ARTICLE

Endocrine stimulation in men with non-obstructive azoospermia and low serum testosterone prior to micro-TESE: hormonal response as a predictor of sperm retrieval

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Background: *Hormonal treatment and response as a predictor of sperm retrieval prior to microdissection testicular sperm extraction (micro-TESE) are not well established in the current literature. This study aimed to investigate the hormonal response as a predictor of sperm retrieval among men with nonobstructive azoospermia (NOA).*

Methods: *Seventy-seven consecutive patients who had testosterone levels ≤ 14 nmol/L were treated medically with an aromatase inhibitor or recombinant human chorionic gonadotropin (rec-hCG) prior to micro-TESE and were included. Thirty-four (44.2%) had unexplained NOA (UNEX), 25 (32.5%) had Klinefelter syndrome (KS), 8 (10.4%) had a history of cryptorchidism (UDT), 4 (5.2%) had microdeletion of the Azoospermia factor C (AZFc), and 6 (7.8%) were treated previously with chemotherapy. Baseline and post-treatment serum hormonal levels were documented. Pre-op testosterone levels were entered into binary logistic regressions with age, Follicle-stimulating hormone (FSH), and Luteinizing hormone (LH) levels to test for significance with sperm retrieval. We then built logistic regression models to identify predictors of successful surgical sperm retrieval (SSR).*

Results: *Forty-five patients (58%) had successful retrieval. In 32 patients (42%), no sperm was retrieved. Both the mean pre-op testosterone and the mean testosterone change between the two groups were significant (p = 0.02 and p = 0.011, respectively). Receiver operating characteristic (ROC) analysis demonstrated an area under the curve (AUC) of 0.785 (95%CI = 0.685–0.886, p < 0.001). The Youden index coefficient was calculated for KS and UNEX. The cut-off point for KS was established at 0.764 (sensitivity = 0.875, false positive rate [FPR] = 0.111), and 0.215 for UNEX (sensitivity = 0.438, FPR = 0.222). We also observed a correlation between age and SSR (p = 0.05). In KS patients, SSR was determined by pre-op testosterone levels irrespective of age.*

Conclusion: *Pre-operative hormonal response is a predictor for SSR in NOA patients who were treated medically. This data may help during pre-operative counselling.*

Key Words: non-obstructive azoospermia (NOA), microdissection testicular sperm extraction (micro-TESE), endocrine stimulation, male infertility, sperm retrieval

Introduction

Azoospermia is defined as the total absence of spermatozoa in the ejaculate, and it occurs in 10%–15% of men who undergo fertility investigation.[1] This needs to be confirmed in repeated tests with vigorous centrifugation of the semen and careful examination of the pellet.[2] Non-obstructive azoospermia (NOA), which is associated with spermatogenic failure, is a challenging form of azoospermia that is managed most commonly by surgical sperm retrieval followed by intracytoplasmic sperm injection (ICSI). Many of these patients present with a hormone profile of high Follicle-stimulating hormone (FSH), normal or high Luteinizing hormone (LH) levels, and normal to low testosterone levels.[3] Intra-testicular testosterone (ITT) is required for several critical steps associated with spermiogenesis, which include meiosis completion, adhesion of elongated spermatids to Sertoli cells, sperm release, and maintenance of the blood-testis barrier.[4,5] Additionally, high ITT is also required for one of the earliest steps of spermatogenesis—the transition from type A to type B spermatogonia.[6,7] In view of the pivotal role of testosterone in the regulation of spermatogenesis and spermiogenesis, elevation of ITT may contribute to the optimization of these processes. Hence, NOA patients who present with low circulating testosterone may benefit from hormonal optimization prior to their surgery.[8,9]

Various sperm retrieval techniques have been used in NOA patients, with significant variability in success rates associated with underlying diagnosis, surgical technique, and several other clinical and laboratory parameters.[10–15] The understandable wish of NOA patients who pursue fertility treatment to understand their chances of successful sperm retrieval dictates thorough preoperative counselling. During such counselling sessions, patients should be presented with as much solid evidence to allow them to make an informed decision.

