

## Hypocalcaemia and Its Role in Traumatic Brain Injury

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### Abstract

**Background:** Despite an overabundance of literature the PubMed database has more than 50,000 hits for the search term “traumatic brain injury” the complex area of TBI is actually somewhat overlooked in both medical training and subsequent general medical and neuropsychiatric practice. We pretend to review the available literature on the effects of hypocalcaemia regarding prognosis in early phases after moderate- severe TBI, to identify the gaps in the literature, and to try filling these gaps by including our proposed pathophysiological schema leading to posttraumatic hypocalcaemia.

**Material and methods:** The data from 282 patients (180 retrospective and 102 prospective) suffering moderate-severe TBI distributed in three different works was analyzed. Patients meeting the following criteria were included: Age: 16 to 87 years, Glasgow Coma Scale (GCS) from 3 to 13 points, Cranial Computed Tomography (CCT) upon admission and Calcium and/or ionized calcium measurements taken on the day of TBI, as well as on days 3 and 7.

**Results:** The expectation that non-ionized serum calcium (serum calcium), as seen in the collective of 122 Mexican patients, would be a significant predictive factor regarding TBI was surprisingly, not the case; rather, in the retrospective and prospective German patient collectives, this factor was non-significant. Instead, a more specific calcium measure, namely ionized serum calcium, was significant as a predictor regarding mortality/morbidity in patients suffering TBI.

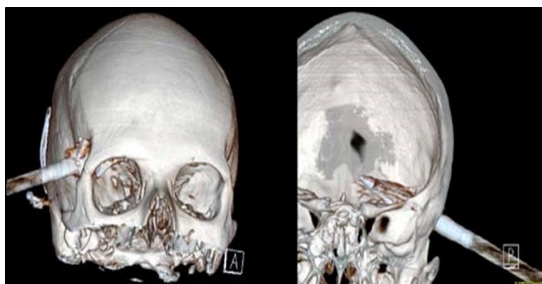
**Conclusion:** Hypocalcaemia is a marker for the depth of brain damage as a result of a cascade of various pathologic mechanisms such as direct mechanical trauma, neuro-inflammation, altered vessel-autoregulation and hypoxia.

### Background

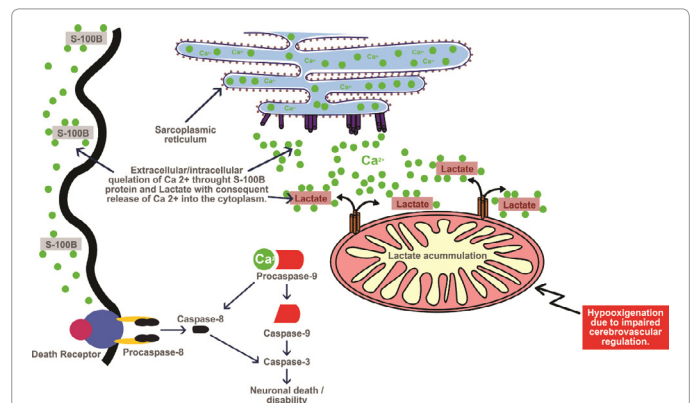
Traumatic brain injury (TBI) is one of the commonest disorders within neuropsychiatry in its widest sense. The incidence of TBI in Germany is approximately 332 per 100 000, in comparison to 182 per 100 000 for strokes [1,2]. Its annual direct and indirect costs amount to roughly 2.5 billion euros [2]. However, despite an overabundance of literature the PubMed database has more than 50 000 hits for the search term “traumatic brain injury” the complex area of TBI is actually somewhat overlooked in both medical training and subsequent general medical and neuropsychiatric practice [3]. Nowadays, answers are missing regarding the diagnosis, prognosis and best possible treatment of traumatic brain injury in its post-acute (Figure 1) and chronic phases.

Traumatic brain injury survivors often suffer from a post-traumatic syndrome with deficits in learning and memory skills [4-6]. Calcium (Ca<sup>2+</sup>) has been implicated in the pathophysiology of induced neuronal death [7-12].

Hypocalcaemia is a hydro-electrolytic disorder distinguished by a serum calcium level of <2.1 mmol/L (8.5 mg/dL) which produces pathophysiological effects. The same occurs as result of a decrease of calcium ionized fraction, with normal levels between 1.10 mmol/L and 1.40 mmol/L (4.4-5.5 mg/dL). Hypocalcaemia could be associated with morbidity and mortality after TBI as a consequence of a reduction of ionized calcium [13-16].



**Figure 1:** Penetrating traumatic brain injury with a shear-blunt object passing through the temporal bone with direct injury to brain tissue.



