CZU: 616.69-008.6-07

MULTIPARAMETRIC DESCRIPTIVE AND COMPARATIVE ANALYSES BETWEEN FERTILE VERSUS INFERTILE MEN WITH SEVERE OLIGOZOOSPERMIA AND AZOOSPERMIA

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https://doi.org/10.52556/2587-3873.2025.3(105).05

Summary

Male infertility represents a major global health concern, often associated with conditions such as severe oligoasthenoteratozoospermia and azoospermia. The aim of the study was to compare clinical, biochemical, and genetic characteristics between infertile men and fertile controls. A prospective case-control study was conducted involving 180 participants, including 90 infertile men (45 with severe oligoasthenoteratozoospermia and 45 with azoospermia) and 90 fertile controls. Semen analysis, testicular ultrasound, vitamin D levels, and genetic testing.were performed. In men with severe oligoasthenoteratozoospermia, significantly reduced mean values were observed for sperm concentration (1.77±2 million/mL), total sperm count (5.59±8 million), total motility (12.64±16%), progressive motility (7.93±12%), vitality (13.64±18%), and normal morphology (1.02±2%) compared to controls. Vitamin D levels were slightly higher in the study group (29.37±9.3 ng/mL) than in controls (25.38±10.2 ng/mL). Average testicular volumes were 12.50±5.47 mL (right) and 12.30±5.09 mL (left). Abnormal echotexture and echogenicity were noted in 24.6% and 31.5% of right testes and 15.6% and 25.5% of left testes, respectively. Y chromosome microdeletions (sY242, sY1291, sY255, sY254) were identified in 4.4% of cases. An abnormal karyotype was found in 7.8% of infertile participants, while 92.2% had a normal karyotype. Compared with fertile men, severe oligoasthenozoospermia and azoospermia show marked alterations in semen, testicular, genetic, and endocrine parameters.

***Keywords**: male infertility, oligoasthenoteratozoospermia, azoospermia, Y chromosome microdeletions, semen analysis, testicular ultrasound*

Rezumat

Analize descriptive și comparative multiparametrice între bărbații fertili versus infertili cu oligozoospermie severă și azoospermie

Infertilitatea masculină reprezintă o problemă importantă de sănătate publică la nivel global, fiind frecvent asociată cu afecțiuni precum oligoastenoteratozoospermia severă și azoospermia. Scopul studiului a fost compararea caracteristicilor clinice, biochimice și genetice între bărbații infertili și sănătoși. A fost realizat un studiu prospectiv de tip caz–control, care a inclus 180 de participanți: 90 de bărbați infertili (45 cu oligoastenoteratozoospermie severă și 45 cu azoospermie) și 90 de bărbați fertili. Au fost efectuate analiza spermei, ecografia testiculară, determinarea nivelurilor de vitamina D și testări genetice. În lotul cu oligoastenoteratozoospermie severă s-au observat valori medii semnificativ reduse ale concentrației spermatozoizilor (1,77±2 milioane/mL), numărului total de spermatozoizi (5,59±8 milioane), motilității totale (12,64±16%), motilității progresive (7,93±12%), vitalității (13,64±18%) și morfologiei normale (1,02±2%), comparativ cu lotul control. Nivelurile de vitamina D au fost ușor ridicate în lotul de studiu (29,37±9,3 ng/mL) față de control (25,38±10,2 ng/mL). Volumul mediu testicular a fost de 12,50±5,47 mL pentru testiculul drept și de 12,30±5,09 mL pentru testiculul stâng. Ecotextura și ecogenitatea anormale au fost observate la 24,6% și 31,5% dintre testiculele drepte și la 15,6% și 25,5% dintre testiculele stângi, respectiv. Microdelețiile cromozomului Y (sY242, sY1291, sY255, sY254) au fost identificate în 4,4% din cazuri. Un cariotip anormal a fost depistat la 7,8% dintre participanții infertili, în timp ce 92,2% au prezentat cariotip normal. Comparativ cu bărbații fertili, oligoastenozoospermia severă și azoospermia prezintă alterări marcate ale parametrilor spermei, testiculari, genetici și endocrini.

***Cuvinte-cheie:** infertilitate masculină, oligoastenoteratozoospermie, azoospermie, microdelеții ale cromozomului Y, analiza spermei, ecografie testiculară*

Резюме

Мультипараметрический описательный и сравнительный анализ между фертильными и бесплодными мужчинами с тяжёлой олигоастено-тератозооспермией и азооспермией

Мужское бесплодие является значимой глобальной проблемой здравоохранения и часто ассоциируется с такими состояниями, как тяжёлая олигоастенотератозооспермия и азооспермия. Целью данного исследования было сравнение клинических, биохимических и генетических характеристик между бесплодными мужчинами и здоровыми контрольными лицами. Было проведено проспективное исследование типа «случай–контроль», включавшее 180 участников: 90 бесплодных мужчин (45 с тяжёлой олигоастенотератозооспермией и 45 с азооспермией) и 90 фертильных контрольных лиц. Были выполнены анализ спермы, ультразвуковое исследование яичек, определение уровня витамина D и генетические исследования. В группе с тяжёлой олигоастенотератозооспермией были выявлены значительно сниженные средние значения концентрации сперматозоидов (1,77±2 млн/мл), общего числа сперматозоидов (5,59±8 млн), общей подвижности (12,64±16%), прогрессивной подвижности (7,93±12%), жизнеспособности (13,64±18%) и нормальной морфологии (1,02±2%) по сравнению с контрольной группой. Уровень витамина D был несколько выше в группе исследования (29,37±9,3 нг/мл), чем в контрольной группе (25,38±10,2 нг/мл). Средний объём яичек составил 12,50±5,47 мл для правого

и 12,30±5,09 мл для левого яичка. Нарушения эхоструктуры и эхогенности отмечались у 24,6% и 31,5% правых яичек и у 15,6% и 25,5% левых яичек соответственно. Микроделеции Y-хромосомы (sY242, sY1291, sY255, sY254) были выявлены в 4,4% случаев. Аномальный кариотип обнаружен у 7,8% бесплодных участников, тогда как у 92,2% кариотип был нормальным. По сравнению с фертильными мужчинами, тяжёлая олигоастенозооспермия и азооспермия характеризуются выраженными нарушениями семенных, тестикулярных, генетических и эндокринных показателей.

