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ORIGINAL ARTICLE

Alcohol consumption affects the late endocrine consequences of mild traumatic brain injury

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Abstract

BACKGROUND: Currently there are no widely applied methods which could identify, at the time of head trauma, those mild traumatic brain injury (mTBI) patients who later develop pituitary dysfunction. The effect of alcohol consumption on post-TBI endocrine dysfunction is unclear.

METHODS: Five hundred and eight TBI patients, 406 of them with mTBI, were studied. Sixty-one patients (46 males, 15 females) were available for follow-up. Admission serum samples were evaluated for S100B protein and markers of alcohol consumption: ethanol level for day-of-injury intake and carbohydrate deficient transferrin (CDT) level for regular alcohol consumption. Regular alcohol consumption was defined as CDT > 1.5%, including both social and heavy drinkers. Admission and one-year follow-up samples were evaluated for pituitary dysfunction.

RESULTS: Newly developed pituitary hormone deficiency was found in 16% of mTBI patients. When cohorts developing and not developing late pituitary dysfunction were compared, 30% and 69% of patients were regular alcohol consumers, respectively ($p = 0.02$). Neither S100B level nor day-of-injury alcohol consumption was predictive of late pituitary dysfunction.

CONCLUSION: The findings of this preliminary study suggest that regular alcohol consumption may protect against the late endocrine consequences of mTBI. Alcohol intake during the weeks preceding mTBI may identify patients at higher risk for late pituitary dysfunction.

Abbreviations:

ACTH	- adrenocorticotropic hormone
CDT	- carbohydrate deficient transferrin
ECLIA	- electrochemiluminescence immunoassay
FSH	- follicule-stimulating hormone
fT4	- free thyroxine
GC	- gas chromatography
GCS	- Glasgow Coma Scale
GGT	- gamma-glutamyl-transferase
GH	- growth hormone
IGF-1	- insulin like growth factor-1
IQR	- interquartile range
LH	- luteinizing hormone
MCV	- mean corpuscular volume
mTBI	- mild traumatic brain injury
NMDAr	- N-methyl-D-aspartic acid receptors
PAI-1	- plasminogen activator inhibitor type 1
SD	- standard deviation
TBI	- traumatic brain injury
TSH	- thyroid stimulating hormone

INTRODUCTION

Traumatic brain injury (TBI) is a major public health concern (Langlois *et al.* 2004). Around 90% of TBI are mild (mTBI) (World Health Organisation, 2006). Despite the high Glasgow Coma Scale (GCS) score of patients with mTBI, severe complications such as fractures and intracranial bleeding as well as permanent impairments, including late pituitary dysfunction, may occur in these patients (Bondanelli *et al.* 2004; Vos *et al.* 2012). After mTBI 15 to 30% of patients may develop permanent pituitary dysfunction (Bondanelli *et al.* 2004; Schneider *et al.* 2007; Tanriverdi *et al.* 2010). This endocrine condition can be detected based on signs and symptoms, while milder cases are to be screened 3 or 6 months and one year after mTBI (Tanriverdi *et al.* 2010). Currently, there are no widely applied methods in clinical practice which could identify, at the time of head trauma, those patients with mTBI who develop pituitary dysfunction 6 to 12 months later.

In TBI, 35-81% of the injured patients are alcohol-intoxicated at the time of injury and 42% of the patients with TBI have a heavy drinking history before injury (Corrigan, 1995). There is a strong correlation between acute alcohol intoxication and injury severity in patients with TBI (Pories *et al.* 1992) but the effects of alcohol on the outcome of those surviving the field and arriving at the hospital is less clear. Some clinical and animal studies seem to suggest a beneficial effect of alcohol on TBI outcome (Lin *et al.* 2014; Opreanu *et al.* 2010; Porter, 2000). Beside the direct measurement of ethanol in blood or serum, there are indirect markers of alcohol consumption e.g. mean corpuscular volume (MCV) of red blood cells, serum gamma-glutamyl-transferase (GGT) and carbohydrate deficient transferrin (CDT) (Andresen-Streichert *et al.* 2018). CDT is an indicator for chronic alcohol abuse. People who drink to excess will typically have a higher proportion of transferrin in the carbohydrate deficient form (Stibler, 1991), which allows of the estimation of alcohol consumption of the past 1-3 weeks (Jeppsson *et al.* 1993). The effect of alcohol intake (acute or chronic) on the development of late pituitary dysfunction after mTBI has not been thoroughly studied. S100B is a calcium binding protein of the astrocytes, its level raises in biological fluids following active neural distress (Michetti *et al.* 2018). S100B has been extensively studied in TBI as a biomarker for neurological outcome (Mercier *et al.* 2013; Undén and Romner, 2010), but not for the development of late pituitary dysfunction.

