

Hepatic, Renal and Cardiovascular Biomarker Variability in Type 2 Diabetes Mellitus Patients with Poor Glycemic Control

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Abstract

Objective: The main aim of the study was to evaluate and compare the variability of the hepatic, renal and cardiovascular biomarkers in type 2 diabetes mellitus patients with poor glycemic control.

Materials and Methods: An analytical cross-sectional study utilizing random sampling technique was used to recruit 103 consenting participants at the Kakamega county general hospital. Approximately 6mls of blood sample was collected and processed for biomarkers of hepatic, renal and cardiovascular function using spectrophotometry and fluorescence-immuno detection. Data was analyzed using the IBM SPSS ver. 22 software. Chi-square and Fisher's exact test were done on categorical variables and Kruskal-Wallis test on the continuous variables. A Bonferroni Post-hoc test was done to determine the differences between the groups.

Results: The study revealed a significant hepatic biomarker variability in gamma glutamyl transferase (GGT) ($P= 0.031$), Total bilirubin ($P< 0.0001$), Direct bilirubin ($P< 0.0001$), albumin ($P= 0.001$) and Aspartate transaminase/alanine transaminase (AST/ALT) ratio ($P< 0.0001$). Renal biomarkers including Urea ($P= 0.002$), potassium ($P= 0.0012$), sodium ($P< 0.0001$) and chloride ($P= 0.007$) showed a significant variability in poor glycemic control. Additionally, Triglycerides ($P< 0.0001$) and total cholesterol ($P= 0.046$) levels were significantly elevated in poor glycemic control.

Conclusion: Poor glycemic control causes elevation in GGT, AST/ALT ratio, potassium, triglycerides and total cholesterol while bilirubin, albumin, sodium and chloride are reduced.


Keywords: Hepatic, Renal, Cardiovascular, Biomarkers, Type 2 diabetes mellitus, Poor glycemic control

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Introduction

Diabetes mellitus (DM) is a group of metabolic disorders characterized with a constant hyperglycemic state due to an absolute or relative deficiency of insulin production or action. Type 2 Diabetes mellitus (T2DM) is a combination of insulin resistance and an inadequate insulin secretion (1). Acute, life-threatening consequences of uncontrolled diabetes are hyperglycemia with ketoacidosis or the non-ketotic hyperosmolar syndrome (2). The chronic hyperglycemia of diabetes mellitus is associated with end-organ damage, dysfunction, and failure, including the eyes, kidney, nervous system, heart, and blood vessels (3). The worldwide prevalence of diabetes is approximately 462 million with the majority living in third world countries. Kenya has an estimated prevalence of 3.5-5% with over 44% of cases still undiagnosed (4).

Poor glycemic control (PGC) is a condition characterized by a constant state of hyperglycemia (Fasting blood sugar (FBS), >7.22 mmol/l or glycated hemoglobin (HbA1c) $>7.0\%$) (5,6). These targets however vary from population to population while American diabetes association(ADA) recommendation of HbA1c targets vary based on clinical case by case presentations of the patient (7). Regulation and control of normoglycemia is a challenge in clinical practice since it's a multifactorial issue involving both patient, healthcare personnel and environmental factors (8). Resource limitations experienced in developing countries including limited healthcare facilities, lack of glucose monitoring devices and lack of awareness leading to non-adherence to medication, polypharmacy and unregulated diet have also contributed to PGC. Kenya has a developed diabetic policy guideline and recommends glycemic targets of HbA1c $<7.0\%$. However, these policy document still has not been reviewed to capture the current diabetic control trends and also was developed with little basis on the local data (9). Uncontrolled/untreated

hyperglycemia in T2DM remains a major predisposing factor in development of both microvascular and macrovascular complications (10). In Kenya, 82% of diabetic patients have PGC which leads to management constrains (9)

Hepatic, Renal and Cardiovascular (CV) function is highly impaired in individuals suffering from T2DM due to various pathophysiological mechanisms (12). Organ injury risk is associated with the development of micro and macrovascular dysfunction, acceleration of atherosclerosis, an impaired endogenous repair system, direct cell metabolism impairment, oxidative stress, vascular and systemic inflammation, inadequate immune response, cardiac biochemical stress, fibrosis, necrosis, and apoptosis as well as thrombophilia and aggregation of blood cells (13,14).

Renal and cardiovascular damage accounts for 80% while hepatic dysfunction accounts for 12.5% of the total mortality cases in T2DM (12,15). PGC accelerates this damage. A high percentage of T2DM patients remain undiagnosed during the early onset of the disease making it difficult to establish early organ injury (16). Early determination of organ damage plays a critical role in the management of the disease thus preventing related complications and mortality.

The use of biomarkers in the diagnosis of organ damage has become a common practice in the recent decade. Conventional hepatic, renal and cardiovascular serum biomarkers such as creatinine, urea, electrolytes, Aspartate amino transferase, alanine aminotransferase, gamma glutamy transferase, albumin, total protein, total bilirubin and direct bilirubin, alkaline phosphates, triglycerides, total cholesterol and microalbumin are being utilized currently as indicators of diabetes organ complications (17,18). However, their dependence is limited and follow up confirmatory invasive histological investigation is required. Diabetes is a

metabolic disorder; the variations in the levels of these biomarkers should not be distinctively attributed to organ damage but rather the metabolic/physiologic changes induced by hyperglycemia. PGC contributes to both organ injury and metabolic disturbances causing the variability.

