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Association between male sex hormones and tramadol abuse

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Abstract

Background: Tramadol dependence is prevalent across Egypt. The allegation that it can improve sexual function is the main reason for its popularity among young men. This study aims to determine the serum level of testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) in tramadol abusers.

Results: Serum testosterone (5.18 ± 1.95) and LH (7.79 ± 1.63) of abusers showed highly significant lower levels than control subjects, while FSH showed no significant difference between abusers and controls. There was no significant difference of hormonal levels in subjects according to the duration of abuse and dose of tramadol.

Conclusions: The results indicate that tramadol abuse causes a pronounced lowering of testosterone and LH levels that is not correlated to the duration of abuse and dose of tramadol.

Keywords: Tramadol, Abuse, Sex hormones, Testosterone, FSH, LH

Background

Tramadol dependence is becoming an increasingly worrying epidemic in Egypt. Because of its accessibility and low cost, tramadol abuse is frequent. In addition, unintentional tramadol abuse media advertising in movies and TV shows had a significant influence in promoting tramadol abuse. Tramadol's reputation as a safe substance stemming from its medicinal use also plays a major role in its abuse [35]. Tramadol is an opioid analgesic that plays a critical role in the treatment of acute and chronic pain, yet it has the potential to be abused because it boosts the reward system [7].

Tramadol is a centrally acting analgesic that has both an opioid and non-opioid component to its effect. It is an opioid receptor agonist that also inhibits serotonin and norepinephrine absorption, increasing the inhibitory effects on pain transmission in the spinal cord. It is used to alleviate pain that ranges from mild to severe [46]. Headache, dizziness, somnolence, nausea, constipation, sweating, itching, and central nervous system stimulation have all been recorded as tramadol adverse effects [31]. Tramadol has a wide tissue distribution and a low plasma protein binding (20%). It is mostly excreted through the liver (where it is converted to O-desmethyl tramadol and N-desmethyl tramadol) and somewhat through the kidney (up to 30% of dose). O-desmethyl tramadol binds to opioid receptors far more strongly than the parent drug, making it a more potent analgesic. The active components' half-lives range from 4.5 to 9.5 h, and tramadol's total plasma elimination rate is relatively high (600 ml/min). Because tramadol has little effect on the disposition of other medications, its interaction potential is deemed negligible [33].

Despite the fact that tramadol appears to have a low risk for abuse, there has been evidence of abuse and withdrawal. Repeated tramadol administration may cause toxic metabolite accumulation, raise the possibility of pharmacokinetic interactions, and/or reduce tramadol elimination, all of which increase the drug's toxicity potential [50]. Chronic tramadol use has been linked to problems with male reproductive tissues. Safarinejad

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et al. [45], for example, found severe reproductive toxicity, such as increased sperm DNA damage caused by testicular oxidative damage.

Despite the fact that tramadol is recommended for the treatment of premature ejaculation and is commonly used by teenagers for sustained libido, an experimental subacute toxicity study found that tramadol has no significant contributory effects on libido but does cause changes in sex hormone levels and alters pituitary-hypothalamus feedback regulation [40]. Tramadol use has also been linked to sperm quality issues, hyperprolactinemia, and hypergonadotropic hypogonadism [23]. The supposed benefits of tramadol in improving premature ejaculation and increasing sexual satisfaction have contributed to its popularity and widespread use, particularly among Egyptian young people [1]. Tramadol has recently gained favor as an erotic drug among young guys [46].

Other abused drugs have been documented to have detrimental effects on male fertility, and alcohol and drug abuse have been linked to negative impacts on male health in recent years [49]. Cannabis has a deleterious impact on male fertility at numerous points along the road. It is been linked to alterations in reproductive hormones, changed sperm parameters, and lower desire and sexual performance [41].

According to Grover et al. [26], males who drink alcohol have lower gonadotropin levels, testicular shrinkage, and lower testosterone and sperm production, all of which might affect fertility. The aim of the current work is to determine the serum level of testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) in tramadol abusers admitted to Addiction Management Unit of Neurology and Psychiatry Hospital at Assiut University.

