Osteoporos Int (2016) 27:405–410
DOI 10.1007/s00198-015-3333-5

SHORT COMMUNICATION

Denosumab increases sublesional bone mass in osteoporotic individuals with recent spinal cord injury

L. Gifre[1] · J. Vidal[2] · J. L. Carrasco[3] · A. Muxi[4] · E. Portell[2] · A. Monegal[1] · N. Guañabens[1,5] · P. Peris[1,5]

Received: 22 June 2015 / Accepted: 18 September 2015 / Published online: 30 September 2015

Abstract
Summary Osteoporosis is a frequent complication related to spinal cord injury (SCI), and data on osteoporosis treatment after SCI is scarce. Treatment with denosumab increases lumbar and femoral BMD and decreases bone turnover markers in individuals with recent SCI. This drug may be a promising therapeutic option in SCI-related osteoporosis.
Introduction Osteoporosis development is a frequent complication related to SCI, especially at the sublesional level. Nevertheless, data on osteoporosis treatment after SCI is scarce, particularly short term after injury, when the highest bone loss is produced. The aim of this study was to analyze the efficacy of denosumab in the treatment of SCI-related osteoporosis.
Methods Fourteen individuals aged 39±15 years with osteoporosis secondary to recent SCI (mean injury duration 15±4 months) were treated with denosumab for 12 months. Bone turnover markers (BTMs) (PINP, bone ALP, sCTx), 25-hydroxyvitamin D (25OHD) levels and bone mineral density (BMD) at the lumbar spine (LS), total hip (TH), and femoral neck (FN) were assessed at baseline and at 12 months. All participants received calcium and vitamin D supplementation.
Results At 12 months, SCI denosumab-treated participants showed a significant increase in BMD at TH (+2.4±3.6 %, p=0.042), FN (+3±3.6 %, p=0.006), and LS (+7.8±3.7 %, p<0.001) compared to baseline values. Denosumab treatment was associated with significant decreases in BTMs (bone ALP −42 %, p<0.001; PINP −58 %, p<0.001, sCTx −57 %, p=0.002) at 12 months. BMD evolution was not related to BTM changes or 25OHD serum levels. No skeletal fractures or serious adverse events were observed during follow-up.
Conclusions Treatment with denosumab increases lumbar and femoral BMD and decreases bone turnover markers in individuals with recent SCI. This drug may be a promising therapeutic option in SCI-related osteoporosis.

Keywords Bone mineral density · Bone turnover markers · Denosumab · Osteoporosis · Spinal cord injury

✉ L. Gifre
lgifre@clinic.ub.es

[1] Metabolic Bone Diseases Unit, Service of Rheumatology, Hospital Clinic of Barcelona, Villarroel 170, Barcelona 08036, Spain

[2] Guttmann Neurorehabilitation Institute, Universitat Autònoma de Barcelona, Badalona, Spain

[3] Public Health Department, University of Barcelona, Barcelona, Spain

[4] Nuclear Medicine Department, Hospital Clinic of Barcelona, Barcelona, Spain

[5] CIBERehd, Madrid, Spain

Abbreviations

SCI	Spinal cord injury
i.v.	Intravenous
25OHD	25-Hydroxyvitamin D
BMD	Bone mineral density
BTMs	Bone turnover markers
BMI	Body mass index
ASIA	American Spinal Cord Injury Association
Bone ALP	Bone alkaline phosphatase

PINP	Propeptide amino-terminal of type I procollagen
sCTx	Serum carboxy-terminal telopeptide of type I collagen
p	*p* value
SD	Standard deviation

Introduction

Spinal cord injury (SCI) is commonly associated with a marked bone loss and increased bone turnover early after SCI, leading to the development of osteoporosis and fractures, especially below the injury level [1–3]. Thus, more than 50 % of patients with complete SCI develop osteoporosis 1 year after injury [1], with a long-term overall prevalence of up to 81 % in these subjects [4]. However, at present, in spite of this well-known common complication, the therapeutic approach of these patients is clearly insufficient with less than 20 % of high-risk patients receiving antiosteoporotic treatment [2]. In addition, although treatment with i.v. or oral bisphosphonates may partly attenuate bone loss after SCI, these drugs have not shown effectiveness in increasing bone mass at sublesional sites, especially in the lower extremities [5–7] where most post-SCI fragility fractures occur [2]. Similarly, osteoanabolic agents such as teriparatide have not demonstrated a positive effect in this specific location [8], thereby indicating the need to improve the therapeutic approach in this clinical complication.

