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Serum Electrolyte Dysregulation and Inflammatory Burden in Type 2 Diabetes: Development of a Novel Electrolyte-Inflammation Risk Score for Predicting Glycemic Control and Cardiovascular Complications

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ABSTRACT

OBJECTIVE This study aimed to develop and validate a novel Electrolyte-Inflammation Risk Score (EIRS) integrating serum electrolytes and high-sensitivity C-reactive protein (hs-CRP), to predict glycemic control and cardiovascular risk in patients with type 2 diabetes mellitus (T2DM).

METHODS A cross-sectional case-control study was conducted at Sri Lalithambigai Medical College, Chennai, involving 100 participants (50 patients with T2DM and 50 age-matched healthy controls). Fasting blood glucose, HbA1c (measured by HPLC using the Bio-Rad D-10 system), serum sodium, potassium, and chloride (measured using an ion-selective electrode on the Roche Cobas), magnesium (measured by the xylidyl blue colorimetric method), and hs-CRP (measured by a particle-enhanced immunoturbidimetric assay) were measured. Statistical analysis included independent t-tests, Pearson correlation, multivariate logistic regression, and ROC curve analysis (SPSS version 28.0; $p < 0.05$).

RESULTS T2DM patients exhibited significant electrolyte imbalances compared with controls: elevated potassium (5.40 ± 0.65 vs. 4.16 ± 0.82 mmol/L), increased sodium (142.6 ± 3.5 vs. 138.2 ± 2.3 mmol/L), reduced magnesium (1.8 ± 0.4 vs. 2.1 ± 0.3 mg/dL), and markedly elevated hs-CRP (4.8 ± 2.1 vs. 1.1 ± 0.7 mg/L; all $p < 0.001$ or $p < 0.05$). Multivariate logistic regression identified elevated sodium (OR = 2.84, 95% CI: 1.23–6.57, $p = 0.015$), elevated potassium (OR = 3.42, 95% CI: 1.45–8.08, $p = 0.005$), elevated hs-CRP (OR = 4.73, 95% CI: 2.15–10.41, $p < 0.001$), and higher BMI (OR = 1.12 per kg/m², 95% CI: 1.01–1.24, $p = 0.031$) as independent predictors of HbA1c > 8%. The EIRS, which is based on the four laboratory parameters, achieved an AUC of 0.847 (95% CI: 0.765–0.929, $p < 0.001$) at an optimal cut-off of ≥ 4 points, with 84% sensitivity and 78% specificity. High-risk patients (score 6–8) had 100% poor glycemic control and a 78% incidence of cardiovascular events, compared with 67% and 33% in moderate-risk and 13% and 8% in low-risk patients, respectively.

CONCLUSION The EIRS effectively identifies patients with T2DM at high risk of poor glycemic control and cardiovascular complications, offering a practical tool for the simultaneous assessment of metabolic and inflammatory risk.

KEYWORDS type 2 diabetes mellitus, electrolyte imbalance, inflammation, risk assessment, glycemic control, C-reactive protein

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a complex metabolic syndrome affecting more than 463 million people worldwide, characterized by chronic hyperglycemia, progressive β-cell dysfunction, and insulin resistance (1). Beyond conventional hyperglycemic manifestations, T2DM contributes significantly to long-term complications and mortality through intricate disturbances in electrolyte homeostasis and inflammatory pathways (2).

Electrolyte dysregulation in T2DM patients arises from multiple mechanisms. Osmotic diuresis induced by hyperglycemia, alterations in renal tubular function, and hormonal imbalances disrupt the balance of sodium, potassium, chloride, and magnesium (3). These electrolyte imbalances are not merely consequences of hyperglycemia; they actively exacerbate insulin resistance, endothelial dysfunction, and cardiovascular complications (4).

Chronic low-grade inflammation, characterized by elevated inflammatory markers such as high-sensitivity C-reactive protein (hs-CRP), plays a crucial role in the pathophysiology and progression of T2DM (5). hs-CRP serves as a robust predictor of cardiovascular events (6) and reflects the inflammatory milieu that contributes to diabetic complications. The intersection of electrolyte dysregulation and inflammatory activation represents a novel therapeutic target and an opportunity for risk stratification. Currently, no comprehensive assessment tools in clinical practice integrate these parameters for exhaustive risk evaluation. While established correlations exist between diabetes and inflammatory markers or electrolyte imbalances, the synergistic effects of electrolyte-inflammation dysregulation on cardiovascular risk and glycemic control remain largely unexplored.

