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MEDICINE

Serum Pentosidine Level in Healthy Ageing and Its Association with Age-Related Disease

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Abstract

Advanced glycation end products (AGEs) arise from non-enzymatic reactions between extracellular proteins and glucose. AGEs' formation occurs during normal ageing but distinctly accelerate with the progression of chronic disease. Pentosidine is a very sensitive marker for all AGEs. We investigated whether serum pentosidine was increased and correlated with healthy elderly individuals (80–102 years) and the disease groups (hypertension 60–77 years; and coronary artery disease 60–77 years). Measurement of serum pentosidine levels in healthy elderly individuals is $n = 38$, hypertensive patients $n = 38$, and coronary artery diseases $n = 31$(treated with drugs). Drugs for the treatment of CAD work as inhibitors of advanced glycation end products. Serum levels of pentosidine are measured by using sandwich ELISA. Serum pentosidine concentrations were significantly higher in hypertensive patients (1910.5 ± 302.6 pmol/ml) in comparison with healthy elderly individuals (1605.1 ± 596.5 pmol/ml) as well as in coronary artery disease (1495 ± 531.8 pmol/ml), $p = .002$. Within the age-dependent serum concentration of pentosidine was higher (2148.5 ± 209.8) $p = 0.988$ in hypertension (> 70 years). A multiple linear stepwise regression analysis concludes that in patients with hypertension, serum pentosidine was significantly influenced with the age (standardized $\beta = 0.440$, 95%CI: 5.49–30.05, $p = .006$). The receiver operating characteristic curves for the presence of hypertension diagnosis had an area under the curve (AUC) of 0.675; (95% CI: 0.575–0.775, $p = .003$). The optimal cutoff value of pentosidine was 1120 pmol/ml with 97.4% sensitivity and 76.8% specificity. Serum pentosidine is significantly associated with hypertension in the study group also within their age group. It may be due to atherosclerosis and arterial stiffness.

Keywords Pentosidine · Advanced glycation end products · Ageing · Hypertension · Coronary artery disease

Introduction

Ageing is a multifaceted process where genetic, endogenous and environmental factors play a key role. Pentosidine is an advanced glycation end products (AGEs) which are a heterogeneous set of macromolecules that are formed by the non-enzymatic glycation of lipids, proteins and nucleic acids [1]. AGEs' formation takes place by binding of reducing sugar, such as glucose or fructose to free lysine or arginine NH_2 residues with proteins in an irreversible mode through the Maillard reaction [2]. Foods that are cooked at high temperature are rich in AGEs, which occurs both exogenously (such as diets) and

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endogenously (within the body) by normal consequence of metabolism [3]. Concerning 10% of dietary, AGEs are absorbed, of which about one third is excreted and two thirds deposited in tissues permanently [4]. Advanced glycation end products play a significant role in the process of normal ageing as well as the development and progression of the chronic disease. As seen in these various diseases diabetes mellitus, chronic renal failure [5], Osteoarthritis [6], atherosclerosis and Alzheimer's disease, cardiovascular disease [7]. The major AGEs include argpyrimidine, *Nε*-carboxyethyl-lysine (CEL), *Nε*-carboxymethyl-lysine (CML), glucosepane, hydroimidazolone and pentosidine. Among these CML, pentosidine are common AGEs in food and human plasma [8].

The injuries between the extracellular matrix (ECM) and cells are stimulated by AGEs in three interesting ways. (1) Accretion of AGEs creates a cross-linking between extracellular matrix and AGEs, and this causes a decrease in elasticity of connective tissue and affects vascular function [9]. (2) There are no enzymes to get rid of the glycated product as of the human body; glycated proteins are generally removed via ubiquitin-dependent 20S proteasome-mediated proteolysis [10]. (3) AGE-RAGE (receptor for AGEs) interaction induces inflammatory signalling pathways. The pathogenic mechanisms include polyol pathways flux, activation of diacylglycerol (DAG)-PKC pathways, increased expression of growth factors, accelerated formation of AGEs, oxidative stress, rennin-angiotensin system activation and subclinical inflammation [11].

The accumulation of pentosidine ultimately contributes to changes in the structure and function of the cardiovascular system and presents as arterial stiffening, endothelial dysfunction, myocardial relaxation abnormalities and formation of atherosclerotic plaque [12]. Previous studies have also confirmed that patients with diabetic retinopathy and diabetic nephropathy were significantly increased Pentosidine level compared with controls groups [13].