Methods

Study design

This case-control study was conducted on 67 male tramadol abusers and 67 male healthy non-abusers as a control group. The sample size was calculated using the Epi Info 2000 statistical package.

Patients

Patients' inclusion criteria

Sixty-seven male inpatients who had been dependent for at least 1 year and who were seeking therapy at the Addiction Management Unit of the Neurology and Psychiatry Hospital at Assiut University

Patients' exclusion criteria

a) Patients with a history of previous renal impairment
b) Patients with a history of hepatitis B/C or HIV infection
c) Patients with a history of autoimmune disease
d) Patients with a history of congenital heart disease
e) Patients with other mental disorders
f) Patients with primary fertility

Ethical considerations

An informed written consent was obtained from each patient or from his parents for inclusion in the study. The confidentiality of all data in this study was protected to the fullest extent possible. All ethical aspects related to research at Assiut University were implicated in this study after the approval of the ethical committee.

Methods

Sociodemographic data and history of drug abuse

Patients were subjected to history taking through fulfilling a modified questionnaire of drug dependence [27].

- Sociodemographic data: included age, occupation, residence, educational level, marital status, birth order, number of family members, and family history of substance abuse
- The history of drug abuse is as follows:
- Type of abused drug
- Method of intake
- History of starting drug abuse
- Duration

Clinical examination

Examination of the abusers was carried out at the time of presentation to the hospital, including a general and systemic examination.

Laboratory investigations

- Sex hormonal assays: LH, FSH, and testosterone
- Sample collection: Five milliliters of venous blood was collected from each subject and transferred into a clean, conical centrifuge tube with no anticoagulant. After the blood sample was centrifuged, the serum was separated and stored at −20 °C to be used for estimation of the serum levels of LH, FSH, and testosterone by using the immunoassay method [38] by the Maglumi 800 (fully automated, random access, immunoassay analyzer).

Kits

- Testosterone was measured by a competitive immunoluminometric assay technique using the MAGLUMI testosterone (CLI) kit with a catalogue number (130202010M) from Shenzhen New Industries Biomedical Engineering Company [30].
- LH was measured by sandwich immunoluminometric assay technique using the MAGLUMI LH (CLIA) kit with a catalogue number (130202002M) from Shenzhen New Industries Biomedical Engineering Company [37].
- FSH was measured by a sandwich immunoluminometric assay technique using the MAGLUMI FSH (CLIA) kit with a catalogue number (130202001M) from Shenzhen New Industries Biomedical Engineering Company [24].

Statistical analysis

Statistical analysis was conducted using the SPSS program version 22. Descriptive statistics were expressed in the form of frequencies, means, and SD, Pearson chi-square, independent sample *T*-test, and Spearman's correlation. A significant *p*-value was considered when it was less than 0.05 and highly significant when it was less than 0.01.

Results

Demographic findings

The age of tramadol abusers ($n = 67$) ranged from 15 to 55 years, with a mean±SD equals 30.46 ± 6.14 years, which was compared with the control age ranged from 16 to 54 with a mean±SD of 29.5 ± 7.6 ($n = 67$). The mean age of starting substance abuse was 21.24 ± 5.9 years (Table 1). Most of the abusers were in the middle age group (25 < 35), which represented 56.7%. Regarding their occupation, nearly two-thirds of them)58.2%(were free workers. As regards residence distribution, 64.2% of them were rural residents. Nearly half of the abusers (46.3%) were technical school graduates, while university graduates and illiterates represent 31.3% and 7.5%, respectively. Married people represented 59.7% of abusers, while singles, divorced, and separated persons represented 32.8%, 6%, and 1.5%, respectively. The largest proportion (43.3%) of abusers was the youngest siblings, while the middle and eldest siblings represented 35.8% and 20.9%. Most of abusers (71.64%) belonged to large families (formed of 5 < 10 members). Furthermore, the majority of abusers (46.3%) lived with non-extended families, while 44.8% lived with extended families and 8.9% lived alone. Regarding duration of abuse, 1 to less than 5 years represented 22.4% while (5 < 10), (10 < 15), and (15–20) represented 32.8%, 26.9%, and 17.9%, respectively. More than half of abusers (52.2%) had a positive family history (Tables 2 and 3).

