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The Value of Composite Measurements of Extracellular Matrix Protein1, Testis- Expressed Gene 101, And Lectin Galactoside-Binding Protein in Predicting Surgical Sperm Retrieval in Men with Non-Obstructive Azoospermia

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ABSTRACT

Background: *The absence of spermatozoa in the ejaculate (azoospermia) is identified in 15% of infertile men and can be classified as obstructive azoospermia (OA) and non-obstructive azoospermia (NOA). OA and NOA are managed by specific medical and/or surgical options. Two highly promising biomarkers for male infertility are testis expressed protein (TEX101) (a protein exclusive to testicular germ cells) and epididymis-expressed protein (ECM-1) (a protein found in the extracellular matrix).*

Aim: *To investigate the relationship between the individual value, as well as the composite measurements of ECM1, TEX 101 and Lectin galactoside-binding soluble 3 binding protein (LAGALS3BP) in predicting surgical sperm retrieval in men with NOA*

Methods: *We conducted a cross section analytical study which included Azoospermia patients who were scheduled for testicular sperm extraction (TESE). We collected essential clinical data including etiology of azoospermia, physical examination for the secondary sex characters, presence of the vas deferens, and clinical varicocele. Hormonal assessment included (FSH, LH, and Testosterone). Primary outcomes included calculating the cut-off level of the following markers ECM, TEX 101 and LAGALS3BP.*

Results: *We found that FSH was significantly higher among patients with TESE findings with p value 0.045, while LH, prolactin, total testosterone, free testosterone, and estrogen levels showed no statistically significant differences according to TESE outcomes. We found that LGALS3BP and TEX101 were significantly higher among patients with TESE positive findings compared to TESE negative group. LGALS3BP and TEX101 were positively and moderately correlated with TESE outcomes. We found that ECM-1 was negatively correlated with TESE outcomes with r= -0.225 and p value= 0.035. LGALS3BP level was significantly higher among patients with Hypo spermatogenesis, normal Spermatogenesis compared to Tubular Hyalinization, SCO, maturation arrest, and mixed Pathology.*

Conclusion: *We finally concluded that Semen biomarkers TEX 101, and LGALS3BP are reliable, sensitive, non-invasive, and cost-effective investigation that can predict outcomes of TESE.*

Keywords: *Testis- Expressed Gene 101, Lectin Galactoside, Non-Obstructive Azoospermia*

1. INTRODUCTION

Infertility is commonly described as the incapacity of a couple to achieve pregnancy even after engaging in unprotected, regular sexual intercourse for a period of one year. Approximately 15% of all couples and a minimum of 180 million couples globally [1]. Male fertility can be influenced by several factors, encompassing both reversible and irreversible disorders. Additional variables that may impact each of the individuals involved include their age, drug usage, surgical background, exposure to environmental pollutants, genetic disorders, and systemic illnesses [2].

The primary objective of assessing a male factor for infertility is to discover the underlying cause and provide treatment options for reversible reasons, ascertain his eligibility for assisted reproductive methods (ART) and give counseling for irreversible and untreatable diseases [3].

Male fertility issues encompass a spectrum of conditions, including reduced sperm production (oligozoospermia) and undetectable levels of sperm in semen (azoospermia), which affects approximately 2% of men in the general population [4]. Testicular biopsy is the sole conclusive diagnostic technique used to differentiate between obstructive (OA) and nonobstructive (NOA) azoospermia, as well as to identify the NOA subcategories of hypo spermatogenesis, maturation

arrest, and Sertoli cell-only syndrome [5].

Two highly promising biomarkers for male infertility are testis expressed protein (TEX101), a protein exclusive to testicular germ cells, and epididymis-expressed protein (ECM1), a protein found in the extracellular matrix. TEX101 and ECM1 clinical tests have the capacity to supplant most diagnostic testicular biopsies, hence enhancing the dependability and efficacy of assisted reproduction approaches [6].

