

Article

Hormonal Profiles and Y Chromosome AZF Microdeletions in Moroccan Azoospermic Men: A Molecular and Endocrine Study

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Abstract

Background/Objectives: Y chromosome microdeletions in the azoospermia factor (AZF) regions are a major genetic cause of severe male infertility, yet their relationship with hormonal profiles in azoospermic men remains unclear. This study aimed to investigate AZF microdeletions and associated hormonal parameters in azoospermic patients. **Methods:** Azoospermic patients were screened for AZFa, AZFb, and AZFc microdeletions using multiplex real-time PCR targeting sequence-tagged site (STS) markers (sY84, sY127, and sY254). Patients were categorized into AZF-negative and AZF-positive groups, with the latter further stratified according to their deletion subtype. Serum follicle-stimulating hormone (FSH), testosterone, and inhibin B levels were measured. Hormonal parameters were compared between groups using the Mann–Whitney U test, and a logistic regression analysis was performed to evaluate associations between hormonal variables and AZF deletion status. **Results:** AZF microdeletions were detected in 18.7% (17/91) of patients. Patients without AZF deletions showed a median FSH level of 17.40 (7.12–31.27) IU/L. In contrast, AZFc deletion carriers exhibited an intermediate median FSH level of 21.10 (16.11–26.10) IU/L and lower median inhibin B concentrations (25.50 [25.25–26.00] pg/mL) compared with AZF-negative patients (56.00 [33.50–106.50] pg/mL). Median testosterone levels in AZFc patients (3.61 [2.87–4.35] ng/mL) remained within the expected physiological range. However, no statistically significant differences were observed between the AZF subgroups for age ($p = 0.262$), FSH ($p = 0.506$), testosterone ($p = 0.615$), or inhibin B ($p = 0.524$). The logistic regression analysis also showed no significant association between hormonal parameters and AZF deletion status. **Conclusions:** Hormonal parameters alone are insufficient to predict the presence of AZF microdeletions in azoospermic men. These findings highlight the importance of routine genetic screening for accurate diagnosis, clinical management, and reproductive counseling in male infertility.



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1. Introduction

Infertility represents a major global reproductive health concern, affecting approximately 10–15% of couples worldwide. Male factors contribute to nearly half of all infertility cases and may arise from a wide range of conditions, including endocrine disorders, anatomical abnormalities, environmental exposures, and genetic defects. Among these causes, severe spermatogenic failure leading to azoospermia represents one of the most challenging clinical forms of male infertility [1,2].

Genetic abnormalities are increasingly recognized as important contributors to male infertility. Among them, microdeletions within the azoospermia factor (AZF) regions of the Y chromosome constitute one of the most common molecular causes of severe spermatogenic impairment. These deletions occur in the long arm of the Y chromosome (Yq11) and involve genes that play essential roles in germ cell development and the regulation of spermatogenesis [3].

The AZF locus is classically divided into three major subregions: AZFa, AZFb, and AZFc. Each region contains genes involved in distinct stages of sperm production. Deletions in AZFa are generally associated with Sertoli cell-only syndrome, whereas AZFb deletions are typically linked to meiotic arrest. AZFc deletions are the most frequently reported and are associated with a broader spectrum of spermatogenic defects, ranging from severe oligozoospermia to complete azoospermia [2,3].

The prevalence of AZF microdeletions among infertile men varies widely between populations, with reported frequencies ranging from 2% to 15% [2,4]. Such variability may reflect differences in patient selection, genetic background, diagnostic approaches, and environmental factors. Despite the growing body of evidence worldwide, data regarding the prevalence and clinical significance of AZF microdeletions in North African populations remain limited [5,6].

In addition to genetic evaluation, hormonal assessment plays a key role in the clinical investigation of male infertility. Hormones such as follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, and inhibin B are essential regulators of testicular function and spermatogenesis. Alterations in these hormones often reflect underlying testicular dysfunction and may provide indirect information about spermatogenic activity. However, the relationship between AZF microdeletions and hormonal profiles remains incompletely understood, particularly in patients with non-obstructive azoospermia [1,7].

