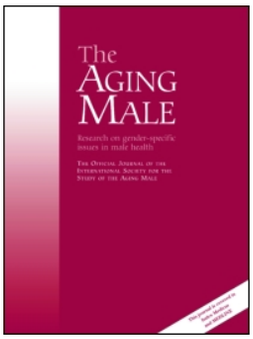

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ORIGINAL ARTICLE

The relationship of salivary testosterone and male sexual dysfunction in opioid-associated androgen deficiency (OPIAD)

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Abstract

Background: Opioids are an effective treatment for chronic non-malignant pain (CNP). Long-term use risks and side effects such as opioid-induced androgen deficiency (OPIAD) exist. This could be measured by saliva testosterone (Sal-T).
Objectives: To evaluate OPIAD in long-term opioid use in CNP patients.
Methods: A cross-sectional study included CNP male outpatients under opioid treatment. Total-Testosterone (Total-T), Free-Testosterone (Free-T), Bio-Testosterone (Bio-T) and Sal-T were measured. Correlations were calculated by Spearman's rho (SPSS 20).
Results: From 2012 to 2014, 134 from 249 (54%) consecutive male outpatients reported erectile dysfunction (ED), 37% of them related to opioids and 19% evidenced OPIAD. A total of 120 subjects (94 cases and 26 matched-controls) were included. A significantly lower luteinizing hormone, Total-T and Free-T were found, as well as, a significant correlation between Sal-T and Total-T ($r = 0.234$, $p = 0.039$), Bio-T ($r = 0.241$, $p = 0.039$), IIEF ($r = 0.363$, $p = 0.003$) and HAD-anxiety ($r = -0.414$, $p = 0.012$) in OPIAD patients. Sal-T levels were significantly lower in patients with severe–moderate ED versus mild ED ($p = 0.045$) and in patients with severe ED versus moderate–mild ED ($p = 0.036$).
Conclusions: These data demonstrate the high prevalence of ED in long-term use of opioids, part of this is associated to OPIAD, which can be tested by Sal-T as a non-invasive approach.

Keywords

Salivary testosterone, sexual dysfunction, erectile dysfunction, opioids, chronic pain, OPIAD

History

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Introduction

Opioid therapy is one of the most effective forms of analgesia currently. Chronic pain adult males exposed to long-use prescription opioids, increase the risk of opioid adverse events such as androgen deficiency (OPIAD) [1–4]. This syndrome is characterized by an inadequate production of sex hormones, particularly testosterone. Symptoms that may manifest include reduced libido, erectile dysfunction (ED), fatigue, hot flashes, anxiety and depression [5,6]. None of these signs and symptoms are specific of OPIAD but may raise suspicion. In fact, opioid-induced endocrinopathy should be considered in any patient receiving daily opioid treatment in an amount equivalent to 100 mg of morphine or more [7]. Patients should be asked routinely about symptoms suggestive of sex hormone deficiency before treatment and at regularly scheduled follow-up medical visits. However, despite its high frequency, OPIAD is rarely considered for treatment, that usually consist in androgen replacement for males and dehydroepiandrosterone (DHEA) supplementation for females [8], and, prevalence of abnormally low serum testosterone levels has historically been scarcely reported, roughly 6% in urology clinics [9–11]. Furthermore, it is well known, that low levels of testosterone in men are related to a higher risk of cardiovascular disease and a decreased survival [12–15].

Serum testosterone concentration is the principal laboratory test used to diagnose male OPIAD. There is no consensus as to when laboratory tests should be ordered, but it is reasonable to do so when patients report one or more suggestive symptoms [16]. Recently, salivary testosterone (Sal-T) has been suggested as a biomarker for androgen deficiency diagnosis [17]. Saliva is a widely accepted sample source for steroid analysis and offers a non-invasive and stress-free, alternative to plasma and serum [18]. In healthy adult men, testosterone circulates in plasma either free

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(Free-T, 2.2%) or bound to serum proteins (albumin, sex hormone binding globulin (SHBG); Total-T, 44%) [19,20], and a highly significant correlation between Sal-T, Total-T and Free-T has been described in eugonadal and hypogonadal men with normal renal function [21,22]. Unfortunately, the usefulness of Sal-T was not further investigated in male sexual dysfunction with androgen deficiency.

The aim of this study was to investigate if Sal-T could become a reliable non-invasive tool to screen androgen deficiency. For this purpose, the following steps were performed: (i) to establish the correlation of Sal-T with circulating Total-T; (ii) to determine the correlation of Sal-T with clinical parameters such as International Index of Erectile Function questionnaire scores (IIEF) and (iii) to detect androgen deficiency through Sal-T analysis.

