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Original Article

Decreased serum leptin levels in male methamphetamine abusers during early abstinence: a cross-sectional study and analysis

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Abstract: Objectives: To examine the differences in serum leptin levels and other relevant factors between male methamphetamine (METH) abusers during early abstinence and healthy controls. Methods: Fifty-five male METH abusers less than 2 weeks after quitting and 50 male healthy controls were enrolled. Abstinence was confirmed by daily negative urine drug screening results. Baseline body data included age, BMI, current smoking, smoking amount, abdominal subcutaneous fat thickness (ASFT), current daily exercise consumption (CDEC), hemoglobin, fasting glucose, total cholesterol, triglyceride, thyrotropin concentrations and other neuroendocrine axis hormones levels. Among these hormones, total testosterone (TT), estradiol, prolactin, cortisol and adrenocorticotropic hormone (ACTH) were measured through chemiluminescent immunoassays, and epinephrine and norepinephrine were detected using radio immunoassay, and leptin was measured using enzyme-linked immunosorbent assays. Results: Compared with the healthy controls, the male METH abusers during early abstinence had lower ASFT, CDEC, leptin, and TT levels and increased daily smoking, estradiol, cortisol, ACTH, and prolactin levels. A nonparametric Spearman's correlation analysis showed that CDEC was positively correlated with serum leptin, but cortisol, ACTH, and norepinephrine were negatively correlated with leptin in male METH abusers. A multivariate stepwise regression analysis indicated that Ln-cortisol and CDEC were independently associated with Ln-leptin in male METH abusers during early abstinence and in the controls. Conclusions: Male METH abusers during early abstinence had low serum leptin, which was associated with their body activity states and specific hormones from the HPA axes. Decreased cortisol levels and HPA axis dysfunction might lead to reduced activity and decreased leptin levels.

Keywords: Methamphetamine, abstinence, leptin, relevant factors

Introduction

Methamphetamine (METH), an addictive psychostimulant used mainly by young people, can elicit negative life behavior alterations or mental disorders, such as short-term excitement, impulsivity, anorexia, autism, and depression [1-3]. These manifestations are closely related to the body's energy metabolism. A report demonstrated that METH exposure impairs glucose uptake and metabolism in human neurons and astrocytes, which presented as neuronal degeneration due to energy depletion [4]. Although energy metabolism was increased [5] and energy regulation in the brain was altered [6] after METH exposure in the model established by injecting METH intraperitoneally, the impact of METH abuse on biological metabolism in humans is poorly understood.

Leptin is an important regulatory factor that reflects the body's energy metabolism [7, 8], but little is known about serum leptin concentration in METH abusers. Previous rat experiments showed that the leptin receptor was present in the hippocampus and leptin exerted some effects on brain tissue neurons and the central nervous system [9-11]. Leptin might have a wide range of peripheral effects and regulate the energy metabolism of the body [12, 13]. A further study reported that METH can activate the hypothalamic-pituitary-adrenal (HPA) axis [14]. Based on these reports, we speculated that the alteration of serum leptin

levels in METH users might be related to stress and energy depletion. The underlying mechanism regarding the relationship among metabolism, energy depletion and hormone regulation in METH abusers has not yet been explored. Therefore, to better understand the potential correlation between leptin and hormonal alterations in the neuroendocrine axes, we conducted a cross-sectional study in male METH abusers during early abstinence.

Materials and methods

Subjects

Fifty-five male METH users between 18 and 40 years of age from the Drug Detoxification and Rehabilitation Center of Kunming were enrolled in a cross-sectional observational study during January 2017-March 2018. The eligibility criteria for male METH abusers to participate in the study were as follows: ① abusers were required to have abused METH (both individually and in combination) within a week before entering into the Drug Detoxification and Rehabilitation Center; and ② abusers were required to have taken METH drugs for more than six months previously. Most of the male METH abusers identified smoking as the primary route of METH administration. Positive urine test results were used for verifying recent METH usage during the initial enrollment period for the abusers, and abstinence was confirmed via daily urine testing and alcohol breath screening. The following exclusion criteria were applied for the enrollment of abusers during early abstinence as subjects in this study: ① past or current serious physical illness (such as liver diseases, renal illness, inflammatory diseases, cardiovascular disease, respiratory diseases, or unstable diabetes); ② metabolic disorders (such as diabetes mellitus, diabetic ketoacidosis, hyperglycemia hyperosmotic syndrome, hypoglycemia, gout, protein-energy malnutrition); ③ severe psychological or cognitive impairment. Specific drug treatment during the withdrawal stage is unnecessary in the treatment of amphetamine-dependent diseases [15]. Moreover, fifty healthy male volunteers were recruited into the center as control subjects from the local community. They had no history of addictive drug abuse, and their urine drug screening tests were negative throughout the study. The exclusion criteria were the same as the exclusion criteria for the male METH abusers.