**Figure 2:** Schematic representation of calcium depletion due to increased chelation to pro-inflammatory molecules/proteins released by injured neurons into the extracellular space after direct trauma leading to a decrease in calcium levels in the intracellular space with consequent Ca<sup>2+</sup> release from the sarcoplasmic reticulum, thereby activating caspases and resulting in cellular death. Notice the lactate production during this process because of disturbances in the aerobic mitochondrial use of ATP with further exacerbation of hypocalcaemia through calcium-lactate chelation.

Two main factors contribute to hypocalcemia in TBI. Mainly, hypocalcemia results from calcium depletion due to increased chelation

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Received May 10, 2017; Accepted May 20, 2017; Published May 25, 2017

**Citation:** Vinas-Rios JM, Sanchez-Rodriguez JJ, Kretschmer T, Medina-Govea FA, Heinen CPG, (2017) Hypocalcaemia and Its Role in Traumatic Brain Injury. J Neurol Disord 5: 342. doi:10.4172/2329-6895.1000342

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Variables	Design	Calcium measurement	n	Outcome
Vinas-Rios et al. [16]	Ambispective	Serum Calcium	122 Retrospective: 81 Prospective: 41	Predictor in mortality in early phase after moderate-severe TBI
Manuel et al. [14]	Retrospective	Ionized serum Calcium	99	Predictor in mortality and severe disability in early phase after moderate-severe TBI
Vinas-Rios et al. [15]	Prospective	Ionized serum Calcium	61	Predictor in mortality and severe disability in early phase after moderate-severe TBI together with protein S-100B and IL-6

**Table 1:** Summary of clinical studies depicting the role of Hypocalcaemia as prognostic factor after moderate-severe TBI.

to pro-inflammatory molecules/proteins released by injured neurons into the extracellular space after direct trauma. This leads to a decrease in calcium levels in the intracellular space with consequent  $Ca^{2+}$  release from the sarcoplasmic reticulum, thereby activating caspases and resulting in cellular death (Figure 2) [17-19]. Moreover, concomitant on-going metabolic acidosis due to impaired post-traumatic intracranial blood vessel regulation contributes to cellular hypo-oxygenation with consequent mitochondrial dysregulation, further disturbing the fine balance by which intracellular calcium activates caspases and intracellular pathways leading to programmed cellular death. Lactate is also produced during this process because of disturbances in the aerobic mitochondrial use of ATP [20,21] with further exacerbation of hypocalcaemia through calcium-lactate chelation (Figure 2). These two processes together lead to a decrease in intracellular calcium with the activation of apoptotic pathways.

The abovementioned pathophysiological mechanisms regarding disturbances in the fine balance between calcium, activating caspases and intracellular pathways leading to programmed cellular death have been demonstrated in canine models [22,23].

The aim of this study was to review the literature on the effects of hypocalcaemia regarding prognosis in early phases after moderate-severe TBI, to identify the gaps in the literature, and to try filling these gaps by including our proposed pathophysiological schema leading to posttraumatic hypocalcaemia.

## Material and Methods

The data from 282 patients (180 retrospective and 102 prospective) suffering moderate-severe TBI distributed in three different works was analysed (Table 1).

Patients meeting the following criteria were included:

1. Age: 16 to 87 years.
2. GCS from 3 to 13 points.
3. Cranial Computed Tomography (CCT) upon admission.
4. Calcium and/or ionized calcium measurements taken on the day of TBI, as well as on days 3 and 7.

The following findings were cause for a patient to be excluded:

1. TBI older than 3 days.
2. Intake of medication or diseases affecting calcium metabolism.
3. Lesions in the brainstem as an isolated finding.
4. Previous treatment at another department.
5. Pregnancy.
6. Hyperphosphatemia ( $>1.32$  mmol/L).
7. Hypomagnesemia ( $<0.61$  mmol/L).
8. Alcoholism.

9. Hypoalbuminemia.

10. Disability prior to TBI.

## Results

An ambispective study including a total of 122 Mexican patients suffering from moderate/severe TBI, which showed significantly lower serum calcium levels on the third day of admission between the survivors and non-survivors patients after moderate/severe TBI significant levels (p-value 0.026) with an OR of 5.2 (CI 95%, 4.48 to 6.032) and an OR in the logistic regression analysis of 3.5 (CI 95% 1.12 to 13.61) [16]. However, morbidity was not assessed.

