

Original article

Relevance of electrolytes, creatinine and uric acid in progression of type 2 diabetes mellitus in Bangladeshi population

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Background: Type 2 diabetes is a chronic metabolic syndrome, with partial beta cell dysfunction, that can lead to serious cardiovascular, renal, neurologic and retinal complications. The knowledge on the diabetic disorders in electrolytes and membrane function in Bangladeshi population is limited.

Objective: This research aimed to analyze the association of serum uric acid, creatinine, and electrolytes as potential risk factors for developing type 2 diabetes mellitus in Bangladeshi population.

Methods: The research performed a prospective case-control study of 79 uncontrolled and 60 controlled type 2 diabetic subjects. Subject's serum was analyzed for electrolytes, glucose, creatinine, uric acid, and HbA1c applying electrolytes analyzer system, glucose-oxidase method, alkaline picrate method, ultraviolet-visible spectrophotometric method, unit root and cointegration analysis (URCA) method based on dimension clinical chemistry system and turbidimetric inhibition immunoassay method (TINIA), respectively.

Results: At the experimental period, systolic blood pressure (SBP) and diastolic blood pressure (DBP) of the uncontrolled type 2 diabetes subjects were significantly different ($P < 0.05$) from those of the controlled type 2 diabetes subjects. HbA1c, sodium ion, potassium ion, bicarbonate ion, serum uric acid level in the uncontrolled type 2 diabetes subjects and the controlled type 2 diabetes subjects were significantly different from those of the controlled type 2 diabetes subjects. However, serum creatinine in the uncontrolled type 2 diabetes subjects and the controlled type 2 diabetes subjects were 1.08 – 0.94 and 1.06 – 0.35 mg/dl, respectively. This showed no significant difference. Na^+ , K^+ , uric acid and HCO_3^- are negatively associated with the uncontrolled type 2 diabetes and Cl^- is positively associated with the controlled type 2 diabetes.

Conclusion: Progression of type 2 diabetes is positively correlated with the increase of glycosylated hemoglobin, uric and creatinine in Bangladeshi population.

Keywords: Creatinine, HbA1c, serum electrolytes, type 2 diabetic mellitus, uric acid, URCA.

Electrolytes play an important role in many body processes, such as controlling fluid levels, acid-base balance (pH), nerve conduction, blood clotting, and muscle contraction. Electrolyte imbalance resulting from kidney failure, dehydration, fever, and vomiting has been suggested as one of the contributing factors toward complications observed in diabetes and other endocrine disorders. ⁽¹⁾ Among the electrolytic ions, sodium regulates the total amount of water in the body and the transmission of sodium into and out of individual

cells. Many processes in the body, especially in the brain, nervous system, and muscles, require electrical signals which are assisted by sodium ions. The movement of sodium is critical in generating these electrical signals. This is why both hyper- and hyponatremic conditions are harmful for human physiology. Potassium in the body regulates the heartbeat and the function of the muscles. A seriously abnormal increase in potassium (hyperkalemia) or decrease in potassium (hypokalemia) can profoundly affect the nervous system and increases the chance of irregular heartbeats (arrhythmias), which, when extreme, can be fatal. Significant increases or decreases in chloride can have deleterious and even fatal consequences.

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Bicarbonate levels are measured to monitor the acidity of the blood and body fluids. The acidity is affected by foods or medications that we ingest and the function of the kidneys and lungs. The bicarbonate test is usually performed along with tests for other blood electrolytes. Disruptions in the normal bicarbonate level may be due to diseases that interfere with respiratory function, kidney diseases, metabolic conditions, or other causes.

Serum uric acid, an end product of purine metabolism, has been shown to be associated with an increased risk of hypertension⁽²⁾, cardiovascular disease⁽³⁾, and chronic kidney disease⁽⁴⁾ in previous epidemiological studies. Also, elevated level of uric acid is risk factor for peripheral arterial disease⁽⁵⁾, insulin resistance, and components of the metabolic syndrome.⁽⁶⁾ Some scientific reports showed a positive association between high serum uric acid levels and diabetes⁽⁷⁾, whereas others reported no association⁽⁸⁾, or an inverse relationship.⁽⁹⁾ However, the putative association between serum uric acid levels and diabetes mellitus is not clear. In this context, the main purpose of our study was to examine the association between serum uric acid and prevalent diabetes.