Ключевые слова: *мужское бесплодие, олигоастенотератозооспермия, азооспермия, микроделеции Y-хромосомы, анализ спермы, ультразвуковое исследование яичек*

Introduction

Worldwide, approximately 15% of reproductive-age couples experience infertility, with male infertility contributing to nearly half of the cases [1]. The age-standardized prevalence of male infertility rate rises by 0.3% per year, with considerable geographical variability ranging from 20% to 70% [2]. Male infertility is a multifactorial condition influenced by genetic abnormalities, endocrine dysfunctions, lifestyle factors, environmental exposures, medical conditions, and medication use. Despite advancements in comprehending male infertility, approximately 30% of cases are still attributed to idiopathic sperm abnormalities, reflecting incomplete understanding of the mechanisms regulating spermatogenesis [3, 4].

In clinical practice, severe oligoasthenoteratozoospermia and azoospermia represent the most pronounced forms of male infertility and are frequently associated with hormonal disturbances, testicular structure alterations and genetic abnormalities. However, it remains insufficiently clarified whether men with confirmed fertility may also present limited or clinically insignificant changes similar to those observed in infertile patients, potentially leading to diagnostic uncertainty.

Conventional semen analysis remains the cornerstone of male infertility evaluation, although its limited ability to reflect testicular structure, endocrine balance and genetic integrity has led to the increasing use of complementary diagnostic tools, including hormonal profiling, scrotal ultrasound and genetic testing [1, 5]. A comprehensive andrological assessment is therefore essential not only for identifying the etiology of infertility but also for detecting associated conditions that may impact long-term health outcomes.

The aim of the study

The purpose of the current research is to compare the profile of the infertile man with the profile of the man whose fertility has been confirmed. Clarifying the characteristics that truly distinguish fertility from severe male infertility may improve the interpretation of uncertain findings, in which certain factors are erroneously assumed to contribute to the inability to conceive.

Materials and methods

A prospective case-control study was conducted from 2021 to 2023, including 180 participants: 90 infertile men (45 with severe oligoasthenoteratozoospermia and 45 with azoospermia) and 90 healthy fertile controls. Inclusion criteria for the study group were sperm concentration ≤5 million/mL, including azoospermia and cryptozoospermia. Control participants were fertile men whose partners had conceived naturally within the last 12 months.

The study involved both descriptive and comparative analyses between groups. Evaluated parameters included age, body mass index, symptom assessments using international questionnaires (International Index of Erectile Function, International Prostate Symptom Score, National Institutes of Health Chronic Prostatitis Symptom Index, and Premature Ejaculation Profile), semen analysis, hormonal profiling, urogenital inflammation status, presence of conditionally pathogenic infections and specific flora in semen and urine, and vitamin D3 levels. Additional assessments for the study group included scrotal ultrasound, genetic testing (karyotyping, azoospermia factor microdeletions, and cystic fibrosis transmembrane conductance regulator mutations), and histological evaluation where appropriate.

Serum follicle-stimulating hormone, luteinizing hormone, and estradiol were measured by electrochemiluminescence (Roche Diagnostics Cobas® e 801 Module). Prolactin, total testosterone, and sex hormone-binding globulin were measured by enzyme-amplified immunoassay (IMMULITE 2000 XPi, Siemens Healthineers). Reference ranges for adult men were as follows: follicle-stimulating hormone, 1.5–12.4 mIU/mL; luteinizing hormone, 1.7–8.6 mIU/mL; Prolactin, 53.0–360.0 mIU/L; total testosterone, 250–1200 ng/dL; Estradiol, 11.3–43.2 pg/mL; sex hormone-binding globulin, 10–57 nmol/L. Free testosterone was calculated using the Vermeulen equation, assuming a fixed albumin concentration of 4.3 g/dL.

For the assessment of oxidative stress in sperm samples, specific biochemical markers of lipid peroxidation and antioxidant activity were used. The level of reactive oxygen species (ROS) was determined using the chemiluminescence method or through specific colorimetric assays adapted for seminal fluid.

Semen samples were obtained by masturbation into sterile containers after 2–7 days of abstinence and analyzed according to the World Health Organization (WHO) 6th edition guidelines. Parameters assessed included sperm concentration (×10^6/mL), total sperm number (×10^6/ejaculate), motility (%), and morphology (% normal forms). Severe oligoasthenoteratozoospermia syndrome was defined by sperm concentration <5 million/mL or total sperm number <10 million/ejaculate, total motility <30%, and normal morphology <4%. Azoospermia was confirmed by two consecutive semen samples lacking spermatozoa. Sediment analysis was performed after 15 minutes of centrifugation at 3000 g, with screening by inverted microscopy at 400× magnification.

Scrotal ultrasound examinations were performed using a GE Logiq E9 system with a 7–15 MHz wideband linear transducer. Both axial and transverse views of the testes were obtained. Testicular volume was calculated using the ellipsoid formula (height × width × 0.523). Echotexture, echogenicity, and presence of calcifications, solid lesions, or epididymal cysts were evaluated for both testes.

