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ORIGINAL INVESTIGATION

Growth hormone deficiency and central hypogonadism in retired professional football players

Gábor László Kovács[1], Piroska Turbucz[1], Éva Rimanóczy[2], Gergely Pánics[3], Katalin Bánáti[1], Miklós Góth[4]

1 1st Department of Internal Medicine, Flór Ferenc Hospital, Kistarcsa Hungary
2 Central Laboratory, Heim Pál Pediatric Hospital, Budapest Hungary
3 Department of Orthopedics and Traumatology, Uzsoki Hospital, Budapest Hungary
4 2nd Department of Internal Medicine, Medical Center, Hungarian Defense Forces, Budapest, Hungary

Corresponding author:
Gábor László Kovács MD, PhD
1st Department of Internal Medicine Flór Ferenc Hospital, Kistarcsa Hungary, 1. Semmelweis Square, Kistarcsa Hungary H-2143; Phone: +36-28-507-600/357; Email: dr.gl.kovacs@gmail.com

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Abstract

Purpose: The aim of this cross-sectional study was to evaluate the possible impact of multiple mild head traumas sustained during a long-term football career on the presence of central hypogonadism and growth hormone (GH) deficiency.
Methods: Twenty-seven retired, former professional male football players were investigated. All subjects were assessed for serum levels of insulin-like growth factor (IGF-1), luteinizing hormone (LH) and total testosterone (TT). Quality of life was quantified using the Assessment of Growth Hormone Deficiency in Adults (QoL-AGHDA) questionnaire.
Results: Subjects had a median age of 48.0 (42.0 – 53.0) years and a median football career of 29.0 years (22.0 – 32.0). One subject had central hypogonadism and none had growth hormone deficiency. Nine subjects reported sport-related head injuries. We found a negative correlation between sport-related head injuries and serum LH (p = -0.459, P = 0.016). Subjects with a history of sport-related head injury had a median LH of 3.3 U/L (2.7 - 3.6), while those without a history of sport-related head injury had a median LH of 4.1 (U/L) (3.6 - 5.7), P = 0.017. However, there were no differences in other hormones between the two groups. Moreover, we did not find any correlation between the duration of the player's career nor their field position with hormone profiles or QoL-AGHDA.
Conclusions: Although retired footfall players with a history of sport-related head injury had lower LH levels, we did not find strong evidence of an increased prevalence of central hypogonadism or GH deficiency in these patients. Our results suggest that a long-term football career, which includes headings and repetitive mild head traumas, does not damage the most vulnerable anterior pituitary cells.

Key words: traumatic brain injury; hypopituitarism; repetitive heading; football

1. Introduction

Mild traumatic brain injuries (TBI), which include injuries classified as concussions, are frequent among young athletes practicing full contact or semi contact martial arts. These injuries have more serious consequences than previously thought, including cognitive, behavioral, and biological deficits [1]. Several investigations have focused exclusively on neurological and social consequences of TBI, like residual disability, behavioral changes, reduced productivity and health costs [2]. It is very difficult to evaluate the severity of TBI, but new biomarkers and neuroimaging approaches are becoming increasingly available for quantitative assessment and classification [3]. TBI is an important public health problem and has been recently recognized as a leading cause of adulthood onset pituitary dysfunction. Approximately 25–50% of the patients with different degrees of pituitary dysfunction have a history of subclinical, repetitive TBI [4,5]. TBI-related hypopituitarism is either complete, i.e. both the anterior and the posterior lobes of the pituitary gland are affected, or partial.

According to several prospective and retrospective studies, close to 70% of adult patients demonstrate variable degrees of hypopituitarism during the first twelve months after severe TBI [6,7]. The neuroendocrine abnormalities in the acute phase following severe or moderate TBI may be transient (e.g. diabetes insipidus), whereas some abnormalities present later, during the recovery period. The most frequent early posttraumatic abnormalities are decreased basal cortisol levels, with a subnormal cortisol response in the glucagon or insulin tolerance test (ITT), central hypogonadism, and hyperprolactinaemia [7]. Growth hormone (GH) deficiency associated low insulin-like growth factor-I (IGF-1) levels was reported to be present in more than 20% of the cases [8]. In addition to GH deficiency, with descending order of frequency, gonadotrophin, adrenocorticotrophic hormone and thyroid stimulating hormone deficiencies have been described [9].