Methods

This protocol was approved by the Ethics Committee for Clinical Research of the University General Hospital of Alicante (Spain). All participants signed informed consents before enrolment in study protocols, and the study were performed according to the Declaration of Helsinki.

Chronic pain patients and controls

A cross-sectional study was developed for two years including consecutive 249 chronic non-cancer pain (CNP) male outpatients with long-use of opioids that spontaneously reported ED; together with 26 controls with the same characteristics and geographical areas but without spontaneous ED report. All subjects came from the Clinic Pain Unit of University General Hospital of Alicante (Spain). Salivary and blood samples from subjects' anterocubital vein were drawn in the morning.

Inclusion criteria were: adult CNP male patient's diagnosed according to International Association for the Study of Pain (IASP)'s criteria [23], receiving oral and/or transdermal opioid treatment for at least one year, and with spontaneous ED in heterosexual patient's reports. Patients with apparent infections, other inflammatory diseases, malignancies or use of testosterone, glucocorticoids, bisphosphonates, calcitonin or parathyroid hormone were excluded from the study. None of the patients were taking hormone medication (supplementation or deprivation) or phosphodiesterase type 5 (PDE5) inhibitors.

Data collection

All the data provided were collected as part of the routine clinical procedure and in line with current guidelines. ED was recorded based on patient's spontaneous notification in routine clinical controls. A physical exam was performed including body mass index (BMI, kg/m^2), blood pressure (mmHg), heart rate (bpm) and the most common comorbidities (hypertension, diabetes, dyslipidaemia or obesity). Baseline socio-demographic and lifestyle characteristics were recorded together with familiar medical history and current intake of abuse drugs including alcohol and nicotine (Table 1 and Supplementary Table 1).

Pain severity was determined using a commonly used self-reported Visual Analogue Scale (VAS), with 0 indicating ''no pain'', and 10 indicating ''the worst possible pain''. Based on this, the pain severity in individuals was classified as mild (VAS $\leq$ 3 cm), moderate (VAS 4–6 cm) or severe (VAS $\geq$ 7 cm). Quality of life standardized measures developed by the EuroQol Group (EQ-VAS) were used in this study. Scores ranged from 0 (the worst health status) to 100 (the best health status). A pain expert psychologist evaluated psychological health by Hospital Anxiety and Depression Scale (HAD). The HAD is comprised of two subscales, Depression and Anxiety. Each subscale has a score ranging from 0 to 21. Items are rated on a four-point Likert-type scale ranging from 0 to 3, generating a scale range of 0–42 points, with higher scores representing greater symptom severity. Scores of 0–7 indicate normal levels; 8–10 indicate borderline abnormal anxiety and depression levels and 11–21 suggest abnormal levels of anxiety and depression.

Patients who reported ED were routinely derived to Andrology Unit for correct physical examination to confirm ED according to the Standard Operating Procedures in Sexual Medicine [24] and International Classification of Diseases (ICD) [25]. Only heterosexual patients were included in this study, to make the results more comparable and to prevent possible bias using the IIEF questionnaire (range 5–75 scores). This questionnaire has 15 items that evaluate different sexual aspects, the most important being Erectile Function domain (IIEF-EF), with a range from 0 to 30 scores which classifies EF as 0–10 severe, 11–16 moderate, 17–25 mild and $\geq$26 normal [26].

Sample collection

Salivette® system was used. It was used for the saliva sample with each swab placed beneath the tongue for at least 3 min. All subjects were instructed not to brush their teeth 2 h prior to saliva collection. Then, salivettes were centrifuged at 570$\times g$ for 2 min and supernatants were frozen at $-20\,^{\circ}$C until processing. Salivary testosterone levels were analysed.

Blood samples were drawn in the morning, after overnight fast, for determination of blood glucose, urea, creatinine, uric acid, total cholesterol, high and low density lipoprotein cholesterol (HDL-cholesterol and LDL-cholesterol), triglycerides, total bilirubin, alanine amino transferase (ALT), aspartate amino transferase (AST), gamma glutamyltranspeptidase (GGT), albumin, total proteins, prostate specific antigen (PSA), thyroid stimulating hormone (TSH), follicular stimulating hormone (FSH), luteinizing hormone (LH), prolactin, total testosterone, SHBG and total testosterone.

To minimize pre-analytical errors, saliva was discarded if contaminated with blood.

