

Estimation of Risk Associated with ADR of Drugs that Cause Urinary Tract Infection in Type 2 Dm Patients: A Retrospective Case Control Study

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ABSTRACT:

Introduction: Diabetes Mellitus is a chronic health condition which if not kept under control can lead to severe complications that could affect the quality of life and even lead to death. UTI is more common and more severe among the Type 2 DM patients.

Objective: To estimate the risk of ADR of drugs such as metabolic disturbances, immunosuppressants, anticholinergics and SGLT2i that cause UTI in Type 2 DM patients.

Materials and methodology: The study was a hospital-based Retrospective case control study conducted in 2713 people with Type 2 DM who were tested for UTI at BCMCH hospital Thiruvalla over a period of 6 months.

Observation and conclusion: The study shows that DM patients who took drugs have more chances of getting UTI than people who don't take the drugs, specifically metabolic disturbants.

KEYWORDS: Type 2 Diabetes Mellitus, Urinary tract infection, ADR, metabolic disturbants, immunosuppressants, anticholinergics, SGLT2i.

INTRODUCTION

India's diabetes prevalence has risen to 7.1% in adults, with urban populations experiencing up to 28% prevalence. This has led to a rise in UTIs, making it a key target population to address. Overweight/obesity is a key risk factor for developing Type 2 Diabetes, which impairs insulin production and leads to elevated glucose levels. A fasting blood sugar level of 99mg/dL or lower is normal, 100 to 125 mg/dL have prediabetes, and 126mg/dL or higher have diabetes. Type 1 and Type 2 diabetes are the main types [1]. Different types of DM includes: **Type 1 diabetes** is caused by an autoimmune reaction, causing the body to stop producing insulin., **Type 2 diabetes** results from insulin resistance, causing blood sugar levels to fluctuate, **Prediabetes**, or impaired glucose tolerance, occurs before Type 2 diabetes, with higher blood glucose levels but not enough to be diagnosed, **Gestational diabetes**, seen in pregnant women, increases

the baby's risk of developing Type 2 diabetes later in life. [2]

Pathophysiology involves:

- Type 1 Diabetes Mellitus : T1DM, also known as insulin-dependent diabetes mellitus, is an autoimmune disorder caused by T-cell destruction of pancreatic β -cells, leading to insulin deficiency and hyperglycemia.
- Type 2 Diabetes Mellitus: Type 2 Diabetes (T2DM), also known as non-insulin dependent diabetes mellitus (NIDDM) or adult-onset diabetes, is characterized by insulin resistance and β -cell dysfunction. Insulin resistance occurs when cellular pathways are disrupted, leading to decreased insulin sensitivity in peripheral tissues.

Risk factors for gestational diabetes include obesity, age over 35, diabetes family history, sedentary lifestyle, prediabetes, and gestational diabetes. Symptoms include frequent urination, excessive thirst, weight loss, extreme hunger, sudden vision changes, tingling, numbness, fatigue, dry skin, and slow-healing sprains. [3,4]. The major diagnostic criteria for Diabetes includes: The Fasting Plasma Glucose (FPG) test, HbA1c test, The random plasma glucose test, The glucose challenge test, The oral glucose tolerance test (OGTT). [3]

The main complications of DM includes:

- MICROVASCULAR COMPLICATIONS: Diabetic retinopathy, Diabetic nephropathy, Diabetic neuropathy [5]
- MACROVASCULAR COMPLICATIONS: Coronary heart disease, Transient ischemic attacks and strokes, Peripheral arterial disease [6]

Treatment includes:

1. Type I Diabetes Mellitus

Insulin and other medications

- It is divided into 4 types: short-acting insulin, rapid-acting insulin, intermediate-acting insulin, and long- and ultra-long-acting insulin. Short-acting insulin starts working after 30 minutes and lasts 4 to 6 hours.