The study was conducted according to the guidelines laid down in the Declaration of Helsinki, and the procedures were approved by the Yunnan Provincial Narcotics Control Commission. Written informed consent was obtained from all subjects.

Experimental procedures

This study used a cross-sectional observational design in which all the participants were evaluated for age, weight (kg), height (m), body mass index (BMI, kg/m^2), abdominal subcutaneous fat thickness (ASFT, mm), current daily exercise consumption (CDEC, kcal/day), current smoking condition (N%) and daily smoking amount (cigarettes/day). According to previous investigations, the early phase of abstinence was defined as less than 2 weeks after withdrawal [16-19]. The interval between the admission day (the day of urine drug screening) and the day of blood sampling was recorded as the post-abstinence days and must be less than 2 weeks in male METH abusers for early abstinence. All the subjects were able to move freely in the center and they could be monitored for calculating energy expenditure. We used ActiGraph activity monitor (ActiGraph wGT3X-BT, USA), which were worn on the wrist by the subjects 24 h a day, to record data for estimating activity energy expenditure. The raw data were analyzed using ActiLife software (ActiLife Mobile2.0.1).

Blood samples were drawn under fasting conditions between 8 a.m. and 10 a.m. to assay hemoglobin (g/L), fasting blood glucose (FBG, mmol/L), total cholesterol (TC, mmol/L), triglyceride (mmol/L), thyrotropin (mIU/L), leptin (ng/mL), total testosterone (TT, ng/mL), estradiol (pg/mL), prolactin (ng/mL), cortisol (nmol/L), adrenocorticotropic hormone (ACTH, pmol/L), epinephrine (pg/mL) and norepinephrine (pg/mL). TT, ACTH, prolactin, cortisol and estradiol were measured using chemiluminescent immunoassays (Elecsys Autoanalyzer, Roche Diagnostics, COBAS 6000). Epinephrine and norepinephrine were measured via radioimmunoassays from KingMed Diagnostics Co., Ltd. All the above assays were performed according to each manufacturer's instructions. With the exception of leptin, the other blood biochemical parameters were all measured in the clinical laboratory of the First Affiliated Hospital of Kunming Medical University or KingMed Diagnostics Co., Ltd.

Table 1. Baseline data characteristics of male METH abusers during early abstinence and the control subjects

	Abstinence (n=55)	Control (n=50)	*p*-value
Age (years)	26.67±5.344	26.00±3.891	0.460
BMI (kg/m^2)	22.01 (20.52-24.66)	23.16 (20.54-25.35)	0.367
Current smoking (N%)	50 (90.9%)	39 (78.0%)	0.101
Smoking amount (cigarette/day)	14 (12-16)	12 (9.5-15)	0.004
Hemoglobin (g/L)	149.64±17.093	148.84±16.416	0.809
ASFT (mm)	10.00 (9.00-11.00)	11 (10.00-12.25)	0.018
CDEC (kcal/day)	129.38±32.06	172.07±34.96	<0.001
Thyrotropin (mIU/L)	2.37 (1.59-3.16)	2.19 (1.57-3.05)	0.875
FBG (mmol/L)	4.78±0.66	4.81±0.61	0.774
TC (mmol/L)	4.33±0.903	4.55±0.965	0.229
Triglyceride (mmol/L)	1.31 (0.81-1.81)	1.26 (0.89-2.14)	0.369
Leptin (ng/mL)	3.29 (2.45-4.26)	4.20 (3.09-5.57)	0.002
TT (ng/mL)	3.58 (2.92-4.38)	4.36 (3.65-5.26)	0.001
Estradiol (pg/mL)	20.85 (16.28-31.21)	16.02 (9.57-25.42)	0.004
Prolactin (ng/mL)	22.57 (17.46-27.82)	19.52 (15.06-23.60)	0.014
Cortisol (nmol/L, 8:00 am)	273.48 (153.62-368.50)	183.64 (95.28-326.71)	0.009
ACTH (pmol/L, 8:00 am)	14.41±6.589	9.41±3.810	<0.001
Epinephrine (pg/mL)	46.42 (19.43-74.19)	45.46 (22.37-70.87)	0.800
Norepinephrine (pg/mL)	193.40 (84.65-324.48)	179.20 (122.87-273.77)	0.758