This study aimed to develop a novel Electrolyte-Inflammation Risk Score (EIRS) to predict glycemic control and cardiovascular risk in individuals with T2DM by integrating serum electrolyte profiles with inflammatory markers.

METHODS

Study design and setting

A cross-sectional case-control study was conducted at Sri Lalithambigai Medical College in Chennai, India, from April 2023 to December 2023. The Institutional Ethics Committee approved the study protocol [Approval No. 002/SBMCH/IHEC/2023/1942]. Before enrolling, each participant provided written informed consent in accordance with the Declaration of Helsinki.

Study population and sample size

We used G*Power 3.1 software to calculate the sample size, which yielded at least 45 participants per group with 80% power, $\alpha = 0.05$, and effect size = 0.8. We enrolled 100 individuals—50 with T2DM and 50 healthy age-matched controls.

Inclusion criteria

Inclusion criteria were patients with T2DM aged 30 to 70 years, diagnosed according to the American Diabetes Association (ADA) criteria (7), with disease duration exceeding one year. Controls consisted of age-matched healthy individuals without acute illness, metabolic syndrome, or diabetes.

Exclusion criteria

The exclusion criteria were type 1 diabetes or secondary diabetes, acute diabetic complications including diabetic ketoacidosis or hyperosmolar hyperglycemic state, chronic kidney disease with estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73m², hepatic dysfunction with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 2 times upper normal limit, acute inflammatory conditions or active infections, medications affecting electrolyte balance including diuretics, angiotensin-converting enzyme (ACE) inhibitors, or potassium supplements within 2 weeks prior to enrollment, and pregnancy or lactation.

Anthropometric measurements

Participants stood barefoot while a wall-mounted stadiometer (Seca 213, Hamburg, Germany) measured their height to the nearest 0.1 cm. Participants wore lightweight attire, and their mass was measured to the nearest 0.1 kg using a calibrated digital scale (Omron HBF-375, Kyoto, Japan). Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared.

Blood pressure measurement

Blood pressure was measured using an automated sphygmomanometer (Omron HEM-7120, Kyoto, Japan) after 5 minutes of rest in a seated position with arm supported at heart level. Three

readings were taken at 2-minute intervals. The mean of the last two readings was recorded.

Sample collection protocol

To minimize circadian variation, venous blood samples (7 mL total) were collected between 8:00 and 10:00 AM after a 12-hour overnight fast. A 21-gauge needle with minimal venous stasis was used to draw blood from the antecubital vein. A 3 mL fluoride oxalate tube (BD Vacutainer, Franklin Lakes, NJ, USA) was used to measure glucose, a 2 mL dipotassium ethylenediaminetetraacetic acid (EDTA) tube (BD Vacutainer, Franklin Lakes, NJ, USA) for HbA1c analysis, and a 2 mL plain tube (BD Vacutainer, Franklin Lakes, NJ, USA) for electrolytes and hs-CRP measurement. All samples were transported to the laboratory at 4°C within 30 minutes of collection and pro-cessed immediately.

Laboratory analysis

Fasting blood sugar (FBS) measurement: the enzymatic colorimetric glucose oxidase-peroxidase method was used (8). The instrument was an Erba Chem-7 semi-automated biochemistry analyzer (Transasia Mannheim, Germany). Reagent: Erba Glucose Kit (Catalog No. 10821). Calibration: Two-point calibration daily using manufacturer-provided standards. **Quality control:** Bio-Rad Lyphochek Diabetes Control was tested with each batch (level 1: 80–100 mg/dL; level 2: 250–300 mg/dL). The assay was performed at a wavelength of 505 nm and a temperature of 37°C. The linearity range was 10–600 mg/dL, with a coefficient of variation (CV) of < 2.5%. Samples were centrifuged at 3,000 rpm (1,500 × g) for 10 minutes. Serum was separated and analyzed within 2 hours of collection.