Creatinine has been found to be a fairly reliable indicator of kidney function. Abnormally high levels of creatinine thus warn of possible malfunction or failure of the kidneys. The kidneys filter out most of the creatinine and dispose of it in the urine. Therefore, it is a precise measure of the kidney function which can be estimated by calculating how much creatinine is cleared from the body by the kidneys. The creatinine level in the blood normally remains essentially unchanged but certain physiological abnormalities are recorded with changes in serum creatinine concentration.

Type 2 diabetes is a chronic metabolic syndrome, with partial beta cell dysfunction, that can lead to serious cardiovascular, renal, neurologic and retinal complications.⁽¹⁰⁾ Several risk factors are identified which may play an important role in the development of type 2 diabetes. The metabolic disturbances and their consequences in diabetes mellitus are well known but still our knowledge on the diabetic disorders in electrolytes and membrane function in Bangladeshi population is limited.⁽¹¹⁾ This study was aimed to investigate the association of electrolytes especially sodium, potassium, bicarbonate, and chloride and creatinine in progression of type 2 diabetes in Bangladeshi population.

Materials and methods

Study place and duration

The study was a prospective case-control study, conducted in the laboratory of Biochemistry in the Research Division of Chittagong Diabetic Hospital, based on the current, reliable and stronger data sources. A total of 139 type 2 diabetes patients (79 uncontrolled and 60 controlled) have been recruited in this study. This study was done during the period of February 2011 to November 2011. The subjects were recruited on the availability regardless of race, religion and socioeconomic status.

Study patient's exclusion criteria

Patients with serious comorbid diseases (infection, stroke, myocardial infarction, major surgery, malabsorption etc.) and history of using drugs seriously affecting glucose metabolism (glucocorticoids, oral contraceptives containing levonorgestrel or high-dose estrogen, phenytoin, high-dose thiazide diuretics etc.) have been excluded from the study. Both types of patients were collected every day of the week except Friday from 8:00 a.m. to 2:00 p.m. from indoor and outdoor units of the hospital.

Preparation and supply of questionnaire

A questionnaire based on demographic, socio-economic and anthropometric data was developed to obtain relevant information. The questionnaire was coded and pre-tested before finalization. As part of anthropometric data, standing height of patients in a fully erect position with the head in the Frankfurt plane was measured using scales (Detect-Medic, Detect scales INC, USA) without shoes. Height was recorded to the nearest 5 mm. Body weight of the patients was also recorded to the nearest 0.5 kg to calculate body mass index (BMI; weight (kg) / [height (m)]²). Blood pressures were measured in sitting position, with calf at the level of the heart. A second reading was taken after 10 min rest. Both systolic and diastolic pressure was recorded according to WHO-IHS.

Blood sample collection

Fasting blood (10 ml) was collected between 8.00 - 9.00 a.m. through venipuncture. Then the patient was given 75 g of glucose in 250 - 300 ml of water and advised to drink in 5 min. The patient was also advised not to smoke, not to take any food and to take rest in a chair for 2h. The next blood sample was taken 2h after glucose load. Serum was separated by

centrifugation for 10 min at 3,000 rpm. Fasting and 2h serum glucose was measured in the same day. Serum was kept frozen at -70°C for future analysis.

Sample analysis

Serum was analyzed for electrolytes by BIOLYTE selective electrolytes (ISE) using BIOLYTE 2000, electrolytes analyzer system. Potentiometer is the measuring principle of ion selective electrodes. To measure the potential of a component in solution, a measuring electrode and a reference electrode are required; these are combined with a conductive bridge. The ion selective electrode of a selective membrane, an internal electrolyte solution, and an internal reference electrode is able to measure a particular ion in solution in the presence of other ions. Cells, particles or colloids in the sample are ignored.

