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The impact of hyperbaric oxygen therapy on erectile functions and serum testosterone levels in patients with erectile dysfunction

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ABSTRACT

Objective: To evaluate the effects of hyperbaric oxygen therapy (HBOT) on erectile functions and serum testosterone levels in patients with erectile dysfunction (ED).

Methods: The patients treated by HBOT for several diseases between July 2017–May 2018 and had erectile dysfunction were included in the study. All patients filled the International Index of Erectile Function (IIEF) questionnaire form; serum total testosterone (TT) and free testosterone (FT) levels were examined before the first day and after the last day of HBOT. The effects of demographic characteristics of patients on erectile functions were evaluated. Patients were categorized according to the risk factors. The IIEF scores, TT and FT levels of patients in first day and after last day of HBOT were compared.

Results: Totally 43 patients were included in the study. The mean post-HBOT IIEF-EF score was significantly higher than the mean pre-HBOT IIEF-EF score of patients (25.4 ± 5.3 vs 20.6 ± 5.1 ; $p < .001$). There was no statistical difference between the pre-HBOT and post-HBOT serum TT and FT levels of patients (4.0 ± 2.3 ng/ml vs 4.1 ± 2.0 ng/ml, $p = .797$; 8.6 ± 3.8 pg/ml vs 8.9 ± 3.5 pg/ml, $p = .658$).

Conclusions: HBOT improved the erectile functions in ED patients however we cannot detect any effect on testosterone levels in our study.

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Erection; erectile dysfunction; hyperbaric oxygen therapy; International Index of Erectile Function (IIEF); testosterone

Introduction

Erectile dysfunction (ED) is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance [1]. ED is a worldwide health problem increasing with aging and has negative impacts on men's quality of life [2]. The prevalence of ED in 40–70 years old men was detected between 25–52% in previous reports [3–6]. Several treatment modalities can be used in ED; first-line treatment of ED includes oral pharmacotherapy with phosphodiesterase type 5 (PDE 5) inhibitors. Intracavernous injections constitute second-line treatment and surgical treatment (penile prostheses) may be offered to patients as a third line therapy for ED. However new treatment modalities have become popular in recent years including low-intensity extracorporeal shock wave therapy (ESWT) and hyperbaric oxygen therapy (HBOT) as an alternative treatment [7–9].

HBOT is a kind of therapy in which the patients breathe 100% oxygen at pressures greater than

normal atmospheric (sea level) pressure (>1 atm). HBOT increases oxygen tensions and oxygen delivery to tissues by extra dissolved content of oxygen in the blood [10]. HBOT had been used in the treatment of several medical conditions during the past 50 years including urological diseases such as interstitial cystitis, radiation-induced hemorrhagic cystitis and Fournier's gangrene (FG) [10–13]. The first reports about the effect of HBOT on erectile functions were published by Müller et al and Yuan et al [8,11]. Both of these studies showed that HBOT improved erectile functions in rat cavernous injury model [8] and in patients with posterior urethral reconstruction [14]. Recent clinical studies showed that HBOT improved the erectile functions in non-surgical patients and this effect was linked to induction of angiogenesis [15,16]. We hypothesized that the improvement in erectile functions may be associated with increasing serum testosterone levels. Passavanti et al showed that HBOT increased the serum total testosterone levels in both non-ED patients and healthy men [17]. However, there

is no clinical study that investigates the effects of HBOT on serum total testosterone (TT) and free testosterone (FT) levels in patients with ED yet. In this study, we aimed to evaluate the effects of HBOT on erectile functions, serum TT and FT levels in patients with ED.

Material and methods

The male patients who were treated by HBOT for several diseases (foot wound, avascular necrosis of the femoral head, sudden hearing loss and sudden loss of vision) between July 2017 and May 2018 were examined. This study was approved by the local ethics committee. Patients were included in the study consecutively. All patients were informed and filled the informed consent form. All patients were heterosexual and did not use PDE-5 inhibitors, intracavernosal injections or any treatment for ED during the study period. Exclusion criteria were; under the age of 18; history of persistent spinal cord or brain diseases; having drug abuse and lack of regular sexual partner. All patients filled the International Index of Erectile Function (IIEF) questionnaire form and serum TT and FT levels were examined before the first day and after the last day of HBOT. A questionnaire including demographic characteristics and medical history was also filled by patients. ED stage improvement was defined as improvement in total IIEF-EF scores; severe to moderate, moderate to mild-moderate, mild-moderate to mild and mild to normal limits.