In Morocco, studies investigating the genetic basis of male infertility remain scarce, and few have explored the association between Y chromosome microdeletions and endocrine parameters. To date, only limited data have been reported, including a study by Rochdi et al. involving a relatively small cohort of patients [8].

Therefore, the aim of the present study was to investigate the prevalence of Y chromosome AZF microdeletions in Moroccan men with azoospermia and to evaluate their association with hormonal profiles in order to better characterize the endocrine features associated with genetic causes of spermatogenic failure.

2. Materials and Methods

2.1. Study Population

This study included male patients undergoing infertility evaluation at a specialized reproductive medicine center. All participants presented with confirmed azoospermia based on semen analysis and were referred for further hormonal and genetic investigations.

Clinical evaluation included a thorough medical history, physical examination, hormonal assessment, and molecular screening for Y chromosome microdeletions. Biological samples (semen and peripheral blood) were collected and processed according to standardized laboratory procedures. Prior to semen collection, patients were instructed to maintain sexual abstinence for 3–5 days.

2.2. Semen Analysis

Semen samples were evaluated for macroscopic and microscopic parameters following World Health Organization (WHO) guidelines. Azoospermia was confirmed using a computer-assisted semen analysis system (Sperm Class Analyzer, SCA) in combination with a Makler® counting chamber (both from Microptic, Barcelona, Spain).

2.3. Hormonal Analysis

Hormonal evaluation focused on parameters involved in the hypothalamic–pituitary–gonadal axis, including follicle-stimulating hormone (FSH), serum testosterone, and inhibin B.

Venous blood samples were collected in dry tubes, preferably in the morning to minimize circadian variation. Serum was obtained after centrifugation at $3000\times g$ for 20 min.

Hormone concentrations were measured using enzyme-linked immunosorbent assay (ELISA) kits (Human Biochemica und Diagnostica GmbH, Magdeburg-Gewerbegebiet Nord, Germany) according to the manufacturer's instructions. Analyses were performed using an automated immunoassay analyzer (COBAS 6000 system; Roche Diagnostics GmbH, Mannheim, Germany), and results were recorded automatically. Hormonal values were interpreted according to the reference ranges established by the laboratory for adult males: FSH (1.0–9.0 IU/L), LH (1–9 IU/L), and total testosterone (1.34–7.42 ng/mL).

2.4. DNA Extraction

Genomic DNA was isolated from peripheral blood specimens using the SaMag Blood DNA Extraction Kit on a SaMag automated instrument (Sacace Biotechnologies, Como, Italy) following the instructions provided by the manufacturer. DNA yield and quality were determined by spectrophotometric measurement at 260 nm. Sample purity was verified through the A260/A280 absorbance ratio, and values ranging from 1.8 to 2.0 were considered indicative of satisfactory DNA quality.

DNA integrity was further verified by agarose gel electrophoresis (1%), followed by visualization under UV illumination.

2.5. Y Chromosome Microdeletion Analysis

Y chromosome microdeletions within the azoospermia factor (AZF) regions (AZFa, AZFb, and AZFc) were investigated following established guidelines for Y chromosome microdeletion screening.

Multiplex real-time PCR was performed using a commercial detection kit (Sacace Biotechnologies, Como, Italy) according to the manufacturer's instructions to confirm Y chromosome microdeletions. Each AZF locus was detected using specific fluorescent channels: FAM channel for AZFa region (sY86/sY84), ROX channel for AZFb region (sY127/sY134), Cy5 channel for AZFc region (sY254/sY255), and JOE/HEX channel internal amplification control. The primer sequences used in the assay (5'–3') were as follows: sY84-F: AGAAGGGTCTGAAAGCAGGT and sY84-R: GCCTACCTGGAGGAGGCTTC; sY86-F: GTGACACACAGACTATGCTTC and sY86-R: ACACACAGAGGGACAACCTC; sY127-F: GGCTCACAACGAAAAAGAA and sY127-R: CTGCAGGCAGTAATAAGGGA; sY134-F: GTCTGCCTCACATACATTAGA and sY134-R: CTCTGTGACACTGAGGCAAC;