Hormone variables

Total serum testosterone can be divided into three components; roughly half of testosterone is bound to the carrier molecule sex hormone-binding globulin (SHBG), almost all of the remainder is bound to albumin, and 1–2% is unbound or free. Testosterone binds so tightly to SHBG that it is functionally unavailable to cells. In contrast, albumin-bound testosterone dissociates readily, meaning that this component and the free component are available for cells. The term ''bioavailable testosterone'' (Bio-T) refers to a combination of the albumin-bound and free portions [27].

Table 1. Summary of clinical and socio-demographical characteristics of the participants.

			Erectile dysfunction ($n = 94$)		
Parameter	Total ($n = 120$)	Control ($n = 26$)	No OPIAD ($n = 76$)	OPIAD ($n = 18$)	p values
Age (years)	58.8 ± 5.8	55.9 ± 14.7	59.8 ± 12.3	58.5 ± 10.3	0.402
Smoke status (%)	31%	35%	29%	33%	0.893
BMI (kg/m^2)	29.3 ± 5.2	27.6 ± 4.9	29.1 ± 4.8	32.5 ± 5.7	**0.014**
Comorbidity (%)	85%	81%	86%	89%	0.499
Total daily opioid dose (mg/day)	113.4 ± 101.8	106.0 ± 64.5	106.2 ± 97.2	153.5 ± 150.8	0.278
Adjuvants	85%	77%	85.5%	94.4%	0.196
Anticonvulsants	70%	68%	67.1%	66.7%	0.924
Antidepressants	39.2%	30.7%	85.5%	50%	0.287
Anxiolytics	22.5%	19.2%	22.3%	27.7%	0.655

The p-values <0.05 are highlighted in bold.

Total-T was measured by chemiluminescent immunoassay (CLIA, UniCel DXI 800, Access testosterone Beckman Coulter). Free-T was calculated by determining Total-T, SHBG (nmol/L) and albumin (kinetic nephelometry, immunochemical systems IMMAGE Beckman Coulter), from the equation $FT = ([T] - (N \times [FT]))/(Kt\{SHBG\text{-}[T]+N[FT]\})$, where Kt ($10^9$ L/mol) is the association constant of SHBG for T, and $N = (Ka[3.6 \times 10^4$ L/mol, association constant of albumin for T]×Ca [albumin concentration, g/L]) + 1, as described by Vermeulen et al. [28].

Bio-T was calculated by adding to the Free-T the testosterone bound to albumin, obtained by the product of KaCa and Free-T. Sal-T was measured by a radioimmunoassay (RIA) for the quantification of Total-T in serum (Coat-A-Count, Siemens) with some in-house modifications in order to adapt it to saliva. In order to increase the sensitivity, the overnight incubation time was prolonged, the reaction volume increased and the calibration curve adapted after successive dilutions of the lower concentration calibrator, achieving an analytical sensitivity of 34 pg/ml and an intraserial CV of 7.9%.

Statistics

Data were expressed as mean ± standard deviation when normally distributed and as median (nonparametric distribution) for parameters with non-normal distribution, unless otherwise specified [29]. Differences were evaluated with one-way analysis of variance or Kruskal–Wallis test, according to normality. Correlations were assessed using Spearman's or Pearson's method when not normally or normally distributed, respectively. Unpaired two-sided Student's t-tests were used for comparison of means of normally distributed parameters. In all other cases, Mann–Whitney U test was used for comparisons between groups. Stepwise multiple linear or logistic regressions were applied for multivariate analysis, for continuous or categorical dependent variable, respectively. All statistical analyses were performed on SPSS (Statistical Package for the Social Sciences; Chicago, IL) for Windows v20. The level of statistical significance was $p < 0.05$.

Results

From 1 May 2012 to 27 July 2014, a total of 747 (249 males, 33%) consecutive patients with long-use of opioids were nursed at the Clinic Pain Unit of University General Hospital of Alicante. In global, 54% (134/249) reported spontaneous ED. Forty of them (30%) were excluded by previously diagnosed hypogonadism or renal insufficiency, hepatic impairment, major psychiatric disorders, and other reasons for ED or chronic debilitating diseases. Patients were also excluded if they were not engaged in steady heterosexual activity.

Finally, a total of 94 patients with ED (37%) were included in the present study (cases, 59.5 ± 11.8 years, 19% OPIAD). Also, 26 non-ED patients (controls, 55.9 ± 14.7 years, $p = 0.402$) were retrieved, according to routine pain screenings. The baseline socio-demographic and clinical characteristics of the participants are reported in Table 1.