A multiplace chamber was used for HBOT (Hiperbot Model 101, 2005, Turkey) and up to ten patients could be treated at the same time. Before the treatment, the chamber was pressurized up to 2.4 atmospheres absolute (ATA) with 100% oxygen for 15 min. and then the patients breathed this oxygen with a mask. The duration of each treatment session was 120 min including; compression at the beginning: 15 min, three oxygenation periods: 75 min (25 min for each), 15 min air breaks (5 min for each period) and decompression of chamber for 15 min. Totally 30 sessions of HBOT were applied to the patients. The HBOT sessions were repeated for six days a week.

The effects of demographic characteristics and medical history of patients on erectile functions were evaluated. Patients were categorized according to the risk factors and the IIEF scores, serum total testosterone and free testosterone levels of patients on first day and after last day of HBOT were compared. Analyses of data were performed with the Statistical Package for the Social Sciences (SPSS, Inc., Chicago IL), version 22, and software for Windows. Data were

presented as mean \pm standard derivation, numbers (*n*) and percent (%). Student Paired T-test was used for comparison of variables before and after HBOT. Statistical significance was set at a *p* values of $<.05$.

Results

HBOT was performed to 175 male patients between July 2017 and May 2018 and 59 patients had ED. Sixteen of these patients did not finish their therapy so they were excluded from the study; finally, 43 patients were included in the study and the mean age was 59.9 ± 11.4 years. The reason of HBOT was foot wound in 19 (44.2%) patients, avascular necrosis of the femoral head in 6 (13.9%) patients, sudden hearing loss in 15 (34.9%) patients, and sudden loss of vision in 3 (7%) patients. Diabetes mellitus and hypertension were the most common co-morbidities in patients (37.2% and 34.9%). Demographic characteristics and medical history of patients were given in Table 1. All patients had a regular sexual partner and 36 (83.7%) of them were married, 6 (14%) of them were single and 1 (2.3%) of them was divorced. IIEF-erectile function (EF) scores showed that 2 (4.7%) patients had severe, 3 (7%) patients had moderate, 15 (34.9%) patients had mild-moderate, and 23 (53.4%) patients had mild ED. The mean post-HBOT IIEF-EF score of patients was significantly higher than the mean pre-HBOT IIEF-EF score of patients (25.4 ± 5.3 vs. 20.6 ± 5.1 ; $p < .001$). The mean post-HBOT IIEF scores of other domains except orgasmic function; including sexual desire, intercourse satisfaction, and overall satisfaction were also significantly higher than pre-HBOT's

Table 1. Demographic characteristics of the patients.

	(mean \pm SD)
Age	59.9 \pm 11.4
BMI	27.1 \pm 3.9
Smoking package/year	14.8 \pm 18.4
Number of co-morbidity	1.0 \pm 1.0
	(<i>n</i> ,%)
The reason of HBOT	
Sudden loss of hearing or vision	18 (41.9%)
Foot wound/avascular necrosis	25 (58.1%)
Total testosterone level	
low	13 (30.2%)
normal	30 (69.8%)
high	0 (0%)
Free testosterone level	
low	21 (48.8%)
normal	22 (51.2%)
high	0 (0%)
Smoking	
Yes	22 (51.2%)
No	21 (48.8%)
Alcohol use	
Yes	21 (48.2%)
No	22 (51.2%)

BMI: body mass index; HBOT: hyperbaric oxygen therapy.

Table 2. Comparison of pre-HBOT and post-HBOT IIEF domain scores, serum total testosterone, and free testosterone levels.

	Pre-HBOT (mean \pm SD)	Post-HBOT (mean \pm SD)	p^a
Erectile function (EF)	20.6 \pm 5.1	25.4 \pm 5.3	<.001 ^a
Intercourse satisfaction	10.7 \pm 3.0	12.3 \pm 2.6	<.001 ^a
Orgasmic function	9.0 \pm 1.5	9.3 \pm 1.4	.058 ^a
Sexual desire	7.0 \pm 2.0	8.0 \pm 1.6	<.001 ^a
Overall satisfaction	7.4 \pm 2.3	8.4 \pm 1.9	<.001 ^a
Total testosterone (ng/ml)	4.0 \pm 2.3	4.1 \pm 2.0	.797 ^a
Free testosterone (pg/ml)	8.6 \pm 3.8	8.9 \pm 3.5	.658 ^a

HBOT: hyperbaric oxygen therapy; IIEF-EF: International Index of Erectile Function-Erectile Function.

^aPaired *t*-test.

scores (Table 2). There were no statistical differences between the pre-HBOT and post-HBOT serum total testosterone and free testosterone levels of patients (4.0 \pm 2.3 ng/ml vs. 4.1 \pm 2.0 ng/ml, $p = .797$; 8.6 \pm 3.8 pg/ml vs. 8.9 \pm 3.5 pg/ml, $p = .658$).

