Patient reported outcome in posttraumatic pituitary deficiency: results from The Danish National Study on posttraumatic hypopituitarism

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Abstract

Objective: Posttraumatic pituitary hormone deficiency is often suggested. The impact of these predominantly mild and often irreproducible deficiencies on outcome is less clear. The aim of the present study was to describe patient reported outcome in a national *a priori* unselected cohort of patients with traumatic brain injury (TBI) in relation to deficiencies identified upon pituitary assessment.

Design and methods: We conducted a nationwide population-based cohort study. Participants were Danish patients with a head trauma diagnosis recorded in the Danish Board of Health diagnostic code registry; 439 patients (and 124 healthy controls) underwent assessment of anterior pituitary function 2.5 years (median) after TBI. Questionnaires on health-related quality of life (QoL) (SF36, EuroQoL-5D, QoL assessment of GH deficiency in adults) and fatigue (MFI-20) were completed in parallel to pituitary assessment.

Results: Patients with TBI had significant detriments in QoL. Impairment (mainly physical scales) related to pituitary deficiency, although only partially confirmed after adjustment for demographic differences. Hypogonadotropic hypogonadism related to several QoL scores. Increasing impairments were observed with declining total testosterone concentrations (men), but not free testosterone concentrations or any other hormone concentrations. Total testosterone was not independently related to impaired QoL and fatigue, after adjustment for demographics, and treatment with antidiabetics, opioids, antidepressants, and anticonvulsants.

Conclusions: Only a very limited relationship between pituitary hormone deficiencies and QoL/fatigue was demonstrated. Due to the dominating influence of concurrent comorbidities, pituitary deficiencies were not independently related to QoL/fatigue. Causality is still to be shown, and whether substitution therapy could be of additional relevance in selected patients needs to be proven.

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Introduction

Traumatic brain injury (TBI) is one of the most common causes of death and disabilities worldwide. The majority of cases are mild (90%), and while most recover within 3 months, many are left with significant functional limitations or psychosocial morbidity. Thus, impairments such as depression, anxiety, fatigue, sexual dysfunction, pain, sleep disorders, cognitive dysfunction, and decreased health-related quality of life (QoL) are all commonly described in TBI survivors.

Within the past 15 years, pituitary hormone deficiency was often described in the immediate and long-term follow-up of TBI patients, which led to recommendations that patients with head trauma should be considered for pituitary assessment (1). However, recent data from large cohorts raised doubt about the evidence behind such recommendations, as they were unable to confirm the previously reported high prevalence of pituitary dysfunction (2, 3, 4). Although severe hypopituitarism may certainly present as a complication to brain injury, mostly mild and often irreproducible deficiencies have been reported.

The impact of post-TBI pituitary insufficiencies has been less addressed. Hypopituitary symptoms highly overlap those observed in TBI patients, and there are data to suggest that hypopituitarism may worsen TBI morbidity including QoL (5, 6, 7, 8), and functional outcome (9), whereas conflicting results exist as to cognitive function impairment (9, 10).

Questioning the impact of the predominantly mild and often irreproducible pituitary hormone deficiencies found by mostly single pituitary function assessment, the objective of this study was to examine patient reported outcome in a national *a priori* unselected cohort of well-characterized patients with TBI, in relation to deficiencies upon single pituitary assessment.

Subject and methods

Participants

We recruited patients hospitalized in 2008 with a head trauma diagnosis recorded in the Danish Board of Health diagnostic code registry, aged 18–65 years, with total length of hospitalization ≥ 24 h; 2014 patients were identified from a background population of 5.5 million DK citizens. By retrospective chart review, 856 patients were eligible for inclusion, meeting the following criteria: loss of consciousness, amnesia, or cranial/cerebral imaging abnormalities, and exclusion criteria published

previously (4). Of these patients, 463/856 (54%) patients accepted and underwent pituitary assessment according to the protocol median 2.5 (range 1.1–4.0) years after the trauma. CT scans available from the time of admission were classified by a radiologist (A W). Baseline trauma-related data registered were based on the clinical description at hospitalization and at the time of endocrine testing. Data on current medication were obtained at the time of endocrine testing.