So far most of the studies compare serum pentosidine between individuals with diabetic mellitus complication with non-diabetic mellitus, coronary heart disease, or severe coronary artery disease (CAD). However, there are limited studies that previously investigated the association of serum pentosidine with healthy aged individuals.

Given because of these considerations, the study aimed to examine, whether serum pentosidine levels were increased with healthy elderly individuals compared with age-related disease, and also investigate their age-dependent association.

Materials and Methods

Participants

A total of 107 patients included in this study. The study was divided into three groups: group 1, healthy elderly individuals (age range 80–102 years) $n = 38$. Group 2 is composed of hypertension $n = 38$ (age range 60–77). Group 3 is composed of coronary artery disease (treated with drugs) $n = 31$(age range 60–77). Group 3 uses drugs for the treatment of coronary artery disease work as inhibitors of advanced glycation end products. All patients are recruited from the Department of General Medicine, Institute of Medical Sciences, Sir Sunder Lal Hospital, Banaras Hindu University Varanasi Uttar Pradesh, India.

Healthy aged participant's categories are based on the following criteria: Charlson Comorbidity Index, Mini Nutritional Assessment (MNA) scores between 24 and 30 normal nutritional grades, 17–23.5 at risk of malnutrition, less than17 malnutrition. Hypertension (HTN) was measured as systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg. Coronary artery disease (CAD) was diagnosed by troponin I and T test as well as ECG (electrocardiography). Patients were classified as CAD according to angiographic results. Exclusion criteria were age below 50 years and patients who do not give consent for the study.

The study was approved by the Institutional Ethics Committee Department of Medicine, Institute of Medical Sciences, Banaras Hindu University ECR/bhu/Inst/UP/2013/Re-registration-2017 dt31.01.2017 (Approval number Dean/2018/EC/336). All methods of this study were in accordance to relevant guideline and regulation. Written informed consent for study participation was obtained from every patient before enrolment and has been approved by ethical committee.

Pentosidine Assay

Venous blood was collected from every subject allowed the blood to clot at room temperature for 30 min. The blood has clotted completely and then centrifuged at 2500–3000 rpm for 10 min. The resulting supernatant serum samples were stored at −80 °C for further analysis. Total pentosidine were quantitatively determined in human serum by sandwich ELISA (enzyme-linked immunosorbent assay) kits provided through MyBioSource catalogue number MBS704095. According to the manufacturer's information's, serum samples were diluted within the detection range of ELISA. The determination range was 31.25 pmol/ml to 2000 pmol/ml with an estimated sensitivity of < 7.81 pmol/ml. The ELISA plate has been pre-coated with an antibody specific to human pentosidine. The samples were added, and later than incubation and washing, the plates were incubated with horseradish peroxidase (HRP), developed with Tetramethylbenzidine (TMB) substrate, and OD 450nm was determined through an ELISA plate reader. Measurements were performed in duplicate, and the results were averaged. The intra-assay and inter-assay coefficients of variation for this ELISA system were < 8 and < 10%, respectively.

Statistical Analysis

The analysis was performed using SPSS version 16.0 software. Data are expressed as the mean ± standard deviation (SD) or median (interquartile range). ANOVA test was used to compare the continuous variables between subgroups. The correlation was determined by linear regression analysis. A receiver operating characteristic (ROC) curve analysis was performed to identify the optimal cutoff points of serum pentosidine concentration for predicting hypertension. The area under the curve (AUC) value was calculated to determine the accuracy of the test. A p value < 0.05 was accepted as statistically significant.

Results

Characteristic of the Studied Population

The main clinical characteristic of the studied population is shown in Table 1. Biological values were statistically different between study groups. The analysis involved age, BMI, SBP, DBP, creatinine, MNA, and pentosidine.

The mean age of the study population with healthy elderly individuals was 89.2 ± 5.5 years, HTN 64.7 ± 7.4 years, and in CAD 63.9 ± 7.1 years. Significant differences were found in age ($p < .001$), BMI ($p < .001$), SBP ($p < .001$), creatinine ($p < .001$) and MNA ($p < .001$), but association of pentosidine was not significantly correlated with DBP ($p = .093$).