In this study, markers of acute and chronic alcohol consumption, i.e., serum alcohol and CDT levels, respectively, as well as serum S100B concentrations were measured in patients with mTBI at the time of injury to assess whether these factors might predict late pituitary dysfunction.

MATERIALS AND METHODS

Patients with TBI (n=508) were enrolled in the study (Figure 1). The study protocol was reviewed and approved by the Regional and Institutional Ethics Committee of the University of Debrecen, approval number: 2977-2009. Written informed consent was obtained from all patients.

Serum and citrated plasma samples were collected from the patients at the time of admission, immediately on presentation to our trauma bay. Samples of the 406 patients diagnosed with mTBI were evaluated, and 116 of them were available for follow-up. Patients under the age of 17 (n=7) or with unknown/long (> 24 hours) time between injury and sample collection (n=15), with repeated head trauma (n=3), known endocrine dysfunction (n=30), stroke (n=2), and brain surgery (n=2) or irradiation of the head and neck region in the past (n=1) were excluded from the study. Follow-up blood samples were collected from those patients who were available for follow-up 6 to 12 months post-injury. All patients with mTBI were evaluated for pituitary function at presentation immediately after admission for TBI and 6 to 12 months after mTBI (for those who were available for follow up). Samples were stored at -70°C until analysed for hormones, S100B, CDT, and serum ethanol levels.

Serum insulin like growth factor-1 (IGF-1), cortisol, S100B and plasma adrenocorticotropic hormone (ACTH) concentrations were measured using chemiluminescence immunoassay (DiaSorin S.p.A., Saluggia, Italy). Serum thyroid stimulating hormone (TSH) and free thyroxine (fT4) concentrations were measured using electrochemiluminescence immunoassay (ECLIA) (Roche Diagnostics GmbH, Mannheim, Germany). Serum follicle-stimulating hormone (FSH), luteinizing hormone (LH) and testosterone levels were measured using ECLIA (Roche Diagnostics GmbH, Mannheim, Germany). Our screening criteria were based on measurements of pituitary hormones simultaneously with their respective regulated endocrine