sY254-F: GGGTGTACCAGAAGGCAAA and sY254-R: GACCGTATCTACCAAAGCTGC; sY255-F: GTTCACATGAAGGGTGTTC and sY255-R: CTCGTCATGTGCAGGCAGGG. Internal control primers were ZFX/ZFY-F: ACCCTRCTGTACTGACTGTGATTACAC and ZFX/ZFY-R: GCACYCTTTGTTACTGACTCTAGTTYC, as well as SRY-F: CTCAGTTTC-CTCGCCTATGC and SRY-R: ACCCCTGGAAGCCTACAACCTGCAT.

Amplification and fluorescence detection were performed using a real-time PCR instrument, and results were interpreted according to the kit's analytical guidelines. The absence of amplification signals in specific channels indicated potential deletions in the corresponding AZF regions.

2.6. Statistical Analysis

All statistical processing and analyses were performed using Python programming language version 3.12.4 (Python Software Foundation, Wilmington, DE, USA; <https://www.python.org/>, accessed on 20 February 2026), employing the pandas, NumPy, and statsmodels libraries. The normality of continuous variables was assessed through the Shapiro–Wilk test. According to the distribution pattern, quantitative data were summarized either as mean $\pm$ standard deviation (SD) for normally distributed variables or as median with interquartile range (IQR) for non-normally distributed variables.

As several variables did not meet the assumptions of normality, the Mann–Whitney U test was used to compare hormonal parameters between patients with and without AZF microdeletions, whereas the Kruskal–Wallis test was applied to compare hormonal parameters among the different AZF microdeletion subtypes.

The associations between hormonal variables and AZF deletion status were evaluated using a binary logistic regression model, and the findings are presented as odds ratios (ORs) accompanied by their corresponding 95% confidence intervals (95% CIs). Statistical significance was established at a threshold of $p < 0.05$.

2.7. Ethical Consideration

All procedures were conducted in accordance with institutional ethical standards and the principles of the Declaration of Helsinki. The study was approved by the competent authorities of the Moroccan Ministry of Health under registration number N°1014/SAE/05/2023. Written informed consent was obtained from all participants prior to sample collection and inclusion in the study.

3. Results

3.1. Baseline Characteristics of the Study Population

A total of 91 azoospermic patients were included in the study. The mean age of the overall study population ($n = 91$) was 37.9 ± 6.8 years. Y chromosome AZF microdeletions were detected in 17 patients (18.7%), whereas 74 patients (81.3%) showed no detectable deletions.

Hormonal measurements were available for a subset of 68 patients. Among this subgroup, 14 patients presented AZF microdeletions, whereas 54 had no detectable deletion. Within the AZF-positive subgroup, AZFa deletions were the most frequent ($n = 5$), followed by AZFc deletions ($n = 4$), while an isolated AZFb deletion was observed in one patient. Combined deletions included AZFa+b ($n = 1$), AZFb+c ($n = 1$), and AZFa+b+c ($n = 2$) (Table 1). FSH and testosterone values were available for 68 patients, while inhibin B measurements were available for 33 patients. Elevated FSH levels were observed in the majority of patients, with approximately 69% presenting high FSH values, consistent with severe spermatogenic impairment in azoospermia. Testosterone concentrations were

predominantly within the normal range. Detailed baseline characteristics are presented in Table 1, which includes only patients with available FSH and testosterone data ($n = 68$).

Table 1. Baseline characteristics of azoospermic patients.