Values are expressed as the mean ± standard deviation, number (%), or median (Q1-Q3). ASFT: abdominal subcutaneous fat thickness; CDEC: current daily exercise consumption; FBG: fasting blood glucose; TC: total cholesterol; TT: total testosterone, ACTH: adrenocorticotropic hormone. Cortisol and ACTH were detected by blood draw at 8:00 am.

A human enzyme-linked immunosorbent assay (ELISA) kit (ab108879, Abcam, Cambridge, MA, USA) was used to detect serum leptin levels. According to the manufacturer's instructions, leptin antibody (500 ng/mL) was diluted and added to a 96-well microplate at 4°C for 12 h. The 96-well microplate was then blocked with 10% goat serum at 37°C for 2 h. Serum samples from the two groups (diluted 1/100 in PBS) were added to the 96-well microplate and incubated at 37°C for 2 h at a constant temperature. After washing with 0.3% PBST, goat anti-human IgG antibodies (diluted 1/10,000 in 0.05% PBST) were added and incubated at 37°C for 1 h. After rinsing with 0.3% PBST, 50 µl of tetramethylbenzidine (TMB)-A and 50 µl of TMB-B were each added to the 96-well microplate, and the plate was subsequently incubated in the dark at room temperature for 5 min. Finally, the reaction was terminated with 2 M H_2SO_4. The optical density was measured at 450 nm using a plate microplate reader (Multiskan MK3; Thermo Fisher Scientific). The serum leptin concentrations were obtained with a standard curve, fitted for the standard value and multiplied by the dilution factor.

For all the above assays, the intra-assay variation coefficient was below 10%, and the interassay variation coefficients were below 15%. All research procedures were approved by the Ethics Committee of the First Affiliated Hospital of Kunming Medical University.

Data statistical analyses

The descriptive statistics of the male METH abusers during early abstinence and the control subjects are presented as the mean and standard deviation for normally distributed variables or the median and quartile ranges for nonnormally distributed variables. The distribution of continuous variables was measured using Shapiro-Wilk's test. For the analyses of quantitative independent data, an independent sample t-test and the Mann–Whitney U-test were used on normal or nonnormal data distributions respectively. For the analyses of qualitative independent data, a chi-square test was used. A statistical comparison of each group was made using Student's *t*-test or Wilcoxon's test for normal or nonnormal data distribution. Spearman's correlation test and multiple step-

Table 2. Spearman's analysis of the correlation between serum leptin levels and other indicators in the two groups separately

Variables	Abstinence group (n=55)		Control group (n=50)	
	Spearman's correlation	*p*-value	Spearman's correlation	*p*-value
BMI	0.114	0.409	0.187	0.194
ASFT	0.035	0.797	0.493	<0.001
CDEC	0.606	<0.001	0.149	0.303
Smoking amount	-0.019	0.892	0.204	0.156
Thyrotropin	0.114	0.409	0.203	0.157
FBG	-0.059	0.668	-0.061	0.675
Hemoglobin	-0.046	0.737	-0.017	0.905
TC	0.067	0.625	0.229	0.109
Triglyceride	0.185	0.177	0.129	0.373
TT	0.264	0.052	0.048	0.740
Prolactin	-0.126	0.360	-0.113	0.433
Estradiol	-0.119	0.388	-0.154	0.285
Cortisol	-0.627	<0.001	-0.202	0.160
ACTH	-0.303	0.024	0.155	0.284
Epinephrine	-0.148	0.279	-0.196	0.172
Norepinephrine	-0.283	0.036	0.069	0.635

ASFT: abdominal subcutaneous fat thickness; CDEC: current daily exercise consumption; FBG: fasting blood glucose; TC: total cholesterol; TT: total testosterone, ACTH: adrenocorticotropic hormone. *P*<0.05 was considered to be statistically significant and *P*<0.001 was considered to be extremely statistically significant.

wise regression analysis were used to determine the correlations of serum leptin levels with influencing factors in two separate groups. *P*<0.05 was considered to indicate statistical significance. All statistics were performed using IBM SPSS Statistics (v. 23.0, Chicago, IL).