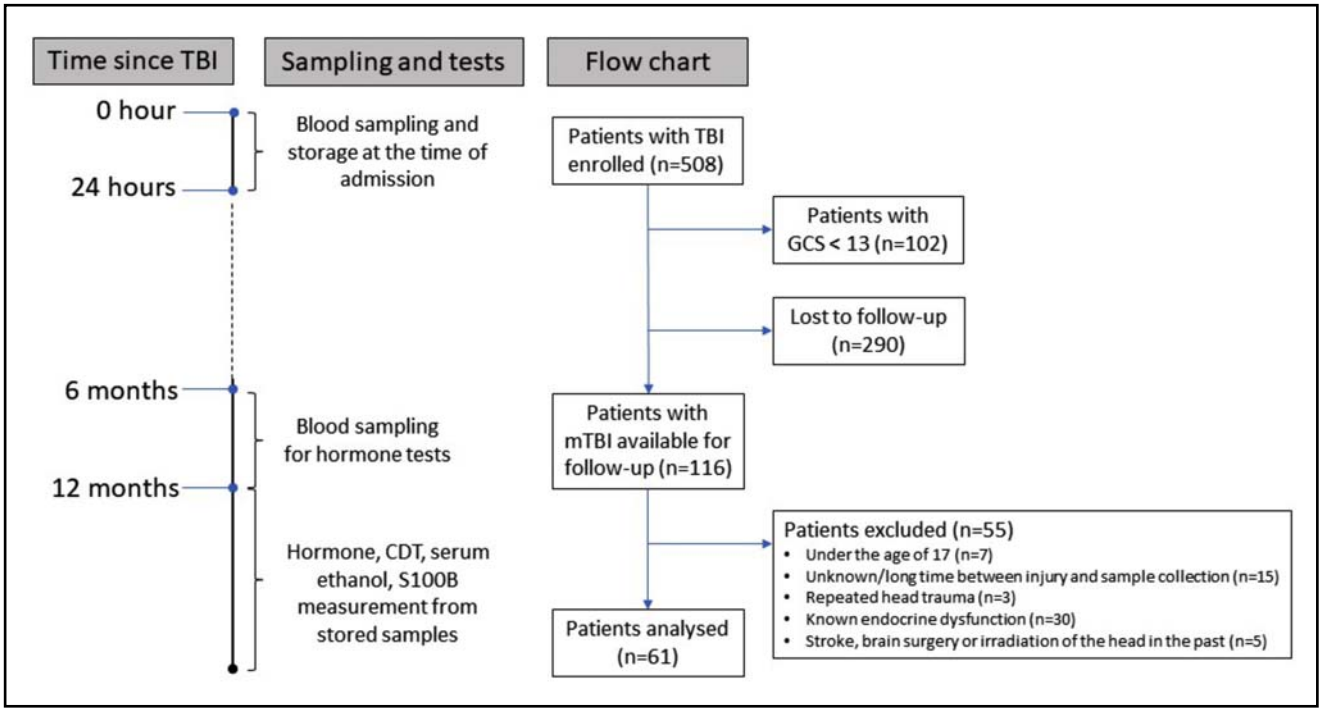

Fig. 1. Study timetable and flow chart.
CDT – carbohydrate deficient transferrin, GCS – Glasgow Coma Scale, mTBI – mild traumatic brain injury

gland hormones, for gonadal, adrenal and thyroid deficiencies, and IGF-1 for growth hormone (GH) deficiency. Pituitary dysfunction was defined as any of the target organ hormones (testosterone, cortisol or fT4) below normal range with the respective pituitary hormone (FSH, LH, ACTH or TSH) in or below normal range. Subnormal age-adjusted IGF-1 was considered dysfunction in any constellation. Normal ranges of hormone levels were defined as follows: testosterone (men): 9.9-27.8 nmol/l, cortisol: 138-690 nmol/l, fT4: 12-22 pmol/l, FSH men: 1.5-12.4 IU/l, FSH women: 1.7-25 IU/l, LH men: 1.7-8.6 IU/l, LH women: 1-85 IU/l, ACTH: 0-75 ng/l, TSH: 0.3-4.2 mU/l. Separate ranges of FSH and LH for pre- and postmenopausal women were used.

Serum CDT was measured by latex-enhanced immuno-nephelometry (Siemens Healthineers, Erlangen, Germany). CDT was expressed as fraction (%) of the total transferrin. Patients with CDT level above 2.5% and between 1.5 and 2.5% were considered heavy drinkers and social drinkers, respectively (Hock *et al.* 2005). Serum transferrin level was measured using an immuno-turbidimetric assay (Roche Diagnostics GmbH, Mannheim, Germany).

Serum ethanol was measured by gas chromatography (GC). Serum ethanol level > 10 mg/dL was considered as proof of alcohol exposure in the last 24 hours.

Statistical analysis was performed by STATISTICA (Statsoft Inc. Tulsa, OK, USA). The distribution of continuous variables was checked by the Kolmogorov–Smirnov test. To compare continuous variables between groups, for normal distributed data, t-test was applied, while for non-normal distributed data Mann-Whitney U test was used. Results were expressed as mean ± standard deviation (SD) in case of normal distributions, or median and interquartile range (IQR) in case of non-normal distributions. The stochastic relationships of discrete variables were analysed by Chi-square test.

RESULTS

Of the 406 patients with mTBI 61 were available for follow-up after the exclusion criteria were applied. The characteristics of the patients are shown in Table 1. Ten out of 61 patients (16%) had pituitary deficiency during the follow-up endocrine screening: 4 patients had GH deficiency, 3 patients had gonadotropin deficiency, and 2 patients had TSH deficiency. One patient had involvement of 2 hormonal axes (combined gonadotropin and TSH deficiency). Patients with deficiency were younger ($p = 0.03$) at the time of mTBI than patients without it, and men were less susceptible to late pituitary deficiency ($p = 0.04$) than women (Table 2). Neither the cause nor the complications (intracranial bleeding, skull fracture, neurosurgery) of mTBI identified patients prone to late pituitary dysfunction (Table 2).