Serum glucose was measured by glucose oxidase method (GOD-PAP, Trinder, 1972) (Randox Laboratories Ltd., UK) using auto analyzer (AUTOLAB, Analyzer Medical system, Rome, Italy). The Auto analyzer was programmed for the estimation of glucose. A 5 µl sample and 500 µl reagent was mixed and incubated at 37°C for 10 min. The reaction occurred in reaction cell or cup. The absorbance of the sample and the standard against the reagent blank were measured at 500 nm within 60 minutes. Glucose concentration (mmol/l) = $(A_{\text{sample}}/A_{\text{standard}}) \times 5.55$.

Serum creatinine was estimated by alkaline picrate method (Randox Laboratories Ltd., UK) where creatinine was reacted with picric acid to form colored complex. The absorbance was taken at 492 nm. The amount of the complex formed is directly proportional to the creatinine concentration calculated by the formula: Serum creatinine concentration (mg/dl) = $(\Delta A_{\text{sample}}/\Delta A_{\text{standard}}) \times 100$. All reagents are supplied and ready to use, stable to expiry date when stored at +15 to 25°C.

Serum uric acid was estimated by the unit root and cointegration analysis (URCA) method used on the dimension clinical chemistry system. URCA method is used on the dimension clinical chemistry system is an *in vitro* diagnostic test intended for the quantitative determination of uric acid in human serum, plasma and urine. Uric acid, which absorbs light at 293 nm is converted by uricase to allantoin, which is non absorbing at 293 nm. The change in absorbance at 293 nm due to the disappearance of uric acid is directly proportional to the concentration of uric acid in the sample and is measured using a bichromatic (293, 700 nm) endpoint technique. Sampling reagent

delivery, mixing, processing and printing of results are automatically performed by the Dimension® system. Standard calibration conditions were maintained to calibrate the device.

Serum HbA1c was determined by Dimension (R) clinical chemistry system which is based on turbidimetric inhibition immunoassay method (TINIA). Briefly, the same aliquot of the lysed whole blood was transferred from the first cuvette to the second cuvette for the Hb measurement of HbA1c. The second cuvette contain and anti-HbA1c antibody in a buffered reagent. Hemoglobin A1c in the sample reacts with anti-HbA1c antibody to form a soluble antigen antibody complex. A polyhapten reagent containing multiple HbA1c epitopes is then added to this cuvette. The polyhapten reacts with excess (free) anti-HbA1c antibodies to form a measured turbidimetrically at 340 nm and blanked at 700 nm and is inversely proportional to the concentration of HbA1c in the sample. At least once in a day, low level of quality control material with known % HbA1c concentrations is analyzed maintain a quality control. The Dimension® System automatically calculates concentration of total Hb and HbA1c using the calculation scheme illustrated in Dimension® Operators Guide. Using these values, the instruments then calculates % HbA1c based as follows:

$$\% \text{HbA1c} = \frac{(\text{g/dl HbA1c})}{(\text{g/dl Hb})} \times 100$$

Sequentially the Dimension® clinical chemistry system calculates a standardized % HbA1c result based on the calculation as shown above. This calculation provides a % HbA1c value that is standardized to the DCCT study result, which is printed on the Dimension® report slip.

Statistical analysis

Statistical analysis was performed using SPSS (Statistical Package for Social Science) software for Windows version 11.5.0 (SPSS Inc. Chicago, Illinois, USA). All the data were expressed as mean ± standard deviation (SD), median (range) and/or percentage (%) where appropriate. The statistical significance of differences between the values was assessed by unpaired *t* - test or Mann-Whitney U test (as appropriate). Correlation was also seen among the parameters. A two-tailed $P < 0.05$ was considered as statistically significant.

Results

A total number of 139 subjects were recruited in this study; 79 of them were identified as uncontrolled type 2 diabetes and 60 were identified as controlled type 2 diabetic subjects. Between them 43.0% of the subjects were males while 57.0% were females uncontrolled type 2 diabetes, 48.0% of the subjects were males while 52.0% were females controlled type 2 diabetes subjects. Baseline characters of the patients are recorded and shown in Table 1.

