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# Prevalence of Pituitary Hormone Dysfunction, Metabolic Syndrome, and Impaired Quality of Life in Retired Professional Football Players: A Prospective Study

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## Abstract

Hypopituitarism is common after moderate and severe traumatic brain injury (TBI). Herein, we address the association between mild TBI (mTBI) and pituitary and metabolic function in retired football players. Retirees 30–65 years of age, with one or more years of National Football League (NFL) play and poor quality of life (QoL) based on Short Form 36 (SF-36) Mental Component Score (MCS) were prospectively enrolled. Pituitary hormonal and metabolic syndrome (MetS) testing was performed. Using a glucagon stimulation test, growth hormone deficiency (GHD) was defined with a standard cut point of 3 ng/mL and with a more stringent body mass index (BMI)-adjusted cut point. Subjects with and without hormonal deficiency (HD) were compared in terms of QoL, International Index of Erectile Function (IIEF) scores, metabolic parameters, and football career data. Of 74 subjects, 6 were excluded because of significant non-football-related TBIs. Of the remaining 68 subjects (mean age, 47.3 ± 10.2 years; median NFL years, 5; median NFL concussions, 3; mean BMI, 33.8 ± 6.0), 28 (41.2%) were GHD using a peak GH cutoff of < 3 ng/mL. However, with a BMI-adjusted definition of GHD, 13 of 68 (19.1%) were GHD. Using this BMI-adjusted definition, overall HD was found in 16 (23.5%) subjects: 10 (14.7%) with isolated GHD; 3 (4.4%) with isolated hypogonadism; and 3 (4.4%) with both GHD and hypogonadism. Subjects with HD had lower mean scores on the IIEF survey ( $p=0.016$ ) and trended toward lower scores on the SF-36 MCS ( $p=0.113$ ). MetS was present in 50% of subjects, including 5 of 6 (83%) with hypogonadism, and 29 of 62 (46.8%) without hypogonadism ( $p=0.087$ ). Age, BMI, median years in NFL, games played, number of concussions, and acknowledged use of performance-enhancing steroids were similar between HD and non-HD groups. In summary, in this cohort of retired NFL players with poor QoL, 23.5% had HD, including 19% with GHD (using a BMI-adjusted definition), 9% with hypogonadism, and 50% had MetS. Although the cause of HD is unclear, these results suggest that GHD and hypogonadism may contribute to poor QoL, erectile dysfunction, and MetS in this population. Further study of pituitary function is warranted in athletes sustaining repetitive mTBI.

**Key words:** growth hormone deficiency; hypogonadism; metabolic syndrome; mild traumatic brain injury; professional football

## Introduction

CONCUSSION IS A WELL-KNOWN HAZARD of all contact sports. It is estimated that between 1.6 and 3.8 million sports-related traumatic brain injuries (TBIs) occur yearly in the United States.<sup>1,2</sup> Recurrent concussion in the National Football League (NFL) is

common. Despite the increased sophistication of helmets and rules to minimize the risk of concussions, mild TBI (mTBI) remains relatively common.<sup>3</sup> Of 1200 NFL concussions that were reported between 1996 and 2007, 29% of players sustained at least 2 or more concussions.<sup>4</sup> More recently, from NFL Injury Surveillance data over the last 4 years ending in 2012, with 256 games per season,

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there was an average of 170 concussions annually (or 0.66 concussions per game; NFL Injury Surveillance). Recurrent concussion in the NFL has been associated with development of depression, cognitive impairment, and poor quality of life (QoL) in retirees.<sup>5,6</sup>

Another potential sequelae of repetitive mTBI is pituitary hormonal dysfunction which is known to occur in 20–40% of moderate and severe TBI (sTBI) patients.<sup>7–18</sup> Prospective cohort studies published since 2000 in moderate and sTBI patients show that growth hormone (GH) and gonadotropin deficiencies are the most common endocrinopathies, whereas hypothyroidism, adrenal insufficiency, and diabetes insipidus are less common.<sup>7–18</sup> To date, there have been no prospective studies addressing the possible relationship between football-related concussion and long-term hypopituitarism. However, a recent case report in an adolescent football player with multiple concussions and anterior hypopituitarism has highlighted this association.<sup>19</sup> Studies in kickboxers and retired boxers also have reported relatively high rates of hypopituitarism; in one report, isolated GH deficiency (GHD) was documented in 45% of subjects, and the severity of GHD correlated with the number of bouts and boxing career duration.<sup>20–23</sup> In another study by Bondanelli and colleagues, chronic hypopituitarism was observed in 37% of mTBI patients.<sup>10</sup>

Given the high rate of repetitive head impact and recurrent concussion in professional football players, and the depression, poor QoL, and obesity that are relatively common among NFL retirees, we hypothesized that pituitary dysfunction could be a contributing factor to their poor physical and mental health status. To address these issues, a prospective study of retired NFL players with relatively low QoL scores was designed. Specifically, we sought to 1) determine the rate of pituitary hormonal dysfunction, sexual dysfunction, and associated metabolic dysfunction in these retirees, 2) compare degrees of poor QoL as well as sexual and metabolic dysfunction in retirees with and without hormonal dysfunction, and 3) determine which, if any, factors of the retirees' football career, including number of concussions sustained, number

