Minor Head Trauma in Soccer and Serum Levels of S100B

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OBJECTIVE: To compare the serum levels of S100B after head trauma with the effect of heading, high-intensity exercise, and playing in a league match. Heading and head trauma in soccer have been suspected to cause brain impairment. The protein S100B is a marker of acute neuronal tissue damage.

METHODS: Baseline S100B was measured in 535 Norwegian professional soccer players. Two hundred twenty-eight head impacts were registered from 352 league matches. Three teams (n = 48) performed a high-intensity exercise session without heading and a low-intensity session with heading exercises. A blood sample was drawn from each participant within 1 hour (B1) after the session, and another sample (B12) was drawn after a match or training session. The players were assigned to four groups: Head Impact (n = 65), Match Control (match participants without head impact, n = 49), High-intensity Exercise (n = 35), and Heading (n = 36).

RESULTS: Serum S100B increased from baseline to B1 for all groups. The increase for the match groups (Head Impact and Match Control) was significantly higher than for both training groups. However, no significant differences between the Head Impact and Match Control groups or between the two training groups were found. A total of 39 players (33.9%) had elevated B1 values (≥0.12 ng/ml) after a match, but these findings were equally distributed between the Match Control and Head Impact groups.

CONCLUSION: Both soccer training and soccer matches cause a transient increase in S100B. There is a possible additive effect of activity with high intensity and heading, but minor head impacts do not seem to cause an additional increase.

KEY WORDS: Brain injury, Closed head trauma, S100 proteins, Soccer

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Soccer is one of the few sports in which the player's unprotected head is used actively for heading and advancing the ball (30). When heading was first introduced in soccer, this feature was considered ludicrous and "not soccer," but it soon became an important part of defensive and offensive play (49). However, during the past two decades, there has been increasing concern that heading could lead to chronic brain injury, as seen in boxing. This was first postulated by Tysvaer (64) in 1992 on the basis of a series of cross-sectional studies including neurological examinations, neuropsychological tests, computed tomographic scans, and electroencephalographic examinations on active and older retired Norwegian soccer players. Since then, some cross-sectional studies have indicated that soccer can cause measurable cognitive impairment (19, 33–35), whereas others have not detected such a relationship (23, 60). Heading duels expose the players to an increased risk of sustaining head trauma (2, 60), and it has been hypothesized that the reported cognitive deficits are more likely to be the result of accidental head impacts that occur during the course of the matches rather than heading (29).

Among injuries related to soccer, 6 to 13% are head injuries (3, 22). The reported incidence of head injuries for men during matches is 1.7 to 3.5 per 1000 player-hours (2, 22). This incorporates all types of head injuries, including facial fractures, contusions, lacerations, and eye injuries, whereas the estimated incidence of concussion is 0.3 to 0.5 per 1000 match-hours (2, 13, 22, 45). However, the rate of brain injuries is difficult to assess (15), and the reported incidences are likely to represent minimum estimates. Andersen et al. (2) identified 192 head impacts on video recordings from elite soccer matches (18.8 per 1000 h), but only five of these were reported as concussions. A study by Delaney et al. (15) revealed that only one in five concussions are recognized by the players after a head impact in a match, indicating that many players continue to play with undiagnosed concussions.

Several different markers for brain injury have been investigated in recent years. On the basis of these studies, Ingebrigtsen and Romner (26) have concluded that the S100B protein is currently the most promising marker for evaluation of traumatic brain injury in patients with minor head injury. Protein S100B is a Ca^{2+}-binding protein mainly attached to the membranes in glial cells in the central and peripheral nervous system (astrocytes or Schwann cells), although it is also expressed in melanocytes, adipocytes, and chondrocytes outside the nervous system (18, 61, 67). The serum levels of S100B increase rapidly after a traumatic brain injury; some studies have reported a 10- to 15-fold increase above baseline levels followed by a significant decrease during the next 4 to 6 hours as a result of its short half-life (10, 27, 28, 38, 48, 62). An increased level of S100B after minor head trauma has been reported to be associated with pathological findings on computed tomographic scans (9, 36), prolonged in-hospital stays (38), prolonged absence from work (59), postconcussive complaints (14, 50), and disability 1 year after the incident (53). In addition, S100B level is associated with the Glasgow Coma Scale score at admission and the outcome after more severe head injury (46, 63). Nevertheless, the specificity of S100B to brain injury has been questioned (4, 17, 32, 40, 43, 57, 65). Highly increased values have been reported after multitrauma and burns without head injury (5), and smaller increases have been detected after swimming (16), running, and boxing (16, 42). Yet, the increase in S100B concentration after exercise was lower than values reported after minor head traumas (9, 12, 14, 27, 36, 41, 48, 53).

S100B levels in soccer players are increased after a soccer match and appear to be related to the number of headers (54, 56). However, no large-scale prospective study has assessed S100B levels after minor head impact in soccer. Thus, this study was designed to assess whether minor head impact in soccer could cause injury to the nervous tissue, measured as an increase in the serum S100B concentration. In addition, we wanted to assess the specific effect of high-intensity exercise and heading on the serum concentration of S100B to control for these factors.