Pentosidine Assay

The mean ± standard deviation (SD) of serum pentosidine in healthy elderly individuals is 1605.1 ± 596.5 pmol/ml, hypertension 1910.5 ± 302.6 pmol/ml, and in CAD 1495 ± 531.8 pmol/ml. There were statistically significantly different ($p = .002$) in serum Pentosidine between all three groups. There is a statistically significant difference between healthy elderly individuals and hypertension ($p = .021$) and also in hypertension and CAD patients ($p = .002$). No significant difference was found among healthy aged individuals and CAD ($p = .624$) in serum pentosidine levels in Fig. 1.

Next, we evaluated the relationship between serum pentosidine levels and their age groups within the study groups. Serum pentosidine concentration markedly increased with > 90-year-old healthy individual's 1833.1 ± 371.6 than 80–90-year-old individuals 1472.1 ± 666.5. As in hypertensive patients, > 70 years had a higher concentration 2148.5 ± 209.8 of serum pentosidine than hypertensive patients with 60–70 years 1847.1 ± 293.9. In CAD group with drug effect (inhibitors of AGEs) showed an increased pentosidine level 1598 ± 508.8 between 60 and 70 years than those with > 70 years 1141.6 ± 483.2 as shown in Table 2.

The ability of serum pentosidine concentrations in distinguishing patients with only hypertension from those without hypertension was assessed using receiver operating characteristic (ROC) curves analysis. The ROC curves for the presence of hypertension diagnosis had an area under the curve (AUC) of 0.675 (95% CI: 0.575–0.775, $p = .003$). The optimal cutoff value of pentosidine was 1120 pmol/ml with 97.4% sensitivity and 76.8% specificity (Fig. 2).

By linear regression analysis, serum pentosidine levels tended to correlate, with serum creatinine but not significantly in healthy aged individuals ($r = 0.172$, $p = 0.303$), hypertensive patients ($r = 0.193$, $p = 0.246$), and serum Pentosidine in CAD showed a negative correlation with serum creatinine ($r = -.226$, $p = 0.221$) in Table 3(A).

In addition, serum pentosidine concentration is negatively associated with mini-nutritional assessment in healthy older individuals ($r = -.136$, $p = 0.414$) and the HTN group ($r = -.078$, $p = 0.640$) with non-significant. Pearson correlation analysis showed that serum pentosidine was a positive correlation with MNA in CAD patients (r= 0.295, p=0.107) in Table 3(B).

Table 1 Clinical and biological parameters of the study subjects

Parameters	Healthy elderly individuals ($n = 38$)	Hypertensive patients $n = 38$	CAD (treated with drugs) $n = 31$	p value
Age (yrs.)	89.2 ± 5.5	64.7 ± 7.4	63.9 ± 7.1	< 0.001
BMI (Kg/m2)	19.3 ± 4	25.2 ± 2.9	25.5 ± 3	< 0.001
SBP (mm Hg)	122.4 ± 14.6	138.8 ± 20	131.2 ± 11.3	< 0.001
DBP (mm Hg)	76.5 ± 11.8	80.8 ± 9.6	80.5 ± 4.9	.093
Creatinine (μmol/L)	1.2 ± 0.6	0.86 ± 0.2	0.8 ± 0.2	< 0.001
MNA Score	16.8 ± 2.5	20.3 ± 2.2	21 ± 1.9	< 0.001
Pentosidine (pmol/ml)	1605.1 ± 596.5	1910.5 ± 302.6	1495 ± 531.8	.002

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MNA* mini-nutritional assessment

