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SM Journal of Orthopedics

Research Article

# Bone Healing and Hormonal Bioassay in Patients with Long Bone Fractures and Concomitant Spinal Cord Injury

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**Article Information**

Received date: Aug 04, 2015
Accepted date: Aug 30, 2015
Published date: Sep 10, 2015

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**Keywords** Acceleration of bone healing; Spine fracture-dislocation; Spinal cord injury; Hormonal control; Sympathetic nervous system

## Abstract

To ensure the possible accelerated osteogenesis of long bone fractures in patients with concomitant spinal cord injury and to investigate the mechanism causing it with the understanding of a possible neuro-hormonal cause, a hormonal bioassay of the blood of 21 of these patients was measured in the prospective controlled study and compared to 20 patients with only spinal cord injuries, 30 patients with only long bone fractures, and 30 healthy volunteers.

The study results showed that Long bone fractures in patients with associated acute traumatic spinal cord injury of quadriplegia or paraplegia heal more expectedly, faster and with exuberant florid union callus ($P>0.001$) and showed statistically significant higher levels of parathyroid hormone and growth hormone ($p<0.005$) and normal corticosteroids levels. Patients with long bone fractures only showed consistent and statistically significant higher level of noradrenaline and adrenaline hormones compared to patients with spinal cord injury alone or associated with long bone fractures ($p<0.001$). Leptin hormone shows statistically significant consistent decrease in patients with spinal cord injury and concomitant long bone fractures compared to healthy subjects ($p<0.001$). We believe, according to the results of this study that bone healing is accelerated in long bone fractures in patients with associated spine fractures and spinal cord injuries. We also can conclude that bone healing has a central neuronal control and a combined neuro- hormonal mechanism with a relative inhibition of the sympathetic nervous system is a possible cause of accelerated healing of long bone fractures in patients with associated spinal cord injury.

## Introduction

The increased rate of fracture healing and abundant callus formation of long bone fractures in patients with concomitant severe acute traumatic head injury is a well-known orthopedic phenomenon, Few studies, however, have reported these phenomena being induced by acute traumatic Spinal Cord Injury (SCI). There is also a well-established clinical relationship between spinal cord injuries and heterotopic ossification [1-5]. The research gap remains to confirm accelerated bone healing in long bone fractures in patients with concomitant SCI and to establish theories about the mechanism causing it.

Early clinical reports in researching the correlation between accelerated bone healing and nervous tissue damage in head and spinal cord injuries were inconclusive and demonstrated no evidence of accelerated union or increased callus formation [6-11]. However, recent researches confirmed accelerated bone healing in patients with concomitant head injuries, but doubted its occurrence in patients with SCI and speculated the cause of these clinical observations to be due either to circulating humoral factors including growth factors, cytokines and other mediators [12-18].

Several studies have addressed the issue of releasing growth factors in brain-injured patients in relation to increased bone healing and they suggest that trauma to the Central Nervous System (CNS) may increase the release of, or decrease uptake by, bone formation mediators that can enter the systemic circulation. Other chemicals may be released from the brain, which act to stimulate local production of BMP or other growth factors or mediators. Investigators hypothesized that BMPs and their receptors are involved in the neuronal plasticity that occurs after Traumatic Brain Injury (TBI). These scenarios would result in a altered bone formation [12-17].

Other possible mechanisms which could be responsible for acceleration of fractures healing in head or spinal cord injured patients include an altered nerve signaling pathway in which a possible physiological central suppressive mechanism on bone healing and remodeling is obliterated due to brain or spinal cord damage and leads either directly or indirectly (through humoral factors) to mobilization, proliferation, and differentiation of undifferentiated mesenchymal stem cells at the fracture site. Accordingly, neuro-hormonal or neuro-humoral mechanisms were suggested [19-32].

In the current study, we proposed and tested a hypothesis that SCI in patients with associated long bone fractures, accelerates bone healing and a neuro-hormonal mechanism is the underlying

cause. This possible mechanism might be indirectly revealed by the variations in the levels of stress hormones: Corticosteroids, adrenaline, and noradrenaline and other hormones, especially with the understanding of possible role of hormones in bone remodeling, which is a type of bone formation [12,32].

