (n: 85) Mean (SD)	Women (n: 19) Mean (SD)	P-value
Physical functioning	29.35 (22.64)	18.82 (12.18)	0.07
Role limitation due to physical problems	71.64 (39.82)	69.44 (40.72)	0.83
Role limitation due to emotional problems	67.48 (42.15)	62.22 (48.72)	0.66
Mental health	76.0 (17.19)	68.70 (19.76)	0.06
Vitality	70.0 (15.72)	61.76 (18.36)	0.12
Social functioning	82.07 (22.52)	69.85 (23.40)	0.046*
Bodily pain	75.12 (24.73)	58.75 (25.67)	0.018*
General health	58.25 (22.24)	54.11 (27.17)	0.50
Physical component summary	58.18 (15.82)	54.19 (19.69)	0.40
Mental component summary	73.91 (18.53)	66.65 (21.72)	0.18
Total score	66.40 (14.70)	60.14 (18.86)	0.17

* Significance at level of $P < 0.05$
P-values stand for one-way analysis of variance (ANOVA) for comparison of means between groups.

significant inverse association between CRP and total score (P: 0.006, $r = -0.29$). However this correlation was lost after adjustment for confounders (P: 0.12). Moreover, the inverse association between CRP and mental health domain (P: 0.03, $r = -0.21$) and MCS (P: 0.03, $r = -0.22$) before adjustments remained significant after controlling for confounders (P: 0.006, $r = -0.35$ and P: 0.005, $r = -0.38$ for MH and MCS, respectively). Table 4 shows the association between serum biomarkers and the scores in domains of SF-36 questionnaire after adjustment for confounders. There was a negative correlation between leptin concentration and role limitation due to physical problems (P: 0.01, $r = -0.16$) as well as with PCS (P: 0.02, $r = -0.30$) however leptin was not a determinant of HRQL total score.

The association between other biomarkers including ferritin, calcitonin, PTH, T3, T4, TSH, FBG, TG, TC, LDL-C, HDL-C and adiponectin with domains of SF-36 questionnaire were insignificant (Table 3).

Discussion

Previous researches have tried to identify biomarkers which correlate with HRQL. The inverse relationship between CRP, as an indicator of inflammation, and quality of life has been demonstrated mostly in chronic diseases. Alishiri *et al.*[33] showed a negative association between SF-36 total score and CRP in patients with rheumatoid arthritis (RA). Park *et al.* showed similar results in hemodialysis patients.[34] Our results do not support the existence of a significant independent association between CRP and HRQL in SCI because the invers correlation between CRP and SF-36 total score in our study was lost after adjustment for injury-related confounders and demographic characteristics. These findings show that CRP cannot be used an independent determinant of HRQL. Previous investigations have illustrated a linear inverse association between CRP and SF-36 total score among patients with rheumatoid arthritis (RA)[33] and chronic kidney diseases[35] which conflicts with our result in SCI. One reason for

Table 4 The association between serum biomarkers and domains of Short Form health survey (SF-36) after adjustment for injury-related confounders and demographic characteristics

Parameter	PF	RF	RE	MH	VT	SF	BP	PCS	MCS	Total
CRP	0.80	0.61	0.97	0.006** (r = −0.35)	0.02 * (r = −0.29)	0.56	0.62	0.66	0.005** (r = −0.38)	0.12
Ferritin	0.41	0.40	0.21	0.69	0.27	0.20	0.48	0.72	0.94	0.67
Calcitonin	0.62	0.43	0.20	0.62	0.13	0.89	0.63	0.66	0.05	0.26
T4	0.97	0.31	0.23	0.55	0.55	0.67	0.38	0.89	0.68	0.85
T3	0.18	0.78	0.79	0.94	0.06	0.69	0.34	0.35	0.34	0.42
TSH	0.82	0.58	0.21	0.38	0.39	0.19	0.35	0.81	0.16	0.57
PTH	0.84	0.63	0.51	0.41	0.77	0.65	0.05	0.80	0.74	0.85
Leptin	0.06	0.01 * (r = −0.16)	0.15	0.85	0.34	0.17	0.30	0.02* (r = −0.30)	0.77	0.09
Adiponectin	0.50	0.86	0.36	0.64	0.29	0.70	0.23	0.28	0.29	0.73
TG	0.13	0.66	0.95	0.83	0.63	0.57	0.98	0.15	0.80	0.24
TC	0.92	0.52	0.79	0.29	0.08	0.75	0.78	0.25	0.18	0.22
HDL-C	0.06	0.84	0.06	0.61	0.42	0.19	0.87	0.37	0.89	0.62
LDL-C	0.45	0.45	0.93	0.21	0.27	0.92	0.92	0.17	0.26	0.23
FPG	0.05	0.19	0.24	0.36	0.95	0.69	0.90	0.44	0.39	0.96