Testicular biopsies were morphologically assessed for absence of seminiferous tubules (tubular sclerosis), absence of germ cells (Sertoli cell-only syndrome), maturation arrest, hypospermatogenesis, and mixed atrophy (global or focal). Spermatogenesis was scored using the Johnsen criteria, with scores ranging from 1 (no germ cells) to 10 (complete spermatogenesis).

Continuous variables were assessed for normality and presented as mean ± standard deviation or median [25th – 75th percentile], as appropriate. Pearson and Kendall rank correlation coefficients were calculated. Statistical significance was set at $p < 0.05$. Data were analyzed using IBM SPSS Statistics version 23. Comparisons between groups were performed using Student's t-test or Mann–Whitney U test for continuous variables, as appropriate, and χ^2 or Fisher's exact test for categorical variables. Where relevant, differences between groups are presented as mean or median differences with corresponding 95% confidence intervals.

The study was approved by the Institutional Ethics Committee of "Nicolae Testemiţanu" State University of Medicine and Pharmacy (decision nr 3 from 26.02.2021).

Results

Participant characteristics: The study group had an average age of 32.83 ± 5 years, compared to 31.39 ± 5 years in the control group. Body mass index was higher in the study group (27.1 ± 4) than in controls (24.9 ± 3), indicating overweight status. International questionnaires assessing lower urinary tract symptoms and sexual dysfunction showed no clinically significant differences. International Index of Erectile Function scores were 21.59 ± 5 in the study group and 21.64 ± 4 in controls. Lower urinary tract symptoms, measured by the International Prostate Symptom Score and the National Institutes of Health Chronic Prostatitis Symptom Index, averaged 1.58 ± 3 and 1.52 ± 3 in the study group, and 5.43 ± 4 and 6.46 ± 6 in controls. Premature Ejaculation Profile scores were 2.91 ± 5 in the study group and 4.77 ± 4 in controls. Statistically significant differences were observed for International Prostate Symptom Score, National Institutes of Health Chronic Prostatitis Symptom Index, and Premature Ejaculation Profile cumulative scores, though values remained within mild or moderate ranges.

Semen Analysis: Average days of abstinence before semen collection were similar between groups (3.73 ± 1 vs. 3.69 ± 1). Seminal volume averaged 3.04 ± 1.4 mL in the study group and 2.92 ± 1.3 mL in controls. Liquefaction time was longer in the study group (31.01 ± 12 minutes) than in controls (28.09 ± 11 minutes). Mean semen pH was 8.07 ± 0.5 in the study group and 7.87 ± 0.5 in controls, with no significant differences. Fertile controls exhibited semen parameters above WHO minimum thresholds: total sperm count 184.74 ± 129 ×10^6, concentration 66.54 ± 45 ×10^6/mL, total mobility 53.82% ± 15, progressive motility 44.60% ± 16, vitality 56.23% ± 12, and normal morphology 5.67% ± 4. Sperm agglutination occurred in 10%, and aggregation in 64.4% of fertile men. Within the study group, severe oligoasthenoteratozoospermia and azoospermia subgroups (45 participants each) were analyzed. Severe oligoasthenoteratozoospermia patients had markedly reduced sperm concentration (1.77 ± 2 ×10^6/mL) and total sperm count (5.59 ± 8 ×10^6), with low total mobility (12.64% ± 16) (mob_total) (figure 1). progressive motility (7.93% ± 12), vitality (13.64% ± 18), and morphology (1.02% ± 2) (figure 2). Agglutination was absent, and mild aggregation was present in 4.4%. Germ cell counts were higher in the study group (4.1 ± 8) than in controls (2.59 ± 3), as were leukocyte counts in semen (1.71 ± 3.3 vs. 0.79 ± 0.9).

Oxidative Stress and Vitamin D: Oxidative stress analysis demonstrated higher levels of reactive oxygen species in infertile men. Elevated and very high reactive oxygen species values (47.8% and 34.4% respectively) predominated in the infertile lot, whereas lower levels (17.8%) were more frequently observed among fertile controls. Vitamin D deficiency was observed in both groups, with mean levels below 30 ng/mL; levels were higher in