Several clinical variables and biomarkers are predictive tools to estimate the likelihood of sperm retrieval in men with NOA.[16–20] In this observational retrospective study, we investigated the surgical outcome in NOA patients who were treated medically prior to their microdissection testicular sperm extraction (micro-TESE), and we assessed the value of their hormonal response as a predictor of SSR.

Materials and Methods

Patients

The records of 117 consecutive NOA patients who underwent micro-TESE by a single surgeon (S.B.) between December 2019 and March 2022 were reviewed retrospectively, and patients who were treated hormonally prior to their operation were identified. Azoospermia was confirmed by two semen analyses according to WHO criteria[2] and two extended sperm searches, as described by Ron-El et al.[21] Diagnosis of NOA was based on the presence of two or more of the following criteria: histopathology that confirmed no spermatogenesis or maturation arrest, the combination of an elevated FSH level greater than 7.6 IU/L and smaller testicular volumes with a long axis of 4.6 cm or less, absence of sperm on initial sperm search and genetic abnormality or chromosomal abnormality known to be associated with NOA (e.g., Klinefelter syndrome [KS]; Yq microdeletions).[22] Patients with proven obstructive azoospermia (i.e., histopathology that confirmed normal spermatogenesis, presence of unilateral or bilateral absence of the vas deferens, presence of an abundant number of sperm on initial sperm search) and men with complete microdeletions on azoospermia factor region (AZF) A or B were excluded from this study.

The study was approved by the local Institutional Review Board of the Assuta Medical Center (No. 0014-22-ASMC). Due to its retrospective nature, informed consent was waived.

Data collection

Patients' ages were recorded. Preoperative evaluation included a complete history, physical examination, and routine scrotal ultrasound. Hormonal evaluation included serum testosterone, estradiol, LH, and FSH hormonal analyses.

Blood samples were collected between 7:00 and 10:00 a.m. after 8–10 h of overnight fasting in serum tubes for the estimation of total testosterone, estradiol, FSH, and LH. The same laboratory and kits were used for all samples. Testosterone, estradiol, FSH, and LH levels were analyzed and quantified by a Siemens ADVIA Centaur® XP (Siemens Healthineers, Forchheim, Germany). The laboratory reference ranges were 6.5–24 nmol/L for total testosterone, <223 pmol/L for estradiol, 1–9 IU/L for LH, and 1.4–18.1 IU/L for FSH. All azoospermic men with testosterone levels ≤14 nmol/L[23] were included in the study.

Treatments

Patients with serum testosterone of ≤ 14 nmol/L were treated with aromatase inhibitors (1 mg anastrozole daily) for ≥ 3 months prior to their surgery. Patients were given oral aromatase inhibitors as first-line treatment regardless of their body mass index (BMI), testosterone/estradiol (T/E) ratio, or estradiol levels. Those who had less than a 15% increase in their testosterone levels after 6 weeks of aromatase inhibitor therapy were converted to recombinant human chorionic gonadotropin (rec-hCG).

Treatment with rec-hCG was initiated at a dose of 2500 IU twice weekly, after 1 month, patients who didn't respond with elevated testosterone levels to normal limits were given a dose of 5000 IU three times weekly. Hormonal treatment was continued until the time of micro-TESE. Median overall treatment time was 5 months (interquartile range [IQR]: 4–7).

Micro-TESE procedure

Micro-TESE procedures were all performed by a single surgeon (S.B.) with over 20 years of experience. The procedure was done as described by Schlegel et al.[24]

Tissue processing and initial and extended sperm search

Seminiferous tubules obtained during micro-TESE were first dissected mechanically under a stereomicroscope with the use of bent 18-gauge needles. The initial search for spermatozoa was performed at $200\times$ magnification with the use of an inverted microscope (Olympus IX81, Olympus Group, Tokyo, Japan).