All subjects ($n = 120$) had documented history of chronic pain with a median duration of 5,5 years and were under long-use of opioid treatment. The most common comorbidity was dyslipidemia (56%, total cholesterol 180 ± 40 mg/dl), followed by hypertension (40%, blood pressure 132/76 mmHg), diabetes (22.3%, fasting glucose 132 ± 36 mg/dl) and obesity (46%, BMI > 30). Patients use: 74% major opioids, 34% tramadol, 40% analgesic, 84% adjuvant drug (most prevalent, 39% antidepressants and 70% anticonvulsants, Supplementary Table 1).

Analysis of pain intensity (VAS), mean quality of life-VAS, HAD-anxiety, HAD-depression, IIEF and IIEF-EF for ED cases and controls are reported in Table 2. In general, pain intensity was mostly severe–moderate with a mean of 5.8 ± 2.5 cm (22% mild, 37% moderate, 41% severe). Most subjects present a normal or borderline result in the HAD-anxiety questionnaire (41% normal, 21% borderline case, 38% case) and depression-HAD (46% normal, 25% borderline case, 29% case). IIEF and IIEF-EF were significantly lower in patients with ED, and especially in patients presenting OPIAD ($p < 0.05$). Most of the patients with ED presented an IIEF-EF score that corresponds to severe conditions (68% severe, 10% moderate, 22% mild).

Blood analysis and Sal-T levels are summarized in Table 3. Total-T, Free-T, SHBG and Sal-T levels were lower in patients presenting OPIAD (Table 3). Furthermore, Total-T and Free-T in these patients were not only significantly lower ($p < 0.01$), but also it was up to two-fold lower than in controls or No-OPIAD patients.

ED and hormone level correlations

Mean hormone values analyzed by ED severity (severe, moderate, mild and normal) are summarized in Table 4.

Table 2. VAS, HAD and IIEF scores for controls and ED patients.

Parameter	Total ($n=120$)	Control ($n=26$)	Erectile Dysfunction ($n=94$)		p values
			No OPIAD ($n=76$)	OPIAD ($n=18$)	
VAS (cm, 0–10)	5.8 ± 2.5	6.4 ± 2.6	5.7 ± 2.4	5.4 ± 3.1	0.417
EQ5-VAS (cm, 0–10)	48.4 ± 24.7	40.2 ± 28.5	48.8 ± 20.8	61.4 ± 30.7	0.072
HAD anxiety (0–21 scores)	9 (5–13)	14 (14–14)	9.5 (5–14.3)	3.5 (2–10)	0.070
HAD depression (0–21 scores)	8 (3.8–11.3)	7 (7–7)	8 (4–12)	6 (1–9.5)	0.501
IIEF (5–75 scores)	27 (16.3–40.8)	60 (43–64)	28.5 (19.3–40.8)	11 (6–28.5)	**0.003**
IIEF-erectile function (0–30 scores)	8 (4–16.8)	28 (27–30)	8 (6–16.8)	3 (1–6.5)	**0.000**

The p-values <0.05 are highlighted in bold.

Table 3. Blood analysis and salivary testosterone levels.