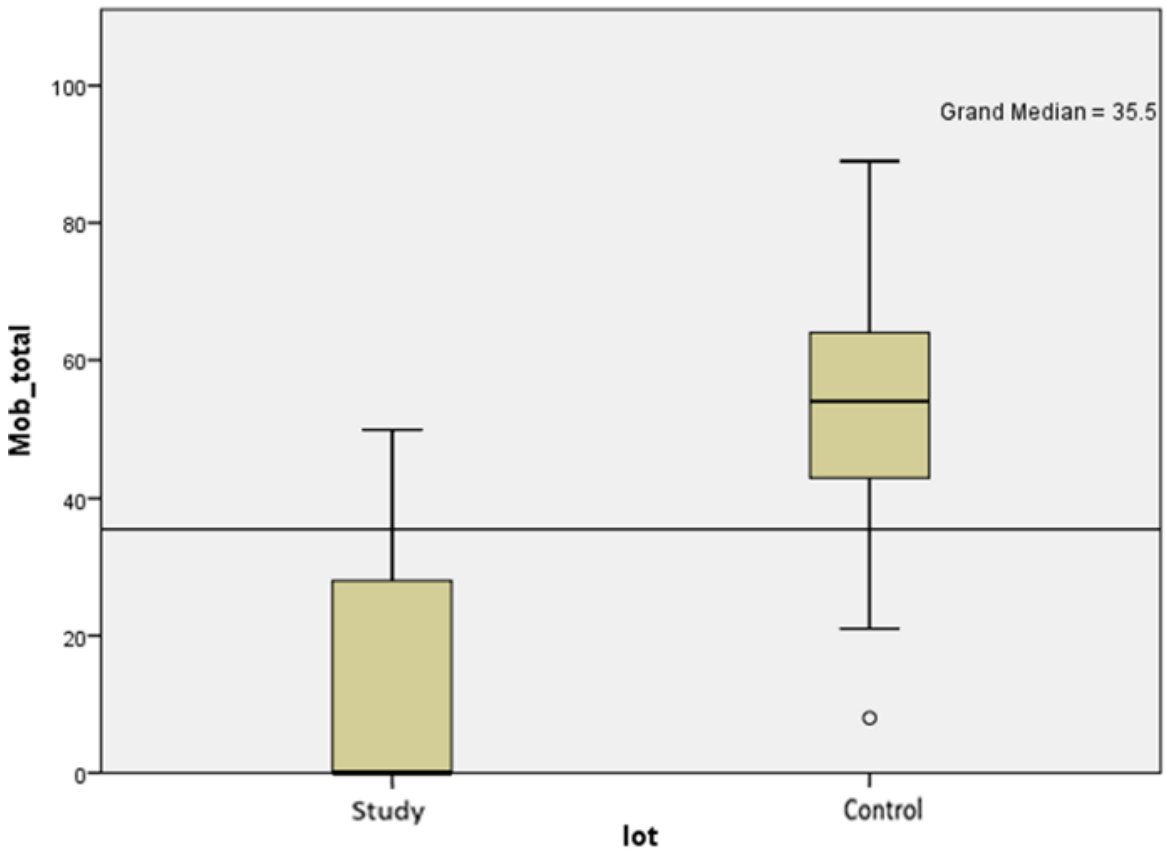

Figure 1. *Total sperm motility in study and control groups*

Note: *Boxplot comparing total sperm motility between study patients and controls. Horizontal line represents the median; whiskers show variability outside the upper and lower quartiles. Outliers are marked as circles. Group differences are statistically significant ($p < 0.05$).*

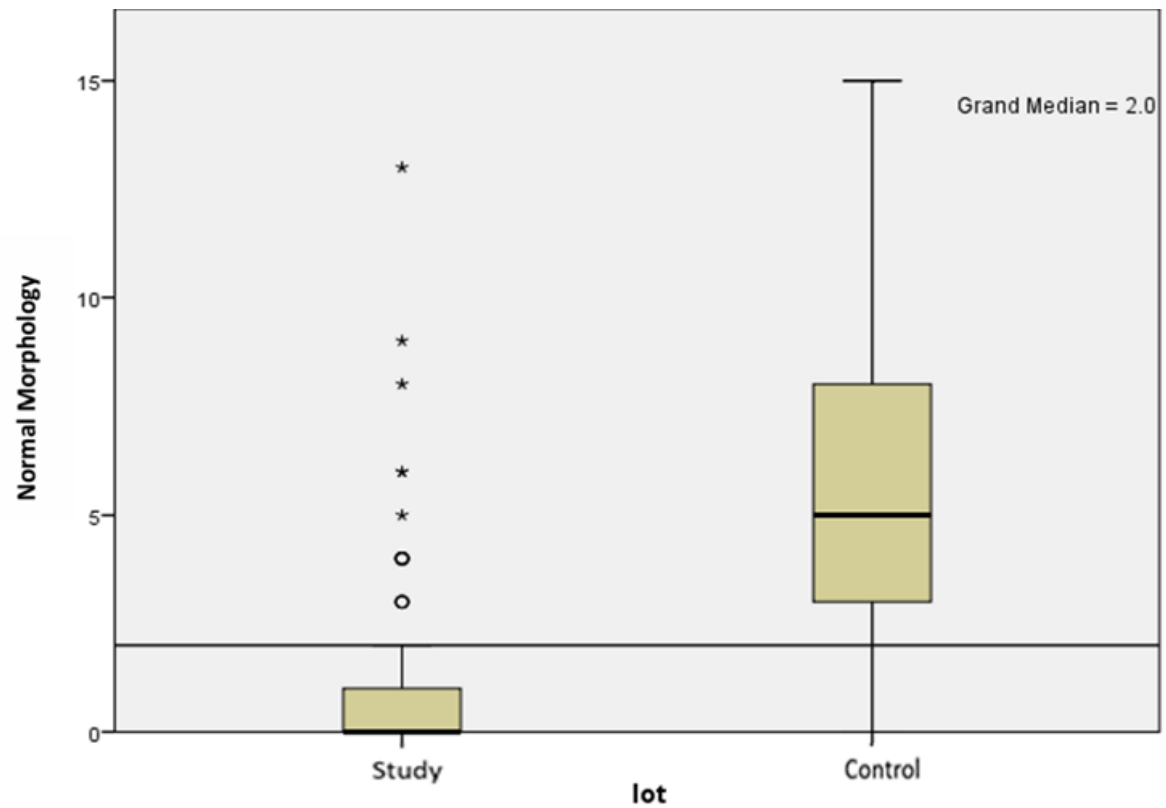

Figure 2. *Normal sperm morphology in study and control groups.*

Note: Boxplot displaying distribution of sperm morphology percentages. Median, quartiles, and outliers are indicated. Study patients show markedly lower normal morphology compared to controls ($p < 0.05$).

the study group (29.37 ± 9.3 ng/mL) than in controls (25.38 ± 10.2 ng/mL) (figure 3).

Infection Screening: The two-glass test (Meares and Stamey) and bacteriological analyses revealed average leukocyte counts of 6.86 ± 7 and 8.12 ± 8 in samples 1 and 2, respectively, with no urine samples showing positive bacterial growth (figure 4). PCR testing for sexually transmitted infections detected Chlamydia trachomatis in 2.2% of the study group and absent in controls. Ureaplasma species were found in 17.8% of patients and 11.1% of controls. Mycoplasma hominis and Mycoplasma genitalium were present in 4.4% and 3.3% of the study group; controls showed 8.9% positivity for M. hominis and no M. genitalium. Trichomonas vaginalis was detected in 1.1% of the study group. Gardnerella vaginalis was identified in 17.8% of patients and 8.9% of controls. Cytomegalovirus, herpes simplex virus, and human papillomavirus were absent in the study group but present at rates of 5.6%, 3.3%, and 1.1% in controls.