The effects of demographic characteristics and erectile dysfunction risk factors including age, body mass index (BMI), comorbidities, smoking, alcohol use etc on HBOT and serum total testosterone and free testosterone levels were given in Table 3. HBOT improved IIEF scores regardless of the presence of risk factors also serum TT and FT levels were not affected by risk factors (Table 3).

Stage improvement in IIEF-EF scores after HBOT was detected in 34 (79%) patients. Our study showed that the most common ED risk factors did not affect stage improvement after HBOT (Table 4).

Discussion

HBOT was first used in decompression patients in 1937 by Behnke and Shaw [18]. However, the modern use of HBOT was started after 1950s by the inhalation of Oxygen in the pressure chamber [19]. HBOT can be applied in a monoplace or a multiplace chamber. In a monoplace chamber, a single patient is taken to the chamber and patient breathes the ambient chamber oxygen directly. In multiplace chamber, two or more patients are taken to the chamber and the chamber is pressurized with compressed air; patients breathe 100% oxygen via masks, endotracheal tubes or head hoods. In our study, we used a multiplace chamber for HBOT.

HBOT was used in several urological disorders including interstitial cystitis, radiation-induced hemorrhagic cystitis and FG [11,13,20–25], however, only a few reports were published about the effect of HBOT on erectile functions [8,14–16]. Müller et al evaluated the effects of HBOT on erectile functions and cavernosal tissue, in the rat cavernous nerve (CN) injury model [8]. They detected that HBOT was a useful and

reliable treatment strategy to preserve or recover EF after CN injury and the mechanism of this effect was connected to expression of neurotrophic and endothelial factors by authors.

Yuan et al. evaluated the effects of HBOT on the recovery of erectile functions after posterior urethral reconstruction [14]. They divided the patients into two groups; group 1 consisted of the patients with only posterior urethral reconstruction and group 2 consisted of the patients with HBOT + posterior urethral reconstruction. Preoperative and postoperative erectile functions were evaluated with IIEF scores. They found the total IIEF, IIEF-EF, IIEF-overall satisfaction (OS) and IIEF-intercourse satisfaction (IS) scores after HBOT were significantly higher in group 2 and they emphasized that HBOT can be useful for improving EF recovery after posterior urethral reconstruction. The effects of HBOT on erectile function may be associated with tissue oxygenation, improvement in eNOS expression and angiogenesis. Sahin et al evaluated the effects of HBOT on erectile functions in patients who had no cavernosal or urethral injury and they showed that all of the IIEF domains increased after HBOT [15]. They emphasized that it can be useful also in normal tissues not only for damaged tissues. In a recent study, Hadanny et al investigated the effects of HBOT on sexual function via IIEF and penile vascular bed via perfusion MRI (magnetic resonance imaging) in non-surgical ED patients [16]. They reported that HBOT significantly improved all IIEF domains by 15–88% and they demonstrated that a significant increase by 153.3 \pm 43.2% of K-trans values in the corpus cavernosum. Similar to these studies all IIEF domains except for orgasmic function were improved in our study. Also, we detected that 79% of ED patients had a stage improvement according to the IIEF-EF scores. In contrast to our results, a recent study by Chiles et al did not find any differences in terms of IIEF scores in prostate cancer patients treated with nerve-sparing robotic radical prostatectomy [26]. They randomized the patients as sildenafil 50 mg daily + HBOT and control

Table 3. The association between HBOT and the demographic characteristics, erectile dysfunction risk factors, and testosterone levels.