Hemoglobin A1c (HbA1c)

Cation-exchange chromatography with gradient elution using HPLC (9) was used. The instrument was a Bio-Rad D-10 Hemoglobin Testing System (Bio-Rad, Hercules, CA, USA). Sample volume was 5 µL of whole blood with a run time of 3.5 minutes per sample, column temperature of 30°C and detection wavelength of 415 nm. Calibration was done with National Glycohemoglobin Standardization Program (NGSP)-certified calibrators. Quality control included Bio-Rad Lyphochek HbA1C controls, which were tested with each batch (level 1: 5.0–5.5%; level 2: 9.5–10.5%). The CV was < 1.5%.

Serum sodium measurement

Serum sodium measurement used an ion-selective electrode with direct potentiometry (10). The instrument was a Roche Cobas 6000 analyzer (Basel, Switzerland). The electrode type was a sodium-specific glass membrane electrode. Sample volume was 100 µL serum and measurement time was 60 seconds. The reference electrode was silver-silver chloride. Calibration included daily two-point calibration with standards at 120 and 160 mmol/L. Quality control using a Roche PreciControl MultiQC was tested twice daily (level 1: 130–135 mmol/L; level 2: 145–150 mmol/L). The linearity range was100–180 mmol/L and CV was < 0.8%.

Serum potassium measurement

Direct potentiometry measurement was done using an ion-selective electrode (10) (Roche Cobas 6000 analyzer, Basel, Switzerland). The electrode was a potassium-selective valinomycin membrane. The sample volume: 100 µL serum. Measurement time: 60 seconds. Calibration: Daily two-point calibration with standards at 2.0 and 8.0 mmol/L. **Quality control:** Roche PreciControl MultiQC was tested twice daily (level 1: 3.5–4.0 mmol/L; level 2: 5.5–6.0 mmol/L). The assay had a linearity range of 1.5–10.0 mmol/L and a CV of < 1.2%.

Serum chloride measurement

Direct potentiometry with ion-selective electrode (10). Instrument: Roche Cobas 6000 analyzer (Basel, Switzerland). Sample volume: 100 µL serum. Measurement time: 60 seconds. Calibration: Daily two-point calibration with standards at 80 and 140 mmol/L. **Quality control:** Roche PreciControl MultiQC was tested twice daily (level 1: 95–100 mmol/L; level 2: 110–115 mmol/L). The assay had a linearity range of 50–160 mmol/L and a CV of < 1.0%.

Serum magnesium measurement

Serum magnesium concentration was measured using the Magnesium Gen.2 (MG2) colorimetric assay (Roche Diagnostics, Basel, Switzerland) on a Roche/Hitachi cobas 6000 analyzer. The assay is based on the reaction of magnesium with xylidyl blue in an alkaline medium containing EGTA, which minimizes interference from calcium. Magnesium forms a purple-colored complex with xylidyl blue, and the resulting absorbance change is measured photometrically. A 3 µL serum sample was used for analysis. The assay was performed using the manufacturer's specified 505/600

nm (sub/main) wavelength configuration and a 2-point endpoint measurement. Calibration was performed using H_2O and Roche Calibrator f.a.s. according to the manufacturer's recommendations. Internal quality control was performed using appropriate Roche PreciControl materials. The manufacturer's measuring range for serum/plasma was 0.10–2.0 mmol/L (0.243–4.86 mg/dL), with an adult reference interval of 0.66–1.07 mmol/L (1.6–2.6 mg/dL) (11).

High-sensitivity C- reactive protein (hs-CRP) measurement: Particle-enhanced immunoturbidimetric assay (12). Instrument: Roche Cobas 6000 analyzer (Basel, Switzerland). Reagent: Roche CRPHS Kit (Catalog No. 04956648). Principle: Latex particles coated with monoclonal anti-CRP antibodies agglutinate C-reactive protein, producing turbidity measured photometrically. Sample volume: 10 µL serum. Wavelength: 570 nm. Temperature: 37°C. **Calibration:** A five-point calibration was performed monthly using the manufacturer's standards. **Quality control:** Roche PreciControl ClinChem Multi was tested twice daily (level 1: 0.8–1.2 mg/L; level 2: 4.5–5.5 mg/L). The assay had a measurement range of 0.15–20.00 mg/L, a functional sensitivity of 0.15 mg/L, and a CV of < 3.5%.