Hormonal Analysis: Follicle-stimulating hormone (14.55 ± 13.22 vs. 4.07 ± 2.13 mIU/mL) and luteinizing hormone (8.42 ± 5.3 vs. 5.03 ± 2.21 mIU/mL) were significantly elevated in the study group ($p < 0.001$) (figure 5). Prolactin (293.97 ± 223 vs. 201.23 ± 157 mIU/L), thyroid-stimulating hormone (2.28 ± 1.26 vs. 1.82 ± 0.97 mIU/L), and estradiol (32.75 ± 17.39 vs. 27.16 ± 10.24 pg/mL), were also higher ($p < 0.05$). Total testosterone levels were similar (352.86 ± 132 vs. 356.87 ± 133 ng/dL) (figure 6).

Scrotal Ultrasound: Scrotal ultrasound performed in infertile men revealed reduced tessticular volumes and frequent abnormalities of testicular morphology. Average testicular volumes were 12.50 ± 5.47 mL (right) and 12.30 ± 5.09 mL (left) (figure 7). Altered echotexture and echogenicity were observed in 24.6% and 31.5% of right testes, and 15.6% and 25.5% of left testes. Testicular calcifications were detected in 4.4% (right) and 7.7% (left). Left-sided varicocele was present in 17.7% of patients.

Genetic Evaluation: Y chromosome microdeletions (sY242, sY1291, sY255, sY254) were found in 4.4% of cases. Normal karyotypes were observed in 92.2%, with 7.8% showing abnormalities, including 46 XX (1 case), 47 XXY (4 cases), and 47 XXY/46 XX (1 case). One patient carried a CFTR gene mutation.

Histological Findings: Among azoospermic patients undergoing microdissection testicular sperm extraction, histological analysis of 35 samples revealed normal spermatogenesis in 25.7%, maturation arrest in 2.9%, Sertoli cell-only syndrome in 45.7%, testicular fibrosis in 8.6%, and mixed atrophy in 17.1%. Johnsen scores of 1–2 were present in 54.3% of samples, while scores of 9–10 were observed in 42.8%.

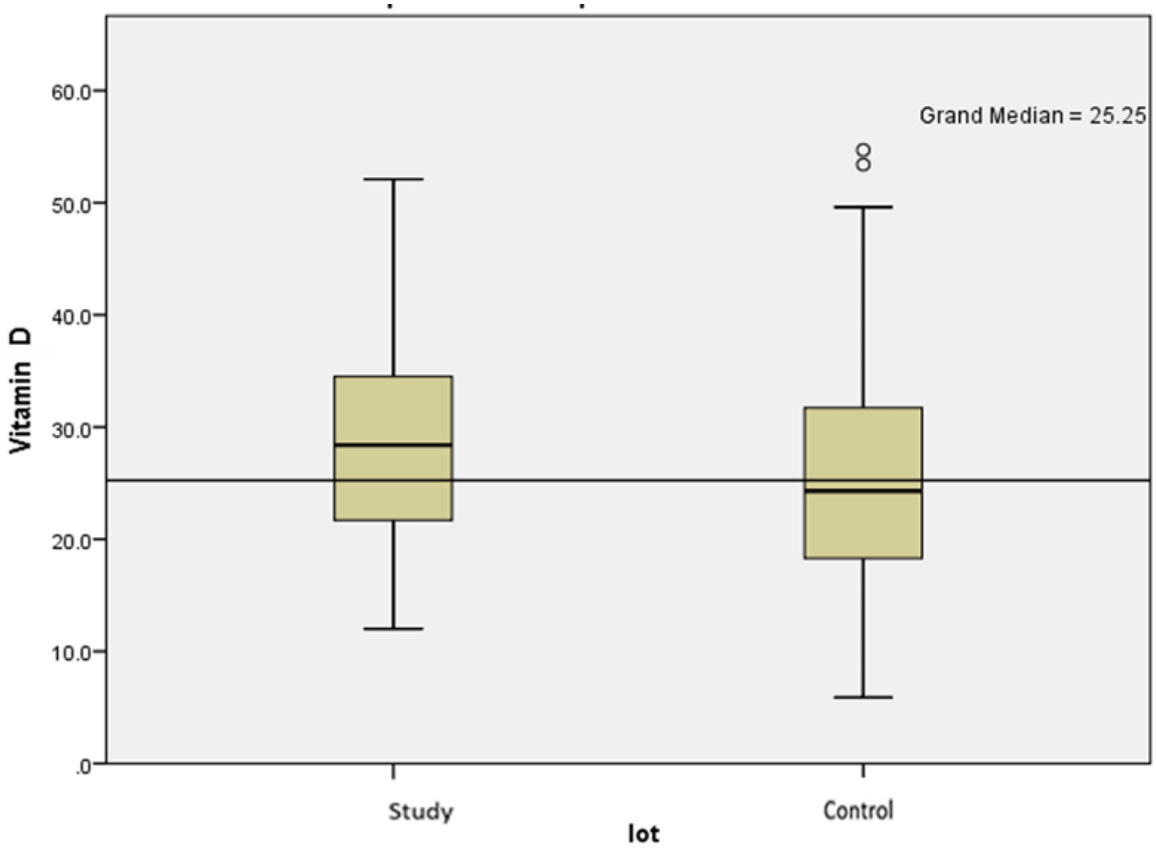

Figure 3 . *Serum vitamin D levels in study and control groups.*

Note: Boxplot showing 25-hydroxyvitamin D concentrations. Both groups present mean levels below the sufficiency threshold (30 ng/mL). Values are presented as median, quartiles, and outliers.

