Protein glycation index and pro-atherogenic indices from laboratory to bedside: Markers of prognostic significance in diabetes mellitus

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Abstract. The aim of the present study was to assess the efficacy of atherogenic indices in prognosis of diabetes mellitus and chronic kidney disease (CKD) and to derive a formula for protein glycation index (PGI) as a marker of aging. The present study evaluated pro-atherogenic indices and glycated proteins in a diabetic population. For the purposes of the present comparative cross-sectional study, 210 subjects were recruited into three groups: Group 1, controls (healthy subjects; n=70); group 2, which included patients with type 2 diabetes mellitus (T2DM; n=70); and group 3, which included patients with T2DM and CKD (n=70). The study comprised 115 male subjects out of the 210 study subjects constituting ~55% of the total study population. Group1 consisted of 31 (44.3%) males, group 2 included 47 (67%) males and group3 had 37 (52.8%) male subjects. The present study enumerated ratios and calculated parameters for the prognosis of T2DM and diabetic neuropathy. The median (25 to 75th percentile) of PGI in the healthy controls was the lowest at 15.99 (8.1-71.4), in patients with T2DM it was 45.01 (17.48-65.29) and in the patients with T2DM and CKD it was 58.2 (33.5-90.0). In addition, a significantly inverse correlation was found between PGI and the anti-aging molecule, Sirtuin1 (-0.823, -0.799 and -0.612 in groups 1, 2 and 3 respectively). Furthermore, there was a significant positive correlation between PGI and carboxymethyl-lysine (0.537, 0.624 and 0.666 groups 1, 2 and 3 respectively). In summary, the present study demonstrates that PGI is a calculated parameter which serve as an index not only for T2DM, but also for other aging-related disorders, since it includes pro-aging molecules and anti-aging molecules. However, further studies using large cohorts with different aging disorders in the same population are required to validate the findings presented herein on PGI.

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Introduction

Uncontrolled diabetes is the primary cause for glycation, which is capable of distorting the cellular skeleton and architecture of vascular tissue, leading to microvascular and macrovascular complications (1). The persistent exposure of cells to the hyperglycemic milieu in type 2 diabetes mellitus (T2DM) leads to the spontaneous non-enzymatic glycation of major macromolecules, such as proteins and lipids (2). The glycation of proteins is termed as advanced glycation end products (AGEs); similarly, poly unsaturated fatty acid (PUFA) glycation is termed as advanced lipoxidation end products (ALEs) (1,3). Therefore, circulating glucose during hyperglycemia affects vascular integrity, causing damage to the end organ. One such end organ examined in the present study is renal tissue, which is affected by increased ALEs, such as carboxymethyl-lysine (CML). By decreasing the action of PUFAs and increasing the levels of pro-inflammatory factors, ALEs are thus formed. Microvascular complications include diabetes with chronic kidney disease (CKD), diabetic retinopathy (DR) and diabetic neuropathy (DN). Macrovascular complications are usually observed in the majority of cases of cardiovascular disease (CVD).

A well-established glycation marker is glycated hemoglobin (HbA1c), which reflects the average glucose level for a period of 120 days (life span of red blood cells) (4). Similarly, glycated albumin, known as fructosamine, can reflect the average glucose level for a period of 21 days (5). Therefore, long- and short-term glucose monitoring aids in the prognosis and management of diabetes mellitus (DM). HbA1c and fructosamine are the endogenously formed glycated products; nevertheless, CML is produced *in vivo* due to the increased consumption of baked, processed and fried fast food, and is hence known as exogenous CML (6). Due to the rapid transformation of lifestyle and food habits in this mechanical era, the monitoring of AGE levels in blood is essential for preventing the onset of aging-related disorders, not only diabetes but also metabolic syndrome, obesity, cancer or thyroid issues.