For an extended sperm search, dissected tubules were dissected further using bent 18-gauge needles for another 20 min and then centrifuged at $1000\times$ g for 15 min. Most of the supernatant was removed, and about 0.5 mL was left above the pellet. The pellet was then resuspended back into the supernatant. Drops of 10–20 μL of the suspension were put in a FluoroDish (FD5040, World Precision Instruments Inc., Sarasota, FL, USA) and covered with light mineral oil (Oil for Embryo Culture; Irvine Scientific, Santa Ana, CA, USA). The extended sperm search was performed with an inverted microscope (Olympus IX81, Olympus Group, Tokyo, Japan) equipped with Nomarski optics, a Uplan Apo X100 or X40 objective lens, and a 0.55 NA condenser lens. Motile or immotile spermatozoa were collected with the use of an injection pipette and Eppendorf TransferMan Nk2 micromanipulator (Eppendorf, Hamburg, Germany). The collected spermatozoa were placed in drops prepared in the same dish made of MHM-C medium (Multipurpose Handling Medium Complete; Irvine Scientific) supplemented with 30% Human Serum Albumin (Irvine Scientific) for further injection into oocytes or cryopreservation.

Statistical analysis

All analyses were performed with SPSS 29 (IBM Corp., Armonk, NY, USA). Descriptive statistics were derived for all variables; normal distribution was tested, and means and standard deviations (SDs) were calculated for hormones and testosterone measures, and paired t-tests were performed between testosterone measures. Following these tests, the pre-op testosterone measure was entered into binary logistic regressions with age, FSH, and LH hormone levels to test for significance with SSR. The predicted sperm retrieval probability was saved for further analysis and entered into a one-way ANOVA to establish the effect of pre-op testosterone level on sperm retrieval for each diagnosis and pre-op treatment. A Least Significant Difference (LSD) post hoc analysis was performed to highlight differences between the pre- and post-treatment groups. The saved predicted sperm retrieval predictor was further processed in a Receiver Operating Characteristic (ROC) analysis to derive Area Under the Curve (AUC) and Youden Index estimates. Age and diagnosis effects on sperm retrieval rates were then derived by sensitivity/specificity analysis.

Results

Seventy-seven patients with NOA who were medically treated prior to their micro-TESE were included in this study (Table 1). The mean age of subjects was 31.4 (range: 20–47). Thirty-four patients (44.2%) presented with unexplained (idiopathic) NOA (UNEX), 25 (32.5%) had KS, eight (10.4%) had a history of cryptorchidism (UDT), four (5.2%) had microdeletion of the AZFc (Yq del), and six (7.8%) were treated previously with chemotherapy (Post Chemo). Sperm was retrieved successfully in 45 patients (58.4%) (SR+) and failed in 32 patients (42%) (SR−). Successful retrieval varied between 47.1% in UNEX cases to 87.5% in UDT ones. Initial, pre-op, and changes in testosterone were analyzed by sperm retrieval (Table 2).

Although initial testosterone differences between the SR+ and SR− groups were small and not significant, both the mean pre-op testosterone and the mean change in testosterone levels between the two groups were significant ($p = 0.02$ and $p = 0.011$, respectively). Because pre-op testosterone accounted for most of the change ($R^2 = 0.656$, $p < 0.001$), it was

TABLE 1. **Characteristics of the study population**

		N (%)	SSR (%)	Mean age (year) (SD)	Mean FSH (mIU/mL) (SD)	Mean LH (IU/L) (SD)
Diagnosis	1 KS	25 (32.5)	16 (64)	27.8 (5.2)	41.62 (12.15)	22.32 (7.26)
	2 Post Chemother-apy	6 (7.8)	3 (50)	36.7 (4.8)	25.82 (10.97)	11.83 (4.68)
	3 UDT	8 (10.4)	7 (87.5)	30.5 (4.6)	26 (11.61)	12.29 (7.27)
	4 UNEX	34 (44.2)	16 (47.1)	33.4 (5.9)	25.61 (15.12)	10.09 (4.82)
	5 Y Deletion	4 (5.2)	3 (75)	30.3 (6.8)	17 (5.72)	6.85 (1.62)
Hormonal Treatment	anastrozole	56 (72.7)	33 (58.9)	31.7 (5.7)	27.56 (14.49)	11.93 (6.42)
	HCG	21 (27.3)	12 (57.1)	30.7 (7.2)	38.03 (14.9)	20.46 (9.07)
Total		77 (100.0)	45 (58.4)	31.4 (6.1)	30.42 (15.42)	14.26 (8.13)

Note. SSR, successful sperm retrieval; SD, standard deviation; FSH, Follicle-stimulating hormone; LH, Luteinizing hormone; KS, Klinefelter syndrome; UDT, undescended testicle; UNEX, unexplained; HCG, human chorionic gonadotropin.