Anthropometrics and clinical characteristics of the study subjects

Age

Age between the uncontrolled type 2 diabetes subject and controlled type 2 diabetes subjects were 52.16 ± 12.31 and 48.66 ± 6.03 years, respectively. Age was significantly higher in the uncontrolled type 2 diabetes subjects than in the controlled type 2 diabetes subjects ($P < 0.05$) (Table 1).

Body mass index

Mean body mass index in uncontrolled type 2

diabetic subjects and controlled type 2 diabetes subjects were 25.44 ± 3.10 and 24.37 ± 2.44 kg/m², respectively. There was no statistically significant difference in body mass index between the groups ($P > 0.05$) (Table 2).

Systolic blood pressure

Systolic blood pressures between the uncontrolled and the controlled type 2 diabetic subjects were 133.00 ± 22.00 and 126.00 ± 14.25 mmHg, respectively and the values were significantly higher in the uncontrolled type 2 diabetes mellitus ($P < 0.05$) (Table 2).

Diastolic blood pressure

Diastolic blood pressure between uncontrolled type 2 diabetes and controlled type 2 diabetes subjects were 84.62 ± 9.23 and 80.47 ± 8.51 mmHg, respectively. It showed that diastolic blood pressure was significantly higher in the uncontrolled type 2 diabetes subjects than in the controlled type 2 diabetes subjects ($P < 0.05$) (Table 2).

Table 1. Baseline characteristics of the patients (n = 139).

Variables	Total number	Percentage (%)
Male : Female	63 : 76	45 : 55
Uncontrolled type 2 Diabetic Subjects (n = 79)		
Uncontrolled Type 2 Male : Female	34 : 45	43 : 57
Controlled type 2 diabetic Subjects (n = 60)		
Controlled type 2 Male : Female	26 : 34	43 : 57
Regular walking		
Yes		
No	9247	6634
Cardiovascular disease		
Yes		
No	4198	2971
Eye problem		
Yes		
No	5980	4258
Hypertension		
Yes		
No	4188	3268
Drug history		
Insulin		
Tablet	8356	6040

Table 2. Anthropometric and clinical characteristics of the study subjects.

Variables	Uncontrolled type 2 diabetes subjects (n = 79)	Controlled type 2 diabetic subjects (n = 60)	P- value
Age (years)	52.16 ± 12.31	48.66 ± 6.03	0.04
BMI (Kg/m ²)	25.44 ± 3.01	24.37 ± 2.44	0.57
SBP (mm/Hg)	133.00 ± 22.00	126.00 ± 14.25	0.01
DBP (mm/Hg)	84.62 ± 9.23	80.47 ± 8.51	0.01

Data are expressed as Mean ± SD. Differences among the groups were calculated using Students *t* - test as the test of significance at 5.0% level. *n* = number of subjects, BMI = Body mass index, SBP = Systolic blood pressure and DBP = Diastolic blood pressure.

**Biochemical status of the study subject
Glycosylated hemoglobin (HbA1c)**

Glycosylated hemoglobin, (%) were expressed as mean ± SD and the value of glycosylated hemoglobin, between the uncontrolled type 2 diabetes and the controlled type 2 diabetes subjects were 11.68 ± 2.68 and 6.41 ± 0.41 respectively. The value of HbA1c was significantly higher in the uncontrolled type 2 diabetes than in the controlled type 2 diabetes subjects (*P* < 0.05) (Table 3).

Serum creatinine

Fasting serum creatinine level in the study between the uncontrolled type 2 diabetes and the controlled type 2 diabetes subjects were 1.08 ± 0.94 and 1.06 ± 0.35 mg/dl. The serum creatinine level was significantly higher in the uncontrolled type 2 diabetes compared to the controlled type 2 diabetes subjects (*P* < 0.05) (Table 3).