Sample processing and storage

Blood samples were collected in appropriate serum-separating tubes and allowed to clot before centrifugation at 3,000 rpm (1,500 × g) for 10 minutes at 4°C using a refrigerated centrifuge (Remi R-8C, Mumbai, India). Serum was separated within 30 minutes of sample collection. All biochemical analyses were completed within two hours of sample processing. Samples requiring repeat testing were stored at −20°C for no longer than 48 hours.

Quality assurance

Laboratory quality assurance included daily calibration checks, analysis of two-level quality control materials with each batch, use of Westgard multi-rule quality control procedures, regular participation in external quality assurance programs, adherence to manufacturer instructions for preventive maintenance of analyzers, and continuous monitoring of analyzer and storage unit temperatures.

Statistical analysis

Data were analyzed using IBM SPSS Statistics version 28.0 (IBM Corporation, Armonk, NY, USA). The Kolmogorov–Smirnov test was used to assess the normality of continuous variables. Continuous variables following normal distribution are presented as mean ± standard deviation (SD). Categorical variables are presented as frequencies and percentages.

For group comparisons, independent samples t-test was used for continuous variables and chi-square test for categorical variables. Pearson correlation coefficient (r) was used for correlation analysis of parametric data. Correlations were categorized as weak (r = 0.1-0.3), moderate (r = 0.3-0.5), and strong (r > 0.5).

Binary logistic regression with backward stepwise method (p-entry < 0.05, p-removal > 0.10) identified independent predictors of poor gly-cemic control. Odds ratios (ORs) with 95% con-fidence intervals (95% CIs) were calculated. Hosmer-Lemeshow goodness-of-fit test assessed model fit.

ROC curve analysis evaluated the discriminatory ability of EIRS. AUC with 95%CIs were calculated. Youden's index (sensitivity + specificity - 1) determined optimal cut-off points. DeLong test compared AUC values.

For all analyses, a two-tailed p-value below 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

The study population comprised 100 participants with comparable age distribution between groups (T2DM: 49.2 ± 12.7 years vs. Controls: 46.8 ± 10.3 years, p = 0.31). T2DM patients exhibited significantly higher BMI compared to controls (28.4 ± 3.2 vs. 23.6 ± 2.1 kg/m², p < 0.001). The mean diabetes duration in T2DM patients was 8.3 ± 4.7 years.

Glycemic parameters and inflammatory markers

T2DM patients demonstrated poor glycemic control with significantly elevated HbA1c (8.8 ± 1.9% vs. 4.5 ± 0.4%, p < 0.001) and FBS (186 ± 42 vs. 98 ± 13 mg/dL, p < 0.001) compared to controls. hs-CRP levels were significantly higher in T2DM patients (4.8 ± 2.1 vs. 1.1 ± 0.7 mg/L, p < 0.001).

Table 1. Biochemical parameters in study participants

Parameter	T2DM (n = 50)	Controls (n = 50)	*p*-value
Age (years)	49.2±12.7	46.8±10.3	0.310
BMI (kg/m²)	28.4±3.2	23.6±2.1	< 0.001
HbA1c (%)	8.8±1.9	4.5±0.4	< 0.001
FBS (mg/dL)	186±42	98±13	< 0.001
Sodium (mmol/L)	142.6±3.5	138.2±2.3	< 0.001
Potassium (mmol/L)	5.40±0.65	4.16±0.82	< 0.001
Chloride (mmol/L)	101.2±5.5	99.7±4.2	0.140
Magnesium (mg/dL)	1.8±0.4	2.1±0.3	< 0.050
hs-CRP (mg/L)	4.8±2.1	1.1±0.7	< 0.001

Data presented as mean ± SD. BMI, body mass index; FBS, fasting blood sugar; hs-CRP, high-sensitivity C-reactive protein. $p < 0.05$ considered statistically significant

Electrolyte profile

T2DM patients demonstrated significant alterations in electrolyte levels. Serum sodium was elevated (142.6 ± 3.5 vs. 138.2 ± 2.3 mmol/L, $p < 0.001$). Serum potassium was elevated (5.40 ± 0.65 vs. 4.16 ± 0.82 mmol/L, $p < 0.001$). Serum magnesium was reduced (1.8 ± 0.4 vs. 2.1 ± 0.3 mg/dL, $p < 0.05$). Serum chloride levels showed no significant difference between groups (101.2 ± 5.5 vs. 99.7 ± 4.2 mmol/L, p = 0.14). Complete biochemical parameters are presented in Table 1.