This current study aimed at determining the serum levels of various biomarkers for hepatic, renal and cardiovascular function, their variability in poorly controlled glycemic state among T2DM patients. This has an overall impact in early organ damage detection, prevention and proper management of T2DM.

Material and methods

Study site and population

The study was conducted at Kakamega county general hospital diabetic clinic located in Kakamega county, Western Kenya. The study was a cross-sectional analytical design where T2DM participants were categorized into two groups (Good glycemic control group (HbA1c <7.0%) and poor glycemic control group ($\geq 7.0\%$)) (5). A healthy control group was also recruited and subjected to the same conditions and measurements as the T2DM group. The study excluded individuals with history of hepatic, renal and cardiovascular disease from a different etiology. Employing convenience sampling design, 103 consenting participants were recruited comprising of (Healthy control, n=27), (T2DM good glycemic control (GGC), n=25) and (T2DM poor glycemic control (PGC), n=51). The sample size was calculated using the modified Cochran formula(19) . The rate of PGC in Kenya is 66% of total T2DM cases (20).

$$\text{PGC} = 66\% \text{ of } 76 = 51$$

$$\text{GGC} = 76 - 51 = 25$$

Healthy controls = approximate ration of 1:1 with GGC = 27

$$\text{Total recruited participants} = 103$$

Collection of anthropometric and demographic data

The sociodemographic data such as age, gender, type of diabetic medication and period

since initial diagnosis were collected using a questionnaire. Height, weight, Body mass index (BMI), hypertension status was collected via scale measurement.

Collection of blood samples

Blood samples for the tests were collected by a trained phlebotomist to ensure the quality of the sample and to minimize the possible risks to the participants. Approximately 6mls of venous blood required was placed in two different blood collection tubes as follows; 3mls in EDTA purple top vacutainer, and 3mls in the red top tube with clot activator BD vacutainer[®] tube (Becton Dickinson, Franklin Lakes, USA) and then labeled with the participant's coded identifiers. Sample from the red top vacutainer was left to clot for about 30 minutes, centrifuged at 3000R/Min for 3 minutes, and then serum separated and placed in well-labeled serum cups then stored at 2-8⁰C as it awaited processing.

Determination of glycemic control

The glycemic control levels were determined by use of a glyated hemoglobin test (HbA1c). The test was done using the Ichroma II immunolyzer instrument that utilizes fluorescent sandwich immunodetection technique. From the results, GGC was defined as HbA1c value of $\leq 7.0\%$ while PGC as HbA1c of $> 7.0\%$.

Quantitative determination of renal and hepatic function biomarkers

Quantitative serum analysis for renal and hepatic biomarkers was by an automated biochemistry analyzer, Humastar 300SR and Humalyte Plus³ (ISE) from Human Biochemical and diagnostics company. Approximately, serum sample of 500 μ l was needed. Calibration and quality control (QC) was done before the samples were processed.

Quantitative determination of cardiac function

Creatinine kinase- MB (CK-MB) levels were determined using an immunolyzer device

Ichroma II which is a point of care (POC) device which uses a fluorescent sandwich immunodetection principle. During the procedure, 10µl of the sample was placed in respective detector diluents, mixed 10 times and 75µl of the mixture pipetted and placed on respective test cartridges. The cartridges were then incubated for 10 minutes at room temperature and then placed on the device to be read. The normal ranges for CK-MB are between 0-7ng/ml.

Determination of Lipid Levels

Lipids profile tests included four basic parameters: total cholesterol, HDL, LDL, and triglycerides. The tests were performed using an automated clinical chemistry analyzer, Humastar 300SR. An approximate 100µl of the serum sample was used.

Data analysis

The data collected was entered on excel, validated, cleaned and analyzed using IBM SPSS 22.0 statistics software (IBM SPSS Inc. Chicago, USA). Sociodemographic variables were analyzed using Chi-square and Fisher's Exact for categorical variables and reported in number(n) and percentages (%) while continuous variables were analyzed using Kruskal-Wallis and reported as medians(M) and interquartile range (IQR). Analysis of hepatic, renal and cardiovascular biomarkers was done using Kruskal-Wallis and results reported as medians (M) and Interquartile range (IQR). The differences were tested at $P \leq 0.05$. A Bonferroni correction post-hoc test was done to all statistically significant results.

Ethical considerations

Ethical approval for the study was sort from the Masinde Muliro University of Science and Technology (MMUST) institutional ethical review committee (IERC) approval number MMUST/IERC/143/2023, National commission for science, technology and innovation (NACOSTI) license number NACOSTI/P/23/25518 and the Kakamega

county general hospital institutional review board(IRB) approval number ERC/200-05/2023 for data collection. Ethical standards as described by the Nuremberg code were maintained throughout the study period.

Results

Demographic and anthropometric characteristics of study participants

A total of 103 adult study participants were enrolled into the study comprising of 42 males (40.8%) and 61 females (59.2%). The participants were categorized into three groups which showed a significant distribution difference age, height, weight, BMI, and hypertension status. Other Demographics such as the hypertension categories, period since diagnosis and medication did not show statistical difference as shown in the Table 1 below.

