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An Observational Study on Serum Carboxy Methyl Lysine, Insulin Resistance and Sensitivity in Type 2 Diabetes Mellitus and Diabetic Nephropathy Cases

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ABSTRACT

Diabetes Mellitus (DM) and one of its types; type 2 diabetes mellitus (T2DM) is more prevalent from adolescent across the globe, invariable of heredity and age. Diet restriction shall cope up and help body metabolism to absorb the required nutrition and eliminate the junk out of body under healthy diet. Masking of insulin action on target cells leads to insulin resistance (IR) and decreased insulin sensitivity (IS) resulting in increased glycated products such, glycated hemoglobin, glycated albumin and other glycated macromolecules called Advanced Glycation End products. Along with AGE and diabetic profiling, BMI, insulin and lipid profiling may help elucidate the correlation between CML and glucose metabolism in diabetics and diabetic nephropathy cases. CML is formed by Glycoxidation and lipoxidation. Thereby, objectives of this study includes correlation of CML with important diabetic and insulin profile to give a supporting evidence for labelling CML as harmful molecule. Basic renal profiling was performed to assess kidney functioning and finding its relation with CML. CML positively correlated with HbA1c, TG and HOMA IR and negatively correlated with QUICKI in group 2 signifying increased damage to tissues due to collective action of glucose, lipid and insulin resistance. Monitoring plasma CML regularly during follow up along with HbA1c may help keep track on plasma glucose status and its deleterious effects on tissues thereby preventing erosion of tissue and vascular lining.

Keywords: Advanced glycation endproduct; diet restriction; glycated hemoglobin; glycoxidation; HOMA IR; lipoxidation

1. INTRODUCTION

Diabetes Mellitus (DM) and one of its types; type 2 diabetes mellitus (T2DM) is more prevalent from adolescent across the globe, invariable of heredity and age [1]. Diet restriction shall cope up and help body metabolism to absorb the required nutrition and eliminate the junk out of body under healthy diet. Since, T2DM is insulin independent, keeping a check on quality of meal we consume everyday may keep plasma glucose levels under control by avoiding carbohydrate rich diet and follow some physical activity.

As suggested by ADA 2018, proper classification of diabetes will help clinicians to decide dosage of drug and insulin administration [2]. Masking of response to insulin and its receptors on target cells by glucose driven consequences, such as, hemodynamic variations, Metabolic alterations, Inflammatory changes and fibrous tissue formation in organs resulting in increased insulin resistance (IR) and decrease Insulin Sensitivity (IS) [3]. There are various mathematical models proposed to calculate IR and IS. HOMA IR was calculated by the formula derived by Mathews et al and insulin sensitivity was calculated by QUICKI implemented by A. Katz et al on a large population to study insulin resistance

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[4,5]. One such factor responsible for resistance and decreased sensitivity considered in this study is the Advanced Glycation End product (AGE) which is a resultant of glycation of macromolecules such as, Proteins, Lipids and Nucleic acids.

AGEs are non- enzymatically formed product from excess, non- metabolized glucose or fructose, through interconvertible Schiff's base and Amadori product called as Maillard reaction [6]. Formation of amadori product is considered the initial step in Maillard reaction where, there can be reversal or stoppage of formation of AGE (Latent step), due to the reactions being interconvertable. Studies proved that diet restriction and decrease in AGE content had impact on HOMA- IR and QUICKI resulting in diabetic control [7]. Increased AGE increases the risk of microvascular and macrovascular complications of DM; therefore, it is essential to monitor concentration of AGE and its types in normal population as well as in diabetes prior to onset of its related complications [8].

Since T2DM is solely dependent on diet, selection of AGE must also be related to food and its metabolism. Carboxy Methyl Lysine (CML) and Pentosidine are one such AGEs whose major route of entry is food [9]. Many in vivo studies had revealed that concentration of CML is high in processed and baked food which contributes more than endogenous CML formed by protein glycation [10]. CML is called the glycoxidation and lipoxidation product meaning, oxidation of glucose and lipid respectively [8]. Along with AGE and diabetic profiling, BMI, insulin and lipid profiling may help elucidate the correlation between CML and glucose metabolism in diabetics and diabetic nephropathy cases. The major lipid involved in lipoxidation is PUFA [10].