Correlation analysis

In T2DM patients, fasting blood sugar correlated with serum sodium ($r = -0.33$, $p = 0.019$) and serum chloride ($r = 0.29$, $p = 0.042$). hs-CRP correlated with fasting blood sugar ($r = 0.45$, $p < 0.01$), HbA1c ($r = 0.52$, $p < 0.001$), serum sodium (r = 0.30, $p = 0.037$), serum potassium ($r = 0.38$, $p = 0.007$), and serum magnesium ($r = -0.40$, $p = 0.004$). Correlations are summarized in Table 2.

Table 2. Correlation of hs-CRP with glycemic and electrolyte parameters in T2DM patients

Parameter	Pearson correlation (r)	*p*-value
Fasting Blood Sugar	0.45	< 0.010
HbA1c	0.52	< 0.001
Sodium	0.30	0.037
Potassium	0.38	0.007
Chloride	0.15	0.290
Magnesium	-0.40	0.004

hs-CRP, high-sensitivity C-reactive protein; T2DM, type 2 diabetes mellitus ; $p < 0.05$ considered statistically significant

Development of electrolyte-inflammation risk score

Multivariate logistic regression analysis was performed to identify independent predictors of poor glycemic control, defined as HbA1c greater than 8%. Variables entered into the model included elevated sodium (greater than 145 mmol/L), elevated potassium (greater than 5.0 mmol/L), elevated hs-CRP (greater than 3.0 mg/L), reduced magnesium (less than 1.8 mg/dL), age, and BMI. Independent predictors identified were elevated sodium (OR = 2.84, 95%CI: 1.23-6.57, $p = 0.015$), elevated potassium (OR = 3.42, 95%CI: 1.45-8.08, $p = 0.005$), and elevated hs-CRP (OR = 4.73, 95%CI: 2.15-10.41, $p < 0.001$). Complete multivariate analysis results are presented in Table 3.

Based on these findings, the EIRS was constructed using weighted point allocation corresponding to the relative strength of association with poor glycemic control. The scoring system assigned 2 points for elevated sodium (serum sodium > 145 mmol/L), 2 points for elevated potassium (serum potassium > 5.0 mmol/L), 3 points for elevated hs-CRP (> 3.0 mg/L), and 1 point for reduced magnesium (serum magnesium < 1.8 mg/dL).

Table 3. Multivariate logistic regression analysis for predictors of poor glycemic control

	Odds ratio	95%CI	*p*-value
Elevated sodium (> 145 mmol/L)	2.84	1.23-6.57	0.015
Elevated potassium (> 5.0 mmol/L)	3.42	1.45-8.08	0.005
Elevated hs-CRP (> 3.0 mg/L)	4.73	2.15-10.41	< 0.001
Reduced magnesium (< 1.8 mg/dL)	1.89	0.82-4.35	0.134
Age (per year)	1.03	0.98-1.08	0.251
BMI (per kg/m²)	1.12	1.01-1.24	0.031

CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; BMI, body mass index. $p < 0.05$ considered statistically significant

Total EIRS ranges from 0 to 8 points. Risk stratification categories were defined as low risk (0-2 points), moderate risk (3-5 points), and high risk (6-8 points).

Performance of Electrolyte-Inflammation Risk Score

Receiver operating characteristic curve analysis was performed to evaluate the discriminatory ability of the EIRS for predicting poor glycemic control. The EIRS demonstrated excellent discriminatory performance with area under the curve of 0.847 (95%CI: 0.765-0.929, $p < 0.001$). The optimal cut-off value was determined to be 4 points or greater, achieving sensitivity of 84% and specificity of 78%. The EIRS performance exceeded that of individual parameters including hs-CRP alone (AUC = 0.723), serum potassium alone (AUC = 0.678), and serum sodium alone (AUC = 0.645). ROC analysis results are summarized in Table 4.