As the GH secreting cells are the most vulnerable cell types of the anterior pituitary, the symptoms of adulthood onset GH deficiency (AOGHD) is the most frequent consequence of TBI. Patients with AOGHD present with variable clinical symptoms, including, but not limited to increased (abdominal) body fat and decreased lean body muscle mass, osteopenia, dyslipidemia, and glucose intolerance. Furthermore, AOGHD may be associated with damaged cardiac muscle structure and function (cardiomyopathy), and reduced physical performance as a consequence of decreased striated muscle mass and strength. Because of these symptoms, patients can experience and report reduced quality of life when assessed with the Assessment of Growth Hormone Deficiency in Adults questionnaire (QoL-AGHDA). Several epidemiological studies have indicated an associated increased mortality risk in patients with hypopituitarism, particularly when all pituitary hormones were replaced with the exception of GH. The action of GH is mediated by IGF-1 produced by the liver. Diminished GH secretion usually results in low IGF-1 levels and the clinical symptoms of AOGHD. Since there is considerable overlap between circulating IGF-1 concentrations in healthy subjects and in patients with AOGHD, normal IGF-1 levels can occur in AOGHD. On the other hand, low IGF-1 levels in combination with deficiencies of more than two pituitary hormones is highly indicative of AOGHD [10]. IGF-1 synthesis is not exclusively regulated by GH but by nutrient supply and other hormones. Low IGF-1 levels with normal or increased GH secretion may reflect peripheral GH resistance. Very low IGF-1 levels in the context of documented hypothalamic or pituitary disease indicate GH deficiency [11].

QoL-AGHDA is a disease-specific, need-based measure, which was based on in-depth interviews with AOGHD patients attending the Christie Hospital in Manchester, UK [12]. Almost all patients were dissatisfied with their body image and more than 90% complained of lack of energy. Additional common complaints were memory loss and impaired concentration (>80%), irritability (70%), lack of strength and stamina (>60%), reduced physical and mental drive (50%) and difficulties with coping with stressful situations and with responding to external stimuli (50%). The questionnaire contained 25 yes or no questions. The QoL-AGHDA score is computed by quantifying a number of recognized problems: each 'yes' answer is assigned a score of 1; therefore, a higher numerical QoL-AGHDA score means poorer QoL [12]. The population normative data for the QoL-AGHDA are available for several countries: England, Wales, Spain, Sweden, Belgium, France, and The Netherlands. Hungarian data have not been published yet, but the official Hungarian translation of the questionnaire is already available and was used in our study. According to the first KIMS results (Pfizer International Metabolic Database for GH Deficiency Patients), before

GH replacement therapy, women with AOGHD had a higher degree of quality of life impairment than men; baseline QoL-AGHDA score was 10.2 (9.1–11.3) and 6.1 (6.0–8.2), for women and men, respectively [12]. A QoL-AGHDA less than 6 is considered normal and argues against untreated AOGHD both in female and male patients.

Sport-related chronic repetitive head trauma due to boxing and kickboxing even among amateur athletes might result in multiple pituitary hormone deficiencies or isolated AOGHD [13,14]. Kelestimur et al. investigated biochemical and basal hormonal parameters including IGF-1 levels in eleven actively competing or retired male boxers with a mean age of 38 years [13]. To assess GH secretory status in boxers and healthy controls, a GHRH (1 microg/kg)+GHRP-6 (1 microg/kg) test was performed. After the GHRH+GHRP-6 test, the peak GH levels in 5 (45%) boxers were found to be lower than 10 μg/L. Thus, they were considered severely GH deficient. In the control group, mean IGF-1 levels (367 ± 18.8 ng/ml) were significantly higher than those measured in boxers (237 ± 23.3 ng/ml) ($p < 0.01$). All other pituitary hormone levels were normal. Based on these findings, a systematic screening for TBI-related AOGHD was recommended among retired boxers. Several mechanisms have been suggested to explain TBI related hypothalamic–pituitary dysfunction, including hypoxic or vascular insult, direct mechanical injury, compression from hemorrhage, and edema of the hypothalamus, pituitary stalk, or the pituitary gland. Autoreactive antibodies directed against damaged and dying neurons in the injured brain can lead to post-traumatic anti-brain immunity with consequent pituitary dysfunction [15], but so far none of these mechanisms have been proven to be the unique causative pathway to TBI. Severe TBI usually results in more pronounced pituitary dysfunction [16], but repetitive minor head traumas are also likely to contribute to pituitary disorder.