TABLE 2. **Sperm retrieval after initial, pre-op, and changes in testosterone levels**

	SSR	No sperm retrieved	Total	*p*-value
Number of patients	45	32	77	/
Mean initial testosterone (SD)	9.36 (3.64)	9.54 (3.81)	9.43 (3.69)	0.84
Mean Pre-op testosterone (SD)	18.18 (5.85)	14.85 (6.37)	16.79 (6.25)	0.02
Mean change in testosterone (SD)	8.81 (6.07)	5.54 (4.24)	7.48 (5.61)	0.01

Note. SSR, successful sperm retrieval; SD, standard deviations.

adopted for further analysis and entered with age, FSH, and LH as independent variables into a binary logistic regression to test sperm retrieval. The saved predicted pre-op sperm retrieval was submitted to a ROC analysis (Figure 1). AUC of 0.785 (95%CI = 0.685–0.886, $p < 0.001$) was obtained, and a Youden Index coefficient was estimated at a 0.524 cut-off point that conformed to a sensitivity of 0.711 and a false positive rate (FPR) of 0.188.

We then calculated the Youden Index Coefficient for the two largest diagnostic categories, KS and UNEX, which together comprised 77% of all cases. The cut-off point for KS was 0.764 (sensitivity = 0.875, FPR = 0.111) and 0.215 for UNEX (sensitivity = 0.438, FPR = 0.222).

To address potential effects of age on sperm retrieval success, the pre-op testosterone predictor was plotted against age and regressed by the observed sperm retrieval (Figure 2). We found a weak, but significant, correlation between age and predicted successful sperm retrieval ($R^2 = 0.109$, $p = 0.05$).

To investigate further the interactions among age, testosterone, and sperm retrieval, patients were coded into "young" (20–30) and "old" (30+), and sperm retrieval results for KS and UNEX groups were plotted and compared to reveal different treatment response dynamics (Figure 3). In both groups, younger patients responded better to the testosterone-raising treatment. Among KS patients, sperm retrieval success was determined predominantly by pre-op testosterone levels, irrespective of age, but in UNEX patients, success, in both young and old, was largely independent of the pre-op testosterone level.
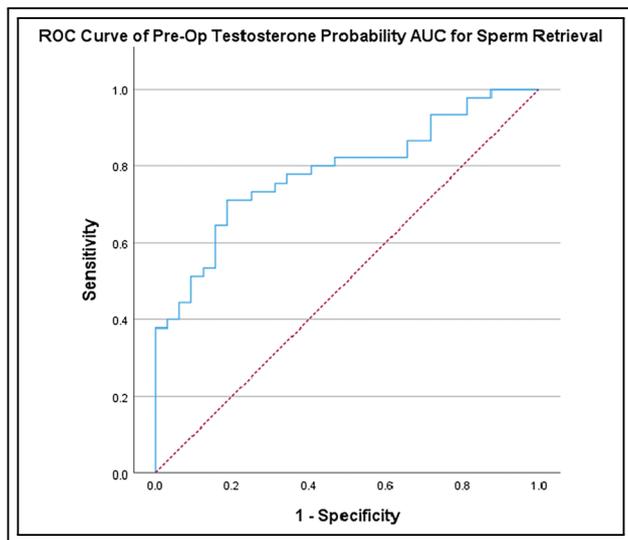
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FIGURE 1. Receiver operating characteristic (ROC) analysis of sperm retrieval by pre-op testosterone level
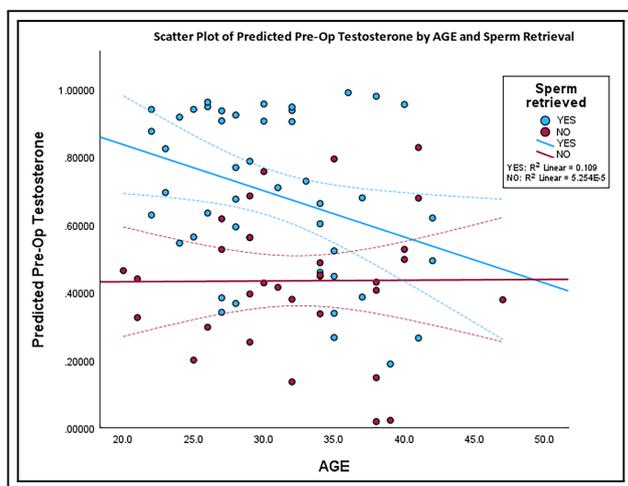