PATIENTS AND METHODS

Study Design

This was a prospective study in a cohort of professional soccer players, in which the serum level of S100B was compared under four different conditions: 1) after a head impact occurring during a regular league match (Head Impact group), 2) after a regular league match with no recorded head trauma (Match Control group), 3) after a high-intensity training session without heading (High-intensity Exercise group), and 4) after a low-intensity training session with heading exercises only (Heading group). The blood sampling protocol in each case included a baseline sample (obtained before the season or before the training session), a follow-up blood sample taken right after the match or training session, and an additional sample taken the next morning.

Participants and Test Procedures

All players in the Norwegian elite soccer league, Tippeligaen, were asked to participate in the study before the 2004 and 2005 seasons. Tippeligaen comprises 14 teams, each with 23 to 28 players on an A-squad contract, yielding a total of 320 to 390 players each season. Written informed consent was obtained from all participants, and the study design was approved by the Regional Committee for Medical Research Ethics, Helse Sør, and the Data Inspectorate.

A total of 289 players in 2004 and 332 players in 2005 consented to participate in the study. Thus, the study covered 621 player-seasons (161 of these players were included in both seasons). Baseline morning blood sampling before both seasons was performed for all teams but one during their preseason training camp at the training center of the Football Association of Norway at La Manga, Spain, in February or March. The final team was tested at their local training facilities in Norway during the same time period. In addition, baseline blood sampling was performed in a subgroup of players (n = 49) on 3 different days during their 2-week training camp to assess the variation in baseline serum S100B concentration. All baseline samples were taken before training between 7:30 and 10:00 AM.

Match Study

During both seasons, all regular league matches were observed live by medical personnel present at the venue. They were asked to record all head impacts during the match. The personnel were either the team's own medical staff covering the match or other local medical personnel recruited by the study administrators. The criteria for including head impacts (Head Impact group) in the sample were: all situations in which 1) a player appeared to receive an impact to the head (including the face and the neck), 2) the match was interrupted by the referee, and 3) the player lay down on the pitch for more than 15 seconds (3).

In any case of a head impact (irrespective of whether or not the player was removed from play), the medical personnel were instructed to draw a blood sample from the player right after the match, preferably within 1 hour after the trauma (B1), as well as a sample the next morning (within 12 h after the match, B12). Video recordings of all matches were provided by the Norwegian Broadcasting Corp. and reviewed the next morning by one of the authors (TMS-N) or a research assistant. When a head impact was identified, the medical personnel of the player's team were contacted by phone to check on the follow-up status and, if necessary, to arrange for B12 blood sampling. A control group of players from six of the teams included in the study was recruited to give blood samples within 1 (B1) and 12 hours (B12) after a regular match in which they had not experienced any head trauma (Match Control group). These six control matches were reviewed on video to verify that no head impacts had occurred to these players and a count was made of the number of headers and other head-accelerating events per player (i.e., falls or collisions that did not qualify as head impacts).

To determine how many of the head impacts resulted in actual time-loss injuries (21), the impacts were also cross-referenced with the injuries reported by the team's medical staff through the injury surveillance system administered by Oslo Sports Trauma Research Centre. This register receives data from all of the teams in Tippeligaen and includes all injuries from all team activities that have resulted in absence from training or match (time-loss injuries) as well as the time and date of the injury, type of match, diagnosis, and number of days before the player returned to training or match (3). The study protocol also included neuropsychological testing of the players the day after the head impact/control match. These results are described in detail in a separate report (Straume-Næsheim et al., unpublished data).

Training Study

Three of the included teams were also asked to participate in two separate training sessions before the 2006 season (n = 48): one high-intensity soccer training session in which heading of the ball was not allowed (High-intensity Exercise group) and one low-intensity training session with heading exercises (Heading group). These sessions were planned in cooperation with the team coach and led by the regular coaching staff. The high-intensity soccer play and heading exercise were organized to be as close to the match situation as possible in terms of the level of intensity or the number and force of the headers. Normal values for the number of headers per player per match was established by counting all headers in matches that were followed live by one of the study administrators during the 2005 season (n = 241 players, two to four matches counted per player). The mean number of headers per player was 5.7 (95% confidence interval [CI], 0–14.8 headers) per match, with large variations between the different playing positions, ranging from 2.8 (95% CI, 0–6.9 headers) for the midfielders to 9.6 (95% CI, 3.9–20.7 headers) for the central defenders. Goalkeepers practically never headed the ball (0.04 [95% CI, 0–0.5 headers]). Thus, no standard number of headers was set for the heading exercise session. However, after both sessions (High-intensity Exercise and Heading), each player was asked to fill out a questionnaire assessing his level of fatigue and how often he headed the ball during the current day's training compared with a regular match (much less, less, a little less, same, a little more, more, or much more). This score was dichotomized to "less" and "same or more" in the analyses. From video recordings of the heading sessions, one or two different players were selected for each of the drills performed, and the number and force (i.e., light, moderate, or hard) of the headers were counted. The number of headers for each drill was then summarized to create an estimate of the mean number of headers per player per training session. New baseline morning samples were drawn before the first training session and subsequently within 1 hour (B1) and the next morning (B12) after each of the two sessions. The training sessions were arranged on separate days and lasted 90 minutes excluding warm up, and no other training was done between collections of the two follow-up blood samples.