Data indicates the numbers (n) and proportions (%) of the participants for the categorical variables while continuous variables presented as median and interquartile range (IQR). Chi-square test and Fisher's exact was done for the categorical proportions while Kruskal-Wallis test was done on continuous variables and significance tested at ($P \leq 0.05$). All the statistical significant P values are in bold.

Hepatic Biomarkers variability in poor glycemc patients

The summary for the hepatic biomarkers variations is summarized in the Table 2. The study results revealed a varied activity of GGT, Total bilirubin direct bilirubin and albumin. Conversely, AST, ALT and total protein levels did not show significant variability among the three groups. However, the AST/ALT ratio indicated a significant difference across the groups.

Data shown indicates the medians and the interquartile range (IQR); Aspartate aminotransferase, AST; Alanine aminotransferase, ALT; gamma-GT, gamma glutamyl transferase; ALP, alkaline phosphatase. Kruskal- Wallis test was used to

compare the levels across the groups at $P < 0.05$. A Bonferroni post-hoc correction test was used for between groups comparisons which was set at ($P < 0.0167$) and significant groups denoted as ^a ($P < 0.0167$ vs Healthy controls) ^b ($P < 0.0167$ vs T2DM good glycemic control). All the statistical significant P values are in bold.

Renal biomarker variability in poor glycemic control patients

The study revealed a significant variation in the levels of urea and electrolytes across the groups. However, creatinine, eGFR and

calcium levels remained similar across the groups. The summary of the data is as shown in Table 3.

Data shown indicates the medians and the interquartile range (IQR); eGFR, glomerular filtration rate; Kruskal- Wallis test was used to compare the levels across the groups at $P < 0.05$. A Bonferroni post-hoc correction test was used for between groups comparisons which was set at ($P < 0.0167$) and significant groups denoted as ^a ($P < 0.0167$ vs Healthy controls) ^b ($P < 0.0167$ vs T2DM good glycemic control). All the statistical significant P are in bold

Table 1. Demographic and anthropometric characteristics of the study participants

Characteristic	Healthy controls n=27	T2DM (GGC) n=25	T2DM (PGC) n=51	P-value
Gender				
Male n (%)	18 (66.7)	11 (44.0)	13 (25.5)	0.002
Female n (%)	9 (33.3)	14 (56.0)	38 (74.%)	
Age, years	23 (2.0)	66 (13.0)	60 (18.0)	<0.0001
Height, Cm	172 (9.0)	163.5 (11.8)	160 (10.5)	<0.0001
Weight, Kg	61 (14.0)	83.1 (19.3)	73.2 (19.6)	<0.0001
BMI Kg/m²	21.3 (3.6)	31.8 (10.8)	28.7 (7.7)	<0.0001
BMI category; n (%)				
Underweight (<18.5 Kg/m ²)	3 (11.1)	0 (0.00)	1 (2.0)	<0.001
Normal (18.5-24.9 Kg/m ²)	21 (77.8)	2 (8.0)	12 (23.5)	
Overweight (25.0-29.9Kg/m ²)	2 (7.4)	6 (24.0)	20 (39.2)	
Obesity (>30.0 Kg/m ²)	1 (3.7)	17 (68.0)	18 (35.3)	
Hypertension status				
Normotensive n (%)	27 (100.0)	4 (16.0)	21 (41.2)	0.001
Hypertensive n (%)	0 (0.00)	21 (84.0)	30 (58.8)	
Hypertension Categories n (%)				
New-5years	N/A	10 (47.6)	14 (46.7)	0.159
6-10 years		5 (23.8)	7 (23.3)	
11-15 years		3 (14.3)	9 (30.0)	
>15 years		3 (14.3)	0 (0.0)	
Period since diagnosis, years	N/A	3 (5.0)	7 (8.0)	0.061
Medication				
Metformin n (%)	N/A	18 (72.0)	42 (82.5)	0.298
Glibenglamide n (%)		10 (40.0)	28 (54.9)	0.222
Other n (%)		6 (24.0)	12 (23.5)	0.964
Combination n (%)		10 (40.0)	32 (62.7)	0.061

Table 2. Hepatic biomarker variability between T2DM (GGC) and T2DM (PGC)

Parameter, Units(Ranges)	Healthy controls n=27	T2DM (GGC) n=25	T2DM (PGC) n=51	P-value
AST, U/L (0-31)	22.0 (9.0)	22.3 (9.0)	19.3 (10.0)	0.059
ALT, U/L (0-34)	17.0 (10.2)	18.5 (8.9)	21.3 (12.2)	0.341
AST/ALT Ratio	1.27 (0.6)	1.13 (0.3)	0.88 (0.3) ^a	<0.0001
Gamma-GT, U/L (0-39)	19.0 (9.1)	24.9 (17.5)	26.9 (23.7)	0.031
ALP, U/L (55-105)	99.8 (55.0)	68.5 (51.1)	83.9 (40.1)	0.076
Total Bilirubin, umol/l (1.71-20.52)	18.4 (12.0)	11.9 (9.2) ^a	11.3 (4.9) ^a	<0.0001
Direct Bilirubin, umol/l (0-3.42)	6.4 (7.09)	3.9 (1.6) ^a	3.2 (1.8) ^a	<0.0001
Total protein, g/l (66-87)	76.2 (5.6)	73.1 (5.7)	72.3 (12.3)	0.080
Albumin, g/l (38-51)	45.6 (3.4)	45.1 (4.8)	42.7 (5.9) ^a	0.001
Albumin/T. Protein	0.59 (0.63)	0.6 (0.07)	0.59 (0.08)	0.323

Cardiovascular biomarkers variability among the study participants

The study also revealed a significant increase in the levels of triglycerides and total cholesterol across the groups. Conversely, HDL, LDL and CK-MB levels remained similar across the groups as shown in Table 4 below.