Renal tissue damage in diabetes is a consequence of constant exposure of nephrons to circulating glucose and AGE. Also, CML has tough association with glomerular cells and tubular cells ceasing their skeletal structure thus, reducing their physiological role [11]. From review consolidating many studies on diabetes, one of the underlying causes for diabetic kidney disease is insulin resistance and insulin insufficiency [12]. Hence, in this study the basic renal profiling were also performed to assess kidney functioning and finding its relation with CML.

2. SUBJECTS AND METHODS

2.1 Subjects

After obtaining Central Ethics Committee (CEC) approval Complying with declaration of Helsinki, subjects recruited for this observational study were the patients attending the general medicine Out Patient Department and admitted as inpatients in RL Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College, a constituent of Sri Devaraj Urs Academy of Higher Education and Research Tamaka, Kolar, India. Healthy volunteers were also selected from the same institute to compare the values. Study subjects were grouped into three categories, Group1 consisting of healthy control (n= 39), Group 2 were cases with T2DM (n= 41) and Group 3 are Diabetic Nephropathy (DN) cases (n= 26), all the individuals with either higher BMI or Increased Total cholesterol or Triglycerides were selected since CML is mainly a lipoxidized product and linked with BMI and Lipids. Patients taking drugs or other factors known to cause diabetes and/ or diabetic nephropathy, Patients undergoing any type of dialysis, acute kidney injury, gestational diabetes mellitus, patients with type 1 DM and monogenic diabetic syndrome were excluded from the study.

2.2 Sample Collection

After clearly explaining the study in subject's understandable language, written informed consent was obtained from all study subjects. Subjects were instructed to fast for minimum of 8 hours and maximum of 12 hours for analysis of Fasting Blood Sugar (FBS), Fasting Insulin (I_0), Lipid profile, Glycated Hemoglobin (HbA1c) and CML, for which 5 mL blood was collected with privacy in a comfortable inclined position in Sodium Fluoride, clot activated and EDTA vaccutainers respectively. Weight was measured using a digital weighing scale in kilograms and height was measured using fixed measuring scale in centimetres. 2 hours after meal 2mL blood was collected to estimate post prandial blood sugar (PPBS) in all study subjects. Plasma was stored at -80ºC till the analysis of CML.

2.3 Methodology

All the routine parameters were analyzed by fully automated Vitros 5, 1 FS (Ortho Clinical Diagnostics, USA), Glycated Hemoglobin (HbA1c) was estimated by BioRad D10 (Bio- Rad USA) based on principle of HPLC, Fasting Insulin (I_0) was analyzed by Vitros electro Chemiluminescence (ECi) and CML was estimated by sandwich ELISA procured from Sincere biotech China. Body Mass Index (BMI), Qualitative Insulin Check Sensitivity Index (QUICKI) Homeostasis Model Assessment-Insulin Resistance (HOMA- IR) and non High Density Lipoprotein (nHDL) were calculated using standard formulae. SBP and DBP were measures using both manual and electronic Sphygmomanometer.

HOMA- IR= fasting insulin (microU/L) x fasting glucose (mg/ dL)/ 405[4]

QUICKI= $1/ [\log(I_0) + \log(G_0)]$[5]

2.4 Statistical Analysis

Statistical package for social sciences (SPSS 20) developed by IBM was used for data analysis. Parametric variables were represented as mean ± S.D, and non- parametric variables were indicated as median (25^{th}- 75^{th} percentile). Probability- value (p- value) for parametric variables were calculated by independent student t test and Mann- whitney U test applied for non parametric variables. P- value < 0.05 was considered significant. Correlation between CML and metabolic syndrome related variables were analyzed by Spearman's rho correlation.