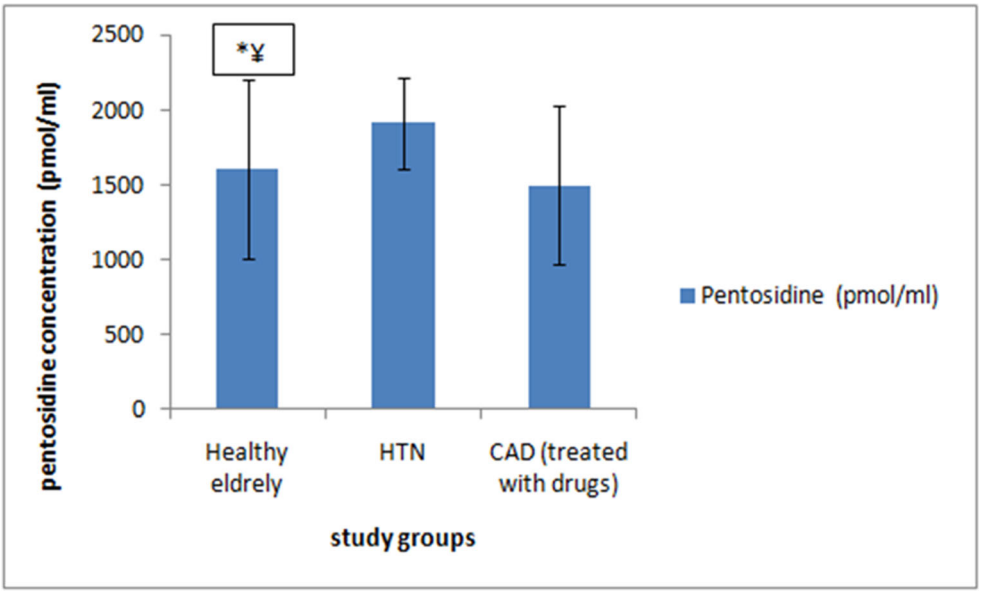

Fig. 1 Concentration of serum pentosidine was compared between healthy elderly individuals and the disease groups. Values are mean ± sSD. * indicates $p = .021$ statistically significant with hypertensive patients. ¥ indicates $p = .624$ statistically not significant with CAD (treated with drugs) group

We constructed a stepwise regression analysis with pentosidine level as dependent variable and age, sex, BMI, SBP, DBP, creatinine and MNA as independent variables. A model that explained a correlation between the concentration of pentosidine and hypertension ($r = 0.68$, i.e. 68%) indicates a good level of prediction. The value of R square ($r^2 = 0.460$), i.e. 46% of the variation of serum pentosidine, can be explained by age, sex, creatinine and DBP in patients with hypertension. Serum Pentosidine was significant influenced the age (standardized β = 0.440, 95%CI: 5.49–30.05, $p = .006$).

Discussion

The main finding of this study is that the concentration of pentosidine levels is higher in hypertensive patients among the three groups. Moreover, the concentration of serum pentosidine level is higher in healthy aged individuals in comparison with coronary artery disease (treated with advanced glycation end products inhibitors).

In hypertensive patients, the increased pentosidine levels due to increased arterial stiffness may contribute to the accretion of pentosidine in the arteries or glycation of their ECM constituents. Because the synthesis of pentosidine involves glycoxidation [14], elevated serum pentosidine concentrations may reflect endothelial dysfunctions and oxidative stress persuade the growth factors according to prior studies [15]. Accumulation of atherosclerotic plaque in blood vessels is also caused by increased Pentosidine levels in hypertensive patients.

Conversely, these studies evaluate the efficacy of assessing the serum concentration of pentosidine in predicting hypertension. No cutoff value of pentosidine to predict the presence of hypertension has been to date. This study revealed best possible cut off of 1120 pmol/ml for Pentosidine (97.4% sensitivity and 76.8% specificity) and suggests that serum concentrations of pentosidine are prospective predictors of the presence of hypertension.

Moreover, we found an optimistic correlation between serum pentosidine and mini-nutritional Assessment in hypertensive patients because nowadays the modern diet contains a high level of AGEs. Diet with increased AGEs consequential an excessive influx of AGEs into the circulatory system, thus enhancing the basal oxidant stress and inflammation. The dietary AGEs levels correlate with the serum concentration of AGEs in equally healthy individuals and people with the disease situation [16].

