RESEARCH PAPER

Role of Metformin on Lipid profile, Lipid ratios, and Insulin Resistance in South Indian Women with Polycystic Ovary Syndrome

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Abstract

Background: Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder in women of reproductive age, often characterized by insulin resistance, hyperinsulinemia, and dyslipidaemia, which increases the risk for cardiovascular diseases. Metformin, an insulin-sensitizing agent, has been widely used to improve insulin resistance in PCOS.

Aim: To evaluate the effect of metformin therapy on and lipid profile, lipid ratios and insulin resistance in South Indian women with PCOS.

Objective: To assess changes in lipid profile (total cholesterol, LDL, HDL, triglycerides), lipid ratios and insulin resistance markers - HOMA-IR before and after metformin treatment in PCOS patients.

Material and Methods: A Case-control study with 104 women with PCOS patients and 95 healthy age matched control subjects were enrolled in the study. Standard- physical method and Chemi Luminescent Immunoassay techniques were employed for measurement of anthropometric parameters and plasma sex hormones respectively in both the groups. Fasting insulin, glucose and lipid profile were measured by standard methods and lipid ratios also calculated from lipid profile. Insulin resistance was measured as HOMA-IR. All 104 PCOS cases received metformin 1500 mg/day for 8 weeks. At the end of 8-week treatment, lipid profile, lipid ratios and insulin resistance and were measured like pre-metformin treatment.

Result: Metformin significantly reduced insulin resistance, reflected by decreased HOMA-IR scores ($p < 0.05$). Significant improvement was observed in lipid profile with a reduction in total cholesterol, triglycerides, LDL- cholesterol and lipid ratios ($p < 0.05$). HDL- cholesterol showed a significance increase ($p < 0.05$).

Conclusion: Metformin therapy significantly improves both insulin resistance, lipid profile and lipid ratios in PCOS patients. These effects may contribute to reducing cardiovascular risk factors associated with PCOS, making metformin an essential therapeutic drug. Further studies may be needed to confirm long-term outcomes.

Keywords: Polycystic ovarian syndrome; Metformin; lipid profile, lipid ratio, South Indian

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Introduction

Polycystic ovary syndrome (PCOS) is one of most common gynecological and endocrine disorder affecting females of the reproductive age, causing infertility with a prevalence of approximately 5-20 %. worldwide (1). It is characterized by menstrual irregularities, hyperandrogenism, and polycystic ovaries, and is often associated with metabolic disturbances such as insulin resistance, obesity, and dyslipidaemia (2). While the causes of PCOS are still unknown. insulin resistance secondary to obesity is strongly correlated to this syndrome. In PCOS, obesity worsens insulin resistance and exacerbates reproductive and metabolic features (3) Dyslipidaemia in PCOS is a well-documented feature, with a typical lipid profile including: Elevated total cholesterol (TC), Increased low-density lipoprotein cholesterol (LDL-C), Higher triglycerides (TG), Reduced high-density lipoprotein cholesterol (HDL-C) (4). Lipid ratios such as TC/HDL-C, LDL-C/HDL-C, and TG/HDL-C are considered more sensitive markers of cardiovascular risk than individual lipid parameters. These ratios are frequently altered in women with PCOS, elevating their risk for cardiovascular disease (5). Recent studies emphasize that metformin, an insulin-sensitizing agent, has been widely used in PCOS management has significant effects on lipid profiles and ratios, which are critical in evaluating cardiovascular risk. Metformin primarily functions by improving insulin sensitivity, reducing insulin levels, and decreasing androgen production in PCOS patients. This insulin-sensitizing effect also positively influences lipid metabolism, leading to beneficial changes in lipid

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profiles (6). Clinical trials have reported significant reductions in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) after three months of metformin therapy in PCOS patients. Furthermore, high-density lipoprotein cholesterol (HDL-C) levels typically improve, albeit modestly. Additionally, metformin has been shown to reduce important lipid ratios such as the LDL-C/HDL-C and TC/HDL-C ratios, which are key markers for cardiovascular risk. This suggests that metformin may help mitigate the cardiovascular complications associated with PCOS **(7)** Another interesting observation is the reduction in the atherogenic index of plasma (AIP), which reflects the balance between TG and HDL-C, further supporting the idea that metformin can positively impact lipid metabolism in PCOS patients **(8).** However, there are only a few studies specifically concerning the effect of Metformin therapy on lipid profile and lipid ratios in women with PCOS **(9)**. However, the effect of metformin on lipid profile and lipid ratios, particularly in South Indian women with PCOS, has not been comprehensively studied. In this background, the aim of our study is to assess the role of metformin treatment on lipid profile and lipid ratios in south Indian women with PCOS.