FIGURE 2. Scatter plot of all cases with pre-op testosterone and age, with regression lines and coefficients for sperm retrieval success and failure

Discussion

This study investigated the surgical outcome in NOA patients who were treated medically prior to their micro-TESE, and we assessed the value of their hormonal response as a predictor of sperm retrieval. Proper counselling of men undergoing micro-TESE is essential. Patients should be presented with solid evidence, so decisions can be made, and the psychological burden managed. Patients with a poor

prognosis might decide to refrain from surgical treatment and consider other options, such as donor sperm or adoption.

Micro-TESE, which is an effective and safe surgical technique, is currently considered a first-line approach for men with NOA undergoing sperm retrieval.[25,26] In a meta-analysis comparing sperm retrieval rates from micro-TESE with traditional surgical techniques, micro-TESE was 50% more likely to retrieve sperm successfully than conventional testicular sperm extraction (cTESE).[27] Elevated ITT levels are essential for the final stage of spermatogenesis, specifically, for differentiation of spermatids into fully developed spermatozoa. Exogenous testosterone administration in humans demonstrated that decreased ITT levels were correlated with inhibition of spermiogenesis.[28,29] NOA patients who presented with hypogonadism may benefit from hormonal stimulation prior to their SSR to maintain sufficient ITT levels, thereby improving the likelihood of effective sperm retrieval.[8,30,31]

Although there are no meta-analyses or large-scale studies that investigated the use of hCG therapy or aromatase inhibitor therapy in men with hypergonadotropic hypogonadism and NOA, our practice, as reflected in the current report, suggested that such hormonal stimulation therapies prior to micro-TESE may improve sperm retrieval rates.

Our analysis consisted of patients with various NOA causes. The prevalence of the different etiologies can be found in the existing literature.[32,33] The current study reports an overall SSR of 58.4%. These findings are consistent with a recent meta-analysis, which recorded an overall SSR success of 47% among NOA subjects.[34]

In the overall study group, our analysis demonstrated that a higher hormonal response was predictive of successful SR in NOA patients who were treated medically prior to their micro-TESE.[35-37] To the best of our knowledge, this is the first report that has investigated the predictive value of post-medical stimulation, pre-operative testosterone levels.

Pre-op testosterone levels had good sensitivity and specificity for predicting sperm retrieval in our medically treated NOA group in total (sensitivity = 71.1%, specificity = 81.2%, and AUC = 0.785). Sensitivity and specificity of pre-op testosterone levels were even better for the KS patient group (sensitivity = 87.5%, specificity = 88.9%).

Although we were unable to fully analyze the underlying determinants of sperm retrieval in the UDT, Yq Deletions, and post-chemo patients due to the limited number of cases, we compared and analyzed the differences between KS and
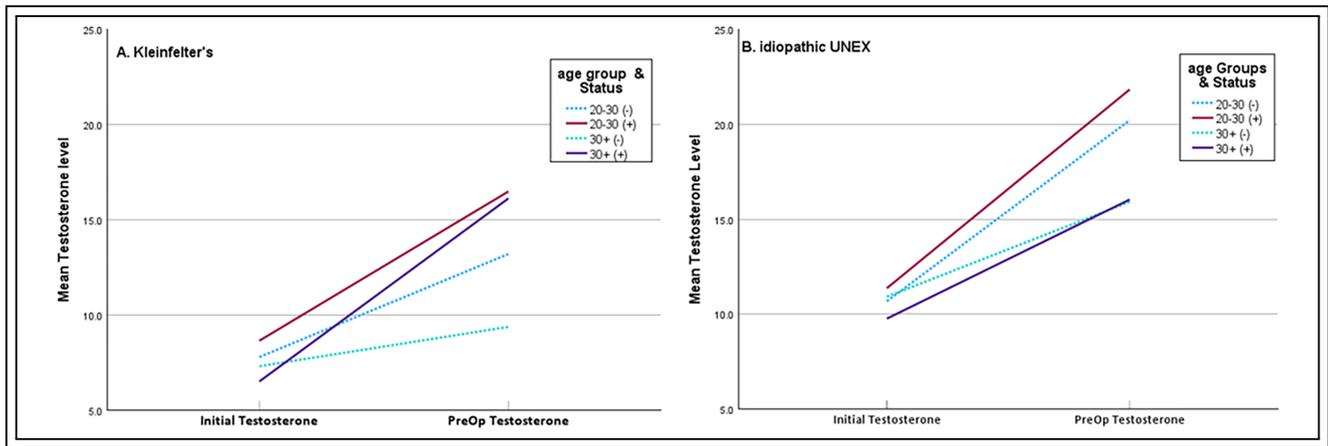
FIGURE 3. Comparison between (**A**) men with Klinefelter's and (**B**) men with unexplained nonobstructive azoospermia (NOA) (idiopathic UNEX) by age, mean initial testosterone, pre-op testosterone, and sperm retrieval. Solid lines denote sperm retrieval success, and dotted lines represent failure