For comparison, 124 healthy gender, BMI, and age group-matched controls recruited by newspaper advertisement or web-based recruiting (www.forsogsperson.dk) were included. Cutoff values for male hypogonadism and for the 250 μ g synacthen test were based on healthy cohorts as previously reported (11, 12).

The protocol was approved by the local ethics committee (J. nr H-B-2008-122). All participants or their closest relatives gave written informed consent before enrolment.

Pituitary assessment and diagnostic criteria

Pituitary hormone assessment was performed at one of four participating centers. All patients were scheduled for baseline evaluation and growth hormone (GH) and adrenocorticotropin (ACTH) stimulation tests by either an insulin tolerance test (ITT) or a pyridostigmin–GH-releasing hormone (PD–GHRH) test + a 250 μ g synacthen test. A GHRH–arginine test was performed in all cases of contraindications to the ITT or PD–GHRH test. The study was made as part of a larger protocol, which included dual testing in some patients. Pituitary status in the present study relates to biochemical results from the first test performed. Assessment of all anterior pituitary axes was performed in 439/463 (95%) patients, whereas 21 (5%) refrained from GH testing, and three patients were tested by baseline evaluation only; 13/439 patients had missing biochemical data (one free thyroxine (T_4); 12 prolactin). The final cohort thus included 426 patients.

Local cutoff values were calculated from healthy controls. Cutoff values for the 250 μ g synacthen test, ITT, PD–GHRH and GHRH–arg tests, and prolactin were defined by the lower 90% confidence limits (CL) of the 2.5th percentile (mean -1.96 s.d.) for each hormone.

Similar definitions were used for fT_4 and testosterone to define central hypothyroidism and male hypogonadism, given thyrotropin (TSH) and luteinizing hormone (LH) below their upper 90% CLs of their 97.5th percentile respectively. Central hypogonadism in premenopausal

women was defined by amenorrhea or oligomenorrhea and low estradiol, while in postmenopausal women by LH/follicle-stimulating hormone (FSH) below the lower reference limits given by the local laboratory as very few healthy postmenopausal women were included for appropriate definition.

Thus, secondary adrenal deficiency was defined as peak cortisol <398 nmol/l (ITT) or as 30 min cortisol <510 nmol/l (synacthen test), hypoprolactinemia as prolactin <61 mU/l, and secondary hypothyroidism as fT_4 <11.1 pmol/l (TSH <4.5 mU/l). GH deficiency was defined as peak GH <1.9 $\mu\text{g/l}$ in response to ITT, or as peak GH <10.3, 2.9, and 1.2 $\mu\text{g/l}$ in response to PD-GHRH/argGHRH in normal weight, overweight, and obese subjects respectively. Male hypogonadotropic hypogonadism was defined as a serum total testosterone <12 mmol/l (waist circumference <102 cm) and <7.5 mmol/l (waist circumference ≥ 102 cm) given LH <6 U/l.

Assays

GH was analyzed by chemiluminescence immunoassay (DPC Immulite 2000; Siemens, calibrated against WHO International Standard 98/574). Lower and upper limits of quantification were 0.05 and 40 $\mu\text{g/l}$ respectively, with analytic sensitivity of 0.01 $\mu\text{g/l}$. The local intra-assay coefficient of variations (CV) were 8 and 9% at concentrations of 2.6 and 6 $\mu\text{g/l}$ respectively. Plasma cortisol, TSH, fT_4 , LH, FSH, and estradiol were analyzed by electrochemiluminescence immunoassay (Modular-E module; Roche, GmbH). The local long-term total assay variations were cortisol 8 and 9% at concentrations of 116 and 978 nmol/l respectively; TSH 4 and 6% at concentrations of 0.9 and 5 mU/l respectively; fT_4 7% at concentrations of 12 and 30 pmol/l; LH 7% at concentrations of 5 and 70 U/l; FSH 7% at concentrations of 8 and 40 U/l; estradiol 10 and 7% at a concentration of 0.2 and 2.5 nmol/l respectively.

Plasma prolactin was analyzed by immunofluorescence (Kryptor; Thermo Fisher, Berlin, Germany) calibrated against 3rd IS WHO 84/50; local total assay CVmax was 8% at a concentration of 120 mU/l.