Insulin delivery devices

- Injections
- An insulin pump [7]

2. Type 2 diabetes mellitus

Medications for type 2 diabetes (antidiabetics) include:

- Metformin
- Sulfonylureas
- Glitazones: Pioglitazone
- Glinides: Nateglinide and Repaglinide
- Gliptins (dipeptidyl peptidase-4 inhibitors): Linagliptin, Saxagliptin, Vildagliptin and Sitagliptin
- Gliflozins (SGLT2 inhibitors): Dapagliflozin, Empagliflozin and Canagliflozin
- Alpha-glucosidase inhibitors: Acarbose [8]

UTI, or urinary tract infection, is the most common bacterial infection among diabetic patients, affecting the kidneys, ureters, bladder, and urethra, with women being less susceptible than men. [13]. It includes Complicated and Uncomplicated UTI. In uncomplicated UTI usually involves the bladder, where bacteria

invade the mucosal wall and cause cystitis. ^[9]. In complicated UTI host factors such as age, catheterization, diabetes mellitus and spinal cord injury can predispose to complicated UTIs. The pathophysiology of complicated UTIs has the following aspects: Structural abnormalities including calculi, infected cysts, renal or bladder abscesses, certain forms of pyelonephritis and catheters, Metabolic or hormonal abnormalities, Impaired host responses, Unusual pathogens, yeast. ^[10]. Symptoms of UTI includes A strong urge to urinate, A burning feeling when urinating, Urinating frequently, and passing small quantities of urine ^[11]. UTI can be diagnosed by: Analysing a urine sample, Growing urinary tract bacteria in a lab, Creating images of the urinary tract, Using a cystoscope to see inside the bladder and performing a cystoscopy ^[12]. The major risk factors includes Previous UTI, Pregnancy, Age, Structural problems in the urinary tract, Poor hygiene. ^[13]

Treatment includes Antibiotics are the primary treatment for urinary tract infections (UTIs), with simple medications like Trimethoprim, sulfamethoxazole, Fosfomycin, Nitrofurantoin, Cephalexin, fluoroquinolones, and levofloxacin used for simple UTIs. For complicated infections, a Fluoroquinolone drug may be prescribed. UTI symptoms usually subside within a few days, but antibiotics may be needed for weeks or more. Preventative measures include consuming antibiotics after coitus and vaginal oestrogen therapy. ^[14].

UTI RISKS ASSOCIATED WITH MEDICATIONS

Drugs associated with an increased risk of UTI development include immunosuppressants, agents affecting voiding processes, drugs promoting lithogenesis, and drugs that reduce glucose reabsorption in the kidneys, causing glycosuria. Drugs like sodium – glucose Cotransporter 2 inhibitors cause UTI due to glycosuria which is caused by the glucose reabsorption. Immunosuppressive agents cause UTI because of poor inflammatory response against the bacteria. ^[15]

OBJECTIVES

To estimate the risk of ADR of drugs such as drugs causing metabolic disturbances, immunosuppressants, anticholinergics and SGLT2i that cause UTI in Type 2 DM patients.

MATERIALS AND METHODOLOGY

The study was a hospital-based Retrospective case control study conducted in 2713 people with Type 2 DM who were tested for UTI at BCMCH hospital Thiruvalla over a period of 6 months (November 2022 to April 2023). It was approved by the Institutional Review Board of Believers Church medical College Hospital, Thiruvalla. The data was collected as Data collection form and Questionnaire format.

Calculating Proportion:

$$N=4PQ/d2$$

Where,

P= Prevalence (from previous studies)

Q= 100-P

STUDY CRITERIA

Inclusion criteria:

- Patients admitted during the study period.

- Patients aged > 18 years.
- Patients of both genders.

Exclusion criteria:

- NIL

STUDY PROCEDURE

The data was collected from all patients who were tested for UTI in the laboratory of BCMCH and was extracted from the Lab Information System (LIS). Their drug history and DM status was extracted from the prescription orders. The data collected were entered in Microsoft Excel-2021 version, statistical analysis was done and the result were obtained.

RESULTS

The study mainly focuses on the comparison between patients having urinary tract infection (case) and non-urinary tract infection (control) in diabetic population. To obtain this objective the results were divided into two sets of data using a statistical approach.