BP: Bodily pain, CRP: C-reactive protein, FPG: Fasting plasma glucose, GH: General health, HDL-C: High density lipoprotein, LDL-C: Low density lipoprotein, MH: Mental health, PF: Physical functioning, PTH: Parathyroid hormone, RE: Role limitation due to emotional problems, RP: Role limitation due to physical problems, SF: Social functioning, T3: Triiodothyronine, T4: Thyroxine, TC: Total cholesterol, TG: Triglyceride, TSH: Thyroid stimulating hormone, VT: Vitality.
The P-values which are presented in this table stand for the partial correlation between variables with controlling for injury-related confounders (level of injury, completeness, ASIA score, type of plegia and time since injury) and demographic characteristics (age, sex and body mass index).
* Significance at level of $P < 0.05$.
**Significance at level of $P < 0.01$.

these conflicting outcomes can be existence of different confounders in each population with a specific disease. Among individuals with SCI, injury-related variables are known to affect HRQL.[19] The reason for the conflicting result between our outcomes and previous literatures can be traced in the characteristics of the investigated population and whether the effects of confounders have been considered. In line with our study, Cummings *et al.*[3] demonstrated that the initial inverse relationship between CRP and HRQL has been lost after adjustment for demographic and disease characteristics in patients with diabetes which suggest that CRP cannot be considered as an independent predictor of HRQL.

Previously, Kalender *et al.*[35] showed that there is a significant negative association between CRP and PCS, MCS and total score of SF-36 questionnaire in patients with chronic kidney disease. Here, we have shown that CRP has and inverse correlation only with MCS among individuals with SCI which illustrates that this biomarker can be more useful in predicting mental component of HRQL in people with disability. However, one reason for insignificant association between CRP and physical component and total score of SF-36 in our study is the fact that physical disability in people with SCI is permanent and even treatment of infections and inflammations does not significantly improve physical abilities. It can be concluded that inflammation deteriorate mental component of HRQL more extensively compared to its influence on physical component and subsequently, treatment of inflammations may mostly improve mental component of quality of life. Another reason for different results observed in people with SCI compared to previous studies on patients with RA33 and chronic kidney disease[35] can be the differences in severity of inflammation among these populations. Although existence of a chronic inflammatory status has been described in SCI,[8,9] it seems that still this chronic inflammatory status is less severe in SCI than other chronic conditions such as RA. The severity of inflammation detected in each medical condition may affect the role of CRP in determining HRQL and therefore leads to such conflicting outcomes between different populations of patients. The reasons behind the association between inflammation and mental component of HRQL (not the physical component) in patients with SCI still remain unknown. Physical disability in individuals suffering from SCI is permanent and therapeutic interventions such as treatment of infections can hardly improve physical disability. Our study shows that the mental component of HRQL is more vulnerable to inflammation and proper treatment to control inflammations in affected individuals are more likely to improve the mental component of HRQL. Further investigations are required to clarify the etiologies of significant

correlation between inflammation and mental component of HRQL. Moreover, it is recommended that the future clinical trials investigate the effect of therapeutic treatments in controlling inflammations on components of HRQL in patients with SCI to confirm our findings.

In line with previous literatures, our results showed higher HDL-C and lower TG level in women,[36] and lower leptin level in men.[37,38] These findings confirmed that sex can have a role as a confounder and therefore all the analyses in the present study were performed with controlling for sex effect as well.