To ensure accelerated healing of long bone fractures in patients with concomitant spinal cord injuries, healing indicators were compared to patients with isolated long bone fractures and to investigate the mechanism causing this accelerated osteogenesis, hormonal bioassay of the blood of these patients were measured in prospective controlled study.

## Patients and Methods

Patients in the age group of 18-60 years with SCI and complete quadriplegia or paraplegia with associated closed diaphyseal humeral, femoral, or tibial long bone fractures, and without history of chronic ill-health or systemic diseases were included in this study. Patients on permanent medications and therapy for chronic disease such as diabetes mellitus, ischemic heart diseases, chronic renal failure, or endocrine diseases, or patients on corticosteroids for bronchial asthma, rheumatoid arthritis, other inflammatory arthritis, and autoimmune diseases were excluded from the study. Patients, with incomplete quadriplegia or incomplete paraplegia after spinal shock stage and patients with history of smoking or with open fractures were also excluded.

Patients were started to be recruited prospectively in this study from 19/09/2011 and were categorized according to their clinical data into the following groups: 20 group (A) patients with acute traumatic spinal cord injuries of complete quadriplegia or paraplegia after spine fractures or fracture-dislocation, without long bone fractures, 21 group (B) patients with SCI of quadriplegia or paraplegia and closed long bone diaphyseal fractures (humerus, femur, and tibia), 30 group (C) patients with long bone fractures only, and 30 group (D) healthy subjects. All long bone fractures in patients of group (B) and (C) were treated surgically by open reduction and dynamic compression plate DCP for humerus shaft fractures and by closed or open reduction and internal fixation by interlocking intra-medullary nails for femoral or tibial diaphyseal fractures. Prophylactic broad spectrum antibiotics have been given intra-venously for all operated patients, with the induction of anesthesia. Spine fractures or fracture-dislocation, whether cervical or dorso-lumbar have been openly reduced and internally fixed.

Assessment of radiological healing of fractures is difficult and controversial, but mostly, radiological union is defined by the presence of bridging callus, disappearance of fracture line or the continuity of cortex in at least in three of the four bone cortices appear in the antero-posterior and the lateral X-ray views, so a score of 3-4 points of one or more of the aforementioned radiological healing criteria defines fracture unionm [8]. The healing of long bone fractures in this study has been followed up by radiological assessment of the fracture in antero-posterior and lateral X-ray views weekly and once the plain X-ray showed fracture union, we use CT to assess the maximal amount of union callus formed at the fracture site if the bridging callus was the main or one of the radiological healing criteria. Delayed union was defined as absence of radiological union criteria 3 months after the occurrence of the long bone fracture, while non-union was defined as no bridging callus and radiologically visible fracture line 6 months after the injury with atrophic or hypertrophic fracture ends. Time to radiological union in weeks, the maximal thickness of the amount of union callus formed in mms as measured in CT scan and the mean healing rate, which is defined as the maximal thickness of union bridging callus in mms divided by the time to healing in weeks, were compared in the two groups of patients: (B) and (C).

Blood samples were withdrawn from the injured patients at: a) 24 hours, b) 72 hours, c) 7days, d) 14 days, and e) 21 days from the time of injury and were withdrawn only once from the healthy volunteers. 10 ml of blood was withdrawn each time. These blood samples were processed by centrifugation and separation of the sera which were preserved at -85$^0$ C.

The blood samples from different patients' groups were used to measure the level of corticosteroids, adrenalin, noradrenaline, parathyroid hormone, growth hormone, and leptin hormone.