Denosumab, a monoclonal antibody against RANKL, is an essential mediator of osteoclast formation and survival, with a marked antiresorptive effect and proven efficacy in increasing bone mass and preventing fractures in osteoporotic subjects [9], with a notable positive effect on cortical bone, such as the proximal femur and forearm [10]. Thus, the use of denosumab may be of especial interest for treating SCI patients with osteoporosis. Indeed, increased bone tissue RANKL expression has been observed in a rodent model of SCI [11] further suggesting the potential therapeutic effect of denosumab for treating this clinical condition.

Herein, we report our experience in a group of individuals with recent complete SCI with associated osteoporosis treated with denosumab for 12 months.

Patients and methods

Study design and subjects

This is an ongoing prospective observational study with the main goal of analyzing the effect of recent SCI on bone mass and bone metabolism in these individuals. The detailed study design and characteristics of the participants has been previously published [1]. Briefly, the participants were recruited at the Neurorehabilitation Guttmann Institute (from June 2010 to December 2013) and followed at the Metabolic Bone Diseases Unit of the Hospital Clinic. Antiosteoporotic therapy was recommended by the attending physician when participants developed densitometric osteoporosis during follow-up. In subjects with low serum values of 25-hydroxyvitamin D (25OHD) (<20 ng/mL), treatment with vitamin D supplements was recommended. Ethical approval was obtained and all participants provided written informed consent.

Forty-two individuals were included in the study with 26 being followed for 12 months. Herein, we present the data on the effect of antiosteoporotic treatment with denosumab in bone mineral density (BMD) and bone turnover markers (BTMs) evolution in those participants who developed osteoporosis during the follow-up. Thus, 14 participants with SCI-related osteoporosis were treated with denosumab (60 mg every 6 months) for up to 12 months.

Methods

Clinical assessment, biochemical determinations, and BMD measurements were performed at baseline and at 12 months of follow-up. Risk factors for osteoporosis were assessed in all participants as well as the body mass index (BMI), and the level (paraplegia/tetraplegia), type (spastic/flaccid), and severity of SCI according to the ASIA score [12]. Skeletal fractures and adverse events were also recorded according to the results of a questionnaire given to patients at the 6- and 12-month control visits and the medical records shared with other hospitals from our geographic area (Catalonia, Spain).

Biochemical measurements included serum creatinine, calcium, phosphate, and 25OHD levels (Liason DiaSorin). The following BTMs were assessed: bone alkaline phosphatase (bone ALP by IDS, Vitro), propeptide amino-terminal of type I procollagen (PINP by Cobas e411, Roche), and serum carboxy-terminal telopeptide of type I collagen (sCTx by Cobas e411, Roche). The intra- and inter-assay coefficients of variation for each marker were as follows: bone ALP 2.9 and 5.8 %, PINP 2.8 and 4.3 %, sCTx 2 and 5.7 %, respectively.

BMD of the lumbar spine, femoral neck, and total hip was measured by dual X-ray absorptiometry (Lunar Prodigy, Radiation Corporation Madison, WI). Osteoporosis was defined according to the WHO criteria [13]. The coefficients of variations for total femur and lumbar spine were 0.6 and 0.8, respectively.

Quantitative variables are described using means and standard deviations and frequencies, and percentages are reported for qualitative variables. To assess the BMD and BTMs evolution, paired *t* tests were applied to compare the 12 months and baseline means. Pearson's correlation coefficient was used to analyze the association between the BMD evolution

and BTM changes. All hypothesis tests with a p value lower than 5 % were considered significant.

Results

The clinical characteristics of the participants included in the study are shown in Table 1. Briefly, most participants were young males (mean age 39 years old) with complete motor involvement (ASIA 12A, 1B, 1C) from C4 to T8, all requiring a wheelchair for mobility. Traffic accidents were the most frequently associated cause of SCI. Biochemical determinations including calcium, phosphate, and 25OHD were within normal range previous to initiating treatment (with a mean time-since-injury at this time of 15.2±4 months), whereas BTMs (bone ALP, PINP, sCTx) were increased at this time (Table 1).

