RESEARCH ARTICLE

Seminal Plasma Interleukin-37 and Interleukin-41 Levels in Infertile Men with Varicocele

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Abstract

Background: Inflammatory processes and cytokines have been implicated in the development of varicocele-associated male infertility. This study aimed to assess the levels of two novel seminal plasma interleukins interleukin-37 (IL-37) and IL-41 among infertile men with varicocele compared to patients without varicocele and fertile controls.

Materials and methods: In this case-control study, 50 infertile men with varicocele, 50 infertile men without varicocele, and 40 fertile controls were recruited for the study. For all participants, semen analysis was performed according to World Health Organization (WHO) 2021 sixth criteria. Seminal plasma levels of IL-37 and IL-41 were measured in all participants using enzyme-linked immunosorbent assay (ELISA) and compared among groups.

Results: Sperm concentration, progressive and total motility were significantly reduced in varicocele group as compared to patients without varicocele ($p < 0.05$, $p < 0.01$, $p < 0.05$, respectively) and fertile controls ($p < 0.001$). Seminal plasma concentrations of IL-37 and IL-41 were higher in varicocele group as compared to patients without varicocele ($p < 0.01$) and fertile controls ($p < 0.001$). Seminal plasma IL-37 and IL-41 levels showed significant inverse correlations with sperm progressive and total motility in patients with varicocele ($r = -0.32$ to -0.46) and inverse significant correlations with sperm progressive motility in patients without varicocele ($r = -0.34$ and -0.3, respectively).

Conclusion: Our study demonstrated significant elevations of seminal plasma IL-37 and IL-41 in infertile men, with the highest levels observed in patients with varicocele. Our findings support role of inflammatory cytokines as key players in varicocele-associated male infertility, and IL-37 and IL-41 may serve as potential new biomarkers of male infertility in patients with varicocele.

Keywords: Cytokines, IL-37, IL-41, Male infertility, Varicocele.

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Introduction

Male infertility is the failure of a couple to achieve conception after 1 year of regular unprotected sexual intercourse. This health problem is a great global challenge as infertility affects 7–12% of couples globally, with the male responsible for infertility in approximately half of cases.[1,2]

The etiology of male infertility is multifactorial, and can be attributed to hormonal disorders, genetic defects, testicular disease, genital infections, genital tract obstruction, or varicocele.[2,3] Further, various factors have been implicated in the decline of semen quality such as environmental, oxidative stress (OS), and lifestyle factors.[4] Therapeutic interventions for infertile men include medical approaches, surgical procedures, and assisted reproduction techniques (ART).[5] Varicocelectomy surgery has improved semen parameters and pregnancy rates in specific subgroups of patients.[6] The implementation of new diagnostic techniques and personalized therapies may lead to improved outcomes for couples with infertility.

Varicocele is defined as an abnormal enlargement of the pampiniform plexus vein of the spermatic cord and is graded by physical examination findings. Varicocele affects approximately 15% of men globally.[7] Scrotal hyperthermia, hypoxia, OS, apoptosis, accumulation of toxins, metabolite reflux, testicular hypoperfusion, sperm deoxyribonucleic acid (DNA) fragmentation, as well as hormonal disturbances are proposed mechanisms underlying varicocele-induced male infertility.[8–10] Multiple studies have reported a link between pro- and anti-inflammatory cytokines, including interleukins IL-1, IL-6, IL-8, IL-10, IL-37, IL-41, TNF-α, and IFN-γ in men with varicocele.[11]

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Cytokines comprise a large and heterogeneous group of small proteins secreted by numerous cell types. Several cytokines and chemokines have been identified and quantified in seminal plasma. Many studies have examined the possible associations between seminal plasma cytokines and sperm parameters.[12] Most studies examine the relationship between seminal plasma cytokines concentration and seminal quality parameters. The levels of cytokines in ejaculates appear to be quite variable among men, and may vary within individuals over time.[5] A higher level of some cytokines has been correlated to leukocytospermia in the ejaculate, which may suggest bacterial, viral parasitic male genital tract infection that may contribute to male infertility. Cytokines contribute to the optimal antimicrobial immune responses and their function in seminal plasma is unknown but they can be used as mediators of inflammation as well as recruitment of leukocytes.[13,14]

Low grade inflammation, which could be responsible for the significant increase in OS and act as a link between varicocele and sperm DNA damage and male factor infertility. Therefore, exploring the function of these inflammatory mediators in varicocele might play a role in the treatment of infertile men. Lifestyle factors may also increase OS and also may impair spermatogenesis and reduce sperm quality.