Table 1: Distribution of Drugs having UTI as ADR among DM Patients

Drugs	Frequency	Percentage
Metabolic disturbants	776	28.6
Immunosuppressants	397	14.6
Anticholinergics	140	5.2
SGLT2i	88	3.2

Figure 1: Distribution of drugs having UTI as an ADR among DM patients

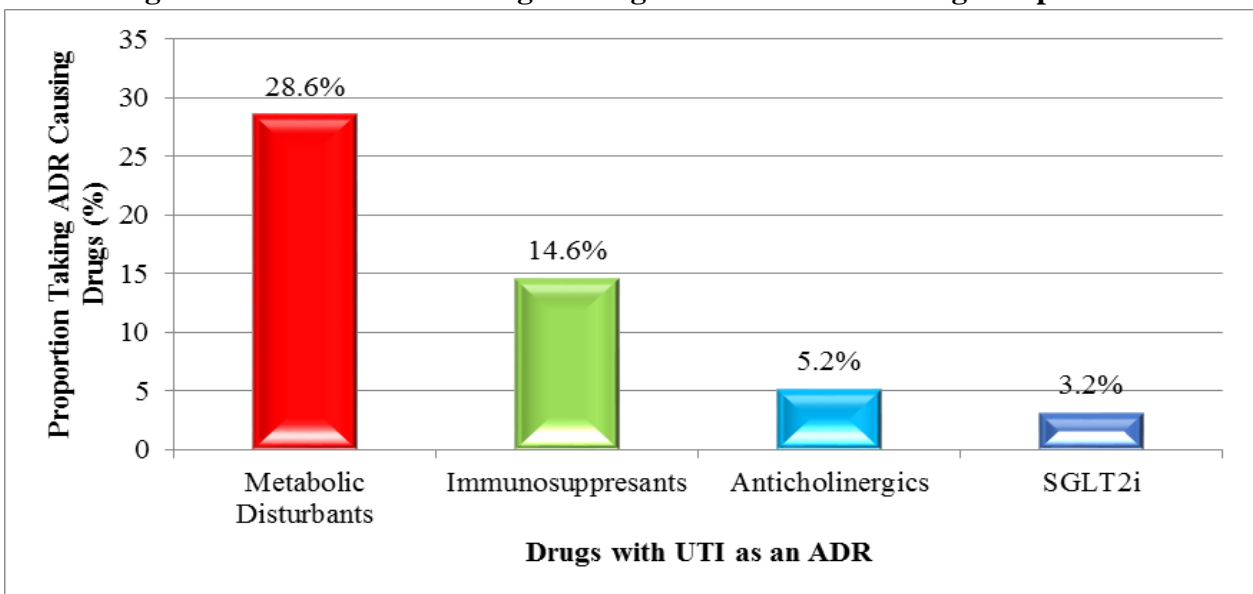
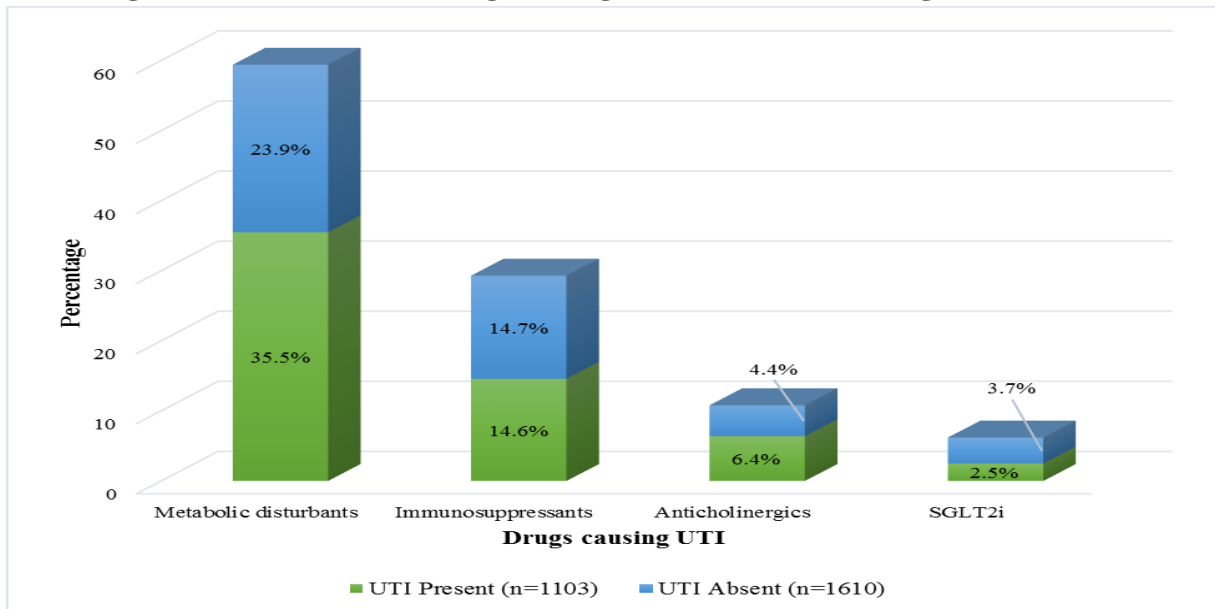