Analyses of total testosterone, SHBG, and free testosterone were performed at Statens Serum Institute, Copenhagen, Denmark. Proteins were precipitated using acetonitrile containing isotopically labelled internal standard. Testosterone was determined by reversed-phase chromatography with tandem mass spectrometry. Calibrators and controls were purchased from Perkin Elmer (Waltham, MA, USA). The sensitivity and the intra- and inter-assay CV were total testosterone 0.1 nmol/l, 9%, and

10% respectively. SHBG levels were determined by immunofluorometric assays using an Abbot Architect. The sensitivity and the intra- and inter-assay CV were 0.1 nmol/l, 4%, and 6% respectively. Free testosterone was calculated from the measurement of total testosterone and SHBG (13).

Patient reported outcome

Outcome questionnaires were completed in parallel to pituitary hormone assessment in patients and healthy controls. Two generic QoL questionnaires (EuroQoL-5D (EQ5D) (14) and Medical Outcomes Study 36-Item Short-Form Health Survey (SF36) (15)), and one specific for GH deficiency (QoLAGHDA) (16) were included. Due to the common complaint of fatigue in TBI patients, the Multidimensional Fatigue Inventory (MFI-20) (17) was added.

Furthermore, non-standardized questions were included as to whether or not patients had experienced changes in symptoms related to pituitary disease including changes of libido, erectile dysfunction, hair growth, menstrual dysfunction, tiredness, cold intolerance, sleep (amount and pattern), thirst, and nycturia. Questions were answered dichotomously.

Statistical analysis

Categorical data are presented as number (%), continuous data as mean (s.d.) if normally distributed and otherwise as median (range). Comparison of categorical data was performed by the χ^2 test or Fisher's exact test in tables with expected frequencies <5. Between-group comparisons were analyzed by unpaired *t*-tests for normally distributed data, otherwise by the Mann-Whitney *U* test. Univariate and multivariate regression analyses were conducted to analyze the association between outcome measures (questionnaire scores) and covariates (pituitary deficiencies, hormone concentrations, demographics, trauma characteristics, and medications). Multivariate analyses were conducted with backward elimination. No interactions were identified. Statistical analyses were performed by SAS version 9.1 (SAS Institute, Inc., Cary, NC, USA). In all cases, a difference was considered significant when $P < 0.05$.

Results

Patient characteristics

The population included 426 patients with full anterior pituitary function assessment (Table 1). Most patients

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Table 1 Characteristics in pituitary sufficient and deficient TBI patients respectively. Data are expressed as number (%) unless specified otherwise.

	<i>n</i>	Deficient patients (<i>n</i> = 84)	Sufficient patients (<i>n</i> = 342)	<i>P</i>
Gender (male)	426	62 (74%)	220 (64%)	0.1
Age (years) ^a	426	48.2 (13.3)	43.6 (14.7)	0.01
BMI (kg/m ²)	426	26.2 (4.8)	26.0 (4.4)	0.92
Trauma cause	426			
Road accident		36 (43%)	154 (45%)	0.90
Fall		32 (38%)	123 (36)	
Assault		5 (6%)	24 (7%)	
Other		11 (13%)	41 (12%)	
Glasgow coma scale	412			
Mild (GCS 13–15)		60 (72%)	234 (71%)	0.9
Moderate (GCS 9–12)		7 (8%)	33 (10%)	
Severe (GCS <9)		16 (19%)	62 (19%)	
Posttraumatic amnesia	418			
Yes		70 (84%)	284 (85%)	0.7
Length (h) ^b		0.5 (0–504)	0.9 (0–144)	0.8
Hospitalization (days) ^b	418	4 (1–108)	4 (1–44)	0.2
Intracerebral lesions (CT)	357			
Axonal injury		2 (3%)	15 (5%)	0.4
Oedema		6 (9%)	40 (14%)	0.3
Midline shift > 4 mm		9 (13%)	34 (12%)	0.8
SAH		14 (20%)	64 (22%)	0.8
EDH		4 (6%)	23 (8%)	0.5
SDH		18 (26%)	77 (26%)	0.9
Contusions		19 (27%)	83 (28%)	0.8
Vault fractures		13 (23%)	45 (20%)	0.6
Base of skull fractures		17 (30%)	63 (28%)	0.7
Glasgow outcome score <5	380	28 (39%)	90 (29%)	0.1
Medication (at the time of pituitary testing)	424			
AEDs		6 (7%)	22 (6%)	0.8
Opioids		10 (12%)	12 (4%)	0.002
Antidepressants		15 (18%)	44 (13%)	0.2
Antidiabetics		9 (11%) ^c	8 (2%)	0.002

AED, antiepileptic drugs; EDH, epidural hemorrhage; SAH, subarachnoidal hemorrhage; SDH, subdural hemorrhage.

