Brief Report

Endocrinological Testicular Dysfunction in Patients with Lepromatous Leprosy and the Impact of Disease on Patient's Quality of Life

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Abstract

Introduction: Leprosy or Hansen's disease poses a drastic impact on the quality of life in affected patients even after successful completion of treatment. The involvement of the endocrine system in leprosy is usually insidious, silent, and under-reported, especially the testicular dysfunction. **Aims and Objectives:** The present study was aimed at evaluating the abnormalities of the primary testicular hormone testosterone and the gonadotrophins LH and FSH in male patients affected with lepromatous leprosy and assessing the impact of the disease on quality of life (QOL). **Materials and Methods:** The study included 43 married male patients diagnosed with lepromatous leprosy. Careful history taking and examination for symptoms of testicular dysfunction were done. Serum concentrations of total testosterone, FSH, and LH were noted. The QOL was evaluated using the WHO Quality of Life-BREF (WHOQoL-BREF). **Results:** The most common clinical manifestation of testicular dysfunction was reduced or loss of libido reported in 12 (27.9%) patients followed by gynaecomastia in 7 (16.3%). Ultrasonographic (USG) analysis revealed reduced testicular volume in 31 (72.1%) patients, and average testicular volume was 11.9 ± 4.9 mL each. Seventeen (39.5%) patients had low serum testosterone levels, 9 (20.9%) had high serum FSH level, and 11 (25.6%) high LH levels. There was a significant negative correlation between testosterone level and FSH as well as LH. There was also a significantly positive correlation between testicular volume and testosterone level. Symptomatic patients with gynaecomastia/gynaecothelia had higher hormonal derangement than those who had other symptoms. On QOL, most patients scored lowest on the domain of "social relationships" (including sexual wellbeing) followed by "psychological health". **Conclusion:** We found a high rate of USG diagnosed testicular atrophy in lepromatous leprosy patients. Therefore, every leprosy patient should be thoroughly examined clinically to rule out features of testicular dysfunction. Testicular function tests should be routinely carried out in all leprosy patients to arrive at an early diagnosis. Leprosy is found to affect all domains of a patient's quality of life.

Keywords: *Hansen's disease, leprosy, testicular dysfunction, quality of life, WHOQOL-BREF*

Introduction

Hansen's disease or Leprosy is a chronic granulomatous and slowly progressive infectious disease, with high rates of disability, which poses a drastic impact on quality of life (QOL) in affected patients even after successful completion of treatment.[1]

Although primarily a disease of the skin and peripheral nerves, leprosy can involve almost any organ of the body. The most commonly involved internal organs include testes, eyes, bones, and lymph nodes.[2]

Testes can get involved in leprosy in following manners: a) by direct invasion of *Mycobacterium leprae*, b) by immune-system mediated destruction, and c) by repeated attacks of epididymal-orchitis during type 2 lepra reaction.[3] Almost all multibacillary patients harbor *Mycobacterium leprae* in their testes due to its lower temperature.[4,5] Testes are favored by *Mycobacterium leprae* owing to their lower temperature.[5] Testicular atrophy is the shrinkage of testes secondary to inflammation or direct invasion leading to a decrease in testicular volume.[6,7] The involvement of seminiferous tubules and Leydig cells leads to an isolated rise in luteinizing hormone (LH) or follicle-stimulating hormone (FSH).[8] Deficient testosterone production causes sexual dysfunction, infertility, and increased risk of osteoporosis and skeletal fracture.

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While male gonadal involvement in leprosy is a well-recognized entity, there is still a dearth of data assessing the underlying hormonal imbalance and consequent sexual dysfunctions, and its impact on QOL in the Indian population.[9-11]

We aimed at evaluating the abnormalities of the primary testicular hormone testosterone and gonadotrophins LH and FSH in male patients affected with lepromatous leprosy and assessing the impact of the disease on patients' QOL using the World Health Organization Quality of life-BREF (WHOQOL-BREF).[12]

Materials and Methods

This cross-sectional, observational study was conducted in our dermatology, venereology, and leprology outpatient department between October 2017 and January 2020.

