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Associations between testosterone and patient reported sexual outcomes among male and female head and neck cancer patients before and six months after treatment: A pilot study

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ABSTRACT

Objectives: To investigate associations between testosterone and patient reported sexual problems and need for sexual care in head and neck cancer patients at time of diagnosis and 6 months after treatment.
Patients and methods: Data and samples were used of 40 patients (20 men, 20 women) before and 6 months after treatment. Outcome measures were total testosterone level (TT) and free testosterone index (FTI), testosterone insufficiency (TI), the EORTC QLQ-HN35 Sexuality subscale, the subscales of the International Index of Erectile Function (IIEF), Female Sexual Function Index (FSFI), and the Sexuality subscale of the Short-Form Supportive Care Needs Survey (SCNS-SF34).
Results: In men, higher FTI before treatment was significantly associated with better IIEF Orgasm ($p = 0.020$) and at 6 months follow-up with IIEF Desire ($p = 0.019$). Before treatment, insufficient testosterone was present in 5 males (25%) and in 3 at follow-up (15%) (2 patients who had TI before treatment plus one). In women, higher TT at follow-up was significantly associated with better EORTC Sexuality ($p = 0.031$) and FSFI Satisfaction ($p = 0.020$); FTI at follow-up was associated with FSFI Satisfaction ($p = 0.012$). Before treatment, TI was present in 2 women (10%) and in 3 (15%) at follow-up (the same 2 patients plus one).
Conclusion: This pilot study showed that testosterone seems to be associated with patient reported sexual outcomes among male and female head and neck cancer patients. It is estimated that 10–25% of HNC patients may have testosterone insufficiency before treatment and/or at 6 months after treatment.

Introduction

Sexual problems often occur in head and neck cancer (HNC) patients with prevalence rates varying between 24% and 100% [1]. A review published in 2016 included 9 studies and showed that several socio-demographic, clinical, symptoms, and health related quality of life factors are associated with sexual outcomes [1]. Since 2016, some more papers were published. Taberna [2] included 262 oral cancer patients.

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From diagnosis to 6 months follow-up, vaginal penetrative sexual activity decreased from 34% to 10% and oral sex from 80% to 25%. Batioglu-Karaaltin [3] reported that 90% of patients after total laryngectomy (TL) and 64% after partial laryngectomy (PL) experienced negative effects of treatment on sexual outcomes (N = 108). Akil [4] found no influence of type of surgery on sexual outcomes when measured with the Arizona Sexual Experiences Scale but a significant difference when measured with the sexuality subscale of the EORTC QLQ-H&N35 (N = 82). Abel [5] found better sexual outcomes in patients 12 months after intensity modulated radiotherapy compared to conventional radiation therapy (n = 207). Bozec [6] reported that among 58 oropharyngeal cancer patients 1 year after treatment, reduced sexual outcome was among the main persistent symptoms. Melissant [7] investigated the course of sexual outcomes in 354 HNC patients treated with primary (chemo)radiation from time of diagnosis to 24 months follow-up, and found that 37% had sexual problems at time of diagnosis which increased to 60% at 6-week follow-up, and returned to baseline level at 12 months follow-up. So [8] reported that many patients have an unmet need for sexual care. Jansen [9] showed that 23% of TL patients (n = 283) had an unmet need for sexual care.

These studies show that the body of evidence on sexual outcomes among HNC patients is growing but far from complete. Moreover, there is a lack of evidence on biological factors that might (partly) explain sexual problems in this population. An important biological factor that influences sexual outcomes is the production of sex hormones. Testosterone is a sex hormone that is produced in the testes, ovaries, and in the adrenal glands. Testosterone makes the sexual system more sensitive to sexual stimuli, in both men and women, and is involved in the regulation of all phases of the sexual response (desire, arousal, orgasm, satisfaction) [10–13]. However, not much is known yet on associations between testosterone and patient reported sexual outcomes among HNC patients. The main objective of this pilot study was to investigate if testosterone is associated with patient reported sexual problems and need for sexual care. A secondary objective was to obtain insight into the prevalence of testosterone insufficiency among HNC patients. The results of this study are relevant to better understand the aetiology of sexual problems in HNC patients.