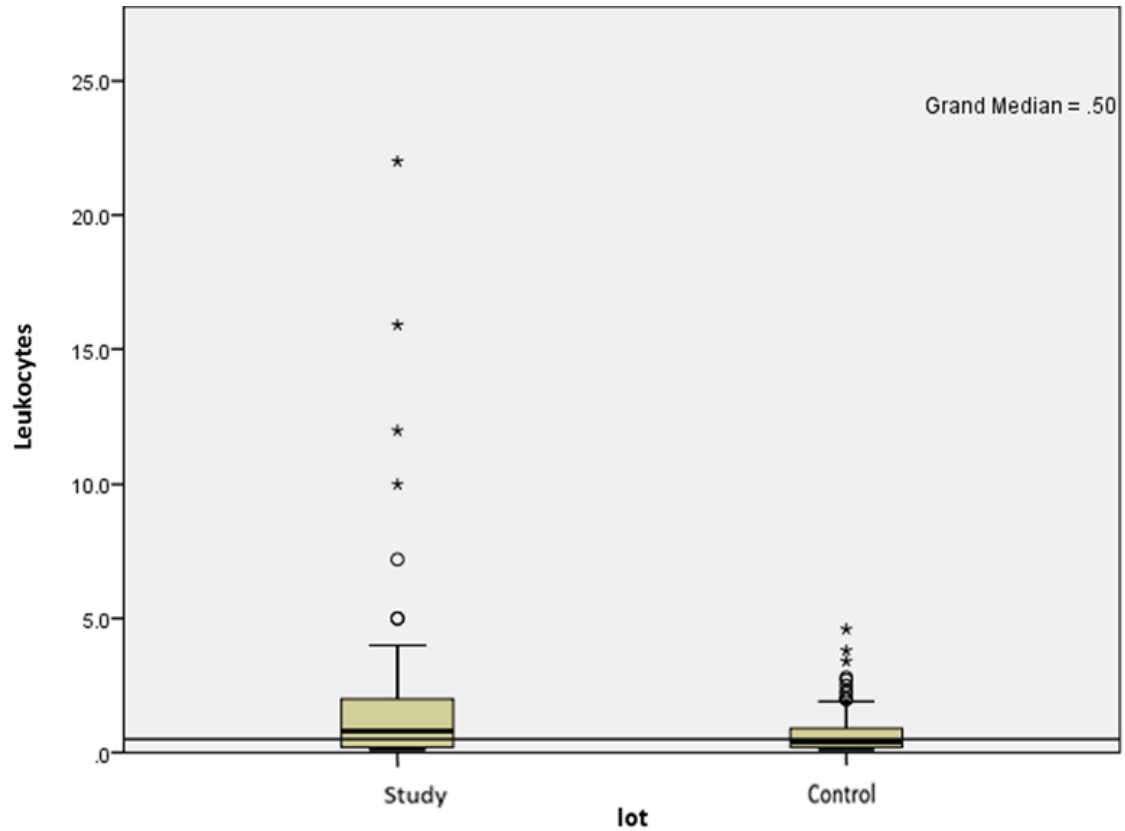

Figure 4 . *Seminal leukocyte counts in study and control groups*

Note: Boxplot illustrating differences in seminal leukocyte concentrations. Medians, quartiles, and outliers are indicated. Elevated leukocyte levels are observed in the study group ($p < 0.05$).

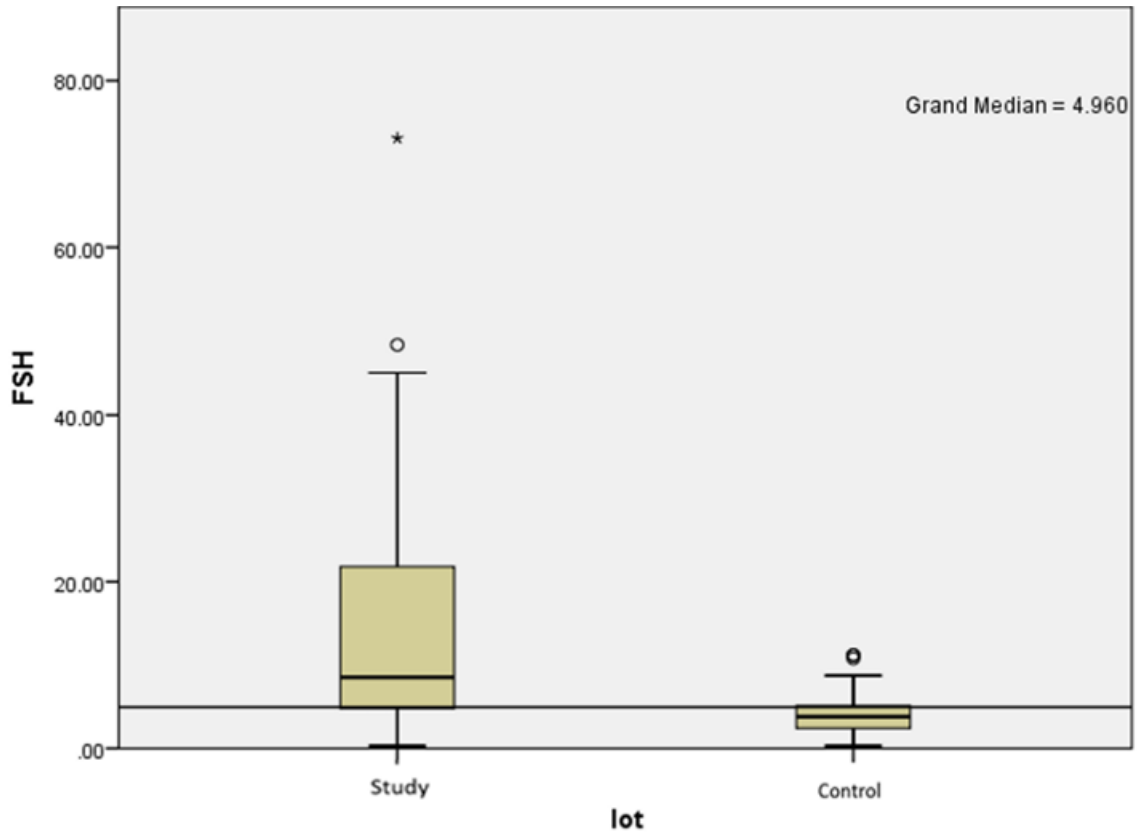

Figure 5. *Serum follicle-stimulating hormone (FSH) levels in study and control groups.*