LGALS3BP, often referred to as Mac-2 binding protein, is a natural ligand of Galectin-3, a β-galactoside binding protein that plays a role in immunology, cellular adhesion, and interactions between pathogens and their hosts. Recent research by has demonstrated the expression of LGALS3BP throughout the whole male genital canal, as well as on the surface of human prostasomes [7]. So, we conducted this cross section analytical study to investigate the relationship between the individual value, as well as the composite measurements of ECM1, TEX 101 and LAGALS3BP in predicting surgical sperm retrieval in men with NOA.

2. PATIENTS AND METHODS

We conducted a cross section analytical study which included Azoospermia patients who were scheduled for testicular sperm extraction (TESE) operation attending at Andrology clinic, Kasr Al Ainy hospital. But we excluded patients with macro-deletion on the Y chromosome (To those accepting the chromosomal study), with obstructive azoospermia, with undescended testis, with hypogonadotropic hypogonadism, with testicular procedures and operations.

2.1. Methods

Selection of infertile patients fulfilling the abovementioned criteria. Collecting the essential clinical data including but not limited to, etiology of azoospermia, physical examination for the secondary sex characters, presence of the vas deferens, and clinical varicocele. Hormonal assessment included (FSH, LH, and Testosterone). Chromosomal Karyotyping and Y chromosome microdeletion analysis was offered to the patients prior to micro testicular sperm extraction (m-TESE). Men refusing Y chromosome microdeletion test or karyotyping, were eligible for enrollment as far as they did not have other exclusion criteria. Semen samples were collected prior to m-TESE operations. Separation of semen plasma and evaluation of ECM, TEX 101 and LGALS3BP values in seminal plasma using ELISA kits. The patients underwent microsurgical testicular sperm extraction (m-TESE). Testicular samples were taken for histopathological evaluation.

2.2. Study outcomes

Primary outcomes included calculating the cut off level of the following markers ECM, TEX 101 and LAGALS3BP, which provided the highest yield in surgical sperm retrieval. Secondary outcomes included the composite use of the selected markers in predicting successful surgical sperm retrieval.

2.3. Sample size

Using PASS 11 sample size calculator; with 0.05 alpha error, confidence interval of 0.95 and power of the study 0.80. To calculate minimum sample size needed to evaluate ECM, TEX 101 and LAGALS3BP in predicting surgical sperm retrieval in men with NOA. According to literature LGALS3BP level concentration below 153ng/mL was associated with a negative TESE outcome with prediction of successful retrieval of spermatozoa after TESE (sensitivity 100%, specificity 45%)[8]. While concentration of TEX101 > 0.9ng/mL and epididymis- specific protein ECM1 > 2.3μg/mL provided 81% sensitivity at 100% specificity for differentiating between anon-obstructive and obstructive azoospermia [9]. The total sample size calculated was 88 patients with NOA.

2.4. Statistical analysis

Statistical analysis was conducted using SPSS 27th edition, categorical variables were presented in count and percent. Graphical and statistical tests were used to explore the continuous data for normality of distribution (Kolmogorov-Smirnova & Shapiro-Wilk). In general, all the data is abnormally distributed except: female age, E2 and ECM1. Testicular histopathology was coded ascendingly from 1 to 6, where one reflects tubular hyalinization and 6 represents obstructive azoospermia. Quantitative variables were presented in mean and standard deviation or medians and percentiles based on the normality of distribution and it was compared between groups using Student T test or the Mann–Whitney U test between 2 groups, and one way ANOVA or Kruskal-Wallis test for comparing between more than 2 groups. ROC curve analysis was used to detect the cut off level for each biomarker. Any p value < 0.05 was considered significant.

2.5. Ethical Considerations

Throughout its implementation, the study complied with the Helsinki Declaration. Approval was taken from Cairo University Institutional ethics committee to achieve this study. An informed and written consent was taken from each patient. All patients in this study were informed about the clinical research and were informed about how the operation is carried out. All data was collected by the researcher himself.

3. RESULTS

We enrolled 88 male patients presented with infertility with a mean age 36.3±7.99 years old, 38.7% were smokers, 88.2% were presented with primary infertility, while 6.5% secondary infertility. Five patients were enrolled as control. Semen analysis was performed for all of the participants included, abnormal semen viscosity was reported in 16.1%, five patients were positive for Klinefelter syndrome (47 XXY in karyotyping). Testicular specimen and histopathology assessment showed that tubular hyalinization was found in 6.5%, SCO in 41.9%, maturation arrest in 16.1%, mixed Pathology in 17.2%, Hypo spermatogenesis in 8.6%, and Normal Spermatogenesis in 4.3% of the included patients. TESE was negative in 42 (45.2%) patients, and positive in 46 (49.5%) patients, and 5 individuals were healthy controls (Table 1).