Results

Participants and blood biochemical parameters

Descriptive statistics of the male METH abusers during early abstinence and the control subjects were recorded as baseline demographic variables. No significant differences between the abstinent abusers and the control subjects with regard to age, BMI, current smoking condition, hemoglobin, thyrotropin, FBG, TC, triglyceride, epinephrine and norepinephrine (**Table 1**). ASFT, CDEC, leptin level and TT concentrations were lower in male METH abusers during their early abstinence than in the control subjects (*P*<0.05). The male METH abusers during their early abstinence had higher daily smoking, and higher cortisol, ACTH, estradiol and prolactin levels than the control group (*P*<0.05) (**Table 1**).

CDEC and cortisol correlated extremely significantly to leptin in the METH abstinence group

To explore potential correlations between serum leptin and the other indicators, we conducted separate nonparametric Spearman's correlation analyses of the two groups (**Table 2**). The analysis of the METH abstinence group revealed that various indicators, including cortisol, ACTH and norepinephrine, were negatively correlated with the serum leptin levels, and CDEC was positively correlated with the serum leptin levels. *P*<0.05 was considered statistically significant and the extremely significantly correlated indicators with leptin were CDEC and cortisol (*P*<0.001). In the control group, only ASFT was correlated with the serum leptin level (**Figure 1**).

Factors affecting serum leptin levels in the two groups separately

Because the value of serum leptin was not normally distributed, we used the natural logarithm of serum leptin (Ln-leptin) as a dependent variable and various other indicators as independent variables. Similarly, the values of some parameters, including BMI, ASFT, thyrotropin, triglyceride, TT, prolactin, estradiol, cortisol, ACTH, epinephrine and norepinephrine, were processed by natural logarithmic conversion (Ln-X). The multivariate stepwise regression analysis indicated that Ln-cortisol and CDEC were independent factors influencing Ln-leptin in male METH abusers during early abstinence and in the control group (**Table 3**). Using the interpretation of percent alteration in the results after natural logarithmic transformation, we can suggest that cortisol was an independent factor influencing leptin in the two groups.

Discussion

Our study demonstrated that compared with the control participants, male METH abusers