Data shown indicates the medians and the interquartile range (IQR); HDL, High density lipoprotein; LDL, low density lipoprotein, CK-MB, Creatine-kinase MB isoenzyme; Kruskal-Wallis test was used to compare the levels across the groups at $P < 0.05$. A Bonferroni post-hoc correction test was used for between groups comparisons which was set at ($P < 0.0167$) and significant groups denoted as ^a ($P < 0.0167$ vs Healthy controls) ^b ($P < 0.0167$ vs T2DM good glycemic control). All the statistical significant P values are in bold.

Discussion

Reported high women prevalence with poor glycemic control can be attributed to adiposity differences where women have more lipogenesis and less fatty acids turnover as compared to males and differences in physical activities which plays a role in increasing insulin sensitivity. Socio-economic differences also play a role in these differences since most women are perceived to have less social

support, more stressed, poor nutritional habits and also likely to be involved in polypharmacy which increases drug-drug interaction reducing diabetic therapy efficacy(11). These findings are in line with a study conducted in Korea which suggests that women are less likely to achieve glycemic control targets when initiated to treatment as compared to males (21). With these findings, a gender based approach should be considered during treatment and management of T2DM.

Poor glycemic control was observed in younger age group. This can be associated to several factors including poor medication adherence, lack of self-glucose monitoring devices, dyslipidemia, obesity and high smoking rates among young patients (22). This finding correlates with a study conducted by S. M. Shamshirgaran in Iran which indicated that older patients were less likely to develop poor glycemic control as compared to young diabetic patients (23).

Low BMI was observed in non-diabetic control group as compared to T2DM group. Being a metabolic disorder, diabetes leads to poor metabolism of fats, causing increased lipogenesis and low fatty acids turnover in diabetes patients thereby affecting adiposity. Obesity has a direct link in development of diabetes through increase of non-esterified fatty acids and glycerol, hormonal imbalances and overproduction of inflammatory

Table 3. Renal Biomarker variability between T2DM (GGC) and T2DM (PGC)

Parameter, units(Ranges)	Healthy controls n=27	T2DM (GGC) n=25	T2DM (PGC) n=51	P-value
Creatinine, umol/l (53.93-99.01)	96.5 (25.6)	103.0 (38.0)	100.4 (30.5)	0.501
Urea, mmol/l (1,83-7.5)	3.4 (1.2)	4.8 (2.5) ^a	3.8 (1.4)	0.002
Potassium[K ⁺], mmol/l (3.5-5.5)	4.02 (0.49)	4.12 (0.55)	4.29 (2.15)	0.012
Sodium[Na ⁺], mmol/l (135-145)	145.8 (2.00)	144.0 (3.10)	142.02 (4.20) ^a	<0.0001
Chloride[Cl ⁻], mmol/l (98-107)	106.9 (3.80)	110.3 (7.55) ^a	106.4 (7.70) ^b	0.007
eGFR (≥90)	92.2 (18.40)	87.0 (29.15)	85.11 (32.80)	0.241
Calcium, mmol/l (2.02-2.6)	2.25 (0.41)	2.42 (0.48)	2.32 (0.55)	0.228

Table 4. Cardiovascular biomarker variability between T2DM (GGC) and T2DM (PGC)

Parameter, units(Ranges)	Healthy control n=27	T2DM (GGC) n=25	T2DM (PGC) n=51	P-value
HDL, mmol/l (1,16-1.55)	1.42 (0.40)	1.33 (0.42)	1.30 (0.60)	0.709
LDL, mmol/l (0-2.59)	2.80 (1.40)	2.85 (1.06)	2.90 (1.31)	0.961
Triglycerides, mmol/l (0.4-1.54)	1.0 (0.15)	1.94 (1.36) ^a	2.05 (3.31) ^{a,b}	<0.0001
Total-cholesterol, mmol/l (0-4.91)	4.00 (1.17)	4.78 (1.48) ^a	5.00 (1.67) ^a	0.046
CK-MB, ng/ml (0-7)	3.00 (1.53)	3.00 (1.53)	3.00 (1.02)	0.961

cytokines. These factors affect the β -islets cells leading to low insulin production and overall insulin insensitivity. The finding is in line with a similar study reporting high levels of BMI in diabetes mellitus (22). The study findings further revealed that individuals with good glycemic control had more weight, height and consequently a high BMI as compared to participants with poor glycemic control. This finding may be attributed to an older age among patients with good glycemic control as compared to those with poor glycemic control. Associated factors include smoking, physical inactivity which leads to increased insulin insensitivity, and fatty acids metabolic disturbances leading to increased peripheral fatty acids and triglycerides deposition (22). Similar findings have been reported with other studies (24).