3. DISCUSSION

3.1 Diabetic Profile

Demographic and diabetic parameters are represented in Table 1. Age is being increased as moving from group1 to group3 since microvascular complications progress as the age progresses. Based on Table 1 between group 1 and group 2 except diabetic parameters in Table 1 all were insignificant indicating blood pressure and body build in normal range. Most of the demographic and diabetic parameters were significant between group 1 and group 3 since subjects of group 3 are diabetic for more than 10years. Insulin sensitivity index calculated by QUICKI was found to be lesser in group 2 and group 3 compared to controls with significant p- value. Systolic blood pressure (SBP) was significantly high in Diabetic nephropathy cases compared to group 1 and group 2. There was no much difference in diastolic blood pressure (DBP) between diabetic and DN group however, there was a significance in the same between group 1 (control) and group 3 (DN). Regularly monitoring blood pressure in diabetes helps preventing renal and cardiovascular complications as demonstrated in various cohort study and based on KDOQI [13]. Standard diagnostic criteria by American Diabetic Association (ADA) 2018 declared that subjects with fasting blood sugar (FBS) < 126 mg/ dL, post prandial blood glucose (PPBS) / RBS < 200 mg/ dL and HbA1c < 6.5% are considered diabetic which was the criteria for finding diabetes cases in this study and categorizing them accordingly as indicated in Table 1 [14]. In addition, it is also stated that PPBS value is precise for diagnosing DM than FBS and HbA1c since both insulin secretion and glucose metabolism place a role after meal14. Surprisingly, it was noted that group 2 had higher HbA1c than the group 3 which may be due to administration of insulin for most of the cases in group 3. Possibly, it must be taken in consideration to control HbA1c levels in group 2 increases incidence of diabetic complication. As stated by Unnikrishnan et al in Indian or Asian population, onset of diabetes was recorded in low BMI adults and children unlike whites who may be due to paucity of trained clinicians or poor knowledge on DM [15]. BMI values in this study supports the above finding, as we move across groups, BMI is significantly being decreased indicating restricted diet and regular exercise in nephropathy and diabetic cases respectively.

Table 1. Demographic data and diabetic profile between study groups

Variables	Group 1 (Controls) n=39	Group2 (T2DM) n= 41	Group 3 (DN) n= 26
	Mean ± S.D		
Age (in years)	42.59 ± 8.39^{ac***}	52.1 ± 8.4^{b*}	55.42 ± 8.03
SBP (mmHg)	123.3 ± 4.97^{a*}	125.31 ± 10.58^{b***}	139.11 ± 16.15^{c***}
DBP (mmHg)	78.74 ± 4.3^{a*}	80.31 ± 14.99^{b*}	87.15 ± 12.66^{c***}
BMI (kg/m^2)	25.76 ± 2.65^{a**}	23.65 ± 1.77^{b**}	22.69 ± 1.6^{c***}
FBS (mg/dL)	95.28 ± 9.53^{ac***}	192.78 ± 74.18^{b*}	181.65 ± 73.98
PPBS (mg/dL)	114.28 ± 12.48^{ac***}	283.22 ± 114.21^{b*}	276.50 ± 101.40
HbA1c (%)	5.56 ± .55^{ac***}	9.25 ± 2.58^{b*}	8.26 ± 1.98
QUICKI¶	0.34 ± .028^{a***}	0.31 ± .032^{b*}	0.32 ± .034^{c**}

*SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, BMI: Body Mass Index, FBS: Fasting Blood Glucose, PPBS: Post prandial Blood Sugar, HbA1c: Glycated Hemoglobin, QUICKI: Qualitative Insulin Check Index, T2DM: Type 2 Diabetes Mellitus, DN: Diabetic Nephropathy. a: comparison of means between group 1 & 2, b: comparison of means between group 2 & 3, c: comparison of means between group 3 &1 . ***: <0.01, **:< 0.05, *: >0.05, ¶: Calculated*