The following routine parameters are considered for the diagnosis of DM: Fasting blood glucose, post-prandial blood glucose and HbA1c; these are considered as the diabetic profile. An extended diabetic profile includes AGEs, fasting insulin, the homeostasis model assessment for insulin resistance and the quantitative insulin sensitivity check index (7). The recommended guidelines for the diagnosis of diabetes

with CKD include the measurement of blood urea, serum creatinine, sodium and potassium levels, which are included in renal function tests (8); cystatin C, urine albumin and the estimated glomerular filtration rate are considered as extended renal profiling to classify the CKD stage (7). The attrition of the vascular structure increases following the increased exposure to glucose and glucose-derived products (9). This pathological condition causes aging, which is not physiological and thereby, the reverting changes are not viable. To prevent irreversible aging, it is recommended that the levels of AGEs are estimated and markers of aging are determined.

DM is classified as one of the aging-related disorders due to poor insulin production and reception (3). One of the markers related to aging, the levels of which are upregulated during calorie restriction, is Sirtuin1, which is a NAD^+-dependent deacetylase enzyme (10). In prolonged uncontrolled hyperglycemia, NAD^+ are depleted due to impaired insulin action (11). Apart from glucose and glucose-derived products, lipid parameters also need to be managed and controlled to prevent arterial stenosis. Therefore, lipid parameters and ratios derived from analyses, such as the atherogenic index of plasma, atherogenic coefficient (AC), Castelli Risk Index I and II and protein glycation index (PGI) serve as surrogate markers for preventing either the onset or the progression of diabetes to microvascular complications (12,13). Dyslipidemia is either a cause or consequence of diabetic complications; thus, the inclusion of lipid calculations may aid in the selection of treatment modalities (13). Several physicians neglect routine lipid profile analyses, such as HbA1c, which is one of the causes for increased numbers of dyslipidemia and diabetic complications.

As per the recent guidelines laid by the KDIGO for the management of diabetes with CKD, dietary management serves as the first line of treatment, as opposed to medication (8). The preferred medication is precision medicine based on the response of the patient to the current therapy prescribed by the treating clinician. Increased levels of lipid components, such as triglycerides and low-density lipoprotein affect the blood circulation to the renal tissue, causing renal dysfunction (14). Apart from lipid profiles, AGEs also play a crucial role in renal health. Therefore, the aim of the present study was to derive a formula for PGI and associate this with anti- and pro-aging molecules.

Materials and methods

Study design and focus. The present study was a comparative cross-sectional study. Patients with T2DM attending the Outpatient Clinic, at the Department of General Medicine and Diabetology at RL Jalappa Hospital and Research Centre, Tamaka, India (constituent of Sri Devaraj Urs Academy of Higher Education and Research) were recruited for the study after fulfilling the inclusion and exclusion criteria. Written informed consent was obtained from all study subjects. The study groups were as follows: Group 1 (n=70), included age- and sex-matched healthy controls; group 2 (n=70), included patients with T2DM without CKD; and group 3 (n=70), included patients with diabetes and CKD, based on the NKF EPI KDIGO guidelines (8).

Inclusion and exclusion criteria. The following inclusion criteria were used: i) Subjects clinically proven to suffer from T2DM, ii) subjects with T2DM with CKD (diabetic kidney disease), and iii) subjects aged between the ages of 35-70 years.

The exclusion criteria were as follows: Patients with other types of DM; ii) patients taking drugs or other factors known to cause diabetes and/or diabetes with CKD; iii) patients undergoing renal dialysis; iv) patients with acute kidney injury due to any cause and other renal pathologies.

Sample collection. After explaining the purpose of study in a language that was understandable to the patient, a written informed consent was obtained, designed according to the Declaration of Helsinki. Under strict aseptic precautions, the study subjects were allowed to be seated in a comfortable position. After the patients underwent 8 h of fasting, blood samples were collected. The blood samples obtained following fasting were divided into parts for biochemical analyses. For the analysis of plasma glucose levels, the samples were segregated into a NaF tube supplied by APR sales (Ortho Clinical Diagnostics). For the analysis of HbA1c levels, whole blood was collected into an EDTA tube supplied by APR sales (Ortho Clinical Diagnostics). For the analysis of routine biochemical parameters and research molecules, serum samples were collected into plain tubes. Post-prandial blood (at 2 h) samples were also collected. Corresponding urine samples were also collected from the study subjects for urine fluoride analysis.