^aMean (s.d.).

^bMedian (range).

^cFour patients had BMI above 30 kg/m² (all diagnosed with isolated hypogonadism), five patients had BMI below 30 kg/m² (isolated GH (*n* = 1), LH/FSH (*n* = 1), and prolactin (*n* = 2) deficiency and GH+prolactin deficiency (*n* = 1)).

(71%) had mild TBI as evaluated by the Glasgow coma scale (GCS). None of the patients were diagnosed with pituitary dysfunction before the protocol and thus none received supplemental substitution therapy. Median 2.5 (1.0–4.0) years after the index trauma, 84/426 (20%) patients were biochemically deficient at one (78/426 (18%)) or two (6/426 (2%)) pituitary axes, with affection of the following: GH: 28/426 (6.6%); LH/FSH: 23/426 (5.4%); prolactin: 20/426 (4.7%); ACTH: 17/426 (4.0%); and TSH: 2/426 (0.5%). None had affection of three or more axes.

Deficient patients were older and more frequently reported daily treatment with opioids and antidiabetics (Table 1). Opioid treatment was more frequent in ACTH-deficient patients (17% vs 4%; *P* = 0.05) and hypogonadal patients (19% vs 4%; *P* = 0.002), whereas use of

antidiabetics was more frequent in hypogonadal patients (19% vs 4%; *P* = 0.002) and hypoprolactinemic patients (15% vs 4%; *P* = 0.06). Deficient and sufficient patients did not differ as to trauma-related factors (Table 1).

QoL and injury-related factors

Patients with moderate to severe TBI (as indicated by GCS <13) had lower EQ5D VAS (*P* = 0.01), increased 'physical and mental fatigue' (*P* < 0.02), decreased 'physical' (*P* = 0.002) and 'social' (*P* = 0.04) function, 'physical' (*P* = 0.01) and 'emotional' (*P* = 0.04) role, relative to patients with mild TBI. Patients with traumatic subarachnoid hemorrhage (SAH) had lower EQ5D VAS, 'general health', 'physical function and activity', and increased 'physical fatigue' (all *P* < 0.05).

Figure 1

Mean (s.d.) EQ-5D VAS and QoL-AGHDA scores in healthy controls (black bars) and in TBI patients with pituitary deficiency (light grey bars) and sufficiency (diagonal striped bars) respectively. EQ-5D VAS measures overall health status on a visual analogue scale, scored 0–100, with 100 denoting the best imaginable health. QoL-AGHDA measures the impact of GH deficiency in one overall score, range from 0 to 25, with higher scores representing worse HRQL. * $P < 0.001$ compared with TBI patients (unadjusted).

relative to those without SAH. Likewise, patients with subdural hemorrhage had increased ‘general fatigue’ ($P = 0.01$), ‘reduced motivation’, ‘vitality’, and ‘mental health’ (all $P < 0.05$). No differences in patient reported outcome were observed in patients with and without epidural hemorrhage, vault or base of skull fractures, cerebral contusions, cerebral edema, or axonal injury.

Patients with Glasgow outcome scale < 5 (i.e. sub-normal recovery) scored worse in all scales ($P < 0.0001$).

QoL and medical treatment

In patients, treatment with antidepressants was related to worse outcome scores in all scales ($P < 0.001$). Opioid treatment was related to worse scores ($P < 0.001$) in all scales but ‘reduced motivation’. Patients medically treated for diabetes had lower ‘physical function’ ($P = 0.002$) and increased ‘physical fatigue’ ($P = 0.01$), whereas those treated with antiepileptic drugs had lower EQ5D VAS ($P = 0.01$), increased ‘physical’ and ‘mental fatigue’ ($P < 0.01$), and decreased ‘physical function’ ($P = 0.002$) and ‘physical role’ ($P < 0.001$).