Materials and Methods

The case control study was conducted on104 women with PCOS and 95 healthy women as controls with regular menstrual cycles aged between 20 to 35 years were recruited from outpatient department of Obstetrics and Gynecology, Jawaharlal Institute of Post Graduate Medical Education and Research (JIPMER) Puducherry, India. The diagnosis of PCOS was made according to the Rotterdam consensus criteria (**10**). It is defined as patient was considered to have PCOS if she fulfilled two out of the following three criteria: oligo- and/or anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries on ultrasonography scan. The study was approved by Institute Research Council Board and followed by Human Ethical Committee, JIPMER, and Puducherry, India (No. Edn.6(10)/2007 and Reg.No.1). The written informed consent was obtained from patients and controls. Patients with diabetes mellitus, thyroid dysfunctions, Cushing's syndrome, congenital adrenal hyperplasia, hyperprolactinemia, androgen secreting tumor, renal and liver dysfunction were excluded from the study by specific laboratory tests. Subjects with medication like ovulation induction agents, antiandrogens, antidiabetic, anti-obesity, hormonal drugs and current or previous use of OC within last 6 months, smoking and alcohol intake were also excluded from the study. All 104 PCOS patients and 95 healthy control underwent full physical examination and anthropometric measurements including weight, height and, waist and hip circumferences. Weight was measured with the subjects wearing light clothing without shoes, and height was measured using a stadiometer. Body Mass Index (BMI) was calculated by using the formula: weight (Kg)/height (meters). Waist circumferences (WC) were measured with the patients standing at a point mid-way between lower costal margin, and ileac crest in the mid- auxiliary line. Hip circumferences were measured at the widest point over the buttocks with the subjects standing and breathing normally. The waist to hip ratio (WHR) were calculated for all subjects = waist circumference/hip circumference After overnight fasting venous blood sample was obtained between 08.00 am and 08.30 am, on the 2nd day of spontaneous progesterone (methoxy progesterone acetate 10mg/day for 7 days) induced withdrawal bleeding for (to carry out the study during the follicular phase we had to induce the menstruation in PCOS women because they were having irregular menstrual cycles) estimation of hormones, IR marker indices and lipid profile. The plasma glucose was determined by glucose oxidase-peroxidase, (GOD-POD) end point method using a commercial kit (Agape diagnostic, India) using clinical chemistry Auto analyzer (Beckman Coulter AU680, Japan). Plasma Insulin was (Bio line, Belgium) estimated by ELISA techniques (Lab system-Multiskan Ascent, Finland) IR was determined by Homeostasis Model Assessment for insulin resistance (HOMA - IR) = Fasting glucose (mg / dl) x fasting insulin (muIU / ml) / 405(**11**). QUICK was calculated as=1/ (log (fasting insulin) +log (fasting glucose) (**12**) Serum LH, FSH, were determined by Chemi Luminescent Immunoassay (CLIA) method using Siemen's Advia Centaur CP kit by Siemens Advia Centaur CP analyzer, Japan. The Testosterone, Androstenedione, Progesterone, Estradiol, DHEAS, SHBG, 17-hydroxy progesterone (17-OHP) were analyzed by competitive immunoassay by Chemi Luminescent Immunoassay method using Siemen's Advia Centaur CP kit by Siemens Advia Centaur CP analyzer, Japan. Total cholesterol, Triglycerides were measured by cholesterol esterase-oxidase end point and glycosol-3-phosphate oxidase-peroxidase, endpoint method respectively by using commercial kits (Agape diagnostic, India) by autoanalyzer (Beckman Coulter AU680, Japan). HDL-cholesterol was estimated by direct immune-inhibition method using commercial kits (Agape diagnostic, India) using autoanalyzer (Beckman Coulter AU680, Japan). VLDL-cholesterol was calculated by dividing the total cholesterol concentration by 5 (**13).** LDL-cholesterol was calculated using Friedwald's formula. LDL-Cholesterol = Total Cholesterol (mg/dl) – [HDL-C + Triglycerides] 5 Non-HDL-cholesterol was calculated by subtracting HDL-cholesterol from total cholesterol. Atherogenic indices as indicated by various risk ratio were calculated using the following calculations: TC (mg/dL)/HDL-C (mg/dL), TG (mg/dL)/HDL-C (mg/dL), LDL-C (mg/dl)/HDL-C(mg/dl), and non-HDL-C(mg/dl) /HDL-C(mg/dl).

