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RESEARCH ARTICLE

DYNAMIC CHANGES ININFLAMMATORY PROFILES OF THYROID DYSFUNCTION: A COMPARATIVE ANALYSIS OF HYPERTHYROIDISM AND HYPOTHYROIDISM

Shikha Paliwal and Ruchi Kant
Department of Medical Laboratory Techniques, College of Paramedical Sciences, Teerthanker Mahaveer University, Moradabad, Uttar Pradesh, India.

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Abstract

Introduction and Aim: The thyroid gland, an endocrine organ, produces vital hormones (T3 and T4) regulating metabolism. Thyroid-stimulating hormone (TSH) controls their release, impacting body tissues. C-reactive protein (CRP), an acute-phase protein, serves as a biomarker, crucial in diagnosing and managing various health conditions, particularly thyroid disorders. Elevated CRP levels often accompany thyroid dysfunction, highlighting the link between inflammation and thyroid disease pathogenesis, essential for diagnosis and management strategies.

Methods: The research was conducted at the College of Paramedical Sciences, Teerthanker Mahaveer University &Teerthanker Mahaveer Hospital & Research Center, Moradabad in India, using random sampling. Blood sample was collected in the vacutainer and serum was separated for the clinical examination of CRP by turbidimetric immunoassay method. Clinical examinations were estimated in the biochemistry lab at the College of Paramedical Sciences by using a Semiautoanalyser.

Results: The CRP levels in both hypothyroid and hyperthyroid groups were found higher as compared to euthyroid individuals, with mean CRP levels of 8.42 mg/dl, 5.67 mg/dl, and 5.05 mg/dl, respectively. A positive correlation between CRP and TSH is observed in hypothyroidism ($r = 0.220$). While hyperthyroidism exhibits slightly elevated CRP levels compared to healthy controls (5.67 mg/dl vs. 5.05 mg/dl), this difference lacks statistical significance ($p>0.05$). Notable variances in serum Hs-CRP levels are observed among individuals with hypothyroidism compared to euthyroidism ($p<0.05$), hyperthyroidism compared to euthyroidism ($p>0.05$), and hyperthyroidism compared to hypothyroidism ($p<0.05$), as determined by statistical analysis.

Conclusion:A notable elevation in CRP levels among individuals with hypothyroidism and hyperthyroidism compared to those with euthyroidism. Additionally, a positive correlation is observed between CRP and TSH levels, particularly in the hypothyroid group. The disparities in Hs-CRP levels among different thyroid conditions underscore the link between thyroid function and inflammatory status.

Corresponding Author:- Shikha Paliwal
Address:- Department of Medical Laboratory Techniques, College of Paramedical Sciences, Teerthanker Mahaveer University, Moradabad, Uttar Pradesh, India.

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Introduction:-

The thyroid gland, an endocrine powerhouse, synthesizes essential thyroid hormones: thyroxine (T4) and triiodothyronine (T3). Initially, T4 is secreted, later converted into T3 by the removal of an iodine molecule [1]. These hormones are pivotal in the body's energy metabolism, governing storage and utilization processes [2]. Regulated by thyroid stimulating hormone (TSH), released by the pituitary gland, T3 and T4 exert their influence on every tissue in the body. Any disruption in their synthesis can disrupt organ function, highlighting their critical role [3]. Thyroid dysfunction manifests primarily as hyperthyroidism and hypothyroidism. Hyperthyroidism sees an overproduction of thyroid hormones, while hypothyroidism witnesses a deficiency. Both conditions can lead to a myriad of health issues, affecting individuals globally, with India bearing a significant burden [4]. Research suggests that around forty-two million individuals in India suffer from thyroid dysfunctions, with a notably higher prevalence among obese females. Multiple factors, including genetics and environment, contribute to these disorders [5].