S100B Assay

Venous blood samples were collected from an antecubital vein and drawn into a standard gel 7-ml tube (BD Vacutainer blood collection tube; Becton Dickinson, Franklin Lakes, NJ) and then allowed to clot for 30 minutes before centrifugation (3000 x *g*) for 10 minutes. The resulting serum was divided between two 1.5-ml Eppendorf tubes (Eppendorf, Hamburg, Germany) and frozen within 2 hours. Serum S100B concentrations were measured using an electrochemiluminescence assay (Roche Elecsys; Roche Diagnostics, F. Hoffmann-La Roche Ltd., Basel, Switzerland). The lower detection limit of the assay is 0.005 ng/ml (per manufacturer's product information). All analyses were performed at the Department of Clinical Chemistry and Clinical Biochemistry, University of Munich, Munich, Germany, according to the procedure described by Mussack et al. (40) and Biberthaler et al. (9). On the basis of previous studies of S100B after minor head trauma (9, 11, 12, 26, 38), a cutoff value of 0.12 ng/ml was used to classify the B1 samples as elevated or within the normal range.

Statistical Analysis

All blood sample data were log-transformed to meet the criteria for normal distribution. The reproducibility for the measurement of the baseline concentration of S100B was assessed using analysis of variance for repeated measurements. The square root of the residual mean square was divided by the joint mean of all three measurement points to create a coefficient of variation.

The main effect variables for the study were the serum concentration of S100B at B1 and B12, the Δ B1 values (change from baseline to postimpact/match/training), and the proportion of players within each group with an elevated B1 sample value. The null hypothesis that there was no difference between groups in S100B serum concentration was tested using repeated measurements analysis of variance with Bonferroni post hoc *P* value adjustments and pairwise *t* test comparisons. Further differences between subgroups were examined using independent sample *t* tests, whereas paired samples *t* tests were used for testing differences within each group. Categorical variables were tested for between-group differences using χ^2 or Fisher exact tests, and bivariate correlations were calculated with the Spearman's ρ correlation coefficient. All S100B concentrations presented in the text are back-transformed values from the log10 values used in the analyses. Descriptive data are presented as the mean and 95% confidence interval (CI) of the distribution, whereas comparative data are presented as the mean and corresponding 95% CI of the mean. Based on the standard deviation from the baseline samples, the lowest true difference between the groups that could be identified was 0.017 ng/ml with at least 25 players in each group with a power of 80% (β = 0.8). All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 13.0; SPSS, Inc., Chicago, IL).

RESULTS

Baseline Characteristics and Compliance

Baseline blood samples were drawn from 255 (88.2%) of the players who consented to participate before the 2004 season and 280 players (84.3%) before the 2005 season. Hence, 535 baseline samples were collected in total, and the mean serum concentration of S100B was 0.045 ng/ml (95% CI, 0.018–0.11 ng/ml). A total of 15 (2.8%) of the baseline samples were equal to or above the cutoff value at 0.12 ng/ml. Three repeated baseline measurements were performed on a total of 49 players, and the mean baseline concentrations of S100B for the three different test days ranged from 0.049 ng/ml (95% CI, 0.026–0.093 ng/ml) to 0.056 ng/ml (95% CI, 0.028–0.11 ng/ml), with a coefficient of variation of 18.4%.

A total of 228 head impacts that met the inclusion criteria were identified on video from 352 matches. Sixty-nine (30.3%) of these were followed up with either a blood sample within 1 hour after the impact (B1, n = 28), a blood sample the next day (B12, n = 3), or both (n = 37). Thus, the total number of B1 and B12 samples were 65 and 40, respectively. The baseline characteristics and compliance with the sampling protocol for all four groups are presented in *Table 1*.

As presented in *Table 2*, only 13 (5.7%) of the 228 impacts were reported as time-loss injuries to the injury surveillance system, including seven concussions (3.1%; 0.6 per 1000 playing hours). In the group that was followed up, a total of 27

TABLE 1. Baseline characteristics and compliance with the sampling protocol for the players who experienced head trauma in a soccer match (Head Impact), the players who participated in a soccer match without experiencing a head trauma (Match Control), the High-intensity Exercise group, which did not practice any heading, and the Heading exercise group