Clinical outcomes according to EIRS categories

Analysis of clinical outcomes stratified by EIRS risk categories revealed significant differences. Among the 50 T2DM patients, 23 (46%) were classified as low risk, 18 (36%) as moderate risk, and 9 (18%) as high risk. High-risk patients demonstrated poor glycemic control with 100% having HbA1c > 8%, compared to 67% in moderate-risk and 13% in low-risk categories. Cardiovascular events were more frequent in high-risk patients (78%) compared to moderate-risk (33%) and low-risk (8%) patients. Mean HbA1c progressively increased across risk categories: 6.8 ± 1.2% in low-risk, 8.9 ± 1.5% in moderate-risk, and 11.2 ± 1.8% in high-risk groups. Complete outcome data are presented in Table 5.

Subgroup validation analysis

The predictive performance of the EIRS was validated across different patient subgroups to ensure robustness and generalizability. Excellent discriminatory ability was maintained across all subgroups examined. For age stratification, patients younger than 50 years showed area under the curve of 0.831 (95%CI: 0.701-0.961, $p = 0.002$) while those 50 years or older showed area under the curve of 0.859 (95%CI: 0.719-0.999, $p = 0.001$). For BMI stratification, patients with BMI less than 30 kg/m² demonstrated area under the curve of 0.824 (95%CI: 0.706-0.942, $p = 0.001$) while those with BMI 30 kg/m² or greater showed area under the curve of 0.873 (95%CI: 0.732-1.000, $p < 0.001$). For diabetes duration, patients with disease duration less than 5 years showed area under the curve of 0.798 (95%CI: 0.627-0.969, $p = 0.016$) while those with duration 5 years or greater demonstrated area under the curve of 0.871 (95%CI: 0.772-0.970, $p < 0.001$). Subgroup analysis results are summarized in Table 6.

Table 4. ROC curve analysis for predicting poor glycemic control

Parameter	AUC	95%CI	p-value	Optimal cut-off	Sensitivity (%)	Specificity (%)
EIRS Score	0.847	0.765-0.929	< 0.001	≥ 4 points	84	78
hs-CRP	0.723	0.621-0.825	< 0.001	> 3.0 mg/L	72	68
Potassium	0.678	0.568-0.788	0.006	> 5.0 mmol/L	65	70
Sodium	0.645	0.532-0.758	0.024	> 145 mmol/L	68	61

ROC, receiver operating characteristic; AUC: area under the curve; CI, confidence interval; EIRS, Electrolyte-Inflammation Risk Score; hs-CRP: high-sensitivity C-reactive protein

Table 5. Clinical outcomes according to EIRS risk categories

EIRS category	n (%)	Mean HbA1c (%)	Poor control (%)[a]	Cardiovascular events (%)
Low risk (0-2)	23 (46)	6.8±1.2	13	8
Moderate risk (3-5)	18 (36)	8.9±1.5	67	33
High risk (6-8)	9 (18)	11.2±1.8	100	78

[a]Poor control defined as HbA1c > 8%; EIRS, Electrolyte-Inflammation Risk Score; CV, cardiovascular

Table 6. Subgroup analysis of EIRS performance

Subgroup	n	AUC	95%CI	*p*-value
Age < 50 years	28	0.831	0.701-0.961	0.002
Age ≥ 50 years	22	0.859	0.719-0.999	0.001
BMI < 30 kg/m²	31	0.824	0.706-0.942	0.001
BMI ≥ 30 kg/m²	19	0.873	0.732-1.000	< 0.001
Diabetes duration < 5 years	18	0.798	0.627-0.969	0.016
Diabetes duration ≥ 5 years	32	0.871	0.772-0.970	< 0.001

EIRS, Electrolyte-Inflammation Risk Score; AUC, area under the curve; CI, confidence interval; BMI, body mass index

DISCUSSION

This study provides a new method for risk stratification in T2DM by creating and validating the EIRS. A useful tool for determining who might have heart problems and poor blood sugar control is the EIRS. It utilizes readily available biochemical parameters.

In individuals with T2DM, elevated sodium levels (142.6 ± 3.5 mmol/L) are a clinically significant finding with significant pathophysiological implications. This increase is likely due to changes in renal sodium handling in diabetics as well as a greater water loss from osmotic diuresis than from sodium loss (13). Acute glycemic fluctuations may temporarily change sodium levels through osmotic water shifts, according to the negative correlation between fasting blood sugar and sodium (r = -0.33, p = 0.019).

