Journal of **R**eproduction & **I**nfertility
Volume 26, Issue no. 2
https://doi.org/10.18502/jri.v26i2.19437

Original Article

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Assessment of Seminal Lactoferrin Levels in Oligoasthenoterato-zoospermic Men with Varicocele

Mahmoud F. Ghaly [1*], Khadiga M. Abougabal [2], Ayman A. Allam [1], Ayad Palani [3,4], Taymour Mostafa [1]

1- Department of Andrology, Sexology and STIs, Faculty of Medicine, Cairo University, Cairo, Egypt
2- Department of Clinical and Chemical Pathology, Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt
3- Department of Basic Sciences, College of Medicine, University of Garmian, Kalar, Iraq
4- Department of Clinical Biochemistry, Zanko Central Laboratory, Kalar, Iraq

Abstract

Background: The association between varicocele and male infertility has always been a subject of ongoing debate. Lactoferrin (LF) belongs to the transferrin family with iron-binding properties and exhibits many beneficial biological properties. The purpose of the current study was to assess seminal levels of LF in infertile oligoasthenoteratozoospermic (OAT) men with varicocele.

Methods: Sixty-nine men were allocated into three groups; healthy fertile men (as controls) (n=20), infertile OAT men without varicocele (n=19), and infertile OAT men with varicocele (n=30). All men underwent history taking, genital examination, semen analysis, and determination levels of seminal LF by ELISA method. Statistical analysis was carried out using Kruskal-Wallis test followed by post-hoc analysis (Conover) for comparisons involving more than two groups, and the Mann-Whitney U test for comparisons between two groups. Spearman correlation test was used to assess the relationship between variables. The $p<0.05$ was set as statistically significant.

Results: The median seminal LF level of the healthy fertile controls demonstrated significantly increased levels compared to both groups of infertile OAT men with or without varicocele ($p<0.000001$). The median seminal LF level of the infertile OAT men with varicocele grade III demonstrated a significant decrease compared to infertile OAT men with grade II ($p=0.0057$). Collectively, seminal LF levels exhibited significant positive correlations with sperm concentration, total sperm motility, and normal sperm morphology.

Conclusion: LF can be an imperative seminal biomarker that decreases in infertile OAT men especially if associated with varicocele.

** Corresponding Author:*
Mahmoud F. Ghaly, Department of Andrology, Sexology and STIs, Faculty of Medicine, Cairo University, Cairo, Egypt
E-mail:
mahmoud.fawzy@kasralainy.edu.eg

Received: 15, Mar. 2025
Accepted: 16, Aug. 2025

Keywords: Male infertility, Lactoferrin, Seminal plasma, Oligoasthenoteratozoospermia (OAT), Varicocele.
To cite this article: Ghaly MF, Abougabal KhM, Allam AA, Palani A, Mostafa T. Assessment of Seminal Lactoferrin Levels in Oligoasthenoterato-zoospermic Men with Varicocele. J Reprod Infertil. 2025;26(2):119-125. https://doi.org/10.18502/jri.v26i2.19437.

Introduction

Infertility is defined as the inability to conceive after at least 12 months of regular and unprotected coitus. This health problem affects about 8-12% of couples worldwide within reproductive age (1). Males are solely responsible for about 20-30% of these cases and are a contributing factor in an additional 30-40% of all infertility cases (2).

Varicocele, the most treatable cause of male infertility, is characterized by dilated, elongated, tortuous, thickened veins of the pampiniform plexus (3). This condition is recognized in up to 35-44% of males with primary infertility, and nearly 45-81% with secondary infertility (4). It

has been recognized that infertile men who were diagnosed with varicocele often have reduced sperm concentration, motility, and normal morphology (5, 6). Additionally, other studies carried out on fertile men identified affected sperm quality even in men with low-grade varicocele (7, 8). However, the association between varicocele and male infertility has been debated as some men with varicocele can still father children, even without intervention (9, 10).