Elevation of ALT indicates an effect of hyperglycemia on hepatic cells due to increased metabolic disturbances leading to fatty acids accumulation in hepatocellular spaces and increased oxidative stress (25). The study findings are in line with other studies done which indicate an elevated ALT levels in poor glycemic control (26). Contrary to these findings, a study conducted by Saligram et al concludes that elevation of the liver enzymes is due to weight and lipids but not glycemic control (27). Contrary to our study, these findings were done only from the newly diagnosed T2DM participants thus, the differences.

In addition, levels of aspartate aminotransferase (AST) reduced in individuals with poor glycemic control as compared to individuals with good glycemic control. This may be attributed to the higher weight in individuals with good glycemic control. Since AST is non-specific to the liver, the elevation maybe due to other diabetic increased factors not related to the liver and glycemic control (27). These findings differ with other studies done which indicate elevation of AST due to liver damage in T2DM (25).

The AST to ALT ratio reduced significantly across the study groups with good glycemic

control having a slightly higher ratio as compared to the poor glycemic control. A possible reason is the inverse relationship witnessed in the levels of individual AST and ALT levels. The reason for this inverse relationship remains unclear, considering that many other study indicates that both the enzymes elevate in case of the hepatocellular damage of any kind (25).

The High γ -glutamyl transferase (GGT) levels reported in poor glycemic control can be attributed to two factors. Firstly, lipid metabolism disturbances that to increased fat deposition in liver cells which consequentially may lead to non-alcoholic fatty liver disease (NAFLD). Such causes pressure to the hepatobiliary cells increasing GGT production (28). Secondly, induction of oxidative stress via increased production of superoxide and reactive oxygen species (ROS) molecules that affects the cell membrane (29). GGT is a transmembrane enzyme and also serves as an anti-oxidant, thus oxidative stress results to increase GGT enzyme production(30). Similar findings have also been reported indicating GGT elevation in T2DM (26).

Bilirubin levels are inversely associated with metabolic syndrome (31). Low bilirubin levels in the body are also considered as a risk factor for development of diabetes and related complications(32). Diabetes is a metabolic disorder which leads to increased oxidative stress. On the other hand, bilirubin is a natural antioxidant thus preventing the cells against diabetic related metabolic deleterious effects on the cells (33). The results in this study were in agreement with a study conducted by Erkus *et al* in 2017 which indicated that low levels of bilirubin were associated with poor glycemic control (34). These findings thus suggest the strong use of bilirubin levels as potential biomarker for glycemic control.

Low total proteins and albumin levels in poor glycemic control are associated to increased proteasome degradation than compromised hepatic synthetic function. In T2DM, there is an increased proteins glycation which results in formation of products such as

advanced glycation end products (AGEs) through a non-enzymatic condensation of amino acids residues and the reducing sugars. These glycated proteins have a shorter half-life than normal protein molecules and they are prone to proteasomal degradation making the total protein levels slightly lower in diabetes and also in poorly controlled diabetes mellitus (35). A study conducted in Ghana in 2019 revealed that poor glycemic control was associated with a reduction in the levels and activities of plasma proteins the results of which are in line with the findings of this study (36). However, the study only focused on three plasma proteins; Protein C (PC), Protein S (PS) and antithrombin III (AT III). Contrary to these findings, a study conducted in Nigeria revealed a higher levels of total proteins in T2DM patients as compared to the healthy control group(37).

A significant high level of urea among the T2DM patients was recorded in the study as compared to healthy controls. Additionally, among the diabetic group, patients with good glycemic control had higher urea levels than patients with poor glycemic control. These results suggest that T2DM is associated with mild azotemia even though the increase is within the normal range. Urea is the main waste formed from the metabolic breakdown of proteins in the liver and is transported to the kidneys for excretion (38). T2DM increases protein glycosylation which in turn leads to increased glycation products in the body. The reaction causes alteration of the proteins which becomes candidates for proteolytic and enzymatic breakdown in the liver (35). High levels of urea is known to be a risk factor for T2DM where it increases insulin secretory defects, impairs glycolysis by increasing the islets protein *O*-GlcNAcylation(39). Similar to the findings of this study, is a study conducted by Dutta et al suggesting ammonia and urea levels elevation in diabetes condition as compared to the non-diabetics (40). Serum urea measurement can serve as useful indicators of poor glycemic control and prediction of diabetic nephropathy.

Diabetes causes DN which result in electrolytes imbalance. These imbalances can further lead to other complications such as cardiovascular, and neuromuscular diseases (41). Hyperkalemia risk in diabetes is brought about by various mechanisms which include compromised K^+ shift back into the cells and impaired excretion due to a deranged tubular function system (42). Diabetes mellitus also leads to a condition known as hyporeninemic hypoaldosteronism which results in a defective RAAS system which thus leads to reduced Na^+ reabsorption and secretion of K^+ into the urinary excretion ducts. This in turn leads to an increase in blood potassium levels (43). Additionally, increased plasma osmolality especially in poor glycemic control leads to water shifting out of the cells. To maintain the balance and revert to the normal state, an opposite electrolyte shift occurs leading to more K^+ ions being pumped outside the cells leading to their increased concentrations (2). Similar results have also been reported in other studies (42). Contrary to the findings of this study, some study indicate that DM leads to hypokalemia especially when there is strong use of diuretics, insulin, beta-2 agonists, antiarrhythmic agents, laxatives and use of glucocorticoids and mineralocorticoids (44). Therefore, in this case the hypokalemia is not directly attributed to hyperkalemia but rather to the use of these treatment agents.

