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Correlation of Hypothyroidism with Polycystic Ovary Syndrome (PCOS): A Hospital-Based Cross-Sectional Study, Benha City, Egypt

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ABSTRACT

Background: The precise relationship between polycystic ovarian syndrome (PCOS) and thyroid gland function is still unknown. However, both conditions share a variety of symptoms, including obesity, menstrual irregularities, hirsutism, infertility, and insulin resistance.

Objectives: To find out the prevalence and the possible link between hypothyroidism and PCOS.

Patients and methods: Our study was conducted on 200 women for the presence or absence of PCO and hypothyroidism. Hormonal assay: (FSH, LH, TSH, FT3, FT4, testosterone) as well as fasting plasma glucose, HbA1c, TPO ab and thyroglobulin ab, HOMA – IR, Neck US, Pelvic-abdominal US were performed to all patients.

Results: Overt hypothyroid patients in PCOS group demonstrated significantly higher PCOS criteria, infertility than those with no hypothyroidism. PCOS patients in hypothyroid group had significantly higher testosterone (0.63 ±0.14 vs 0.39 ±0.05 ng/dl), TPO antibody (median = 489 vs 203 IU/ML), and TG antibody (362.5 vs. 98 IU/ML) than patients without PCOS. Our results revealed that insulin resistance is a common finding in both condition that is inferred from the following: Patients with hypothyroidism in PCOS group demonstrated significantly higher weight (94.6 ±22.8 vs. 80.3 ±20.5 kg), BMI (34.7 ±8 vs. 30.5 ±7.5), and waist circumference (101 ±15 vs. 94 ±15 cm). Meanwhile, in hypothyroidism group, PCOS patients had higher fasting plasma glucose (127 ±30 vs 88 ±17), HBA1C (6.32% ±0.95 vs 5.07% ±0.59), HOMA-IR (median = 3.05 vs 0.9).

Conclusion: There is an association between PCOS and hypothyroidism per se, neither related to the underlying etiology nor to clinical presentation.

Keywords: Hypothyroidism, PCOS, TSH, TPO ab. and TG ab, testosterone.

INTRODUCTION

About 5-10% of reproductive women are affected by PCOS, the most prevalent kind of persistent anovulation linked to an excess of androgen [1]. The 2003 Rotterdam ESHRE/ASRM updated consensus is currently used as the diagnostic standard for PCOS [2]. After ruling out alternative causes of anovulation and hyperandrogenism, at least two of the following criteria—chronic oligo/anovulation, clinical and/or biochemical evidence of hyperandrogenism, and the presence of polycystic ovaries on ultrasound—are necessary to make the diagnosis. The link between PCOS and hypothyroidism is receiving more attention. The most prevalent pathogenic hormone shortage is primary hypothyroidism, with overt and subclinical illness prevalences of 0.3% and 4.3%, respectively [3].

Anovulation and/or luteal phase defects lead to clinical symptoms such as irregular menstruation and decreased fertility [4]. Although the precise relationship between PCOS and thyroid function is still unknown, both conditions are difficult to diagnose because they share a number of symptoms, such as obesity, menstrual irregularities brought on by anovulation, acne, hirsutism, infertility, miscarriages, and carbohydrate intolerance in the form of insulin resistance. It has been shown that PCOS and hypothyroidism are related. The majority of the time, while examining PCOS for the first time, subclinical hypothyroidism is found [5].

It is plausible that a potential imbalance in thyroid function may cause, maintain, or exacerbate the PCOS symptoms based on the link between hypothyroidism, insulin resistance, and reproductive diseases. Our aim was to assess the prevalence of hypothyroidism in women with polycystic ovary disease and to determine the prevalence of polycystic ovary in women with hypothyroidism. We also aimed to explore the possible link and associated pathogenic mechanism between hypothyroidism and polycystic ovary.

SUBJECTS AND METHODS

This cross-sectional study was conducted at Benha University Hospital. It comprised 200 female subjects of 18-40 years old. Participants were divided into two groups; one group constituted 100 women with PCOS (participants were assessed for the presence or absence of true hypothyroidism) and another group containing 100 with true hypothyroidism (participants were assessed for the presence or absence of PCOS). Diagnosed PCOS subjects were recognized in the outpatient clinic of gynecology and obstetrics, while hypothyroid patients were recognized in the outpatient clinic of endocrinology. Females were categorized as PCOS as per Rotterdam criteria 2003 [2].