C-reactive protein (CRP) is an acute-phase reactant protein synthesized by the liver in response to inflammatory stimuli [6]. It serves as a key biomarker of systemic inflammation and is widely used in clinical practice to assess and monitor inflammatory processes. [7]. CRP levels increase rapidly in response to tissue injury, infection, or other inflammatory conditions, making it a valuable tool for diagnosing and monitoring a wide range of diseases [8]. In addition to its role as a marker of inflammation, CRP has been implicated in the pathogenesis of various diseases, including cardiovascular disease, rheumatoid arthritis, and certain types of cancer. Elevated CRP levels have been associated with an increased risk of cardiovascular events, such as heart attack and stroke, suggesting that CRP may play a role in the development and progression of atherosclerosis and other cardiovascular disorders [9]. Moreover, CRP has been proposed as a prognostic marker in several diseases, with higher CRP levels often indicating a worse prognosis. For example, in patients with sepsis or acute respiratory distress syndrome (ARDS), elevated CRP levels have been associated with increased mortality rates. This highlights the potential utility of CRP as a prognostic indicator in critically ill patients [10].

Changes in inflammatory profiles accompany thyroid dysfunction, reflecting the intricate interplay between the immune system and the thyroid gland. Inflammation plays a pivotal role in the pathogenesis of thyroid disorders, influencing disease progression and clinical manifestations [11]. Thyroid dysfunction, encompassing hypothyroidism and hyperthyroidism, triggers a cascade of inflammatory responses mediated by various cytokines, chemokines, and acute-phase reactants [12]. Studies have demonstrated that patients with thyroid dysfunction often exhibit altered levels of inflammatory markers, including C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) [13]. These dynamic changes in inflammatory profiles contribute to the systemic manifestations of thyroid disorders, such as cardiovascular complications, metabolic abnormalities, and autoimmune phenomena. Understanding the dynamic nature of inflammatory profiles in thyroid dysfunction is essential for elucidating disease mechanisms, identifying biomarkers for diagnosis and prognosis, and developing targeted therapeutic interventions. Further research into the temporal dynamics and functional implications of inflammatory mediators in thyroid disorders is warranted to advance our understanding and improve patient care.

Materials and Methods:-

Study setting and design:

Aprospective, cross-sectional study was conducted in northwestern Uttar Pradesh, district of Moradabad.

Sample size and sampling technique:

The research was conducted at the Study Center of the College of Paramedical Sciences, Teerthanker Mahaveer University, and Teerthanker Mahaveer Hospital and Research Center in Moradabad, Uttar Pradesh, India. The simple random sampling technique was used to select samples from Teerthankar Mahaveer University Hospital and Research Centre.The study criteria outlined inclusion and exclusion criteria. Inclusion criteria encompassed patients with thyroid dysfunction aged 18 years and above. Exclusion criteria included patients with diseases other than thyroid, those above 65 years, individuals with surgeries affecting thyroid function, and pregnant women.

Ethics, consent, and permissions:

The study conducted at Teerthanker Mahaveer College of Paramedical Sciences in Moradabad, Uttar Pradesh, India, has received approval from the College Ethics Committee. The approval was granted during the Ethics Committee Meeting held on January 19, 2023, at the Committee Room of the College of Paramedical Sciences, Teerthanker

Mahaveer University, Moradabad. The study protocol, outlined in Annexure I to V, was approved by both the College Ethics Committee members and Academic Board members. Before participation, all patients were provided with a patient information sheet, and informed consent in both Hindi and English was obtained from each patient. The study is registered with the College Ethics Committee under reference PM/ETHICAL/COPS/2023/022.

Data collection:
From 2022 to 2023, a cross-sectional study was conducted among the thyroid population in Moradabad District, India. The study included 225 participants from Teerthankar Mahaveer Hospital and Research Centre, Moradabad, categorized into 75 Hypothyroid, 75 Hyperthyroid, and 75 Euthyroid individuals, aged between 18-65 years. Participants with thyroid dysfunction were involved, and a pre-validated questionnaire, both closed and open-ended, was administered after obtaining informed consent. The questionnaire, validated by experts, was translated into Hindi and back-translated to English to ensure tool reliability.