Markers of alcohol consumption, i.e. serum ethanol level and CDT, were examined at the time of admission: 36% of patients had measurable amount of ethanol in their serum ranging from 33 mg/dL to 287 mg/dL. Detectable serum ethanol levels, i.e. acute pre-injury alcohol consumption was not significantly different in groups with and without acquired pituitary dysfunction

Tab. 1. Characteristics of the study population (n=61)

Age (years); mean ± SD, min-max	44 ± 19, 17 – 81
Sex, male/female	46/15
Cause of TBI, n (%)	
Fall	32 (52)
Motor vehicle accident	19 (31)
Other/unknown	10 (17)
TBI Severity, n (%)	
GCS = 15	50 (82)
GCS = 14	6 (10)
GCS = 13	5 (8)
Neurosurgery intervention, n (%)	3 (5)
Intracranial bleeding, n (%)	15 (25)
Skull fracture, n (%)	25 (41)
Time to initial blood sampling after injury (hours); median (IQR), min-max	3.5 (2.0-6.0), 1.0 – 24.0
Time to follow-up blood sampling after injury for hormone tests (months); median (IQR), min-max	7.5 (7.0-9.5), 6.0 – 12.0

GCS – Glasgow Coma Scale, IQR – interquartile range, SD – standard deviation, TBI – traumatic brain injury

(Table 2). On the other hand, CDT levels had been significantly lower ($p = 0.02$) in patients who later developed pituitary deficiency, compared to patients with normal pituitary function during follow-up (Figure 2).

Heavy (CDT level above 2.5%) and social (CDT level between 1.5–2.5%) alcohol consumptions together were more frequent in the group with normal pituitary function (Table 2).

Day-of-injury alcohol consumption was more prevalent in regular drinkers, i.e. in the group of patients with CDT level above 1.5%, than in patients with CDT level below or equal to 1.5% (53% vs 9%, $p < 0.001$). Neither acute nor chronic pre-injury alcohol consumption differed in groups with distinct injury severity ($p = 0.2$ for both), based on computer tomography findings (negative or not performed, positive without midline shift, and positive with midline shift).

There was no difference in the level of serum S100B protein between patients with and without pituitary dysfunction (Table 2). Further, S100B was not different in groups with distinct computer tomography findings ($p = 0.1$). No correlation was found between S100B level and serum alcohol concentration ($p = 0.8$) or S100B and CDT levels ($p = 0.7$).

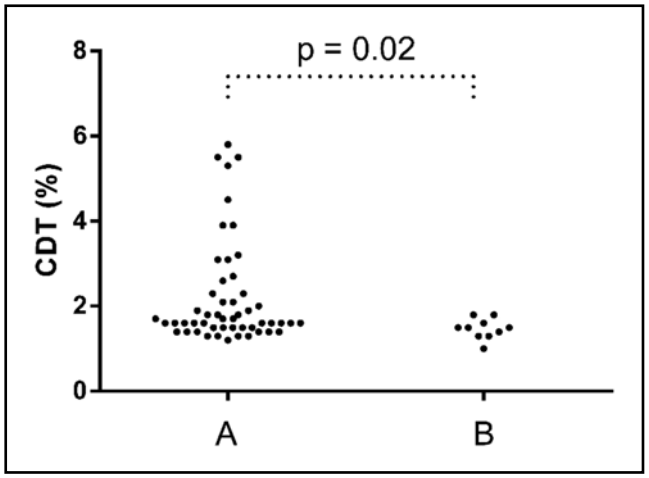

Fig. 2. Carbohydrate deficient transferrin (CDT) levels of patients with mild traumatic brain injury (mTBI) who did not (A) and did (B) develop pituitary dysfunction during follow up. GCS – Glasgow Coma Scale