The study included 43 married male patients aged 18–59 years, diagnosed with lepromatous leprosy based on clinical presentation, clinical tests, histopathological analysis, and slit skin smear examination. The patients were either newly diagnosed, already on treatment, or released from treatment. Unmarried patients or those with comorbidities like diabetes, renal or hepatic dysfunction, tuberculosis, immunosuppression, etc., were excluded. Additionally, patients with traumatic, surgical, or congenital testicular abnormalities were also excluded.

A careful history taking in the form of physical examination, external genital examination, clinical tests, lab investigations, and ultrasonography (USG) examination of testes was done. The patient details were recorded in a proforma. The family and personal history of patients, loss of libido, and erectile dysfunction were noted after building rapport with the patient. Disease-related parameters like disease duration, bacteriological index at diagnosis, history of type 2 lepra reaction, grading of disability as well treatment history were noted. Detailed testicular examination and assessment of density and presence or absence of androgen-dependent hair growth pattern on pubic and axillary areas as well as gynaecomastia (breast enlargement) and gynaecothelia (enlargement of nipple areola complex) was done.

The battery of lab investigations apart from routine investigations included specific hormonal profiles to assess testicular function. Serum concentrations of total testosterone, FSH, and LH were recorded. For the estimation of serum total testosterone, LH, and FSH chemiluminescent immunoassay was used. Normal ranges of total testosterone, FSH, and LH were noted as 6–7.5 ng/mL, 2–20 IU/L, and 1.8–8.4 IU/L, respectively. Ultrasonographic (USG) analysis of testicular volume was done as follows: normal testicular volume- ≥15 mL; testicular atrophy- <15 mL each.

The World Health Organization Quality of life BREF (WHOQoL-BREF) questionnaire:[12]

The quality of life of patients was evaluated using the WHOQoL-BREF Hindi-validated questionnaire, after taking formal approval from the developers, assessing the perception of the patient in the last 2 weeks. It involved four domains, namely physical health, psychological health, social relationships, and environment. The domains of psychological health and social relations were modified according to the symptoms of testicular dysfunction.

Following score interpretation was employed: score ≤45, low QOL; 46 to 65, moderate QOL; and score >65, relatively high QOL.

Ethical considerations

All the male patients gave their written informed consent to be a part of the study. Additionally, due approval was also obtained from the institutional ethical board before initiating the study. Permission was obtained to use the Hindi-validated version of WHOQoL BREF.

Statistical analysis

Statistical analysis of the data was done using SPSS version 19. Mean and standard deviation (SD) were used to find the distribution of the continuous numbers while proportion or percentages were used for qualitative variables. *r*-value for correlation and *t*-test along with T value were used as required. $P < 0.05$ was considered statistically significant.

Results

This study included 43 married male patients between the ages of 18 and 59. The mean age of patients was 34.1 ± 11.2 years. Thirty-one (72.1%) patients have had children before the onset of disease. The mean duration of illness was 3.4 ± 2.1 years (range-6 months to 10 years). Sixteen (37.2%) patients had ≥5 bacteriological index (BI). Eleven (34.4%) patients gave a history of symptoms consistent with orchitis, either during the episodes of erythema nodosum leprosum (ENL) or anytime after the onset of disease. The baseline parameters of study participants have been tabulated in Table 1.

USG analysis revealed reduced testicular volume in 31 (72.1%) patients while the average testicular volume was 11.9 ± 4.9 mL each. On lab investigation, the mean serum total testosterone level was 6.14 ± 0.95 ng/mL, with a low testosterone level in 17 (39.5%) patients. The mean FSH and LH levels were 12.43 ± 13.52 IU/L and 11.50 ± 7.99 IU/L, respectively. While 9 (20.9%) patients had high serum FSH levels, 11 (25.6%) patients had high LH levels. Out of the total 43 patients, 21 (48.8%) had a normal hormonal profile while 4 patients had normal testosterone with high FSH, 3 had normal testosterone and elevated LH level [Table 2]. There was a significantly negative correlation of total testosterone level with FSH as well as LH, i.e., FSH and LH rose linearly with fall in

level of testosterone [FSH vs Testosterone *r* score = -0.36, *P* value = 0.018; LH vs Testosterone *r* score = -0.39, *P* value = 0.009] [Figures 1 and 2]. Similarly, FSH and LH were also significantly positively correlated (*r* score = 0.49, *P* value <0.001) [Figure 3].