Clinical Examination:
The subject's fresh fasting blood sample was collected by a phlebotomist in a red top vacutainer by venipuncture for the analysis of thyroid profile (T3, T4, and TSH) and CRP. Triiodothyronine (T3) is a vital thyroid hormone influencing growth, metabolism, and body temperature regulation. The Quanti Microlisa method offers a precise enzyme immunoassay for quantifying T3 levels in serum samples. Competitive ELISA methodology is employed, where anti-triiodothyronine antibodies coat microwells, enabling the detection of T3 bound with enzyme-conjugated T3. The procedure involves serial addition of standards and samples, followed by incubation, washing, substrate addition, and stop solution. Accurate T3 measurements at 450 nm facilitate research on thyroid dysfunction. Thyroxine (T4), another crucial thyroid hormone regulating metabolism, growth, and development, is quantified using the sensitive Quanti Microlisa method. Competitive ELISA is employed, with anti-thyroxine antibodies coating microwells. Sample addition allows T4 binding with enzyme-conjugated T4 for detection. Similar to T3 quantification, the procedure involves serial addition of standards and samples, incubation, washing, substrate addition, and stop solution, with absorbance measured at 450 nm. Thyroid Stimulating Hormone (TSH), a glycoprotein hormone crucial for thyroid function assessment, is quantified using the effective Quanti Microlisa method. Sandwich ELISA is employed, with microwells coated with anti-TSH antibodies. Sample addition enables TSH binding with enzyme-conjugated anti-TSH for detection. The procedure involves serial addition of standards and samples, incubation, washing, substrate addition, and stop solution, with absorbance measured at 450 nm.

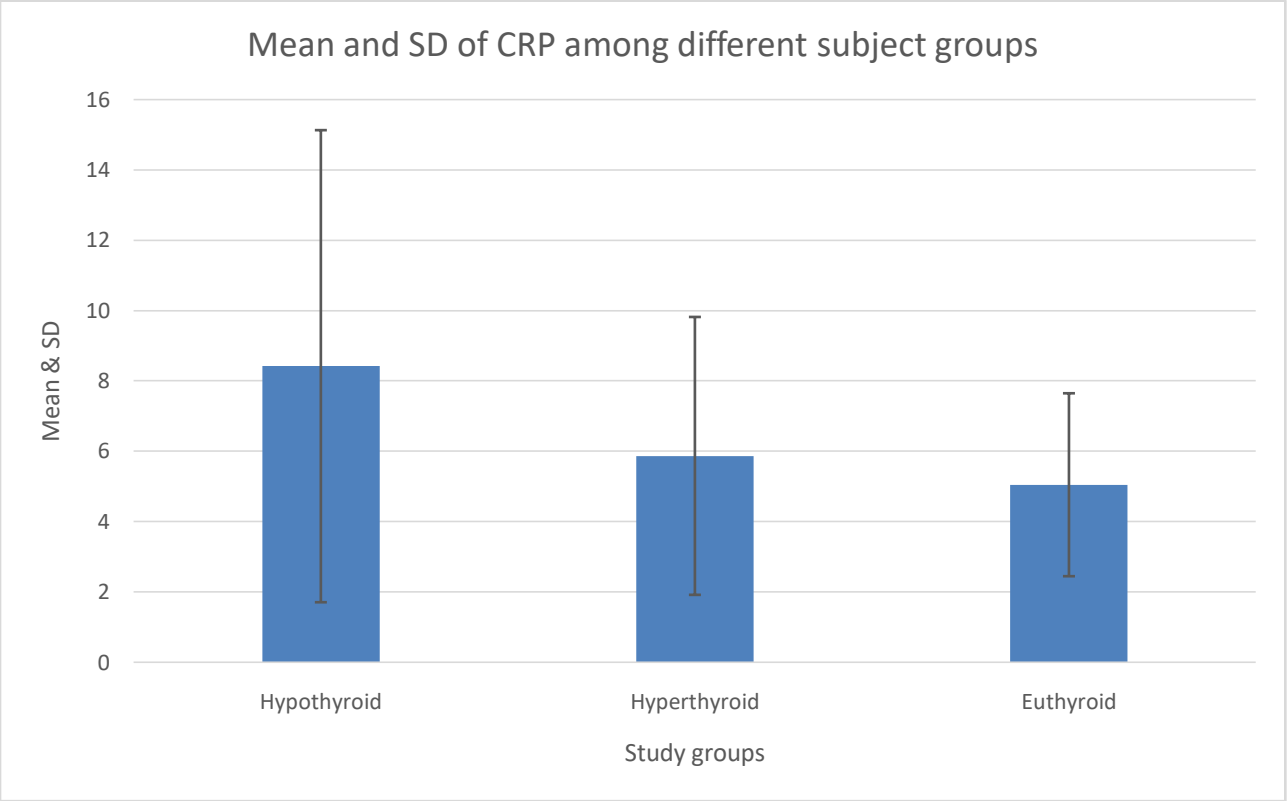
Plasma C-reactive protein (CRP) serves as a vital biomarker reflecting systemic inflammation. The Turbilyte-CRP kit employs a turbidimetric immunoassay method for precise CRP testing. Patient serum or plasma is mixed with specific antibodies labeled with particles, inducing turbidity proportional to CRP concentration. The kit includes activating buffer (R1) and latex particles conjugated with anti-CRP antibodies (R2) crucial for immune complex formation. Calibration solutions ensure accurate quantification. This literature kit comprehensively explores CRP's significance, from its role as an acute-phase reactant to its emerging associations with various health conditions. Through critical analysis, it navigates the intricate landscape of CRP in diagnostic medicine, empowering readers with a nuanced understanding of its diagnostic utility and potential in medical research and practice.