Variable	Head impact (n = 69)	Match control (n = 56)	High-intensity exercise (n = 48)	Heading (n = 46)
Age (yr)	28.1 (22.5–35.0)	26.2 (19.0–33.0)	26.1 (18.5–33.6)	26.1 (18.4–33.7)
Height (cm)	185 (175–194)	183 (172–191)	182 (171–195)	183 (171–195)
Weight (kg)	81.6 (70.8–93.0)	79.2 (70.0–90.0)	78.1 (63.5–94.1)	78.2 (63.0–94.4)
Nationality				
Norwegian or Scandinavian	55 (79.7%)	43 (87.8%)	39 (81.3%)	37 (80.4%)
Playing position				
Goalkeeper	4 (5.8%)	3 (6.1%)	6 (12.5%)	6 (13.0%)
Central defender	22 (31.9%)	13 (26.5%)	11 (22.9%)	11 (23.9%)
Full wingback	11 (15.9%)	9 (18.4%)	5 (10.4%)	5 (10.9%)
Central midfielder	11 (15.9%)	12 (24.5%)	13 (27.1%)	12 (26.1%)
Midfielder	4 (5.8%)	4 (8.2%)	6 (12.5%)	5 (10.9%)
Striker	16 (23.2%)	8 (16.3%)	7 (14.6%)	7 (15.2%)
No. of headers				
Respective match/training	—	6.8 (0.0–16.0)	—	18.9 (7.0–33.0)
Compliance with test protocol				
Baseline sample	60 (87%)	49 (88%)	48 (100%)	46 (100%)
B1 sample	65 (94%)	49 (88%)	35 (73%)	36 (78%)
B12 sample	40 (58.0%)	46 (82.1%)	33 (69%)	28 (61%)
Post training questionnaire	—	—	36 (75%)	35 (76%)
Time (range) from impact/end of match/training to B1 (min)	77.7[a] (32.3–53.3) (n = 29[b])	33.2 (20.0–80.0) (n = 48)	26.3 (12.6–45.8) (n = 35)	23.0 (9.7–40.8) (n = 36)
Time (range) from impact/end of match/training to B12 (h)	14.9 (10.5–24.8) (n = 20[b])	13.3 (11.4–14.7) (n = 46)	20.6 (17.7–22.1) (n = 33)	18.6 (16.7–22.5) (n = 28)

[a] Significantly different ($P < 0.02$).
[b] The exact sample time was not available for all the samples in the Head Impact group.

players (39.1%) reported having symptoms directly after the impact, but only nine (33.3%) of these were taken out of play.

Two players experienced a head impact during the heading exercise session and were consequently excluded from further analyses. The serum concentration of S100B at baseline was not significantly different for any of the four groups (analysis of variance, $P = 0.408$).

Changes in the Serum Concentration of S100B

All groups had a significant increase in serum concentration of S100B between baseline and B1 and a similar significant decrease from B1 to B12 (*Fig. 1*). Both match groups displayed higher B12 values compared with baseline, but only the B12 value for the Head Impact group was significantly different from baseline (baseline: 0.041 ng/ml [95% CI, 0.034–0.051 ng/ml]; B12: 0.051 ng/ml [95% CI, 0.43–0.59 ng/ml], $P = 0.040$). For both training groups, the B12 value had returned to the baseline level. However, it has to be emphasized that the time from the end of the activity until B12 sampling the next morning was on average 5.8 hours (95% CI, 5.0–6.6 h) longer for the training groups compared with the match groups ($P < 0.001$), because the matches usually were played in the evenings, whereas the training sessions took place around noon.

No significant differences were seen between the two training groups or between the two match groups for any of the sampling time points. The joint match groups (Match Control and Head Impact groups, taken together) had a significantly higher mean serum S100B concentration at B1 compared with the joint training groups (*Fig. 1*). A similar pattern was evident for the Δ B1 values, in which the joint match groups had a significantly higher increase from baseline compared with the joint training groups (Δ B1: training groups: 0.026 ng/ml [95% CI, 0.020–0.031 ng/ml], match groups: 0.062 ng/ml [95% CI, 0.052–0.073 ng/ml], $P < 0.001$). However, within the match and training groups, there were no significant differences in the Δ B1 values.

TABLE 2. Reported injuries and retrospectively classified concussions based on the Vienna concussion definition for the identified head impacts (n = 228)

	Postmatch follow-up status group	
	Not followed up	Head impact S100B
No.	159	69
Reported time loss injuries	3 (1.9%[a])	10 (14.5%)
Concussion	2 (1.3%)	5 (7.2%)
Facial fracture	1 (0.6%)	2 (2.3%)
Other	0	3 (4.3%)
Loss of consciousness	1 (0.6%)	4 (5.8%)
Posttraumatic amnesia	—	2 (2.9%)
Classified as concussions (Vienna definition)[b]	—	27 (39.1%)
Taken out of play as a result of concussion	—	9 (13.0%)

[a] Percentages are reported within each group, the followed up cases, and the group not followed up.
[b] Retrospective classification based on symptoms reported by the medical personnel or the players themselves.

For the soccer players in the joint match group, a total of 39 B1 samples (34.2%) scored equal to or slightly above the cutoff value ($\geq$0.12 ng/ml), but they were equally distributed between the Head Impact and the Match Control groups (χ^2: $P = 0.48$). Based on the symptoms reported either by the team medical personnel or by the players themselves, a total of 26 (37.7%) of the followed up impacts in the Head Impact group were classified as concussions according to the criteria set by the First International Conference on Concussion in Sports in Vienna in 2001 (i.e., any impairment to neurological function after a head trauma) (7). Ten (38.5%) of these scored equal to or above the cutoff value for B1, versus 14 (35.9%) of the 39 impacts that did not classify as concussions (χ^2, $P = 0.83$). Only five B1 samples in the training group were equal to or above the cutoff value for B1. Although four of these were within the High-intensity Exercise group, the numbers were too small to test for any significant differences in the distribution.