Table 2 The comparison between serum pentosidine levels and their age groups within the study groups

Study groups	Age groups (in years)	Pentosidine mean ± (SD)	p value
Healthy elderly individuals	80–90	1472.1 ± 666.5	
	> 90	1833.1 ± 371.6	.428
Hypertensive patients	60–70	1847.1 ± 293.9	
	> 70	2148.5 ± 209.8	.988
Coronary Artery Disease (treated with drugs)	60–70	1598 ± 508.8	
	> 70	1141.6 ± 483.2	.846

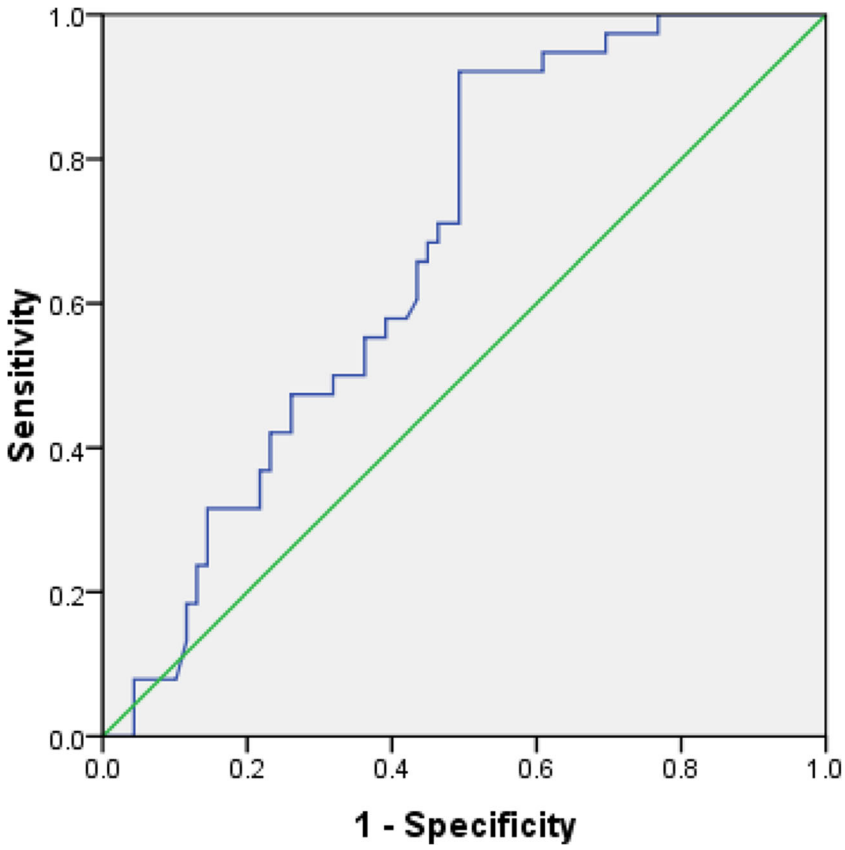

Fig. 2 Receiver-operating characteristic (ROC) curve analysis of the predictive value of serum pentosidine concentration in the presence of Hypertension. The area under the ROC curve is 0.675; 95% CI: 0.575–0.775, $p = .003$

Earlier studies have reported that serum pentosidine was significantly privileged in patients with diabetes mellitus compared with non-diabetic controls. In diabetic patients, serum pentosidine level was significantly higher in patients who had proliferative diabetic retinopathy (PDR) those with non-proliferative diabetic retinopathy (NPDR) [11].

M Kerkeni et al. demonstrated that the concentration of CML and pentosidine were increased both in non-CAD and CAD patients compared with control subjects, and CML further increased in patients with diabetes compared with patients without diabetes [17].

Table 3 Correlation between serum pentosidine levels with study groups (A) serum creatinine (B) mini-nutritional assessment

Study groups	Correlation between Pentosidine and serum creatinine (A)		Correlation between pentosidine and mini-nutritional assessment (B)	
	r	*p*	*r*	*p*
Healthy elderly individuals	0.172	0.303	−.136	0.414
Hypertensive patients	0.193	0.246	−.078	0.640
CAD (treated with drugs)	−.226	0.221	0.295	0.107

r: pearson's correlation *p*:<.05 statistically significant

This shows that in the case of diseased condition, concentration of pentosidine increases. But in our study, the level of pentosidine decreases in CAD patients because CAD patients were under routine medications for the treatment of CAD. Drugs which are used in the treatment of reducing CAD also work as inhibitors for the formation of AGEs. The drugs which were used in the study for the treatment of CAD are benfotiamine, angiotensin converting enzyme (ACE) inhibitors (Ramipril), angiotensin receptor blockers (ARB) and atorvastatin [18].