There was also a significantly positive correlation between testicular volume and serum total testosterone levels (*r* value = 0.57, *P* value <0.001) [Figure 4].

Clinical manifestations of reduced testicular volume were seen in 20 (46.5%) patients with some patients having more than one manifestation. The most common clinical manifestation was reduced or loss of libido reported in 12 (27.9%) patients. While 7 (16.3%) patients had both gynaecomastia [Figure 5a] and gynaecothelia, in 3 (6.9%) patients only gynaecothelia [Figure 5b] was observed. However, 1 (2.3%) study subject, aged 41 years also reported erectile dysfunction. One (2.3%) patient had female pattern of pubic hair [Figure 5c]. Infiltration or nodular lesions on genitalia were seen in 8 (18.6%) patients [Figure 5d and e].

Table 1: Demographic profile, disease duration, status of type 2 reactions, and disability grading of patients

	Number of patients
Age Distribution (In Years)	
18-37	29 (67.4%)
38-57	13 (30.2%)
≥58	1 (2.4%)
Mean age	34.1±11.2 years
Disease Duration (In Years)	
<1	5 (11.6%)
≤5	30 (69.8%)
>5	8 (18.6%)
History Of ENL	
Absent	11 (25.6%)
Present	32 (74.4%)
History Of Orchitis	
Present	11 (25.6%)
Absent	32 (74.4%)
Grading Of Disability	
Grade 0	6 (13.9%)
Grade 1	18 (41.9%)
Grade 2	19 (44.2%)

Table 2: Hormone profile of study participants

Hormonal Profile	Number of Patients (%)
Serum Testosterone	
Normal	26 (60.5%)
Decreased	17 (39.5%)
Serum FSH	
Normal	34 (79.1%)
Elevated	9 (20.9%)
Serum LH	
Normal	32 (74.4%)
Elevated	11 (25.6%)

While comparing these symptomatic patients, those with gynaecomastia and gynaecothelia (*n* = 10) had higher mean levels of FSH (15.3 IU/L) and LH (16.4 IU/L) and a slightly lower level of mean testosterone (5.79 ng/mL), than who had other symptoms (*n* = 10) [FSH-13.9 IU/L, LH-14.5 IU/L and Testosterone-5.67 ng/mL), although statistically insignificant.

WHOQoL-BREF scoring

Most patients scored lowest on the two domains specific for testicular dysfunction, i.e.: "social relationships" with a low QOL in 30 (69.7%) patients, followed by the domain of "psychological health" in 24 (55.8%) patients. However,

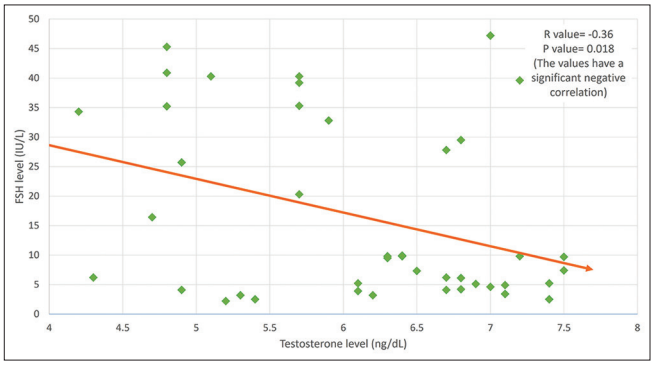

Figure 1: Statistically significant negative correlation of total testosterone level with FSH (*r* score = -0.36, *P* value = 0.018)

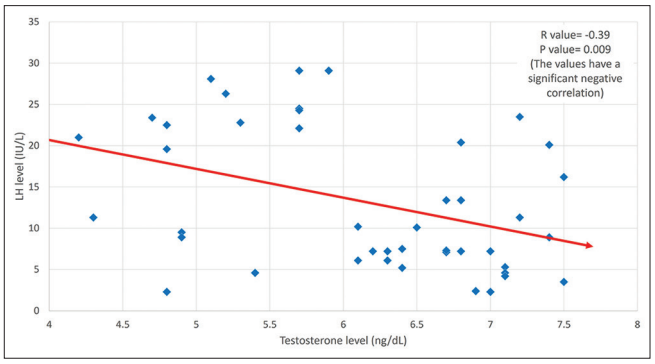

Figure 2: Statistically significant negative correlation of total testosterone level with LH (*r* score = -0.39, *P* value = 0.009)