HRQL in patients and controls

Age- and gender-adjusted EQ5D, SF36, QoLAGHDA, and MFI-20 scores were significantly worse in both sufficient

and insufficient patients, relative to healthy controls (all $P < 0.0001$) (Figs 1 and 2).

HRQL and pituitary function

Patients with pituitary deficiencies ($n = 84$) had increased ‘physical fatigue’ ($P = 0.03$), worse ‘physical component score’ ($P = 0.03$), and ‘physical function’ ($P = 0.01$) relative to patients with intact pituitary function (Figs 1 and 2).

Figure 2

Mean (s.d.) SF-36 and MFI-20 scores in healthy controls (black bars), and TBI patients with pituitary deficiency (light grey bars) and sufficiency (diagonal striped bars) respectively. SF-36 consists of 36 items summated into eight scales measuring different dimensions of health. The eight scales are further condensed into two summary component scores of mental and physical health. Within the SF-36 scores, low values denote a lower self-rated general health. Data quality of the SF-36 responses was determined using QualityMetric Health Outcomes Scoring Software 4.5 (QualityMetric, Lincoln, RI, USA). MFI-20 consists of five scales based on different modes of expressing fatigue (general fatigue, mental fatigue, reduced activity, reduced motivation, and mental fatigue). Scores range from 4 to 20, with high scores representing increased fatigue. * $P < 0.001$ compared with both sufficient and insufficient TBI patients; ** $P < 0.05$ comparing deficient and sufficient TBI patients (unadjusted).

Gender, age, and waist circumference explained 14–21% of the total variation in physical fatigue, function, and component score in healthy controls. Adjustment for these covariates removed the relationship between pituitary deficiency and questionnaire scores for all but 'physical function' ($\beta = -2.5$; $P=0.03$).

Patients with untreated hypogonadotropic hypogonadism (19 men and four women) had worse 'physical component score' ($P=0.02$), 'physical functioning' ($P=0.004$), and 'social functioning' ($P=0.05$) and increased 'physical fatigue' ($P=0.05$) compared with eugonadal patients. 'Physical function' ($\beta = -5.2$; $P=0.005$) and 'social function' ($\beta = -5.7$; $P=0.02$) remained significantly related to gonadal insufficiency after adjustment for gender, age, and waist circumference. Hypogonadism did not remain significantly related to any of the scale scores by further adjustment for medical

treatment with opioids, antidepressants, and antidiabetic agents (Table 2).

Patients with GH deficiency ($n=28$) had decreased overall health perception on the EQ5D VAS ($P=0.03$), which was further strengthened after adjustment for the above covariates ($P=0.01$; $R^2=0.14$) (Table 2). However, GH deficiency was not related to any of the other scale scores, including the QoLAGHDA.

Neither ACTH, TSH nor prolactin deficiency was independently related to any of the questionnaire scores.

In univariate analysis, lower physical component score was related to lower total ($\beta=0.35$; $P<0.001$) and free ($\beta=2.99$; $P=0.03$) testosterone in men. Increased fatigue (general and physical), worse physical SF36 scores (physical fatigue, bodily pain, and role physical), and EQ5D VAS were significantly related to lower total testosterone but not to free testosterone. Total but not

Table 2 Multiple regression analyses on the relationship between EQ5D VAS, SF36, and MFI-20 physical scores and (A) pituitary deficiencies and (B) hormonal concentrations. Data are presented as β -coefficients. Lower coefficients denote greater impairment to HRQL (EQ5D and SF36), whereas higher coefficients denote greater fatigue (MFI-20). Multiple regression analyses with EQ5D VAS, SF36, and MFI-20 physical scores entered as the dependent variable and gender (men=1, women=0), age, waist circumference, Glasgow coma scale, medications (yes=1, no=0) together with either (a) hypogonadotropic hypogonadism or GH deficiency (yes=1, no=0), or (b) testosterone or IGF1, entered as independent variables in each model.