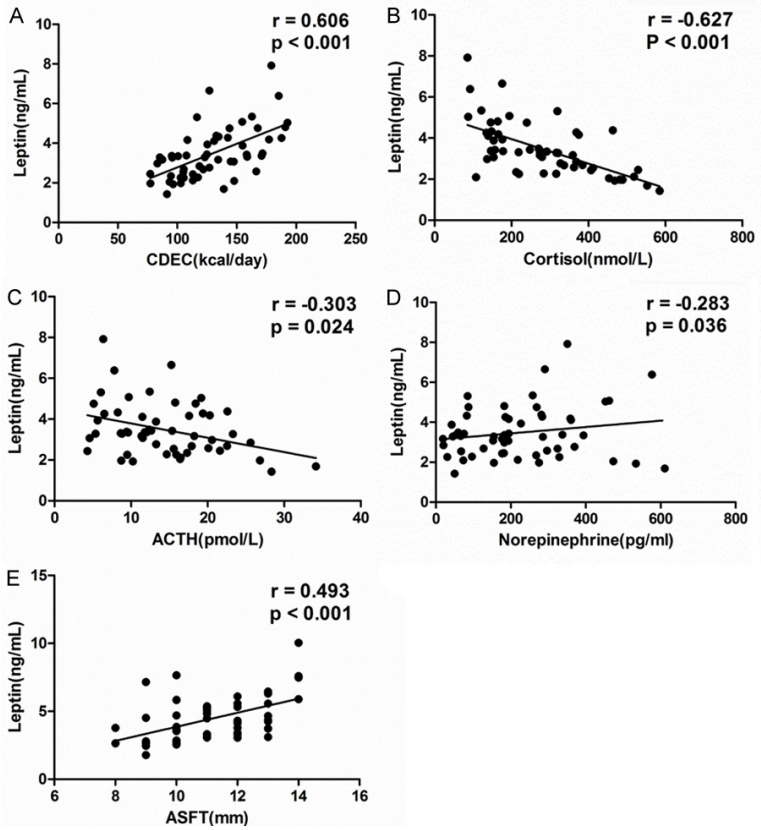

Figure 1. Correlation between serum leptin levels and other parameters. A. Correlation between serum leptin levels and CDEC in the abstinence group. B. Correlation between serum leptin levels and cortisol in the abstinence group. C. Correlation between serum leptin levels and ACTH in the abstinence group. D. Correlation between serum leptin levels and norepinephrine in the abstinence group. E. Correlation between serum leptin levels and ASFT in the control group. CDEC: current daily exercise consumption; ACTH: adrenocorticotropic hormone; ASFT: abdominal subcutaneous fat thickness.

during early abstinence showed significantly lower serum leptin levels, less subcutaneous fat, and less activity. These results indicated that METH abusers might exhibit a poor metabolic state during the early withdrawal period. Leptin is secreted by adipose tissue mainly from abdominal or subcutaneous fat [20]. Moreover, leptin is associated with fat metabolism and redistribution, reflecting metabolic changes in the body [21, 22]. METH is a powerful stimulant drug that increases synaptic levels of monoamine neurotransmitters [23], giving the abusers feelings of energy, confidence, euphoria, and improved attention, impulsivity, and aggressiveness [24]. METH abusers experience hyperactivity and perform repetitive actions [25], which results in excessive body energy consumption and fat mobilization and leads to the redistribution of subcutaneous fat and body fat [26]. As a result, low energy expenditure after excess energy consumption and decreased leptin levels were detected at the initiation of abstinence. According to our results, we hypothesized that the decreased serum leptin levels might reflect the body's energy metabolic state in the abstinence period because the major physiological function of leptin is to signal states of negative energy balance and decreased energy stores [27]. For male METH abusers during early abstinence, the serum leptin level appeared to undergo a progression from increasing to decreasing accompanied by energy expenditure.

METH exposure can have lasting effects on the HPA axis, a finding which is supported by a study concluding that the HPA axis-associated regions are affected by METH [28]. In a previous study, cortisol levels were shown to be elevated in abusers of METH [29]. Cortisol and norepinephrine are closely related to oxidative stress [30, 31], which is marked by a sustained release of cortisol [32]. In METH users during early abstinence, oxidative damage is still manifested with a high level of 8-hydroxy-2'-deoxyguanosine and does not normalize [33]. Therefore, high cortisol levels are maintained in male METH abusers during early abstinence due to oxidative stress. However, METH abusers can experience gradual fatigue and depression due to prolonged and increased strength activities. After considerable activities for METH abusers, the cortisol levels in abusers are elevated [34] and sustained to regulate the body's activities. Continuous high cortisol levels can contribute to depression and the inhibition of physical activity [35, 36]. Less physical activity was observed in male METH abusers during early abstinence in our study. Fatigue, depression and reduced activity are relevant to the dysfunction of the HPA axis and energy metabolism [37, 38]. Our results show that cortisol and

Table 3. Determinants of Ln-cortisol by multivariate stepwise regression analysis in the two groups separately

Parameters	B	Std.error	*t*	*p* value
Abstinence group				
Constant	2.575	0.614	4.196	<0.001
Ln-cortisol	-0.331	0.088	-3.779	<0.001
CDEC	0.003	0.001	2.354	0.022
Control group				
Constant	2.585	0.366	7.065	<0.001
Ln-cortisol	-0.310	0.048	-6.412	<0.001
CDEC	0.003	0.001	2.394	0.021

In the multivariate stepwise regression model in the two groups, Ln-BMI, Ln-ASFT, Ln-smoking amount, Ln-thyrotropin, fasting blood glucose, Hemoglobin, TC, Ln-triglyceride, Ln-TT, Ln-estradiol, Ln-prolactin, ACTH, Ln-epinephrine and Ln-norepinephrine were also included as covariates, but they were not independently associated with Ln-leptin. $P<0.05$ was considered significant. ASFT: abdominal subcutaneous fat thickness; CDEC: current daily exercise consumption.