Age < 18 years and > 40 years, known cases of congenital adrenal hyperplasia, pregnant and lactating patients, and any patient receiving hormonal therapy were excluded. Data recruited from each participant included; Age, marital status, a history of infertility (either primary or secondary), menstrual history, including any history of oligomenorrhea, irregular periods, or amenorrhea, and any prior sonographic

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examinations that had shown PCOS. Body mass index (BMI) was computed using anthropometric measures.

The body mass index (BMI) thresholds for obesity and overweight in this study were ≥30kg/m^2 and ≥25kg/m^2, respectively. The modified Ferriman-Gallwey (FG) score was used to determine hirsutism; a score of 8 or below was utilised as the diagnostic threshold [6].

Normal references values of biochemical features were as follows; serum fasting glucose (70–100 mg/dl), HbA1c (4–5.6%), TSH (0.35–4.94 mIU/L), free T4 (fT4) (0.89–1.76 ng/dl), fT3 (2.3–4.2 pg/ml), TgAb (0–100 IU/mL), TPO ab (0–35 IU/mL), FSH (1.5–12.4 mlU/mL), LH (2.00–15.00 mL), serum testosterone (3,5-8.6 ng/ml), and HOMA–IIR = (fasting insulin mIU/mL * fasting glucose mM)/22.5. Insulin resistance was diagnosed when HOMA was > 2.5.

Ethical approval:

Medical Ethics Committee of Benha Faculty of Medicine gave its approval to this study (number RS. 11-12-2020All participants gave written consent after receiving all information. The Helsinki Declaration was followed throughout the study's conduct.

Statistical analysis: The SPSS version 28, was used for data management and statistical analysis. To evaluate the normality of quantitative data, the Kolmogorov-Smirnov test, the Shapiro-Wilk test, and direct data visualisation techniques were utilised. Quantitative data were summarised using medians and ranges or means±standard deviations in accordance with normality. The use of numbers and percentages was used to express a categorised collection of data. To compare data based on hypothyroidism or PCO status for normally and non-normally distributed quantitative data, the independent t-test or Mann-Whitney U test was used. The Chi-square test or Fisher's exact test were applied to compare categorical data. There are two sides to every statistical test. P values of 0.05 or less was considered significant.

RESULTS

Table (1) shows clinical features according to the presence or absence of overt hypothyroidism in PCOS group. Patients with overt hypothyroidism demonstrated significantly higher weight, BMI, and waist circumference. Age-related changes were not significantly different; SBP, and DBP. In addition, overt hypothyroidism patients revealed significantly higher PCOS criteria; infertility, and manifestations of hypothyroidism than those with no hypothyroidism. In contrast, patients with overt hypothyroidism had much reduced rates of hirsutism than in those without hypothyroidism. No significant differences were observed concerning the pattern of menstruation and other hyperandrogenism symptoms.

Table (1): Clinical characteristics according to state of thyroid function in PCOS group

		Overt hypothyroidism		
		Yes (n = 50)	**No (n = 50)**	**P-value**
Age (years)	**Mean ±SD**	**26 ±5**	**25 ±4**	**0.272**
Marital status				
Single	**n (%)**	**18 (36)**	**30 (60)**	**0.016***
Married	**n (%)**	**32 (64)**	**20 (40)**	
Weight (kg)	**Mean ±SD**	**94.6 ±22.8**	**80.3 ±20.05**	**0.001***
Height (cm)	**Mean ±SD**	**164 ±4**	**162 ±4**	**0.014***
BMI (Kg/m2)	**Mean ±SD**	**34.7 ±8**	**30.5 ±7.5**	**0.008***
WC (cm)	**Mean ±SD**	**101 ±15**	**94 ±15**	**0.022***
SBP (mmHg)	Mean ±SD	129 ±14	129 ±17	1.0
DBP (mmHg)	Mean ±SD	82 ±7	83 ±8	0.507
Pattern of menstruation				
Irregular	n (%)	36 (72)	38 (76)	0.847
Oligomenorrhea	n (%)	8 (16)	8 (16)	
Regular	n (%)	6 (12)	4 (8)	
Hirsutism	n (%)	24 (48)	38 (76)	**0.004***
Other hyperandrogenism symptoms	n (%)	16 (32)	14 (28)	0.663
PCOS criteria on US	n (%)	48 (96)	40 (80)	**0.014***
Infertility	n (%)	26 (81.3)	10 (50)	**<0.001***
Clinical Manifestation of hypothyroidism	n (%)	38 (76)	0 (0)	**<0.001***