### Post- operative rehabilitation and follow up

Patients in groups (B) and (C) were subjected to an intensive program of physiotherapy including continuous passive motion CPM exercises, whether in paralyzed, group (B) patients or patients with long bone fractures only, group (C). Patients with spinal cord injury were allowed to be mobilized on a wheel chair when all their fractures were fixed, while patients in group (C) actively exercised their limbs and were allowed to walk partial or full weight bearing with crutches or walker, once their femoral or tibial fractures were fixed. The mean period of follow up for patients in the two groups was 15 and the range (13-18) months.

**Statistical Analysis:** Results were analysed with Statistical Package for the social sciences SPSS for Windows (Version 16). Means and standard deviations were determined. Mean scores between the two groups of patients were compared using chi square and the Student t-test. p value < 0.05 was considered statistically significant.

## Results

20 patients have been recruited in group (A). The mean age of the patients in this group was 32.7 range (18-49) years. These 20 patients included 16 (80%) males and 4 (20%) females with a ratio of 4:1. All the patients in this group have been involved in high energy trauma with 12 patients (60%) in RTA accidents and 8 patients (40%) in falling from height accidents.

Cervical spine injuries of fracture-dislocation have occurred in 9 patients (45%) and burst vertebral body fracture or fracture-subluxation of dorso-lumbar spine have occurred in the remaining 11 patients (55%), more details about spine injuries in this group has been shown in Table 2. Regarding, the neurological deficits in this group of patients: 9 patients (45%) had complete quadriplegia, 11 patients (55%) had complete paraplegia, as shown in Table 1. In all group (A) patients spine surgery procedures of open reduction, decompression, cage, plate fixation, trans-pedicular screws posterior fixation, and or fusion have been done in cervical and dorso- lumbar spine injuries.

21 patients have been recruited in group (B). The mean age in this group was 33.5, range (22-48) years. There were 18 (85.7%) males and 3 (14.3%) females with a ratio of 6:1. All the patients of this

group had been involved in high velocity trauma: 17patients (81%) in RTA and four (19%) in falling from height accidents. In this group 8 patients had cervical spine injuries with complete quadriplegia (38%) and 13 patients sustained dorso-lumbar spine injuries with complete paraplegia (62%), as shown in Table 1. These injuries included: burst vertebral body fracture, fracture-dislocation, or subluxation of cervical or dorsolumbar spine, more details about spine injuries in this group has been shown in Table 2.

**Table 1:** Patients' biodata and characteristics of injuries in patients' all groups.

| Groups | | A | B | C | D |
|---|---|---|---|---|---|
| No. Recruited | | 20 | 21 | 30 | 30 |
| Mean Age Years | | 32.7 | 33.5 | 33 | 39 |
| Age Range Years | | 18-49 | 22-48 | 18 -60 | 20-60 |
| Sex | M | 16 | 18 | 25 | 22 |
| | F | 4 | 3 | 5 | 8 |
| Cause of Injury | Road Traffic Accident RTA | 12 | 17 | 27 | 0 |
| | Fall from height | 8 | 4 | 3 | 0 |
| Type of Spine Injury | Cervical | 9 | 8 | 0 | 0 |
| | Dorso-Lumber | 11 | 13 | 0 | 0 |
| Neurological Spinal Cord Injury | Quadriplegia | 9 | 8 | 0 | 0 |
| | Paraplegia | 11 | 13 | 0 | 0 |
| Type of Fracture | Humerus | 0 | 2 | 5 | 0 |
| | Femur | 0 | 12 | 17 | 0 |
| | Tibia & fibula | 0 | 8 | 14 | 0 |
| Status of Patient | Alive / Dead | 20/0 | 21/0 | 30/0 | 30/0 |

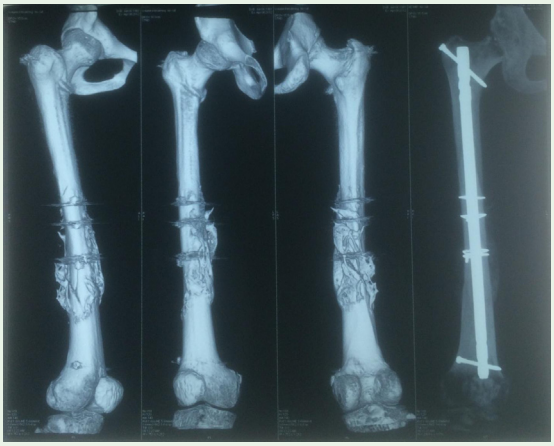

**Figure 1:** 3D CT scan and X-ray of femur with accelerated union of diaphyseal fracture with abundant callus formation 5 weeks post-surgery and 5.8 weeks post-injury in a group (B) patient with cervical spine fracture-dislocation and quadriplegia.

