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Original Research Paper

Biochemistry

REINVENTION OF CLINICAL USE OF URINE GLUCOSE TEST AS A PREDICTOR OF GLUCOSE LOWERING EFFICACY OF SGLT2 INHIBITOR THERAPY AS ORAL HYPOGLYCEMIC AGENT IN TYPE 2 DIABETES MELLITUS.

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ABSTRACT

Backgrounds: To reinvent the clinical use of Urine glucose test as a predictor of glucose lowering efficacy of oral SGLT2 inhibitor therapy in Type 2 diabetes mellitus.

Methods: Forty-six (Group A) new T2DM & 42 (Group B) new T2DM with urine glucose test results (+) & (+++) respectively were given 2000 mg of metformin sustained release & 10 mg of dapagliflozin (SGLT2 inhibitor) per day who have baseline HbA1c of 7.8 ± 0.3% & 7.9 ± 0.3% respectively and fasting plasma glucose of 180 ± 15mg/dl & 184 ± 14mg/dl respectively. They were followed up at an interval of three months up to six months with HbA1c, fasting plasma glucose & urine glucose test.

Results: Better HbA1c and fasting plasma glucose reduction was seen in Group A than Group B patients.

Conclusion: urine glucose testing can predict the glucose lowering efficacy of oral SGLT2 inhibitor therapy in Type 2 diabetes mellitus.

KEYWORDS : Sodium–glucose linked transporter type 2 (SGLT2), dapagliflozin, urine glucose testing.

Introduction:

Type 2 diabetes mellitus (T2DM) is associated with many cardiovascular and renal complications.1 Current guidelines propose metformin as the preferred initial pharmacological agent for T2DM.2 However, many patients do not tolerate metformin or do not achieve the glycemic goal and the addition of a second oral agent or insulin, is usually needed.

Gliflozins (empagliflozin, canagliflzin, dapagliflozin etc) are selective reversible inhibitors of sodium–glucose linked transporter type 2 (SGLT2) and have been recently approved for the treatment of patients with T2DM. SGLT2 mediates approximately 90% of active renal glucose reabsorption in the S1 segment of early proximal tubule of the kidney.3 SGLT2 inhibitor leads to a significant reduction in glucose reabsorption and decrease of serum glucose concentration in an insulin-independent manner.4 It also improves insulin sensitivity but enhances endogenous glucose production in patients with T2DM.5, 6 The reduction in glucose reabsorption has been associated with a reduction in body weight possibly owing to the decrease of body calories. Furthermore, the drug has been shown to reduce blood pressure levels through its action as an osmotic diuretic and the associated body weight reduction.7 Earlier urine glucose testing was the major method used to monitor glycemic control in diabetes mellitus. It was convenient, noninvasive, inexpensive, and useful.8 Measurement of glucosuria was an indirect index of the blood glucose concentration. However the social stigma sometimes associated with handling a body waste product9 can be a consideration in terms of patient acceptance of the monitoring technique. These limitations, together with the home capillary blood glucose monitoring, glycated hemoglobin measurement, and frequent plasma glucose determinations have led to a decline in the use of urine glucose for monitoring in diabetes mellitus.

The aim of this study is to see whether Urine glucose test can be used to predict the glucose lowering efficacy of SGLT2 inhibitor therapy as oral hypoglycemic agent in Type 2 diabetes mellitus

Materials & methods:

Patients were asked to empty their bladders before their visit to phlebotomists. Urinary samples were collected just before drawing blood samples. The study protocol used was approved by the institutional ethics committee according to the Declaration of Helsinki. Written informed consent was obtained from each participant. 88 recent new onset Type 2 diabetes mellitus patients (50 males & 38 females) attending the outpatient department of IPGME&R-SSKM Hospital, Kolkata were included in the study. 46 patients (Group A) were having urine glucose test result (+) & 42 patients (Group B) were having urine glucose test result (+++). They were given 2000 mg of metformin sustained release & 10 mg of dapagliflozin per day with baseline HbA1c 7.8 ± 0.3% & 7.9 ± 0.3% respectively and fasting plasma glucose 180 ± 15mg/dl & 184 ± 14mg/dl respectively. They were followed up at an interval of three months up to six months with HbA1c, fasting plasma glucose & urine glucose test. Eight (8) patients did not turn up for follow-up but 43 patients from Group A & 37 patients from Group B completed the study. A detailed questionnaire on family history, social status, and dietary habits, including other habits such as smoking, alcohol intake, history of systemic diseases, and drug history was completed by all the study subjects prior to their inclusion in the study. Hypertension, cardiovascular disease, renal disease, liver disease, serum electrolyte disturbance and drug exposure (that interfere urine glucose testing) were ruled out in the present study based on the biochemical tests apart from the questionnaire.

Venous blood samples were collected into tubes containing ethylene di-amine tetra- acetic acid (EDTA) for HbA1c measurement and sodium fluoride for plasma glucose measurement. Plasma was separated from whole blood from sodium fluoride containing tubes within 1 hour after collection. Plasma glucose concentrations were determined according to the glucokinase method10 using Auto analyzer (Beckman Coulter) and HbA1c levels of the patients were determined using a Bio-Rad D-10 HPLC instrument, whose compliance with the latest Diabetes Control and Complications Trial (DCCT) reference method has been documented by the National Glycohemoglobin Standardization Program (NGSP).11 Two levels of Bio-Rad calibrators and controls were used for the calibration of the instrument. Both the intra- and interassay coefficients of variation were < 2.6% & < 3%. Statistical analysis was performed using the Student's t-test and SPSS version 11.5 (SPSS Inc., Chicago, IL, USA).