Football is indisputably the single most popular team sport around the world. The FIFA (Fédération Internationale de Football Association) has 209 member federations, and approximately 240 million people play this game day-by-day. Football-related head injuries may typically occur in four ways: head contact with the ball (heading), contact with another player (head, foot, arm), contact with the ground, and contact with stationary objects (goal posts). As a consequence of heading or other head traumas, concussion with nausea, vomiting, headache, visual field defects, confusion, personality changes or paresthesia can appear. Furthermore, it has been suggested that repeated sub-concussive beats to the head can cause equivalent damage than a single mild concussive event [17]. There is an increased risk of TBI when heading is performed improperly or results in a head-to-head contact with another player. The duration of a professional football player's active career is usually more than 20 years. In the course of their careers, the players receive thousands of blows to the head [18]. Witol et al. published data about the long-term neuropsychological effect of repetitive headings. Players with the highest lifetime estimates of heading had poorer scores on scales measuring attention, concentration, cognitive flexibility and general intellectual functioning [18]. Poorer neuropsychological findings can be associated with pituitary deficiency in these cases. Ives et al. reported a case of hypopituitarism after multiple concussions in a junior football player [1]; a 14-year-old previously healthy male athlete suffered four head traumas over a 4-month period and the fourth trauma was a medically diagnosed concussion suffered during football play. After assessing the full endocrine panel (including IGF-1), complete anterior pituitary gland deficiency was diagnosed. The most vulnerable hormone system to physical injuries is the GH-IGF-1 axis, but there are some reports about isolated gonadotropin deficiency after multiple concussions as well. Auer et al. published a case-study of a 27-year-old male with symptoms of loss at libido, erectile dysfunction and fatigue [19]. He had been playing football from the age of 7, for the last 10 years as a high-level professional. During that time repeated mild head-trauma without loss of consciousness had occurred, mainly triggered by excessive header training and occasional mild head traumas. Serum testosterone and luteinizing hormone levels were low. Further pituitary hormone deficiencies were excluded.

In the present study, we aimed to assess the prevalence of central hypogonadism and GH deficiency in professional football players and to correlate serum hormone levels with career duration and history of sport-related head trauma.

Patients and methods

Twenty-seven former professional male football players were recruited. All of them had resigned from active playing. After signing the informed consent, the

participants filled out a questionnaire about their main football position and history of sport-related and unrelated head injuries. All subjects were tested for IGF-1 (Cisbio Bioassay I-125 immunoradiometric assay, calibration: 1st IRR WHO 87/518), LH (ABBOTT chemoluminescent microparticular immunoassay, calibration: WHO 80/552 2nd, reference range 0.57-12.07 IU/L) and total testosterone (ABBOTT chemoluminescent microparticular immunoassay; calibration internal reference standard; reference range 5.76 - 30.4 nmol/L). The assays were used according to the manufacturer's instructions. The IGF-1 SDS score was calculated according to the formula of Blum et Schweizer [20]. The normal range of IGF-1 SDS is between 0 - 2. The subjects' quality of life was assessed with the QoL-AGHDA scoring system; the official Hungarian questionnaire was used. The upper normal cutoff score of the test was set at 5 according to Koltowska-Häggström et al. [12]. Central hypogonadism was defined as decreased serum testosterone level along with normal or low LH level. GH deficiency was defined as decreased IGF-1 SDS along with abnormal QoL-AGHDA.