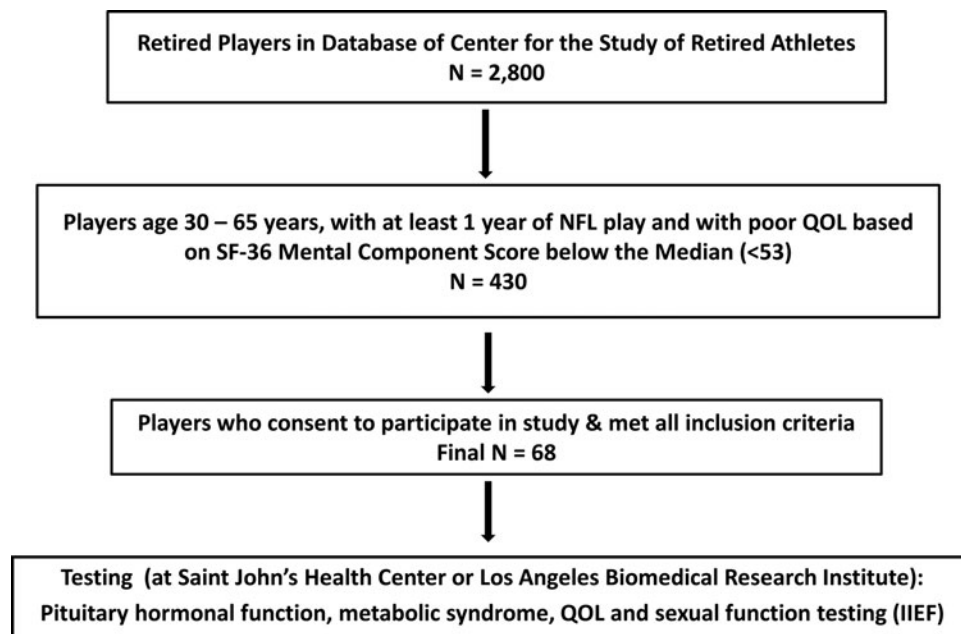
of years played, games played, and positions played, were associated with hormonal dysfunction.

## Methods

### *Initial screening, eligibility, and exclusion criteria*

Subjects were recruited from a database developed over 9 years at the Center for the Study of Retired Athletes (CSRA) in collaboration with the National Football League Players' Association. From this database of over 2800 retirees, 430 retired NFL players were identified who meet the following criteria: 1) age 30–65 who played at least 1 year in the NFL; 2) completed the CSRA Health Survey of Retired NFL Players questionnaire<sup>5,6,24</sup> the Short Form 36 (SF-36) quality-of-life assessment and the International Index of Erectile Function (IIEF) survey; and 3) had poor QoL based on an SF-36 Mental Component Score (MCS) of <49 (Fig. 1). Although an MCS of 49 represents the 25th percentile and below which corresponds to a significantly impaired QoL in U.S. men, the criteria was relaxed near the end of the study to an MCS of <53, which is the median for adult men, to allow completion of enrollment.<sup>16,17</sup> These 430 players were contacted by mail inviting them to participate in this study. If agreeable, they were asked to provide a medication list and complete a questionnaire regarding prior history of treatment for any pituitary hormonal disorders and prior hormone and steroid use, including performance-enhancing steroids during their NFL career. Study exclusion criteria included terminal illness (e.g., advanced cancer or acquired immune deficiency syndrome), recent glucocorticoid use (within the last 3 months), diagnosis of pituitary insufficiency made before NFL retirement, and history of pituitary surgery or irradiation.

The CSRA Health Survey of Retired NFL Players questionnaire, which has been utilized in many previous reports of retired NFL players, asked for a detailed concussion history, including concussions sustained in high school, collegiate, and professional football.<sup>5,6,24</sup> A concussion was clearly defined for study participants as follows: "a concussion is a blow to the head followed by a variety of symptoms that may include any of the following: headache, dizziness, loss of balance, blurred vision, 'seeing stars',



**FIG. 1.** Flow diagram for subject recruitment, eligibility, and enrollment. QOL, quality of life; IIEF, the International Index of Erectile Function.

feeling in a fog or slowed down, memory problems, poor concentration, nausea, or throwing-up. Getting 'knocked out' or being unconscious does NOT always occur with a concussion." In addition to the number of concussions sustained, the survey asked about how many times a physician or athletic trainer evaluated them after a concussion, how many times there was a loss of consciousness (LOC) and/or memory loss, and how often they returned to play immediately after a concussion. Using the same concussion definition, Guskiewicz and colleagues observed high reliability in the self-reporting of earlier concussions (~25 years earlier) when surveyed 18–24 months apart among former NFL players.<sup>5</sup> Kerr and colleagues observed moderate reliability in the self-reporting of a similar cohort of former NFL players when surveyed 9 years apart.<sup>25</sup>

#### Testing of enrolled subjects

Consented subjects were tested at Saint John's Health Center, Santa Monica, or Los Angeles Biomedical Research Institute (LABioMed) at Harbor-UCLA Medical Center (Torrance, CA), beginning with hormonal and metabolic function testing in the morning followed by a brief interview addressing TBI history in and outside their NFL career, as well as other relevant demographic information (e.g., education level), completion of structured questionnaires, and psychological and neuropsychological testing in the afternoon. We report on QoL and erectile function data from this assessment; additional data from the assessment will be reported in other articles.

#### Pituitary hormonal testing

After an overnight fast, all participants were admitted to the testing center at 7 AM to obtain weight, height, and vital signs and for an intravenous (i.v.) catheter insertion. Testing began at 8 AM with baseline blood draws at -30 min and time zero. These initial blood draws included 1) luteinizing hormone (LH), follicle-stimulating hormone (FSH), and free and total testosterone to assess gonadal function, 2) free T4, total T4, and thyroid-stimulating hormone (TSH) to assess thyroid function, 3) prolactin level to assess for lactotroph dysfunction, and 4) serum and urine sodium and osmolality and urine specific gravity were also collected to assess posterior pituitary function. Testing for GHD and adrenal insufficiency were assessed sequentially using stimulation tests. For GHD, at time zero, an insulin-like growth factor 1 (IGF-1) level was drawn, then a glucagon (1 mg; 1.5 mg, if >90 kg) i.v. push was given to assess for GHD with serial measurements of GH at 90, 120, 150, and 180 min. For adrenal insufficiency, adrenocorticotrophic hormone (ACTH) and cortisol levels were drawn at time zero, then a Cortrosyn™ 250 µg i.v. push was administered at time 180 min with serial measurements of cortisol at 210 and 240 min after baseline.