The action of drugs used in this study benfotiamine is able to completely prevent micro- and macrovascular dysfunction induced by an AGE-rich test meal in patients with type 2 diabetes [19]. Atorvastatin, a lipid-lowering agent, prevents first cardiovascular events including stroke, in patients with T2DM without low density lipoprotein cholesterol [20].

Angiotensin converting enzyme (ACE) inhibitors decrease angiotensin formation, prevents breakdown of bradykinin, and may also act on other peptides of the rennin-angiotensin system. Thus, these agents have many effects that can potentially protect the coronary and peripheral vasculature. Ramipril has potent effects on atherosclerosis regression and plaque stabilization as well as on myocardial structure and also improves glucose metabolism. Ramipril reduced fluorescent AGEs' reduction in blood pressure and proteinuria [21].

Due to multidrug effects, the interaction between AGE and RAGE on the plasma membrane triggers the downstream signalling which inhibited and prevents AGEs' formation in diseased treatment condition. That is why the concentration of pentosidine decreases in CAD patients [22].

The concentration of pentosidine in serum is higher in the case of healthy aged individuals than CAD group. The cause behind these increased levels of pentosidine is merely physiological ageing at the molecular level, because healthy aged individuals did not have any major chronic illness and they are not under any routine medications.

A growing body of evidence has linked age-associated vascular changes, with enlarged artery thickening and stiffness as well as endothelial dysfunction, with a high risk of developing clinically manifest atherosclerosis. It has been observed that individuals over the age of 80 are more likely to decrease glomerular filtration rate, the most important determination ofpentosidine in body fluids [23].

Table 2 showed that pentosidine concentration accelerates along with the advancing age of humans. In age-dependent serum, > 90 year-old-individuals have distinctly higher serum concentration of pentosidine than 80–90-year-old individuals. In hypertension > 70 years patients have higher pentosidine level than 60–70 years patients.

But in the CAD group, concentration of pentosidine is lower in > 70 years patients and higher in 60–70 years patients; ythis reverse effect may be due to decreased level of the receptor of AGEs by the use of inhibitors of the advanced glycation end products for the treatment of CAD. The following possible confines of our comparatively small study populations, short follow-up period, and diverse medications may affect the results.

Conclusions

Pentosidine is a classic form of AGEs with an extended half-life which is primarily found in the ECM. It has now been well established that glycation contributes equally to physiological aging and age-related disease. The present study is one to compare serum concentrations of pentosidine in healthy aged individuals and patients having the disease. We demonstrate that the hypertensive group has markedly higher serum Pentosidine level between the study groups. The presence of drugs led to a decrease in the concentration of pentosidine in the coronary artery disease group. Considering the overall result of this study, anti-AGEs' drugs would be a striking clinical option shortly soon. A further rising point is that pentosidine measurement has still not taken a crucial and prevalent role in clinical practice. Pentosidine level indeed adds new information for the development and succession of hypertension with CAD.

There was a non-significant correlation between healthy aged individuals and serum pentosidine level in this study. With limited preceding publications, there has been a propensity to believe that serum levels of Pentosidine increase with age. This study does not sustain the idea that pentosidine represents an important marker of ageing and for the disease. The level of serum Pentosidine wasn't an independent risk factor in aging and disease. This suggests that traditional risk factors may take part in causing disease events and the serum pentosidine level has low prognostic value. Our result alone cannot be considered the evidence for the involvement of pentosidine in healthy ageing and disease in humans, but they raise a hypothesis and may give rise to further investigations. Further studies are needed, particularly in a larger population to corroborate this finding suggested by the current study.

Authors' Contributions Conceptualization: Dr. Indrajeet Singh Gambhir and Neelam Tia, Methodology: Neelam Tia, Chandra Shekhar Azad and Pritee Chaudhary, Formal analysis and investigation: Neelam Tia and Moti Lal, Writing: Neelam Tia, Writing - review and editing: Neelam Tia, Manish Singh, Funding acquisition: National Programme for Healthcare of the elderly (NPHCE) government of India and the University Grant Commission Rajiv Gandhi National Fellowship (UGC-RGNF). Supervision: Dr. Indrajeet Singh Gambhir

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Compliance with Ethical Standards

Conflict of Interests NT, ML, CSA, PC, MS and ISG have no conflict of interests that are directly relevant to the contents of this article.

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