The study reported lower levels of sodium (Na^+) in T2DM patients. Glucose is a metabolically active substance which means it draws water towards it. High glucose levels as witnessed in diabetes causes a directional water flow out of the cells thus over diluting the extracellular milieu. This dilution mechanism subsequently lowers the levels of sodium in blood. Uncontrolled diabetes can also lead to hypovolemic hyponatremia via induced diuresis. The results of these study correlate with other studies which also report low levels of sodium in T2DM and poorly controlled T2DM (43). Contrary findings were reported in a study conducted in Nigeria which suggested that sodium levels increased in

T2DM patients as compared to non-diabetic patients (45). A study conducted among the Chinese population also revealed that serum sodium levels were significantly decreased in diabetic patients. However the decrease was more significant in diabetic patients with normal glucose regulation as compared to those impaired glucose regulation (46).

The levels of chloride [Cl⁻] were low in poorly controlled DM as compared to good glycemic control. Serum chloride levels are affected by the balance in other electrolytes especially sodium with the main mechanism leading to hypochloremia being as a result of increased osmolality due to high glucose levels leading to extracellular chloride dilution due to high water movement outside the cells (47). Similar findings were reported in India where among 342 study participants, 31% had hypochloremia and it was significantly common among subjects with uncontrolled DM (48).

Serum electrolyte measurement remains essential biomarker for determining renal function and related complications in T2DM. However, due to differences in mechanisms leading to the variability as seen in this study and various other studies, their clinical use and interpretation should be coupled with clear clinical history and presentation of the patient.

Triglycerides levels were significantly high in poor glycemic control. Several studies suggest the importance of serum triglycerides determination since is a more useful independent predictor of atherosclerotic cardiovascular disease in people with T2DM. Impaired/ abnormal triglycerides levels can be attributed to various mechanisms which occur concurrently in diabetes state. Firstly, increased insulin insensitivity leads to compensatory hyperinsulinemia elevated VLDL-TG secretion. Secondly, absolute insulin deficiency leading to increased hepatic secretion of VLDL-TG and lastly, severe chylomicronemia due to deficiency in insulin dependent Lipoprotein Lipase. Similar to these findings indicating high triglycerides levels

were reported in a study in Chinese diabetic population (49).

Elevation of total cholesterol levels in PGC is an indication of poor lipid metabolic control similar to that of TGs. In line with these findings, a study conducted in Iran among T1DM patients also reported an increase in total cholesterol levels in poorly regulated glycemic condition. Similar results indicating dyslipidemia among poorly controlled diabetes was also reported in a study conducted in Iraq in 2020 (18,50). Additionally, the study indicated no significant variation in LDL and HDL levels across the diabetic groups. However, their measurement remains to be key in the management of diabetes and monitoring of related vascular complications.

The study only utilized HbA1c as the only index to classify glycemic control. Additional markers of poor glycemic control such as glycated albumin, fructosamin and 1,5-anhydroglucitol used in combination could have improved the classification.

Conclusion

Poor glycemic control causes an elevation in GGT and AST/ALT ratio while bilirubin levels are lowered. The variation however does not indicate a significant hepatic damage.

The levels of urea, potassium and chloride increased significantly while sodium levels reduced in PGC. However, Hyperglycemic osmolality and increased protein turnover are the major causes of acute variability in levels as compared to renal injury.

The levels of triglycerides and total cholesterol were significantly increased in poor glycemic control. Thus PGC in T2DM causes dyslipidemia which affects cardiovascular functioning.

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Conflict of Interest

The authors declare that there are no conflicts of interest.

Authors' contributions

Conception or design: K.S, G.G and N.Sh.

Data collection, analysis and interpretation: K.S, V.K, T.W and N.Sh.

Drafting the work or revising: N.Sh, G.G, F.M and E.B.

All authors read and approved the final manuscript.