Study methodology. The present study was ethically approved by the Central Ethics Committee of Sri Devaraj Urs Academy of Higher Education and Research (Kolar, India) recognized by the Science and Industrial Organization of the Ministry of Science and Technology prior to the commencement of the study (ethics certificate no. SDUAHER/KLR/CEC/35/2018-19). All the routine investigations were carried out using a fully automated Vitro 5, 1 FS, a fusion analyzer, maintained by Ortho Clinical Diagnostics. HbA1c levels were estimated using a Bio-Rad D10 hemoglobin testing system (Bio-Rad Laboratories, Inc.) based on the principle of HPLC at the Biochemistry Section of Central Diagnostic Laboratory Services of the study hospital. Manual parameters were analyzed at the Research Laboratory of the Department of Biochemistry Sri Devaraj Urs Medical College.

For the diagnosis of DM and one of its microvascular complications, namely CKD, the following parameters were analyzed: i) Diabetic profile: Fasting and post-prandial blood sugar levels and glycated hemoglobin; ii) extended diabetic profile: Carboxymethyl-lysine and fructosamine levels; iii) renal profile parameters in serum: Creatinine and urea levels. These parameters were analyzed using the following methods.

ELISA. Serum Sirtuin1 (ng/ml) levels were measured using a kit procured from Sincere Biotech, Co., Ltd. [E13651608 (Type II)]; serum CML levels (ng/ml) were measured using a kit procured from Sincere Biotech, Co., Ltd. [E13651946 (Type II)]; and serum fructosamine (ng/ml) levels were also measured using a kit procured from Sincere Biotech (QY-E01291).

HPLC. HPLC was performed using a Bio-Rad D10 hemoglobin testing system (Bio-Rad Laboratories, Inc.) for measuring the HbA1c levels (%).

Table I. Anthropometric data of the study subjects.

Parameter	Group 1 (n=70)	Group 2 (n=70)	Group 3 (n=70)	P-value
Age (years)	50.71±9.2	53.1±8.2	56. 04±8.2	0.08
SBP (mmHg)	122.1±5.4	124.1±14.2[a]	135.3±20.5[a-c]	<0.001
DBP (mmHg)	80.12±5.6	83.2±8.64[a,c]	86.7±10.2[a-c]	<0.001

Data are presented as the mean ± SD. [a]Comparison with group 1 (healthy controls); [b]comparison with patients with type 2 diabetes mellitus; [c]P<0.05, significant difference. Group 1, healthy control; group 2, patients with type 2 diabetes mellitus; group 3, patients T2DM with CKD. SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table II. Diabetic and renal parameters of the study subjects.

Parameter	Group 1 (n=70)	Group 2 (n=70)	Group 3 (n=70)	P-value
HbA1c (%)	5.6±0.6	9.0±2.3[a,c]	8.4±2.1[a-c]	<0.001
Blood urea (mg/dl)	20.5±7.6	26.4±10.14[a,c]	69.03±27.5[a-c]	<0.001
Serum creatinine (mg/dl)	0.7±0.09	0.71±0.2	3.4±1.5[a-c]	<0.001
Serum albumin (g/dl)	4.1±0.41	4.32±0.91	2.8±0.8[a-c]	<0.001

Data are presented as the mean ± SD. [a]Comparison with group 1 (healthy controls); [b]comparison with patients with type 2 diabetes mellitus; [c]P<0.05, significant difference. Group 1, healthy controls; group 2, patients with type 2 diabetes mellitus; group 3, patients with diabetes and CKD. HbA1c, glycated hemoglobin.

Other parameters. An autoanalyzer (Vitros 5,1 Fs) (all reagents were procured from Ortho Clinical Diagnostics) was used to measure the serum urea (mg/dl), serum creatinine (mg/dl), serum triglycerides (TG; mg/dl), serum total cholesterol (TC; mg/dl), serum high density lipoprotein (mg/dl) and serum albumin (mg/dl) levels. The following parameters were also calculated: i) Non-high-density lipoprotein (nHDL) (15)=total cholesterol-HDL; ii) AC (16)=nHDL/HDL; and iii) PGI (g/dl), which is defined as a marker for measuring aging and for the prognosis of DM. The following equation was used to derive value of the index, [(∑glycated proteins)-serum albumin]/anti-aging molecule (Sirtuin1)].