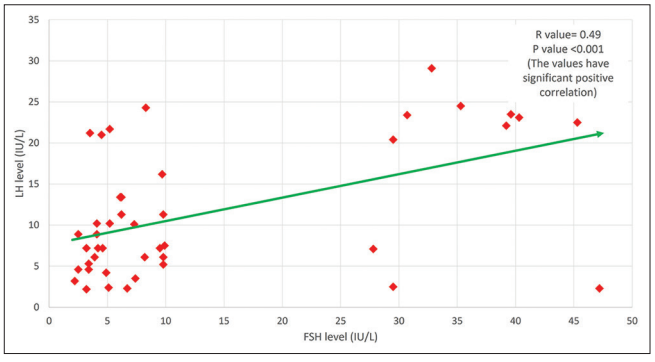

Figure 3: Statistically significant positive correlation of FSH with LH (*r* score = 0.49, *P* value <0.001)

overall only 13 (30.2%) and 11 (25.6%) patients had a low QOL in domains of physical health and environment [Figure 6].

The patients were divided into two groups: group A-with symptoms of testicular dysfunction (n = 20), and group B-without symptoms of testicular dysfunction (n = 23). There was a significant difference between the scores of 3 out of four domains amongst patients of both groups, namely social well-being, psychological, and physical health. Patients in group A scored significantly low on domains of physical health, psychological health, and social relations [Figure 7]. Under the domain of social well-being, the mean scores of groups A and B were 34.7 ± 17.7 and 49.7 ± 19.9, respectively (P value = 0.007). The component of conjugal relations had the lowest scorefollowed by sexual activity while social support was only mildly affected. In the domain of psychological health the most severe effect was seen on the perception of bodily image, namely breast enlargement and shrinking of testicles followed by self-esteem and feelings (group A-37.5 ± 16.3; group B-58.3 ± 22.5; P value-0.001). The physical health scores of group A and B were 51.4 ± 21.8 and 64.3 ± 12.6, respectively (P value = 0.011). However, there was a statistically nonsignificant difference between scores of environment domain amongst the two groups (group A-63.6 ± 13.2; group B-65.9 ± 19.2; P value-0.332).

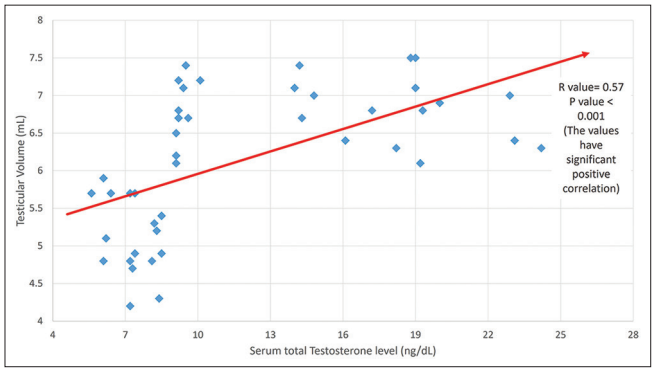

Figure 4: Statistically significant positive correlation between testicular volume and serum total testosterone levels (r value = 0.57, P value <0.001)

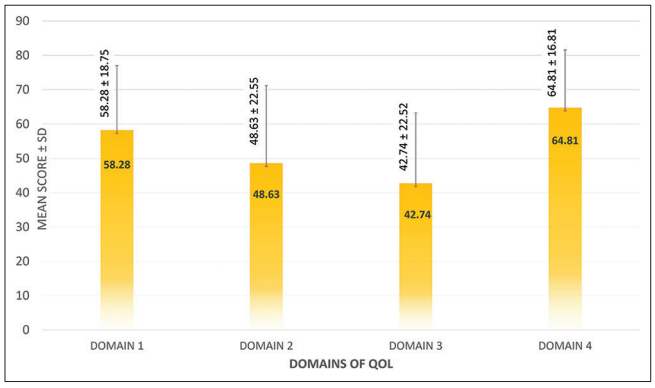

Figure 6: Mean score and standard deviation of patients for the four domains of WHOQOL-BREF

Discussion

The involvement of testes in leprosy was reported for the first time in 1952 by Grabstald and Swan.[2] In our study, 39.5% of patients had a low testosterone level. While 9 (20.9%) patients had high serum FSH levels and 11 (25.6%) patients had high LH levels. These findings were in close approximation with the studies conducted by Gunawan *et al*.,[2] Hasan *et al*.,[13] and Abd-Elkawi *et al*.[14] to name a few.