Table 1 The mean age of tramadol abusers and control subjects and mean ages for onset of abuse

	Mean±SD (years) (minimum-maximum)
Age of abusers (*N* = 67)	30.46 ± 6.14 (15–55)
Age of control subjects (*N* = 67)	29.5 ± 7.6 (16–54)
Age of onset of substance abuse	21.24 ± 5.9

Abusers were classified into tramadol only ($n = 26$), which had a mean age of onset ±*SD* of 23.65 ± 5.46, while multiple substance abusers ($n = 41$) had 19.80 ± 5.75 years. Tramadol and cannabis were the most prevalent combination of polysubstance abuse, 25.37% of them (Tables 4 and 5). Less than a quarter of abusers (20.9%) used injection as a method for substance administration (Table 6).

Analysis of sex hormones in abusers and controls showed highly significant lower levels of testosterone and LH in abusers, while FSH levels showed no significant difference between abusers and controls (Table 7). No significant difference was revealed between the testosterone, LH, and FSH levels of tramadol abusers and multiple substance abusers (Table 8).

Table 9 shows that there was no significant relation between the duration of abuse and levels of testosterone, LH, and FSH. Table 10 shows that there was no significant relation between the number of tramadol tablets taken daily by tramadol abusers and levels of testosterone, LH, and FSH.

Discussion

Due to the quickly developing and changing pattern of substance usage in Egypt, addiction is a big issue [28]. Tramadol is a commonly abused narcotic, particularly among the young and middle aged [47].

The current study is a case-control study involving 67 tramadol male abusers hospitalized to Assiut University Hospital between January 1 and June 30, 2017, and 67 healthy male non-abusers. The abusers' average age was30.46 ± 6.14 years, and more than half of them (56.7%) were between the ages of 25 and 35. This finding was similar to another study done by Maruf et al. [36] in Dhaka, Bangladesh, which found that about half of the abusers (50.5%) were between the ages of 21 and 30, while about a quarter were between the ages of 31 and 40. This could be explained by the fact that persons over the age of 40 are not frequently exposed to new medications

Table 2 Age distribution and sociodemographic characteristics of the studied tramadol abusers

	Number $N = 67$	Percentage (%)
Age categories (years)		
15 < 25	11	16.4%
25 < 35	38	56.7%
35 < 45	17	25.4%
45 < 55	1	1.5%
Occupation		
Free work	39	58.2%
Government employee	12	17.9%
Do not work	11	16.4%
Student	5	7.5%
Residence		
Rural	43	64.2%
Urban	24	35.8%
Educational level		
Secondary technical	31	46.3%
University	21	31.3%
Illiterate	5	7.5%
Preparatory	5	7.5%
Secondary general	3	4.5%
Primary	2	2.9%
Marital status		
Married	40	59.7%
Single	22	32.8%
Divorced	4	6%
Separated	1	1.5%
Birth order in the family		
The oldest	14	20.9%
In the middle	24	35.8%
The youngest	29	43.3%
Number of family members		
1 < 5	15	22.39%
5 < 10	48	71.64%
≥ 10	4	5.97%
Family structure		
Living alone	6	8.9%
Non-extended family	31	46.3%
Extended family	30	44.8%
Duration of abuse		
(1 < 5)	15	22.4%
(5 < 10)	22	32.8%
(10 < 15)	18	26.9%
(15–20)	12	17.9%

in the same way that young people are [53]. Furthermore, young individuals are more prone to be active substance abusers and to be affected by substance abuse issues [54].