Statistical analysis. SPSS version 20 software (IBM Corp.) was used to perform the statistical analyses. The normality of distribution of variables was assessed using the Kolmogorov-Smirnov test. All the variables which are normally distributed (parametric) are presented as the mean ± SD and those which are non-parametric are presented as the median (25 to 75th percentile). Parametric tests were carried out as follows: The data are presented as the mean ± standard deviation (mean ± SD) for normally distributed data. One-way analysis of variance (ANOVA) followed by the Tukey's and post hoc test, was used to compared the three groups. In addition, the following non-parametric tests were performed: Non-parametric data, based on the frequency of data distribution, were divided into quartiles with the 25 and 75th percentile and presented as the median (25 to 75th percentile). The Bonferroni's correction was applied after the Kruskal-Wallis test and Mann-Whitney U test to determine any significant differences. Spearman's correlation analysis [Rho (ρ)] was used for correlation analyses. A value of P<0.05 was considered to indicate a statistically significant difference.

Results and Discussion

The study comprised 115 males among 210 study subjects, constituting ~55% of the total study population. Group 1 consisted of 31 (44.3%) males, group 2 included 47 (67%) males and group 3 comprised of 37 (52.8%) male subjects.

The integration of mathematics with the markers of diagnostic importance in DM may aid in improving the management of the disease. The outcomes of treatment may help implement the same prognostic tool in other aging-related disorders, such as cancer, metabolic syndrome, CVD and Alzheimer's disease. Some researchers have focused on atherogenic indices, since lipid deposition causes various deleterious effects on organ systems (16,17). Therefore, the consumption of foods rich in lipids causes arterial changes and leads to diabetic microvascular complications.

The anthropometric measures and basic profiles for diabetes and renal function of the subjects in the present study are presented in Tables I and II. Xie *et al* (17) demonstrated that blood pressure in patients with diabetes and CKD was increased; this was also found in the present study, with significant differences (P=0.08 for age and P<0.001 for blood pressure) across groups 1, 2 and 3. Similarly, the levels of other diabetic parameters and renal profiles were significantly increased across the groups, indicating the progression of T2DM. The levels of HbA1c were increased in group 3 compared with the control.

In order to evaluate the atherogenic status of the study subjects, lipid profiles were analyzed (Table III). Statistically

Table III. Lipid profiles of the study subjects.

Parameter (reference range)	Group 1 (n=70)	Group 2 (n=70)	Group 3 (n=70)	P-value
Total cholesterol, mg/dl (120-200)	172±39	161.6±60[b,c]	184±59.3	0.007
HDL, mg/dl (40-60)	40.01±09.1	28±10.5[a-c]	41±14	<0.001
nHDL, mg/dl (<130)	132±40.01	126.1±59	145±56.9	0.077
TG, mg/dl (44-150)[d]	141 (93-193.5)	148 (114.5-211)	184 (119.5-215.5)[a,c]	0.033
Atherogenic coefficient[e]	3.6±0.5	4±0.2	5.1±0.4[a-c]	<0.001

[a]Comparison with group 1 (healthy controls); [b]comparison with patients with type 2 diabetes mellitus; [c]P<0.05, significant difference; [d]Data are not normally distributed and are presented as the median (25 to 75th percentile); [e]data are presented as the mean ± SEM. Group 1, healthy controls; group 2, patients with type 2 diabetes mellitus; group 3, patients with diabetes and CKD. HDL, high-density lipoprotein; nHDL, non-high-density lipoprotein; TG, triglycerides.

Table IV. Lipid indices of the study subjects.

Parameter	Group 1 (n=70)	Group 2 (n=70)	Group 3 (n=70)	P-value
Atherogenic index	0.54±0.03	0.63±0.03	0.74±0.03[a,c]	<0.001
Castelli risk index 1 (CRI 1)	4.5±0.16	4.9±0.2	6.4±0.42[a-c]	0.001
Castelli risk index 2 (CRI 2)	2.5±0.11	2.9±0.17	3.6±0.3[a-c]	0.007

[a]Comparison with the healthy controls; [b]comparison with patients with type 2 diabetes; [c]P<0.05, significant difference. Group 1, healthy controls; group 2, patients with type 2 diabetes mellitus; group 3, patients with diabetes and CKD.