In our study, we found that 31 (72.1%) patients had a reduction in their testicular volume. Various studies in the past have reported testicular atrophy in 51%–93.75% patients.[2,15] There was also a negative correlation between disease duration and testicular volume. Testicular atrophy is attributed to disease duration, BI, delay in seeking treatment, severity, and degree of testicular inflammation resulting from lepra reactions.[14,15]

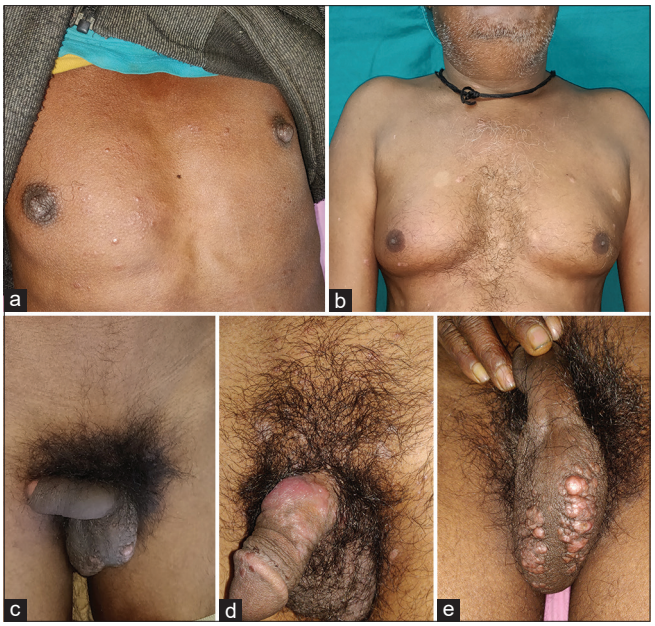

Figure 5: Clinical features of testicular dysfunction (clockwise from top left) (a) Gynaecothelia, (b) Gynacomastia, (c) Female pattern of pubic hair growth with testicular atrophy, (d) Infiltration of penis with testicular atrophy, (e) Nodular leprosy lesions of scrotum

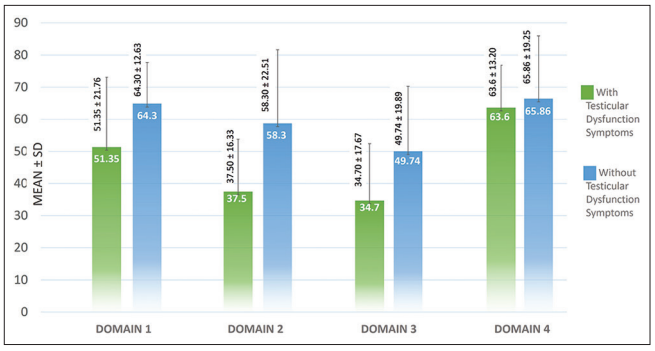

Figure 7: Mean score and standard deviation of patients between groups A and B for the four domains of WHOQOL-BREF

Another interesting finding of our study was a significant correlation between testicular volume (calculated using ultrasonography) and serum testosterone level. Out of the 31 patients who had testicular atrophy, 9 had ENL attacks in the past. During acute episodes of type 2 reaction, the sudden influx of inflammatory infiltrates with edema in the granuloma can also result in a sudden testicular hypofunction. Patients with history of recurrent type 2 reaction (n = 8) had higher rate of testicular atrophy (n = 8, 18.6%).

The histological events in testicular tissue during leprosy were classified by Grabstald *et al*.[16] into 3 stages, i.e., vascular (active orchitis), interstitial, and obliterative. Initially, there is testicular pain and swelling, which gradually changes to the typical picture of chronic epididymal-orchitis with firm to hard testes in a few cases. However, in most cases these events stay silent with testes getting soft, followed by a reduction in volume, and eventually testicular atrophy sets in.[5] In such chronic cases, the fertility is said to get significantly low. In these cases, histology is consistent with the presence of a lepromatous granuloma.