In all group (B) patients, spine surgery procedures have been done. In this group, there were 22 fractured long bones, which were treated surgically by fixation with DCP or static reamed interlocking intra-medullary nail. The 22 fractured long bones in this group included 2 humeral shaft fractures (in patients with complete quadriplegia with C4-C5 fracture-dislocation), 12 femoral shaft fractures, and 8 tibia & fibula shaft fractures, as shown in Table 1.

The mean time to union in this group was 6.3, range (3.7-7.5) weeks. There are no cases of non-union of long bones in this group.

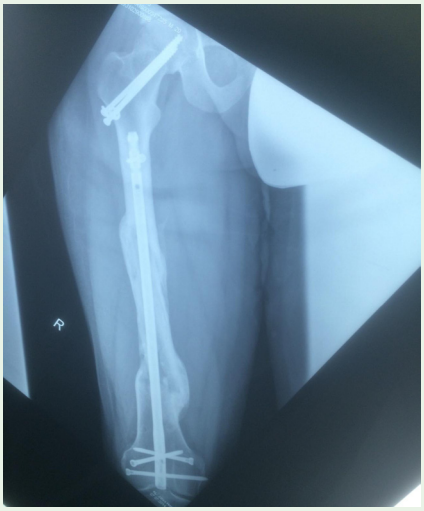

**Figure 2:** X-ray of accelerated union of comminuted femoral shaft fracture with ipsilateral neck fracture 6.2 weeks post-injury with abundant diaphyseal callus formation and healing of both fractures in a group (B) patient with spine fracture-dislocation and SCI of paraplegia, this injury is well known to have delayed or nonunion in one of the two fractures sites, healing of femoral neck fracture has not been considered or counted in the statistical analysis of the study.

**Table 2:** Types of spine injuries seen in groups (A) and (B) patients.

| Types of spine injury | Group A | | Group B | |
|---|---|---|---|---|
| | No of patients | % | No of patients | % |
| Cervical spine injuries | 9 | 45 | 8 | 38.1 |
| C3-C4 fracture dislocation | 2 | 10 | 2 | 9.5 |
| C4-C5 fracture dislocation | 2 | 10 | 3 | 14.3 |
| C5-C6 fracture dislocation | 5 | 25 | 3 | 14.3 |
| Fracture pedicle or lamina | 5 | 25 | 3 | 14.3 |
| Dorso-lumber spine injuries | 11 | 55 | 13 | 61.9 |
| Unstable burst fracture DV | 5 | 25 | 8 | 38.1 |
| Fracture-dislocation DV | 5 | 25 | 4 | 19 |
| Fracture-dislocation D-LJ | 1 | 5 | 1 | 4.8 |

The mean maximal thickness of union bridging callus as shown in X-rays, figure (1) or CT scan was 29, range (10-48) mm. The mean healing rate was 4.7, range (2.6-7.5) mm/week, as shown in table (3) and Figures 1 & 2.

30 patients finished their follow-up in group (C); the mean of their age was 33, range (18-60). There were 25 (83.3%) males and 5 (16.7%) females with a ratio of 5:1. The type of accident was high energy trauma, RTA in 27 (90%) and falling from height in 3 (10%). There were 36 long bone diaphyseal fractures in this group: 5 of humerus, 17 of femur and 14 of tibia & fibula which all have been treated surgically by closed or open reduction and skeletal stabilization of DCP for humerus fractures and static reamed interlocking intra-medullary nails for femoral or tibial fractures, as shown in Table 1.