Interleukin-37 is an anti-inflammatory cytokine of the IL-1 family and inhibits innate inflammatory and immune responses.[15,16] Interleukin-37 mediates biologic functions through dual mechanisms: The intracellular one when it binds to Smad3 and moves into the nucleus on an extracellular basis, IL-37 forms a complex with extracellular IL-18 receptor alpha (IL-18Rα) and IL-1R8.[16,17] It also inhibits the synthesis of IL-1, 1L-6, TNF-α, and other inflammatory components. Interleukin-41, also known as meteorin-like (Metrnl), subfatin, or cometin, is a new class of secreted protein that possesses immunomodulatory properties involved in regulating inflammation, energy metabolism and tissue homeostasis.[18,19] In contrast to typical cytokines, IL-41 shows context-dependent effects, with either pro- or anti-inflammatory properties in different pathophysiological settings and targeted cells.

In male infertility and varicocele, new studies have shown dysregulation of both cytokines among patients. Zeinali et al. demonstrated elevated seminal plasma IL-37 in infertile individuals with varicocele compared with fertile controls, indicating a compensatory anti-inflammatory response to the chronic inflammation induced by varicocele.[20] Recently, IL-41 has also been described as a possible biomarker in male reproductive diseases and changes in its serum levels were correlated to impaired semen quality, suggesting a contribution of this cytokine in reproductive immunology and potential diagnostic usefulness.[21] Such findings indicate the intricate cytokine interrelationships in male fertility. The purpose of this study was to evaluate the concentrations of IL-37 and IL-41 in seminal plasma between infertile men with varicocele and without varicocele, as well as fertile controls. The induction of inflammatory signaling pathways, such as the NLR family pyrin domain containing 3 (NLRP3) pathway, disrupted blood-testis barrier (BTB) and perpetuated dysregulation of the inflammatory loop, ultimately leading to a loss of male fertility potential.[11] Data on the level of IL-41 in infertile men with varicocele are limited, and our study is the first study to explore the set of IL-37 and IL-41 in infertile men with varicocele. Therefore, this study aimed to assess IL-37 and IL-41 levels in seminal plasma in infertile patients with varicocele compared with those without varicocele and fertile controls.

Materials and Methods

In this case-control study, 50 infertile men with varicocele, 50 infertile men without varicocele and 40 fertile controls (age-matched) were recruited for the study. The participants were recruited from Babil Fertility Clinic, Babyl, Iraq from February to August 2024. Infertile men had not achieved pregnancy in 12 months or more and have abnormal semen analysis. In patients' group with varicocele, varicocele was diagnosed by scrotal examination in upright positions before and during Valsalva's maneuver (grades I–III) and was confirmed by Doppler sonography. Patients with known predisposing factors for male infertility such as undescended testicles, endocrinopathies, systemic diseases, genital infection, smoking, alcoholism, and recent antioxidant intake were excluded. Fertile controls must have fathered a child in the previous 2 years and have normal semen analysis. Ethical approval was issued by the University of Babylon (EC/1882-24) and informed consent was received before the start of the study.

Semen Analysis

Semen samples were collected from participants following an abstinence period of 3–5 days by masturbation. Following collection, the semen sample was held at 37°C for liquefaction and then analyzed according to World Health Organization (WHO) 2021 sixth criteria for all semen parameters.[3] All the analyses were undertaken by the same investigators, and for all participants two semen samples were assessed and their average value was used for this study.