Serum and urine samples for all subjects were stored at -20°C before assay and then measured in the Endocrine and Metabolic Research Laboratory at LABioMed using previously published validated methods.<sup>26,27</sup>

As detailed in Table 1, pituitary hormonal deficiencies were defined as follows: corticotroph axis: peak cortisol levels after Cortrosyn below the 5th percentile (< 12.0 µg/dL); thyrotroph axis: total T4 levels below the 5th percentile (< 4.9 µg/dL); and gonadotroph axis: total testosterone levels below the 5th percentile (< 265 ng/mL). Prolactin levels either above or below the reference range were noted (3–15.4 ng/mL). Criteria for GHD using a control cohort is described below.

#### Control cohort for defining growth hormone deficiency and adjusting for body mass index

Whereas weight per se has not been shown to be a factor in GH responsiveness, central obesity has been well documented to reduce

TABLE 1. ANTERIOR PITUITARY HORMONAL TESTING BATTERY

Axis	Test	Normal range
Thyroid	TSH, total T4	total T4: 4.9–11.7 µg/dL
Adrenal	Cortrosyn stimulation	peak cortisol: 12.0–25.7 µg/dL
Gonadal	LH, FSH, total testosterone	total T: 265–973 ng/dL
GH	Glucagon stimulation	peak GH: BMI < 25: ≥ 3 ng/mL BMI 25–30: ≥ 0.9 ng/mL BMI > 30: ≥ 0.5 ng/mL
Lactotroph	Prolactin	prolactin 3.0–15.4 ng/mL

TSH, thyroid-stimulating hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; BMI, body mass index; GH, growth hormone.

24-h endogenous GH secretion and lower peak GH levels in response to GH stimulation testing.<sup>28–30</sup> Consequently, BMI-adjusted cut points for GH stimulation testing test have been proposed and are currently recommended by several consensus guidelines.<sup>31,32</sup> Because of this known inverse relationship with BMI and peak GH after stimulation testing with glucagon, GHRH/arginine, and insulin tolerance testing, GHD was defined at 3 cut points, adjusted for BMI using a normal non-head-injured control cohort referred to the Dynamic Endocrine Testing Unit at the Oregon Health & Science University (Portland, OR) for assessment of possible GHD with low normal to low serum IGF-1 levels.<sup>27,33–36</sup> From 119 men tested, individuals were excluded if they had a previous history of pituitary or hypothalamic tumor, other hypothalamic or pituitary disorder, pituitary surgery or irradiation, or TBI. Thirty individuals from these 119 men met the criteria and made up the control group. Of these 30 control subjects, 7 had primary hypothyroidism, 5 had primary hypogonadism, and 1 had secondary ACTH deficiency from previous glucocorticoid exposure for Crohn's colitis. All subjects at the time of glucagon stimulation testing were on adequate replacement of thyroid, testosterone, and glucocorticoid hormones. In this cohort, a strong inverse correlation was found between BMI and peak GH. A reference range for BMI < 30 and BMI ≥ 30 used the 5th percentile as the cutoff for defining GHD. From this analysis, the cut points for defining GHD by peak GH after glucagon stimulation testing are: BMI < 25 kg/m<sup>2</sup>: < 3 ng/mL; BMI 25–30 kg/m<sup>2</sup>: < 0.9 ng/mL; and BMI > 30 kg/m<sup>2</sup>: < 0.5 ng/mL. The Results section shows the overall HD rates using the standard cut point of 3 ng/mL for defining GHD as well as with a more stringent BMI-adjusted cut point for defining GHD. However, for all comparisons of the HD versus non-HD cohorts, the more stringent BMI-adjusted cut point for defining GHD was used.

Criteria for the presence of central diabetes insipidus were urine specific gravity ≤ 1.005, urine osmolality < 500 mOsm/kg, and serum sodium > 140 mmol/L in the setting of frequent urination (at least two times per night and excessive/chronic thirst).

#### Metabolic syndrome definition

Fasting glucose, insulin, and lipid panel were calculated by the homeostatic model assessment for insulin resistance and urine microalbumin. Insulin assays were performed at the Endocrine and Metabolic Research Laboratory. MetS was considered present when three or more of the following seven parameters met the following thresholds: fasting glucose > 110 mg/dL; high-density lipoprotein cholesterol < 40 mg/dL, triglycerides > 150 mg/dL or on treatment for hyperlipidemia; systolic blood pressure > 130 mm Hg; diastolic blood pressure > 85 mm Hg; or on antihypertensive medication; and waist circumference > 102 cm.<sup>37</sup>

### Demographic and NFL play information

Demographic data included age, education level, number of seasons and games played, positions played, number of concussions sustained during professional football, collegiate, and high school play (obtained from the CSRA Health Survey of Retired NFL Players questionnaire), as well as non-sports-related TBIs. If, on detailed questioning, subjects had sustained a significant TBI outside their football career (defined as an LOC of 30 min or greater), they were excluded.

### Quality of life and erectile function

The SF-36 data and IIEF survey, well-established widely validated self-assessment tools, were utilized in the current study. Subjects were considered to have erectile dysfunction if their IIEF score was <25 (score range, 5–75).<sup>16,17,38,39</sup> Subdomain analysis was also performed for IIEF: erectile function (questions 1 through 5 and 15; possible total score, 1–30); orgasmic function (questions 9 and 10; possible total score, 0–10); sexual desire (questions 11 and 12; possible total score, 2–10); intercourse satisfaction (questions 6, 7, and 8; possible total score, 0–15); and overall satisfaction (questions 13 and 14; possible total score, 2–10).<sup>39</sup>

### Approval

The institutional review boards of each participating center approved this study, and all participants voluntarily consented to study participation by signing an informed consent form.