All 104 PCOS Patients received metformin 1500 mg/day (C.I Laboratories, Calcutta-700653) along with food for 8 weeks. Patients were instructed not to modify their eating habits, lifestyles, and active level during this study. At the end of 8 weeks treatment blood sample

were collected and lipid profile, lipid ratios and insulin resistance markers were measured like pre-metformin treatment.

Statistical Analysis:
All the statistical analysis were carried out the Statistical Package for the Social Sciences (SPSS) version 24.0, for Windows (SPSS, Inc., Chicago). All the quantitative data were expressed as mean ± standard deviation (SD). The unpaired Student's t–test was used to compare the values of PCOS *vs* Controls. Pearson's correlation coefficient test was used to assess the association between the parameters in PCOS patients. Statistical significance was considered as $P < 0.05$

Results
Table-1 Shows anthropometric parameters in control groups and PCOS groups. In this study all women were in the age group of 25-35 years for both cases and controls. The BMI was found to be more in PCOS patients and statistically significant when compared to the control subjects ($p<0.01$). The waist to hip ratio was more in PCOS cases and statistically significant when compared to the control subjects ($p<0.05$)

Table 1: **Anthropometrics parameters in control and PCOS Cases.**

Variables	Control (n = 95)	PCOD (n = 104)
Age (years)	27±4	27.33 ± 3.30 NS
Weight (Kg)	57±12	68 ± 4**
Height (Cm)	1.59±0.05	1.58 ± 3.38 NS
BMI (Kg / m^2)	22.08±1.75	27.39 ± 1.45**
Waist circumference (Cm)	75±4	89 ± 3*
Hip circumference (Cm)	91±5	104 ± 4*
Waist-hip ratio	0.82±0.02	0.85 ± 0.01*

Values on shown in mean ± standard deviation
* $p < 0.05$ and ** $p < 0.01$ compared to controls
NS=Not significant
The hormonal data of women with PCOS and controls are shown in Table 2. The hormones such as LH, total Testosterone androstenedione was significantly higher in women with PCOS than controls ($p < 0.01$) and similarly, LH/FSH ratio and progesterone, 17 OHP, DHEAS were also significantly higher in women with PCOS than healthy controls groups ($p < 0.05$). On the other hand, patients with PCOS had significantly lower levels of FSH, estradiol and SHBG than control groups ($P < 0.05$)

Table-2 Hormonal profiles in control and PCOS cases

Variables	Control (n = 95)	PCOD (n = 104)
LH (μIU/ml)	5.98±1.03	13.10±7.00**
FSH (μIU/ml)	5.74±1.16	4.61±1.85*
LH / FSH	1.05±0.11	2.83±0.76*
TT (ng/dl)	36.60±8.15	63.98±16.65**
A_4 (ng/dl)	1.47±0.45	3.64±0.87**
Progesterone (ng/dl)	0.45±0.40	0.61±0.39*
17 OHP (ng/dl)	0.53±0.02	0.84±0.18*
E_2 (pg./ml)	58.92±17.21	39.03±11.51*
SHBG (nmol/L)	62.39±8.35	42.98±11.44*
DHEAS (μg/dl)	173.12±44.72	262.64±72.33**

Values are shown in mean ± standard deviation and
* $p < 0.05$ and ** $p < 0.01$ compared to controls
Table 3: depicts the insulin resistance indices in control and PCOS groups. The fasting plasma glucose was significantly increased in PCOS cases when compared to control groups ($p < 0.05$) The fasting plasma insulin and HOMA-IR were significantly increased in PCOS patients compared to control groups ($p < 0.01$) The fasting plasma glucose and insulin ratio was significantly decreased in PCOS group than control subjects ($p < 0.01$) The QUICKI was significantly lowered in patients than in control subjects ($p < 0.05$)

Table-3: Insulin resistance parameters in women with PCOS and healthy controls.