Table V. Special parameters of the study subjects.

Parameters	Group 1 (n=70)	Group 2 (n=70)	Group 3 (n=70)	P-value
Sirtuin1(ng/ml)	47.16 (12-97)	33.5 (25.1-53)[b,c]	50.1 (33.7-102.01)	0.002
Carboxymethyl-lysine (ng/ml)	900 (625.6-1,306)	1,815 (1,100-2,592.03)[a,c]	1,869 (1,155.1-2,272.5)[a,c]	<0.001
Fructosamine (ng/ml) (yet to be derived)	100 (56-172)	245.9 (98-341)[a,c]	330 (131.2-418.2)[a,c]	<0.001
PGI	15.99 (8.1-71.4)	45.01 (17.48-65.29)[a,c]	58.2 (33.5-90.0)[a,c]	<0.001

Data are presented as the median (25 to 75th percentile). [a]Comparison with the healthy controls; [b]comparison with patients with type 2 diabetes; [c]P<0.05, significant difference. Group 1, healthy controls; group 2, patients with type 2 diabetes mellitus; group 3, patients with diabetes and CKD. PGI, protein glycation index.

significant differences were found (0.007, <0.001, 0.033 and <0.001) across the groups for the levels of TC, HDL, TG and AC, respectively, indicative of future diabetic complications due to dyslipidemia, such as CVD.

The data presented in Table IV depict the mean ± standard error of the mean (SEM) for the entire population from which the study subjects were recruited. It is the crucial part of the study which portrays the importance of numerical values, which shall act a surrogate marker during any type of paucity.

Currently, lipid ratios are gaining importance as they can directly associate 'bad' with 'good' cholesterol. The values of lipids and advanced biomarkers are presented in Tables IV and V, respectively. Mathematical indices currently play a major role in planning strategies to manage disorders and outbreaks. The reason behind this is that the number implies a greater significance of the disease severity and progression (18). There are several mathematical designs, such as regression analysis, risk ratios, etc., out of these the simplest one is the arithmetic ratios of parameters whose values may serve a greater purpose when correlated (18).

In medicine, beginning from diagnosis to therapeutics, mathematical interpretations play a vital role in disease prognosis and management. Therefore, the present study enumerates the ratios and calculated parameters, which shall be considered in the prognosis of T2DM and DN. The values of anti-aging molecules (e.g., Sirtuin1) and pro-aging molecules (e.g., CML and fructosamine) are presented in Table V. These three are the major determinants used to assess the magnitude of aging. The PGI, is the novelty of the present study. PGI is defined as the index which measures

Table VI. Correlation analysis of protein glycation index with Sirtuin1 and CML.

Parameters	Group 1 (n=70)	P-value	Group 2 (n=70)	P-value	Group 3 (n=70)	P-value
Sirtuin1 (mg/ml)	-0.823[a]	<0.001	-0.799[a]	<0.001	-0.612[a]	<0.001
CML (ng/ml)	0.537[a]	<0.001	0.624[a]	<0.001	0.666[a]	<0.001

Correlation analysis was performed using Spearman's correlation and Rho values are presented. Group 1, healthy controls; group 2, patients with type 2 diabetes mellitus; group 3, patients with diabetes and CKD. CML, carboxymethyl-lysine. [a]P<0.01, significant difference.