Patients and methods

Study population and procedures

We used data and samples of HNC patients who participated in the "Netherlands Quality of life and Biomedical Cohort Study on head and neck cancer" (NET-QUBIC) [14]. The purpose of NET-QUBIC is to advance interdisciplinary research that aims to optimize diagnosis, treatment, and supportive care for HNC patients. Using an extensive assessment protocol (electronic clinical record form, patient reported outcomes (PROs) and fieldwork (interviews and physical tests)), clinical data and data on health related quality of life, demographic and personal, physical, psychosocial, and social factors are stored in the data warehouse. A longitudinal biobank is built with tumor tissue, blood and blood components, saliva samples, and oral rinses. Patients fill out PROs before treatment and at 3, 6, 12, 24, 36, 48, and 60 months after treatment. The interviews, physical tests and biological sample collection are before treatment and 6, 12, and 24 months after treatment. In total, 739 HNC patients were included in 5 out of the 8 HNC centers in the Netherlands. Detailed information can be found in the protocol paper [14]. The study protocol was approved by the Institutional Review Board of the coordinating research center (Amsterdam UMC (location VUmc)) (2013.301(A2018.307)-NL45051.029.13). All patients provided written informed consent to use and re-use their data and samples in studies that aim to research quality of life and improved diagnosis and treatment of HNC.

In this pilot study on the associations between testosterone and patient reported sexual outcomes, we selected a random sample (using SPSS software) of 20 men and 20 women who had completed blood samples and patient reported sexual outcome measures before treatment and 6 months follow-up. Other inclusion criteria in the NET-QUBIC study were: newly diagnosed squamous cell carcinomas in the head and neck (oral cavity, oropharynx, hypopharynx, larynx, unknown primary; all stages); age > 18 years; treatment with curative intent; all treatment modalities (surgery, radiotherapy, chemotherapy and combinations); able to write, read, and speak Dutch. Exclusion criteria were: other tumors in the head and neck (e.g. lymphoma, skin malignancies, thyroid cancer); patients unable to understand the questions or test instructions; and severe psychiatric co-morbidities (i.e. schizophrenia, Korsakoff's syndrome, severe dementia), or unable to understand informed consent. Patients were treated according to the current standard in the Netherlands as defined in national guidelines on diagnosis, treatment, and follow-up care.

Outcome measures

Sociodemographic and clinical data were retrieved from medical files: age, sex, tumour site (ICD-10) and type of treatment (surgery, radiotherapy, chemotherapy).

Blood samples were used to extract total testosterone (TT) and sex hormone-binding globulin (SHBG) levels. Testosterone circulates in the bloodstream and consists of free testosterone and testosterone bound to SHBG. SHBG inhibits the function of testosterone. TT and SHBG values were determined in serum (750 μl serum (2 serum tubes) per sample) at the lab in Amsterdam UMC. TT was measured using an in-house assay and SHBG using one reagent (one reagent lot). Non-bound free testosterone and bound testosterone were extracted (in nmol/L based on a LC-MS/MS assay). The interassay variation was 5–8%. SHBG was measured using an automated non-competitive (sandwich) immunoassay (Abbott, Architect i2000) with an interassay variation of 5%. Free testosterone index (FTI) was calculated as 100 × TT/SHBG. In men, testosterone insufficiency (TI) was defined as TT ≤ 12 nmol/L or FTI ≤ 0.225 nmol/L. In women, TI was defined as TT ≤ 0.3 nmol/L if SHBG levels were within the normal range (<100 nmol/L), and as TT*FTI ≤ 0.5 nmol/L in patients with elevated SHBG levels (>100 nmol/L)) [15–19].

The EORTC QLQ-HN35 module covers specific health-related quality of life issues related to HNC. The questionnaire comprises seven subscales including a scale on sexual interest and enjoyment (2 items). All items, refer to the last week. All scales range in score from 0 to 100, higher scores indicate a higher level of symptoms (e.g. less sexual interest and enjoyment). The EORTC QLQ-HN35 is developed in a cross-cultural setting and is a valid and reliable instrument for quality of life assessments in HNC patients [20].

The 15-item International Index of Erectile Function (IIEF) was used to assess male sexual functioning across five domains, including erectile function (6 items), orgasmic function (2 items), sexual desire (2 items), intercourse satisfaction (3 items), and overall satisfaction (2 items). All items refer to the past four weeks. On each of the domains a total sum score is calculated. A higher score indicates better functioning, while a domain score of zero indicates no sexual activity during the four weeks. The IIEF has been validated, including in the Dutch language [21,22].

Sexual function in women was evaluated by means of the 19-item Female Sexual Function Index (FSFI) across six domains: desire (2 items), arousal (4 items), lubrication (4 items), orgasm (3 items), satisfaction (3 items), and pain (3 items). All items refer to the last four weeks. For each of the domains a total score is calculated by summing scores of all items and multiplying this by its corresponding weight. In addition an overall total score is calculated by summing total scores of all domains. A higher score indicates better functioning. Psychometric properties of the FSFI have been investigated in Dutch women with and without sexual complaints [23].