	Questionnaire			
	EQ-5D	Short Form-36		MFI-20
	VAS	PCS	Physical function	Physical fatigue
(A) Multivariate, adjusted R^2	0.18	0.16	0.22	0.18
Gender (women)	-5.83 [†]	-3.40 [†]	-3.72 [†]	1.71 [†]
Age (10 years)	1.33	-0.28	-0.40	0.03
Waist (10 cm)	-2.36 [†]	-1.12 [†]	-0.95 [†]	0.67 [†]
GCS	5.73 [†]	-2.59*	-3.54 [†]	1.59 [†]
Antidepressants	-10.34 [†]	-4.87 [†]	-3.74 [†]	1.96 [†]
Opioids	-18.40 [†]	-10.60 [†]	-9.15 [†]	4.02 [†]
Antidiabetics	-5.84	-1.54	-4.21*	2.30*
AEDs	-11.57 [†]	-1.96	-1.37	2.07*
Hypogonadotropic hypogonadism ^a	2.64 ^{<i>P</i>=0.58}	-1.05 ^{<i>P</i>=0.67}	-3.32 ^{<i>P</i>=0.10}	-0.23 ^{<i>P</i>=0.84}
GH deficiency	-10.84 ^{<i>P</i>=0.01}	-3.44 ^{<i>P</i>=0.09}	-2.19 ^{<i>P</i>=0.22}	1.54 ^{<i>P</i>=0.10}
(B) Multivariate (adjusted R^2)	0.14	0.16	0.20	0.18
Gender	-	-	-	-
Age (10 years)	0.90	-0.50	-0.64	0.05
Waist (10 cm)	-1.61	-0.57	-0.66	0.40
GCS	-5.60*	-1.98	-3.03 [†]	1.61*
Antidepressants	-13.00 [†]	-5.13 [†]	-6.03 [†]	2.80 [†]
Opioids	-4.32	-6.63*	-4.16	-0.03
Antidiabetics	-7.90	-4.79	-6.11 [†]	3.64 [†]
AEDs	-7.94	-1.75	-2.17	0.51
Testosterone	0.25 ^{<i>P</i>=0.21}	0.21 ^{<i>P</i>=0.04}	0.08 ^{<i>P</i>=0.35}	-0.09 ^{<i>P</i>=0.06}
IGF1	-0.01 ^{<i>P</i>=0.85}	0.003 ^{<i>P</i>=0.64}	0.004 ^{<i>P</i>=0.65}	-0.002 ^{<i>P</i>=0.78}

AED, antiepileptic drugs; GCS, Glasgow coma scale; VAS, visual analogue scale; PCS, physical component score. Data are presented as β -coefficients, adjusted R^2 ; * $P<0.05$ and [†] $P<0.001$.

^aMen and women, all untreated.

free testosterone remained related to worse 'physical component score', 'bodily pain', and 'general health perception' ($\beta=0.12$ – 0.24 ; $P<0.05$; R^2 0.09–0.13) after adjustment for age, waist circumference, and medical treatment with opioids, antidepressants, and antidiabetic agents (Table 2).

Age- and gender-adjusted IGF1 was related to physical functioning ($\beta=0.03$ and $P=0.04$), which did not remain after further adjustment for waist circumference (Table 2).

None of the other hormone concentrations were independently related to any of the questionnaire scores.

Pituitary symptom questionnaire

The symptoms addressed were commonly acknowledged by the patients, with a particularly high prevalence of fatigue ($>60\%$), changed sleep pattern ($>50\%$), and decreased libido ($>25\%$). Decreased libido ($P=0.03$), erectile function ($P=0.03$), and hair growth ($P=0.01$) and increased fatigue ($P=0.01$) and sleep pattern changes ($P=0.03$) were more commonly acknowledged by deficient compared with sufficient men. Only decreased hair growth was independently related to male hypogonadotropic hypogonadism ($P=0.01$; adjusted for age, waist circumference, and medical treatment with opioids, antidepressants, and antidiabetic agents). The frequency of acknowledged symptoms was similar in deficient and sufficient women.

Use of antidepressants was the strongest predictor for decreased libido ($P=0.001$), erectile function ($P<0.001$), and fatigue ($P=0.01$), whereas GCS <13 was the strongest predictor for change in sleep pattern.

Discussion

In a population-based TBI cohort, we explored different aspects of patient reported outcome in relation to pituitary deficiency.