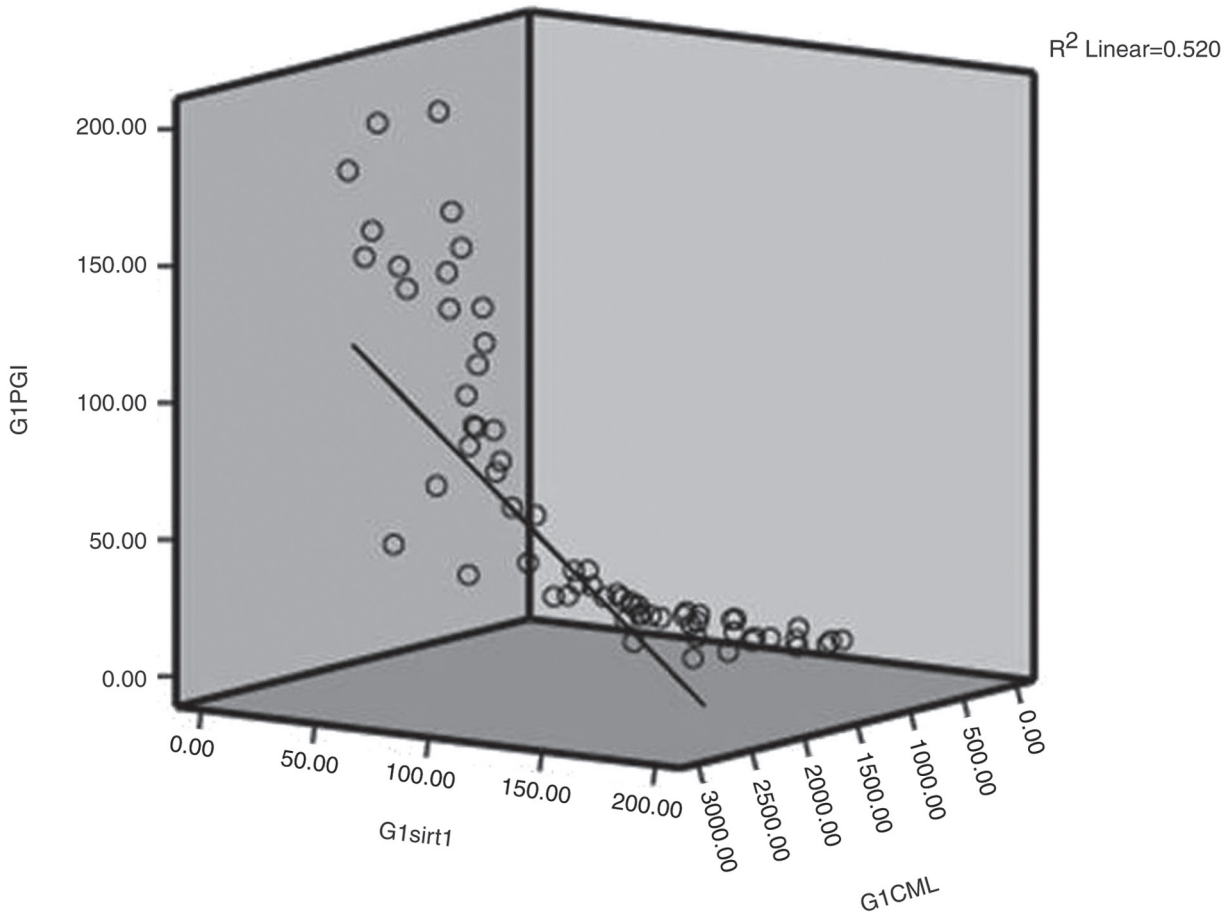

Figure 1. Correlation between PGI, sirtuin 1 and CML in group 1. The graph depicted is a triple-axis graph. The z-axis represents the PGI values, the y-axis represents sirtuin1 and the x-axis represents CML. PGI, protein glycation index; CML, carboxymethyl-lysine.

the amount of major protein glycated (pro-aging) alongside the anti-aging protein. The median (25 to 75th percentile) of PGI in the healthy controls was 15.99 (8.1-71.4); in the patients with T2DM it was 45.01 (17.48-65.29); and in the patients with T2DM and CKD it was 58.2 (33.5-90.0). When comparing the PGI between the groups with the disease and controls, statistically significant differences were found. Therefore, an increase in PGI increases aging, which is well-defined and evident from the data presented in Tables V and VI.

The results of Spearman's correlation analysis revealed a significant an inverse correlation between PGI and the anti-aging molecule, Sirtuin1 (-0.823, -0.799 and -0.612 in groups 1, 2 and 3; shown in Figs. 1-3, respectively). Similarly, the analysis of the correlation between PGI and CML revealed a significant positive correlation (0.537, 0.624 and 0.666 in groups 1, 2 and 3; shown in Figs. 1-3, respectively). As a result, to calculate PGI, the serum albumin concentration, and any one of the glycated protein concentrations, an anti-aging molecule concentration is required.

