

# Galectin-1 (Gal-1) and Galectin-3 (Gal-3) levels in seminal plasma and serum in azoospermic patients versus fertile men: A cross-sectional study

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## Summary

**Introduction:** Galectin-1 (Gal-1) and galectin-3 (Gal-3) are expressed by many immune cells and receive considerable attention in the context of immunity. We aimed to compare between seminal plasma and serum levels of Gal-1 and Gal-3 in azoospermic patients and fertile men.

**Materials and methods:** This cross-sectional study was conducted at the andrology outpatient clinic from January (2022) to September (2022). A total of 90 participants were enrolled and divided into two equal groups: azoospermic and normal group. Semen analysis was done for all participants. Hormonal profile including FSH, LH, serum prolactin, total testosterone and estradiol was performed as well as assessment of serum and seminal levels of Gal-1 and Gal-3 by ELISA commercial kits. Finally, scrotal Duplex was done in standing and supine position.

**Results:** Serum and seminal levels of Gal-1 and Gal-3 were statistically significant higher in azoospermic patients compared with normal individuals ( $p < 0.001$  for all). In addition, in healthy individuals there were statistically significant positive correlations between serum levels of Gal-1 and age, FSH, LH levels ( $r = 0.296$ ,  $p = 0.005$ ;  $r = 0.333$ ,  $p < 0.001$ ;  $r = 0.312$ ,  $p = 0.003$ , respectively) and serum levels of Gal-2 and FSH and LH ( $r = 0.436$ ,  $p < 0.001$ ;  $r = 0.350$ ,  $p < 0.001$ , respectively), whereas serum Gal-3 showed a borderline positive correlation with age ( $r = 0.2$ ,  $p = 0.059$ ). Additionally, statistically significant positive correlations between seminal levels of Gal-1 and Gal-3 and free testosterone in healthy individuals were reported ( $r = 0.205$ ,  $p = 0.053$ ;  $r = 0.219$ ,  $p = 0.038$ , respectively).

On the other hand, there were negative correlations between serum and seminal levels of Gal-1 and Gal-3, total and progressive sperm motility, sperm count and abnormal sperm forms in healthy individuals ( $r = -0.382$ ,  $p < 0.001$ ;  $r = -0.405$ ,  $p < 0.001$ ;  $r = -0.376$ ,  $p < 0.001$ ;  $r = -0.364$ ,  $p < 0.001$ ) ( $r = -0.394$ ,  $p < 0.001$ ;  $r = -0.467$ ,  $p < 0.001$ ;  $r = -0.413$ ,  $p < 0.001$ ;  $r = -0.433$ ,  $p < 0.001$ ); ( $r = -0.372$ ,  $p < 0.001$ ;  $r = -0.377$ ,  $p < 0.001$ ;  $r = -0.317$ ,  $p = 0.002$ ;  $r = -0.311$ ,  $p = 0.003$ ) ( $r = -0.445$ ,  $p < 0.001$ ;  $r = -0.498$ ,  $p < 0.001$ ;  $r = -0.453$ ,  $p < 0.001$ ;  $r = -0.463$ ,  $p < 0.001$ , respectively).

Furthermore, statistically significant positive correlations between serum levels of Gal-1 and Gal-3 and age in azoospermic patients were reported ( $r = 0.511$ ,  $p < 0.001$ ;  $r = 0.390$ ,  $p = 0.008$ , respectively). On the other hand, there were negative correlations between seminal Gal-1 and estradiol (E2) and seminal Gal-3 and FSH and LH in azoospermic patients

( $r = -0.318$ ,  $p = 0.033$ ;  $r = -0.322$ ,  $p = 0.031$ ;  $r = -0.477$ ,  $p < 0.001$ , respectively). Also, negative correlations between serum Gal-3 and total and free testosterone in azoospermic patients were detected ( $r = -0.396$ ,  $p = 0.007$ ;  $r = -0.375$ ,  $p = 0.011$ , respectively).

**Conclusions:** Elevated serum and seminal levels of Gal-1 and Gal-3 have detrimental effects on spermatogenesis. Furthermore, the current study demonstrated potential regulatory effects of reproductive hormones on Gal-1 and Gal-3. Thus, future studies are needed to confirm such findings.