Parameter	Total ($n=120$)	Control ($n=26$)	Erectile dysfunction ($n=94$)		p values
			No OPIAD ($n=76$)	OPIAD ($n=18$)	
Total testosterone [3–10 ng/mL]	3.3 ± 1.6	3.4 ± 2.1	3.4 ± 1.6	1.4 ± 0.6	**0.000**
Free testosterone (ng/mL)	27.7 ± 15.0	30.3 ± 10.7	29.7 ± 16.1	15.8 ± 8.9	**0.002**
SHBG [4–72 nmol/L]	48.2 ± 24.1	50.7 ± 31.9	49.6 ± 22.1	39.7 ± 20.1	0.259
Salivary testosterone (pg/mL)	125.1 ± 67.1	101 ± 59.1	132.9 ± 69.8	104.1 ± 51.9	0.222
Glucose [74–106 mg/dL]	115.1 ± 62.3	130.0 ± 92.0	111.0 ± 56.0	110.0 ± 27.0	0.402
Urea [10–50 mg/dL]	39.4 ± 15.8	37.4 ± 10.3	40.0 ± 15.0	38.0 ± 23.0	0.703
Creatinine [0.7–1.20 mg/dL]	0.9 ± 0.2	0.8 ± 0.1	0.9 ± 0.3	0.79 ± 0.1	0.480
Uric acid [3.4–7 mg/dL]	5.3 ± 1.3	5.2 ± 1.2	5.5 ± 1.4	4.8 ± 1.3	0.685
Total cholesterol [110–200 mg/dL]	181.3 ± 41.2	186 ± 45	183.0 ± 39.0	167.0 ± 43.0	0.282
Triglycerides [50–200 mg/dL]	149.3 ± 88.0	148.8 ± 118.2	142.0 ± 76.0	181.0 ± 84.0	0.268
Total bilirubin [0.1–1.2 mg/dL]	0.5 ± 0.2	0.5 ± 0.18	0.5 ± 0.2	0.4 ± 0.2	0.456
AST [10–40 U/L]	20.0 ± 6.3	20.0 ± 6.0	20.0 ± 7.0	20.0 ± 7.0	0.608
ALT [10–41 U/L]	20.1 ± 6.3	23.0 ± 13.0	19.0 ± 8.0	19.0 ± 8.0	0.765
GGT [7–60 U/L]	35.0 ± 19.6	35.0 ± 20.0	35.0 ± 20.0	36.0 ± 17.0	0.752
Albumin [3660–5100 mg/dL]	4292.9 ± 418.8	4348.0 ± 375.0	4260.0 ± 401.0	4349.0 ± 536.0	0.563
TSH [0.38–4.84 mU/L]	2.2 ± 1.2	2.3 ± 1.1	2.2 ± 1.2	1.9 ± 1.2	0.452
Prolactin [4.6–21.0 ng/mL]	12.4 ± 12.9	9.7 ± 5.5	12.2 ± 12.4	9.0 ± 5.0	0.150
FSH [1–8 U/L]	6.1 ± 2.7	5.9 ± 3.1	6.4 ± 2.8	5.5 ± 1.8	0.302
LH [2–11.2 U/L]	5.5 ± 3.5	5.8 ± 4.1	5.9 ± 3.3	3.6 ± 2.0	**0.043**

The p-values <0.05 are highlighted in bold.

Table 4. Testosterone levels in ED patients according to ED severity.

	Severe	Moderate	Mild	p values (1)	p values (2)	p values (3)
Total testosterone [3–10 ng/mL]	2.9 ± 1.3	3.8 ± 1.3	4.2 ± 1.5	**0.010**	**0.012**	**0.004**
Free testosterone (ng/mL)	25.0 ± 13.2	39.4 ± 17.1	37.8 ± 19.7	**0.010**	**0.034**	**0.003**
Bio-T (ng/mL)	9.4 ± 3.9	12.9 ± 4.4	14.7 ± 4.9	**0.002**	**0.003**	**0.001**
SHBG [4–72 nmol/L]	47.8 ± 24.3	36.2 ± 14.1	46.2 ± 19.1	0.473	0.766	0.585
Salivary testosterone (pg/mL)	122.3 ± 59.4	152.6 ± 67.9	170.0 ± 80.1	0.093	**0.045**	**0.036**
IIEF (5–75 scores)	21 (8–28)	37 (29–42)	50 (42–53)	**0.000**	**0.000**	**0.000**
IIEF-EF (0–30 scores)	6 (2–8)	14 (11–14)	21 (18–24)	**0.000**	**0.000**	**0.000**

p values (1): comparison between all groups; p values (2): severe–moderate versus mild; p values (3): severe versus moderate–mild.
The p-values <0.05 are highlighted in bold.

Total-T, Free-T, Bio-T and Sal-T levels were significantly lower in patients with severe ED (Figure 1 and Table 4).

In addition, we analyzed correlations between testosterone levels and HAD-anxiety and IIEF/IIEF-EF results in the samples and in ED patients (Supplementary Table 2 and 3, respectively). In our sample, we observed a significant correlation ($p<0.05$) between Sal-T and Total-T ($r=0.234$, $p=0.039$), Bio-T ($r=0.241$, $p=0.039$), IIEF ($r=0.363$, $p=0.003$), and HAD-anxiety ($r=-0.414$, $p=0.012$) (Figures 1 and 2, and data not shown). Also, a positive correlation was found between Total-T and IIEF ($r=0.268$, $p=0.021$) (Figure 2), HAD-anxiety ($r=0.370$, $p=0.017$), and HAD-depression ($r=0.337$, $p=0.033$); and between Bio-T and Free-T ($r=0.501$, $p=0.000$), IIEF ($r=0.299$, $p=0.011$) (Figure 2), and HAD-anxiety ($r=0.357$, $p=0.026$).