Table 2. Comparison of lipid profile, HOMA- IR and carboxy methyl lysine between study groups

Variables	Group 1 (Controls) n=39	Group2 (T2DM) n= 41	Group 3 (DN) n= 26
	Median (25th- 75th percentile)		
I_0 (U/ mL)	10.5 (6.87- 14.6)^{abc*}	12 (7.095- 16.5)	9.92 (5.27- 15.27)
HOMA- IR¶	2.5 (1.5- 3.3)^{a***}	5.5 (3.1- 7.7)^{b*}	4.18 (2.3- 7.1)^{c**}
BU (mg/dL)	21 (16- 25)^{a**}	25 (18.5- 38)^{b***}	65 (40.75- 80.75)^{c***}
SC (mg/dL)	0.7 (0.5- 0.9)^{a*}	0.7 (0.5- 0.8)^{b***}	3.6 (2.1- 4.62)^{c***}
TC (mg/dL)	182 (157- 208)^{a**}	210 (175.5- 242.5)^{b*}	198.5 (156- 234)^{c*}
TG (mg/ dL)	147 (122- 235)^{a**}	210 (188- 247.5)^{b*}	219 (199.5- 249)^{c**}
HDL (mg/ dL)	37 (30- 46)^{a*}	41 (33- 49.5)^{b***}	28 (18- 37.25)^{c**}
LDL (mg/ dL)	108 (85- 131)^{a*}	110 (87.5- 133.5)^{b*}	101.4 (58.5- 132.25)^{c*}
nHDL (mg/ dL)	148 (120- 168)^{a**}	164 (135.5- 194.5)^{b*}	166 (121- 203.5)^{c*}
CML (ng/ mL)	911.5 (651.5- 1126)^{a***}	1840 (1034- 2275)^{b*}	1860 (1094.1- 2682.5)^{c***}

*I_0: Fasting Insulin, HOMA- IR: Homeostasis Model Assessment- Insulin Resistance, SC: Serum Creatinine, BU: Blood Urea, TC: Total Cholesterol, TG: Triglyceride, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, nHDL: non- High Density Lipoprotein, CML: Carboxy Methyl Lysine, T2DM: Type 2 Diabetes Mellitus, DN: Diabetic Nephropathy. a: comparison of means between group 1 & 2, b: comparison of means between group 2 & 3, c: comparison of means between group 3 & 1 . ***: <0.01, **:< 0.05, *: >0.05, ¶: Calculated*

3.2 Renal Profile

Table 2 depicts renal, insulin and lipid profile along with CML. Fasting insulin can alone not be a marker to assess glucose breakdown consequently, HOMA IR and QUICKI which are calculated based on fasting insulin and FBS clarifies the action of insulin on plasma glucose. Apart from increased blood pressure, serum creatinine and blood urea, based on NKF- KDOQI 2012 guidelines, uACR (spot urine albumin to creatinine ratio) of < 30 mg/g and/ or eGFR (estimated glomerular filtration rate) 60 ml/min per 1.73 m^2 are considered as renal incompetency [16]. Renal function is initially assessed by measuring creatinine and urea concentration in serum, increase in serum creatinine > 1.5 mg/ dL and blood urea > 45 mg/ dL indicates renal damage which is significantly high in group3 subjects and within normal range in group 1 and group 2 subjects [17].

3.3 Insulin Profile

From Table 2, HOMA- IR is significantly being increased in group 2 than other groups similar to QUICKI. Since, increase in serum creatinine and blood urea is gold standard for renal dysfunction, Table 2 also confirms the same with significant p- values between controls and DN and between Diabetic and DN. However, lipid parameters of group 3 is less than group 2 which may be due to

controlled diet in diabetic nephropathy cases. The key molecule; CML is found decreased in control group than the other groups demarcating the groups with diabetes and healthy controls.