**KEY WORDS:** Gal-1; Gal-3; Azoospermia; Normal spermatogenesis.

Submitted 11 May 2023; Accepted 20 June 2023

## INTRODUCTION

Non-obstructive azoospermia (NOA) is one of the most important causes of male infertility. It characterized by the absence of sperm in semen repeatedly (1). At present, its pathogenesis is complex and can be categorized into primary and secondary testicular failure (1).

About 10-15% of people of childbearing age are infertile in the world, of which male infertility accounts for about 50% (2). NOA is a type of male infertility caused by spermatogenic dysfunction of testicular tissue. Patients with NOA cannot produce sperm or can only produce a very small amount of sperm. In patients with NOA, the structure of the seminiferous tubules in the testis is disordered, while the maturation of spermatogenic cells is blocked, and the meiosis of spermatogenic cells is arrested (3). Galectins are a family of soluble carbohydrate-binding proteins that regulate cell phenotype and function in development and disease (4). Galectin-1 (Gal-1) and Galectin-3 (Gal-3) are expressed by many immune cells and receive considerable attention in the context of immunity (5, 6). Gal-1 was the first member of the lectin family, reported more than 3 decades before, as a +15 kDa protein existing in a non-covalent homodimer form that was previously known as electrolectin,  $\beta$ -galactosidebinding lectin, galaptin or L-14 (4). Different organs and tissues secrete it including thymus (7), spleen (8), smooth muscle (9), colon (10), ovary (11) and also the nervous system (12). It is an endogenous

protein that might play a key role in Leydig cell biology as well as potential control of the development of normal Leydig cells through autocrine and paracrine mechanisms (13). However, cells such as Sertoli or peritubular cells might be responsible for Gal-1 regulation in Leydig cell functions (13). In contrast, Gal-3 is the most commonly reported type (14). Gal-3 is approximately 30kDa protein that acts several roles in cell to cell interaction, cancer progression, pathogenesis of infections, and immunomodulation (15). In male reproductive tract, Gal-3 is present in testes, epididymis, vas deferens, prostate, seminal vesicles and in semen (15).

Early reports demonstrated that extracellular Gal-3 signals apoptosis via cytochrome c-release and caspase-3 activation independent of caspase-8 activation (16), with more recent data suggesting that Gal-3 activates caspase-9 upstream of caspase-3 through phosphorylation of *extracellular signal-regulated kinase* (ERK) (17).

Differences in the pro-apoptotic signaling pathways activated by extracellular Gal-1 and Gal-3 may arise because they recognize different cell surface glycoproteins by way of their selectivity for different oligosaccharide ligands (18). Gal-3 expression has been identified in human Sertoli cells where it is under *follicle stimulating hormone* (FSH) control (19, 20). A potential role of Gal-3 in germ cell survival/regeneration is suggested based on its increased expression one month after a transient germ cell death process (20). Although *luteinizing hormone* (LH)/testosterone and FSH potentially exert their control on spermatogenesis via identified components, there are still other hormonally regulated Sertoli cell factors which remain unknown (20). We aimed in the current study to compare between seminal plasma and serum levels of Gal-1 and Gal-3 in azoospermic patients and fertile men. Also, we aimed to find out the potential relationships between reproductive hormones and Gal-1 and Gal-3.

## METHODS

This cross-sectional study was conducted at the andrology outpatient clinic from January 2022 to September 2022. A total of 90 participants were enrolled and divided into two equal groups as follows: azoospermic and normal group. All participants signed an informed consent. The ethical committee approved the study that conforms to Helsinki declaration (2013) (21) (MS-197-2022).

### Inclusion criteria

Any azoospermic patient or fertile individual aged 20-50 years old was included.

### Exclusion criteria

Any azoospermic patient with abnormal karyotyping was excluded. Also, any participant with chronic medical condition was excluded.

All participants were evaluated by history taking as well as general and local examinations. Testicular volume (V) was calculated from measurements of *length* (L) and *width* (W) according to the formula, ( $V = \pi/6 \times L \times W^2$ ) using a plastic ruler or caliper. Two semen analyses with an interval of 1 month were obtained. Hormonal profiles including: FSH, LH, serum prolactin, total testosterone,

and estradiol were performed. Scrotal Duplex in standing and supine position was done.