Discussion

This study shows a high prevalence of ED spontaneously reported in 37% of males with chronic pain under long-use of opioids, 19% of them with OPIAD. Some studies demonstrated a direct correlation between testosterone deficiency and chronic opioid use but this is the first study that demonstrates the value of Sal-T in the diagnosis of androgen deficiency [30]. In fact, Sal-T levels were significantly lower in patients with severe–moderate ED compared to patients with mild IIEF-EF score.

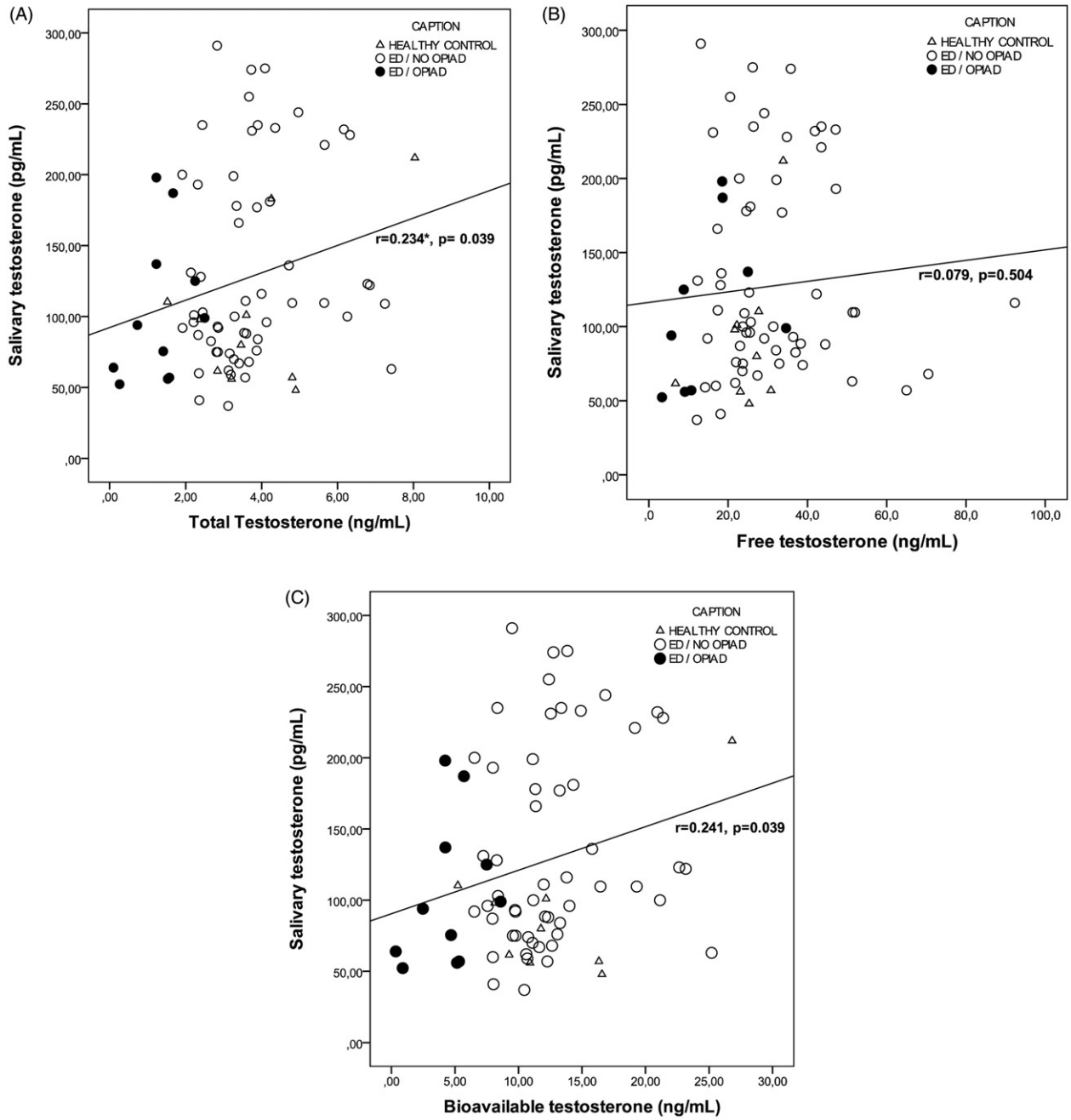

Figure 1. Correlation analysis of salivary testosterone with total (A), free (B) and bioavailable testosterone (C). Each dot corresponds to a different participant. *Correlation is significant ($p \leq 0.05$).