In leprosy, the infiltrates involve both the seminiferous tubules (exocrine part) and interstitial cells (endocrine part). However, the seminiferous tubules get involved early, whereas the involvement of interstitial cells (Leydig cells), which produce testosterone, sets in late. Exocrine atrophy leads to aspermatogenesis manifesting with sterility and change in secondary sexual characters, like the female pattern of pubic hair but without loss of sexual potency. Although in untreated cases over the course of time, the Leydig cells leads to reduction in testosterone causing impotence and erectile dysfunction.[14,17,18]

A study by Migam *et al*.[6] had observed sexual dysfunctions in 56.6% of patients. Our findings were in accordance with them with symptoms of testicular dysfunction in 46.5% of patients.

Generally, the testicular atrophy occurs bilaterally and the observations of our study were no exception. All our cases had bilateral atrophy (n = 31). After 40 years of age the production of the most important androgen in males, testosterone, reduces by about 1% per year due to physiological testicular atrophy with increasing age while the levels of FSH and LH increase due to loss of negative feedback as a consequence of a reduction in testosterone secretion.[19] Damage to the Leydig cells manifests as an increase in LH levels.[5] In our study 17 (39.5%) had low testosterone levels, although 3 (6.9%) had only high LH levels with normal testosterone levels. An isolated rise in LH with normal testosterone generally occurs in case of only mild Leydig cell destruction indicating an early onset testicular atrophy.[2,19]

Similarly, the sertoli cells of seminiferous tubules produce inhibin, which inhibits mammotropic hormone and FSH.[20] Loss of this negative feedback causes a rise in FSH production. The consequence of this unchecked rise is gynaecomastia and gynaecothelia.[16] Over the years the rate of gynaecomastia in lepromatous leprosy (LL) cases has been reported to range from 6.25% to 27%.[2,14,15] Ten (23.3%) patients in our study had either gynaecomastia or gynaecothelia or both.

Leprosy is perhaps the most stigmatized dermatosis owing to the external physical appearance of patients. It poses a great impact on patients' QOL as reported by a handful of studies in the past.[9-11]

We made similar observation in our study. Most of the patients scored the lowest on the domain of social relationships (including sexual wellbeing) followed by the domain of psychological health and physical health [Figure 6]. The scores were higher in patients with a long duration of disease and a history of recurrent ENL.

On a detailed analysis of WHOQoL-BREF, there was a staggeringly significant difference in the domain of social relationships between patients with symptoms of testicular dysfunction and patients without any such symptoms (P-value 0.007). These symptomatic patients also scored significantly low on domains of physical health and psychological health [Figure 7].

QOL is one aspect of leprosy, which has just recently been addressed. Apart from the social and physical burden, our study also found a significant toll of the disease on patient's sexual wellbeing and the impact of disease in causing conjugal tensions. Such patients must be counseled and educated about the nature of the disease. The National Leprosy Eradication Program, India, is one such program, which has devised the much-needed strategies to deal with the taboo attached to the disease and focuses on providing the information, education, and communication activities to the diseased and their families.[21]

To the best of our knowledge, our study is the first of its kind to assess the parameters of testicular involvement and estimating the impact of the same on QOL of lepromatous leprosy patients in the Indian population simultaneously. However, our study was limited by small sample size, absence of a control group, lack of semen analysis, or evaluation of secondary infertility in study participants. Though there is still a dearth of data on testicular atrophy in leprosy patients, our study could prove to be a useful tool for studies to come in the future.

Conclusion

We found a high rate of testicular atrophy in lepromatous leprosy patients with a high percentage of symptomatic patients. Factors like ENL, disease duration, and degree of testicular involvement were found to contribute to testicular dysfunction. Therefore, every leprosy patient should be thoroughly examined clinically for the involvement of

testes, breasts, and androgen-dependent areas of hair growth. Testicular function tests should be routinely carried out in all leprosy patients. We also found that leprosy poses a significant effect on a patient's QOL and these psychological factors should be carefully considered when treating a patient with leprosy infection.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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