Note: Boxplot comparing FSH concentrations. Median and variability are shown. Study group demonstrates significantly higher values ($p < 0.001$).

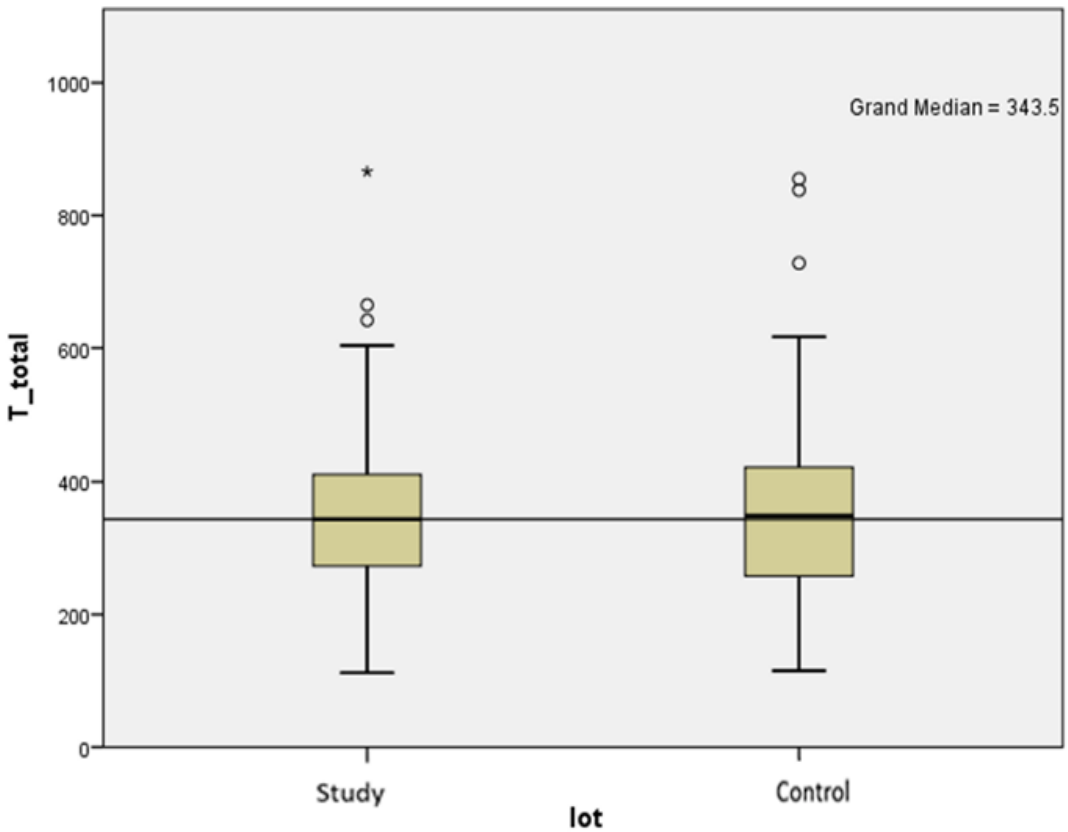

Figure 6. *Total testosterone concentrations in study and control groups.*

Note: *Boxplot showing serum testosterone levels. Median, quartiles, and outliers are displayed. No statistically significant difference was observed between groups.*