### Statistical analysis

Hypopituitarism, metabolic syndrome, and body mass index. Subjects were considered hormonally deficient (HD) for a given axis if their values were below the normal range, as defined in Table 1. Deficiency rates for the cohort for each hormonal axis were calculated. Mean values for the HD and non-HD groups were calculated for each hormonal axis. Rates of MetS (chi-square test) and mean BMI (Student's *t*-test) were compared between the HD and non-HD subjects. The change in BMI over time since retirement was also examined and compared between the HD and non-HD subjects using mixed model with random effect (subjects) and fixed effects (HD group and years since retirement).

Differences in quality of life and erectile function. Results from SF-36 and IIEF survey were compared in the HD and non-HD using the Student's *t*-test (for continuous variables) and the chi-square test (for categorical variables).

Risk factor assessment for hormonal deficiency. The number of self-reported concussions in NFL and non-NFL football seasons (including collegiate and high school), number of professional football games played, years in the NFL and other professional football leagues, as well as age and position played were compared in the HD and non-HD groups using the Student's *t*-test (for continuous variables) or chi-square test (for categorical variables). Position played was compared between the two groups using the chi-square test. The primary position played was also assessed by comparing high-frequency impact (offensive line, defensive line, linebacker, and special teams) versus low-frequency impact positions.<sup>40</sup> *p* values <0.05 were deemed statistically significant. Data are represented as mean ± standard deviation (SD).

## Results

In total, 74 of 430 (17%) invited professional football retirees were studied. On detailed questioning, 6 subjects had sustained significant non-sports-related TBIs outside of their football careers

and were excluded from analysis. None of the 6 excluded subjects had hypopituitarism based on hormonal testing. Demographic, hormonal, metabolic, and QoL testing results are presented on the remaining 68 subjects. As shown in Table 2, the 68 subjects ranged in age from 30 to 65 years, with a median number of years in the NFL of 5 (range, 1–17); 62 of 68 (91.2%) had an SF-36 MCS of ≤49. Only 3 (4.4%) subjects reported having sustained no concussions, and 37 (54.4%) reported having 3 or more NFL career concussions.

### Pituitary hormonal dysfunction, metabolic syndrome and body mass index

Using a standard peak GH cutoff of <3 ng/mL to define GHD, 28 of 68 (41.2%) subjects were GH deficient, however, using a more stringent BMI-adjusted definition of GHD, 13 of 68 (19.1%) were GH deficient. Using this more stringent definition for GHD, overall, HD was found in 16 (23.5%) of 68 subjects, including 10 (14.7%) with isolated GHD, 3 (4.4%) with isolated hypogonadism, and 3 (4.4%) with both GHD and hypogonadism. In total, GHD was found in 13 (19.1%) using the BMI-adjusted definition and hypogonadism in 8.8% (Table 2). Of the 6 subjects with hypogonadism, all had normal or low gonadotropins (LH and FSH), indicating a pituitary/hypothalamic origin. No patients had hypothyroidism, adrenal insufficiency, hyperprolactinemia, or diabetes insipidus. Comparing the HD versus the non-HD subjects (using the BMI-adjusted definition for GHD), mean IGF-1 levels, IGF-1 *z*-scores (adjusted for age), and total testosterone levels were significantly lower in the HD subjects, but all other mean hormonal levels, including those of total T4, free T4, peak cortisol, and prolactin, were similar between the two groups (Table 3).

Using the BMI-adjusted definition of GHD, MetS was present in 34 (50.0%) subjects, including 9 (56.3%) and 25 (48.1%) of HD and non-HD subjects, respectively, (*p*=0.568). Categorized by hormonal deficiency, MetS was present in all subjects with both GHD

TABLE 2. DEMOGRAPHICS, HORMONAL DEFICIENCY AND METABOLIC SYNDROME IN 69 NFL RETIREES

Variable	Mean ± SD or median (range)
Age	47.3 ± 10.2 (30–65)
BMI	33.8 ± 6.0 (24–51)
Years since retirement	18.5 (2–41)
Years in NFL	5 (1–17)
NFL games played	54 (0–241)
	Frequency (%)
GH deficiency <sup>a</sup>	13 (19.1)
Testosterone deficiency	6 (8.8)
GH and testosterone deficiency	3 (4.4)
Any hormonal deficiency	16 (23.5)
Metabolic syndrome	34 (50.0)
BMI > 30	45 (66.2)
High-frequency impact position <sup>b</sup>	44 (64.7)

<sup>a</sup>If GH deficiency criteria had not been adjusted for BMI, and the standard cutoff of peak GH <3 ng/mL had been used, 28 of 68 (41.2%) subjects would have been classified as GH deficient. No subjects had hypothyroidism, adrenal insufficiency, or diabetes insipidus.

<sup>b</sup>Guskiewicz and colleagues.<sup>33</sup>

NFL, National Football League; BMI, body mass index; GH, growth hormone; SD, standard deviation.



TABLE 3. HORMONAL TEST RESULTS IN HORMONALLY DEFICIENT AND NONDEFICIENT RETIREES

Hormonal test	Nonhormone Deficient (n=52)	Hormone deficient (n=16)	p value
Peak GH after GST	6.9±5.7	1.0±1.9	<0.0001
IGF-1	174.1±67.3	127.1±61.4	0.015
IGF-1 z-score, age	2.9±1.9	1.6±1.6	0.020
Total testosterone	486.2±129.9	340.9±115.1	0.0002
Prolactin	7.4±3.2	8.5±3.5	NS (0.243)
Total T4	7.0±1.5	7.6±1.3	NS (0.172)
Peak cortisol	28.2±3.6	29.1±6.6	NS (0.622)

Values are shown as mean±standard deviation. GH, growth hormone; GST, glucagon stimulation test; IGF-1, insulin-like growth factor 1; NS, not significant.

and hypogonadism (n=3), 66.7% of subjects with isolated hypogonadism (n=3), 40% with isolated GHD (n=10), and 48.1% in those with no hormonal deficiency (n=52). Compared to the 62 subjects without hypogonadism, the 6 subjects with hypogonadism had a higher rate of MetS (83.3% vs. 46.8%; p=0.087) and higher BMI (36.0±6.6 vs. 33.6±5.9; p=0.338), but these differences were not statistically significant.