Statistical analysis:
The data was analyzed utilizing SPSS software, and the normality of continuous data distribution was assessed through the Kolmogorov-Smirnov test. Descriptive statistics were employed to showcase the demographic and fundamental clinical parameters of the study participants. In terms of statistical analysis, inferential methods i.e. the Paired t-test, Pearson correlation, and ANOVA test were utilized. The significance level (alpha) was established at 5%, and the study's power was set at 80%.

Results:-

This perspective, clinical-based, cross-sectional, and single-centered study aimed to investigate and compare CRPinthe blood of 225 subjects, categorized into three groups: 75 individuals with hypothyroidism, 75 with hyperthyroidism, and 75 with euthyroid (normal thyroid function). The study was conducted at Teerthanker Mahaveer Hospital & College of Paramedical Sciences in Moradabad over two years, from 2022 to 2023.The parameteranalyzed in the blood samples includes CRP (C-reactive protein). The parameter was selected to provide a comprehensive understanding of the subjects' metabolic and thyroid health. The sample collection process was carried out under the prescription of an endocrinologist, ensuring a standardized and controlled approach to sample acquisition. The age range of the subjects included in the study varied from 18 to 65 years.Additionally, the

specified time frame of the study ensures that the observations are confined to a specific period, reducing the impact of potential external factors.Overall, this study contributes valuable insights into the relationships between thyroid function, metabolic parameters, and immune responses in a diverse subject population, shedding light on potential correlations and distinctions between hypothyroid, hyperthyroid, and euthyroid individuals.