Unmet need for sexual care was measured using the 34-item Short-Form Supportive Care Needs Survey (SCNS-SF34). The SCNS-SF34 measures the need for supportive care from the patient's perspective

in the last month on a 5-point, two-level response scale. The first level consists of two broad categories of need, i.e. 'no need' and 'some need'. The 'no need' scale is further subdivided into '1 = not applicable' for issues that were no problem to the patient and '2 = satisfied' for issues on which a patient needed support but the support was satisfactory. The 'some need' level has three categories indicating the level of need for additional care: 3 = low, 4 = moderate and 5 = high. A total score per subscale is calculated and converted to a 0–100 score, with a higher score indicating a higher level of care needs. The SCNS-SF34 has good validity and reliability among HNC patients [24–26].

Statistical analyses

Descriptive statistics were generated to describe the study population. Frequency and percentage were used for categorical data, median and interquartile range (IQR) for continuous data. Spearman's correlation coefficients were used to test associations between TT and FTI and scores on subscales of the patient reported outcome measures. A p-value of < 0.05 was considered to be statistically significant. Statistical analyses were performed using the IBM SPSS Statistics version 26 (IBM Corp, Armonk, NY, USA).

Results

Study population

An overview of patient characteristics and study outcomes is provided in Table 1. Mean age was 60 years in men and women. In men, tumor subsite was oral cavity (25%), oropharynx (45%), larynx (30%); 35% was treated by surgery, 80% by radiotherapy, 20% by chemotherapy. In women, tumor site was oral cavity (63%), oropharynx (32%), larynx (5%); 60% was treated by surgery, 60% by radiotherapy, 30% by chemotherapy.

Testosterone

In men, median TT before treatment was 14.5 (IQR 10.9 – 16.7) and 14.9 (IQR 12.3 – 21.3) at 6 months after treatment. Median FTI before treatment was 32.9 (IQR 26.6 – 43.2) and 36.1 (IQR 30.6 – 40.2) at follow-up. Before treatment, TI was present in 5 patients (25%) and in 3 patients at follow-up (15%) (2 patients who had TI before treatment plus one). In women, median TT before treatment was 0.59 (IQR 0.47 – 0.80) and 0.63 (IQR 0.48 – 0.93) at follow-up. Median FTI before treatment was 1.2 (IQR 0.99 – 1.8) and 1.5 (IQR 0.88 – 2.0) at follow-up. Before treatment, TI was present in 2 patients (10%) and in 3 patients (15%) at follow-up (the same 2 patients plus one).

An overview of all associations between TT and FTI and scores on the subscales of the PROs is presented in Table 2. In men, FTI before treatment was significantly associated with the IIEF subscale Orgasm ($p = 0.020$)) and at 6 months follow-up with the IIEF subscale Desire ($p = 0.019$). In women, FTI at 6 months follow-up was significantly associated with the FSFI subscale Satisfaction ($p = 0.012$). TT was significantly associated with EORTC sexuality ($p = 0.031$) and FSFI satisfaction ($p = 0.020$).

Table 1
. Overview of the study population.