In conclusion, as per the American Diabetes Association guidelines, fasting, post-prandial measurements and HbA1c levels are of diagnostic significance as markers for DM. Following several analyses and comparisons with other parameters, any one of the AGE and calculated lipid indices (atherogenic indices) may serve as prognostic tools in DM for the prevention of DM-related complications, particularly diabetes with CKD and CVD. PGI is a calculated parameter, which serves as an index not only for DM, but also for other aging-related disorders, since it includes pro- and anti-aging

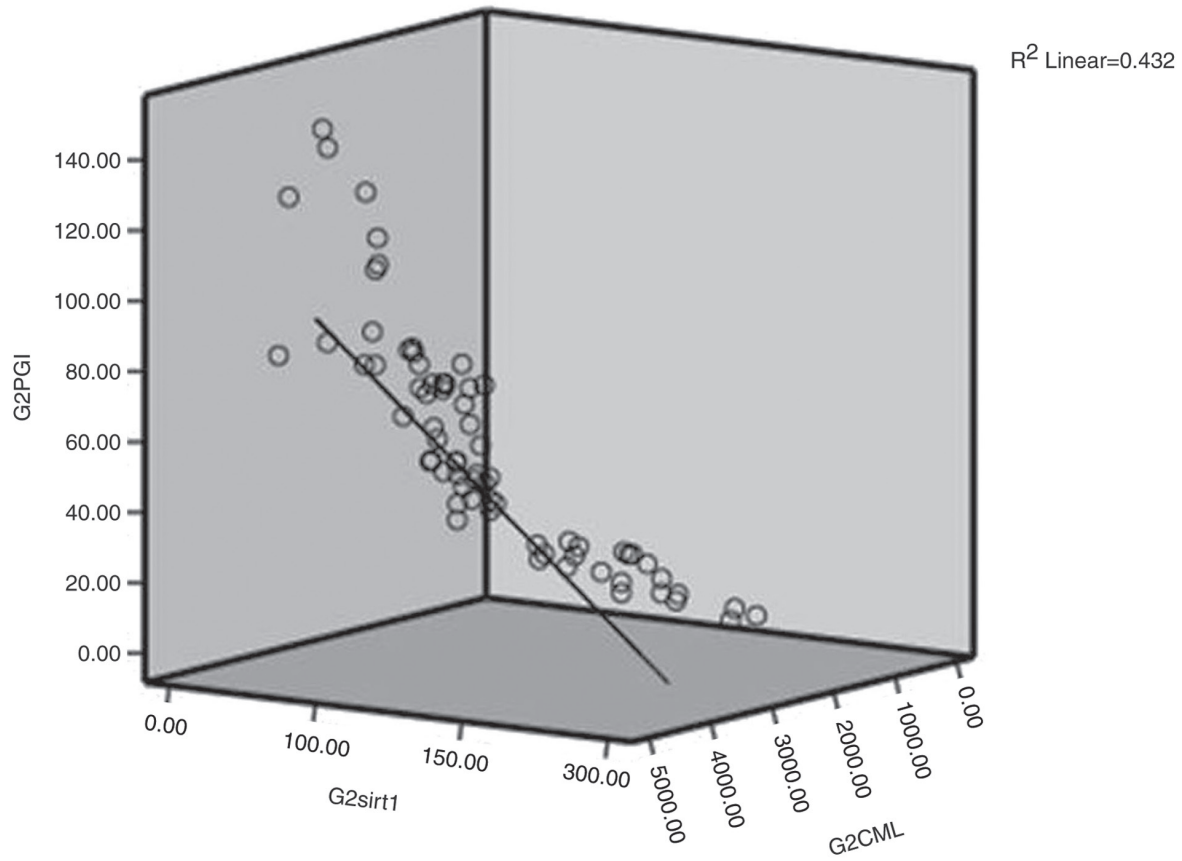

Figure 2. Correlation between PGI, sirtuin 1 and CML in group 2. The graph depicted is a triple-axis graph. The z-axis represents the PGI values, the y-axis represents sirtuin1 and the x-axis represents CML. PGI, protein glycation index; CML, carboxymethyl-lysine.