Seminal Plasma IL-37 and IL-41 Measurement

Following centrifugation at 3,000 rpm for 5 minutes, seminal plasma was collected and kept at –20 °C for further biochemical tests. Seminal plasma levels of IL-37 and IL-41 in were measured in all participants using enzyme-linked immunosorbent assay (ELISA) kit (Sunlong Biotech, China) and following manufacturer's recommended instructions.

Statistical Analysis

Statistical analysis of data was performed with MedCalc software (v.22). Data normality was assessed with Kolmogorov–Smirnov test. The results were expressed as mean ± standard deviation (SD). Analysis of variance (ANOVA) test was used for comparing the means of semen parameters and IL-37 and IL-41 levels among groups. Pearson's correlation coefficient was used to correlate semen parameters and interleukin levels. $p < 0.05$ was considered statistically significant.

Results

The mean age was comparable across all groups (39.3 ± 9.8 years in controls, 36.2 ± 9.7 years in the patients without varicocele, and 34.2 ± 12.1 years in the varicocele group) (Table 1). The mean duration of infertility was similar between infertile groups (7.8 ± 6.75 years in patients without varicocele and 6.7 ± 5.2 years in patients with varicocele). Semen analysis revealed significant impairments in both infertile groups compared to controls (Table 1). Sperm concentration was markedly reduced in both patients without varicocele and the varicocele group compared to controls ($p < 0.001$). Furthermore, sperm concentration was significantly lower in the varicocele group compared to the patients without varicocele ($p < 0.05$). Progressive motility was severely impaired in infertile men compared to controls (both $p < 0.001$). The varicocele group demonstrated significantly lower progressive motility than the patients without varicocele ($p < 0.01$). Total motility was also lower in infertile men as compared to fertile controls ($p < 0.001$). Total motility was significantly reduced in the varicocele group compared to patients without varicocele ($p < 0.05$).

Both IL-37 and IL-41 levels were significantly elevated in infertile men compared to controls (Table 2). Seminal plasma IL-37 concentrations were 109.63 ± 18.95 pg/mL in controls, 180.24 ± 26.18 pg/mL in patients without varicocele ($p < 0.001$), and 265.46 ± 34.02 pg/mL in the varicocele group ($p < 0.001$) (Fig. 1). Notably, IL-37 levels were significantly higher in patients with varicocele compared to those without varicocele ($p < 0.01$). Similarly, IL-41 level was 86.42 ± 25.41 pg/mL in controls, 144.35 ± 38.12 pg/mL in patients without varicocele ($p < 0.001$), and 231.2 ± 40.26 pg/mL

Table 1: Patients characteristics and semen analysis

Parameter	*Controls (n = 40)*	*Patients without varicocele (n = 50)*	*Patients with varicocele (n = 50)*
Age (years)	39.3 ± 9.8	36.2 ± 9.7	34.2 ± 12.1
Duration of infertility (years)		7.8 ± 6.75	6.7 ± 5.2
Sperm concentration (million/mL)	65.2 ± 32.34	8.4 ± 2.7*	7.1 ± 3.04*†
Sperm progressive motility (%)	58.4 ± 21.6	17.8 ± 7.9*	14.5 ± 6.61*‡
Sperm total motility (%)	65.34 ± 19.3	22.4 ± 7.1*	19.2 ± 6.46*†
Normal morphology (%)	9.86 ± 3.7	8.91 ± 4.41	7.7 ± 3.4

*$p < 0.001$ compared to controls; †$p < 0.05$ compared to no varicocele group; ‡$p < 0.01$ compared to no varicocele group

Table 2: Correlations between semen parameters and seminal plasma IL-37 and IL-41 levels in patients with varicocele