	men (N = 20)		women (N = 20)	
Age (mean, standard deviation)	60.2	10.1	59.8	7.9
Clinical factors	**n**	**%**	**n**	**%**
tumor site - oral cavity	5	25	12	63
tumor site - oropharynx	9	45	6	32
tumor site - larynx	6	30	1	5
treatment - surgery	7	35	12	60
treatment - radiotherapy	16	80	12	60
treatment - chemotherapy	4	20	6	30
Sexual hormones	**median**	**IQR**	**median**	**IQR**
Total testosterone before treatment	14.5	10.9–16.7	0.59	0.47–0.80
Total testosterone six months follow-up	14.9	12.3–21.3	0.63	0.48–0.93
SHBG before treatment	37.0	19.8–37.0	55.1	37.6–65.7
SHBG six months follow-up	42.6	32.6–59.1	51.0	36.7–70.8
Free Testosterone Index before treatment	32.9	26.6–43.2	1.2	0.99–1.8
Free Testosterone Index six months follow-up	36.1	30.6–40.2	1.5	0.88–2.0
	N	**%**	**n**	**%**
Testosterone insufficiency before treatment	5	25	2	10
Testosterone insufficiency six months follow-up	3	15	3	15
PROs before treatment [range domain]	**mean**	**SD**	**mean**	**SD**
EORTC Hn Sx subscale [0–100]	23.3	27.3	43.3	40.2
SCNS Sx subscale [0–100]	16.7	18.5	8.1	13.9
IIEF - desire [2–10]	5.6	1.9	n.a.	n.a.
IIEF - erectile function [1–30]	18.9	10.9	n.a.	n.a.
IIEF – orgasm [0–10]	6.8	3.9	n.a.	n.a.
IIEF - intercourse satisfaction [0–15]	6.6	5.3	n.a.	n.a.
IIEF - overall satisfaction [2–10]	6.1	2.9	n.a.	n.a.
FSFI – desire [1.2–6]	n.a.	n.a.	2.3	1.3
FSFI – arousal [0–6]	n.a.	n.a.	2.1	2.5
FSFI – lubrication [0–6]	n.a.	n.a.	2.4	2.8
FSFI – orgasm [0–6]	n.a.	n.a.	2.4	2.7
FSFI – satisfaction [0.4–6]	n.a.	n.a.	3.2	2.1
FSFI – pain [0–6]	n.a.	n.a.	2.6	2.9
FSFI – total score [1.6–36]	n.a.	n.a.	14.9	13.6
PROs six months follow-up [range domain]				
EORTC Hn Sx subscale [0–100]	21.9	24.2	37.7	39.2
SCNS Sx subscale [0–100]	5.8	14.1	9.4	19.6
IIEF - desire [2–10]	6.0	2.0	n.a.	n.a.
IIEF - erectile function [1–30]	18.9	11.4	n.a.	n.a.
IIEF – orgasm [0–10]	6.9	4.1	n.a.	n.a.
IIEF - intercourse satisfaction [0–15]	7.8	5.5	n.a.	n.a.
IIEF - overall satisfaction [2–10]	6.9	2.6	n.a.	n.a.
FSFI – desire [1.2–6]	n.a.	n.a.	2.5	1.2
FSFI – arousal [0–6]	n.a.	n.a.	2.0	2.5
FSFI – lubrication [0–6]	n.a.	n.a.	2.1	2.6
FSFI – orgasm [0–6]	n.a.	n.a.	2.1	2.5
FSFI – satisfaction [0.4–6]	n.a.	n.a.	3.0	2.2
FSFI – pain [0–6]	n.a.	n.a.	2.4	3.0
FSFI – total score [1.6–36]	n.a.	n.a.	14.0	12.9

IQR: interquartile range; SHBG: sex hormone-binding globulin; PROs: patient reported outcomes;
EORTC: European Organisation for Research and Treatment of Cancer; SCNS: supportive care needs survey
FSFI: female sexual function index; IIEF: the international index of erectile function

Discussion

The aim of this pilot study was to investigate whether testosterone is associated with patient reported sexual problems and need for sexual care in male and female HNC patients. Among a group of 40 HNC patients of whom 10–25% had testosterone insufficiency, testosterone was significantly associated with sexual problems before as well as 6 months after treatment, but not with need for sexual care. As expected, we found that testosterone was associated with all phases of the sexual response: sexual desire, arousal, orgasm, and satisfaction. More specifically, in men, FTI was significantly associated with orgasm before treatment and with desire at 6 months follow-up. In women, testosterone was not significantly associated with sexual problems before treatment. At 6 months after treatment, TT was significantly associated with sexuality and intimacy, and satisfaction, and FTI with satisfaction.

Obviously, a limitation of this pilot study was the relatively small

Table 2
Correlations between testosterone and patient reported sexual outcomes outcomes.