Serum uric acid

Serum uric acid level in the study between the uncontrolled type 2 diabetic subjects and the controlled type 2 diabetic subjects were 5.04 ± 1.28 and 4.56 ± 1.17 mg/dl. The value of serum uric acid was significantly higher in the uncontrolled type 2 diabetes (*P* < 0.05) than in the controlled diabetic subjects (*P* < 0.05) (Table 3).

Electrolytes status of the study subjects

Serum sodium

Serum Sodium ion (Na⁺) level between the uncontrolled type 2 diabetic subject and the

controlled type 2 diabetic subjects were 140.49 ± 5.97 and 143.68 ± 4.02 mmol/l, respectively; and, the value of serum Na⁺ was significantly lower in the uncontrolled type 2 diabetic subjects than in the controlled type 2 diabetic subjects (*P* < 0.00) (Table 4).

Serum potassium

Serum potassium ion level between the uncontrolled type 2 diabetic subjects and the controlled type 2 diabetic subjects were 4.28 ± 0.38 and 4.43 ± 0.32 mmol/l. In this case, the value of serum K⁺ was significantly lower in the uncontrolled type 2 diabetic subjects than in the controlled type 2 diabetic subjects (*P* = 0.018) (Table 4).

Serum chloride

Serum chloride level between the uncontrolled type 2 diabetic subjects and the controlled type 2 diabetic subjects were 106.35 ± 4.05 and 104.51 ± 3.12 mmol/l, respectively. The value of serum Cl⁻ was significantly higher in the uncontrolled type 2 diabetic subjects than in the controlled diabetic subjects (*P* < 0.05) (Table 4).

Serum bicarbonate

Fasting serum bicarbonate level between the uncontrolled type 2 diabetic subjects and the controlled type 2 diabetic subjects were 21.28 ± 4.76, and 25.87 ± 5.06 mmol/l, respectively. Fasting serum HCO₃⁻ level in the uncontrolled type 2 diabetic was significantly higher than in the controlled type 2 diabetic subjects (*P* < 0.008) (Table 4).

Table 3. Biochemical status of the study subjects.

Variables	Uncontrolled type 2 diabetes subjects (n = 79)	Controlled type 2 diabetic subjects (n = 60)	P - value
HbA1c %	11.68 ± 2.68	6.41 ± 0.41	0.001
Screa (mg/dl)	1.08 ± 0.94	1.06 ± 0.35	0.910
SUA (mg/dl)	5.04 ± 1.28	4.56 ± 1.17	0.020
FG (nmol/l)	9.98 ± 1.56	5.37 ± 0.81	0.001

Data are expressed as Mean ± SD and Median (range) as appropriate. Differences between the groups were calculated using Students *t*-test and Mann Whitney test, HbA1c = Glycosylated Hemoglobin, Screa = Serum Creatinine, SUA = Serum Uric Acid, FG = Fasting glucose.

Table 4. Serum electrolytes status of the study subjects.

Variables	Uncontrolled type 2 diabetes subjects (n = 79)	Controlled type 2 subjects (n = 60)	P - value
Na ⁺ (mmol/l)	140.49 ± 5.97	143.68 ± 4.02	0.001
K ⁺ (mmol/l)	4.28 ± 0.38	4.43 ± 0.32	0.018
Cl ⁻ (mmol/l)	106.35 ± 4.05	104.51 ± 3.12	0.004
HCO ₃ ⁻ (mmol/l)	21.28 ± 4.76	25.87 ± 5.06	0.001

Data are expressed as Mean ± SD and Median (range) as appropriate. Differences between the groups were calculated using ANOVA (Bonferroni *t*-test) *P*-value were calculated using log transformed value. Na⁺ = Sodium, K⁺ = Potassium; Cl⁻ = Chloride; HCO₃⁻ = Bicarbonate