Effect of Heading and High-intensity Exercise on Serum S100B

As shown in *Table 3*, the players in the Heading group who reported the same number or more headers in the training session compared with a regular league match had significantly higher Δ B1 values than the other players. However, this finding resulted from a significantly lower baseline serum level of S100B for the subgroup who reported the same or more frequent heading intensity. There was no significant difference in the serum concentration of S100B at B1 between the two subgroups. Within the High-intensity Exercise group, no differences were discovered with respect to the effect of the exercise intensity level compared with a regular match (*Table 3*).

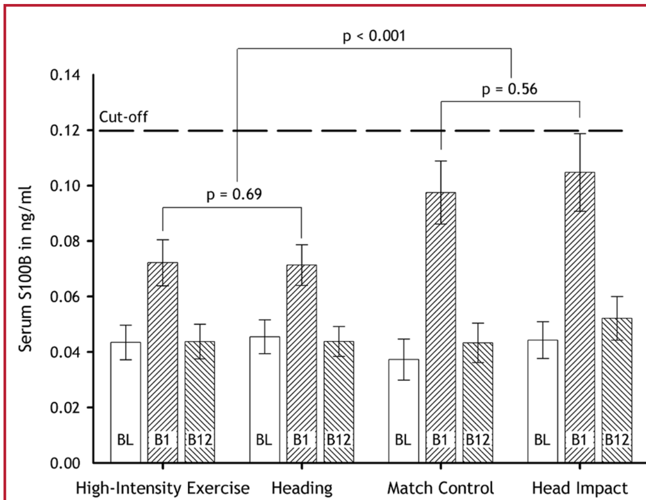

FIGURE 1. *Mean S100B values (in ng/ml) for the Head Impact, Match Control, Heading, and High-intensity Exercise groups shown at baseline (BL), 1 hour (B1), and 12 hours postimpact/match/training (B12). The* error bars *represent the 95% confidence interval of the mean.*

For the players in the Match Control group, there was a trend toward a positive correlation between the number of headers in the respective match and serum S100B at B1 (Spearman's $\rho = 0.28$, $P = 0.056$), but not for Δ B1 (Spearman's $\rho = -0.20$, $P = 0.89$). However, the players who headed 10 times or more during the respective match (upper quartile: 0.045 ng/ml [95% CI, 0.033–0.061 ng/ml]) exhibited a trend toward a higher serum S100B concentration at baseline compared with the players who headed three times or less (lower quartile: 0.029 ng/ml [95% CI, 0.019–0.044 ng/ml], $P = 0.11$). When the number of all other head-accelerating events and the number of headers were added, a significant correlation with serum S100B at B1 was found (Spearman's $\rho = 0.36$, $P = 0.012$), but there was still no correlation with Δ B1 (Spearman's $\rho = 0.025$, $P = 0.87$).

DISCUSSION

This study followed elite soccer players for two seasons to determine whether minor head traumas in soccer cause detectable brain tissue injury. The serum concentration of S100B after head trauma was compared with the effect of heading, high-intensity exercise, and playing a regular league match without any head trauma. Our main finding was that all conditions led to a moderate but significant increase in serum S100B concentration, which returned to baseline levels within the next day. Although the increase was higher for the two match conditions compared with the two training conditions, there were no significant differences between the two match groups at any time point.

TABLE 3. Serum concentration of S100B (in ng/ml) at all three test points for the High-intensity Exercise and Heading groups[a]

S100B sample	High-intensity exercise group: Level of fatigue versus match, Less (n = 19, 53%)	High-intensity exercise group: Level of fatigue versus match, Same or more (n = 17, 47%)	*P* value	Heading group: No. of headings versus match, Less (n = 10, 29%)	Heading group: No. of headings versus match, Same or more (n = 25, 71%)	*P* value
Baseline	0.043 (0.035–0.053)	0.045 (0.036–0.056)	0.82	0.061 (0.043–0.087)	0.039 (0.034–0.045)	0.009
B1 sample	0.070 (0.060–0.081)	0.075 (0.061–0.092)	0.57	0.078 (0.057–0.11)	0.066 (0.060–0.072)	0.16
B12 sample	0.041 (0.035–0.048)	0.047 (0.036–0.062)	0.40	0.052 (0.036–0.075)	0.041 (0.036–0.048)	0.20
Δ B1	0.025 (0.011–0.038)	0.032 (0.019–0.045)	0.73	0.016 (–0.005–0.036)	0.025 (0.020–0.031)	0.022

[a] Both groups are dichotomized according to self-reported level of fatigue or number of headers compared with a regular match.

S100B and Minor Head Trauma

The postmatch serum S100B levels after head trauma were not different from levels measured after playing 90 minutes of professional soccer without experiencing any head impacts. The increase in both match groups was comparable to serum S100B levels measured in Swedish professional male and female soccer players after playing a regular match (54, 56). In addition, there was no difference between the Match Control group and the Head Impact group in the proportion of players with elevated serum S100B levels. Even for the impacts that were classified as concussions on the basis of their symptoms, the proportion of players with elevated levels was not different from the remaining Head Impact group or the Match Control group.