Variables	Control (n = 95)	PCOS (n = 104)
Fasting glucose (mg/dl)	83.76±6.67	106.64±12.56*
Fasting Insulin (μIU/ml)	14.27±2.92	35.61±5.31**
Glucose / Insulin	6.20±1.79	3.01±0.33**
HOMA-IR	2.92±0.53	9.49±2.36**
QUICKI	0.33±0.09	0.28±0.09*

Values are shown in mean standard deviation
* $p < 0.05$ and
** $p < 0.01$ compared to controls

Table-4 depicts the insulin resistance parameter in PCOS patients before and after treatment with metformin. The fasting insulin and HOMA-IR were significantly lowered ($p<0.05$) and fasting glucose and insulin ratio was significantly increased ($p<0.05$) in PCOS patients by metformin treatment. However, QUICKI was not significantly altered.

Table 4: Insulin resistance parameters in PCOS cases (Before and After Metformin Treatment)

Variables	PCOS (n = 104) Before Treatment	PCOS (n = 104) After Treatment
Fasting glucose (mg/dl)	106.64±12.56	80.31±11.44*
Fasting Insulin (μIU/ml)	35.61±5.31	21.18±8.87*
Glucose / Insulin	3.01±0.33	4.48±1.91*
HOMA-IR	9.49±2.36	4.16±1.73*
QUICKI	0.28±0.09	0.31±0.02 NS

Values are shown in mean ± standard deviation
* $p < 0.05$ compared to before treatment
NS = Not significant

Table-5 Shows lipid profile atherogenic index, of PCOS patients, before and after metformin treatment. The total cholesterol, triglycerides, LDL-cholesterol, and were significantly reduced ($p<0.05$) and HDL-cholesterol was significantly increased ($p<0.05$) in PCOS patients after metformin treatment. Atherogenic index such us non-HDL-cholesterol, total cholesterol/HDL-cholesterol, TG/HDL-cholesterol, and LDL-cholesterol/HDL-cholesterol were significantly decreased by metformin treatment in PCOS patients($p<0.05$).

Table 5: Lipid parameters in PCOS cases (Before and After Metformin Treatment)

Variables	PCOS (n = 104) Before Treatment	PCOS (n = 104) After Treatment
Total cholesterol (mg/dl)	181.66±30.30	164.68±28.47 *
Triglycerides (mg/dl)	139.41±35.41	112.35±52.13*
HDL-C (mg/dl)	34.42±7.69	46.55±9.09*
LDL-C (mg/dl)	119.36±21.27	105.67±32.32*
Non HDL-C (mg/dl)	147.24±25.23	128.13±13.15*
TG / HDL-C	4.11±0.75	2.51±1.3*
TC / HDL-C	5.41±0.86	3.95±1.31*
LDL-C / HDL-C	3.60±0.81	2.45±1.3*

Values are shown in mean ± standard deviation
* $p < 0.05$ compared to before treatment

Table-5 Shows lipid profile atherogenic index, of PCOS patients, before and after metformin treatment. The triglycerides, LDL-cholesterol and VLDL-cholesterol were significantly reduced ($p<0.05$) and HDL-cholesterol was significantly increased ($p<0.05$) in PCOS patients after metformin treatment. Atherogenic index such us non-HDL-cholesterol, total cholesterol/HDL-cholesterol, TG/HDL-cholesterol, and LDL-cholesterol/HDL-cholesterol were significantly decreased by metformin treatment in PCOS patients.