Gal-1 and Gal-3 were assessed in seminal plasma and serum. Serum and semen were used for determination of Gal-1 using ELISA kit provided by *Bioassay Technology Laboratory with Cat. No E2989Hu* (Zhejiang, China). Serum and semen were used for determination of Gal-3 using ELISA kit provided by *Bioassay Technology Laboratory with Cat. No E3449Hu* (Zhejiang, China). *Serum separator tubes* (SST) were used, and samples were allowed to clot for 30 min at room temperature before centrifugation for 15 min at 1000 x g. Serum was removed and assayed immediately or divided into aliquot and stored at  $\leq -20^\circ\text{C}$ . Repeated freeze-thaw cycles were avoided. The ejaculates were obtained after 4 days of sexual abstinence into sterile containers for immediate analysis. Semen was examined according to 5<sup>th</sup> guidelines WHO guidelines (2010) (22). Seminal plasma was centrifuged for 15 min at 1000 x g within 30 min of collection. Next, it was assayed immediately or divided into aliquot and stored at  $\leq -20^\circ\text{C}$ . Repeated freeze-thaw cycles were avoided.

### Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 23.0 (SPSS Inc., Chicago, Illinois, USA). The quantitative data were presented as mean  $\pm$  standard deviation and ranges. Qualitative variables were presented as number and percentages. Data were explored for normality using Kolmogorov-Smirnov and Shapiro-Wilk Test. Independent-samples t-test of significance was used when comparing between two means. Mann Whitney U test was used for two-group comparisons in non-parametric data. Chi-square ( $\chi^2$ ) test of significance was used in order to compare proportions between qualitative parameters. Spearman's rank correlation coefficient (rs) was used to assess the degree of association between two sets of variables if one or both of them was skewed. Values of two variables are plotted along two axes as scatter plots showing the presence of correlations. The confidence interval was set to 95% and the margin of error accepted was set to 5%.

## RESULTS

The current study did not reveal any statistically significant difference among participants regarding age. There were statistically significant higher means of Gal-1 and Gal-3 in azoospermic patients compared to healthy individuals ( $p < 0.001$  for all) (Table 1).

In addition, in healthy individuals there were statistically significant positive correlations between serum levels of Gal-1 and age, FSH, LH levels ( $r = 0.296$ ,  $p = 0.005$ ;  $r = 0.333$ ,  $p = < 0.001$ ;  $r = 0.312$ ,  $p = 0.003$ , respectively) and serum levels of Gal-2 and FSH and LH ( $r = 0.436$ ,  $p < 0.001$ ;  $r = 0.350$ ,  $p < 0.001$ , respectively), whereas serum Gal-3 showed a borderline positive correlation with age ( $r = 0.2$ ,  $p = 0.059$ ) (Table 2).

Additionally, statistically significant positive correlations between seminal levels of Gal-1 and Gal-3 and free testosterone in healthy individuals were observed ( $r = 0.205$ ,  $p = 0.053$ ;  $r = 0.219$ ,  $p = 0.038$ , respectively) (Table 2). On the other hand, there were negative correlations

between serum and seminal levels of Gal-1 and Gal-3, total and progressive sperm motility, sperm count and abnormal sperm forms in healthy individuals ( $r = -0.382$ ,  $p < 0.001$ ;  $r = -0.405$ ,  $p < 0.001$ ;  $r = -0.376$ ,  $p < 0.001$ ;  $r = -0.364$ ,  $p < 0.001$ ) ( $r = -0.394$ ,  $p < 0.001$ ;  $r = -0.467$ ,  $p < 0.001$ ;  $r = -0.413$ ,  $p < 0.001$ ;  $r = -0.433$ ,  $p < 0.001$ ) ( $r = -0.372$ ,  $p < 0.001$ ;  $r = -0.377$ ,  $p < 0.001$ ;  $r = -0.317$ ,  $p = 0.002$ ;  $r = -0.311$ ,  $p = 0.003$ ) ( $r = -0.445$ ,  $p < 0.001$ ;  $r = -0.498$ ,  $p < 0.001$ ;  $r = -0.453$ ,  $p < 0.001$ ;  $r = -0.463$ ,  $p < 0.001$ , respectively) (Table 2). Furthermore, statistically significant positive correlations between serum levels of Gal-1 and Gal-3 and age in azoospermic patients were reported ( $r = 0.511$ ,  $p < 0.001$ ;  $r = 0.390$ ,  $p = 0.008$ , respectively) (Table 3). On the other hand, there were negative correlations between seminal Gal-1 and estradiol (E2) and seminal Gal-3 and FSH and LH in azoospermic patients ( $r = -0.318$ ,  $p = 0.033$ ;  $r = -0.322$ ,  $p = 0.031$ ;  $r = -0.477$ ,  $p < 0.001$ , respectively) (Table 3). Also, negative correlations between serum Gal-3 and total and free testosterone in azoospermic patients were detected ( $r = -0.396$ ,  $p = 0.007$ ;  $r = -0.375$ ,  $p = 0.011$ , respectively) (Table 3).