Data from the league injury surveillance system, which is administered by the Oslo Sports Trauma and Research Center, showed that 13 of the recorded head impacts caused an injury (i.e., concussion or facial fracture) that kept the player away from regular matches and training from 1 to 21 days or more. However, B1 samples were available for nine of these impacts, and none of these samples was above the theoretical maximum serum level of S100B that can be achieved by stress- or exercise-induced failure of the blood–brain barrier only (32). In addition, the Head Impact group's mean B1 level was below the values reported for patients admitted to the hospital with minor head trauma (Glasgow Coma Scale score of 13–15) (9, 12, 27, 36, 41, 48, 53), and under half the mean serum S100B levels reported for minor head trauma patients with abnormalities on the computed tomographic and/or magnetic resonance imaging scan (9, 12, 41).

Some limitations of this study must be borne in mind when interpreting the results. First, a possible source of bias is that only 69 (30%) of the 228 head impacts were followed up. After numerous efforts toward the teams and their medical personnel, we ascertained that the main reason for the low compliance was that the players were reluctant to be tested after the match mainly because they regarded the impacts as trivial. Analyses of all the impacts identified from the match videos revealed that 24.6% of the players who were followed up with blood samples after a head impact did not return to play compared with 8.8% of the cases in which the impacts were not followed up. Thus, a player who was taken out of play was nearly three times more likely to be followed up as one who returned to play. Consequently, the followed up group was likely to include a higher proportion of more severe impacts and, accordingly, 39.1% of these were retrospectively classified as concussions. Nevertheless, the majority returned to play after the head impact, indicating that both the players and the team medical personnel regarded the majority of the impacts as benign.

Second, the samples of both the Head Impact and the Match Control groups were drawn within 1 hour after the end of the match, although the head impacts occurred on average 56 minutes before the end of the match. The biological half-life of S100B in serum has been reported to be as short as 25.3 minutes (95% CI, 15.3–35.3 min) (28), and consequently, an increase in S100B caused by the head impact would decrease substantially during the time from the impact until the end of the match. Nevertheless, even when considering these limitations, the head impacts did not have an additive effect on the S100B concentration when compared with playing a soccer match only, indicating that the head impact did not cause substantial nervous tissue injury.

S100B and Soccer Play

The present study showed an increase in serum S100B after playing a regular match irrespective of whether the players had experienced any head impacts. In addition, in approximately 35% of these cases, the values were above the suggested cutoff level (0.12 ng/ml) used for severity screening of patients with minor head trauma in hospitals (12). A somewhat smaller increase was found after high-intensity exercise without heading. Comparable increases in serum S100B have been reported after various physical activities in which head traumas and other sudden head-accelerating events like heading are rare, such as long-distance running (42), swimming (16), and basketball (55). The effect of physical activity on the serum level of S100B and the source of S100B release into the serum under these circumstances are unresolved (4, 5, 17, 54, 56). Extracerebral sources of S100B are well known (e.g., chondrocytes, melanocytes, and fat cells [67]), but the concentrations in these cells are very small compared with those in astroglial and Schwann cells (24, 27). Although an increase of S100B has been reported in patients with multitrauma (5) or isolated single bone fractures (65) without an obvious direct head injury, this does not exclude an indirect disturbance of nerve cells by inflammatory factors like cytokines released in high amounts in these trauma situations (20, 31, 37). Similar short-term cell-activating effects may occur during an intensive physical workout and could explain the increases reported after exercise, indicating that the source for S100B in serum may indeed be the nervous tissue (44, 54, 58).

Severe damage to the brain is typically accompanied by a breakdown of the blood–brain barrier function (32), but recent studies have established that the blood–brain barrier also can be disrupted under conditions of physical activity such as prolonged moderate exercise in warm conditions (66) and 30 minutes of forced swimming (animal study [52]). Based on mathematical modeling of the S100B kinetics across the blood–brain barrier, Marchi et al. (32) proposed that up to a level of 0.34 ng/ml, serum S100B is primarily a marker of increased blood–brain barrier permeability, whereas higher values are associated with neuronal damage and poor patient outcome. In comparison, the highest value in our study was 0.33 ng/ml, and this sample was drawn 20 minutes after a league match from a midfield player in the Match Control group. He did not head the ball during that particular match, and his baseline and B12 samples were normal.

Exertion, stress, and increased circulating levels of epinephrine have also been shown to increase blood–brain barrier permeability (1, 25, 51), thus enabling an increase in serum S100B levels. Playing a competitive match is associated with high levels of stress, adrenaline, and physical intensity, which are difficult to mimic in a regular training session. This was reflected in the posttraining questionnaire, in which 53% of the players reported a lower level of fatigue after the training session compared with a league match. Hence, the higher B1 values for the match groups compared with the training groups in our study could be attributable to a different level of exertion only.

Properties of the S100B measurement procedure could also have affected the results. The measured S100B in this study refers to the summed concentrations of the S100B monomers in S100A1B and S100BB. A recent study has found a higher increase in S100A1B in patients with minor head traumas than in patients with minor orthopedic injuries, whereas the increase in S100B was equal for the two different groups (41). Nevertheless, although the specificity for brain injury after minor head trauma seems to be higher for S100A1B, the sensitivity to detect brain tissue damage is comparable for S100B.