Table 1 Clinical, biochemical, and densitometric characteristics of SCI participants at baseline

	Normal range	SCI participants (n=14)
Clinical characteristics		
Age (years)		39±15 (19−65)
Men/women		14/0
BMI (kg/m^2)		23±4 (16−32)
Dietary calcium intake (mg/day)		539±378
Current alcohol consumption (%)		14
Current tobacco consumption (%)		14
Type and cause of SCI		
Time-since-injury (months)		15.2±4.0 (8–21)
Severity of SCI (by ASIA score)		12 A/1 B/1 C
Wheelchair users (%)		100
Paraplegia/tetraplegia (%)		43/57
Spastic/flaccid (%)		86/14
Cause of SCI (%)		
Traffic accident		85.7
Fall from height		7.1
Sports accident		7.1
Biochemical determinations		
25OHD (ng/mL)	>20	29.8±27.4
PINP (ng/mL)	22–63	71±28
Bone ALP (ng/mL)	6.0–14	16.8±5.0
sCTx (ng/mL)	0.14–0.48	0.68±0.43
Baseline BMD (g/cm^2)		
Lumbar		1.168±0.127
Femoral neck		0.751±0.085
Total hip		0.718±0.072

Results are expressed as mean±SD, %, or n

BMI body mass index, *SCI* spinal cord injury, *25OHD* 25-hydroxyvitamin D, *PINP* propeptide amino-terminal of type I procollagen, *bone AP* bone alkaline phosphatase, *sCTx* serum carboxy-terminal telopeptide of type I collagen, *BMD* bone mineral density

At 12 months, SCI participants treated with denosumab showed a significant increase in BMD at total hip (+2.4± 3.6 %, p=0.042), femoral neck (+3±3.6 %, p=0.006), and lumbar spine (+7.8±3.7 %, p<0.001) compared to baseline values (Fig. 1a). In addition, denosumab treatment was associated with a significant decrease in BTMs (bone ALP −42 %, p<0.001; PINP −58 %, p<0.001, sCTx −57 %, p=0.002) at 12 months (Fig. 1b). BMD evolution was not related to BTM changes or to 25OHD serum levels.

No skeletal fractures were observed during follow-up and no serious treatment-related adverse events were noted during the study. In addition, no local site reactions nor skin infections or respiratory infections were observed. A soft tissue infection after traumatic skin abrasion was observed in one individual, which was resolved with oral antibiotic therapy. Moreover, 9 participants developed a total of 29 urinary tract infections during the 12-month follow-up period of treatment with denosumab. However, all of these individuals had also presented episodes of urinary tract infection during the period prior to initiating treatment with denosumab with no significant difference in the frequency of infections between the two periods of time (before denosumab treatment: 85.7 vs. 64 % during denosumab treatment, p=0.649). No autonomic dysreflexia was reported during the 12-month follow-up period.

Discussion

This preliminary observational study shows for the first time the efficacy of denosumab in the treatment of SCI-related osteoporosis early after injury. Thus, treatment with denosumab increased lumbar and femoral BMD and decreased BTMs in these participants, suggesting the usefulness of this agent in the treatment of this common clinical complication.

In the present study, treatment with denosumab decreased bone turnover and not only prevented BMD loss after SCI but also significantly increased BMD 1 year after initiating treatment in all the locations evaluated, the lumbar spine and proximal femur. Thus, BMD increased about 3 % at the proximal femur including both the femoral neck and total hip, and ~8 % at the lumbar spine. Although the specific mechanism related to the maintained increase in cortical bone mass areas, such as the proximal femur, with denosumab treatment are not fully understood, recent studies have attributed this finding to both an increase in bone modelling, mostly affecting