## DISCUSSION

The current cross-sectional study was conducted at andrology outpatient clinic. The current study had shown that serum and seminal levels of Gal-1 and Gal-3 were statistically significant higher in azoospermic cases compared to fertile individuals. This finding is attributed to the fact that Gal-3 expression and/or its subcellular localization could be modified in the human infertile testes as Gal-3 immunostaining appears more intense in the infertile testes with an absence of germ cells (Sertoli cell-only syndrome) (20). Furthermore, animal studies on rat testes had revealed that Gal3 levels are increased in severely damaged spermatogenesis (20).

These findings could be seen in agreement with *GamalEl Din et al.* who evaluated seminal plasma and serum levels of Gal-1 in NOA patients (23). The aforementioned case-control study that included in total 48 NOA patients and 50 age matched healthy controls demonstrated that seminal plasma levels of Gal-1 were higher in NOA men versus healthy controls (23). Consistently, Gal-3 levels are increased in oligozoospermic cases (24). In addition, there

	Azoospermic cases (n = 45)			Healthy individuals (n = 45)			p-value
	Mean	SD	range	Mean	SD	range	
Serum Galectin 1 (ng/ml)	13.79	± 10.14	6.7-56	7.35	± 1.12	5.2-9.3	< 0.001
Seminal plasma Gal-1 (ng/ml)	12.11	± 6.24	3.6-27.4	7.25	± 0.90	5.7-8.7	< 0.001
Serum Gal-3 (pg/ml)	402.56	± 295.59	153.8-1300	230.11	± 59.33	120-312.3	< 0.001
Seminal plasma Gal-3 (pg/ml)	404.15	± 300.11	114.6-1230	152.77	± 22.50	120.6-198.2	< 0.001

*P* value was calculated using Mann-Whitney test.

**Table 1.**

Shows levels of seminal plasma and serum Gal-1 and Gal-3 in azoospermic cases and healthy individuals.

Parameters	Gal-1 (ng/ml)				Gal-3 (pg/ml)			
	Serum		Seminal plasma		Serum		Seminal plasma	
	r	p-value	r	p-value	r	p-value	r	p-value
Age (years)	0.296	0.005	0.013	0.904	0.200	0.059	-0.092	0.387
Sperm count	-0.382	< 0.001	-0.394	< 0.001	-0.372	< 0.001	-0.445	< 0.001
Total sperm motility	-0.405	< 0.001	-0.467	< 0.001	-0.377	< 0.001	-0.498	< 0.001
Progressive sperm motility	-0.376	< 0.001	-0.413	< 0.001	-0.317	0.002	-0.453	< 0.001
Abnormal sperm forms	-0.364	< 0.001	-0.433	< 0.001	-0.311	0.003	-0.463	< 0.001
FSH	0.333	< 0.001	0.319	0.002	0.436	< 0.001	0.151	0.155
LH	0.312	0.003	0.337	< 0.001	0.350	< 0.001	0.007	0.951
Total testosterone	-0.139	0.191	0.046	0.666	-0.184	0.082	0.054	0.614
Free testosterone	-0.111	0.298	0.205	0.053	-0.197	0.063	0.219	0.038
PRL	0.033	0.757	0.120	0.260	0.032	0.765	0.008	0.940
E2	0.053	0.622	-0.151	0.155	0.079	0.460	-0.049	0.645

*P* value calculated using Spearman's rank correlation coefficient.

**Table 2.**

Shows correlation between Gal-1 (ng/ml) and Gal-3 (pg/ml) with age and different sperm parameters and reproductive hormones.

