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Original Article

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Correlation Study to Associate Serum Glycaemic Status Markers with Uric Acid–HDL Cholesterol Ratio among Gestational Diabetes Mellitus and Normal Pregnancy

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Abstract

***Background & Aims*:** Pregnancy is a diabetogenic state characterized by hyperinsulinemia and insulin resistance. The primary goal of identifying gestational diabetes mellitus (GDM) is to detect women at risk for adverse perinatal outcomes. Proper diagnosis of this condition and its complications is essential for the benefit of both maternal and child health. The uric acid/HDL-C ratio (UHR), which combines two metabolic parameters—serum uric acid and HDL-C— is a powerful predictor of metabolic deterioration. The present study aims to understand the role of metabolic derangement in the development of GDM in pregnant women and to compare these findings with those of healthy controls. The objectives of the study are to compare the serum UHR in the GDM and control populations and to correlate UHR in each group with glycemic status markers and BMI.

***Materials & Methods*:** Based on inclusion and exclusion criteria, a total of 30 cases and 30 age-matched controls were selected for the study. The age range was 18 to 35 years. All serum parameters were analyzed using a Beckman Coulter AU-480 fully automated analyser. UHR was calculated from serum uric acid and HDL-C values using the formula: UHR = UA/HDL-C.

***Results*:** The results show that patients with GDM had higher uric acid levels and UHR and lower HDL-C levels than healthy controls, suggesting significant metabolic derangement in this group.

Conclusion: Routine use of UHR as an early screening tool can help identify metabolic abnormalities in GDM. This will also aid in early pharmacological intervention, thereby preventing future complications for both the mother and foetus.

***Keywords*:** Hyperinsulinemia, Insulin resistance, Uric acid/HDL-c ratio (UHR)

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Introduction

Pregnancy is a diabetogenic state characterised by hyperinsulinemia and insulin resistance. The definition of gestational diabetes (GDM) is any degree of glucose intolerance that occurs or is first recognized during pregnancy. GDM can be classified as A1GDM and

A2GDM. Gestational diabetes that is managed without drugs and responds to nutritional therapy is diet-controlled gestational diabetes (GDM) or A1GDM. On the other hand, GDM treated with medication to achieve adequate glycaemic control is A2GDM (1). The most recent meta-analysis by Saeedi et al. reported that the global prevalence of GDM was 14.7% based on the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria, the most used screening method worldwide (2). In 2019, a meta-analysis using the same criteria reported that the highest pooled prevalence (11.4%) of GDM was in South Asia (Bangladesh, India, and Sri Lanka) compared to the rest of the world (3.6–6.0%) (3). In India, the prevalence rate of GDM is estimated to be 10-14.3%, which is much higher than in Western countries (4).

The American Diabetes Association recommends screening for undiagnosed type 2 diabetes at the first prenatal visit in women with diabetes risk factors. In pregnant women not known to have diabetes, GDM testing should be performed at 24 to 28 weeks of gestation. In addition, women with diagnosed GDM should be screened for persistent diabetes 6 to 12 weeks postpartum. It is also recommended that women with a history of GDM undergo lifelong screening for the development of diabetes or prediabetes at least every three years.

According to the criteria of the International Association of Diabetes and Pregnancy Study Groups (IADPSG), the problem of preventing gestational diabetes is increasingly becoming the focus of research in recent years, given the many short-and long-term side effects associated with GDM in mothers and their offspring. In women, GDM is associated with an increased risk of preeclampsia during pregnancy and a significantly increased risk of type 2 diabetes (T2D) and comorbidities such as cardiovascular disease after pregnancy (5). Intrauterine hyperglycaemia during pregnancy potentially affects many aspects of the offspring's lifelong health. For example, babies born to mothers with GDM are larger for their gestational age and therefore more likely to experience birth trauma (6).

Uric acid is the end product of the catabolism of purines. It is mainly synthesized in the liver, intestine, kidneys, muscles, and vascular endothelium and eliminated by the kidneys and intestines. It exhibits the properties of both pro-oxidants and antioxidants. It is responsible for two-thirds of the total antioxidant capacity of plasma. Uric acid is also responsible for the chelation of transition metals. The generation of nitric oxide in endothelial cells is impaired by soluble uric acid, thereby inhibiting the relaxation of vascular endothelium. Thus, increased uric acid levels can cause endothelial dysfunction. Hyperuricemia is associated with insulin resistance (7). Similarly, lipid profile, is a panel of tests performed to interpret lipoprotein and cholesterol metabolism. It is a well-known cardiac metabolic risk factor (8).