Statistical analyses

Patient's characteristics were assessed with descriptive statistics presented as median with interquartile range values. Independent variables were compared using the Mann–Whitney test, and Kruskal-Wallis test and Fisher's exact test, when appropriate. Correlation analyses were performed using the Spearman's correlation coefficient. Statistical analyses were performed using SPSS, ver. 20.0. P value <0.05 was considered statistically significant.

Table 1. Characteristics of the study population

	Median (interqartile range)
Age (years)	48.0 (42.0 – 53.0)
Duration of sports career (years)	29.0 (22.0 – 32.0)
IGF-I (ng/ml)	395.4 (324.0 – 440.2)
SDS	2.3 (1.9 – 2.7)
LH (U/l)	3.9 (3.0 – 5.0)
testosterone (nmol/l)	17.1 (12.5 – 21.2)
QoL- AGHDA	1.0 (0.0 – 3.0)
	N (%)
Sport associated head injuries	9 (33.3%)
Other head injuries	5 (18.5%)
Player position	
Goal keeper	4 (14.8)
Defense	9 (33.3)
Mid-field	3 (11.1)
Striker	11 (40.7)

Results

Subjects had a median age of 48.0 (42.0 – 53.0) years and a median football career of 29.0 (22.0 – 32.0) years. The remaining characteristics are presented in Table 1. Nine of the 27 players reported sport-related head injuries, three of them with further head traumas (traffic accident related traumas). We found a negative correlation between sport-related head injuries and serum LH (ρ = -0.459, P = 0.016). Subjects with a history of sport-related head injury had median LH of 3.3 U/L (2.7 - 3.6), while those without had median LH of 4.1 U/L (3.6 - 5.7), P = 0.017 (Figure 1). However, there were no differences in other hormones between the two groups (Table 2). Moreover, we did not find any correlation between the career duration or the player's field position with hormone profiles or QoL-AGHDA. All subjects had > 0 IGF-1 SDS value and only two had < 1. The median QoL - AGHDA score was 1.0 (0.0 – 3.0). Only four out of 27 subjects scored > 5, and two of them reported head trauma. One subject had central hypogonadism along with a high QoL-AGHDA score, but his IGF-1 SDS was normal, i.e., not indicative for GH deficiency.

Table 2. Comparsion of the subject characteristics between patients with and without the history of sport-related head injury (continous variables are presented as median with interquartile range)

	History of sport-related head injury		
	Absent (N = 18)	**Present (N = 9)**	**P**
Age (years)	49.5 (44.0 – 56.0)	48.0 (42.0 – 49.0)	0.275
Duration of sports career	29.0 (22.0 – 32.0)	29.0 (23.0 – 30.0)	0.743
LH (U/l)	4.1 (3.6 – 5.7)	3.3 (2.7 – 3.6)	0.017
testosterone (nmol/l)	16.2 (13.2 – 21.2)	17.7 (12.5 – 21.1)	0.900
IGF-I (ng/ml)	395.4 (324.0 – 432.4)	389.5 (330.2 – 445.4)	0.820
SDS	2.4 (1.9 – 2.6)	2.2 (1.9 – 2.7)	0.820
QoL- AGHDA	0.5 (0.0 – 2.0)	2.0 (0.0 – 5.0)	0.322
Other head injuries n(%)	2 (11)	3 (33)	0.295
Player position n(%)			
Defense n(%)	5 (27.8)	4 (44.4)	0.422
Goal keeper n(%)	2 (11.1)	2 (22.2)	0.581
Mid-field n(%)	2 (11.1)	1 (11.1)	0.988
Striker n(%)	9 (50.0)	2 (22.2)	0.231