Discussion

The exact cause of PCOS is not clear, however IR certainly plays a major role in PCOS and its repercussion are responsible for all aspects of PCOS namely the metabolic, endocrine, reproductive, and long-term risk

factor (**14**). IR and secondary hyperinsulinemia affect approximately 65-70% of women with PCOS (**15**). Hyperinsulinemia is a predictor of CAD, IR has been proposed as a key factor linking to hypertension, glucose intolerance, obesity, lipid abnormalities and coronary heart disease (**16**). The present study showed that PCOS women had higher degree of IR in terms of increased HOMA-IR, fasting glucose, and fasting insulin and decreased QUICKI and glucose / insulin ratio compared to the control group and results were consistent with other previous studies. In many studies performed in PCOS women, HOMA-IR and QUICKI were used as markers of insulin resistance. Several studies confirmed that both obese and non-obese women with PCOS have a higher incidence of insulin resistance and hyperinsulinemia than age-matched controls, however, obese women with PCOS have significantly decreased insulin sensitivity compared with non-obese PCOS women (**17**,**18**). Reports of the prevalence of insulin resistance in women with PCOS vary dependent on the sensitivity and specificity of the tests employed and the heterogeneity of PCOS. Since IR and hyperinsulinemia play a major role in the pathophysiology of PCOS, the use of insulin sensitizers such as Metformin, may be vital in its management **(19).** Several studies have been published investigating the effect of metformin on IR in women with PCOS. The first study was by Velazque EM et al., (1994) in USA found that metformin treatment in 26 obese PCOS women with mean BMI of 29 Kg/m^2 for 8 weeks showed that reduced hyperinsulinemia, systolic blood pressure, and improved hormonal and reproductive abnormalities (**20).** Diamanti-Kandarakis E et al., (1998) found that a significant reduction in fasting glucose and fasting insulin and same result were obtained by the Finish group (**21**). A reduction in fasting glucose and insulin levels after treatment with metformin was reported by investigators in both obese (**22**) and non-obese (**23**). In a meta-analysis of 13 controlled studies, in different ethnic populations, it was confirmed that metformin has a significant effect in reducing fasting insulin levels, associated with a small reduction of fasting glucose (**24.**). It was shown that treatment with 1500mg of metformin for 8 weeks decreases the levels of serum insulin **(25,26**). In a double-blind study by Moghetti P et al., (2000) and Acbay O and Gundogdu S (1996) found that no difference in insulin and glucose levels with metformin treatment. (**27,28**) Not all studies have shown consistent improvement of insulin sensitivity with metformin therapy. Possible explanation for this discrepancy may be variability in the doses of metformin and the effect of metformin on BMI. Our study also indicated that the fasting glucose and fasting insulin and HOMA-IR were reduced and QUICKI and glucose / insulin ratio were increased with metformin therapy and consistent with reports like Velazquez et al., (1994), De leo V et al., (1998) and Awartani KA et al., (2002). (**29,30,31**) The possible mechanism for metformin action for lowering insulin resistance by inhibiting hepatic glucose production, by gluconeogenesis by, direct inhibition of gluconeogenic enzymes decrease intestinal glucose uptake and increase insulin sensitivity in peripheral tissues. Metformin has antilipolytic effects and lower circulating free fatty acids concentration, which ultimately reduce the gluconeogenesis and IR (**32**). Metformin affects ovarian function by improving insulin sensitivity and inhibiting androgen synthesis by theca cells, directly impacting ovarian steroid hormone synthesis (**33).**

Numerous studies have shown that metformin improves various lipid parameters in PCOS women, although the degree of change can be modest. Metformin plays a crucial role in addressing dyslipidaemia, a common issue in women with Polycystic Ovary Syndrome (PCOS). PCOS is associated with insulin resistance, which can lead to an abnormal lipid profile, increasing the risk of cardiovascular diseases. Metformin, by improving insulin sensitivity, directly and indirectly influences lipid metabolism, resulting in more favourable lipid profiles (**34).**

Several studies have shown that metformin significantly reduces total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C). These changes are particularly important because high levels of LDL-C are a major risk factor for atherosclerosis and cardiovascular disease (**35,36).**