DISCUSSION

Acute alcohol intoxication is common in TBI (Parry-Jones *et al.* 2006), and may affect the morbidity and mortality associated with head trauma (Corrigan, 1995; Lin *et al.* 2014; Opreanu *et al.* 2010; Pories *et al.* 1992; Porter, 2000). Clinical studies assessing acute or late effects of acute or chronic pre-injury alcohol consumption, including functional outcomes in patients with TBI, have shown no consistent results. The majority of these studies have focused on moderate to severe TBI (Alexander *et al.* 2004; De Guise *et al.* 2009; Kaplan & Corrigan, 1992; Lange *et al.* 2008; Ponsford *et al.* 2013; Schutte and Hanks, 2010; Wilde *et al.* 2004). Further, the findings have varied with the types of outcomes examined. Up till now, the impact of alcohol consumption on the development of late pituitary dysfunction following mTBI has not been studied.

We found that 36% of patients with mTBI had measurable level of alcohol in their serum at the time of admission. This pre-injury alcohol intoxication did neither affect injury severity nor the prevalence of late pituitary dysfunction.

Chronic alcohol intake biomarkers remain positive in blood for a more prolonged time period (Fleming *et al.* 2009). CDT is the most specific laboratory marker of chronic alcohol abuse, therefore, for evaluation of pre-injury long-term alcohol intake, we measured serum CDT. CDT is a transferrin that lacks one or two complete carbohydrate side-chains or show incomplete side-chains (Arndt, 2001). Since alcohol affects the enzymes that regulate transferrin glycosylation, an alcohol intake of 50-80 g daily for at least one week results in a rise in CDT (Stibler, 1991). CDT normalizes within several weeks of abstinence (Stibler, 1991). Chronic consumption of small amounts of alcohol (up to 20 g/day) increases CDT levels within the normal range, while short-term intake of large amounts does not (Whitfield *et al.* 1998). In addition to alcohol consumption, rare congenital disorders of glycosylation and severe liver disease may also result in increased levels of CDT (Arndt, 2001).

Patients with CDT levels below 1.5%, i.e. those who did not consume alcohol regularly, were more likely to develop late pituitary dysfunction after mTBI. Our data suggest that regular alcohol consumption leading

Tab. 2. Characteristics of the patients without and with late pituitary deficiency

Late pituitary deficiency after mTBI (n)	Absent n =51	Present n=10	*p*
Known pituitary deficiency in medical history	no	no	
Age (years), mean ± SD, min - max	46 ± 18, 17 - 81	32 ± 18, 17 - 68	0.03
Sex, male/female	41/10	5/5	0.04
Cause of TBI, n (%) fall motor vehicle accident other/unknown	 26 (51) 17 (33) 8 (16)	 6 (60) 2 (20) 2 (20)	0.7
Severity of TBI, n (%) GCS = 15 GCS = 14 GCS = 13	 42 (82) 6 (12) 3 (6)	 8 (80) 0 (0) 2 (20)	0.2
Neurosurgery procedure performed, n (%)	3 (6)	0 (0)	0.4
Intracranial bleeding, n (%)	14 (28)	1 (10)	0.2
Skull fracture, n (%)	21 (41)	4 (40)	0.9
Time to initial blood sampling after injury (hours); median (IQR), min - max	3.5 (2.3-6.0), 1.0 – 24.0	3.5 (1.0-5.0), 1.0 – 12.0	0.5
Time to follow-up blood sampling after injury for hormone tests (months); median (IQR), min-max	7.5 (7.0 – 9.5), 6.0 – 12.0	7.5 (7.0 – 10.0), 6.5 – 10.5	0.9
S100B (μg/l); median (IQR), min - max	0.36 (0.16-0.88), 0.05 – 7.13	0.23 (0.14-1.89), 0.05 – 8.17	0.8
Acute alcohol consumption; serum ethanol > 10 mg/dL, n (%)	21 (41)	1 (10)	0.07
CDT, median (IQR), min - max	1.6 (1.5-2.3), 1.2 – 5.8	1.5 (1.3-1.6), 1.0 – 1.8	0.02
Heavy drinkers; CDT > 2.5%, n (%)	12 (24)	0 (0)	0.09
Social drinkers; CDT > 1.5 and ≤ 2.5%, n (%)	23 (45)	3 (30)	0.4
Heavy and social drinkers combined; CDT > 1.5%, n (%)	35 (69)	3 (30)	0.02

CDT – carbohydrate deficient transferrin, GCS – Glasgow Coma Scale, IQR – interquartile range, mTBI – mild traumatic brain injury, SD – standard deviation

to higher CDT levels may protect against late pituitary dysfunction after mTBI. Both heavy and social drinking were protective in this regard. Injury severity of the patients with high and low CDT levels was not different.