Opioid-induced endocrinopathy is one of the most common, yet least often, diagnosed consequences of prolonged opioid therapy. More or less, all guidelines suggest chronic opioid use as a common cause of hypogonadism [5]. It has been shown that prolonged opioid therapy affects testosterone plasma levels. Although wide interindividual variations exist, mean testosterone levels decline with age, and differences between populations have been observed [31–36]. At age 75, the mean Total-T level in the morning is about two-thirds of the mean level in men aged 20–30 years, whereas the mean Free-T and Bio-T levels are only 40% of the mean levels in younger men. Furthermore, the circadian rhythm of serum testosterone levels is generally lost or attenuated in elderly men [37,38]. In fact, some groups in developing countries exhibit significantly lower Sal-T levels compared to industrialized western populations as well as more attenuated age related declines [39–41].

While there are no current standards for monitoring these patients, the available evidence suggests that we should routinely screen patients on opioid treatment for manifestations of hypogonadism and determine testosterone levels [5,42,43]. This study supports the usefulness of morning Sal-T testing as a non-invasive approach to screen androgen status in men with ED and CNP.

Campbell et al. [44,45] reported some differences in aging patterns in association with different life styles, cultures and ethnic groups. Also, patterns of age related decline of male testosterone are variable depending on the measurements

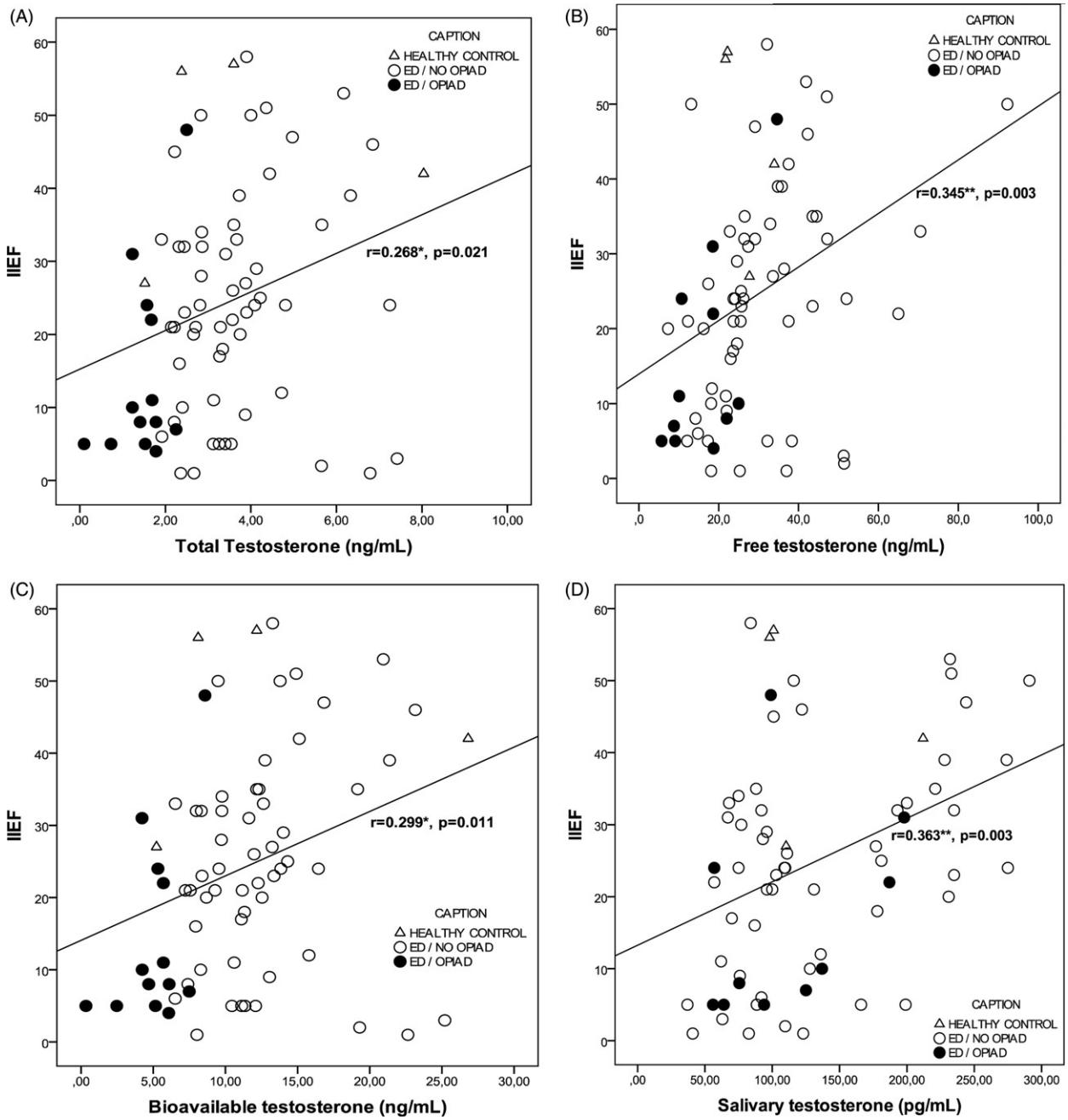

Figure 2. Correlation analysis of IIEF with total (A), free (B), bioavailable (C) and salivary (D) testosterone. Each dot corresponds to a different participant. *Correlation is significant ($p \leq 0.05$). **Correlation is very significant ($p \leq 0.01$).

used (serum Total-T, Free-T), and on the age ranges in question [46–49]. Inter- and intraindividual testosterone variations are also associated with illness severity and body composition such as amount of skeletal muscle [50–53], as well as adipose tissue deposition and distribution [54–57]. These results suggest that the commonly reported decline of testosterone values after the third decade of life observed in western countries may not be caused by aging *per se*. Instead, any association between testosterone and age may be a result of various factors, including energy availability and utilization during maturation, body composition, as well as age-related life style or illness [58,59]. Even more, males with anxiety mood also tend to show lower testosterone levels indicating that hormones and pain perception are changed by anxiety [60]. In our study, a significant correlation was found between Sal-T, IIEF and anxiety symptoms.

Chronic administration of painkillers, such as opioids, requires the physician to be aware of both the consequences that can develop due to long-term testosterone impairment and the available means to restore and maintain physiological testosterone levels. It has been shown that even a single administration of morphine in men was able to reduce enormous testosterone levels in few hours inducing a dramatic hypogonadism that persists throughout the treatment [61,62]. Unfortunately, OPIAD remains known just as the effect of many medications on sexual function, since patients and professionals are often uncomfortable discussing about sexuality, thus, it remains under-recognized and under-treated [63]. Testosterone has an appreciable role where adequate