Among the 36 fractured long bones in the 30 patients of this group, 30 fractures (83.3%) united and 6 (16.7%) went into atrophic nonunion. The mean healing time in this group of patients was 22.5, range (14-42) weeks. The mean maximal thickness of callus in the united fractures in this group was 8, range (2-20) mm. The mean healing rate was 0.41, range (0.25 – 1) mm/week, as shown in Table 3.

The results of the study did not show any statistically significant difference due to variables of age or gender in healing indicators

in long bone fractures in patients of both groups (B) and (C). The level of spine fracture or fracture-dislocation and the level of SCI also, did not seem to affect healing of long bone fractures in these patients. Authors of the current study have a good understanding of autonomic dysreflexia, which develops in patients with SCI at or above the sixth thoracic vertebral level (T6) and are familiar with the

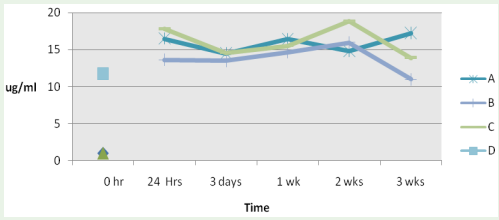


**Figure 3 a & b:** Serum corticosteroids hormones levels in patients' groups A to D in (ug/ml).

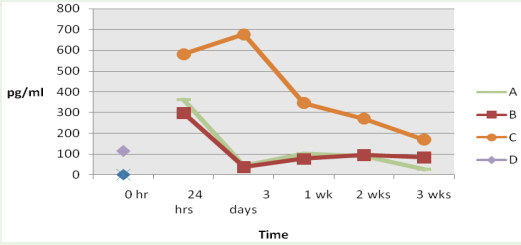


**Figure 4 a & b:** Serum noradrenaline levels in patients' groups A to D in (pg/ml).

signs and symptoms of this potentially life-threatening condition, and despite of the presence of 13 (61.9%) among the 21 patients with their SCI levels were higher than T6, the results of the study did not show any statistically significant difference due to this variable in healing indicators in long bone fractures in comparison to patients with SCI levels below T6 in group (B). The trauma series X-rays of patients in both groups (B) and (C) did not show radiological signs of osteoporosis or even, to suspect it to go forward to test Bone Mineral Density (BMD), may be due to the small number of middle aged and old people in the study (only one male patient in group B and two male patients in group (C)).

All groups showed normal levels of corticosteroids compared to healthy subjects, without statistically significant difference along the whole three weeks period of follow-up as shown in Figure 3.

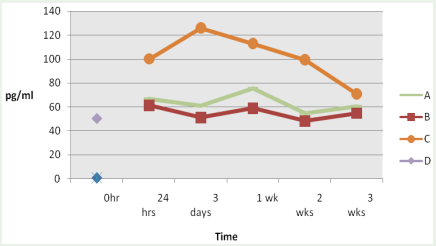


**Figure 5 a & b:** Serum adrenaline levels in patients of all groups.

**Table 3:** Comparison of healing indicators between groups (B) and (C) of patients.

| Patients" Groups | Union Percent % | Healing Time | Thickness of Maximal Union Callus | Healing Rate |
|---|---|---|---|---|
| B | 100% | Mean 6.3 weeks Range (3.7-7.5) | Mean 29 mm Range (10-48) | Mean 4.7 mm/week Range (2.6-7.5) |
| c | 83.30% | Mean 22.5 weeks Range (14-42) | Mean 8 mm Range (2-20) | Mean 0.41 mm/week Range (0.25 – 1) |

Patients with long bone fractures only showed consistent and statistically significant higher level of noradrenaline hormone compared to patients with spinal cord injury alone or associated with long bone fractures, and healthy subjects ($p<0.001$). The levels of noradrenaline in patients of head injury with or without long bone fractures, during the three weeks of follow-up, were comparable to the hormone levels in healthy subjects, without any statistical significant difference, as shown in Figure 4.