Our results showed that treatment with metformin caused a significant increase in HDL-C and a decrease in total cholesterol, triglyceride, VLDL-C and LDL-C levels in PCOS patients. Our result is in accordance with recent studies by Prithiv Raj et al. (2024), Johanna Melin et al. (2023), Ghalia M. Attia et al.(2023), Geetika Singh et al (2017),Rachana Mehandiratta et al (2016), Singh B et al (2010), Costantino D et al (2009),Karimzadeh et al (2007), and Ibanez L et al. (2007) (**37,28,29,40,41,42,43,44,45)** where metformin has been shown to improve the lipid profile. Glueck et al (2003) reported that a significance decreases in triglycerides levels as well as HDL-C in PCOS patients on metformin treatment (**46).** Therefore, treatment with metformin may cause the prevention of CVD through correcting lipid profile changes. Other studies done by Rautio et al (2005) Moghetti et al (2000) and Valazquez et al (1994) showed that no significance changes in serum cholesterol, triglycerides, and LDL-C in women with PCOS **(47,48).** On the other hand, some other studies have shown that only a negligible or on effect on lipid profile in women with PCOS (**49,50**). In a meta-analysis of by Harborne L et al (2003) by metformin therapy, no difference in total cholesterol, HDL -C or LDL-C cholesterol were observed (**51**). These discrepancies in the result among researches could be explained by difference in the study population or by different duration of treatment in various studies.

The mechanism of the effect of metformin on lipid profile is not clear and may be due to improvements in insulin sensitivity. Its principal clinical function is to inhibit the production of hepatic glucose, increasing insulin sensitivity in peripheral tissues and decreasing intestinal glucose uptake (**52**). Additionally, it inhibits

mitochondrial respiratory chain complex 1 by interfering with cellular respiration, which imitates a cell starvation condition by decreasing intracellular ATP. Accordingly, the adenosine monophosphate (AMP) pool increases, activating the AMP- activated protein kinase (AMPK) (**53).** The AMPK stimulation also increases the translocation of glucose transporters (GLUT) to the cell membrane and increases the transport of glucose into the cell

The activation of AMPK also results in a reduction in the activity of acetyl-CoA carboxylase (ACC) which in turn reduces oxidation of fatty acids and suppresses lipogenic enzymes. Suppression of fatty acid oxidation results in decreased hypertriglyceridemia, thus reducing the availability of energy for gluconeogenesis. This is linked with increased clearance of very low-density lipoprotein (VLDL) and decreased synthesis. Lipolysis inhibition and reduction in triglyceride levels will lead to increased insulin sensitivity through reduced lipotoxicity (**54**).

In our study shown that atherogenic index like non-HDL-C, TG/HDL-C, TC/HDL-C and LDL-C / HDL-C were reduced in PCOS patient with metformin treatment. Lipid ratios such as TC/HDL-C, LDL-C/HDL-C, and TG/HDL-C are considered more sensitive markers of cardiovascular risk than individual lipid parameters. **(55).** Metformin has been shown to reduce these ratios, indicating an overall improvement in the balance between harmful and protective lipids (**56).** Our results were in line with previous studies on lipid ratios in PCOS, where metformin has been shown to improve lipid ratios (**57,58).** A lower LDL-C/HDL-C ratio is particularly valuable because it reflects reduced atherosclerotic risk. Atherogenic Index of Plasma (AIP), calculated as the log of the triglyceride/HDL-C ratio, is a sensitive indicator of cardiovascular risk. Metformin significantly lowers AIP, providing further evidence of its protective role in reducing cardiovascular complications in PCOS patients (**59**). In summary, metformin therapy has shown consistent benefits in improving lipid profiles and lipid ratios and reducing cardiovascular risk in PCOS patients by targeting key metabolic abnormalities linked to insulin resistance and dyslipidaemia. Long-term use of metformin in PCOS patients is associated with sustained improvements in lipid profiles, along with other metabolic benefits such as weight reduction, decreased androgen levels, and improved menstrual regularity. These combined effects make metformin a cornerstone therapy for managing both metabolic and reproductive issues in PCOS. **(60)**

Conclusion

Metformin plays an essential role in improving the lipid profile in PCOS patients by addressing the underlying issue of insulin resistance. Its effects on reducing total cholesterol, triglycerides, LDL-C, and improving HDL-C and lipid ratios contribute significantly to reducing the cardiovascular risk in insulin resistance women with PCOS. Given its benefits on both metabolic and reproductive aspects of PCOS, metformin is a cornerstone of therapy for managing the syndrome's complex symptoms.

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Conflicts of interest

There is no conflict of interests to declare

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