*: Significant

Laboratory and radiological findings of overt hypothyroid in PCOS patients were assessed in table 2. Overt hypothyroidism patients demonstrated significantly lower testosterone but higher TPO antibodies than those with no

true hypothyroidism. Furthermore, neck US significantly differed according to hypothyroidism status, with 44% and 56% of hypothyroidism patients having diffuse and nodular goiter, respectively. Regarding fasting blood sugar, no notable variations were found; HBA1C, HOMA-IR, FSH, LH, and TG antibody.

Table (2): Laboratory and radiological findings according to state of thyroid function in PCOS group

		Overt hypothyroidism		
		Yes (n = 50)	**No (n = 50)**	**P-value**
Fasting plasma glucose(mg/dl)	Mean±SD	101 ±17	100 ±24	0.737
HbA1C (%)	Mean±SD	5.67 ±0.53	5.55 ±0.9	0.444
HOMA-IR	Median (range)	2.8 (0.5 - 3)	2 (0.5 - 3.5)	0.318
FSH (mlU/mL)	Median (range)	6.8 (0.1 - 9.8)	6.8 (0.1 - 9.7)	0.912
LH (mlU/mL)	Median (range)	2.9 (0.1 - 7.53)	3.9 (0.1 - 9.53)	0.978
TSH (mlU/mL)	Median (range)	11 (6.21 - 120)	1.47 (0.4 - 6.9)	**<0.001***
Free t3 (pg/ml)	Median (range)	2.3 (1.1 - 3.94)	3.4 (0.84 - 3.8)	**0.009***
Free t4 (ng/dl)	Mean±SD	1.04 ±0.25	1.48 ±0.36	**<0.001***
Testosterone (ng/dl)	Median (range)	0.5 (0.35 - 0.82)	0.78 (0.33 - 1.5)	**0.006***
TPO antibody (IU/mL)	Median (range)	296.5 (3 - 1300)	4.8 (3.5 - 5.5)	**<0.001***
TG antibody(U/mL)	Median (range)	53.2 (2.3 - 1000)	38 (36 - 51)	0.238
Neck u/s				
No goiter	n (%)	0 (0)	50 (100)	**<0.001***
Diffuse goiter	n (%)	22 (44)	0 (0)	
Nodular goiter	n (%)	28 (56)	0 (0)	

Median and range: non-parametric test.*: Significant

Table (3) shows clinical findings in Hashimoto thyroiditis status in PCOS group. Patients with Hashimoto thyroiditis demonstrated non-significant difference in BMI, HbA1C and testosterone than patients without Hashimoto disease. No significant differences were observed regarding SBP, DBP, HOMA-IR, fasting plasma glucose, pattern of menstruation, hirsutism, other hyperandrogenism symptoms, and PCOS criteria on US.

Table (3): Clinical findings according to Hashimoto thyroiditis status in PCOS group

		Hashimoto		
		Yes (n = 30)	**No (n = 20)**	**P-value**
BMI (Kg/m2)	Mean ±SD	32.96 ±8.13	37.18 ±7.24	0.066
SBP (mmHg)	Mean ±SD	129 ±14	129 ±14	1.0
DBP (mmHg)	Mean ±SD	81 ±8	84 ±7	0.179
HbA1C (%)	Mean ±SD	5.55 ±0.38	5.85 ±0.66	0.047*
HOMA-IR	Median (range)	2.8 (0.5 - 3)	2.75 (0.7 - 3)	0.522
Fasting plasma glucose(mg/dl)	Mean ±SD	99 ±15	105 ±21	0.256
Pattern of menstruation				
Irregular	n (%)	22 (73.3)	14 (70)	0.811
Oligomenorrhea	n (%)	4 (13.3)	4 (20)	
Regular	n (%)	4 (13.3)	2 (10)	
Hirsutism	n (%)	17 (56.7)	7 (35)	0.133
Other hyperandrogenism symptoms	n (%)	7 (23.3)	9 (45)	0.108
PCOS criteria on US	n (%)	29 (96.7)	19 (95)	1.0
Testosterone	Median (range)	0.71 (0.35 - 0.82)	0.42 (0.35 - 0.79)	0.087