		Total testosterone		Free testosterone Index	
		Spearman's correlation	p-value	Spearman's correlation	p-value
Before treatment					
men	EORTC Sexuality	−0.18	0.44	0.36	0.12
	SCNS Need for sexual care	−0.01	0.97	0.44	0.054
	IIEF - Desire	0.28	0.24	0.31	0.18
	IIEF - Erectile function	0.13	0.60	0.44	0.061
	IIEF - Orgasm	0.23	0.32	0.52	0.020*
	IIEF - Intercourse satisfaction	0.12	0.64	0.32	0.18
	IIEF - Satisfaction	0.08	0.74	0.13	0.60
women	EORTC Sexuality	0.24	0.30	−0.14	0.56
	SCNS need for sexual care	0.20	0.41	0.00	1.00
	FSFI - Desire	0.02	0.92	0.38	0.10
	FSFI - Arousal	−0.08	0.73	0.24	0.31
	FSFI - Lubrication	−0.05	0.84	0.18	0.44
	FSFI - Orgasm	−0.06	0.80	0.24	0.30
	FSFI - Satisfaction	0.08	0.72	0.40	0.078
	FSFI - Pain	−0.08	0.74	0.13	0.60
	FSFI - Total score	0.00	0.99	0.29	0.21
Six months follow-up					
men	EORTC Sexuality	−0.06	0.81	0.01	0.95
	SCNS Need for sexual care	0.02	0.92	0.01	0.97
	IIEF - Desire	0.03	0.90	0.52	0.019*
	IIEF - Erectile function	0.21	0.38	0.33	0.15
	IIEF - Orgasm	0.08	0.74	0.36	0.12
	IIEF - Intercourse satisfaction	0.13	0.60	0.34	0.15
	IIEF - Overal satisfaction	0.38	0.094	−0.15	0.53
women	EORTC Sexuality	−0.50	0.031*	−0.32	0.18
	SCNS Need for sexual care	−0.23	0.34	0.29	0.21
	FSFI - Desire	0.24	0.31	−0.02	0.94
	FSFI - Arousal	0.26	0.27	0.18	0.46
	FSFI - Lubrication	0.32	0.18	0.18	0.46
	FSFI - Orgasm	0.27	0.24	0.28	0.23
	FSFI - Satisfaction	0.52	0.020*	0.55	0.012*
	FSFI - Pain	0.25	0.28	0.23	0.33
	FSFI - Total score	0.35	0.13	0.23	0.33

EORTC: European Organisation for Research and Treatment of Cancer; SCNS: supportive care needs survey.
IIEF: the international index of erectile function; FSFI: female sexual function index.

sample size. Therefore, associations between testosterone and patient reported sexual outcomes were not investigated in relation to other factors such as age, treatment modality, other endocrine and stress-related biomarkers, and the female androgen insufficiency syndrome (FAIS) (women) or late onset hypogonadism (men).

In the general population, testosterone level decreases with increasing age. HNC patients are typically between 40 and 80 years old. In the European Male Aging Study, with a study population also aged 40–80 years, a 0.4% per year decrease in total testosterone was found and a 1.3% per year decline in FTI [13]. In women, testosterone levels decline gradually in the 20 years after adolescence but remain stable across menopause and beyond [27]. Natural menopause does not seem to lead to a significant decrease in total testosterone level in contrast to surgical (bilateral oophorectomy) menopause [16].

Cancer treatment may also negatively impact sexual outcomes. Radiotherapy and chemotherapy may induce sexual problems directly by damage to the vessels and nerves in the pelvic region, or indirectly by metabolic or hormonal changes in cancer patients in general. Surgery in the region of the hypothalamus, pituitary gland, or thyroid may also induce sexual problems [28]. The hypothalamus-pituitary–gonadal (HPG) axis, the hypothalamus–pituitary–thyroid (HPT) axis, and the hypothalamus–pituitaryadrenal (HPA) axis are three pathways in which neuroendocrine function including testosterone is directed. Hypothyroidism is common after HNC treatment, particularly when neck nodal levels are within the radiation field. The incidence of radiation-related hypothyroidism in HNC varies between 15% and 50% [29–33], but it is unknown whether this impacts testosterone level or patient reported sexual outcomes in HNC patients.

Sexual problems are often associated with other patient reported problems or symptoms. In women, criteria of FAIS include low FTI and impaired sexual function (reduced sexual desire, decreased sexual receptivity and pleasure), as well as poor well-being, dysphoric mood, and possibly also fatigue, vasomotor instability, vaginal dryness, decreased muscle strength, poor memory, and bone loss [34]. Laan et al (2019) also reported that TI is associated with decreased sexual desire, fatigue, impaired cognitive function, reduced physical activity and function, increased distress, and symptoms of depression [18]. In men, late onset hypogonadism is a clinical syndrome that includes TI in combination with symptoms as erectile dysfunction, reduced sexual desire, erectile dysfunction, decreased spontaneous erections, decreased vigorous activity, difficulty walking $>$ 1 km, decreased bending, low mood, decreased motivation, and fatigue [11].

Finally, also due to the small sample size, we investigated the associations before treatment and at 6 months follow-up separately. In future research it would be interesting to also investigate the course of sex hormones in relation to the course of sexual problems from time of diagnosis to short and long-term follow-up.

Conclusion

Based on this pilot study, testosterone seems associated with patient reported sexual outcomes among male and female HNC patients. It is estimated that 10–25% of HNC patients may have testosterone insufficiency before treatment and/or at 6 months after treatment. Further research is needed to verify these findings, using a larger cohort and more biopsychosocial factors that might moderate or mediate the association between testosterone and patient reported sexual outcomes among HNC patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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