Table (1): Baseline clinical characteristics and pathological findings among the included males

Mean			**SD**
Age in years		36.3	**7.99**
		N	%
Smoking	Non-smoker	52	**55.9%**
	Smoker	36	**38.7%**
Type of infertility	1ry	82	**88.2%**
	2ry	6	**6.5%**
	Control (normal semen)	5	**5.4%**
Semen viscosity	abnormal	15	**16.1%**
	normal	78	**83.9%**
Karyotyping	Not done	62	**66.7%**
	46 xy	26	**28.0%**
	47 xxy	5	**5.4%**
Pathology	Tubular Hyalinization	6	**6.5%**
	SCO	39	**41.9%**
	Maturation arrest	15	**16.1%**
	Mixed Pathology	16	**17.2%**
	Hypo spermatogenesis	8	**8.6%**
	Focal Spermatogenesis	4	**4.3%**
TESE outcomes	Negative	42	**45.20%**
	Positive	46	**49.50%**
	Control	5	**5.40%**
		Mean	**SD**
Testicular sperm concentration		**2404.349**	**6412.374**

Table (2) shows that there was no statistically significant difference in age according to TESE outcomes, however, patients with TESE negative findings showed significantly higher volume of semen compared to TESE positive patients with p value 0.027. FSH was significantly higher among patients with negative TESE findings with p value 0.045, while LH, prolactin, total testosterone, free testosterone, and estrogen levels showed no statistically significant differences according to TESE outcomes. LGALS3BP and TEX101 were significantly higher among patients with TESE positive findings with p values 0.004, 0.003 respectively compared to TESE negative group. While ECM1 was insignificantly higher among TESE negative group. P value 0.077.

Table (2): Comparison of age, semen characteristics, hormonal profile and study biomarkers according to TESE outcomes

	TESE outcomes				**P-value**
	Positive		Negative		
	Mean	SD	Mean	SD	
Age	36.913	8.03831	35.6905	7.99844	**0.477**
Vol	2.2196	0.86657	2.9976	2.04957	**0.027**
PH	7.4522	0.2268	7.5	0.01	**0.160**
FSH	15.3146	10.48141	21.7631	17.85893	**0.045**
LH	10.5818	6.49983	11.3914	8.38846	**0.685**
PRL	13.6011	8.31417	11.9341	6.00036	**0.397**
TT	4.9502	4.0689	4.1067	1.99074	**0.215**
FT	29.6784	24.45013	122.3569	588.9017	**0.359**
E2	35.5381	11.8426	74.4376	278.2639	**0.395**
ECM1	681.1957	360.2533	815.8095	344.9934	**0.077**
LGALS3BP	122.937	165.4718	45.2367	52.41672	**0.004**
TEX101	**88.2235**	**135.8291**	**20.5775**	**53.82227**	**0.003**

Table (3) shows that there was a statistically significant negative correlation between total number of samples and TESE outcomes with r= -0.477 and p value≤.001, testicular sperm concentration and Pathology were positively correlated with TESE outcomes with r= 0.921, 0.414 and p value≤0.001, <0.001 respectively. ECM1 was negatively correlated with TESE outcomes with r= -0.225 and p value= 0.035. LGALS3BP, and TEX101 were positively and moderately correlated with TESE outcomes with r= 0.394, 0.377 p values ≤0.001, and <0.001 respectively.