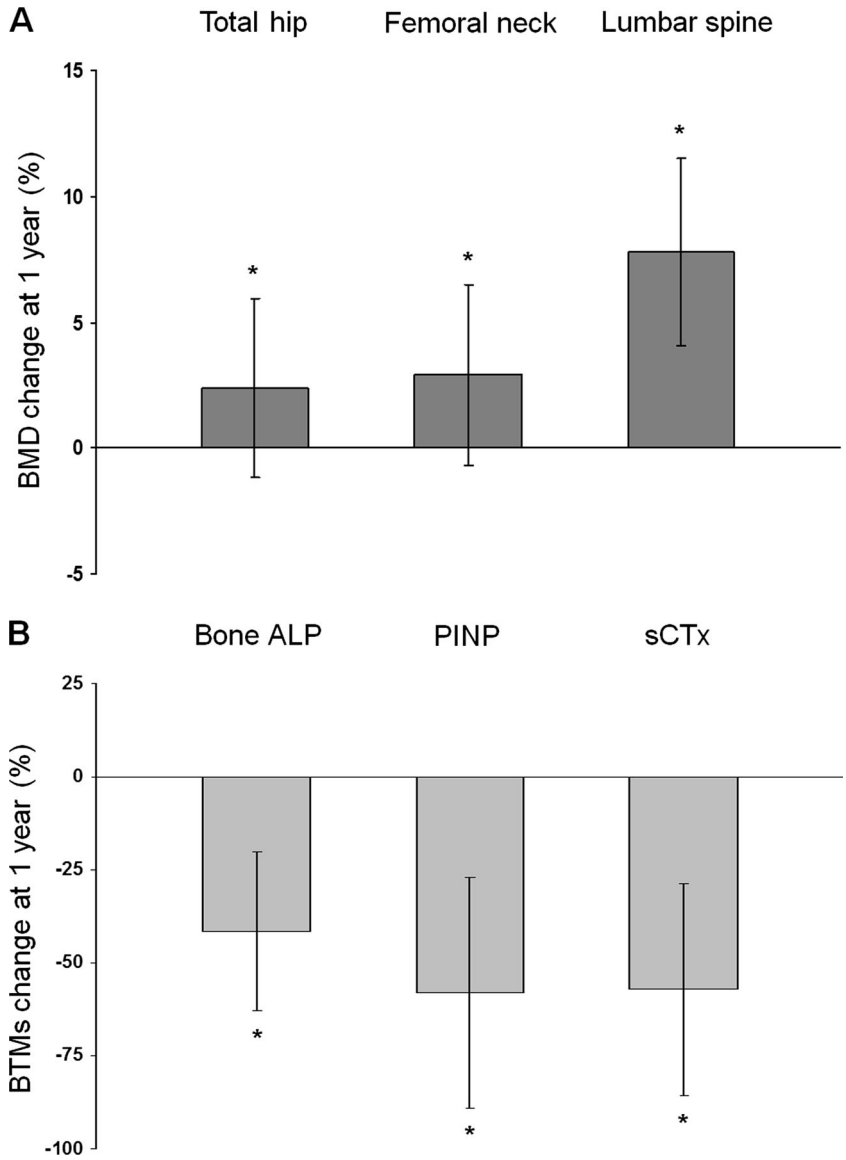

Fig. 1 Percentage of changes (±standard deviation) in BMD at the proximal femur and lumbar spine (**a**) and in the BTMs values (**b**) at 12 months of denosumab treatment. *$p<0.05$ compared with baseline values

endocortical and periosteal surfaces, and a decrease in bone remodelling [14]; the latter explaining the marked reduction in BTMs with this treatment. On the other hand, it should be noted that the spontaneous BMD evolution in other locations after SCI such as the lumbar spine may differ. Indeed, maintenance or a slight increase in BMD in this location has been described after SCI, in relation to the continued weight-bearing function in this site in these individuals [15, 16]. Although we cannot totally rule out a spontaneous BMD increase in this specific location, the magnitude of the increase (~8 %) and the absence of radiological artefacts in the DXA scans in these subjects (none had undergone surgical instrumentation in the lumbar spine) further suggest an additional effect of the antiosteoporotic treatment.

Notably, although this is a preliminary study, denosumab increased BMD at the sublesional level in our participants, thereby being the first antiosteoporotic treatment able to improve bone mass in subjects with osteoporosis related to recent SCI to date. Thus, our participants had an early complete SCI with a mean time since SCI of 15 months, when the highest bone loss after SCI is known to be produced [3, 15, 16] and when no previous antiosteoporotic treatment has demonstrated prevention of BMD loss at the sublesional level, especially in the lower extremities. In this sense, several oral or intravenous bisphosphonates, such as alendronate, pamidronate, or zolendronate, or even osteoanabolic agents such as teriparatide have only shown an attenuation of bone mass loss at the lower extremities early after SCI [5–8]. Indeed, preventive effects in BMD loss have only been observed

with these agents long-term after SCI when either the magnitude of the BMD loss and/or the increase bone turnover markers is much lower [5, 6].