LF is a highly glycosylated medium-molecular weight globular glycoprotein of 690 amino acid residues belonging to the transferrin family with iron-binding properties (11). This multifunctional protein deserves to be termed a "miracle molecule", as it exhibits many valuable properties such as anti-pathogenic, anti-inflammatory, immunomodulatory, and DNA-regulatory activities (12). Human body cells can produce LF which has been detected in the kidneys, gallbladder, lungs, intestine, pancreas, liver, saliva, prostate, tears, sperm, urine, bronchial secretions, cerebrospinal fluid, vaginal discharge, synovial fluid, blood plasma, and immune cells (13).

LF was first identified in the human seminal plasma (14) as being secreted by the seminal vesicles and the prostate (15). However, few studies, mainly in animal models, have investigated seminal LF relationships. Martins et al. demonstrated that LF increases sperm membrane functionality in frozen equine semen (16). Thaler et al. suggested that some LF molecules in seminal plasma are free and that others are associated with LF-binding molecules that change their physicochemical properties, influencing their affinity to sperm (17). Additionally, Su et al. showed that LF is an important protein during cryopreservation, and its addition to a cryoprotective extender can significantly improve the function of frozen ram sperm (18). In humans, LF was spotted in human oviductal secretion where it can bind to oocytes and sperm, and modulate gamete interaction (19). Hamada et al. reported that LF functions as an antioxidant by chelating iron to prevent lipid peroxidation, with its levels being elevated in samples lacking oxidative stress (20). The purpose of the current study was to assess seminal LF levels in infertile OAT men with varicocele.

Methods

This study was carried out from the 1st of June 2022 to the 31st of December 2022. Overall, 69 male Egyptian subjects with matched age and Caucasian ethnicity were investigated. These subjects were recruited from the Andrology Outpatient Clinic at the University Hospital following institutional review board approval and after obtaining written informed consent. Inclusion criteria were infertile OAT men with/without varicocele (sperm concentration $<15\times10^6/ml$, sperm motility <42%, normal sperm morphology <4%) and fertile normozoospermic men without varicocele (sperm concentration $>15\times10^6/ml$, sperm motility >42%, normal sperm morphology >4%) who had fathered a child within the previous year, with normal female partner factors.

Exclusion criteria were azoospermia, leukocytospermia, smoking, previous testicular disorders (torsion, trauma, infection), history of chemotherapy or radiotherapy, chronic debilitating disease, and previous varicocelectomy. The sample size was estimated to require at least 60 measurements to achieve a 95% confidence level, ensuring that the true value lies within ±5% of the measured value. The subjects were divided into three groups: Group I (n=20), healthy fertile normozoospermic men without varicocele (control group); Group II (n=19), infertile OAT men without varicocele; and Group III (n=30), infertile OAT men with varicocele.

All cases underwent history taking, genital examination, and semen analysis. The genital examination was carried out to evaluate testicular size and assess the spermatic cord for the clinical diagnosis of varicocele, which was confirmed radiologically using scrotal ultrasound (Mindray Z5; Mindray Bio-Medical Electronics Co., China). Semen analysis was carried out twice, two weeks apart, after 4–5 days of sexual abstinence in a clean aseptic wide-pored container according to WHO guidelines (21). Clinical examination was done in the standing position with/without the Valsalva maneuver. Scrotal color Doppler ultrasonography (ACUSON 128XB; Siemens Healthineers, USA) was carried out to diagnose varicocele, defined as a venous diameter >3 *mm* on duplex imaging. Varicocele was classified clinically as grade I (only palpable during Valsalva maneuver), grade II (palpable distension when standing upright), and grade III (visible through the scrotal skin) (22). All cases had peroxidase-positive leukocytes at a concentration of $<1\times10^6/ml$ of semen (23). Seminal LF estimation was carried out by an Enzyme-Linked Immunosorbent Assay (ELIZA) kit with a sensitivity of 0.19 *ng/ml* (Elabscience, USA).

Statistical analysis: Statistical analysis was carried out using the MedCalc® Statistical Software version 20 (MedCalc Software Ltd, Belgium). Kolmogorov–Smirnov test was used to test normal distribution. Data were presented with medians, and interquartile range (IQR). Statistical analysis was performed using the Kruskal–Wallis test followed by post-hoc analysis (Conover) for comparisons among more than two independent groups with non-parametric data, and the Mann–Whitney U test for comparisons between two independent groups with non-parametric data. Spearman correlation test was used to assess correlations between variables. The $p<0.05$ was set as statistically significant.