Covariate	Category	Pre-HBOT Mean IIEF-EF	Post-HBOT Mean IIEF-EF	<i>p</i> ^a	Pre-HBOT Mean TT level	Post-HBOT Mean TT level	<i>p</i> ^a	Pre-HBOT Mean FT level	Post-HBOT Mean FT level	<i>p</i> ^a
Age	<50	22.9 ± 2.8	28.1 ± 3.8	<.001	3.8 ± 1.6	4.0 ± 1.3	.621	8.9 ± 3.7	9.6 ± 2.4	.384
	≥50	18.4 ± 5.8	22.8 ± 5.2	<.001	4.3 ± 2.8	4.2 ± 2.6	.519	8.4 ± 4.0	8.3 ± 4.2	.875
BMI	<25	21.2 ± 7.0	25.9 ± 6.6	<.001	3.7 ± 1.8	3.7 ± 1.6	.918	8.3 ± 3.2	9.0 ± 4.0	.390
	≥25	20.4 ± 4.2	25.2 ± 4.8	<.001	4.2 ± 2.5	4.2 ± 2.2	.815	8.8 ± 4.1	8.9 ± 3.3	.899
Smoking	No	22.1 ± 4.1	27.0 ± 4.4	<.001	3.6 ± 1.4	3.5 ± 1.3	.591	8.9 ± 3.6	8.3 ± 3.1	.465
	Yes	19.1 ± 5.5	23.8 ± 5.6	<.001	4.5 ± 2.9	4.7 ± 2.4	.531	8.4 ± 4.1	9.5 ± 3.7	.257
Alcohol drinking	No	20.2 ± 5.6	24.9 ± 5.5	<.001	3.6 ± 1.3	3.8 ± 1.4	.440	8.5 ± 2.8	8.5 ± 3.3	.988
	Yes	21.0 ± 4.5	25.9 ± 5.1	<.001	4.5 ± 3.0	4.4 ± 2.5	.883	8.8 ± 4.7	9.3 ± 3.6	.606
Comorbidities	Absent or just one	21.7 ± 4.2	26.5 ± 4.8	<.001	4.1 ± 2.4	4.2 ± 1.9	.586	8.8 ± 4.2	9.5 ± 3.4	.404
	At least two	18.0 ± 6.0	22.8 ± 5.7	<.001	4.0 ± 2.3	3.8 ± 2.3	.564	8.2 ± 2.8	7.6 ± 3.3	.570
The cause of HBOT	Sudden loss of hearing or vision	22.3 ± 2.6	27.6 ± 3.6	<.001	4.0 ± 1.9	4.1 ± 1.9	.603	7.7 ± 3.4	9.0 ± 3.3	.204
	Foot wound/ avascular necrosis	19.4 ± 6.0	23.8 ± 5.7	<.001	4.1 ± 2.6	4.1 ± 2.2	.969	9.3 ± 4.0	8.9 ± 3.7	.572

HBOT: hyperbaric oxygen therapy; TT: total testosterone; FT: free testosterone; IIEF-EF: International Index of Erectile Function-Erectile Function.

^aPaired *t*-test.

Table 4. The association between ED risk factors and stage improvement after HBOT.

	Stage improvement (–)	Stage improvement (+)	<i>p</i>
Age (mean ± SD)	46.0 ± 12.6	48.0 ± 11.2	.645
BMI (mean ± SD)	27.1 ± 4.1	27.2 ± 3.9	.950
Smoking (<i>n</i> ,%)			
No	3 (7%)	18 (42%)	.252
Yes	6 (14%)	16 (37%)	
Alcohol drinking (<i>n</i> ,%)			
No	5 (11.7%)	17 (39.5%)	.532
Yes	4 (9.3%)	17 (39.5%)	
Comorbidities (<i>n</i> ,%)			
Absent or just one	3 (7%)	14 (32.5%)	.489
At least two	6 (14%)	20 (46.5%)	

group (sildenafil 50 mg daily + normal air) after nerve-sparing robotic radical prostatectomy. Hereby, all participants had used sildenafil 50 mg daily. The effect of HBOT might be better compared with control group if both of the groups did not use sildenafil therapy. The HBOT procedure of their study including 10 sessions however 30 sessions were performed to our patients. The different results can be also connected the HBOT procedures.

Previous reports showed that sex steroid hormones had an impact on wound healing processes in patients [27]. Although the effects of HBOT are linked to induction of oxygen; the efficiency of HBOT is also mediated by indirect changes such as the increase of testosterone levels like the Passavanti et al's study [17]. They linked the effects of HBOT on modifying testosterone to the increase in blood oxygenation increases testosterone synthesis or decreases testosterone metabolism; so that hyperoxygenation of gonadal

tissue improves Leydig cell functions, resulting in an increase of testosterone synthesis. However in a previous study Nakada et al investigated the effects of HBOT on testicular activity in rats at 1986 and they did not find any significant differences between pre-HBOT and post HBOT in terms of serum testosterone concentrations and the amounts of collagen, non-collagenous protein or elastin in testis [28]. We evaluated the pre and post-HBOT testosterone levels in ED patients; we noted that serum total and free testosterone levels were minimally increased but not statistically significant. We can conclude that from our results HBOT improves IIEF scores regardless of the risk factors and testosterone levels.

This study has some limitations; there was no control group in our study and the patient sample was heterogeneous in terms of HBOT indications. Further studies including control groups and more homogeneous patient samples can be designed. Psychiatric conditions of patients might be evaluated at the beginning and end of the HBOT with a scale.

HBOT improved the erectile functions in ED patients however we could not detect any effect on testosterone levels in our study. HBOT seems to be a good alternative or supportive treatment modality for patients with erectile dysfunction. Further studies with larger sample size are required to clearly identify the effects of HBOT on testosterone levels in ED patients.

Disclosure statement

There is no conflict of interest to disclose.

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