The Uric Acid/HDL-c ratio (UHR), which combines two metabolic parameters, serum uric acid and HDL-C, is a powerful predictor of metabolic deterioration. The UHR was associated with many metabolic-inflammatory diseases such as hypertension, thyroiditis, and hepato-steatosis, and is associated with complications in diabetic mellitus (9). Detection of GDM could be a way of early identification of the risk of developing metabolic syndrome, maintaining good health and avoiding T2DM and CVD later in life (10).

The primary goal of identifying GDM is to detect women at risk for adverse perinatal outcomes. There is evidence that women who receive intensive treatment during pregnancy can achieve near-normal macrosomia. Proper diagnosis of this condition and its complications is important as it requires dietary control and pharmacological intervention, as well as careful monitoring of the pregnancy, foetus, and its long-term effects on maternal and child health (11, 12). Hence, the present study was conducted to compare and correlate the serum glycaemic status markers (FSG, PPSG) in GDM patients and normal pregnancies with UHR (uric acid-HDL-C ratio), to undermine the role of glycaemic status in the development of metabolic syndrome.

Aims & objectives

The present study aims to understand the role of metabolic derangement in the development of GDM in pregnant women and compare it with that of healthy controls.

The objectives of the study are:

(a) To compare the serum UHR in the GDM and control populations.

(b) To correlate UHR in each group with glycaemic status markers and BMI.

(c) To observe the changes in the association between UHR to glycaemic status markers, and BMI in the study groups.

Materials & Methods

(i) Study Design: This is a cross-sectional study conducted at Rangaraya Medical College/Government General Hospital, Kakinada, AP.

(ii) Study Area: The study was conducted among pregnant women attending the Obstetrics and Gynaecology Department and healthy controls for whom investigations were done in the Central Lab, Department of Biochemistry, Government General Hospital.

(iii) Study period: The study was conducted over a period of 3 months, from April 2023 to July 2023.

(iv) Study subjects: A total of 60 individuals, aged between 18 and 35 years, were included in the present study. They were divided into two groups as follows:

Group 1: 30 newly diagnosed GDM patients

Group 2: 30 pregnant women who were age-matched controls with normal GTT results.

(a) Inclusion criteria: Newly diagnosed GDM (undergoing GTT test, with GTT results showing serum glucose: fasting > 95 mg/dl, first hour sample > 180 mg/dl and second hour sample > 155 mg/dl) identified during the first and second trimesters of pregnancy.

(2) All individuals who gave consent or were willing to participate in the present study.

(b) Exclusion criteria: Individuals with hypothyroidism on medication, preeclampsia, eclampsia, anemia, previous history of GDM, and other complications during pregnancy. Those in the third trimester of pregnancy. Individuals who did not give consent or were not willing to participate in the present study.

(v) Ethical approval and Informed consent: Ethical approval was obtained from the Institutional

Ethical Committee before the start of the study. Informed consent was obtained from the study subjects before blood sample collection.

(vi) Sample collection and Processing: Study participants were advised to fast overnight to undergo the GTT test to identify their glycaemic status. The first blood sample, collected in the morning in a red-topped vacutainer, was used for the estimation of fasting serum glucose, uric acid, and lipid profile. The second and third blood samples were collected after 1hr and 2hrs post-glucose load (75 g of anhydrous glucose dissolved in 100 ml of water) in a red vacutainer for postprandial plasma glucose estimation. After properly mixing the sample, it was left at room temperature for 15-20 minutes for clot formation. The vacutainer was then centrifuged at 3000-5000 rpm for 15 minutes for the separation of clear serum. The serum was aliquoted into Eppendorf tubes, analyzed immediately, and stored at -4^{0}C until the completion of the study period.