Table 3 Family history of substance abuse among the studied tramadol abusers

Family history of substance abuse	Number (percentage) $N = 67$
Yes	**35 (52.2%)**
No	**32 (47.8%)**

Table 4 Distribution of abused substance/substances among the studied tramadol abusers

Abuse substance	Number $N = 67$	Percentage (%)
Tramadol only	**26**	**38.81%**
Multiple substance abuse (tramadol with other substances)	**41**	**61.19%**
■ Tramadol and cannabis	17	25.37%
■ Tramadol, opium, and cannabis	8	11.94%
■ Tramadol and opium	7	10.45%
■ Tramadol and heroin	3	4.48%
■ Tramadol, cannabis, heroin, and benzodiazepine	4	5.97%
■ Tramadol, opium, cannabis, and heroin	1	1.49%
■ Tramadol, opium, cannabis	1	1.49%
■ Benzodiazepine and alcohol		

Table 5 Age of onset substance abuse among the studied abusers

Substance abuse	Age of onset (mean±SD)	*p*-value
Tramadol	23.65 ± 5.46	**0.008***
Tramadol and other substances	19.80 ± 5.75	

P-value (0.008) of independent *T*-test is significant

Table 6 Prevalence of injection of substance abuse among the studied abusers

Method of substance abuse	Number $N = 67$	Percentage (%)
Injection	14	20.9%
Noninjection)oral, inhalation)	53	79.1%

In the current study, the majority of abusers (58.2%) were unemployed. These findings were supported by Colpaert et al. [14], who stated that the high prevalence of substance abuse among free workers (e.g., mechanics and technicians) can be attributed to their lower education and socioeconomic status, as well as the relatively high income that is directed to substance use rather than other productive activities.

Table 7 The means of sex hormones among studied abusers compared to nonabusers

Sex hormone	Abusers $N = 67$	Nonabusers $N = 67$	*p*-value
Total testosterone (ng/ml)	5.18 ± 1.95	7.79 ± 1.63	0.002*
LH (m IU/ml)	4.67 ± 2.43	7.80 ± 1.99	0.003*
FSH (m IU/ml)	3.76 ± 2.82	3.28 ± 1.03	0.682

P-value (0.002 and 0.003) of independent *T*-test is statistically highly significant. *N* = number. Normal range for total testosterone (2.62–15.9 ng/ml), for LH (1.7–11.2 m IU/ml), for FSH (2.0–18.6m IU/ml)

Table 8 The means of sex hormones among tramadol-only abusers compared to tramadol and other substance abusers

Sex hormone	Tramadol only $N = 26$	Tramadol and other substances $N = 41$	*p*-value
Total testosterone (ng/ml)	4.62 ± 2.08	5.53 ± 1.97	0.06
LH (m IU/ml)	4.3 ± 2.77	4.9 ± 2.19	0.33
FSH (m IU/ml)	3.68 ± 2.55	3.8 ± 3.01	0.86

P-value of independent *T*-test < 0.05* is statistically significant. *N* = *number*. Normal range for total testosterone (2.62–15.9 ng/ml), for LH (1.7–11.2 m IU/ml), for FSH (2.0–18.6m IU/ml)

backgrounds were the least likely to use substances in Egypt, including Upper Egypt.

In terms of educational attainment, nearly half of the abusers (46.3%) were secondary-technical school graduates, with university graduates accounting for 31.3%. This conclusion matched a cross-sectional research of students from secondary or technical schools in Assiut province, which found that 11.6% of pupils tested positive for bango misuse [55]. In contrast to the current findings, a study conducted in Zagazig found no statistically significant link between substance abusers and their degree of education [39]. Another study in Damghan, Iran's Semnan region, found no link between tramadol addiction and academic performance [43].

In terms of marital status, married people made up 59.7% of the sample, while singles, divorced people, and separated people made up 32.8, 6, and 1.5%, respectively. The off-label usage of tramadol to improve premature ejaculation and increase sexual satisfaction could explain these findings [47]. Those findings are similar to those published by Dawood [17], who found that 49.2% of relapsed drug dependents in Baghdad were married, with the author attributing this to an inability to confront marital problems.