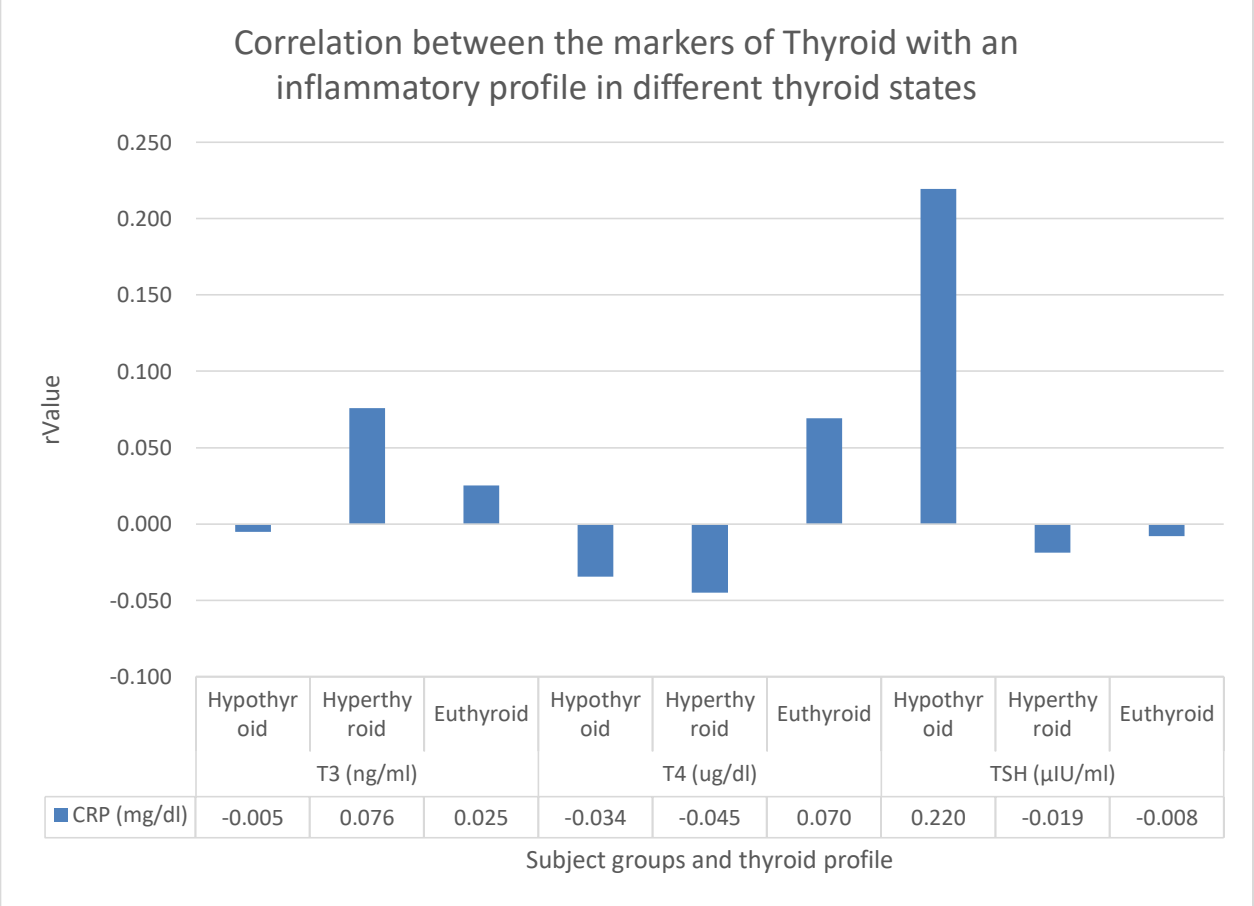
Graph3.1:- Mean and SD of CRP among different subject groups.

The above graph shows that, in hypothyroid individuals, the mean CRP concentration was markedly elevated at 8.42 mg/dl, with a standard deviation of 6.71. Conversely, individuals with hyperthyroidism exhibited a substantially lower mean CRP level of 5.87 mg/dl, accompanied by a standard deviation of 3.95, Euthyroid individuals, with a CRP mean concentration of 5.05 mg/dl and standard deviation of 2.60.

Group	**Two sample t-test with p-value Hypo Vs Euthyroid**	**Two sample t-test with p-value Hyper Vs Euthyroid**	**Two sample t-test with p-value Hypo Vs Hyperthyroid**
CRP (mg/dl)	<0.05	>0.05	<0.05

Table3.1:- p Value of two-sample t-tests comparing CRP levels between different subject groups.

The analysis presents the results of two-sample t-tests comparing CRP levels between different groups: Hypothyroid vs. Euthyroid p-value <0.05, Hyperthyroid vs. Euthyroid p-value >0.05, and Hypothyroid vs. Hyperthyroid p-value <0.05. The p-values indicate the statistical significance of the differences observed between the groups.



Graph3.2:- Correlation between the markers of Thyroid with an inflammatory profile in different thyroid states

The above Graph consists of correlation coefficients (r values) between thyroid hormones (T3, T4, TSH) and CRP (C-reactive protein) levels in different thyroid conditions (Hypothyroid, Hyperthyroid, Euthyroid).

a) T3 and CRP: In individuals with hypothyroidism, the correlation coefficient of -0.005 between T3 and CRP signifies an extremely weak negative correlation. Conversely, in hyperthyroidism, the correlation coefficient of 0.076 suggests a weak positive correlation. In euthyroidism, the correlation coefficient of 0.025 indicates a very weak positive correlation.

b) T4 and CRP: In hypothyroidism, the coefficient of -0.034 suggests a weak negative correlation. Conversely, in hyperthyroidism, the coefficient of -0.045 indicates a slightly stronger negative correlation. In euthyroidism, the coefficient of 0.070 reveals a moderate positive correlation.

c) TSH and CRP: In hypothyroidism, the coefficient of 0.220 indicates a strong positive correlation. Conversely, in hyperthyroidism, the coefficient of -0.019 suggests a weak negative correlation. In euthyroidism, the coefficient of -0.008 indicates a very weak negative correlation.