(vii) Biochemical analysis: A Beckman Coulter AU 480 clinical chemistry analyzer was used for analysis. The instrument was calibrated, and calibration was checked using appropriate controls. After completing the maintenance of the auto-analyzer, the accuracy and precision of each parameter were tested using QC material. When QC results were within the range, sample analysis was performed. Grossly hemolyzed, lipemic, or icteric samples were not used for analysis in the present study and were discarded. The obtained values were recorded in an Excel sheet**.**

- Uric acid was estimated in serum samples by a modification of the Fossati method, i.e., the Uricase-Peroxidase method, on an AU480 clinical chemistry analyzer.

- Serum glucose was estimated in fasting and postprandial samples using the hexokinase- G6PD method.
- Total cholesterol was estimated using the cholesterol oxidase-peroxidase method; serum triglycerides were estimated using the glycerol oxidase method; HDL-C was estimated using the HDL CH esterase and peroxidase method. VLDL-C and LDL-C were calculated using Friedewald's formula.
- UHR was calculated from serum uric acid and HDL-C values using the formula UA/HDL-C.

(viii) Statistical analysis: Data collected for each variable in the two groups were tested for normal distribution and summarized as Mean ± SD. Mean ± SD was compared between the two groups for statistical difference using student's t-test, with *P-values* < 0.05 considered statistically significant and *P-value* < 0.001 considered highly statistically significant. The association of UHR with other variables in each group, such as BMI, TC, TG, LDL-C, FSG, and PPSG was calculated using Pearson's correlation, with the strength of the correlation expressed as the *R-value*.

Demographic information (age, height, weight, BMI) of cases and controls was noted in data collection tables. Height was measured in meters from displayed charts, and weight was measured using a weighing scale. BMI was calculated using the formula weight in kg/ height in meters^2.

Results

The results of the present study are shown in Table 1 and Table 2 as follows:

Table 1. Mean ± SD values in GDM and Controls along with *P-value*

S No	Parameter	Controls	Cases	*P-value*
1	Age (Years)	25.8 ± 4.2	30.2 ± 4.6	< 0.001
2	BMI (Kg/m^2)	25 ± 2.6	31.1 ± 5.0	< 0.001
3	FSG (mg/dl)	82.1 ± 8.5	123.7 ± 21.4	< 0.001
4	PPSG (mg/dl)	110.4 ± 10	209.7 ± 36.7	< 0.001
5	Total Cholesterol (mg/dl)	156 ± 25.9	210.4 ± 15.2	< 0.001
6	Triglycerides (mg/dl)	117.7 ± 26.8	177.5 ± 28.4	< 0.001
7	HDL-C (mg/dl)	47.7 ± 5.1	42.8 ± 4.6	< 0.001
8	LDL-C (mg/dl)	85.7 ± 24.2	133.2 ± 15.8	< 0.001
9	VLDL-C (mg/dl)	23.5 ± 5.4	35.5 ± 5.7	< 0.001
10	Uric Acid (mg/dl)	5.2 ± 0.9	6.8 ± 0.7	< 0.001
11	UHR	0.1121 ± 0.02	0.1609 ± 0.023	< 0.001

The mean age of GDM patients is 30.2 ± 4.6 years, compared to 25.8 ± 4.2 years in the control group, showing a statistically significant difference (*P-values* < 0.001). GDM patients have a higher mean age than the control group. The mean BMI in GDM patients was 31.1 ± 5 kg/m^2, compared to 25 ± 2.6 kg/m^2 in the control group, showing a statistically significant difference (*P-values* < 0.001). GDM patients have a higher BMI compared to the control group.

Glycaemic parameters: FSG in GDM patients has a mean value of 123.7 ± 21.4 mg/dl compared to normal pregnancy, where the mean value is 82.1 ± 8.5 mg/dl. PPSG in GDM patients is 209.7 ± 36.7 mg/dl compared to normal pregnancy controls at 110.4 ± 10 mg/dl. These values show a statistically significant difference between the two groups.

Lipid profile parameters: Serum lipid profile values in GDM show a dyslipidemic pattern, with increased TC, TG, LDL-C, VLDL-C, and decreased HDL-C.

Uric acid: Mean serum uric acid levels in GDM patients are 6.8 ± 0.7 mg/dl compared to 5.2 ± 0.9 mg/dl in normal pregnancy. There is a statistically significant elevation of serum uric acid in GDM patients compared to controls (*P-values* < 0.001).