Variable	Total Population ($n = 68$)
Age (years), mean $\pm$ SD	38.1 $\pm$ 6.3
Type of AZF microdeletion, n (% of total)	
AZFa	5 (7.4%)
AZFb	1 (1.5%)
AZFc	4 (5.9%)
AZFa+b	1 (1.5%)
AZFb+c	1 (1.5%)
AZFa+b+c	2 (2.9%)
FSH (IU/L), median (IQR)	19.4 (7.2–32.0)
FSH classification, n (%), $n = 68$	
Low	2 (2.9%)
Normal	19 (27.9%)
High	47 (69.1%)
Testosterone (ng/mL), median (IQR)	5.1 (3.2–8.1)
Testosterone classification, n (%), $n = 68$	
Low	16 (23.5%)
Normal	42 (61.8%)
High	10 (14.7%)
Inhibin B (pg/mL), median (IQR)	56.0 (32.5–97.5)

Values are presented as mean $\pm$ standard deviation (SD) or median (interquartile range, IQR) for continuous variables and number (percentage) for categorical variables. FSH and testosterone measurements were available for 68 patients. Inhibin B measurements were available for 33 patients. AZF: azoospermia factor; IQR: interquartile range.

3.2. Baseline Characteristics According to AZF Deletion Status

Comparisons between patients with and without AZF microdeletions were performed among the 68 patients with available FSH and testosterone measurements (Table 2). No significant differences were observed between the two groups regarding age, FSH levels, or testosterone levels. Patients carrying AZF deletions tended to show higher median FSH levels and lower median testosterone levels, although these differences did not reach statistical significance.

Table 2. Baseline characteristics according to AZF deletion status.

Variable	No AZF Deletion ($n = 54$)	AZF Deletion ($n = 14$)	p -Value
Age (years), mean $\pm$ SD	38.1 $\pm$ 6.4	38.0 $\pm$ 6.0	0.944
FSH (IU/L), median (IQR)	17.40 (7.12–31.27)	25.1 (14.2–47.8)	0.292
Testosterone (ng/mL), median (IQR)	5.3 (3.2–8.3)	4.6 (2.7–5.3)	0.252

IQR: interquartile range. FSH and testosterone data were available for 68 patients. Comparisons were performed using the Mann–Whitney U test.

Inhibin B concentrations were available for 33 patients (Table 3). No significant difference was observed between patients with and without AZF microdeletions ($p = 0.345$). Nevertheless, patients carrying AZF deletions tended to exhibit lower inhibin B concentrations compared with non-deleted patients.

Table 3. Inhibin B concentrations according to AZF deletion status.

Variable	No AZF Deletion	AZF Deletion	p-Value
Inhibin B (pg/mL), median (IQR)	56.0 (33.5–106.5)	51.5 (28.5–73.8)	0.345

IQR: interquartile range. Inhibin B data were available for 33 patients. Comparisons were performed using the Mann–Whitney U test.

To further evaluate the association between hormonal parameters and AZF deletion status, binary logistic regression analysis was performed (Table 4). None of the evaluated hormonal variables were significantly associated with AZF deletion status.

Table 4. Logistic regression analysis of factors associated with AZF deletion.

Variable	OR	95% CI	p-Value
FSH (IU/L)	0.986	0.935–1.039	0.589
Testosterone (ng/mL)	0.951	0.699–1.294	0.751
Inhibin B (pg/mL)	0.985	0.961–1.01	0.233

OR: odds ratio; CI: confidence interval. Odds ratios and 95% confidence intervals were estimated using logistic regression analysis. No statistically significant association was observed between AZF deletion and the studied hormonal parameters ($p > 0.05$).

3.3. Hormonal Characteristics According to AZF Deletion Subtype

The hormonal distribution according to AZF deletion subtype is summarized in Table 5. Patients without AZF deletions showed a median FSH level of 17.40 (7.12–31.27), consistent with severe spermatogenic impairment in azoospermic individuals.

Table 5. Hormonal characteristics according to AZF microdeletion subtype.