	IL-37 (pg/mL)		*IL-41 (pg/mL)*	
Parameter	*r-value*	*p-value*	*r-value*	*p-value*
Age	0.124	0.39	0.09	0.49
Sperm concentration	−0.268	0.05	−0.24	0.09
Sperm progressive motility	−0.46	0.005*	−0.38	0.01*
Sperm total motility	−0.41	0.008*	−0.32	0.04*
Sperm normal morphology	−0.215	0.13	−0.18	0.18

r, Pearson's correlation coefficient; *Significant correlations

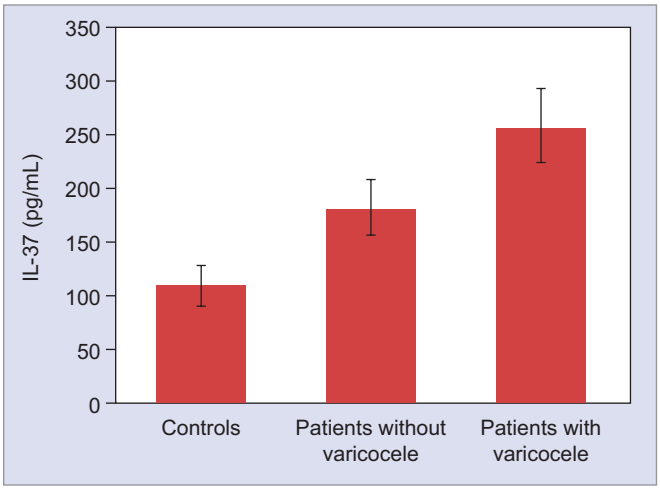

Fig. 1: Seminal plasma interleukin-37 (IL-37) level in study groups. Results are expressed as mean ± SD

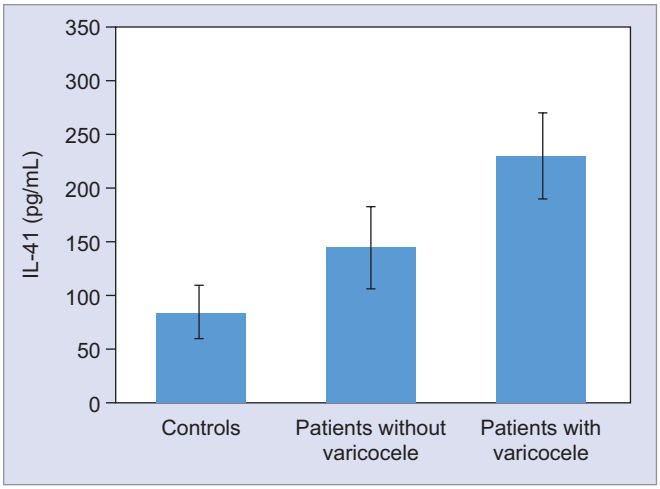

Fig. 2: Seminal plasma interleukin-37 (IL-41) level in study groups. Results are expressed as mean ± SD

Table 3: Correlations between semen parameters and seminal plasma IL-37 and IL-41 levels in patients without varicocele

	IL-37 (pg/mL)		*IL-41 (pg/mL)*	
Parameter	*r-value*	*p-value*	*r-value*	*p-value*
Age	0.087	0.548	0.112	0.438
Sperm concentration	−0.198	0.168	−0.176	0.222
Sperm progressive motility	−0.34	0.01*	−0.30	0.04*
Sperm total motility	−0.287	0.053	−0.263	0.064
Sperm normal morphology	−0.142	0.326	−0.128	0.376

r, Pearson's correlation coefficient; *Significant correlations

in the varicocele group ($p < 0.001$) (Fig. 2). The varicocele group demonstrated significantly higher IL-41 levels than patients without varicocele ($p < 0.01$).

In patients with varicocele, IL-37 levels showed significant negative correlations with progressive motility ($r = -0.46$, $p = 0.005$) and total motility ($r = -0.41$, $p = 0.008$) (Table 2). Interleukin-41 levels also demonstrated significant negative correlations with progressive motility ($r = -0.38$, $p = 0.01$) and total motility ($r = -0.32$, $p = 0.04$). In patients without varicocele, IL-37 levels showed a significant negative correlation with progressive motility ($r = -0.34$, $p = 0.01$) while IL-41 levels correlated negatively with progressive motility ($r = -0.30$, $p = 0.04$) (Table 3).