A retrospective study developed by Manuel et al. compiled data from 99 German patients suffering moderate and severe TBI. Significant difference was found in ionized serum calcium levels on the third day of admission between patients with a Glasgow Outcome Score (GOS)  $\leq 3$  and  $>3$  (disability/death) in ionized serum calcium levels on day three (p $<0.008$ ). According to this result, the lower calcium levels were correlated with the group with the worse outcome (GOS  $\leq 3$ ). The best logistic regression model in this study included: absent pupillary reactivity, hypocalcaemia of ionized serum calcium ( $<1.10$  mmol/L) on day three and serum sodium dysregulation on day seven. These variables substantiated poor Glasgow Outcome Scores in 28.08% ( $R^2=0.2808$ , p $<0.0002$ ) [14].

The majority of the patients with Glasgow Outcome Score $>3$  had normal values of serum ionized calcium on third day; therefore, maximum specificity was at the level of 1.28 mmol/L. The cut-off for higher sensitivity (83.76%) and specificity (66.66%) of serum ionized calcium on third day was at the level of 1.11 mmol/L [14].

The authors noticed that the value of 0.95 mmol/L of serum ionized calcium on the third day following trauma was associated with death or moderate/severe disability in all patients (sensitivity: 100%, PNV=1). Another crucial value was at the level of 1.06 mmol/L with a sensitivity of 94% (PNV=0.77). Moreover they calculated an Odds Ratio (OR) of 6.6 (95% CI: 2.28-40.36) (p $<0.0009$ ) for the association of hypocalcaemia of serum ionized calcium ( $<1.10$  mmol/L) on third day and the disability/death group [14].

However, the retrospective data collection limited the validity of the findings because of possible inherent bias. This possibly could be attributed to diverse primary clinical documentation or inconsistencies in data registration.

In a prospective study developed by Vinas-Rios et al. the importance of calcium regarding prognosis in mortality-morbidity after moderate-severe TBI in 61 German patients who suffered moderate and severe TBI could be assessed again [15]. This time the serum levels of ionized calcium on day three was empowered with Protein S100 b and IL6 also on day three as part of the theory that calcium is diminished due to neuro- and systemic-inflammation. They calculated a Relative Risk (RR) of 3.14 (95% CI: 2.49-3.78) (0.05) for the association of hypocalcaemia of serum ionized calcium ( $<1.10$  mmol/L) on third day and the Disability/Death group [15].

The best logistic regression model included: age, absent pupillary reactivity, hypocalcaemia of ionized serum calcium (<1.10 mmol/L), Protein S100 b and IL6 on day three. These variables substantiated poor Glasgow Outcome Scores in 34.08% ( $R^2=34.3\%$ ,  $p=0.001$ ). Age is a well-known factor for unfavorable outcome in patients suffering TBI, being significant in this study ( $p=0.001$ ) between studied groups. Nevertheless, serum ionized calcium was an independent finding regarding age and therefore considered as potential selection bias [15].

According to the hypothesis that proinflammatory proteins and molecules may be the cause of hypocalcaemia after TBI, protein S-100B (a marker of neuronal damage) and IL-6 (a pro-inflammatory cytokine) levels upon admission, day 3 and 7 after TBI was assessed, being significant ( $p=0.002$  and  $p=0.007$  respectively) between studied groups on day three after TBI [15].

## Discussion

The expectation that non-ionized serum calcium (serum calcium), as seen in the collective of 122 Mexican patients, would be a significant predictive factor regarding TBI was surprisingly, not the case; rather, in the retrospective and prospective German patient collectives, this factor was non-significant. Instead, a more specific calcium measure, namely ionized serum calcium, as this form interacts with intracellular cellular death signaling pathways and may serve as a prognostic factor, was significant as a predictor regarding mortality/morbidity in patients suffering TBI.

The overall results between the two patient collectives (retrospective and prospective) were strikingly very similar, and each study supported the other. The clinically relevant factors in these studies in patients with a poor outcome were monovalent cations such as sodium and potassium on day 7 after TBI and pH on day 3 [14,15]; the latter supports the theory of metabolic acidosis due to mitochondrial dysfunction and consequent lactate accumulation, disrupting the fine balance of intracellular calcium activating programmed cellular death (Figure 2). This was likely significant only in the prospective phase probably due to more controlled and accurate manner of data collection.

In the collective of 160 German patients, non-ionized serum calcium alone was not significant regarding mortality/morbidity [15,24], as seen in the study on 122 patients from the Mexican population. Back then, the authors evaluated only mortality (and not morbidity) and ionized calcium was not assessed [16].