The elevated level of leptin in patients with SCI has been previously demonstrated.[39,40] In this study, we have shown that leptin can be a predictor of poorer physical component summary in HRQL. Previously Maalej *et al.*[41] reported that leptin is associated with more severe asthma and therefore may contribute to poorer HRQL among affected individuals. Here we have shown the similar outcomes among people with SCI. However, leptin was only associated with PCS and was not a predictor of total score. A correlation between leptin level and "role limitations due to physical health problems" has been also demonstrated by Dubey *et al.*[42] in obstructive sleep apnea syndrome patients which is similar to our findings in people with SCI. It has been well-documented that increased levels of leptin are mostly observed among overweight people.[42] "Being overweight" has also the potential to reduce physical functioning. We hypothesized that the inverse association between leptin level and physical component of HRQL is due to obesity-induced physical limitations but our study showed that the negative correlation between leptin and physical component of HRQL remained significant after adjustment for weight. It seems that the relationship between leptin and HRQL is not mediated only through increased weight. On the other hand leptin has been shown to be increased in inflammatory processes and its increased production by inflamed visceral fat has been reported.[43] Although leptin has been shown to be increased in inflammations, many other non-inflammatory conditions have been related to increased level of leptin. For instance, leptin levels are higher in people with obesity[44] (leptin has been shown to balance lipogenesis.[45] Leptin is increased in people with obesity as a physiologic response of body to control weight). Overweight is a major factor known to restrict physical abilities in general population. One reason that leptin was associated with poorer scores in physical component of HRQL is perhaps the correlation between leptin and obesity.

However, leptin level was not correlated to mental component of HRQL. One reason is that there are numerous factors affecting the level of leptin (not only the inflammation) including insulin level,[46] high and low environmental temperature, stress[46] and hormonal interactions.[47] It seems that the effect of leptin level on HRQL cannot only be explained through inflammatory interactions but a more complex model should be described when addressing the association between leptin level and HRQL. Further investigations should be performed to assess the biological pathways through which leptin may be associated with HRQL.

The majority of participants in our study were men. Previously, it has been demonstrated by Rahimi-Movaghar *et al.*[48] that about 83% of individuals with SCI in Iran are men which is similar to sex distribution in our study sample. The very low prevalence of SCI among women in Iran compared to men results in such unbalances in sex distribution of study samples. Future studies with oversampling of female subjects are required to clarify the factors associated with quality of life among women.

Lower scores in social functioning scale of quality of life among women compared to men has also been described by Guallar-Castillón *et al.*[49] in healthy population of Spain. Here, we have observed similar results in Iranian women with SCI. However, the small sample size of women compared to men also suggests that there is a possibility that the confounding effect of sex is probably an artifact of lack of diversity in the sample of women with SCI. Therefore, it is recommended that further studies with adequate sample size of women be performed. Furthermore, sex socialization is certainly affected by a nation's culture. Although SCI itself reduces social functioning as a consequence of disability and difficulties to access work places in both men and women, still it seems that in the Iranian population women tend to have more reduced social functioning compared to men. Future studies with consideration of culture-specific factors, life style, religion and environmental factors should be performed to assess the reasons behind the lower social functioning among women with SCI compared to male individuals.

Higher prevalence of SCI among men compared to women is almost a constant finding reported by many investigations in various regions and nations. Men are more prone to SCI in most countries, although the sex ratios vary considerably—1.73 in China to 7.55 in Pakistan.[50] Similarly, our study showed that 82% of patients with SCI were men. Although the reasons behind this sex difference have not yet been fully

described in Iran, it seems that men are more involved in violence (including fights and martial arts). Moreover, Iranian men are more frequently recruited as labor power in specific jobs which require transportation of heavy objects or performing risky activities in heights during building process of edifices and buildings. This sex difference in the type of occupations assigned to men and women may play a role in higher prevalence of SCI among men. In this regard, epidemiological studies are required to confirm these assumptions in Iran.

This study shows that CRP can be used a predictor of mental component of health-related quality of life whereas leptin can be considered as a determinant of physical component of HRQL. However, none of these two biomarkers had significant association with total score of SF-36 questionnaire. The combined consideration of these two markers may be helpful in predicting HRQL among individuals with SCI.

Conclusion

This investigation tries to identify determinant biomarkers of HRQL among individuals with SCI. The inverse association between CRP and total score of SF-36 questionnaire was lost after adjustment for injury-related confounders and demographic characteristics which illustrate that CRP cannot be used as an independent determinant of HRQL. However, the inverse association between CRP and MCS remained significant after controlling for confounders. Leptin level was negatively related with PCS. While CRP and leptin showed to have predictor value for MCS and PCS, respectively, none of them were associated with total scores. The combined consideration of these two biomarkers may help to predict HRQL among people with SCI.

Study Limitation

The unbalanced sex distribution in the sample of this study may results in misjudgments especially among population of women. Therefore, it is possible that that the confounding effect of sex is an artifact of lack of diversity in the sample of women with SCI. Moreover, reduced social functioning among women may be affected by culture-specific factors. It is recommended that further investigations with consideration of factors related to culture and religion be performed with higher sample size of female participants to render more reliable results of quality of life assessment in Iranian population.

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Conflict of interest None declared.

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