Median and range: non-parametric test. *: Significant

Table (4) illustrates clinical features of PCOS in hypothyroidism group. Patients with PCOS had significantly higher weight, BMI, waist circumference. Also, Patients with PCOS had significantly higher SBP, and DBP. The pattern of menstruation significantly differed according to the presence of PCOS; the most frequent patterns in PCOS patients were irregular and oligomenorrhea, while in patients without PCOS, the most frequent pattern was regular menstruation. Additionally, PCOS patients had significantly higher hirsutism, other manifestations of hyperandrogenism, and PCOS criteria on US. Regarding infertility, there were no discernible changes and manifestations of hypothyroidism.

Table (4): Clinical features of PCOS in hypothyroid group

		PCOS		
		Yes (n = 24)	**No (n = 76)**	**P-value**
Age (years)	Mean ±SD	29 ±7	29 ±5	1.0
Marital status				
Single	n (%)	9 (37.5)	25 (32.9)	0.678
Married	n (%)	15 (62.5)	51 (67.1)	
Weight (kg)	Mean ±SD	100.1 ±15	81.4 ±18.8	**<0.001***
Height (cm)	Mean ±SD	166 ±4	165 ±4	0.288
BMI (Kg/m2)	Mean ±SD	36.3 ±5.3	30.1 ±6.8	**<0.001***
WC (cm)	Mean ±SD	107 ±12	94 ±14	**<0.001***
SBP (mmHg)	Mean ±SD	139 ±13	120 ±15	**<0.001***
DBP (mmHg)	Mean ±SD	88 ±7	79 ±9	**<0.001***
Pattern of menstruation				
Irregular	n (%)	11 (45.8)	4 (5.3)	**<0.001***
Menorrhagia	n (%)	2 (8.3)	11 (14.5)	
Oligomenorrhea	n (%)	11 (45.8)	0 (0)	
Regular	n (%)	0 (0)	61 (80.3)	
Hirsutism	n (%)	6 (25)	0 (0)	**<0.001***
Other hyperandrogenism manifestation	n (%)	3 (12.5)	0 (0)	**0.013***
PCOS criteria on US	n (%)	21 (87.5)	0 (0)	**<0.001***
Infertility	n (%)	4 (26.7)	22 (43.1)	0.293
Clinical manifestation of hypothyroidism	n (%)	24 (100)	69 (90.8)	0.192

*: Significant

Table (5) reveals laboratory and radiological findings according to the presence or absence of PCOS in hypothyroid group. PCOS patients had significantly higher fasting blood, HBA1C, HOMA-IR, testosterone, TPO antibody, and TG antibody than patients without PCOS. In contrast, FSH was significantly lower in PCOS patients. Additionally, neck US findings significantly differed according to PCOS, with PCOS patients having higher nodular goiter and lower diffuse goiter compared to patients without PCOS.

Table (5): Laboratory and radiological findings of PCOS in hypothyroid group

		Polycystic ovary		
		Yes (n = 24)	**No (n = 76)**	**P-value**
Fasting blood glucose (mg/dl)	Mean ±SD	127 ±30	88 ±17	**<0.001***
HbA1C (%)	Mean ±SD	6.32 ±0.95	5.07 ±0.59	**<0.001***
HOMA-IR	Median (range)	3.05 (2.3 - 3.3)	0.9 (0.5 - 3.99)	**<0.001***
FSH (mlU/mL)	Mean ±SD	7.47 ±1.64	8.4 ±0.86	**<0.001***
LH (mlU/mL)	Mean ±SD	4.29 ±1.03	4.44 ±0.81	0.458
TSH (mlU/mL)	Median (range)	16 (6.26 - 46.03)	15.13 (6.12 - 88.02)	0.401
Free t3 (pg/ml)	Median (range)	1.3 (1.1 - 3.6)	1.33 (1.1 - 3.4)	0.774
Free t4 (ng/dl)	Mean ±SD	0.99 ±0.16	1 ±0.33	0.914
Testosterone(ng/dl)	Mean ±SD	0.63 ±0.14	0.39 ±0.05	**<0.001***
TPO antibody (IU/mL)	Median (range)	489 (5.8 - 654)	203 (3 - 1300)	**0.025***
TG antibody (U/mL)	Median (range)	362.5 (31 - 650)	98 (1.7 - 1387)	**0.042***
Radiological findings				
Neck US				
No goiter	n (%)	0 (0)	0 (0)	**0.005***
Diffuse goiter	n (%)	5 (20.8)	41 (53.9)	
Nodular goiter	n (%)	19 (79.2)	35 (46.1)	