Increase in HOMA IR value indicates increases insulin resistance by cells and values less than 0.32 spells diabetic with decreased insulin sensitivity [4,5] which is proved true with significant difference between groups. Like HbA1c, though there is increased insulin in group 2 HOMA IR and QUICKI are not up to the normal range in comparison with group 2 which may again be due to insulin administration in DN, thereby giving favourable HOMA- IR and QUICKI values.

Major aspect with respect to diabetes and accumulation of AGE is the lipid profile which aids aggravating diabetic consequences. Under criteria of scoring defined by National Cholesterol Education Program guidelines, LDL,100 mg/ dL are considered at 10- years risk for coronary heart disease (CHD) and triglycerides (TG) >200 mg/dL shall be considered for treatment with drugs lowering TG [18,19]. Diabetic group in this study had shown a comparative high Triglycerides (TG) and Total Cholesterol (TC) levels indicating a risk of either renal or cardiac disorder and/ or diabetic vascular complication. Further, Group3 cases were under cholesterol lowering drugs and hence, showing borderline TC and TG levels. Low Density Lipoproteins (LDL) are considered the bad cholesterol due to its action of easy penetration into arterial intima resulting in plaque formation leading to increased blood pressure and various complication to blood pumping and filtering organs [20]. High Density Lipoprotein (HDL) counteracts with LDL in surrendering the cholesterol to liver for metabolism preventing its accumulation in rest of the body parts and arteries [20].

3.4 Carboxy Methyl Lysine

Carboxy methyl lysine (CML), oxidized form of AGE under research since its source mainly is through diet and harming renal tubules in diabetes [21]. Increased AGE is naturally observed in diabetes due to hyperglycemia [21]. According to this study, increase of CML in group 2 is due to increase in all other diabetic parameters and through diet, in contrary, increase of CML in group 3 is mainly due to hyperglycemia and increased lipids but not diet since, they are under restricted food intake. It is also known that CML is excreted through urine and hence chances of decreased urinary output of CML may also be one of the reasons for increased CML in group 3 [22]. Although there are many studies on CML, this is one among the studies where CML is estimated after the onset of disorder and also compared between Diabetes and its complication. Since, dialysis cases were excluded sample size was decreased which is a limitation of this study.

Correlation of CML with important diabetic parameters was performed, giving a supportive evidence for labelling CML as harmful molecule. CML positively correlated with HbA1c, TG and HOMA IR and negatively correlated with QUICKI in group 2 signifying increased damage to tissues due to collective action of glucose, lipid and insulin resistance. On the other hand in group 3, HbA1c and QUICKI were positively correlated unlike HOMA IR and TG, reason being diet restriction and good long- term glycaemic control since they are under insulin therapy [22].

Table 3. Correlation of CML with HbA1c, Triglyceride (TG), HOMA IR and QUICKI

Parameters	Group II ρ- value	Group III ρ- value
HbA1c (%)	0.023	0.74
TG (mg/dL)	0.63	-0.184
HOMA IR	0.7	-0.051
QUICKI	-0.118	0.083

CML: Carboxy Methyl Lysine, HbA1c: Glycated Hemoglobin, HOMA- IR: Homeostasis Model Assessment- Insulin Resitance, QUICKI: Quantitative Insulin Sensitivity Check Index

4. CONCLUSION

CML being called as 'auto oxidized AGE' of protein and lipid, shall be also considered as marker of oxidation in diabetes and complications of diabetes. Monitoring plasma CML regularly during follow up along with HbA1c may help keep track on plasma glucose status and its deleterious effects on tissues thereby preventing erosion of tissue and vascular lining. Also, AGE; CML can be considered as a biomarker along of extent of glycation in comparison with glycated proteins. Since, major portion of CML pool in body reserve is said to be through food, food restriction and regular exercise may decrease glucose availability thereby combats the CML formation. Interventional studies with low glycation index and raw food intake may help assess to select food which aids decreasing glycated end products levels. This scenario can be curtailed upon decreasing calorie intake especially, decreasing baked, fried and processed and/or packed food.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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