Discussion

The results of this study support the adverse impact of varicocele on the quality of semen. The highly reduced sperm concentration progressive and total motility observed in both infertile groups with a more severe decline in the varicocele group are supported by findings in the literature showing an association of varicocele and impaired spermatogenesis.[11] The decline of semen parameters in varicocele patients with the progressing severity found in the present study is in agreement with previous reports demonstrated that all three sperm parameters decrease in these

patients.[22] It is noteworthy that we did not find difference in sperm morphology between the three groups included in our study. This finding indicates that the effect of varicocele is more profound on sperm production and motility than on their morphological characteristics.

The marked increase of IL-37 and IL-41 in seminal plasma of infertile men, especially those with varicocele, suggests that inflammation is a key player in varicocele-associated male infertility. These results are consistent with other studies, which showed enhanced proinflammatory cytokines in male infertility.[12–14] The detrimental effects of proinflammatory cytokines on spermatogenesis and function have been demonstrated in the male reproductive system in previous studies.[22,23] Our results are also in agreement with the study of Zeinali et al. who also found high levels of IL-37 in seminal plasma of infertile men with varicocele with respect to healthy controls.[20] The authors speculated that increased expression of IL-37 could be a compensatory response to counterbalance pro-inflammatory cytokines such as IL-18, and this compensation is not enough for maintaining normal fertility. Similarly, Fraczek et al. found that infertile men have increased levels of anti-inflammatory cytokine IL-10 and transforming growth factor (TGF)-β, which could represent the body's response to counteract inflammatory stimuli.[24] Yet, this compensatory reaction seems not to be fully effective against the deleterious effects on spermatogenesis and sperm function.

Oxidative stress is a consequence of prooxidants/antioxidants disequilibrium. A diverse antioxidant therapies have attempted to ameliorate OS, reactive oxygen species (ROS), and sperm DNA fragmentation (SDF), and in turn to decrease in SDF-dependent. and change in semen parameters and seminal antioxidant markers.[6] Antioxidant treatment is undermined by the absence of consensus on the type, dose, and duration of antioxidant treatment.[4] Many cytokines contribute to the optimal antimicrobial immune responses. IFN-γ, is normally found in seminal fluid, though they are endogenously secreted.[25] Their function in seminal plasma is unknown, but they can be used as mediators of inflammation as well as to recruit leukocytes *in-situ*. Therefore, knowledge of the role of these chemical mediators in the varicocele disease might play a role in the treatment of male infertility. Lifestyle factors may also increase OS and impair spermatogenesis and sperm quality.

This study also showed a significant negative relationship observed between IL-37 and IL-41 with sperm progressive and total motility. These associations were detected in varicocele and non-varicocele infertile men, indicating that inflammatory events are causally related to sperm motility irrespective of the presence of varicocele.[20] The more significant reduction in the varicocele group than the non-varicocele groups indicate a possible enhancement of OS by the phenomenon and inflammation that is toxic to sperm.

Pro-inflammatory cytokines may thus have a direct impact on spermatozoa by various mechanisms, including enhanced generation of cytotoxic ROS, altered mitochondrial membrane potential, and disturbance in sperm plasma membrane integrity.[22] It has been shown that inflammatory cytokines such as IL-6, can impair sperm motility, possibly by an overproduction of nitric oxide (NO).[26] Furthermore, Eggert-Kruse et al. found that higher levels of seminal TNF-α and IL-1β were negatively associated with sperm parameters during an infertility investigation.[27] Zhang et al. also observed complex cytokine networks which can be involved in OS and changes in sperm function.[28]