The majority of clinical studies have indicated beneficial effects of pre-injury acute alcohol consumption on short-term outcomes, complications or mortality during acute care, while studies examining functional outcomes following TBI in patients with acute or chronic alcohol intake show mixed results (Taylor & Sutton, 2015). The mechanism behind the putative beneficial effect of regular alcohol intake on endocrine outcome in the present series of patients with mTBI is unknown. Various mechanism have been suggested for neuroprotective effects of alcohol, including inhibition of N-methyl-D-aspartic acid receptors (NMDAr) or sympathetic response (Opreanu *et al.* 2010). A major aim of TBI management is to reduce the secondary brain injury and protect the brain from ischemia. Several medications such as sedatives, mannitol and hypertonic saline are used in the treatment of increased intracranial pressure caused by TBI (Alnemari *et al.* 2017); we suspect that the diuretic effect of alcohol may contribute to its protective effect.

We have shown earlier that higher plasminogen activator inhibitor type 1 (PAI-1) levels may protect against pituitary dysfunction (Frendl *et al.* 2017). Both alcohol (van de Wiel *et al.* 2001) and PAI-1 are inhibitors of fibrinolysis, which may point to a common background of their protective effect.

In addition to pre-injury acute and chronic alcohol intake, the potential role of the astrocyte-derived S100B protein level in prediction of late pituitary dysfunction after mTBI was examined. The concentration of S100B raises following brain injury due to its release from astrocytes through the disrupted blood-brain barrier, and can be used as a screening, monitoring and prediction tool in the management of patients with TBI (Thelin *et al.* 2017). Neurotoxic effects of chronic alcohol abuse can also increase the serum level of S100B protein (Liappas *et al.* 2006). In our study,

S100B levels of patients with mTBI did not correlate with the severity of brain injury or with CDT levels, and S100B protein level did not differ between groups of patients with or without late pituitary dysfunction.

One major limitation of our prospective study is the low number of patients available for long-term follow-up. This, however, is a general issue with trauma patients as they are often lost to long-term follow-up. This, on the other hand, enhances the value of a predictive biomarker measured at the time of admission. CDT may be useful for the prediction of pituitary dysfunction that may require treatment 6-12 months later. Such powerful tool could also increase patient compliance for follow-up as they could be specifically forewarned about these subsequent health issues. Another limitation is the criteria applied in this study to define pituitary dysfunction. Normal or low pituitary hormones with their respective target gland hormones below normal range, or subnormal age-adjusted IGF-1 level, are not diagnostic but screening tools which can identify patients who require more detailed endocrine testing. Third, the lack of effect of one-time acute alcohol consumption may have been related to the small size of the patient cohort. Further, the number of alcohol intoxicated patients at the time of injury may have been underestimated since the median time interval between injury and blood sampling at admission was 3.5 hours (Table 1); acute blood alcohol levels fall at a rate of 15 mg/dL per hour due to the rapid metabolic clearance of alcohol from blood (Paton, 2005). The individual rate of alcohol metabolism is a major confounding factor in studies where pre-injury acute alcohol consumption is verified by laboratory methods at the time of admission. The type of alcohol consumed was not surveyed, therefore a conclusion cannot be drawn regarding this from our results.

In summary, we have shown for the first time that chronic alcohol exposure, both social and heavy drinking, has favourable impact on late endocrine outcome in patients with mTBI. Patients with complete abstinence for 2-4 weeks pre-injury are more prone to pituitary dysfunction after mTBI. Drinking habits of the patients in the last month before mTBI may identify subgroups of patients at higher risk for post-injury pituitary dysfunction. Subsequent studies with larger patient cohorts will be required to confirm our preliminary findings.

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CONFLICT OF INTEREST

Authors have no financial interests in this manuscript and no affiliations (relationships) to disclose.

