Unraveling biochemical hypogonadism in men with nonobstructive azoospermia: insights, discrepancies, and future avenues

Nonobstructive azoospermia (NOA), characterized by the absence of sperm in semen due to spermatogenic failure, is a concern for 5%–15% of men seeking help for infertility, accounting for approximately 60% of all men with azoospermia (1). A comprehensive assessment should aim to identify genetic factors, treatable causes, and associated conditions, such as hypogonadism (1). Additionally, the evaluation of men with NOA should look for physical signs, such as gynecomastia, small testes, lack of secondary sexual characteristics, or any signs of hormonal imbalance, that could suggest an underlying cause (1). Moreover, men with NOA may have concurrent biochemical hypogonadism, defined as a total testosterone (T) concentration of <300 ng/dL, suggesting possible Leydig cell insufficiency, pituitary insufficiency, or a combination of the two (2–4). In men who have NOA in addition to biochemical hypogonadism, there might be a decrease in intratesticular testosterone (ITT) concentrations that can impair spermatogenesis (5). In a recent study, Achermann et al. (2) investigated the prevalence of biochemical hypogonadism in a cohort of 767 consecutive patients with normogonadotropic or hypergonadotropic NOA. It is important to note that the investigators excluded men with any identifiable genetic cause of NOA. Patients were then segregated into those considered eugonadal (19.2%) vs. those defined as hypogonadal (80.8%). A T cutoff of 350 ng/dL was used. Upon analyzing the study data, it was evident that among men with biochemical hypogonadism, a substantial number likely had luteinizing hormone (LH) levels <8 IU/L, indicating secondary hypogonadism (pituitary insufficiency), while a smaller proportion likely had LH levels >8 IU/L, suggesting primary hypogonadism (testicular insufficiency) (2). The median LH level for patients with biochemical hypogonadism was 6.2 IU/L, with an interquartile range of 5.0–8.9 IU/L, indicating that 50% of the patients fell within that range. Given the upper limit of the interquartile range, it is reasonable to infer that most patients had LH levels <8 IU/L, indicative of secondary hypogonadism, thus pituitary insufficiency (2). In this context, men with secondary hypogonadism can be eligible for medical therapies such as selective estrogen receptor modulators (SERMs) and human chorionic gonadotropin (hCG), whereas men with primary hypogonadism (high LH level) will likely not benefit from SERMs and hCG unless their T-to-estradiol (E) ratio is abnormal (estrogen blockers would be a potential therapy if this was identified) (3). As such, a considerable proportion of men with NOA in the hypogonadal group would have been considered eligible for SERM and hCG therapy. Furthermore, important differences were detected between the men with low T concentration and men with eugonadal status. On the one hand, as expected, hypogonadal men had significantly lower testicular volume; lower baseline serum levels of E, T, and free T; and a lower T-to-E ratio (2). On the other hand, they had higher baseline serum levels of follicle-stimulating hormone and LH (2). Notably, testicular histopathology was also documented, showing that hypogonadal patients had higher rates of Sertoli cell–only syndrome or hypospermatogenesis, compared to eugonadal patients, who exhibited spermatogenic maturation arrest more often, suggesting that presence of germ cells would suggest appropriate Leydig cell function. Furthermore, the sperm retrieval (SR) rates varied across groups, with the highest being in normogonadotropic eugonadal patients at 63.1% (2). The investigators concluded that their study demonstrated a significant prevalence of biochemical hypogonadism, affecting approximately 80% of men with NOA seeking medical help for infertility (2). This high prevalence can be explained by factors such as testicular volume, E levels, paternal age, testicular histopathology, and possibly ethnicity. Similarly, other studies have investigated the hypogonadism prevalence rates among patients with NOA. For instance, Bobjer et al. (4) analyzed 65 men with NOA and revealed that 40% of these individuals exhibited T levels lower than the threshold of 10 nmol/L. However, the investigators' inclusion of patients with Klinefelter syndrome and other genetic abnormalities in their cohort makes their results difficult to compare with those of the study by Achermann et al. (2). Reifsnyder et al. (3) investigated the impact of preoperative medical therapy on men with NOA undergoing microdissection testicular sperm extraction. Their study included 736 men with NOA, 47% of whom had initial T levels <300 ng/dL. They observed higher serum follicle-stimulating hormone levels and a greater proportion of patients with Klinefelter syndrome among men with low T levels (3). Moreover, among men with hypogonadal NOA, testicular spermatozoa were retrieved in 52% of cases (3). Interestingly, there were no significant differences in clinical pregnancy rates, live birth rates, or SR rates between patients with low T levels and those with normal levels, regardless of whether the men with low T levels were treated or not. Furthermore, no differences were observed in testicular histology between eugonadal and hypogonadal patients (3). These findings contrast with those of Achermann et al. (2), who reported higher rates of Sertoli cell–only syndrome or hypospermatogenesis in patients with hypogonadal NOA, suggesting that those with biochemical hypogonadism have higher rates of spermatogenic failure than men with eugonadal NOA (3).

Because ITT is crucial for spermatogenesis and difficult to measure, we have proposed serum 17-hydroxyprogesterone (17-OHP) as a reliable biomarker for ITT status (5). In this context, the findings of Lima et al. (5) support using serum 17-OHP as a reliable indicator of ITT levels. Future research on hypogonadism rates in men with NOA should consider evaluating 17-OHP as a reliable marker for ITT and spermatogenesis status. Taken together, these studies highlight the need for more extensive research on the prevalence and characteristics of hypogonadal men with NOA. The study by Achermann et al. (2) stands out owing to its large and homogeneous cohort of

patients with NOA without genetically determined causes that could have biased the results of previous studies. Their research reveals a significant prevalence of hypogonadal NOA, with 80% of patients with NOA exhibiting T levels <350 ng/dL. It is worth noting that the choice of the 350 ng/dL cutoff might be influencing this high prevalence. Interestingly, had the investigators opted for a 300 ng/dL cutoff, their findings would have been more closely paralleled with the hypogonadal rates reported in previous studies involving men with NOA. Now that the prevalence of biochemical hypogonadism is more established, future clinical studies should focus on whether treating it with medications such as SERMs, estrogen blockers (anastrozole), and/or hCG would improve chances of sperm appearing in the ejaculate or chances of surgical SR. Overall, the findings of Achermann et al. (2) remain important because they provide a clearer understanding of the differences between eugonadal and hypogonadal men with NOA and stimulate additional research in the field.

CRediT Authorship Contribution Statement

Edoardo Pozzi: Conceptualization, Writing – original draft, Writing – review & editing. **Ranjith Ramasamy:** Supervision.

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