S100B and Heading

In our heading exercise session, the idea was to minimize the effect of physical activity and subsequently tease out the effect of heading only. However, after correcting for the difference in the S100B baseline values within the Heading group, we could not detect any relationship between S100B and perceived heading intensity. Furthermore, we found no correlation between the observed number of headers and head-accelerating events and the Δ B1 values, as previously reported in the studies on Swedish soccer players (54, 56). Yet, a closer examination of the baseline levels for the upper quartile compared with the lower quartile with respect to the number of headers in the match revealed a trend toward higher baseline levels for those who headed most frequently, and consequently this could cause a subsequent bias of the Δ values for our Match Control group. A plausible explanation could be that the baseline samples were collected at a training camp where the players had two or three training sessions per day, and, although the baseline blood sampling was performed in the morning before training, there could be some effects left from the training sessions the day before for the players experiencing the most frequent headers.

The goalkeepers also represent a problem in these correlations. Goalkeepers practically never head the ball, and their level of exertion during a match is lower compared with the outfield players (6, 47). Consequently, the goalkeepers are grouped among the low-frequency headers, and there is a chance that the correlation between the number of headers and the increase in S100B would be confounded by differences in physical activity during the match. The studies by Stålnacke et al. (54, 56) provide no information regarding the goalkeepers, and their results are therefore difficult to compare directly with ours.

In contrast to our results from the heading session, Mussack et al. (39) found that an exercise session with repetitive controlled headers led to a higher transient increase in serum S100B than an exercise session only. However, this study was performed on young amateur players and a significant increase was seen only for the youngest group of players (age range, 12–15 yr). According to Kirkendall and Garrett (29), coaches do not incorporate heading in the training sessions until the players are 12 years of age or older. Consequently, in the study of Mussack et al. (39), controlled repetitive heading for 55 minutes was most likely a heavier exposure for the youngest players compared with the more experienced 16- to 17-year-old players. This is in line with biomechanical studies of heading in which brain accelerations during normal heading by adult players have been estimated to average less than 0.1% of the accepted levels required to produce brain injury in a single impact, whereas "accidental" heading and heading with poor technique could cause brain accelerations within the concussive range (8).

CONCLUSION

The serum level of S100B increases transiently after soccer training and soccer matches. There is a possible additive effect of heading and high-intensity exercise, but minor head impacts do not seem to cause an additional increase in S100B beyond the levels seen after a regular game. Thus, there is no evidence suggesting that there is significant brain tissue injury after these minor head impacts in soccer. However, for clinical use, S100B is not an ideal marker for brain injury in athletes because of the confounding effect of exercise alone.

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COMMENTS

The authors should be congratulated for performing this very large study, which was funded by the International Federation of Association Football, the sport's controlling body in Europe. The study included a large number of elite soccer players (535), there appears to be no bias in the presentation, and the statistics seem appropriate to me. There are two main messages to be drawn from this work. First, as the authors primarily conclude, there is no strong evidence in this sample, 228 identified and reported head impacts, that soccer, even with seven concussions, causes any minor head injury. This was judged mainly by the fact that the biomarker S100B did not increase more than it did for strenuous exercise alone, as seen in soccer practice. There is a second conclusion which is, in my view, more robust (i.e., this large study confirms the failure of S100B as a marker of mild traumatic brain injury). The real salient fact here is that the S100B levels in those patients with confirmed concussion sufficient to remove the player from play was no different than the levels seen in players who simply exercised vigorously. Thus, this is important evidence that S100B is not a valid marker of mild and moderate traumatic brain injury. As the authors note, S100B increased to levels within the "borderline" range for head injury, (0.12–0.34ng/ml), even in the strenuous exercise control group. This accords with other studies showing that S100B increases with long bone fractures and no head injury (1) and that its increase may be an indicator of the blood-brain barrier, rather than of neuronal damage per se (2).

The main feature that weakens the first conclusion of the study, namely that soccer does not cause mild head injury, is that not all of the patients who had significant head impacts in this study were actually followed up with further S100B measurements and psychometric testing. Nevertheless, the authors have made a major contribution to the study of mild traumatic brain injury and S100B as a biomarker.

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1. Anderson RE, Hansson LO, Nilsson O, Dijlai-Merzoug R, Settergren G: High serum S100B levels for trauma patients without head injuries. **Neurosurgery** 48:1255–1258, 2001.
2. Kleindienst A, Ross Bullock M: A critical analysis of the role of the neurotrophic protein S100B in acute brain injury. **J Neurotrauma** 23:1185–1200, 2006.

In this interesting study, a low plasma level of S100B protein was found to be unrelated to heading a soccer ball because even players who did not head the ball demonstrated mild serum elevations of S100B. Previous investigations have shown the lack of specificity of this protein as a marker of TBI; even systemic trauma can increase S100B levels in the absence of central nervous system injury. This study suggests that heading a soccer ball is not associated with any elevation of serum S100B levels beyond that seen with vigorous exercise. It remains unclear whether other serum markers would have better specificity.

Alex B. Valadka
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In this prospective study of professional soccer players, S100B levels were measured in four different groups of athletes before and after playing. The study indicates that S100B levels rise transiently in all four groups, with the greatest increase seen in both the Head Impact (TBI) and Match Control groups (league game without recorded TBI).