The elevated potassium level (5.40 ± 0.65 mmol/L) in our T2DM cohort is in line with recent studies that demonstrate diabetic patients, particularly those with hyporeninemic hypoaldosteronism, have a propensity to retain potassium in their bodies (14). Diabetes is often the cause of this problem, which is characterized by normal cortisol secretion and selective hypoaldosteronism. This is brought on by diabetic autonomic neuropathy, which prevents renin from being released and inhibits the synthesis of angiotensin II. High potassium levels in diabetics are clinically significant due to the increased risk of heart arrhythmias and sudden cardiac death, in addition to electrolyte imbalance.

Patients with diabetes have lower magnesium levels (1.8 ± 0.4 mg/dL) because diabetes is frequently linked to increased renal magnesium excretion and impaired gastrointestinal absorption (15). In diabetics, magnesium deficiency can exacerbate insulin resistance, affect the function of pancreatic β-cells, and cause problems with the endothelium. The resulting vicious cycle speeds up the onset of diabetic complications and makes it impossible to properly control blood sugar levels.

One of the main characteristics of diabetes is chronic low-grade inflammation, as evidenced by the marked increase in hs-CRP in T2DM patients (4.8 ± 2.1 mg/L). The strong correlation between hs-CRP and HbA1c (r = 0.52, p < 0.001) indicates a reciprocal relationship between inflammation and glucose control. Accordingly, chronically high blood sugar levels cause inflammation through oxidative stress and advanced glycation end products, while inflammation itself decreases insulin sensitivity in a number of ways (16).

The recently discovered associations between hs-CRP and electrolytes (sodium: r = 0.30; potassium: r = 0.38; magnesium: r = -0.40) suggest that inflammatory processes may act as a unifying mechanism connecting electrolyte imbalances and metabolic dysregulation. This observation supports the notion that various organ systems, particularly renal electrolyte management mechanisms, are impacted by systemic inflammation (17). Inflammatory cytokines directly affect renal tubular ion transport mechanisms, aldosterone sensitivity, and epithelial sodium channel activity.

The area under the curve for the EIRS is 0.847, which is significantly greater than the area under the curve for each parameter. This suggests that it can detect when glycemic control is insufficient. This performance highlights the importance of a comprehensive evaluation that elucidates the intricate relationship between inflammatory activation and electrolyte dysregulation. The optimal cut-off for identifying high-risk patients is four points or more. There is a clinically significant balance between sensitivity (84%) and specificity (78%).

The EIRS's ability to differentiate between various risks is astounding. Patients at high risk (6–8 points) had a significantly worse glycemic control (100% with HbA1c > 8%) and a significantly higher rate of cardiovascular events (78%). This study outlines a patient population that is especially at risk and advocates for comprehensive intervention strategies that include precise electrolyte replacement, stringent glycemic control, anti-inflammatory medication, and general cardiovascular risk reduction.

The EIRS is easy to use in clinical practice because it utilizes lab tests that are already available in most healthcare settings. You can decide how aggressive the treatment should be and how often to check on people by using the scoring system to sort them by risk. More frequent lab and clinic visits, targeted treatments for particular electrolyte imbalances and inflammatory markers, drug therapy optimization with an eye toward medications that help with inflammation and glycemic control, and comprehensive cardiovascular risk management that includes lipid and blood pressure control all would be beneficial for patients with moderate to high risk scores.

The combination of electrolyte and inflammatory parameters in the EIRS indicates the presence of underlying cooperative and interconnected pathophysiological mechanisms. Chronic hyperglycemia triggers inflammatory pathways by producing more pro-inflammatory cytokines, activating protein kinase C (PKC), increasing oxidative stress, and producing advanced glycation end products (AGEs). Additionally, hyperglycemia causes osmotic diuresis by altering the kidneys' ion reabsorption capacity, leading to urinary sodium and water loss, impaired cellular ion channels and transporters, and aldosterone resistance.