The adrenaline hormone shows the same pattern of noradrenaline with a statistically significant higher level of adrenaline in patients with long bone fractures only compared to patients with spinal cord injury with or without long bone fractures and normal subjects ($p<0.001$). Again, the levels of adrenaline in patients with spinal cord injury with or without long bone fractures, during the three weeks of follow-up, were normal or subnormal compared to healthy subjects, with a statistically insignificant difference, as shown in Figure 5.

Spinal cord injury with or without Long bone fractures resulted in statistically significant higher levels of parathyroid hormone compared to patients with long bone fractures only or the healthy controls ($p<0.005$). Patients with spinal cord injury combined with long bone fractures had higher level of parathyroid hormone compared with patients with spinal cord injury and no long bone fractures ($p<0.005$). In all groups of patients the parathyroid hormone normalized to the levels in normal healthy subjects at the end of the third week.

Growth hormone was found elevated statistically significant in patients with spinal cord injuries with or without long bone fractures compared to healthy subjects ($p<0.005$). Patients with spinal cord

injury associated with long bone fractures showed sustained, consistent, and the highest elevation, which remained till the third week ($p<0.005$). Patients with long bone fractures only after their statistically significant elevation for the first two weeks declined to normal levels at the end of the third week ($p<0.05$).

Assessment of leptin hormone shows statistically significant decrease along the three weeks of follow-up of its levels in blood samples of all groups of patients compared to healthy subjects ($p<0.001$).

## Discussion

Patients with central nervous tissue damage have been noticed to have an increased incidence of heterotopic ossification and this phenomenon has been extensively described [6-9]. The idea that acceleration of fracture healing occurs in long bone fractures in patients with spinal cord injury remains a controversial subject. Research on this topic has been, mostly from studies and authors who denied the presence of this relationship. The only abnormality of bone formation that was detected was an unusually high incidence of heterotopic ossification without an effect on clinical or radiological fracture union [1-11].

The results of this study showed that long bone fractures of humerus, femur and tibia, in spinal cord injury patients group B healed faster and united within a shorter period of time than in patients from group C with long bone fractures only. The study also showed that long bone fractures in patients with spinal cord injury united more expectedly and all healed without a single case of nonunion or delayed union. However, 6 (16.7%) long bone fractures among the 36 fractures in the 30 patients of group C had atrophic nonunion. Long bone fractures in group B patients united with the mean time to union was 6.3, range (3.7-7.5) weeks compared to 22.5, range (14-42) weeks in group C patients, a statistically significant difference ($p<0.001$). Another important finding of our study is that long bone fractures in spinal cord patients group B healed with more exuberant and florid callus formation compared with patients with long bone fractures only group C patients. The mean maximal thickness of union bridging callus as shown and measured in CT scan in group B patients was 29, range (10-48) mm compared to 8, range (2-20) mm in group C patients which is a statistically significant difference ($p<0.001$). The mean healing rate was also faster, statistically significant, in group B compared to group C {4.7, range (2.6-7.5) mm/week versus 0.41, range (0.25 – 1) mm/week}. These data, which all were statistically significant, indicate that in all probabilities, patients with spinal cord injuries have accelerated bone healing of concomitant long bone fractures with the underlying mechanism causing it, remains to be revealed.

Researching the underlying mechanism causing this acceleration of bone healing in long bone fractures in patients with associated acute traumatic SCI of complete quadriplegia or paraplegia, we investigated the bioassay of corticosteroids, adrenaline, noradrenaline, parathyroid hormone, growth hormone, and leptin hormone in patients with SCI of post-traumatic quadriplegia or paraplegia and long bones fractures in comparison to control groups of patients with spinal cord injuries only, patients with long bones fractures only, and normal subjects. To the best of our knowledge, except for leptin hormone this is the first study to investigate the role of hormones in accelerated osteogenesis in central nervous tissue damage patients with associated long bone fractures.