References

- American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes care*. 2010;33(Supplement_1):S62-9.
- Adeyinka A, Kondamudi NP. Hyperosmolar Hyperglycemic Syndrome. <http://www.ncbi.nlm.nih.gov/books/NBK482142/>
- Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes research and clinical practice*. 2017;128:40-50.
- Mohamed SF, Mwangi M, Mutua MK, Kibachio J, Hussein A, Ndegwa Z, et al. Prevalence and factors associated with pre-diabetes and diabetes mellitus in Kenya: results from a national survey. *BMC public health*. 2018;18:1-1.
- Alzahrani SH, Baig M, Aashi MM, Al-Shaibi FK, Alqarni DA, Bakhamees WH. Association between glycated hemoglobin (HbA1c) and the lipid profile in patients with type 2 diabetes mellitus at a tertiary care hospital: a retrospective study. *Diabetes, metabolic syndrome and obesity: targets and therapy*. 2019:1639-44.
- Kohnert KD, Heinke P, Vogt L, Salzsieder E. Utility of different glycemic control metrics for optimizing management of diabetes. *World journal of diabetes*. 2015;6(1):17-29.
- Assessment G. 6. Glycemic targets: standards of medical care in diabetes—2022. *Diabetes Care*. 2022;45:S83.
- Haghighatpanah M, Nejad AS, Haghighatpanah M, Thunga G, Mallayasamy S. Factors that correlate with poor glycemic control in type 2 diabetes mellitus patients with complications. *Osong public health and research perspectives*. 2018;9(4):167-74.
- Shiroya V, Neuhaan F, Müller O, Deckert A. Challenges in policy reforms for non-communicable diseases: the case of diabetes in Kenya. *Global health action*. 2019;12(1):1611243.
- Chawla A, Chawla R, Jaggi S. Microvascular and macrovascular complications in diabetes mellitus: distinct or continuum?. *Indian journal of endocrinology and metabolism*. 2016;20(4):546-51.
- Wanjohi MM. Factors Affecting Glycemic Control Among Type II Diabetics Attending Machakos Level Five Outpatient Clinic. (Doctoral dissertation, University of Nairobi). 2018.
- Papatheodorou K, Banach M, Bekiari E, Rizzo M, Edmonds M. Complications of diabetes 2017. *Journal of diabetes research*. 2018;2018:e3086167.
- Fowler MJ. Microvascular and macrovascular complications of diabetes. *Clinical diabetes*. 2008;26(2):77-82.
- Charlton A, Garzarella J, Jandeleit-Dahm KA, Jha JC. Oxidative stress and inflammation in renal and cardiovascular complications of diabetes. *Biology*. 2020 ;10(1):18.
- Tolman KG, Fonseca V, Dalpiaz A, Tan MH. Spectrum of liver disease in type 2 diabetes and management of patients with diabetes and liver disease. *Diabetes care*. 2007;30(3):734-43.
- Pálsson R, Patel UD. Cardiovascular complications of diabetic kidney disease. *Advances in chronic kidney disease*. 2014;21(3):273-80.
- Gowda S, Desai PB, Kulkarni SS, Hull VV, Math AA, Vernekar SN. Markers of renal function tests. *North American journal of medical sciences*. 2010 ;2(4):170.
- AL-Bahrani SM, Yassin BA. Lipid Profile and Glycemic Control in Type 2 Diabetic Patients. *Arab Board Medical Journal*. 2022;23(1):21-7.
- Pastakia SD, Nuche-Berenguer B, Pekny CR, Njuguna B, O'Hara EG, Cheng SY, et al. Retrospective assessment of the quality of diabetes care in a rural diabetes clinic in Western Kenya. *BMC endocrine disorders*. 2018;18:1-9.
- Otieno FC, Mikhail T, Acharya K, Muga J, Ngugi N, Njenga E. Suboptimal glycemic control and prevalence of diabetes-related complications in Kenyan population with diabetes: cohort analysis of the seventh wave of the International Diabetes Management Practices Study (IDMPS). *Endocrine and Metabolic Science*. 2021;3:100093.
- Choe SA, Kim JY, Ro YS, Cho SI. Women are less likely than men to achieve optimal glycemic control after 1 year of treatment: A multi-level analysis of a Korean primary care cohort. *PLoS One*. 2018;13(5):e0196719.
- Mamo Y, Bekele F, Nigussie T, Zewudie A. Determinants of poor glycemic control among adult patients with type 2 diabetes mellitus in Jimma