Parameters	Serum Gal-1 (ng/ml)		Seminal plasma Gal-1 (ng/ml)		Serum Gal-3 (pg/ml)		Seminal plasma Gal-3 (pg/ml)	
	r	p-value	r	p-value	r	p-value	r	p-value
Age (years)	0.511	< 0.001	0.064	0.674	0.390	0.008	-0.102	0.505
FSH	0.077	0.615	-0.024	0.874	0.265	0.078	-0.322	0.031
LH	0.093	0.546	0.053	0.731	0.152	0.320	-0.477	< 0.001
Total testosterone	-0.236	0.118	0.045	0.769	-0.396	0.007	0.127	0.405
Free testosterone	-0.207	0.173	0.224	0.138	-0.375	0.011	0.293	0.051
PRL	0.077	0.613	0.279	0.064	0.032	0.834	0.046	0.765
E2	-0.011	0.945	-0.318	0.033	0.004	0.980	-0.173	0.256

*P* value calculated using Spearman's rank correlation coefficient.

**Table 3.**

Shows correlation between Gal-1 (ng/ml) and Gal-3 (pg/ml) with age and reproductive hormones among azoospermic patients.

were statistically significant positive correlations between serum and seminal levels of Gal-1 and Gal-3, age, FSH, LH and abnormal sperm forms. Similarly, it should be noted that FSH enhances Gal-3 expression probably through the classical cAMP/PKA/CREB transducing pathway (20). Furthermore, *CAMP responsive element* (CRE) and activator protein complex (AP1) have been detected in gal-3 promoter, a finding which agrees with the potential direct stimulatory actions of FSH and EGF, respectively. On the contrary, Gal-1 has been detected in interstitial cells in mouse testis (25) where it might modulate Leydig cell growth through its multivalent binding and cross-linking properties as well as its ability to interact with extra cellular matrix causing changes in cell adhesivity (26). In the same context, the same study had reported that Gal-1 induces changes in Leydig cell morphology and reduces cell viability and testosterone production (26). Furthermore, this is the first time that an endogenous protein, Gal-1, is shown to possess apoptosis-inducing activity on Leydig cells. Also, there were negative correlations between Gal-1, Gal-3, total and progressive sperm motility and sperm count. We agreed with *Mentesoglu and colleagues* (2021) who assessed the correlation between semen parameters and galectin-3 levels of infertile men (24). Moreover, the possible role of Gal-3 and sperm motility in the current study is also supported by the negative correlation between Gal-3 levels and total progressive motile sperm.

Consistently, Gal-3 levels were found to be negatively correlated with total progressive sperm count in oligozoospermic patients (24). Furthermore, there was a highly statistically significant positive correlation between serum Gal-1 and Gal-3 and age in azoospermic patients that could be seen contradictory to the study conducted by GamalEl Din et al who failed to demonstrate any correlation between serum Gal-1 and age in NOA patients (23). Furthermore, there was a statistically significant negative correlation between seminal plasma Gal-1 and estradiol (E2) in azoospermic patients. Similarly, *Perzelova et al.* demonstrated an inverse relation between Gal-1 and estrogen as they showed that the pharmacological activation of estrogen receptor- $\beta$  led to a significant alteration in the pattern of differentiation and the proliferation activity of keratinocytes including Gal-1 (27). Interestingly, there were statistically significant negative correlations between serum Gal-3, total testosterone and free testosterone in azoospermic patients. These findings could be seen contradictory to a recent study that was conducted on rats and revealed the favorable effect of testosterone administration to halt the progression of cavernosal fibrosis by decreasing Gal-1 through enhancing the expression of miR-22-3p (28). Furthermore, there were statistically significant negative correlations between seminal plasma Gal-3, FSH and LH in azoospermic patients.

Remarkably, there are several points of strength of the current study that can be summarized as follows. It clearly demonstrates the detrimental effects of Gal-1 and Gal-3 on spermatogenesis. Also, it highlights the horizons for a potential regulatory effect of reproductive hormones on these proteins. Admittedly, lack of immunohistochemistry can be seen as the major limitation of the current study. Also, small sample size can be added as another

limitation. Finally, five cases of the healthy individuals suffering from hypothyroidism and diabetes mellitus and hypertension and disc prolapsed were included.

## CONCLUSIONS

Elevated serum and seminal levels of Gal-1 and Gal-3 have detrimental effects on spermatogenesis. Furthermore, the current study demonstrated potential regulatory effects of reproductive hormones on Gal-1 and Gal-3. Thus, future studies are needed to confirm such findings.

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**Conflict of interest:** The authors declare no potential conflict of interest.