Results

The median seminal LF level of the healthy fertile control group demonstrated significant increases compared to both infertile OAT men with/without varicocele. Also, the median seminal LF in fertile men without varicocele exhibited a significant increase compared to infertile OAT men with/without varicocele (p=0.000001) (Table 1, Figure 1). Among infertile OAT men with varicocele, cases with grade II exhibited a significant increase in the median seminal LF compared to those with grade III (p=0.0057) (Table 2, Figure 2). Collectively, seminal LF demonstrated significant positive correlations with sperm concentration (ρ=0.365, p=0.0021), total sperm motility (ρ=0.463, p=0.0001), normal sperm morphology (ρ=0.552, p=0.0001), but no significant correlations with age (ρ=0.0221, p=0.8572) or semen volume (ρ=0.233, p=0.0536).

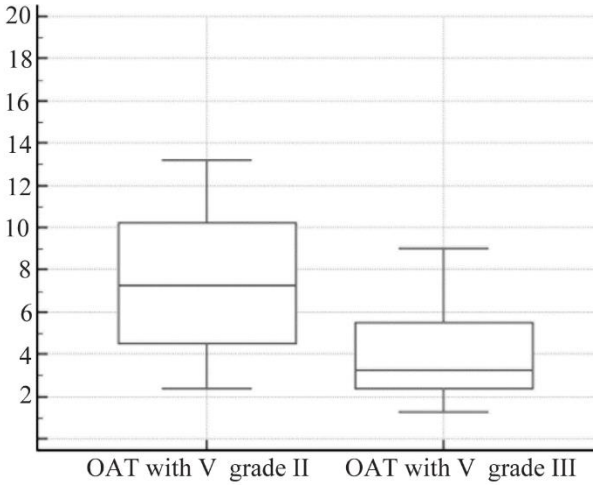

Figure 1. The median seminal LF levels in different investigated groups

Discussion

The current study demonstrated significantly decreased median seminal LF levels in the infertile OAT men, with/without varicocele compared to healthy fertile controls, along with significant positive correlations with sperm concentration, total sperm motility, and normal sperm morphology. These outcomes could be interpreted in the context of well-recognized characteristics of LF as a molecule with antioxidant, anti-apoptotic, anti-autophagic, as well as anti-inflammatory properties (24, 25). In this context, varicocele is well-known for its association with elevated seminal reactive oxygen species (ROS), as well as increased apoptotic and autophagic markers, as reported in numerous studies (26-31).

ROS are fundamental for spermatogenesis, but excessive levels can impair the fertility potential. Indeed, ROS induce lipid peroxidation of the sperm membrane, leading to sperm DNA damage and promoting gamete apoptosis (32). Recently,

Table 1. Comparison of the mean data of the investigated groups (median, IQR)

	Fertile controls without varicocele	Infertile OAT men without varicocele	Infertile OAT men with varicocele	Kruskal-Wallis test p-value
n	20	19	30	
Age (years)	31.0 (4.5)	30.0 (5.7)	29.0 (4.0)	0.200322
Semen volume (*ml*)	2.4 (2.7)	2.8 (2.0)	2.4 (1.5)	0.487496
Sperm concentration (10^6/*ml*)	49.8 (27.1)	5.3 (5.7)	4.8 (5.15)	0.000001 *
Total sperm motility (%)	57.5 (10.0)	20.0 (10.0)	25.0 (10.0)	0.000001 *
Normal sperm morphology (%)	8.5 (1.0)	2.0 (1.0)	2.0 (1.0)	0.000001 *
Seminal lactoferrin (*ng/ml*)	18.8 (8.1)	13.6 (9.46)	5.1 (5.68)	0.000001 *

IQR: Interquartile range. Significant statistical difference at $p<0.05$

Table 2. Comparison of seminal parameters in infertile OAT men with varicocele according to varicocele grade (median, IQR)