Table 9 The means of sex hormones in relation to duration of abuse

	cat1 (1 < 5) $n = 15$	cat2 (5 < 10) $n = 22$	cat3 (10 < 15) $n = 18$	cat4 (15–20) $n = 12$	*p*-value
Testosterone	5.47 ± 1.35	5.72 ± 1.92	4.78 ± 2.33	4.43 ± 1.85	0.210
LH	5.55 ± 2.49	4.71 ± 2.65	4.06 ± 1.87	4.43 ± 2.68	0.366
FSH	3.46 ± 1.41	3.71 ± 2.91	3.25 ± 2.47	4.99 ± 4.18	0.392

P-value of ANOVA test < 0.05* is statistically significant. *N* = number. Normal range for total testosterone (2.62–15.9 ng/ml), for LH (1.7–11.2 m IU/ml), for FSH (2.0–18.6 m IU/ml)

Table 10 The means of sex hormones in relation to the number of tramadol tablets taken daily by tramadol abusers

	cat1 (1–5) $n = 42$	cat2 (6–10) $n = 20$	cat3 (11–15) $n = 2$	cat4 (16–20) $n = 3$	*p*-value
Testosterone	5.07 ± 1.82	5.31 ± 2.40	5.13 ± 0.98	5.18 ± 0.26	0.978
LH	4.77 ± 2.23	4.80 ± 2.99	2.54 ± 0.02	3.37 ± 1.63	0.541
FSH	3.91 ± 2.90	3.54 ± 2.98	4.14 ± 1.32	3.51 ± 1.35	0.965

P-value of ANOVA test < 0.05* is statistically significant. *N* = number. Normal range for total testosterone (2.62–15.9 ng/ml), for LH (1.7–11.2 m IU/ml), for FSH (2.0–18.6 m IU/ml). One tablet of tramadol = 100 mg

The majority of abusers (64.2%) in the current study came from rural areas, while the rest came from metropolitan areas (35.8%). This may be due to the fact that rural populations make up 72.8% of the Assiut Governorate's population [21]. This was in contrast to Hamdi's [28] findings, which revealed that those from rural

In terms of conventional family structure, the biggest percentage of abusers (46.3%) lived with non-extended family, followed by 44.8% who lived with extended family and 8.9% who lived alone in the current study. This finding corroborated Dew et al. [18] findings, which

suggested that changes in conventional family structures and the weakening of parental connections may contribute to substance dependence. Furthermore, in most Arabic countries, most young adults live with their parents until they marry, and familial relationships are highly prized [25].

In this study, the youngest siblings accounted for nearly half of the abusers (43.3%), whereas the middle siblings and eldest siblings accounted for 35.8% and 20.9%, respectively. Last-born children had the highest risk of becoming drug dependents and are overrepresented in psychiatric populations, according to Eckstein and Kaufman [19]. This risk is explained by the fact that younger siblings are frequently reared as pampered children, robbing the youngster of his or her independence. Psychological dependence can lead to substance abuse, and older siblings may expose a later-born child to abused substances at a younger age [9].

The current study found that in 71.64% of cases, the number of family members were between 5 and 10. Due to the parents' inability to control their children, the size of the family plays an essential role as a risk factor for substance misuse [22]. Inept parenting exposes children to a variety of threats, including substance misuse and other crimes [3].

According to the findings, 52.2% of the participants had a positive family history of substance misuse. This could be due to adolescent maltreatment, which is prevalent solely because of family history [2].

Early initiation of substance misuse raises the chance of psychosocial issues in a variety of areas of life, including behavior, psychiatric disorders, family, peer relationships, and work adjustment [42]. The current investigation discovered a strong relationship between the average age of first substance abuse and the substance utilized. Single substance abusers (tramadol only) had a greater age (23.65 ± 5.46 years) than multiple substance abusers (19.80 ± 5.75 years). Early-onset substance abuse has been linked to a high rate of polysubstance misuse [52]. Injection was employed as a technique of abuse by 20.9% of abusers, according to our findings. By using needles and equipment previously used by others, injection is linked to greater rates of sickness and mortality, primarily due to bacterial, fungal, or viral infection [34].

One of the major areas of research around the world is the effects of drug dependence on sexual functioning and sex hormones [29]. In humans, opioids have been shown to lower testosterone levels [12]. Not all opioids have the same effect on testosterone levels; tramadol had no effect on plasma testosterone levels in rats [11]. In the current study, measurement of sex hormones in all subjects in the sample found that abusers had considerably lower testosterone and LH levels than non-abusers. There was no statistically significant difference in the mean value of FSH between abusers and non-abusers, on the other hand.