As expected, treatment with denosumab was associated with a significant decrease in all the bone turnover markers evaluated in our study (bone ALP, PINP, and sCTx) with nearly a 60 % decrease in their values at 1 year of follow-up. However, since a spontaneous decrease in BTMs was observed during the first years after SCI, we cannot totally rule out an influence of the natural evolution of BTMs after injury. Nevertheless, the magnitude of the decrease in these markers was similar to that previously reported in postmenopausal osteoporotic women and men with osteoporosis treated with this agent (~60 % for sCTx and/or PINP) [9, 10, 17], thereby suggesting a similar response in our participants.

Since RANKL is expressed on activated T and B lymphocytes and lymph nodes, a RANKL inhibitor such as denosumab could theoretically increase the risk of infection. Nevertheless, apart from skin infections (cellulitis), the overall incidence of infections in previous studies of patients treated with denosumab for osteoporosis was not increased [9], and similar results were observed in individuals treated with cancer-related complications, in whom the dose given and the periodicity of administration of denosumab are much greater [18]. In our study, one of the concerns about using denosumab for treating osteoporotic SCI subjects was its effect on the possible increased risk of infections, especially in the urinary tract, a well-known clinical complication of SCI [19]. Although this was an observational non-controlled study with a limited number of participants and length of follow-up, which is the main limitation to assess side effects, we did not observe serious adverse events related to this treatment. Thus, no local site reactions nor skin or respiratory infections were observed in our participants. Additionally, although 64 % of participants developed at least one urinary tract infection during the 12-month denosumab treatment, this figure was similar to that observed prior to initiating treatment and was also similar to the reported expected incidence in subjects with complete SCI [19, 20]. Nevertheless, the non-randomized nature of the present study and the small sample size prone to increased risk of infection require controlled randomized clinical trials to further address this issue.

In conclusion, our results indicate that in individuals with SCI-associated osteoporosis treatment with denosumab early after injury increases lumbar and femoral BMD 1 year after initiating therapy. Therefore, this agent might represent a promising therapeutic option for treating this clinical complication. Nonetheless, in view of the present results, further prospective randomized controlled studies analyzing the long-term efficacy of denosumab in a larger number of participants are needed.

Acknowledgments This work was funded by the Fundació La Marató de TV3.

Compliance with ethical standards The procedures followed were in accordance with the Ethical Standards of the Helsinki Declaration.

Funding This work was funded by a grant from Fundació La Marató de TV3.

Conflicts of interest None.

Ethics approval Ethical approval was obtained from the Hospital Clinic of Barcelona and from the Neurorehabilitation Guttmann Institute Ethics Committees.

Consent to participate All participants provided written informed consent prior to the initiation of this study.