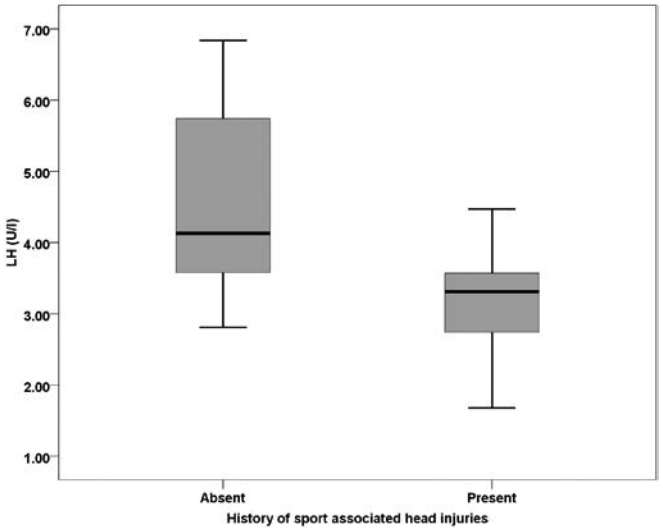

Figure 1. LH levels in patients with and without the history of sport related head trauma.

Discussion

To our knowledge, this is the first study focused on traumatic brain injuries among retired football players. In this study, the long-term effects of mild or severe head traumas on pituitary function, as well as the effect of repetitive minor traumas (thousands of headings or head to head contacts) during a long-term sports career on hypothalamic-pituitary function was assessed. The GH-IGF-1 axis and the LH-testosterone axis are known to be the most vulnerable parts of the pituitary regulatory circuits. Mild, repetitive head traumas may result in partial or complete pituitary dysfunction. The gold standard stimulation test to assess GH secretory capacity is the ITT. Diagnostic alternatives are the GHRH-arginin test and the glucagon test. These tests are either troublesome for the patient or expensive (GHRH-arginin test) and require multiple blood sampling for GH determination. A screening test should be clinically robust and inexpensive. Therefore, we chose IGF-1, LH and total testosterone determinations to test our hypothesis. The additional QoL-AGHDA scoring is a reliable non-invasive approach to provide further evidence of GH deficiency. These tests are inexpensive, simple and reliable for AOGHD screening. Based on the literature, we assumed that IGF-1 SDS around the upper limit of the normal range (up to 2) and QoL-AGHDA scores below 6 would most probably exclude AOGHD.

The two athletes with IGF-1 SDS below 1 (but still within the normal range) had normal QoL-AGHDA scores, making the presence of AOGHD very unlikely. The assessment of the LH - testosterone axis also showed an almost intact system. All but one player showed normal testosterone and LH levels suggesting an appropriate regulation of this feedback and secreting mechanism. One subject with high QoL-AGHDA and low testosterone and LH, had reported a positive history of sport-related head injury, but his IGF-1 SDS was still above 2, making GH deficiency highly unlikely. However, it prompts further dynamic endocrinological investigation. Only 9 (33.3%) subjects had a history of sport-related head traumas, which is relatively low considering a median football career of 29.0 (22.0 – 32.0) years. The biochemical/endocrine data of this subgroup showed comparable results to that of the study subjects without a reported head trauma, as there were no differences in IGF-1 SDS value, testosterone levels and QoL-AGHDA scores. Interestingly, subjects with a positive history of sport-related head trauma had lower LH levels, without the clinical signs of hypopituitarism and similar testosterone levels when compared with subjects without a history of head trauma.

In conclusion, our results suggest that long-term football playing, which includes headings and repetitive mild head traumas, does not damage the most vulnerable anterior pituitary cells. However, larger studies should include dynamic endocrinological evaluation in order to confirm these findings and in order to elucidate the clinical implications of decreased LH in football players with a positive history of sport-related head trauma.

Authors' contributions

GLK created the conception and design of the study, and drafted the article. PT participated in organizing the study and recruited the study subjects; additionally she analysed the data. ÉR organized the laboratory testing of blood samples. Furthermore she did the analysis and interpretation of the data. GP participated in organizing the study and recruited the study subjects; additionally, he analysed the study data. KB handled the questionnaires and informed consents filled by the study subjects; she helped in the acquisition of data. MG revised the article for important intellectual content and analysed the study data. All authors have approved the final version of the article.

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