Median and range: non-parametric test.*: Significant

DISCUSSION

The two endocrine problems, PCOS and hypothyroidism, have been linked to one another for a very long time. According to our research, 30% of PCOS patients had Hashimoto's thyroiditis and 20% had non-immune hypothyroidism. A number of articles that have noted an increased frequency of thyroid issues in girls with PCOS corroborate this evidence. The first was a thorough prospective investigation on the prevalence of autoimmune thyroid diseases in PCOS by **Janssen *et al.*** [7]. The other research by **Garelli *et al.*** [8] confirmed the increased prevalence of Hashimoto's thyroiditis in PCOS; 27% of PCOS patients (with an average age of 24 years) had the condition, compared to 8% of controls.

The pathophysiological link between these two disorders has not yet been identified with certainty. The higher BMI and insulin resistance that are shared by both of these conditions may be the most obvious link. In the majority of these cases (54-68%), an increase in BMI is a key component of PCOS [9]. Leptin-based pathway has been proposed to account for this finding. It has been hypothesised that elevated leptin levels in obesity directly affect the hypothalamus, increasing TRH secretion [10]. Our study showed that true hypothyroid patients in PCOS group demonstrated significantly higher PCOS criteria on US (96% vs. 80%, P = 0.014) and infertility (81.3% vs. 50%, P = 0.018) than without. Infertility issues are a defining trait of PCOS. In between 75 and 85 percent of PCOS patients, ovarian abnormalities are identified, in which 30% of cycles were ovulatory [11]. Excessive androgen concentration in the ovary may contribute to premature luteinization of granulosa cells. Oocyte maturation may be hampered by further variation in the paracrine secretion of growth factors in the ovary [12]. Polycystic ovary syndrome and systemic hormone disorders such hypothyroidism and hyperinsulinemia can also play a part in this type of monthly irregularity. In our results hirsutism was significantly lower in hypothyroid compared to euthyroid patients (48% vs. 76%). According to our study, testosterone levels were considerably lower in hypothyroid patients (median = 0.5 vs. 0.78). Low total testosterone levels have been linked to hypothyroidism and are thought to be caused by low SHBG levels [13]. But it has also been shown that low free testosterone levels can normalise when hypothyroidism is addressed [14].

Our results showed that hypothyroid patients in PCOS group had higher median levels of TPO antibodies than euthyroid patients (median = 296.5 vs. 4.8). The prevalence of thyroid autoimmunity is higher in PCOS patients. When compared to controls, women with PCOS had greater thyroid antibody levels, bigger thyroid volumes, and thyroids that are more hypoechogenic (compatible with thyroiditis) [7]. In comparison to controls, 27% of patients were found to have thyroid peroxidase antibodies [8].

Our study revealed that 24% of hypothyroidism patients had polycystic ovarian disease. Our findings matched the results of with study by **Hu *et al.*** [15], which discussed PCOS prevalence and risk in patients with Hashimoto's thyroiditis. The mean prevalence of PCOS in patients with Hashimoto's thyroiditis was 24.15%. Our study showed that the pattern of menstruation significantly differed according to the presence of PCO in hypothyroid patients; the most frequent patterns of menstrual abnormality in PCOS patients were irregular cycles and oligomenorrhea (45.8% for each), while in patients without PCO, the most frequent pattern was regular cycles (80.3%). Additionally, PCOS patients had significantly higher hirsutism (25% vs 0%), other manifestations of hyperandrogenism (12.5% vs 0%), and PCOS criteria on US (87.5% vs 0%).