REFERENCES

1 Alexander S, Kerr ME, Yonas H, Marion DW (2004) The effects of admission alcohol level on cerebral blood flow and outcomes after severe traumatic brain injury. J Neurotrauma. **21**(5): 575–83.
2 Alnemari AM, Krafcik BM, Mansour TR, Gaudin D (2017) A Comparison of Pharmacologic Therapeutic Agents Used for the Reduction of Intracranial Pressure After Traumatic Brain Injury. World Neurosurg. **106**: 509–28.
3 Andresen-Streichert H, Müller A, Glahn A, Skopp G, Sterneck M (2018) Alcohol Biomarkers in Clinical and Forensic Contexts. Dtsch Arztebl Int. **115**(18): 309–15.
4 Arndt T (2001) Carbohydrate-deficient transferrin as a marker of chronic alcohol abuse: a critical review of preanalysis, analysis, and interpretation. Clin Chem. **47**(1): 13–27.
5 Bondanelli M, De Marinis L, Ambrosio MR, Monesi M, Valle D, Zatelli MC et al. (2004) Occurrence of pituitary dysfunction following traumatic brain injury. J Neurotrauma. **21**(6): 685–96.
6 Corrigan JD (1995) Substance abuse as a mediating factor in outcome from traumatic brain injury. Arch Phys Med Rehabil. **76**(4): 302–9.
7 De Guise E, Leblanc J, Dagher J, Lamoureux J, Jishi AA, Maleki M et al. (2009) Early outcome in patients with traumatic brain injury, pre-injury alcohol abuse and intoxication at time of injury. Brain Inj. **23**(11): 853–65.
8 Fleming M, Bhamb B, Schurr M, Mundt M, Williams A (2009) Alcohol biomarkers in patients admitted for trauma. Alcohol Clin Exp Res. **33**(10): 1777–81.
9 Frendl I, Katko M, Galgoczi E, Boda J, Zsiros N, Nemeti Z et al. (2017) Plasminogen Activator Inhibitor Type 1: A Possible Novel Biomarker of Late Pituitary Dysfunction after Mild Traumatic Brain Injury. J Neurotrauma. **34**(23): 3238–44.
10 Hock B, Schwarz M, Domke I, Grunert VP, Wuertemberger M, Schiemann U et al. (2005) Validity of carbohydrate-deficient transferrin (%CDT), gamma-glutamyltransferase (gamma-GT) and mean corpuscular erythrocyte volume (MCV) as biomarkers for chronic alcohol abuse: a study in patients with alcohol dependence and liver disorders of non-alcoholic and alcoholic origin. Addiction. **100**(10): 1477–86.
11 Jeppsson JO, Kristensson H, Fimiani C (1993) Carbohydrate-deficient transferrin quantified by HPLC to determine heavy consumption of alcohol. Clin Chem. **39**(10): 2115–20.
12 Kaplan CP and Corrigan JD (1992) Effect of blood alcohol level on recovery from severe closed head injury. Brain Inj. **6**(4): 337–49.
13 Lange RT, Iverson GL, Franzen MD (2008) Effects of day-of-injury alcohol intoxication on neuropsychological outcome in the acute recovery period following traumatic brain injury. Arch Clin Neuropsychol. **23**(7–8): 809–22.
14 Langlois JA, Rutland-Brown W, Thomas KE, National Center for Injury Prevention and Control (U.S.). Division of Injury and Disability Outcomes and Programs. (2004) Traumatic brain injury in the United States : emergency department visits, hospitalizations, and deaths. Atlanta, Ga.: Dept. of Health and Human Services, Centers for Disease Control and Prevention, Division of Acute Care, Rehabilitation Research and Disability Prevention, National Center for Injury Prevention and Control.
15 Liappas I, Tzavellas EO, Kariyannis C, Piperi C, Schulpis C, Papassotiriou I et al. (2006) Effect of alcohol detoxification on serum S-100B levels of alcohol-dependent individuals. In Vivo. **20**(5): 675–80.
16 Lin HL, Lin TY, Soo KM, Chen CW, Kuo LC, Kin YK et al. (2014) The effect of alcohol intoxication on mortality of blunt head injury. Biomed Res Int. **2014**: 619231.
17 Mercier E, Boutin A, Lauzier F, Fergusson DA, Simard JS, Zarychanski R et al. (2013) Predictive value of S-100β protein for prognosis in patients with moderate and severe traumatic brain injury: systematic review and meta-analysis. BMJ. **346**: f1757.