	Infertile OAT men with varicocele grade II	Infertile OAT men with varicocele grade III	Mann-Whitney U test p-value
n	16	14	
Age (years)	29.0 (2.25)	29.5 (5.0)	0.5304
Semen volume (*ml*)	2.4 (1.55)	2.3 (1.37)	0.9333
Sperm concentration (10^6/*ml*)	3.2 (5.05)	5.6 (4.3)	0.4411
Total sperm motility (%)	25.0 (6.25)	20.0 (13.75)	0.0160 *
Normal sperm morphology (%)	2.0 (1.0)	2.0 (1.0)	0.9803
Seminal lactoferrin (*ng/ml*)	7.3 (5.62)	3.3 (2.89)	0.0057 *

IQR: Interquartile range. Significant statistical difference at $p<0.05$

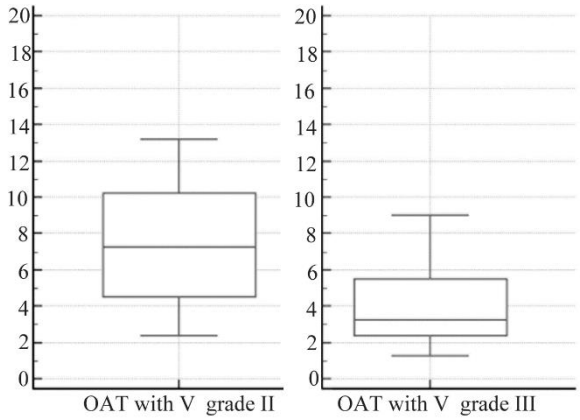

Figure 2. Median seminal LF levels in infertile OAT men with varicocele according to clinical grade

He et al. (33) demonstrated that LF mitigates spermatogenic dysfunction in mice through extracellular signal-regulated kinase 1/2 (ERK1/2)-mediated, ubiquitin-dependent degradation of P62, a classical autophagy receptor.

Previously, Autiero et al. (34) indicated that LF is raised in a cohort of asthenozoospermia as well as oligozoospermia but the number of cases in their study was relatively small, and it was unclear whether the asthenospermic group had normal sperm density or not. Along with their study, Buckett et al. (35) reported that seminal LF levels were elevated in a cohort of oligozoospermia and oligoasthenozoospermia samples, with no significant differences between asthenozoospermic men with normal sperm density and normozoospermic controls; however, leukocytes were present in most of the investigated ejaculates. Although the median LF concentration was higher, in Buckett et al.'s (35) study, there was no significant difference between samples exhibiting leukocytospermia and those that did not. In the current study, leukocytospermia was excluded in all cases.

In the current study, infertile OAT men associated with grade III varicocele demonstrated significantly decreased median seminal LF levels compared to the infertile OAT cases with grade II varicocele. Moreover, Alkan et al. (36) showed that cases of grade III varicocele had significantly higher superoxide anion and total ROS levels than cases with grade II varicocele and fertile controls. Additionally, many studies pointed to the decreased seminal antioxidant levels with increased varicocele grade (37-39).

Recently, numerous oral antioxidants have been introduced as a treatment for male infertility, either as single agents or in combination, with varying outcomes (40-42). LF shows the potential as a supplementary antioxidant for the management of male infertility. To date, most studies on LF have been conducted in reproductive animal models, where it demonstrated beneficial effects (43-45). Recently, He et al. (33) demonstrated that LF alleviates spermatogenic dysfunction in mice via ERK1/2-mediated ubiquitin-dependent degradation of P62, a classical autophagy receptor, which also involves the restoration of apoptosis, reduction of oxidative stress, and normalization of autophagic flux. These authors suggested that the signaling pathways and molecules involved could expand the scope of LF research and its potential applications. However, investigations of these effects in humans remains largely unexplored.

LF demonstrates promising potential as a supplementary antioxidant in the management of male

infertility by mitigating oxidative stress, supporting sperm quality, and protecting against apoptotic and autophagic damage. However, this study has certain limitations, including a relatively small sample size. Previous studies have consistently highlighted the significant benefits of varicocele repair in improving seminal parameters and reducing oxidative stress and apoptotic markers (46, 47).

Conclusion

It is concluded that LF is an imperative seminal biomarker that is decreased in infertile OAT men especially if associated with varicocele. As a novel antioxidant with anti-apoptotic, anti-autophagic, and anti-inflammatory properties, LF has the potential to be utilized in various studies addressing male infertility in general, and varicocele-associated infertility in particular.

Conflict of Interest

None.

Funding: This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

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