Uric acid-HDL Cholesterol Ratio: UHR in GDM is 0.1609 ± 0.023 compared to 0.1121 ± 0.02 in controls, showing a statistically significant elevation in GDM (*P-values* < 0.001) compared to controls (Figure 1).

Fig. 1. parameters of the case group and the control group

Table 2. Correlation between UHR and other parameters in GDM and controls

***R-value* of UHR**	**Cases**	**Controls**
BMI	0.7615	0.6233
FSG	0.5302	0.505
PPSG	0.5424	0.502
TC	0.3712	0.343
TG	0.3212	0.388
LDL-C	0.4295	0.332

This data shows that there is a linear positive relationship between UHR and TC, TG, LDL-C, FSG, PPSG, and BMI in GDM.

UHR has a strong association with BMI (r value = 0.76), a moderate association with FSG (r value = 0.53), PPSG (r-value = 0.50), and LDL-C (r value = 0.43), and a weak association with TC (r value = 0.37) and TG (r-value = 0.32) in GDM. In controls, UHR is strongly correlated with BMI (r-value = 0.62), has a moderate association with FSG (r-value = 0.505) and

PPSG (r-value = 0.502), and is weakly associated with TC (r-value = 0.343), TG (r value = 0.388), and LDL-C (r-value = 0.332).

When comparing the degree of association of UHR with other parameters between the two groups, UHR is strongly associated with BMI in both GDM and controls. It is moderately associated with FSG and PPSG in both groups. It is weakly associated with the lipid profile in controls, but in GDM cases, it is moderately associated with LDL-C and weakly associated with TC and TG. The above data is illustrated in scatter plots showing the relationship between UHR and other parameters in both cases and controls (Figure 2-7).