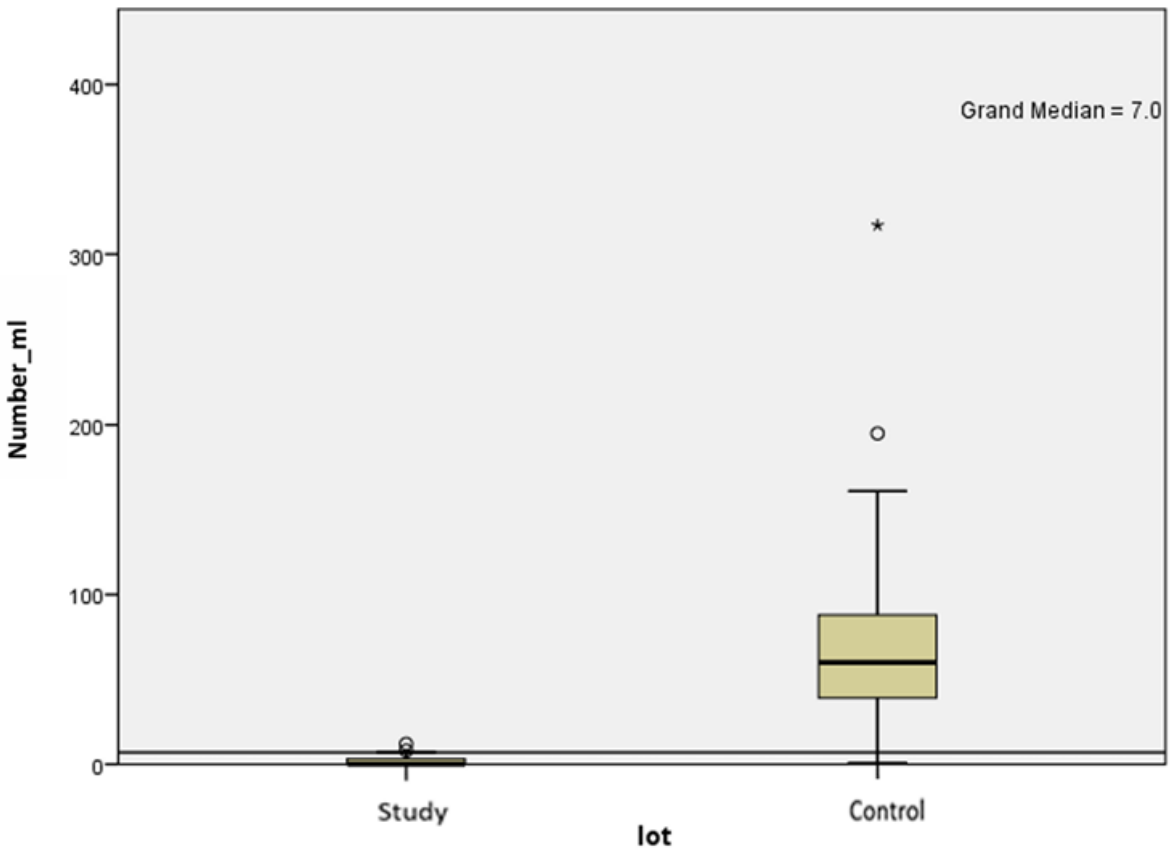

Figure 7. *Testicular volumes in study and control groups.*

Note*: Boxplot showing average testicular volumes (right and left). Medians, quartiles, and outliers are indicated. Study patients exhibited significantly reduced testicular volumes compared to controls ($p < 0.05$).*

Discussions

Male infertility of unknown etiology is frequently linked to obesity, impaired vitamin D homeostasis, oxidative stress, and genetic factors. Our study observed a higher prevalence of overweight status among infertile men compared to fertile controls, consistent with prior reports. Obesity has been described as a major factor impairing male fertility through reductions in testicular volume, spermatogenesis, and semen quality [6–9]. Its prevalence varies geographically and socioeconomically, with lifestyle factors such as sedentary behavior contributing to increased obesity rates [10].

Obesity disrupts endocrine balance, affecting sex hormone regulation and inducing heat stress that impairs mitochondrial function in Sertoli cells, ultimately reducing testosterone synthesis [11, 12]. Lower levels of free and total testosterone in obese men correlate with increased risks of erectile dysfunction and other reproductive impairments, which may further diminish fertility by reducing sexual activity [13].

Vitamin D deficiency was prevalent in both infertile and fertile men in our cohort, reflecting regional insufficiency. While vitamin D is recognized for its diverse genomic and non-genomic roles in male reproductive physiology [14], human clinical studies on its impact on fertility remain inconclusive. Vitamin D appears to influence bioavailable testosterone more than total levels and has been associated with improvements in semen quality, particularly sperm motility, likely through modulation of intracellular calcium and sperm function pathways [15].

Oxidative stress, characterized by an imbalance between reactive oxygen species (ROS) and antioxidant defenses, was detected at high levels even among fertile men in our study. This finding highlights the complexity of ROS's role in male fertility. Although oxidative stress has been implicated in idiopathic male infertility [16,17], its direct causative role remains debated, with various environmental and lifestyle factors contributing to altered redox status [18]. Leukocytes and immature spermatozoa are major sources of ROS, potentially exacerbating oxidative damage in seminal fluid [19]. Although a formal distinction between idiopathic and non-idiopathic infertility was not performed, the presence of oxidative stress, subclinical hormonal alterations, and structural testicular changes suggests that a proportion of cases classified as idiopathic may harbor underlying pathophysiological mechanisms.

Genetic abnormalities were present in a subset of infertile patients, with Y chromosome microdeletions detected in 4.4% and chromosomal anomalies in 7.8%. These findings align with large retrospective studies identifying diverse genetic causes of non-obstructive azoospermia, including Klinefelter syndrome, Sertoli cell-only syndrome, maturation arrest, and Y microdeletions [20–22].

Ultrasound findings of testicular asymmetry, measured via the Testicular Asymmetry Ratio (TAR), further support the association between structural testicular changes and severe idiopathic oligoasthenoteratozoospermia, potentially serving as a non-invasive marker for spermatogenic dysfunction. Recent evidence also suggests that testicular asymmetry negatively correlates with serum testosterone and follicle-stimulating hormone, linking structural abnormalities to hormonal dysfunction in idiopathic infertility [23].

Male infertility is a multifactorial and polyetiological condition involving urologic, endocrine, and genetic factors, underscoring the need for comprehensive evaluation beyond semen analysis. Detailed diagnostic workups enable tailored treatment strategies and identification of concomitant conditions affecting patient quality of life [24]. This study highlights key distinguishing features between fertile and infertile men that may guide personalized diagnostic and therapeutic approaches in cases of idiopathic infertility.

Conclusions

Our study underscores the complex and multifactorial nature of male infertility, By integrating clinical, biochemical, hormonal, genetic, and imaging parameters, we demonstrate that several underlying contributors, such as obesity, vitamin D deficiency, oxidative stress, and testicular asymmetry, are often present even in the absence of overt pathology. These findings support the necessity of expanding routine diagnostic protocols beyond basic semen analysis to include targeted evaluation of metabolic, hormonal, and genetic factors. Multidimensional approach not only refines the diagnostic process but also opens avenues for more personalized and potentially effective interventions in male infertility management.

Declaration of interests

The authors declare that they have no conflicts of interest.

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