serum levels are required in males and females for libido and sexuality; cellular growth; maintenance of muscle mass and bone; healing; blood–brain barrier; and for central nervous system maintenance [64]. Also, it has been suggested that androgen insufficiency disrupts cellular signalling pathways and produces pathological alterations in penile tissues leading to ED. Even more, OPIAD persistence is important not only because of the endocrine aspect of the illness, but also because it cannot be excluded that OPIAD in chronic pain patients could determine increasing pain sensitivity [65]. Due to the pivotal role of testosterone, adequate serum levels are required for multiple functions such as muscle mass maintenance, cellular growth or sexuality. In order to maintain adequate serum levels, testosterone replacement therapy should be considered, however, there is no rule regarding when to start treatment. It is important to establish when to start testosterone replacement treatment therapy and which candidates can benefit from the treatment [64]. Testosterone replacement therapy has been shown to improve body composition, pain sensitivity, sexual desire and aspects of quality of life [66], however, men on long-term testosterone treatment should be monitored periodically for secondary effects.

Also, testosterone deficiency appears to be even more underdiagnosed in women [67,68]. Women receiving chronic opioid therapy may manifest a similar constellation of symptoms related to testosterone deficiency as men; however, these symptoms may be undiagnosed due to underappreciation of this phenomenon by both patient and practitioner. Pending problems to use Sal-T are related to the certainty of reference ranges (potential influence of gender, age, ethnicity, genotype and pathologic deviations), duration of effects, dose–response correlations and potential induction of binding proteins after long-term opioid use. Potential interferences from blood leakage into the buccal mucosa should be considered, e.g. by determination of blood related proteins.

The initial assessment of men with ED and/or diminished libido should include determination of testosterone level. These symptoms, with or without a testosterone deficiency, might be related to co-morbidities [5]. Thus, patients with long use of opioids should be routinely screened for ED due to its high prevalence. The findings of our study suggest the usefulness of morning Sal-T analysis as a non-invasive approach to screen androgen status in men with ED and CNP. Further research is needed to determine if treatment is beneficial in improving sexual dysfunction symptoms and OPIAD. Also, studies of longer duration could demonstrate continued and further improvement in long-term ED symptoms.

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Declaration of interest

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