BMI at time of testing was inversely correlated with peak GH after glucagon stimulation testing, as shown in Figure 2. However, BMI was similar between the HD and non-HD groups (34.0±6.2 vs. 33.7±6.0; p=0.853). The percent of obese subjects (BMI > 30) at the time of testing was also similar (56.3% for HD and 69.2% for non-HD subjects). Based on subjects' reported weight at retirement, BMI increased significantly for the cohort overall from time of retirement to time of testing (p=0.001), but the change in BMI over time was similar between the HD and non-HD groups (p value from linear mixed model=0.214; Fig. 3).

Quality of life and erectile function

Comparing the HD and non-HD groups (using the BMI-adjusted definition for GHD), there was a trend toward lower mean SF-36 MCS (32.9±10.5 vs. 37.4±9.6, respectively; p=0.113), although SF-36 PCS scores were similar (44.1±13.4 vs. 43.0±10.5, respectively; p=0.740; Table 4). IIEF scores were lower in the HD group (42.8±20.0 vs. 55.2±16.8; p=0.016), but the rate of erectile dysfunction (IIEF score < 25) in the HD and non-HD groups was similar (18.8% vs. 9.8%; p=0.336). Of 6 retirees with low testosterone, 3 (50%) had IIEF scores under 25, compared to 5 of 61 (8.2%) retirees with normal testosterone (p=0.003). Subdomain analyses of IIEF (sexual desire, overall satisfaction, erectile function, orgasmic function, and intercourse satisfaction) showed no significant differences between HD and non-HD groups. Retirees with low testosterone levels had significantly lower erectile function (19.00±7.75 vs. 25.47±5.06; p=0.021) and orgasmic function (6.75±2.87 vs. 8.79±1.75; p=0.035) scores, compared to the eugonadal group. Those who had MetS had lower IIEF score, compared to those who did not have MetS (55.81±13.86 vs. 61.90±8.55; p=0.057) and significantly lower erectile function subdomain score (23.21±6.36 vs. 26.76±3.76; p=0.014).

Risk factors for hormonal deficiency: demographics, concussion history, and steroid use

As shown in Table 5, the HD and non-HD groups (using the BMI-adjusted definition for GHD) were similar in terms of mean age, median seasons in the NFL, games played, and number of concussions sustained in both NFL and non-NFL leagues (including high school and collegiate). The non-HD group had a higher mean years of play in the NFL, compared to the HD group (6.1±4.0 vs. 3.9±2.8; p=0.045). The distribution of high- versus low-frequency impact positions was also similar between the two groups.

Regarding performance-enhancing steroid use, in total, 9 of 68 (13.2 %) subjects acknowledged steroid use, including 3 of 15 in