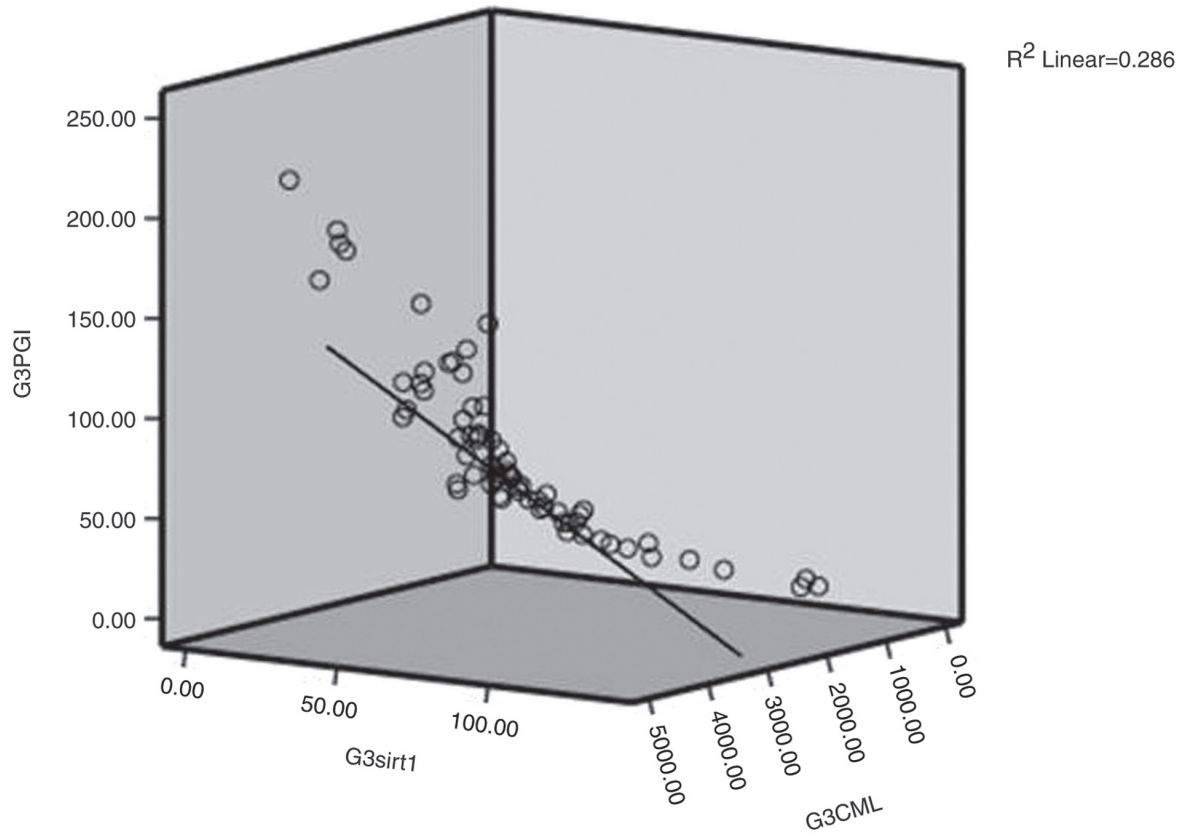

Figure 3. Correlation between PGI, sirtuin 1 and CML in group 3. The graph depicted is a triple-axis graph. The z-axis represents the PGI values, the y-axis represents sirtuin1 and the x-axis represents CML. PGI, protein glycation index; CML, carboxymethyl-lysine.

molecules. However, further studies with larger cohorts examining different aging-related disorders in the same population are required to confirm the findings of the present study regarding PGI.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SDRM was involved in sample collection, data analysis, statistical analysis and interpretation of the data, and in the writing of the manuscript. SKN was involved in subject recruitment, sample collection and in the reviewing of the manuscript. SDRM and SKN confirm the authenticity of all the raw data which is preserved as an excel master chart. Both authors have read and approved the final manuscript.

Ethics approval and consent to participate

The Central Ethics Committee of Sri Devaraj urs Academy of Higher Education and Research with it affiliated institution Sri Devaraj Urs Medical College approved the study as per the Declaration of Helsinki (approval no. SDUAHER/KLR/CEC/35/2018-19). Informed consent was obtained from all the study subjects after explaining them the study in understandable language through patient information sheet.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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