- University Medical Center, Jimma zone, south west Ethiopia: a case control study. *BMC endocrine disorders*. 2019;19:1-1.
23. Shamshirgaran SM, Mamaghanian A, Aliasgarzadeh A, Aiminisani N, Iranparvar-Alamdari M, Ataie J. Age differences in diabetes-related complications and glycemic control. *BMC endocrine disorders*. 2017;17(1):25.
 24. Hassan MR, Jamhari MN, Hayati F, Ahmad N, Nawi AM, Sharif KY, et al. Determinants of glycaemic control among type 2 diabetes mellitus patients in Northern State of Kedah, Malaysia: a cross-sectional analysis of 5 years national diabetes registry 2014-2018. *Pan African Medical Journal*. 2021;39(1):206.
 25. Noroozi Karimabad M, Khalili P, Ayoobi F, Esmaeili-Nadimi A, La Vecchia C, Jamali Z. Serum liver enzymes and diabetes from the Rafsanjan cohort study. *BMC Endocrine Disorders*. 2022;22(1):127.
 26. Islam S, Rahman S, Haque T, Sumon AH, Ahmed AM, Ali N. Prevalence of elevated liver enzymes and its association with type 2 diabetes: A cross-sectional study in Bangladeshi adults. *Endocrinology, diabetes & metabolism*. 2020;3(2):e00116.
 27. Saligram S, Williams EJ, Masding MG. Raised liver enzymes in newly diagnosed Type 2 diabetes are associated with weight and lipids, but not glycaemic control. *Indian journal of endocrinology and metabolism*. 2012;16(6):1012-4.
 28. Williams KH, Shackel NA, Gorrell MD, McLennan SV, Twigg SM. Diabetes and nonalcoholic fatty liver disease: a pathogenic duo. *Endocrine reviews*. 2013;34(1):84-129.
 29. Giacco F, Brownlee M. Oxidative stress and diabetic complications. *Circulation research*. 2010;107(9):1058-70.
 30. Gohel MG, Chacko AN. Serum GGT activity and hsCRP level in patients with type 2 diabetes mellitus with good and poor glycemic control: An evidence linking oxidative stress, inflammation and glycemic control. *Journal of Diabetes & Metabolic Disorders*. 2013;12:1-8.
 31. Zhu B, Wu X, Bi Y, Yang Y. Effect of bilirubin concentration on the risk of diabetic complications: a meta-analysis of epidemiologic studies. *Scientific reports*. 2017;7(1):41681.
 32. Yang M, Ni C, Chang B, Jiang Z, Zhu Y, Tang Y, et al. Association between serum total bilirubin levels and the risk of type 2 diabetes mellitus. *Diabetes research and clinical practice*. 2019;152:23-8.
 33. Fu YY, Kang KJ, Ahn JM, Kim HR, Na KY, Chae DW, et al. Hyperbilirubinemia reduces the streptozotocin-induced pancreatic damage through attenuating the oxidative stress in the Gunn rat. *The Tohoku journal of experimental medicine*. 2010;222(4):265-73.
 34. Erkus E, Aktas G, Kocak MZ, Duman TT, Atak BM. Serum bilirubin level is associated with diabetic control in type 2 diabetes mellitus. *Blood Heart Circ*. 2018;2(2):1-2.
 35. Raupbach J, Ott C, Koenig J, Grune T. Proteasomal degradation of glycated proteins depends on substrate unfolding: Preferred degradation of moderately modified myoglobin. *Free Radical Biology and Medicine*. 2020;152:516-24.
 36. Addai-Mensah O, Annani-Akollor ME, Nsafoah FO, Fondjo LA, Owiredo EW, Danquah KO, et al. Effect of poor glycaemic control on plasma levels and activity of protein C, protein S, and antithrombin III in type 2 diabetes mellitus. *PLoS One*. 2019;14(9):e0223171.
 37. Analike RA, Ihim A, Iweanya S, Ogbodo E, Onah C, Asomugha A, et al. Assessment of glycated haemoglobin, total protein and albumin levels in patients with type 2 diabetes mellitus visiting NAUTH, Nnewi. *Indian Journal of Pathology and Oncology*. 2019;6(4):700-3.
 38. Higgins C. Urea and the clinical value of measuring blood urea concentration. *Acutecaretesting Org*. 2016;22:1-6.
 39. Al-Musawi HS, Al-Lami M, Al-Saadi AH. Assessment of Glycemic Control, Renal Function, and Oxidative Stress Parameters in Type 2 Diabetes Mellitus Patients. *Iraqi Journal of Science*. 2021:4628-38.
 40. Dutta T, Kudva YC, Persson XM, Schenck LA, Ford GC, Singh RJ, et al. Impact of long-term poor and good glycemic control on metabolomics alterations in type 1 diabetic people. *The Journal of Clinical Endocrinology & Metabolism*. 2016;101(3):1023-33.
 41. Pipeleers L, Wissing KM, Hilbrands R. Acid-base and electrolyte disturbances in patients with diabetes mellitus. *Acta Clinica Belgica*. 2019;74(1):28-33.
 42. Goia-Nishide K, Coregliano-Ring L, Rangel ÉB. Hyperkalemia in diabetes mellitus setting. *Diseases*. 2022;10(2):20.
 43. Sousa AG, de Sousa Cabral JV, El-Feghaly WB, de Sousa LS, Nunes AB. Hyporeninemic hypoaldosteronism and diabetes mellitus: pathophysiology assumptions, clinical aspects and implications for management. *World journal of diabetes*. 2016;7(5):101.
 44. Coregliano-Ring L, Goia-Nishide K, Rangel ÉB. Hypokalemia in diabetes mellitus setting. *Medicina*. 2022;58(3):431.
 45. Unachukwu MN, Engwa GA, Nwalo FN, Attama TJ, Abonyi C, Akaniro-Ejim EN, et al. Influence of type 2 diabetes on serum electrolytes and renal function indices in patients. *Journal of Clinical and Diagnostic Research*. 2018;12(6):BC13 - BC16.

46. Wang S, Hou X, Liu Y, Lu H, Wei L, Bao Y, Jia W. Serum electrolyte levels in relation to macrovascular complications in Chinese patients with diabetes mellitus. *Cardiovascular diabetology*. 2013;12:1-0.
47. Khan RN, Saba F, Kausar SF, Siddiqui MH. Pattern of electrolyte imbalance in Type 2 diabetes patients: Experience from a tertiary care hospital. *Pakistan Journal of Medical Sciences*. 2019;35(3):797.
48. Karuppan A, Sahay Mi, Ravindranathan R, Haripriya P, Sriram Dk, George M. Electrolyte Disturbances among Diabetic Patients Admitted in a Multi-Specialty Hospital in Southern India. *Journal of Clinical & Diagnostic Research*. 2019;13(2):OC12-OC15.
49. Wang S, Ji X, Zhang Z, Xue F. Relationship between lipid profiles and glycemic control among patients with type 2 diabetes in Qingdao, China. *International Journal of Environmental Research and Public Health*. 2020;17(15):5317.
50. Mostofizadeh N, Hashemipour M, Roostazadeh M, Hashemi-Dehkordi E, Shahsanai A, Reisi M. The impact of poor glycemic control on lipid profile variables in children with type 1 diabetes mellitus. *Journal of education and health promotion*. 2019;8(1):6.