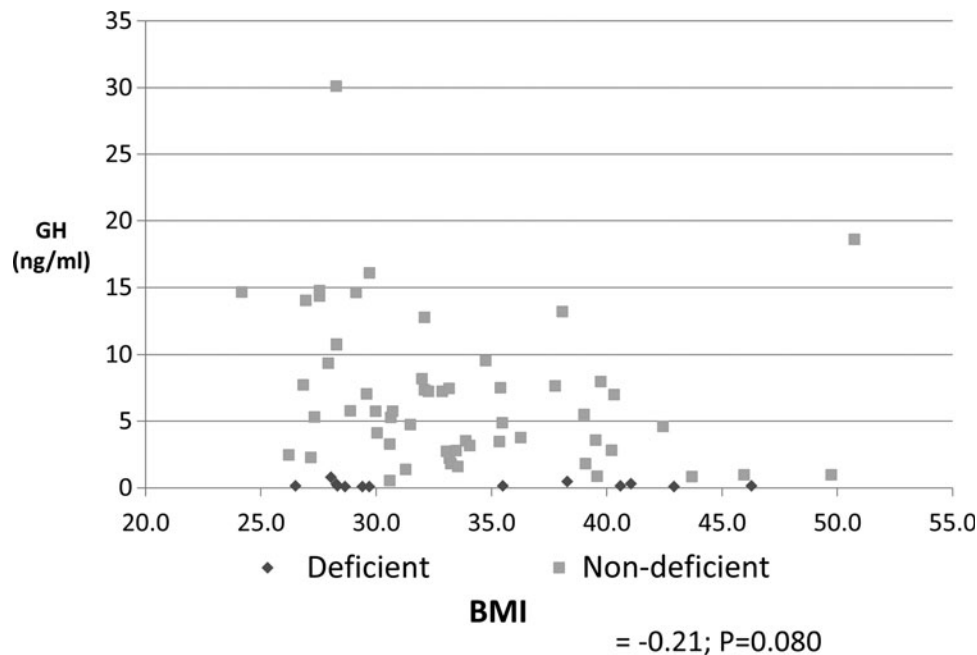
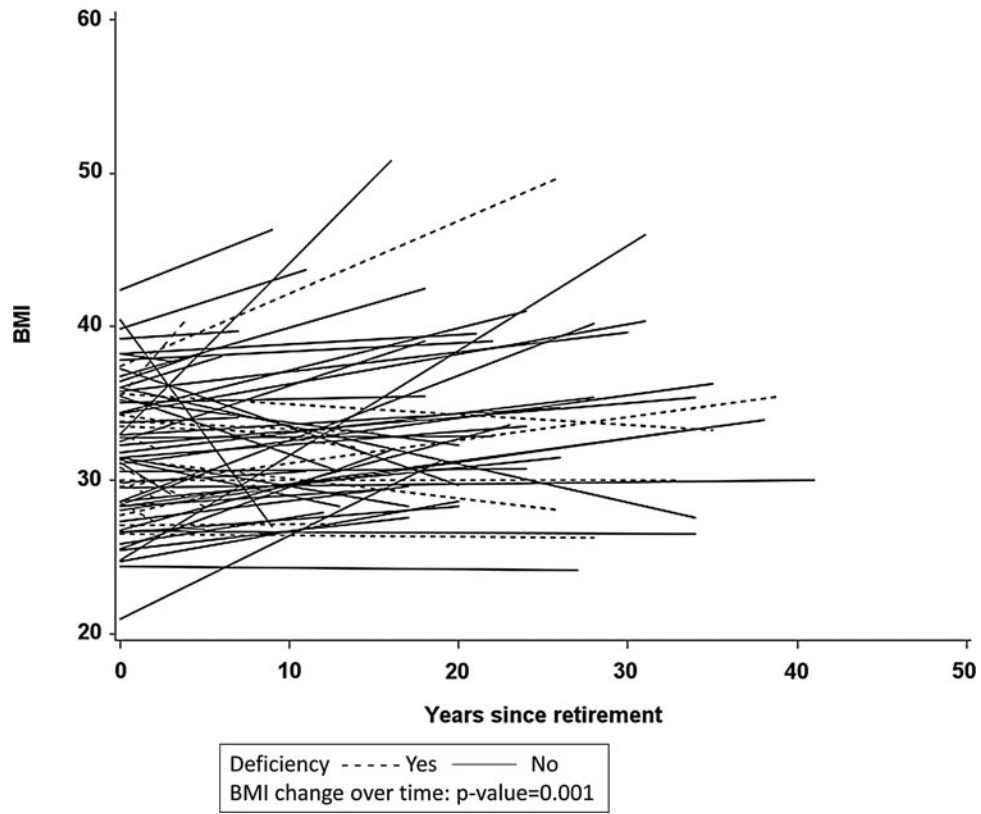
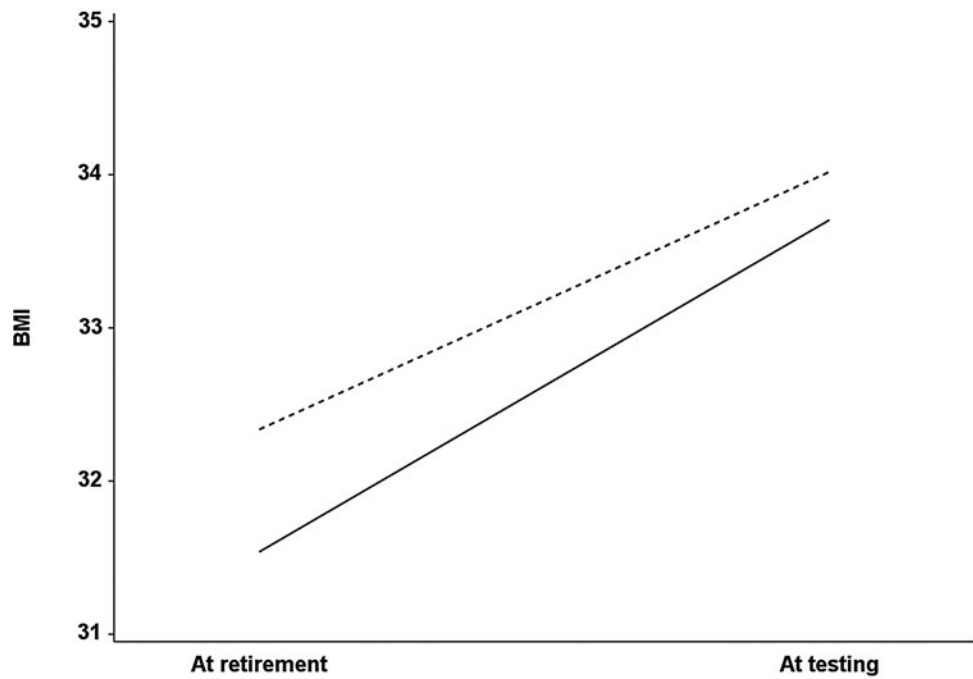


FIG. 2. Peak GH after glucagon stimulation as a function of BMI. The 13 subjects with GH deficiency denoted by diamonds; non-GH deficient are denoted by squares. GH, growth hormone; BMI, body mass index.



**FIG. 3A.** Changes in BMI since retirement to time of testing for all 58 subjects. Subjects with hormonal deficiency are shown by dashed lines and subjects without hormonal deficiency with solid lines. BMI, body mass index.



**FIG. 3B.** Change in BMI since retirement to time of testing grouped for subjects with hormonal deficiency (dashed line) and without hormonal deficiency (solid line). BMI, body mass index.

**TABLE 4. SF-36 AND ERECTILE FUNCTION SCORES IN HORMONALLY DEFICIENT AND NONDEFICIENT RETIREES**

<i>Factor</i>	<i>Nondeficient (n=52)</i>	<i>Deficient (n=16)</i>	<i>p value</i>
QOL: SF-36 MCS, mean ± SD	37.4 ± 9.6	32.9 ± 10.5	0.113
QOL: SF-36 PCS, mean ± SD	43.0 ± 10.5	44.1 ± 13.4	0.740
Erectile function (IIEF) < 25	9.8%	18.8%	0.336
Erectile function score, mean ± SD	55.2 ± 16.8	42.8 ± 20.0	0.016

QOL, quality of life; SF-36, the Short Form 36 quality-of-life assessment; MCS, Mental Component Score; SD, standard deviation; PCS, Physical Component Summary; IIEF, the International Index of Erectile Function.

the HD group (20%) and 6 of 52 (11.5%) in the non-HD group (*p* = 0.4075; Fisher’s exact test); 1 subject in the HD group did not answer the question on his survey. Of the 3 HD subjects who acknowledged steroid use, duration was given as 1 year for each subject and all subjects had been retired for at least 10 years at the time of hormonal testing. In the 6 non-HD subjects, duration of steroid use ranged from 1 month to 7 years.