The resulting inflammatory state further reduces insulin sensitivity by blocking insulin receptor substrate (IRS) phosphorylation, triggering stress-activated kinases, increasing inflammatory adipokine production, and accelerating lipolysis with elevated free fatty acids. These inflammatory effects increase electrolyte imbalances by directly altering renal tubular transport mechanisms, changing hormone sensitivity, and exerting systemic effects on fluid and electrolyte distribution.

The renin-angiotensin-aldosterone system (RAAS) constitutes a key element of these interrelated processes (18). Inflammatory cytokines directly affect ion transport mechanisms in renal tubules, whereas hyporeninemic hypoaldosteronism associated with diabetes causes potassium elevation. These complex relationships form the foundation for the integrated assessment methodology displayed in the EIRS and provide insight into the connections between inflammatory markers and electrolyte imbalances.

Limitations

There are several limitations that must be acknowledged. Because of the cross-sectional design, a causal relationship between the evaluated parameters and clinical outcomes cannot be established. Longitudinal studies are required to conclusively ascertain whether electrolyte and inflammatory dysregulation foreshadows and predicts the onset of poor glycemic control and its associated complications. The moderate sample size of 50 T2DM patients may limit the findings' generalizability. To confirm the EIRS's effectiveness across racial and ethnic groups, geographic locations, and healthcare settings, more comprehensive studies in a variety of populations are required.

The study population's limited geographic applicability may be due to its focus on Chennai, India. It is essential to validate across various centers and populations. We cannot ascertain whether the score can forecast long-term outcomes such as the onset of diabetes complications, cardiovascular issues, and mortality because there is no long-term follow-up. To evaluate the prognostic significance of the EIRS, prospective studies with long follow-up are required.

Future directions

The EIRS serves as the foundation for customized diabetes care plans. Mechanistic studies to clarify the molecular pathways linking electrolytes and inflammation at the cellular and molecular levels; prospective intervention studies to determine whether EIRS-guided therapy improves clinical outcomes in comparison to standard management; comprehensive validation studies in diverse populations to evaluate performance across a range of ethnic groups, geographic locations, and healthcare settings; future research directions include examining temporal changes in EIRS and their relationship to treatment re-

sponse and prognosis, as well as integrating them into clinical decision support systems to enable broad adoption and real-time risk assessment.

CONCLUSIONS

This study introduces the Electrolyte-Inflammation Risk Score as a valuable instrument for the comprehensive assessment of metabolic and inflammatory status in individuals with type 2 diabetes. The EIRS has an area under the curve of 0.847 and works best when the cut-off is 4 points or higher. This means that it is very good at predicting which patients are most likely to have bad glycemic control and heart problems.

The results underscore the significance of considering inflammatory burden and electrolyte dysregulation as interconnected pathophysiological processes in T2DM. The EIRS framework encourages a comprehensive methodology for diabetes management that acknowledges the intricate characteristics of diabetic pathophysiology and transcends traditional glycemic-focused strategies.

The EIRS's use in clinical practice may lead to better patient outcomes by improving risk stratification, focused interventions, and individualized monitoring plans. The EIRS finds patients who are at high risk and need intensive care. This care includes aggressive cardiovascular risk reduction, targeted electrolyte correction, anti-inflammatory medication, and thorough metabolic control. This integrated assessment approach is a big step toward precision medicine in the treatment of diabetes.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest related to this study.

AUTHOR CONTRIBUTIONS

S.D.: conceptualization, methodology, data curation, formal analysis, writing — original draft preparation, writing — review & editing, project administration, correspondence; V.M.S.: conceptualization, methodology, investigation, clinical supervision, resources, writing — review & editing; A.K.S.: data curation, investigation, sample analysis, validation, writing – original draft preparation; V.S.K.: supervision, methodology, validation, writing — review & editing, project administration; T.J.: supervision, formal analysis, validation, statistical consultation, writing — review & editing.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author (sarguru2@gmail.com) upon reasonable request.

INSTITUTIONAL REVIEW BOARD STATEMENT

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of Sri Lalithambigai Medical College, Dr. MGR Educational & Research Institute (approval 002/SBMCH/IHEC/2023/1942, approved on April 29, 2023).

INFORMED CONSENT STATEMENT

Informed consent was obtained from all subjects involved in the study. All participants provided written informed consent in accordance with the Declaration of Helsinki before enrollment in the study.

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