Compared with matched controls, patients with TBI had significant and substantial detriments in their QoL and symptom scores. Although controversies may exist concerning the disabilities associated with mild TBI (18), it is generally agreed that survivors of moderate-to-severe TBI are at increased risk of various degrees of permanent disability. Our cohort included patients with mild, moderate, and severe TBI and still showed QoL impairment, sleep disturbances, fatigue, depression, and sexual dysfunction at comparable rates to previous reports (19).

Patients with pituitary deficiencies had increased impairment of various mainly physical scales relative to

patients with intact pituitary function. These differences were only partially confirmed upon adjustment for differences in gender, age, and waist circumference, in keeping with previous observations that gender, age (15), and body composition (20) have to be considered to avoid considerable bias analyzing QoL data.

As pituitary deficiencies may affect QoL differently, axis-specific relations were sought for. Patients with hypogonadotropic hypogonadism (men and women) had worse physical and social functioning and increased physical fatigue compared with eugonadal patients. Our data also suggested increasing impairments with declining total testosterone concentrations in men. However, the observed relations were only modest, and overall not reproduced for free testosterone. Consistently, androgen deficiency was neither identified as the sole nor the most important cause of impaired QoL and fatigue in TBI patients, after adjustment for significant covariates including medication known to influence endocrine pathways.

Impaired QoL and fatigue are common in androgen deficiency (21). Androgen deficiency is, however, related to several comorbidities including obesity, diabetes, depression, and opioid treatment, all of which are independently related to decreased QoL (22, 23, 24). In healthy elderly men, bioavailable testosterone was only modestly associated with QoL, whereas more closely associated with central fat mass (20). In our study, additional to age and waist circumference, medication with antidepressants, opioids, anticonvulsants, and antidiabetics were more closely associated with QoL and fatigue than total and free testosterone levels. Decreased testosterone concentrations in obesity and diabetes mellitus are linked to decreased SHBG (21), whereas opioids may cause inhibition at the hypothalamic, pituitary, and end-organ level (25). Anticonvulsants used in TBI patients for treatment of pain and epilepsy may among other influences increase testosterone metabolism via induction of hepatic enzymes in men (26). Lower testosterone levels in depressive illness are probably linked to activation of the general stress response (27), which in turn may be responsible for down-regulated testosterone biosynthesis in the Leydig cell (28). Consequently, since testosterone concentrations are closely associated with age, body composition, and above medications, it may not have an independent effect on QoL. However, as many of the covariates display a mutual relationship, it may be difficult to discern which dysfunction is causal if any. While only total but not free testosterone was independently related to QoL in this study, it may theoretically remain an important and treatable syndrome in selected

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patients. Hypogonadism has complex physiology and relating testosterone concentrations to QoL may be too simplified, as androgen receptor polymorphisms, and posttranscriptional factors cannot be taken into account in such analyses.

Patients with GH deficiency had worse EQ5D VAS scores, whereas the QoLAGHDA score specific to GH deficiency did not differ from patients with intact GH secretion. IGF1 levels did not relate to QoLAGHDA or any other scale scores. Decreased QoL including lowering of the QoLAGHDA score was previously reported in post-traumatic GH deficiency (5, 7). The reason that we were unable to identify such relations in the present cohort is unclear. A possible explanation is the high risk of irreproducible GH test outcomes (4, 29), which could have led to misdiagnosis (false positive), thus blurring the statistical analyses, not only in the present but also in all previous studies relying on single testing.

QoL is increasingly used for patient assessment and treatment evaluation. It is a complex entity integrating the patient's physical, mental, and social well-being, and due to its nature susceptible to many often coexisting conditions. In this study, medical treatment by antidepressant, opioids, and antiepileptic drugs reflected persistent physical and mental sequelae to the index trauma, which may be more important for the QoL than any hormonal deficiency *per se*. Symptom clusters including fatigue, depression, pain, and sleep disorders strongly predict lower QoL in various disease states other than pituitary deficiency (30, 31), which might explain the modest or even absent associations between hormonal deficiencies and QoL after adjustment for above covariates with a possible overpowering dominant influence.