The traditional view understands that bone healing and remodeling are regulated by autocrine/paracrine. Recent works suggested the influence of a possible higher integrating neuronal pathway. Several neuropeptides, neurotrophins, and classical neurotransmitters, as noradrenaline and serotonin, were described as possible neuromediators [19-32].

Khare, et al. [22] proposed a new hypothesis to explain excessive callus formation seen after injury to brain or spinal cord. Nervous tissue is very active metabolically and when damaged or inflamed it extracts, utilizes and inactivates most of the corticosteroids and other anti-inflammatory substances present in the blood. Therefore very little active corticosteroids are left to exhibit the inhibitory effect on callus formation. This leads to faster fracture healing with excessive callus formation in head or spinal cord injured patients.

Afan, et al. [25] concluded in their study of the anatomical analysis of the innervation of murine femora and the effects of denervation of these femora on the cellularity of the femoral bone marrow and the mobilization of the osteo-progenitor stem cells into peripheral blood, that the nervous system has an important role in the selective control of bone marrow cellularity and the denervation leads to decrease in the femoral bone marrow cellularity and mobilization of progenitor cells to the peripheral blood. The study also indicates a possible nervous control of cell proliferation within the bone marrow [23-30].

From results of the hormonal bioassay of blood samples from patients and healthy subjects recruited in this study, we believe that the consistent and statistically significant higher levels of parathyroid hormone and growth hormone, may suggest a possibility of hormonal or neuro-hormonal mechanism to explain accelerated healing of long bone fractures in patients with associated spinal cord injury.

The statistically significant higher level of noradrenaline and adrenaline hormones in patients with long bone fractures only, may reflect a relative inhibition of nerve signaling of the sympathetic nervous system via neuromediators of possible neurotrophins or neuropeptides in spinal cord injury patients with or without long bone fractures. This in turn may lead, according to Afan and others, to mobilization of undifferentiated mesenchymal stem cells and osteoprogenitor cells to peripheral circulation in abundance to induce accelerated abundant healing of long bone fractures, indicating a combined neuro- hormonal mechanism to explain accelerated healing [23,26,30].

The results of normal levels of corticosteroids in spinal cord injury patients with concomitant long bone fractures may again reflect a relative neuronal inhibition of the supra-renal cortex in producing the anti-osteogenic corticosteroids, releasing the inflammatory condition, which is mandatory to bone healing [20].

The statistically significant low blood level of leptin hormone in patients with spinal cord injury and associated long bone fractures may confirm its anti-osteogenic effect due to its down-regulation in the environment of accelerated osteogenesis.

Karsenty, et al. [32] have characterized the mechanism by which leptin regulates bone mass, and they showed that the sympathetic nervous system is the intermediate between leptin and osteoblasts and they, also suggested that B-blockers, drugs that are used routinely to treat high blood pressure, could also help reverse osteoporosis.

We believe that the results of this study, have shed some light on a possible regulatory system of bone healing, and that the bone healing is controlled neuronally and centrally via sympathetic nervous system pathway, through neuromediators of neurotransmitters, neuropeptides, or neurotrophins. Accordingly, we understand that sympatholytic medications as B-blockers and others may enhance bone healing and may have therapeutic potentials in treatment of fracture complications as in delayed union and non-union and also may be used from the very beginning in the treatment of severely open fractures and other complicated fractures, which its clinical and radiological pictures predict high probability for these complications to happen, but this should remain for further experimental research work.

## Conclusion

Our findings from this current study demonstrated that long bone fractures in patients with concomitant spinal cord injuries heal more expectedly, at a faster rate, and with exuberant and florid callus formation compared to patients with long bone fractures only. We can conclude, also that bone healing has a central neuronal control and a combined neuro- hormonal mechanism with a relative inhibition of the sympathetic nervous system may mobilize the undifferentiated mesenchymal stem cells from distant bone marrow to peripheral circulation to home to the fracture site and induce accelerated abundant bone healing in patients with SCI and long bone fractures.

## Acknowledgement

This study was funded “fully” by Kuwait Foundation for the Advancement of Sciences under project code: 2010/1302/04.

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