Discussion

This study tried to explore the association of serum electrolytes, uric acid and creatinine with the progression of type 2 diabetes mellitus of Bangladeshi population. In this cross-sectional study, the observed reduction of serum Na⁺ and K⁺ in diabetic subjects might be a result of electrolyte loss arisen due to dehydration or a result of kidney dysfunction caused by diabetes. ⁽¹²⁾ As the body is trying to flush out excess glucose due to hyperglycemia, water is also flushed out continuously through the kidney tubules. This water loss is accompanied by Na⁺ and K⁺ loss. Such rapid loss of sodium and potassium, if continued could soon bring about depletion of base in the body sufficient to cause dehydration of the tissues which may result in death. ⁽¹³⁾ Sodium and potassium depletion are common features of essential hypertension and type II diabetes. ⁽¹⁴⁾ The significant elevation of serum chloride and reduction in HCO₃⁻ in diabetic subjects might be due to diabetic ketoacidosis. ⁽¹⁵⁾ The low serum insulin levels in diabetics signal the body to produce more glucose via gluconeogenesis, glycogenolysis and ketogenesis which results in excess production of ketone bodies. In this condition, ketone bodies in the blood are

elevated and blood bicarbonate may fall to near zero, with resultant severe acidosis. ⁽¹⁶⁾ The reduction in blood pH caused by ketoacidosis might result in acid base imbalance which may lead to elevation of chloride by the system in order to compensate for the anion loss. ⁽¹⁷⁾ This electrolytes imbalance might also occur due to inhibition of the rennin-angiotensin-aldosterone system, which plays a key role in the regulation of fluid and electrolyte balance. This enzyme system has been reported to be affected in many endocrine and cardiovascular diseases particularly diabetes. ⁽¹⁸⁾

Therefore, HbA1c is a very important biochemical parameter that provide long term status of blood glucose levels and monitoring tool for measuring glycemic control in type – 2 diabetic patients. ⁽¹⁹⁾ HbA1c in general, developed when the hemoglobin joined with glucose in the blood and become glycated. According to many studies, HbA1c levels could be used as an independent risk factor for stroke and cardiovascular disease (CVD) in both healthy and diabetic populations. The current research is complying the above clinical evidences for type diabetes patients as well that of Bangladesh. ^(19 - 21)

Variations in uric acid levels have been increasingly associated with insulin resistance, hyperinsulinemia, and diabetes. ⁽²²⁾ Diabetic patients who are hyperuricemic appear to have an increased risk for developing diabetic complications, especially renal and cardiovascular disease. ⁽²³⁾ Recently, Chunlei Y, *et al.* ⁽²⁴⁾ reported that two-thirds of subjects with type 2 Diabetes mellitus suffer from elevated uric acid levels. In type 2 diabetes, hyperuricemia seems to be associated with the insulin-resistance syndrome, impaired glucose tolerance, and an early onset of nephropathy, while hypouricemia is associated with nonadequate metabolic control, hyperfiltration, and a late onset of overt nephropathy. ⁽²⁵⁾ Serum creatinine in our study has been insignificantly varied from the controlled to the uncontrolled type 2 diabetes mellitus while the recent literatures reported that uric acid/creatinine might be a novel predictor of chronic kidney disease progression in type 2 diabetes mellitus patients. ⁽²⁶⁾

Since diabetes is primarily a genetic disease, the symptoms, disease progression and consequences, to some extent, vary in context of demographical variation. This study unfolded the association and progression of type 2 diabetes mellitus in Bangladeshi population. Hardly the phenomenon has previously been tried to be unveiled for the people of studied region. However, it could be more comprehensive if the study design could have covered a large sample size of population in this study. Additionally, the genetic analysis of the serum for target subject could incorporate a more precise reflection of diabetes predisposing factors of Bangladeshi population. The future endeavor undertaking the aforesaid issue will undoubtedly find out very decisive factors associated with diabetes for Bangladeshi people.

Authors' contributions

MAR designed the experiments, coordinated the study and participated in analysis and interpretation of data. MSB performed experiments, participated in analysis and interpretation of data. MAR, MAH, DH, WE, AAM participated in drafting and critically revising the manuscript. DH, WE and AAM partially contributed funds for conducting research. All authors read and approved the final version of the manuscript and MAR approved the submission of manuscript for publication.

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Conflict of interest

The authors, hereby, declare no conflict of interest.

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