18 Michetti F, D'Ambrosi N, Toesca A, Puglisi MA, Serrano A et al. (2018) The S100B story: From biomarker to active factor in neural injury. J Neurochem. **148**(2): 168–84.
19 Opreanu RC, Kuhn D, Basson MD (2010) Influence of alcohol on mortality in traumatic brain injury. J Am Coll Surg. **210**(6): 997–1007.
20 Parry-Jones BL, Vaughan FL, Miles Cox W (2006) Traumatic brain injury and substance misuse: a systematic review of prevalence and outcomes research (1994-2004). Neuropsychol Rehabil. **16**(5): 537–60.
21 Paton A (2005) Alcohol in the body. BMJ. **330**(7482): 85–7.
22 Ponsford J, Tweedly L, Taffe J (2013) The relationship between alcohol and cognitive functioning following traumatic brain injury. J Clin Exp Neuropsychol. **35**(1): 103–12.
23 Pories SE, Gamelli RL, Vacek P, Goodwin G, Shinozaki T, Harris F (1992) Intoxication and injury. J Trauma. **32**(1): 60–4.
24 Porter RS (2000) Alcohol and injury in adolescents. Pediatr Emerg Care. **16**(5): 316–20.
25 Schneider HJ, Kreitschmann-Andermahr I, Ghigo E, Stalla GK, Agha A (2007) Hypothalamopituitary dysfunction following traumatic brain injury and aneurysmal subarachnoid hemorrhage: a systematic review. JAMA. **298**(12): 1429–38.
26 Schutte C, Hanks R (2010) Impact of the presence of alcohol at the time of injury on acute and one-year cognitive and functional recovery after traumatic brain injury. Int J Neurosci. **120**(8): 551–6.
27 Stibler H (1991) Carbohydrate-deficient transferrin in serum: a new marker of potentially harmful alcohol consumption reviewed. Clin Chem. **37**(12): 2029–37.
28 Tanriverdi F, Unluhizarci K, Kelestimur F (2010) Pituitary function in subjects with mild traumatic brain injury: a review of literature and proposal of a screening strategy. Pituitary. **13**(2): 146–53.
29 Taylor AN, Sutton RL (2015) Evidence for Beneficial and Adverse Effects of Alcohol in Animal Models and Clinical Studies of Traumatic Brain Injury. in: Brain Neurotrauma: Molecular, Neuropsychological, and Rehabilitation Aspects. Boca Raton (FL): CRC Press/ Taylor & Francis; Chapter 48.
30 Thelin EP, Nelson DW, Bellander BM (2017) A review of the clinical utility of serum S100B protein levels in the assessment of traumatic brain injury. Acta Neurochir (Wien). **159**(2): 209–25
31 Undén J, Romner B (2010) Can low serum levels of S100B predict normal CT findings after minor head injury in adults?: an evidence-based review and meta-analysis. J Head Trauma Rehabil. **25**(4): 228–40.
32 van de Wiel A, van Golde PM, Kraaijenhagen RJ, von dem Borne PA, Bouma BN, Hart HC (2001) Acute inhibitory effect of alcohol on fibrinolysis. Eur J Clin Invest. **31**(2): 164–70.
33 Vos PE, Alekseenko Y, Battistin L, Ehler E, Gerstenbrand F, Muresanu DF et al. (2012) Mild traumatic brain injury. Eur J Neurol. **19**(2): 191–8.
34 Whitfield JB, Fletcher LM, Murphy TL, Powell LW, Halliday J, Heath AC et al. (1998) Smoking, obesity, and hypertension alter the dose-response curve and test sensitivity of carbohydrate-deficient transferrin as a marker of alcohol intake. Clin Chem. **44**(12): 2480–9.
35 Wilde EA, Bigler ED, Gandhi PV, Lowry CM, Blatter DD, Brooks J et al. (2004) Alcohol abuse and traumatic brain injury: quantitative magnetic resonance imaging and neuropsychological outcome. J Neurotrauma. **21**(2): 137–47.
36 World Health Organisation (2006) Neurological Disorders: Public Health Challenges. Geneva: World Health Organisation Press.