Opioids bind to specific receptors in the hypothalamus and pituitary gland, impair the pulsatile release of corticotrophin-releasing hormone and adrenocorticotropic hormone, and interfere with the generation of cortisol and androgen precursors, according to Auernhammer et al. [5]. Testosterone levels are also lowered as a result of direct testosterone production inhibition in the testes [15]. Chan et al. [13] further suggest that tramadol may cause adrenal insufficiency as a result of continuous use, which would explain the decrease in serum testosterone levels. Chronic tramadol administration causes considerable harm to testicular tissue, according to [4]. Tramadol has been shown to impact male reproductive hormones by lowering serum testosterone and gonadotrophins while raising estradiol and prolactin levels.

A case-control study conducted at Ain Shams University in Cairo, Egypt, to assess the effect of bhang and opium addiction on hypothalamic pituitary gonadal axis hormones found a significant decrease in serum total testosterone, FSH, LH, and prolactin in male addicts when compared to the control group [48]. In addition, a study on adult male Albino rats found that tramadol administration resulted in a considerable fall in testosterone levels, as well as a gradual decline in LH and FSH, as compared to the control group [56].

In tramadol-treated mice, Salah et al. [46] found a drop in blood testosterone, FSH, and LH levels as well as a rise in serum prolactin. Furthermore, long-term tramadol administration has been shown to have negative effects on sperm quality and testicular tissues in mice, with dose-dependent effects [6]. Both endogenous and exogenous opioids are known to cause hypogonadism via binding to opioid receptors in the hypothalamus and pituitary gland. This causes GnRH to be released less frequently, resulting in less LH and FSH being released from the pituitary and, as a result, less testosterone being produced [44].

An experimental investigation on laboratory rabbits, in contrast to the current study, found that tramadol administration resulted in a large drop in FSH while a considerable increase in LH. The effect of opioids on sex hormone release was found to be poorly understood, according to these experts [40].

The results of this investigation showed that there was no link between tramadol dependence and hormone decrease. Tramadol was found to significantly suppress testosterone, LH, and FSH in male rats after 20 and 30 days of therapy, corroborating the current findings [20]. Another study found a decrease in testosterone levels in male Sahel goats in Maiduguri, Nigeria, during the

first week of tramadol administration [8]. Caju [10] found that albino rats exposed to acute and chronic morphine dosages have less Sertoli and Leydig cells. In contrast to our findings, a case-control research conducted at Assiut University Hospital in Assiut, Egypt, to investigate the effect of tramadol dependence on sex hormones found a statistically significant link between the severity of male sex hormone reduction and the duration of tramadol misuse [16].

In contrast to our study, another case-control study conducted at Tanta University in Tanta, Egypt, to assess the impact of chronic tramadol administration on sexual functions in tramadol-dependent males found that as tramadol daily dose and duration increased, there was a significant decrease in serum testosterone and an increase in serum prolactin level [32], and other case-control study conducted at Benha University in Benha, Egypt, to determine the possible gonadotoxic effects of tramadol dependence on seminal fluid parameters, prolactin, and testosterone hormone levels revealed a significant increase in erectile dysfunction (ED) and decreased libido in the tramadol-dependent group. In addition, the serum testosterone level in this group was lower, although the serum prolactin level was significantly greater. Except for aberrant forms, which were high in the dependent group, all semen parameters were low in the dependent group. The preceding parameter became more negative when the tramadol dose was raised, whereas ED, libido, semen volume, and concentration remained the same. Increased tramadol treatment time was similarly associated with a worsening of these measures [51].

Conclusions

The present work revealed that tramadol abuse has possible adverse effects on male sex hormones that are poorly correlated to the addiction duration.

Abbreviations

FSH: Follicle-stimulating hormone; GnRH: Gonadotropin-releasing hormone; HIV: Human immunodeficiency virus; LH: Luteinizing hormone; N: Number; SD: Standard deviation.

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Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by SA and NZ. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All data are available on request.

Declarations

Ethics approval and consent to participate

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

Consent for publication

For all details relating to all patients, written informed consent for the publication of these details was obtained from these patients. The consent was for publication of their details under the Creative Commons Attribution License 4.0.

Competing interests

The authors declare that they have no competing interests.

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