The detection of glucose by test strips is based on the enzymatic reaction of glucose oxidase.12 This enzyme catalyses the oxidation of glucose by atmospheric oxygen to form D-glucono-δ-lactone and hydrogen peroxide. A second linked reaction, mediated by a peroxidase, catalyses the reaction between the peroxide and a chromogen orthotoluidine (a substance that acquires colour after a chemical reaction) to form a coloured compound that indicates the glucose concentration.

Results:

Group A cases have got better HbA1c and fasting plasma glucose reduction in comparison to Group B patients although both have similar urine glucose test results at the end of the study (Table-1).

Discussions:

Nearly all the glucose removed in the glomerulus is reabsorbed in the proximal convoluted tubule under normal conditions. If the blood glucose level increases in diabetes mellitus, the capacity of the convoluted tubule to reabsorb glucose is exceeded (an effect

known as renal reabsorption threshold). For glucose this threshold is between 160–180 mg/dl.

In our study we showed that dapagliflozin have greater hypoglycemic effect in group A patients than group B patients and this can be explained by its greater glucosuric effect in group A than group B as evident from the urine glucose test results which showed that low glucosuric patients in group A were benefitted more than the high glucosuric patients in group B. This was because of probable increase in expression of sodium–glucose linked transporter type 2 protein in group A patients than group B patients at the beginning of the study. Reductions in the HbA1c & FPG between three months & six months in each group are there but not significant. These reductions in spite of the same glucosuric effect in both groups at the end of six months can be explained by the weight reducing effect of dapagliflozin thereby improving the insulin sensitivity which was not probably there in the initial period of study.

In conclusion our study proved the routine use of simple, noninvasive, convenient & inexpensive urine glucose testing to be made mandatory prior to the initiation of SGLT2 inhibitor therapy to predict the glucose lowering efficacy of SGLT2 inhibitor therapy as oral hypoglycemic agent in Type 2 diabetes mellitus.

Limitations: Urine glucose test is specific for glucose, as occurs in all enzymatic reactions, but it can provide some false positive results due to the presence of traces of strong oxidizing agents or peroxide from disinfectants used on laboratory instruments.

Conflicting interest:

The Authors declare that there is no conflict of interest.

Table-1. Follow up of SGLT 2 inhibitor therapy on HbA1c and fasting plasma glucose & urine glucose test results.

	Group A (n=43)		Group B (n=37)			
	HbA1c%	Fasting Plasma Glucose mg/dl	urine glucose test	HbA1c%	Fasting Plasma Glucose mg/dl	urine glucose test
Initiation of study	7.8 (0.3)	180 (15)	+	7.9 (0.3)	184 (14)	+++
Three months after the study	5.9 (0.2)*	92 (10)*	++++	6.5 (0.2)†	120 (10)†	++++
Six months after the study	5.7 (0.2)*‡	87 (9)*‡	++++	6.3 (0.2)†	110 (9)†	++++

*$p < 0.005$ in response to initiation of study; † $p < 0.05$ in response to initiation of study; ‡ $p < 0.05$ in response to Group B.

Reference:

1. Leong A., Dasgupta K., Chiasson J., Rahme E. Estimating the population prevalence of diagnosed and undiagnosed diabetes. Diabetes Care 2013; 36: 3002–8.
2. American Diabetes Association Standards of medical care in diabetes. Diabetes Care. 2014; 37(1): S14–S80.
3. Vallon V., Platt K., Cunard R., Schroth J., Whaley J., Thomson S., et al. SGLT2 mediates glucose reabsorption in the early proximal tubule. J Am Soc Nephrol. 2011; 22: 104–12.
4. Balakumar P., Sundram K., Dhanaraj S. Dapagliflozin: glucuretic action and beyond. Pharmacol Res. 2014; 82: 34–9.
5. Merovci A., Solis-Herrera C., Daniele G., Eldor R., Fiorentino T., Tripathy D., et al. Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. J Clin Invest. 2014; 124: 509–14.
6. Mudaliar S., Henry R., Boden G., Smith S., Chalamandaris A., Duchesne D., et al. Changes in insulin sensitivity and insulin secretion with the sodium glucose cotransporter 2 inhibitor dapagliflozin. Diabetes Technol Ther. 2014; 16: 137–44.
7. Oliva R., Bakris G. Blood pressure effects of sodium-glucose co-transport 2 (SGLT2) inhibitors. J Am Soc Hypertens. 2014; 8: 330–9.
8. Alberti KGMM, Worth R, Home PI. 1982. Home blood glucose monitoring: Does it improve diabetic control per se? In Peterson CM, ed., Diabetes Management in the 80's, New York, Praeger Publishers.
9. Valenta CL. Urine testing and home blood-glucose monitoring. Nurs Clin North Am. 1983; 18: 645-59.
10. Trinder P. Determination of blood glucose using an oxidase-peroxidase system with a non-carcinogenic chromogen. J Clin Pathol. 1969; 22(2): 158-61.
11. Hoelzel W, Weykamp C, Jeppsson JO, Miedema K, Barr JR, Goodall I, Hoshino T, John WG, Kobold U, Little R, Mosca A, Mauri P, Paroni R, Susanto F, Takei I, Thienpont L, Umemoto M, Wiedmeyer HM. IFCC reference system for measurement of hemoglobin A1c in human blood and the national standardization schemes in the United States, Japan, and Sweden: a method-comparison study. Clin Chem. 2004; 50(1): 166-74.
12. Bandi ZL, Myers JL, Bee DE, James GP. Evaluation of determination of glucose in urine with some commercially available dipsticks and tablets. Clin Chem. 1982; 28: 2110–5.