UNEX patients—the two major groups. In both groups, younger age predicted a better response to testosterone-raising treatment. However, in KS patients, sperm retrieval success was determined predominantly by pre-operative testosterone levels, regardless of age. Conversely, in UNEX patients, success was largely independent of pre-operative testosterone levels for both "young" and "old" individuals.

We hypothesize that the higher preoperative testosterone levels among successful KS NOA patients reflected more intact seminiferous tubules, which contained functionally normal Leydig cells with a preserved capacity to secrete testosterone.

The current UNEX data suggest that sperm retrieval success may also be determined by other variables that have not yet been identified. The heterogeneous nature of the idiopathic NOA group makes the identification of clear determinants of sperm retrieval in this group extremely challenging.

We believe that NOA patients may benefit from an individualized pre-op counselling approach. We suggest three supporting pillars for such counselling:

1. The likelihood of a successful SSR based on current relevant literature;
2. The likelihood of a successful SSR based on the specific experience of the clinic/surgeons who are conducting the treatment (local up-to-date database);
3. Individual hormonal response (change in testosterone levels) when pre-op medical treatment is indicated and implemented. This can be used as a stand-alone predictive parameter or as an addition to predictive models developed previously.

The limitations of this study were related primarily to its relatively small sample size. Given its retrospective design, it was not immune to selection bias. Although we didn't notice a major difference between patients with or without preoperative therapy, scoring methods such as the Johnsen's score were not available while interpreting the data due to the retrospective nature. Additionally, the patient cohort featured homogeneous ethnicity, which suggested that our findings might not extend to NOA patients across diverse ethnic backgrounds. Consequently, we advocate for further research that involves larger cohorts to ascertain definitively the predictors of successful sperm retrieval in NOA patients. Lastly, we did not measured ITT intraoperatively. Despite these limitations, this study stands as the first report that assesses the predictive significance of post-medical stimulation, pre-operative testosterone levels for successful sperm retrieval, which marks an important contribution to the field.

Conclusions

This study demonstrated that a favorable hormonal response was predictive of successful SR in medically-treated NOA patients, and it distinguished between patients with a good or a poor prognosis. SR success was associated with the change between pre- and post-treatment testosterone levels. We propose using this predictive parameter as part of individualized counselling and to consider its implementation in predictive models that were developed previously.[38–40]

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Author Contributions

Shlomi Barak designed the study, conducted the data analysis and drafted and revised the manuscript. Netanel Waldenberg, Aharon Peretz and Reut Bartoov assisted with the data analysis and revised the manuscript. Guy Bar designed the study and revised the manuscript. Snir Dekalo assisted with the data analysis and revised the manuscript. All authors reviewed the results and approved the final version of the manuscript.

Availability of Data and Materials

Data will be made available when contacting the corresponding author.

Ethics Approval

The study was approved by the local Institutional Review Board of the Assuta Medical Center (No. 0014-22-ASMC). Due to its retrospective nature, informed consent was waived.

Conflicts of Interest

The authors declare no conflicts of interest to report regarding the present study.

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