Group	n	Age (Years)	FSH (IU/L)	Testosterone (ng/mL)	Inhibin B (pg/mL)
No AZF deletion	54	38.13 ± 6.37	17.40 (7.12–31.27)	5.34 (3.25–8.32)	56.00 (33.50–106.50)
AZF _a	5	40.80 ± 3.63	28.10 (5.50–54.30)	5.12 (2.15–11.40)	36.00 (24.00–56.00)
AZF _b	1	33.00	5.80	3.59	–
AZF _c	4	40.25 ± 6.55	22.60 (17.40–26.30)	3.40 (2.62–4.39)	26.00
AZF _a +b	1	31.00	23.70	8.12	87.00
AZF _b +c	1	26.00	78.00	2.98	–
AZF _a +b+c	2	38.50 ± 3.54	52.55 (38.33–66.78)	5.22 (5.17–5.27)	67.00
p-value		0.262	0.506	0.615	0.524

Values are expressed as mean ± SD for age and median (IQR) for hormonal parameters. Hormonal variables were compared using the Kruskal–Wallis test. Results from subgroups with very small sample sizes ($n \leq 2$) should be interpreted with caution.

Patients with AZF_c deletions exhibited an intermediate hormonal profile relative to other deletion groups. Their median FSH level (21.10 [16.11–26.10] IU/L) was lower than that observed in AZF_a deletion carriers (25.10 [16.95–42.70] IU/L) and substantially lower than in the AZF_b+c deletion case (78.00 IU/L). Median inhibin B levels were reduced in AZF_c carriers (25.50 [25.25–26.00] pg/mL) compared with patients without deletions (56.00 [33.50–106.50] pg/mL), which may suggest reduced Sertoli cell function.

Median testosterone concentrations in AZF_c patients (3.61 [2.87–4.35] ng/mL) were lower than those observed in patients without deletions, although values remained within the physiological reference range.

Despite these observed trends, statistical comparisons between AZF subgroups did not reveal significant differences for age ($p = 0.262$), FSH ($p = 0.506$), testosterone ($p = 0.615$), or inhibin B ($p = 0.524$).

4. Discussion

The present study investigated the relationship between hormonal parameters and Y chromosome microdeletions in a cohort composed exclusively of azoospermic men. Because azoospermia represents the most severe form of spermatogenic failure, the hormonal profile observed in this population provides important insights into the endocrine consequences of testicular dysfunction.

4.1. Hormonal Profiles and AZF Microdeletions

Previous studies have suggested that Y chromosome microdeletions can influence male hormonal physiology, particularly affecting FSH, LH, and testosterone levels [3,6]. For instance, combined AZFb+c+d deletions have been associated with markedly elevated FSH levels, reflecting severe impairment of spermatogenesis [9,10]. These hormonal alterations are thought to result from disrupted testicular function and altered feedback mechanisms within the hypothalamic–pituitary–gonadal axis [11].

In our cohort, no statistically significant association was observed between hormonal parameters (FSH, testosterone, and inhibin B) and the presence of AZF microdeletions. This is consistent with several previous studies [11,12] and may be explained by the relatively homogeneous endocrine profile observed in azoospermic men, in whom FSH is often elevated irrespective of genetic status. However, non-significant trends were observed, including higher FSH levels and lower inhibin B concentrations in patients with AZF deletions, particularly AZFa carriers. These findings suggest a possible gradient of testicular dysfunction, although the heterogeneity of the data and small subgroup sizes limit definitive conclusions [13,14].

4.2. Hormonal Patterns According to AZF Deletion Subtype

Subgroup analysis revealed distinct hormonal patterns according to AZF deletion subtype. Patients with AZFc deletions showed a non-significant trend toward higher FSH levels and reduced inhibin B concentrations compared with non-deleted individuals, suggesting impaired but heterogeneous spermatogenic activity. In contrast, AZFa deletions tended to be associated with higher FSH levels, although this difference did not reach statistical significance, likely due to the small sample size; this finding is consistent with previous reports linking AZFa deletions to severe testicular phenotypes, including Sertoli cell-only syndrome [3,15]. The heterogeneity observed among AZFc carriers is in line with previous reports indicating a broad spectrum of spermatogenic phenotypes, with possible residual focal spermatogenesis [10,16].