Group	**Hypothyroid**	**Hyperthyroid**	**Euthyroid**	**F ratio value**	**p-value**
	Mean ± SD	**Mean ± SD**	**Mean ± SD**		
CRP (mg/dl)	8.42 ± 6.71	5.87 ± 3.95	5.05 ± 2.60	10.34682	<0.05

Table 3.2:- p Value of ANOVA test comparing mean CRP levels across the three thyroid groups

This table appears to present data related to levels of C-reactive protein (CRP) across different thyroid statuses: hypothyroid, hyperthyroid, and euthyroid. value indicates the statistical significance of the F ratio value. In this case, the p-value <0.05, indicates a highly significant difference in CRP levels between the three thyroid groups. Specifically, hypothyroid individuals tend to have much higher CRP levels compared to both hyperthyroid and euthyroid individuals.

Discussion:-

The current research demonstrates a notably elevated CRP level in both hypothyroid and hyperthyroid groups when compared to the euthyroid group (with mean CRP levels of 8.42 mg/dl, 5.67 mg/dl, and 5.05 mg/dl, respectively).**Hammo Y et al (2019) &Savas E et al. (2016)**discovered that CRP levels were notably elevated in both the hypothyroid and hyperthyroid groups in comparison to the control group (with mean CRP levels of 5.62 mg/dl, 5.75 mg/dl, and 3.59 mg/dl, respectively) [14, 15].

In our current study, we also observed a positive correlation between CRP and TSH levels in the hypothyroid group when compared to the euthyroid group (with an r-value of 0.220). **Jouda J et al. (2019)** determined that there was a significant positive correlation between CRP levels and thyroid profile in the thyroid group compared to the euthyroid group [16].

In this study, we observed slightly elevated CRP levels in individuals with hyperthyroidism compared to those in the healthy control group (mean CRP levels were 5.67 mg/dl and 5.05 mg/dl, respectively). However, this variance did not reach statistical significance ($p>0.05$). **PopBawska-Kita A et al (2013)** observed marginally elevated CRP levels among individuals with hyperthyroidism compared to healthy controls (average CRP levels were 3.6 mg/dl in subclinical hyperthyroidism and 3.2 mg/dl in the control group), but this discrepancy did not reach statistical significance [17].

In this study, we observed notable variances in serum Hs-CRP levels among individuals with hypothyroidism compared to those with euthyroidism ($P<0.05$), individuals with hyperthyroidism compared to those with euthyroidism ($p>0.05$), and individuals with hyperthyroidism compared to those with hypothyroidism ($p<0.05$), as determined by statistical analysis.**Czarnywojtek A et al (2014)** identified significant disparities in serum Hs-CRP levels across various thyroid conditions: hypothyroidism versus euthyroidism ($p = 0.001$), hyperthyroidism versus euthyroidism ($p = 0.007$), and hyperthyroidism versus hypothyroidism ($p = 0.001$), as indicated by statistical analysis[18].

Conclusion:-

In conclusion, the study revealed a significant increase in CRP levels among individuals with both hypothyroidism and hyperthyroidism compared to those with euthyroidism also noted a positive correlation between CRP and TSH levels specifically within the hypothyroid group compared to the euthyroid group. significant differences were noted in serum Hs-CRP levels across various thyroid conditions i.e. between hypothyroidism and euthyroidism & hyperthyroidism and hypothyroidism. These findings underscore the potential association between thyroid function and inflammatory status as indicated by Hs-CRP levels.

Limitations of the study

We advocate for further investigations with larger sample sizes to validate our findings regarding the association between thyroid hormones and inflammatory markers. While our study offers insights, its cross-sectional nature warrants caution in interpretation. Future studies should explore associations between Mean Platelet Volume (MPV) and thyroid hormone levels in hypothyroidism, considering variables like sex and age. It's crucial to note that correlation doesn't imply causation, necessitating deeper research into underlying mechanisms and clinical implications.

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Conflict Of Interest

We declare that there is no conflict of interest in this research work.

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