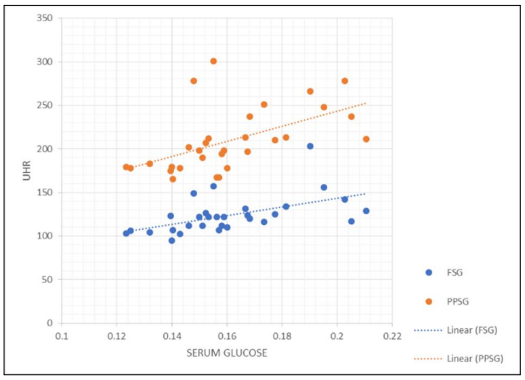

Fig. 2. Relationship b/w Glucose and UHR in GDM

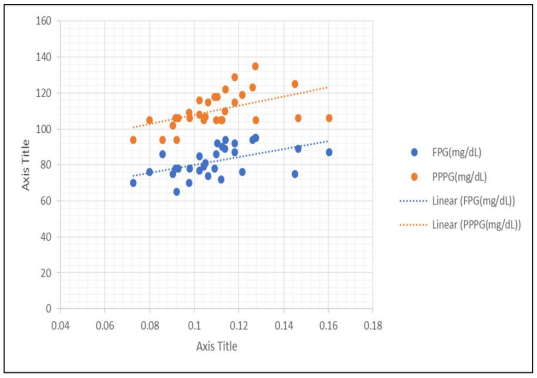

Fig. 3. Relationship b/w Glucose and UHR in Controls

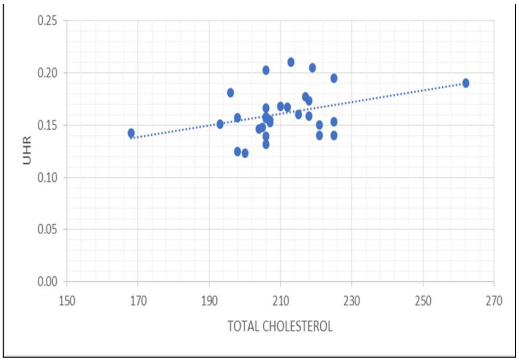

Fig. 4. Relationship b/w TC and UHR in GDM

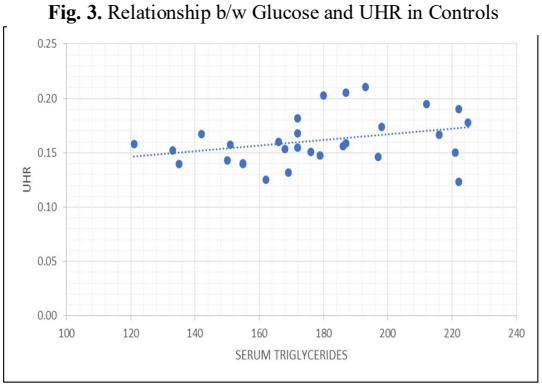

Fig. 5. Relationship b/w TGL and UHR in GDM

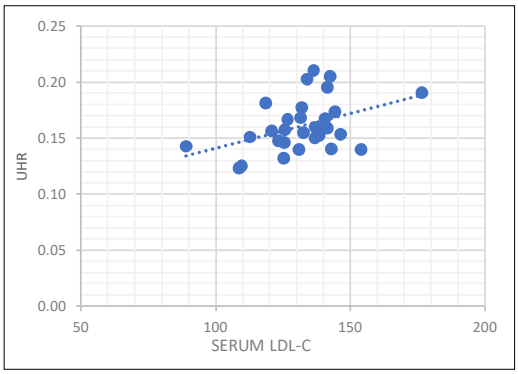

Fig. 6. Relationship b/w LDL and UHR in GDM

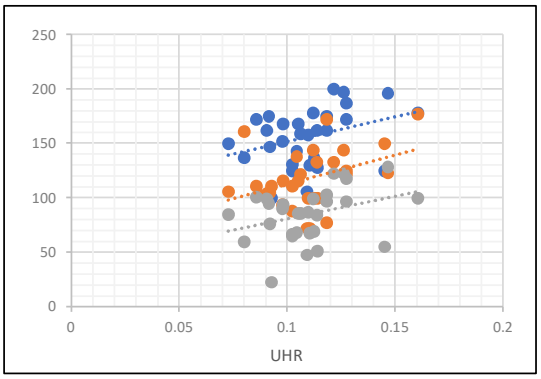

Fig. 7. Relationship b/w LP and UHR in Controls

TC = Total Cholesterol; TGL = Triglycerides; LP = Lipid Profile

Discussion

The present study aims to associate the role of metabolic derangements in the development of GDM. The prevalence of GDM is increasing nowadays. Pregnant women with GDM are at an increased risk of future complications such as T2DM, metabolic syndrome, cardiovascular accident.

The mean age of GDM cases in our study was 30.2 ± 4.6 years compared to the Prakash et al. study "Maternal and neonatal outcome in mothers with gestational diabetes", where the average age was 28 years (13). The mean age was significantly higher in cases compared to controls (25.8 ± 4.2 years). The increased age group of pregnant women carries a risk for GDM similar to the systematic review article by Li et al., where the authors demonstrated an increased risk of GDM with advancing maternal age. The exact mechanism associating increased maternal age with an increased risk of GDM is not clear, but possible explanations include high levels of adipocytokines, high insulin resistance, and inflammatory markers (14).

The mean BMI of GDM cases, 31.1 ± 5 kg/m^2, is significantly elevated compared to the BMI of control group pregnant women. The increased BMI in pregnant women carries an increased risk for GDM. Our study findings are similar to the conclusions of Martin, et al., who reported that increasing maternal age is a significant risk factor for GDM. GDM and increased BMI conditions both share a similar metabolic milieu i.e., increased insulin resistance, hypertriglyceridemia, hypercholesterolemia, hyperglycaemia and low-grade chronic inflammation. Adipose tissue, plays a critical role in innate immune sensing and secretes adipocytokines, which mediate insulin resistance (15).

Fasting serum glucose and post prandial serum glucose values are significantly elevated in GDM compared to controls because of the hyperglycaemia observed in GDM, which is the basis for the diagnosis.

Lipid profile values in GDM show a dyslipidaemia pattern (increased TC, TG, LDL-C and decreased HDL-C) in our study. These findings are supported by fthose of Ghodke et al., and Wang et al. where similar results were reported (16, 17). However, Lenin et al.'s study reported decreased serum TC levels in GDM compared to controls (18).