Some concerns related to the study should be addressed. First, this is an observational study from which causality cannot be inferred. Due to the dominant effect of trauma sequelae and coexisting morbidities often mutually related to hormonal deficiencies, causality may remain difficult to prove. Until now, data on treatment effect in posttraumatic hypopituitarism remain limited and comes from small non-randomized intervention studies (8, 32) and reports from the KIMS database (33).

Second, only indirect information on depression and diabetes was obtained from the use of medications at the time of testing. The prevalence of depression in the Danish background population is 3–4%, but considerably increased after TBI (34); 14% of our patients were treated with antidepressants, which is in keeping with previous reports (35), indicating that severe underestimation is

unlikely. Further, only patients receiving antidiabetics fulfilled the diagnostic criteria for diabetes mellitus.

Yet another concern could be a potential invalidity of the posttraumatic QoL scores. The cerebral lesions in TBI patients often involve the frontal lobe region, and therefore the patients may lack awareness and insight into their own dysfunctions. QoL items reporting of these dysfunctions may consequently be underestimated (36). As posttraumatic QoL scores from significant others (closest relatives) were only random, we were not able to correct for this potential bias.

The primary strength of this study is its size and standardized protocol ensuring fasting morning sampling in well characterized patients enabling appropriate adjustment for significant comorbidities. Further, all samples from healthy controls and patients were frozen and analyzed by the same assays within few batches. Total testosterone was determined by the gold standard reverse-phase chromatography with tandem mass spectrometry, from which free testosterone was calculated. Local assay-specific cutoff values were calculated from healthy controls further minimizing the risk of methodological bias. Cutoff values generally resembled those from the literature, although peak cortisol in response to ITT was significantly lower than that usually applied, in keeping with previous reports (37, 38). Accordingly, 15% of our controls failed the general cutoff of 500 nmol/l. False-positive cases were also acknowledged by Vestergaard *et al.* (37), who described peak cortisol during ITT ranging from 448 to 775 nmol/l in healthy controls. Also, Simsek *et al.* (38) recently reported significantly lower peak cortisol during ITT compared with ACTH and glucagon tests in hypopituitary patients and defined a local peak cortisol response for the ITT of <300 nmol/l for determining adrenal failure. As to the appropriateness of the applied cutoff value in the present cohort, 12 of 208 (6%) patients undergoing ITT were diagnosed as sufficient, although failing a cutoff value of 500 nmol/l; ten had a 30 min plasma cortisol ranging from 540 to 770 nmol/l in response to synacthen stimulation, whereas two patients might have been misclassified as they had insufficient 30 min plasma cortisol concentrations of 481 and 486 nmol/l respectively. On the other hand, five patients had a peak cortisol below 398 nM, but a normal synacthen test with a 30 min cortisol ranging between 589 and 718 nmol/l, which underline the complexity of the diagnosis where in some cases the clinical context and repeated testing has to be considered for the final decision as to whether or not a patient is considered insufficient. Cutoff values always reflect the balance

between test sensitivity and specificity, and have to be addressed in the clinical context. The use of 398 nmol/l in the present study was justified by assessment in a low-risk population, although a risk of diagnostic uncertainty is acknowledged.

In conclusion, compared with matched controls, patients with TBI have significant and substantial detriments in their QoL. The relationship between pituitary hormone deficiencies upon single unconfirmed testing and QoL was modest compared with that of various TBI sequelae and related non-hormonal comorbidities. For patients with TBI, our results suggest that the presence of concurrent comorbidities plays a significant role in QoL and that identifying these comorbidities should be of greater priority than focus on pituitary function. Causality is still to be shown, and whether hormonal substitution therapy could be of additional relevance in cases of mild deficiencies needs to be proven. However, in cases of overt posttraumatic multiple pituitary hormone deficiencies, treatment effect is expected of similar efficacy as in any other cause of pituitary deficiency and thus needs to be considered.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

M Klose made primary contributions to data collection and analysis, interpretation of results, and writing of the manuscript. M Klose, U Feldt-Rasmussen, J S Christiansen, M Andersen, P Laurberg, and K Stochholm contributed to the study conception and design. J Janukonyté and L L Christensen contributed to data collection, A S Cohen and A Wagner contributed to data collection/analyses. All authors contributed to interpretation of results, all revised the manuscript critically for important intellectual content and all approved the final manuscript. M Klose is the guarantor.

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