This is explained by menstrual cycle disruption may develop from hypothyroidism alone, without hyperprolactinemia, interfering with normal hypothalamus pituitary ovarian activity. Menorrhagia is typical in less severe cases of hypothyroidism. Amenorrhea is frequently linked to long-lasting or severe hypothyroidism, especially if it is accompanied by hyperprolactinemia [16].

Our study showed that PCOS patients in hypothyroid group had significantly higher testosterone (0.63 ±0.14 vs 0.39 ±0.05), TPO antibody (median = 489 vs 203), and TG antibody (362.5 vs. 98) than patients without PCO. Neck US findings in our study showed that PCO patients have higher nodular goiter (79.2%) and lower diffuse goiter (20.8%) compared to patients without PCO (46.1% and 53.9%, respectively). The main issue with PCOS is excessive androgen synthesis by the ovaries, which stimulates a lot of follicles and prevents the appropriate quantity of FSH from working. A dominant follicle will therefore seldom develop [17]. Various human [18], and animal [19] research. According to cases, testosterone levels increase after PCOS due of hormonal abnormalities. The prevalence of thyroid autoimmunity is higher in PCOS individuals. When compared to controls, women with PCOS had greater thyroid antibody levels, bigger thyroid volumes, and more hypoechogenic thyroids [7].

Our study showed that FSH was significantly lower in PCO patients (7.47 ±1.64 vs. 8.4 ±0.86, P = 0.013). The increased activity of hypothalamic GnRH in PCOS-affected women may be the cause of the relative reduction of FSH production. As an alternative, the persistent estrogen production that is a feature of this illness may have a negative feedback effect, resulting in a drop in circulating FSH. However, PCOS women's granulosa cells have enhanced FSH binding and are easily stimulated by FSH both in vitro and in vivo [20].

Our study showed that metabolic alterations seen in PCOS and hypothyroidism are frequently connected.

This could be inferred from the following:

Patients with true hypothyroidism in PCOS group demonstrated significantly higher weight (94.6 ±22.8 vs. 80.3 ±20.5 kg, P = 0.001), BMI (34.7 ±8 vs. 30.5 ±7.5, P = 0.009), and waist circumference (101 ±15 vs. 94 ±15 cm, P = 0.022), but no significant differences were observed regarding fasting blood glucose (P = 0.737), HBA1C (P = 0.444), HOMA-IR (P = 0.318). Patients with PCOS in hypothyroidism group had significantly higher weight (100.1 ±15 vs. 81.4 ±18.8, P <0.001), BMI (36.27 ±5.26 vs. 30.08 ±6.83, P <0.001), waist circumference (107 ±12 vs. 94 ±14, P < 0.001), systolic blood pressure (139 ±13 vs. 120 ±15, P <0.001), and diastolic blood pressure (88 ±7 vs. 79 ±9, P < 0.001), compared to patients without PCOS. Furthermore, they had significantly higher fasting plasma glucose (127 ±30 vs 88 ±17, P < 0.001), HBA1C (6.32 ±0.95 vs 5.07 ±0.59, P < 0.001), HOMA-IR (median = 3.05 vs 0.9, P < 0.001). Patients with overt or subclinical hypothyroidism exhibit metabolic problems in Hashimoto's disease, which are more evident than in those who are euthyroid and using T4 replacement treatment [21]. It appears then that they are primarily linked to thyroid dysfunction and improve with normal hormone levels [21]. When Hashimoto's thyroiditis and PCOS combine, the metabolic alterations may be more severe than those caused by either condition alone. Actually, girls suffering from both PCOS and Hashimoto's thyroiditis had higher values of: BMI, fasting glucose level, HOMA-IR index and cholesterol contrasted to girls with Hashimoto's thyroiditis only or a control group[22].

CONCLUSION

Our study shows that there was a relationship between PCOS and hypothyroidism per se, independent of the underlying cause or the kind of clinical manifestation (overt or subclinical). Our hypothesis is that one of the two illnesses makes the other more common. The intricacy of the etiologies of both diseases may be the cause of the link's current ambiguity. But insulin resistance is present in both circumstances.

LIMITATIONS

The absence of a healthy control group in either patients with PCOS or patients with hypothyroidism was the major limitation of the study.

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Competing interests: Nil.

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