Plasma lipid profile values change during normal pregnancy due to increased estrogen levels and insulin resistance. During the first two-thirds of gestation, there is an increase in maternal fat accumulation due to hyperphagia and increased lipogenesis. In the last third of gestation, increased lipolytic activity and reduced lipoprotein lipase activity lead to a decrease in maternal fat storage or even cessation. These changes reflect maternal physiological adaptation to the energy demands of the fetus and prepare for delivery and lactation. However, it is difficult to differentiate between physiological and pathological lipid profile changes during pregnancy. Hypertriglyceridemia and decreased HDL-C levels are associated with insulin resistance in GDM. These metabolic derangements in GDM carry a long-term inherent risk for metabolic syndrome, hyperlipidemia, and T2DM in the mother (19).

Uric acid levels in our present study are significantly elevated in GDM compared to controls, similar to the findings of Murthy et al. and Zhao et al. The higher range of serum uric acid observed in the present study compared to other studies may be due to differences in the study population and methods of estimation. However, all the above-mentioned studies observed elevated serum uric acid levels in GDM compared to controls (20, 21).

Elevated serum uric acid may result in impaired endothelial integrity, decreasing vascular response to nitric oxide. Increased blood glucose levels in GDM may increase the formation of oxygen free radicals and oxidative stress, resulting in increased uric acid concentrations, which account for a considerable proportion of the antioxidant activity of plasma. GDM is characterized by an amplification of the low-grade inflammation that already exists in normal pregnancy. Increased inflammation is another mechanism contributing to the production of free radicals (22).

UHR is associated with metabolic syndrome, as UA and HDL-C are indicators of metabolic derangements. UHR is commonly estimated in diabetes, where it has

been linked to the development of long-term complications (23, 24). There are no studies comparing UHR in GDM and pregnant women. Our study shows that there is a statistically significant elevation of UHR in GDM compared to normal pregnancy, suggesting the presence of metabolic derangements in GDM.

Similar to the findings of Aktas et al., who reported a positive correlation between UHR and FPG, as well as BMI, in type 2 diabetes, the present study findings also show a positive correlation between UHR and FSG, as well as UHR and BMI, in GDM. UHR and BMI in normal pregnancy appear to be better markers of metabolic syndrome than other indicators (25).

UHR is also considered as significant indicator of glycaemic control as the above study findings suggest positive correlation between UHR and HBA1C. The plausible mechanism being increased BMI, increased adipose tissue, release of Adipocytokines, increased insulin resistance, increased blood glucose levels, dyslipidaemia changes, increased oxidative stress and increased uric acid levels. These above changes may be responsible for increased UHR in GDM.

UHR is also positively correlated with changes in TC, TG, and LDL-C, as these pathological metabolic changes are driven by insulin resistance in GDM.

Limitations

The main limitation of this study is the small sample size and short duration. Additionally, as a cross-sectional study, we could only determine the degree of association between UHR and glycaemic status markers and BMI in GDM and normal pregnant women. To better elucidate the diagnostic role of UHR in determining long-term complications, a cohort study is recommended. Lastly, the degree of association between HbA1c and UHR was not assessed in this study.

Conclusion

Our study found that UHR was significantly elevated in GDM compared to normal pregnancy, with positive correlations to FSG and BMI. These findings suggest that UHR may have potential as an early screening tool for metabolic abnormalities in GDM. If validated in larger studies, UHR could potentially be used to identify GDM patients at higher risk of metabolic complications, enabling targeted interventions. Although limited by its small sample size and cross-sectional design, this study provides a foundation for further research. Longitudinal studies are needed to evaluate the predictive value of UHR for long-term metabolic outcomes in women with a history of GDM. By improving our ability to identify and monitor metabolic abnormalities in GDM, we may be able to reduce the long-term risks of T2DM, metabolic syndrome, and cardiovascular problems in this population.

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None.

Ethical statement

This study was approved by the Institutional Ethics Committee (IEC/RMC/2023/031).

Data availability

The data supporting this study's findings are available from the corresponding author upon reasonable request.

Author contributions:

Author 1: Conceptualization, data collection, data analysis, draft manuscript

Author 2: Study design, data analysis, data interpretation, manuscript preparation

Author 3: Data Analysis, data interpretation, manuscript revision, proof reading

Corresponding Author: Manuscript preparation, manuscript revision, proof reading, correspondence

* All authors reviewed the results and approved the final version of the manuscript.

Conflict of interest

None.

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