**Discussion**

*Summary of findings*

The most important finding in this prospective study was that pituitary dysfunction and MetS are relatively common in retired professional football players and may be significant contributors to their poor QoL. However, years played in the NFL and concussion history were not associated with these hormonal and metabolic dysfunctions. In this cohort of 68 NFL retirees with poor, QoL based on SF-36 MCS, 23.5% had pituitary hormonal dysfunction, including 19.1% with GHD, 8.8% with hypogonadism, and 4.4% with both GHD and hypogonadism. In addition, MetS was present in 50.0%. Notably, there was a relatively high rate of GHD, despite using very stringent BMI-adjusted definitions of the glucagon stimulation test to confirm the presence of GHD. The 6 subjects with low testosterone had a high rate of sexual dysfunction (50.0%), including decreased erectile and orgasmic function, MetS (83.3%), and obesity (83.3%; BMI > 30). Including all 16 subjects with either low testosterone and/or GH deficiency, there was a trend toward lower QoL based on the SF-36 MCS. There were no clear risk factors for hormonal deficiency related to concussion history or position played, although 64.7% of retirees played positions with a high frequency of head impact. The implications of these findings are discussed below.

*Defining hormonal deficiency*

In this study, standard pituitary hormonal testing was used, including stimulation testing for the corticotroph and somatotroph axes.<sup>41</sup> For GHD, we utilized the glucagon stimulation test, which is a well-validated test for this purpose.<sup>32,33,36,42–44</sup> Given that a majority of this cohort was obese and that peak GH levels are negatively correlated with BMI for all types of GH stimulation testing, including glucagon, GHRH/arginine, and the insulin tolerance tests, it was necessary to use a BMI-adjusted definition for GHD with a control cohort of overweight subjects.<sup>27,34–36</sup> Without a BMI adjustment and

**TABLE 5. POTENTIAL DEMOGRAPHIC AND PROFESSIONAL FOOTBALL RISK FACTORS FOR HORMONAL DYSFUNCTION**

<i>Factor</i>	<i>Nondeficient (n=52)</i>	<i>Deficient (n=16)</i>
Age, mean ± SD	47.1 ± 10.7 years	48.1 ± 8.4 years
Years in NFL (median, IQR)	5 (3–8.5)	4 (1–6)
Years in NFL (mean ± SD; <i>p</i> = 0.045)	6.1 ± 4.0	3.9 ± 2.8
NFL games played (median, IQR)	64 (22.5–107.5)	48 (2–70)
NFL concussions (median, IQR)	3 (2–5)	2.5 (1.0–6.5)
All concussions (median, IQR) <sup>a</sup>	5 (3–10)	4.5 (1.5–12.5)
Position played <sup>b</sup> (high- vs. low-frequency)	63.5%	68.8%

<sup>a</sup>Includes NFL, collegiate, and high school concussions.

<sup>b</sup>High-frequency impact positions include offensive line, defensive line, linebacker, and special teams, according to Guskiewicz and colleagues.<sup>33</sup> SD, standard deviation; NFL, National Football League; IQR, interquartile range.

using the standard cutoff for GHD, the rate of GHD in this cohort would have been over 40%. With this more stringent and appropriate criteria for GHD, the rate of GHD was 19.1%. Because gonadotropin and thyrotropin-releasing hormones are no longer available commercially in the United States, pituitary stimulation tests using these hormones cannot be performed and is generally not necessary for the clinical diagnosis of central hypogonadism or hypothyroidism.

*Previous studies on postconcussive hypopituitarism*

Previous studies indicate that the somatotroph and gonadotroph axes are the most vulnerable to the primary and secondary insults of moderate and sTBI, with deficiency rates ranging from 8% to 38% and 0% to 29%, respectively.<sup>7–15,45,46</sup> In contrast, corticotroph, thyrotroph, and posterior pituitary deficiencies are less common, with rates averaging 8%, 5%, and 2% respectively.<sup>7–15,45,46</sup> In the present study of mTBI subjects who sustained repetitive head impact with a median of 5 concussions in their football career, a similar pattern of hormonal deficiency was observed involving the somatotroph and gonadotroph axes with sparing of corticotroph, thyrotroph, and posterior pituitary function. GHD remained the most common HD in our cohort, despite adjustment for BMI for the diagnostic cut point for GHD. Relatively few studies have addressed the association between sports-related mTBI and hypopituitarism.<sup>47</sup> Small case series in boxing and kickboxing have shown a high rate of GHD, and one case report highlighted the association between repeat concussion in an adolescent athlete and subsequent anterior hypopituitarism.<sup>15,19,21–23,48</sup>

*Quality of life, erectile dysfunction, metabolic syndrome, and obesity*

In this study, not surprisingly, men with low testosterone had lower erectile and orgasmic scores, compared to eugonadal men, based upon the IIEF. Hormonally deficient subjects with either GHD or low testosterone also had lower average IIEF scores than those without HD. Whereas there was only a trend toward lower SF-36 MCS in the hormonally deficient group, the overall cohort reported a poor QoL, with over 90% having an SF-36 MCS of < 49. These findings are consistent with previous reports of TBI patients

with GHD and/or low testosterone. Both GHD and hypogonadism have been associated with poor QoL.<sup>49–60</sup>

In addition to poor QoL, both GHD and hypogonadism can contribute to decreased lean body mass, increased fat mass (in particular, visceral fat), and poor exercise capacity that further contribute to poor QoL, obesity, and MetS, increasing cardiovascular disease (CVD) risk.<sup>51,54,57,61–70</sup> Studies have shown that MetS is associated with, and predicts the development of, low serum testosterone levels in men.<sup>62,64,65,71</sup> Five of 6 subjects with hypogonadism had MetS and obesity. However, whereas obesity was present in 65% of subjects and MetS in 49% of subjects, these rates were statistically not different in subjects with and without any hormonal deficiency. Thus, it is likely that other factors, such as football-related orthopedic injuries, diet, and exercise habits, and other medical comorbidities, contributed to subjects' development of obesity and MetS and CVD risk.