Furthermore, the patient collective from the German population in comparison with the Mexican collective were treated with different health standards and treatment quality in a completely different context, i.e., in a hospital and a health care system in a first world country. It is quite likely that German patients who have a severe disability after surviving a critical health condition that could cost their lives (such as moderate/severe TBI) has not concluded in a fatal outcome thanks to complex treatment in the ICU. If these patients had been treated in the Mexican health care system, i.e., in a developing country with deficiencies and financial shortcomings associated with the treatment of critical patients, such as those with moderate/severe TBI, the trauma could have been fatal.

Nevertheless, despite the expectations, in the German collective of 160 patients, there were 17 deaths (10.6%) while in the collective of 122 Mexican patients; there were 9 (7.3%) deaths [14-16]. Outcomes regarding morbidity (severe disability) between these two collectives were not analyzed. Nonetheless, the overall death rates provide a rough estimation of outcomes, and were comparable in the two patient collectives.

In support of these results and in order to clarify this rough approximation, a more advanced and sensitive method of calcium measurement (ionized serum calcium) was assessed. This measure is quicker and easier to assess and plays a more important role regarding the intracellular biomolecular signaling processes in programmed cell death. The correlation with hypocalcaemia in ionized serum calcium in the collective of 160 German patients was striking: over 95% (70/73) of the patients with GOS scores  $\leq 3$  and with low ionized calcium died or had a poor outcome with severe disability, while in the collective of Mexican patients, 8 of the 9 patients (88.8%) who presented hypocalcaemia in non-ionized serum calcium on day 3 after trauma died. Findings like this should alert physicians treating patients suffering from moderate/severe TBI.

Changes in the epidemiological patterns of TBI show that the median age of individuals who experience TBI is increasing, and falls have now surpassed road traffic incidents as the leading cause of this injury in developed countries [24]. Age is a well-known factor predisposing to unfavorable outcomes in patients with TBI [25]. Elderly TBI patients, in general, have a deteriorated medical condition before injury, compared to younger adults. Other aging-related changes include cerebrovascular atherosclerosis and decreased free radical clearance [26]. This deficiency in free radical clearance could increase the risk of injury or cause a secondary insult, thereby activating neuronal programmed death. As seen in the prospective study results [15] and according to global trends, most of the patients included in that work were older than 65 years of age at the time of TBI. These patients more often had a severe disability or even died ( $GOS \leq 3$ ). This findings could lead to a selection bias as elderly people tend to have worse outcomes overall, mainly due to a deteriorated medical condition and deficient free radical clearance with the accumulation of pro-inflammatory proteins/cytokines that activate cellular death following TBI [26].

Referent to markers in serum the S100 b protein, has gained weight to be a marker together with the clinical parameters such as grade of trauma and associated lesions for the evaluation in the degree of brain injury following trauma. In TBI the expression of S100 is upregulated and therefore could be responsible for hypocalcaemia by elevated calcium binding [19,27].

In addition, prompt and adequate treatment regimens, such as maintaining adequate cerebral blood perfusion [13,28], avoiding large disturbances in serum glucose levels and neurosurgical procedures (decompressive hemicraniectomy or craniotomy with evacuation of an acute subdural or epidural hematoma) taking into account the host defense reaction, may improve oxygen delivery at the neuronal level and influence S100B and pro-inflammatory cytokines release, thereby preventing the cascade of damage leading to inflammation and disturbances in fine intracellular calcium equilibrium, particularly in the aerobic mitochondrial phase, which would decrease  $Ca^{2+}$  concentrations, activate caspases and consequently lead to cellular death [18,19,29].

Another marker that depicts the grade of neuro-inflammation and regulates the liberation of S-100 protein with consequent calcium binding is the cytokine Interleukin-6 (IL-6) [18]. This interleukin acts as a pro-inflammatory cytokine. It is secreted by T cells and macrophages and stimulates the immune response during infection and after trauma, especially with tissue damage, and thereby promotes inflammation. It is capable of crossing the blood-brain barrier and stimulating the synthesis of acute phase proteins such as tumor necrosis factor alpha (TNF- $\alpha$ ) [30,31]. IL-6 can be used as an indirect indicator of the liberation of S100B and therefore  $Ca^{2+}$  chelation [15].

## Conclusion

In conclusion, hypocalcaemia is a marker for the depth of brain damage after TBI as a result of a cascade of various pathologic mechanisms such as direct mechanical trauma, neuro-inflammation, altered vessel-auto-regulation and hypoxia. Hypocalcaemia looks like being an epiphenomenon of several factors and seems to play a role as prognosticator, however, not as leverage point for therapy. Calcium administration has not been proven yet to have a potential influence in neuronal death.

## Conflict of Interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

## Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

## Informed Consent

Informed consent was obtained from all individual participants included in the studies.

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