Table (3): Correlation matrix showing the association between age, hormonal levels, pathology findings, semen biomarkers according to TESE findings

	TESE Outcome	
	r	**P value**
Age	0.070	**0.517**
Vol	-0.155	**0.149**
PH	-0.146	**0.176**
FSH	-0.167	**0.119**
LH	-0.059	**0.665**
PRL	0.070	**0.610**
TT	0.080	**0.458**
FT	0.146	**0.238**
E2	0.217	**0.061**
Total Number of Samples	-0.477	**<0.001**
Testicular sperm concentration	0.921	**<0.001**
Pathology	0.414	**<0.001**
ECM1	-0.225	**0.035**
LGALS3BP	0.394	**<0.001**
TEX101	**0.377**	**<0.001**

Table (4) shows the comparison between azoospermia and control groups and showed that there was no statistically significant difference in terms of ECM-1 and LGALS3BP levels between groups, while TEX101was significantly higher among control groups compared to azoospermia with p value 0.001.

Table (4): Comparison of age, semen characteristics, and semen biomarkers among study groups

	Azoospermia		**Control**		**P value**
	Mean	SD	Mean	SD	
Age	36.3295	7.99673	36.8	4.60435	**0.840**

Vol	2.5909	1.58771	3.5	2.23607	**0.418**
ECM1	745.4432	357.4797	640.4	163.5827	**0.247**
LGALS3BP	85.8527	130.3107	117.2	30.16123	**0.125**
TEX101	**55.9379**	**109.8308**	**349.8**	**93.5131**	**0.001**

Table (5) shows the comparison between TESE negative, TESE positive, and control groups showed that volume of semen was significantly lower among TESE positive compared to negative, and controls with p value 0.037. LGALS3BP was significantly higher among controls and TESE positive groups compared to negative group. TEX101was significantly higher among control and TESE positive groups compared to TESE negative with p value <0.001.

Table (5): Comparison of age, semen characteristics, semen biomarkers between study groups

	TESE Negative		**TESE Positive**		**Control**		**P value**
	Mean	SD	Mean	SD	Mean	SD	
Age	35.7	8.0	36.9	8.0	36.8	4.6	**0.763**
Vol	3.0	2.0	2.2	0.9	3.5	2.2	**0.037**
ECM1	815.8	345.0	681.2	360.3	640.4	163.6	**0.160**
LGALS3BP	45.2	52.4	122.9	165.5	117.2	30.2	**0.013**
TEX101	**20.6**	**53.8**	**88.2**	**135.8**	**349.8**	**93.5**	**<0.001**

Table (6) shows LGALS3BP level was significantly higher among patients with Hypo spermatogenesis, normal Spermatogenesis compared to Tubular Hyalinization, SCO, maturation arrest, and mixed Pathology with (P-value < 0.001). As well, TEX101 level was significantly higher among Hypo spermatogenesis, normal Spermatogenesis compared to other findings Tubular Hyalinization, SCO, maturation arrest, and mixed Pathology with (P-value < 0.001).

Table (6): Comparison of semen biomarkers levels according to pathology findings

		Tubular Hyalinization	**SCO**	**Maturation arrest**	**Mixed Pathology**	**Hypo spermatogenesis**	**Normal Spermatogenesis**	**P value**
ECM1	Mean	831.0	761.4	741.4	681.0	680.3	865.0	**0.901**
	SD	442.2	364.3	358.3	356.3	329.3	375.9	
LGALS3BP	Mean	10.5	34.5	114.8	97.4	266.1	184.5	**<0.001**
	SD	6.0	40.7	51.5	62.8	345.3	104.3	
TEX101	Mean	3.1	11.4	79.2	74.9	162.7	193.1	**<0.001**
	SD	**1.7**	**15.0**	**118.4**	**134.4**	**187.0**	**134.8**	

Table (7) shows that LGALS3BP and TEX101-2 can significantly predict negative TESE outcomes with cutoff value 618.5, 30.5, and 4.725, sensitivity 71.7%, and 71.7%, specificity 69.0%, and 64.3% respectively. On the other hand, ECM-1 cannot predict TESE outcome (AUC=0.37, sensitivity 50% and specificity 33.3%).