References

1. Gifre L, Vidal J, Carrasco J, Filella X, Ruiz-Gaspà S, Muxi A, Portell E, Monegal A, Guañabens N, Peris P (2015) Effect of recent spinal cord injury on Wnt signaling antagonists (sclerostin and Dkk-1) and their relationship with bone loss. A 12-month prospective study. J Bone Miner Res 30:1014–1021
2. Gifre L, Vidal J, Carrasco J, Portell E, Puig J, Monegal A, Guañabens N, Peris P (2014) Incidence of skeletal fractures after traumatic spinal cord injury: a 10-year follow-up study. Clin Rehabil 28:361–369
3. Frey-Rindova P, de Bruin ED, Stüssi E, Dambacher MA, Dietz V (2000) Bone mineral density in upper and lower extremities during 12 months after spinal cord injury measured by peripheral quantitative computed tomography. Spinal Cord 38:26–32
4. Shojaei H, Soroush MR, Modirian E (2006) Spinal cord injury-induced osteoporosis in veterans. J Spinal Disord Tech 19:114–117
5. Bryson JE, Gourlay ML (2009) Bisphosphonate use in acute and chronic spinal cord injury: a systematic review. J Spinal Cord Med 32:215–225
6. Chang KV, Hung CY, Chen WS, Lai MS, Chien KL, Han DS (2013) Effectiveness of bisphosphonate analogues and functional electrical stimulation on attenuating post-injury osteoporosis in spinal cord injury patients—a systematic review and meta-analysis. PLoS One 8, e81124
7. Bauman WA, Cirnigliaro CM, La Fountaine MF, Martinez L, Kirshblum SC, Spungen AM (2015) Zoledronic acid administration failed to prevent bone loss at the knee in persons with acute spinal cord injury: an observational cohort study. J Bone Miner Metab 33:410–421
8. Gordon KE, Wald MJ, Schnitzer TJ (2013) Effect of parathyroid hormone combined with gait training on bone density and bone architecture in people with chronic spinal cord injury. PM R 5: 663–671
9. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, Delmas P, Zoog HB, Austin M, Wang A, Kutilek S, Adami S, Zanchetta J, Libanati C, Siddhanti S, Christiansen C, Trial FREEDOM (2009) Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 361:756–765
10. McClung MR, Lewiecki EM, Cohen SB, Bolognese MA, Woodson GC, Moffett AH, Peacock M, Miller PD, Lederman SN, Chesnut CH, Lain D, Kivitz AJ, Holloway DL, Zhang C, Peterson MC, Bekker PJ, AMG 162 Bone Loss Study Group (2006)

Denosumab in postmenopausal women with low bone mineral density. N Engl J Med 354:821–831
11. Jiang SD, Jiang LS, Dai LY (2007) Effects of spinal cord injury on osteoblastogenesis, osteoclastogenesis and gene expression profiling in osteoblasts in young rats. Osteoporos Int 18:339–349
12. Waring WP 3rd, Biering-Sorensen F, Burns S, Donovan W, Graves D, Jha A, Jones L, Kirshblum S, Marino R, Mulcahey MJ, Reeves R, Scelza WM, Schmidt-Read M, Stein A (2010) 2009 review and revisions of the international standards for the neurological classification of spinal cord injury. J Spinal Cord Med 33:346–352
13. (1994) Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. World Health Organ Tech Rep Ser 843:1-129
14. Ominsky MS, Libanati C, Niu QT, Boyce RW, Kostenuik PJ, Wagman RB, Baron R, Dempster DW (2015) Sustained modeling-based bone formation during adulthood in cynomolgus monkeys may contribute to continuous BMD gains with denosumab. J Bone Miner Res 30:1280–1289
15. Giangregorio L, McCartney N (2006) Bone loss and muscle atrophy in spinal cord injury: epidemiology, fracture prediction, and rehabilitation strategies. J Spinal Cord Med 29:489–500
16. Jiang SD, Dai LY, Jiang LS (2006) Osteoporosis after spinal cord injury. Osteoporos Int 17:180–192
17. Orwoll E, Teglbjærg CS, Langdahl BL, Chapurlat R, Czerwinski E, Kendler DL, Reginster JY, Kivitz A, Lewiecki EM, Miller PD, Bolognese MA, McClung MR, Bone HG, Ljunggren Ö, Abrahamsen B, Gruntmanis U, Yang YC, Wagman RB, Siddhanti S, Grauer A, Hall JW, Boonen S (2012) A randomized, placebo-controlled study of the effects of denosumab for the treatment of men with low bone mineral density. J Clin Endocrinol Metab 97: 3161–3169
18. Stopeck AT, Lipton A, Body JJ, Steger GG, Tonkin K, de Boer RH, Lichinitser M, Fujiwara Y, Yardley DA, Viniegra M, Fan M, Jiang Q, Dansey R, Jun S, Braun A (2010) Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol 28:5132–5139
19. Adriaansen JJ, Post MW, de Groot S, van Asbeck FW, Stolwijk-Swüste JM, Tepper M, Lindeman E (2013) Secondary health conditions in persons with spinal cord injury: a longitudinal study from one to five years post-discharge. J Rehabil Med 45:1016–1022
20. Noreau L, Proulx P, Gagnon L, Drolet M, Laramée MT (2000) Secondary impairments after spinal cord injury: a population-based study. Am J Phys Med Rehabil 79:526–535