4.3. Prevalence of AZF Microdeletions

The overall prevalence of AZF microdeletions in our cohort (18.7% (17/91)) is consistent with previously reported frequencies in azoospermic populations, typically ranging from 10% to 20% [8,17,18]. This supports the robustness of our cohort selection and reflects the expected enrichment of genetic abnormalities in non-obstructive azoospermia.

4.4. Clinical Implications for Genetic and Hormonal Evaluation

From a clinical perspective, identification of AZF deletion subtypes remains essential for reproductive prognosis. In our cohort, patients with AZF deletions showed a non-significant elevation of FSH levels, again highlighting the limited utility of hormonal markers alone in predicting genetic status [11]. Although AZF subtypes have been reported in the literature to be associated with different degrees of spermatogenic impairment, such outcome-based parameters were not assessed in the present study [9,16]. These findings are

consistent with previous reports indicating that hormonal evaluation alone cannot reliably distinguish between patients with or without AZF microdeletions.

Therefore, AZF genetic screening remains essential in the diagnostic work-up of azoospermic patients, and an integrated approach combining clinical assessment, hormonal profiling, and genetic testing is recommended for accurate etiological classification and patient counseling [19].

4.5. Strengths and Study Limitations

This study benefits from the inclusion of a clinically well-defined cohort restricted to azoospermic men, providing a robust model of advanced spermatogenic failure and minimizing phenotypic heterogeneity. The integration of hormonal profiling with molecular screening for Y chromosome microdeletions enhances translational relevance by linking endocrine alterations to underlying genetic defects. In addition, the use of standardized laboratory procedures and validated PCR-based assays strengthens the internal validity and reproducibility of the findings.

Nevertheless, several limitations must be acknowledged. The relatively small number of AZF-positive cases, combined with limited subgroup sizes across deletion types, reduces statistical power and may obscure clinically meaningful associations. The incomplete availability of inhibin B data further limits the comprehensive assessment of Sertoli cell function. Moreover, the cross-sectional design restricts the analysis to associative observations, precluding causal inference. The absence of standardized testicular volume measurements also represents an important limitation. Since testicular volume is closely associated with the pituitary–gonadal axis [19], the lack of these data limited the evaluation of volume–hormone phenotypes. Finally, the absence of histopathological correlation and longitudinal reproductive outcomes limits the clinical applicability of the findings, particularly regarding the prediction of sperm retrieval success.

Future research should prioritize larger, well-stratified cohorts integrating detailed genetic subtypes, comprehensive hormonal profiling, standardized testicular volume assessment, and histopathological as well as longitudinal clinical outcomes to better elucidate the complex interplay between AZF microdeletions and testicular function.

5. Conclusions

In this cohort of azoospermic men, hormonal parameters including FSH, testosterone, and inhibin B were not significantly associated with the presence of Y chromosome AZF microdeletions. Although patients with AZFc deletions exhibited hormonal patterns consistent with impaired spermatogenesis, endocrine markers alone were insufficient to predict genetic abnormalities.

These findings highlight the importance of routine molecular screening for AZF microdeletions in the diagnostic evaluation of severe male infertility. Overall, our results support the use of an integrated diagnostic approach combining hormonal assessment with genetic testing to improve etiological diagnosis and patient counseling in azoospermia.

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Abbreviations

The following abbreviations are used in this manuscript:

AZF	Azoospermia factor
AZFa	Azoospermia factor a region
AZFb	Azoospermia factor b region
AZFc	Azoospermia factor c region
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
FSH	Follicle-stimulating hormone
IQR	Interquartile range
LH	Luteinizing hormone
OR	Odds ratio
PCR	Polymerase chain reaction
SD	Standard deviation
SCA	Sperm class analyzer

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