Table 2: Association of drugs having UTI as ADR among DM Patients

Drugs causing UTI as ADR	UTI			p value	OR (95% CI)
	Total (n=2713)	Present (n=1103)	Absent (n=1610)		
Metabolic disturbants	776 (28.6%)	392 (35.5%)	384 (23.9%)	>0.00001	1.8(1.5-2.1)
Immunosuppressants	397 (14.6%)	161 (14.6%)	236 (14.7%)	0.9	1.0(0.8-1.2)
Anticholinergics	140 (5.2%)	70 (6.4%)	70 (4.4%)	0.02	1.5(1.1-2.1)
SGLT2i	88 (3.2%)	28 (2.5%)	60 (3.7%)	0.08	0.7(0.4-1.1)

Figure 2: Association of Drugs having UTI as an ADR among DM Patients.



As shown in Table 1 and Figure 1, among the 2713 DM patients observed, some have used drugs that could cause UTI as an adverse drug reaction. More than a quarter of them, that is, 776 (28.6%) used drugs that cause metabolic disturbances, 397 (14.6%) used Immunosuppressants, 140 (5.2%) used Anticholinergics and 88 (3.2%) used SGLT2 Inhibitors. In Table 2 and Figure 2, more patients with confirmed UTI (35.5%) had taken drugs for metabolic disturbances than those without (23.9%). And this difference was highly significant ($p < 0.00001$). That is those who took drugs for metabolic disturbances had 1.8 (1.5-2.1) times higher risk of having UTI than those who did not take this drug. Similarly, more patients with confirmed UTI (6.4%) had taken anticholinergics than those without (4.4%). And this difference was significant ($p = 0.02$). That is those who took anticholinergics had 1.5 (1.1-2.1) times higher risk of having UTI than those who did not take this drug. Figure 2. Other drugs such as Immunosuppressants and SGLT2 inhibitors were not significantly associated with UTI in DM patients. However there seems to be an apparent protective inhibitors effect for those who took SGLT2i (OR (95% CI): 0.7(0.4-1.1)).

OBSERVATIONS AND DISCUSSIONS

• THE DISTRIBUTION OF DRUGS WITH UTI AS ADR AMONG DM PATIENTS BY DIAGNOSIS OF UTI

The study shows that, a quarter of the patients, that is, (28.6%) used metabolic disturbants, (14.6%) used

Immunosuppressants, (5.2%) used Anticholinergics and (3.2%) used SGLT2 Inhibitors. Among these 35.5% had confirmed UTI with use of drugs that cause metabolic disturbances which was highly significant, 14.6% had confirmed UTI with anticholinergics which was significant, 6.4% UTI with immunosuppressants and 2.5% with SGLT2i which was not significantly associated with UTI in DM patients. The study conducted by, Lukasz Dobrek, inferred that the use of certain class of drugs such as immunosuppressive agents, anticholinergics, drugs that cause metabolic disturbances led to the development of UTI. ^[15]

CONCLUSION

Diabetes is a chronic health condition and the risk of diabetes depends on age, gender, comorbid conditions and complications. One of major complications of Diabetes is recurrent UTI. Certain drugs such as metabolic disturbances, immunosuppressants, anticholinergics and SGLT2i can cause UTI as ADR in Type 2 DM patients. In our case study it shows DM patients who took drugs for metabolic disturbances had more chances of getting UTI than any other drugs.

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CONFLICT OF INTEREST:

The authors declare that the case report was conducted in the absence of any commercial financial relationships that could be constructed as a potential conflict of interest.

ABBREVIATIONS

UTI: URINARY TRACT INFECTION

T2DM: TYPE 2 DIABETES MELLITUS

ADR: ADVERSE DRUG REACTION

NIDDM: NON-INSULIN-DEPENDENT DIABETES MELLITUS

SGLT2i: SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITORS

FPG: FASTING PLASMA GLUCOSE

OGTT: ORAL GLUCOSE TOLERANCE TEST

LIS: LAB INFORMATION SYSTEM

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