Animal studies show that cytokines can also enhance fertility by inducing an immune response in seminal fluid.[25] The presence of seminal plasma can affect embryo development to a large extent, endometrial transformation, and implantation and thereby modulating placental growth and fetal health. Seminal plasma cytokines can have either a pro- or anti-inflammatory effects, suggesting that the homeostasis of immune regulatory mechanisms in the seminal plasma is crucial.[5] Recent WHO guidelines suggest that examination of some cytokines in seminal plasma might be helpful for diagnosis of male infertility.[3]

Identifying the role of pro-inflammatory cytokines in physiological processes of male fertility as well as their role in male infertility, is valuable for the development of future markers and therapies for infertile men. Different cytokines increase or decrease in the setting of varicocele-associated male infertility, suggesting that cytokines could play a dual role in enhancing or reducing fertility potential in men with varicocele.[14] Understanding the effects of various cytokines on altering different semen parameters, sperm function as well their effect on fertilization and pregnancy, is essential to guide future research. Modulating cytokine levels could be a promising therapeutic target in men with infertility and varicocele. While the surgical approach remains the main treatment modality for varicocele, alteration of the levels of these cytokines may supply an alternative therapeutic window to overcome this condition with global impact.[29] In addition, these cytokines may be added to the assessment panel of tests in infertile men and may provide prognostic data in these patients. In addition, these markers could provide indication of the severity of inflammatory processes in infertile men with varicocele and provide both quantitative as well as qualitative assessments for these processes.

Current treatment modalities for male infertility encompass medical, surgical, and assisted reproductive technologies. While medical therapies have been used in the treatment of endocrine disorders, genital tract infection, and idiopathic male infertility, surgical treatment is required for other contributing factors for male infertility, such as varicocele, cryptorchidism, and surgical sperm retrieval.[30] Varicocele embolization has also been tried to treat varicocele in infertile men, but the success rate is variable and increased risk of recurrence.[31] Treatment of varicocele in infertile men enhances the environment for optimal spermatogenesis and reduces the adverse effects of hypoxia, hyperthermia, OS, and reflux of toxic metabolites in infertile men.[32,33]

The upregulation of IL-37 and IL-41 in infertile men especially with varicocele, could have multiple clinical implications. The cytokines could be potential biomarkers in estimating the severity of varicocele associated with infertility and predicting a treatment response. Further, the association between levels of cytokines and sperm motility indicates that anti-inflammatory treatments might assist surgical varicocelectomy in ameliorating fertility outcomes. A few studies have already reported that anti-inflammatory agents can relieve varicocele-induced pathogenesis in animal models.[11] Furthermore, determination of cytokine levels in seminal plasma may improve the diagnostic work-up of male infertility. Fraczek et al. suggested that measurement of different interleukins in serum and seminal plasma could help differentiate causes of various etiologies of infertility.[23]

Limitations of the current study encompass the cross-sectional nature of the study means that we cannot infer causal relationships

between cytokine levels and infertility. Prospective cohorts that track longitudinal changes in cytokines following varicocelectomy would be helpful to determine whether or not these inflammatory mediators can predict varicocele repair. We also did not analyze OS parameters, which would have allowed for a more thorough evaluation of the inflammatory-OS phenomenon in the patients group.

Conclusion

In summary, in the present study, we have shown that seminal plasma IL-37 and IL-41 are increased significantly in infertile men, with the most marked increases among those affected by varicocele. Our data augments previous reports on the essential role of inflammatory cytokines in varicocele-related male infertility. Therefore, IL-37 and IL-41 may represent diagnostic/therapeutic targets of varicocele-related male infertility. Further prospective and large-scale studies on infertile varicocele patients are needed to strengthen the evidence provided in the present study.

Declaration

Ethics Approval

The study was approved by the Institutional Ethics Committee, University of Babylon (Approval No. EC/1882-24).

Informed Consent

Written informed consent was obtained from all participants prior to their enrolment in the study.

Clinical Trial Registration

Not applicable.

Data Availability Statement

The data generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Artificial Intelligence (AI) Use Declaration

The authors declare that no AI tools were used in the preparation of this manuscript.

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Authors' Contributions (CRediT)

Ahmed T Alahmar: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review and Editing.

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