However, there was also a significant rise in the High Intensity Exercise Group without heading the ball and in the Heading Group (low intensity exercise with heading). This is another study addressing the utility of S100B levels as a marker of concussion in athletes showing that vigorous exercise alone can cause significant S100B level elevations. The present study further confirms that the increase in S100B is not specific to heading or minor head impacts. Although this study could be interpreted to indicate that there is no significant brain tissue injury after minor head impacts in soccer, it also suggests that S100B may not be the ideal marker for detecting such minor TBI. Given the increasing evidence that repetitive concussion is linked to subsequent depression and mild cognitive impairment in retired professional athletes, a continued search for more predictive markers of acute brain injury after concussion is warranted (1, 2).

Daniel F. Kelly
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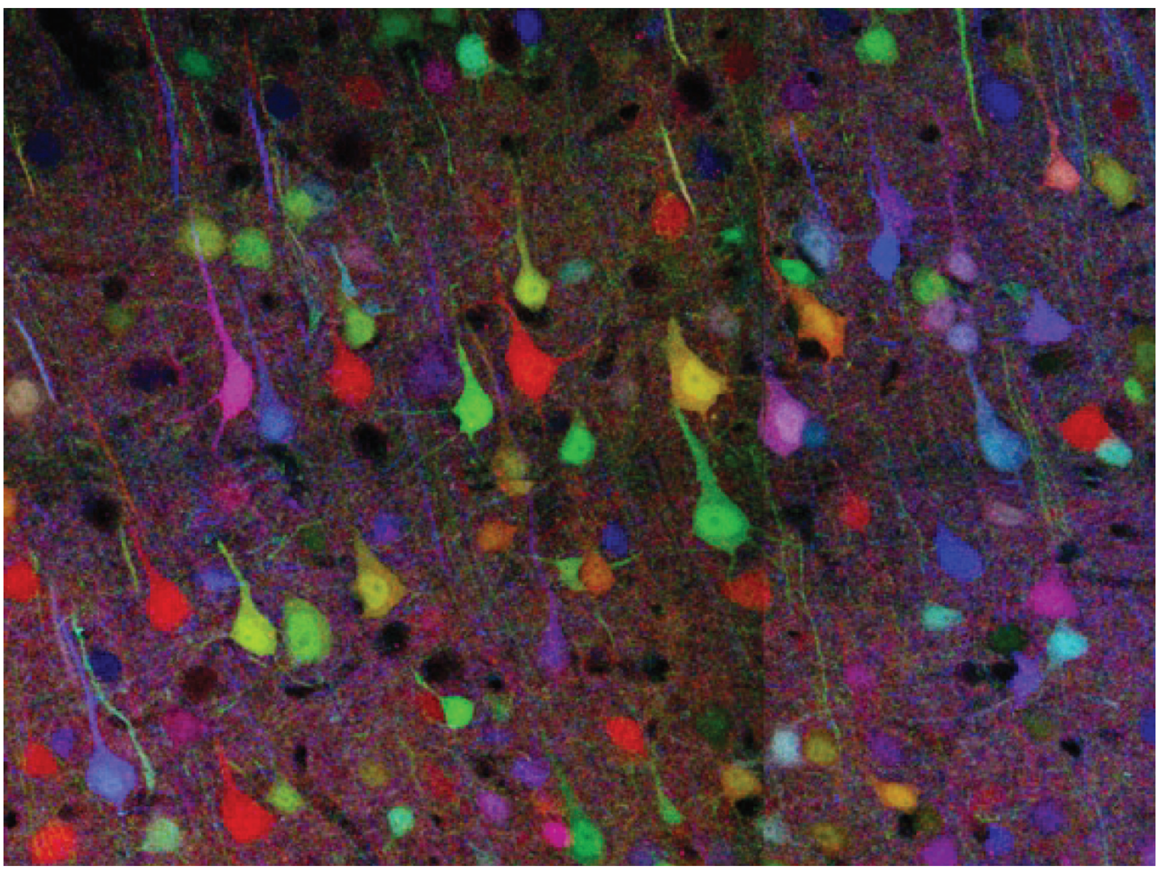
1. Guskiewicz KM, Marshall SW, Bailes J, McCrea M, Cantu RC, Randolph C, Jordan BD: Association between recurrent concussion and late-life cognitive impairment in retired professional football players. **Neurosurgery** 57:719–726, 2005.
2. Guskiewicz KM, Marshall SW, Bailes J, McCrea M, Harding HP Jr, Matthews A, Mihalik JR, Cantu RC: Recurrent concussion and risk of depression in retired professional football players. **Med Sci Sports Exerc** 39:903–909, 2007.

This article presents a well prepared project that looked at the changes in serum levels of S100B as it relates to minor head trauma during soccer games. The study attempted to prospectively evaluate the effect of minor head injury in soccer using the S100B protein as a marker. As the authors mentioned in the text, the main challenge this study encounters is the low specificity of the S100B protein because there are many factors that may increase its levels during activity. The authors made a good effort by dividing the patients in the study into four different groups and obtaining blood samples 1 hour (B1) and the following morning (B12) after a match/training session to improve on the specificity problem. The study suggests that there was no significant change in S100B protein levels as a result of mild head impacts during soccer games. The question remains whether S100B has any clinical value because the authors conclude that, for clinical use, S100B is not an ideal marker for brain injury in athletes due to the confounding effects of exercise alone.

Ali F. Krisht
Little Rock, Arkansas



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