#### *Etiology of hypopituitarism in mild traumatic brain injury*

No correlation was found between the development of hormonal dysfunction and the number of self-reported football-related concussions sustained in the NFL or throughout their football career from high school through the NFL. This finding was somewhat surprising, given that earlier studies by our group have shown a strong association between recurrent concussion and lifetime depression and mild cognitive impairment. In two studies by Guskiewicz and colleagues, they reported that retired players reporting 3 or more concussions (24.4%) were 3 times more likely to be diagnosed with depression and 5 times more likely to be diagnosed with mild cognitive impairment than those who had not sustained NFL concussions.<sup>5,6,25</sup> In a follow-up study by Kerr and colleagues, of 1044 members of the NFL Retired Players Association, 10% reported being clinically diagnosed with depression, which ranged from 3% in those with no concussions to 27% for those with 10 or more concussions.<sup>72</sup> Notably, in the present study, other measures of head impact exposure, including years in the NFL, games played, and position played, similarly did not predict development of subsequent hormonal dysfunction. This lack of correlation between concussion history and hypopituitarism raises the issue of what other factors might lead to eventual hormonal deficiencies in these retired athletes. It is possible that multiple subconcussive impacts sustained over a long career could lead to eventual hormonal dysfunction.<sup>73</sup> Other non-football-related etiologies of GHD and hypogonadism, such as age-related and obesity-associated decline in serum testosterone and GH, may also be important factors to consider in this population of retired athletes. The acknowledged use of performance-enhancing steroids, which was documented in a minority of subjects, was not associated with any hormonal dysfunction. Notably, the overall rate of admitted steroid use in this cohort (13%) was similar to the 9% rate from a larger cohort of over 2552 retirees in an earlier study by our group.<sup>24</sup>

#### *Study limitations and future investigations*

Although the current study is the first to evaluate hormonal dysfunction in retired NFL players, it is not without some limitations. First, a larger sample size would be beneficial to determine whether these preliminary findings are valid in a larger population of NFL retirees and may have allowed for comparison of subjects with different types of hormonal dysfunction. Second, only 17% of the retirees invited to take part in the study ultimately did participate, which introduces a selection bias. Third, it would be important to determine the rate of hypopituitarism in a cohort of NFL retirees

with a good QoL based on their SF-36 scores or similar validated QoL measures. Fourth, a more comprehensive assessment of concussion history, including severity and interval between concussions, may have provided new insights regarding the relationship between mTBI and hormonal dysfunction.<sup>25</sup> Fifth, additional information regarding subjects' football-related orthopedic injuries and medical comorbidities as well as diet and exercise regimens may have helped to unravel the potential relationships between concussion, obesity, and QoL. Sixth, despite our attempts to determine whether retirees used performance-enhancing (anabolic) steroids during their NFL career, we cannot be certain that some subjects did, in fact, use such substances and failed to admit this fact. In a subset of subjects, it is also possible that steroid use had a lasting effect on pituitary function, especially with a prolonged duration and high-dose use. However, in the 3 subjects with HD who did acknowledge such use, the duration of 1 year or less, and at least a decade interval between such use and their hormonal testing, would suggest that steroid use was not an important factor in their development of HD. Finally, in future studies, brain and pituitary magnetic resonance imagings may be helpful in documenting the long-term structural effect of repetitive sports-related concussions on both brain and hypothalamic-pituitary function.

#### *Clinical implications*

Retired professional football players have a relatively high rate of poor QoL, depression, and other neurocognitive deficits, compared to the general population.<sup>5,6,72</sup> Though the cause of hormonal dysfunction in this selected subset of NFL retirees remains somewhat unclear, the finding of GHD in almost 20% of retirees and hypogonadism in almost 10% of retirees is significant. Given the well-documented clinical manifestations of untreated GHD and low testosterone, these hormonal deficits may be contributing factors to poor QoL, erectile dysfunction, obesity, and MetS, as well as to cognitive decline and depression, in these retired athletes. Although preliminary, these findings have implications for all active and retired athletes exposed to repetitive head impact and sports-related concussion. For such individuals who exhibit symptoms and signs of hypopituitarism, pituitary hormonal testing should be considered. Specific complaints and signs typically associated with GHD and hypogonadism, such as weight gain, decreased exercise capacity, fatigue, low libido, depression, and cognitive decline, should trigger a pituitary hormonal evaluation. Documented GHD, low testosterone, or other deficiencies, such as hypothyroidism or adrenal insufficiency, should be appropriately treated in consultation with an endocrinologist. Specifically, because it relates to the findings of GHD and hypogonadism in this study, GH replacement is known to improve QoL in patients with adult-onset GHD and helps reduce fat mass and improve exercise capacity.<sup>51,52,54,55,74–80</sup> The benefits of testosterone therapy for men are clear and considered standard practice.<sup>50,57,81</sup> In addition, the high prevalence of MetS in retired football players is important because lifestyle changes may reverse some of these findings and improve the cardiovascular and metabolic disease risks that are associated with MetS. Lifestyle changes to reduce weight with appropriate hormonal supplement in these former athletes may improve not only QoL, but also decrease disease risks.

#### **Conclusions**

In this cohort of retired professional football players, using a stringent BMI-adjusted definition of GHD, chronic hypopituitarism was present in 23.5% of subjects and MetS in 50%. Over 50% of



our subjects suffered 3 or more concussions during their NFL career. As observed in other types of TBI, the somatotroph and gonadotroph axes appear to be the most vulnerable to sports-related concussion and repetitive head impact. Though a causative link between repetitive mTBI and hormonal dysfunction has not been proven in this study, these hormonal deficiencies and metabolic disturbances may be important factors in the overall poor QoL and general health of many retired football players. Further study of pituitary function involving a larger number of subjects is warranted in athletes sustaining repetitive head impact.

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