Table (7): Sensitivity analysis showing semen biomarkers predictability for negative TESE outcomes

Test Result Variable(s)	**AUC**	**P value**	**95% Confidence Interval**	**Cutoff**	**Sensitivity**	**Specificity**
ECM-1	0.37	0.036	0.253-0.488	618.5	50.0%	**33.3%**
LGALS3BP	0.728	<0.001	0.621-0.835	30.5	71.7%	**69.0%**
TEX101	**0.718**	**<0.001**	**0.61-0.825**	**4.725**	**71.7%**	**64.3%**

4. DISCUSSION

Infertility is commonly described as the incapacity of a couple to achieve pregnancy even after engaging in unprotected, regular sexual intercourse for a period of one year. Approximately 15% of all couples and a minimum of 180 million couples globally [1]. Male fertility can be influenced by several factors, encompassing both reversible and irreversible disorders. Additional variables that may impact each of the individuals involved include their age, drug usage, surgical background, exposure to environmental pollutants, genetic disorders, and systemic illnesses [2].

The primary objective of assessing a male factor for infertility is to discover the underlying cause and provide treatment options for reversible reasons, ascertain his eligibility for assisted reproductive methods (ART), and give counseling for irreversible and untreatable diseases [3]. Two highly promising biomarkers for male infertility are testis expressed protein (TEX101), a protein exclusive to testicular germ cells, and epididymis-expressed protein (ECM1), a protein found in the extracellular matrix. TEX101 and ECM1 clinical tests have the capacity to supplant most diagnostic testicular biopsies, hence enhancing the dependability and efficacy of assisted reproduction approaches [6].

LGALS3BP, often referred to as Mac-2 binding protein, is a natural ligand of Galectin-3, a β-galactoside binding protein that plays a role in immunology, cellular adhesion, and interactions between pathogens and their hosts. Recent research by has demonstrated the expression of LGALS3BP throughout the whole male genital canal, as well as on the surface of human prostasomes [7].

We conducted a cross section analytical study to investigate the relationship between the individual value, as well as the composite measurements of ECM1, TEX 101 and LAGALS3BP in predicting surgical sperm retrieval in men with NOA. We enrolled 88 male patients presented with infertility with a mean age 36.3±7.99 years old, 38.7% were smokers, 88.2% were presented with primary infertility, while 6.5% secondary infertility. Five patients were enrolled as health control. Abnormal semen viscosity was reported in 16.1%, five patients were positive for Klinefelter syndrome (47 XXY in karyotyping).

We found that testicular specimen and histopathology assessment showed Tubular Hyalinization was found in 6.5%, SCO in 41.9%, Maturation arrest in 16.1%, Mixed Pathology in 17.2%, Hypo spermatogenesis in 8.6%, and Normal Spermatogenesis in 4.3% of the included patients. Testicular sperm extraction was successful in 46/88 (55.7%). We found that FSH was significantly higher among patients with negative TESE findings with p value 0.045, while LH, prolactin, total testosterone, free testosterone, and estrogen levels showed no statistically significant differences according to TESE outcomes.

These findings are consistent with Banerjee et al. who reported that FSH > 20mIU/mL was associated with very low of TESE positive retrieval accounting for 15% [10]. Cissen et al. conducted a study that analyzed data from 1371 TESE operations. They discovered that lower levels of FSH were indicative of a higher likelihood of successful sperm retrieval [11].

In retrospective research conducted by Friedler et al. it was shown that there was no association between FSH levels and the presence or lack of testicular sperm after TESE in 123 individuals [12]. In a prospective cohort investigation conducted by Saccà et al. patients with non-obstructive azoospermia (NOA) had traditional testicular sperm extraction. The study revealed a sperm retrieval rate of 47.6%. Additionally, no significant statistical difference was seen between the mean follicle-stimulating hormone (FSH) levels and the percentage of sperm retrieval [13].

An isolated rise of FSH often indicates significant damage to the germ cell epithelium. Significantly increased levels of (FSH) and (LH), along with testosterone levels that are within the lower end of the normal range or below normal, indicate widespread dysfunction of the testes. This dysfunction might be due to either congenital condition (such as Klinefelter syndrome) or an acquired cause [14].