CDEC are independent factors influencing leptin. It has long been known that cortisol is stimulated by ACTH. Although ACTH is negatively associated with leptin levels according to our data, the affecting factors did not include ACTH. Chronic use of METH might lead to a negative feedback regulation of cortisol to ACTH and dysfunction from the HPA axis after abstinence [39]. In METH abusers during early abstinence, inhibition of the HPA axis might result in decreased activity and low energy expenditure, accompanied by a reduction in leptin.

In addition to cortisol from the adrenal cortex, norepinephrine from the adrenal medulla is known to induce the formation of reactive oxygen species and is related to the progression of oxidative stress [40]. Moreover, a previous study showed that adrenergic agonists, particularly norepinephrine, play a suppressive role in leptin secretion [41] and leads to energy depletion [42]. These views are in accord with our results that the plasma NE levels are higher and significantly negatively correlated with serum leptin levels in male METH abusers during early abstinence. However, NE was not an independent factor affecting serum leptin in our results, which might be mainly related to the occurrence of acute stress without continuous secretion in chronic METH abusers.

A strong association between adipose tissue and the activity of the HPA axis has been reported [43]. Leptin is released by adipose tissue and simultaneously suppresses cortisol secretion during the stress-related activation of the adrenal axis [44], such as METH exposure. Interestingly, in the initial abstinence period, after the leptin release reduction, the inhibition of cortisol secretion cannot recover completely; thus, the level of cortisol might be low, which appears to be in contrast to our results. Even so, this might be consistent with the progression of energy expenditure from exhaustive activity to reduced activity or fatigue. Further study is needed to explore the alteration of cortisol levels throughout the abstinence period.

Although glandular hormones from the HPG axis, including TT, estradiol, and prolactin, changed in METH abusers during early abstinence compared with the control subjects, our results did not show a significant correlation between these hormones and leptin. There was reciprocal interaction between the HPG and HPA axes: hormones in the two secretory axes participate in the regulation of the function of the other axis at different levels [45]. The plasma luteinizing hormone levels, other than testosterone, had a significant effect on leptin release and might have an increased effect on plasma leptin [46]. Currently, there are few studies on testosterone affecting serum leptin levels. In addition, estrogen was found to upregulate the levels of leptin receptors in the arcuate nucleus and ventromedial nucleus in a rat model, which increased the sensitivity of the hypothalamus to leptin [47]. However, to date, there is no definitive study showing that male METH abusers have elevated or decreased estradiol levels in peripheral plasma. In fact, estrogen is an important modulator of energy balance, and estrogen deficiency causes increased feeding and reduced energy expenditure [48], similar to the function of leptin. In view of this, we consider that the above gonadotropins and leptin might affect energy metabolism and balance through different pathways.

Our study had several potential limitations: First, this study did not measure other hormones at different levels from neuroendocrine axes, such as luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which are disturbed by various factors, including the feedback effect of gonadal hormones; second, due

to the difficulty associated with surveying various observed populations and the confounding factors involved in the recovery process of abusers after withdrawal, we did not conduct a longitudinal follow-up at different times for measuring the biochemical indicators; third, the measurement time of all biochemical parameters, particularly ACTH and cortisol, was done between 8:00-10:00 am without the circadian rhythm to avoid other metabolic factors such as physical activities. Finally, our results cannot be generalized to female METH abusers owing to hormonal differences between the sexes.

The effect of leptin on energy homeostasis is two-way. When the body is in an energy-consuming state, fat is mobilized, and leptin secretion increases, which suppresses eating, and a reduced energy metabolism is thereby achieved to maintain the energy metabolism balance [49]. As a regulatory factor of energy metabolism, lower leptin levels were observed in METH abusers during early abstinence and served as an indicator for evaluating energy consumption and the metabolic state. The detection of serum leptin levels in these populations might endow a positive significance for the guidance of body recovery after withdrawal. The recognition that hormone regulation and low leptin levels existed in these populations after withdrawal is beneficial to our understanding the disorder of energy metabolism among METH abusers. Further, it provides new insight into the mechanisms underlying damage to the peripheral tissues due to METH abuse.

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Disclosure of conflict of interest

None.

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