We found that LGALS3BP and TEX101 were significantly higher among TESE positive patients compared to TESE negative group. LGALS3BP and TEX101 were positively and moderately correlated with TESE outcomes with r= 0.394, 0.377 p values = < 0.001, and < 0.001 respectively. Additionally, our data showed that LGALS3BP can significantly predict positive TESE outcomes using cutoff point 30.5, with sensitivity 71%, specificity 69%, AUC 0.728 and p-value <0.001. TEX101 can significantly predict positive TESE outcomes using cutoff point 4.7, with sensitivity 71.7%, specificity 64%, AUC 0.718 and p-value <0.001.

Freour et al. reported that patients who had a positive outcome of testicular sperm extraction (TESE) showed notably elevated levels of lectin galactoside-binding, soluble 3 binding protein (LGALS3BP) in the seminal plasma. The threshold of 153ng/mL was documented with a sensitivity of 100% and a specificity of 45%. Nevertheless, the study conducted by Freour et al. was marred by a significant drawback: the small sample size of only 40 instances, resulting in a reduced AUC value [8].

Araujo & Bertolla propose that LGALS3BP has the potential to serve as a prognostic indicator for the success of testicular sperm extraction (TESE) in patients with non-obstructive azoospermia (NOA) prior to intracytoplasmic sperm injection (ICSI) [15].

Drabovich et al. reported that TEX101 5μg/ml as a cutoff level for differentiation between OA and NOA with 73% specificity, at 100% sensitivity [16]. Jarvi et al. reported that TEX101 level < 0.2ng/mL is a very accurate indicator of the likelihood of failed sperm retrieval in men with normal karyotypes and non-obstructive azoospermia (NOA). It is currently the most powerful non-invasive predictor of sperm retrieval failure that has been published [17]. Korbakis et al. stated that ≥ 0.6 ng/mL of TEX101 as a cutoff point for predicting sperm or spermatid retrieval in patients with NOA by TESE with 73% sensitivity at 64% specificity [18].

Al Dulaimy et al. reported that levels of TEX101 were substantially greater in patients with non-obstructive azoospermia (NOA) compared to patients with obstructive azoospermia (OA), with a p-value <0.001. The receiver operating characteristic (ROC) curve demonstrates that TEX101 cutoff values over 0.9ng/ml are indicative of being a suitable candidate for the sperm retrieval procedure [19].

We found that ECM-1 was negatively correlated with TESE outcomes with r= -0.225 and p value= 0.035. Al Dulaimy et al. reported that levels of ECM1 were substantially greater in patients with non-obstructive azoospermia (NOA) compared to patients with obstructive azoospermia (OA), with a p-value of 0.007. The receiver operating characteristic (ROC) curve demonstrates that ECM1 protein has a threshold value of >943.11 pg/ml for distinguishing between NOA and OA [19]. Drabovich et al. ECM1 can accurately differentiate between abnormal spermatogenesis (OA) and normal spermatogenesis with 100% specificity by applying a cutoff threshold of 2.3μg/ml [16].

In the current study, LGALS3BP level was significantly higher among patients with Hypo-spermatogenesis, normal Spermatogenesis compared to other findings Tubular Hyalinization, SCO, maturation arrest, and mixed Pathology with p-value < 0.001. Also, TEX101 level was significantly higher among Hypo spermatogenesis, normal Spermatogenesis compared to other findings Tubular Hyalinization, SCO, maturation arrest and mixed Pathology with p-value <0.001. Drabovich et al. found that TEX101 at a threshold > 5ng/mL, could differentiate NOA underlined by Sertoli-cell only syndrome from NOA due to other testis histology: hypospermatogenesis, with a 67% specificity and a 100% sensitivity, or maturation arrest, with a 54% sensitivity and a 100% specificity) [16].

5. CONCLUSION

TEX101, and LGALS3BP are reliable, sensitive, non-invasive and cost-effective investigation that can predict outcomes of TESE.

6. Limitations

The current study showed limitations of small number of normal spermatogenesis groups. Lack of universal standardization of the measuring units of ECM-1. TEX101 and LGALS3BP which made it difficult to compare our findings to other western studies. We did not use qualitative assessment of testicular pathology using the Johnsen score, instead we use ranked testicular pathology ascendingly from tubular hyalinization to normal spermatogenesis by assuming equal difference (Δ) between different types.

Conflict of interest

All authors have no conflicts of interest that are directly relevant to the content of this review.

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