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THE RISK OF HYPERGLYCEMIA ASSOCIATED WITH THE USE OF PRESCRIBED MEDICATIONS

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ABSTRACT: Hyperglycemia is a deleterious consequence of uncontrolled diabetes and an adverse effect of many common therapeutic drugs. Identification of drug-induced hyperglycemia is necessary for reducing morbidity or mortality associated with high blood glucose levels. The aim of the present study was to assess risk of unrecognized drug-induced hyperglycemia in patients admitted to King Abdulaziz Medical City (KAMC) in Riyadh, Saudi Arabia. All cases pertaining to hyperglycemia were identified from medical record archive of a random sample of patients admitted to KAMC, from January 2015 to December 2015. Patients with a previous history of diabetes were excluded from the study. The case/non-case method was employed to find association between identified drugs and hyperglycemia. The hyperglycemia risk was estimated by calculating the reporting odds ratios (ROR). The results reveal about one fifth of study population was admitted primarily due to hyperglycemia. A significant association for hyperglycemia has been shown with corticosteroids, immunosuppressants and anticholinergic agents with ROR = 2.63; 95% CI (1.26-5.51), ROR = 8.38; 95% CI (2.33-30.16) and ROR = 4.11; 95% CI (1.39-12.20), respectively. In contrast, the proton-pump inhibitors (omeprazole and esomeprazole) were associated with a significant reduction in hyperglycemia risk with ROR of 0.13 (95% CI 0.06-0.29). Although, there is no consistency in the reported hyperglycemic risk associated with some immunosuppressants or anticholinergic agents, the present results advocate this risk, particularly with mycophenolate mofetil, tropicamide, and cyclopentolate. Thus, further investigational studies may be required to confirm of present results and to assess the hyperglycemic risk of other drugs.

INTRODUCTION: Diabetes is a chronic disease that has dramatically increased over the past few decades. According to the global report on diabetes published by World Health Organization in 2016, the prevalence of diabetes has steadily increased from 4.7% in 1980 to 8.5% in the adult population in 2014, with a total global estimate of 422 million diabetic patients [1].

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This massive increase in the disease burden was even worse in the Eastern Mediterranean countries, with a prevalence rate of 13.7% in 2014. Such immense increase in prevalence of diabetes was mainly due to the increase in the average age of the general population and obesity [1].

The prevalence rate of hyperglycemia and diabetes has been reported to be increased substantially in the last decade. It was estimated that 347 million people have diabetes worldwide [2]. Such dramatic increase is mainly caused by changes in human lifestyle and diet over the last century [3]. Several studies have suggested a high association between hyperglycemia and adverse clinical consequences. Hyperglycemia was recognized to promote

oxidative stress, which contribute to the increase risk of cardiovascular [4] and renal [5] diseases, even in non-diabetic subjects.

A number of drugs or classes of drugs has been demonstrated to be associated with an increased risk of metabolic deterioration, which significantly elevate blood glucose concentrations leading to hyperglycemia including β-blockers [6], thiazide diuretics [7], corticosteroids [8], atypical antipsychotics [9], immunosuppressants [10], calcium channel blocker [11], statins [12] and niacin [13]. Moreover, new drugs have been also recently identified to elicit hyperglycemia in non-diabetic patient. For example, it had been reported that an elderly non-diabetic patient had developed severe hyperglycemia after receiving gatifloxacin, a fluoroquinolone antibiotic, which was resolved after discontinuation of the drug[14]. Therefore, it is always pivotal to recognize situations or drugs attributed to the hyperglycemic complications in order to identify patients who are in risk for such deleterious consequences.

New-onset hyperglycemia has been identified in patients who received such medications over an extended period of time. Therefore, it is very important to reduce the likelihood of developing hyperglycemia or glucose intolerance to prevent complications and to ensure a healthy lifestyle whilst the patients are on the medication. Some physicians imply that it may be plausible to reduce this risk by using the smallest effective medication dose for shorter periods of time where possible. However, some studies have demonstrated an increased risk of acute hyperglycemia associates with even short-term use of atypical antipsychotics[15]. Early identification of drug-induced hyperglycemia is important to reduce morbidity or mortality by controlling high blood sugar and possibly avoiding the future complications or development of diabetes mellitus.

The aim of the present study was to assess the risk of new-onset hyperglycemia associated with the use of prescribed medications and the unrecognized drug-induced hyperglycemia among patients at King Abdulaziz Medical City (KAMC) in Riyadh.

Study Design: The design of the present study was a retrospective cross-sectional patients chart review. According to the American Diabetes Association criteria for the diagnosis of hyperglycemia [16], patients with fasting blood glucose level ≥ 100 mg/dL (5.6 mmol/L) and/or glycosylated hemoglobin (HbA1C) level ≥ 5.7% (39 mmol/mol) or a random plasma glucose ≥ 140 mg/dL (7.8 mmol/L) were identified. Patients with a previous history of diabetes mellitus were excluded from the diagnosis of new-onset hyperglycemia (or possibly drug-induced hyperglycemia). Infants and terminally ill patients were also excluded. For each patient, a baseline demographic data including gender, age, and weight, in addition to past medical history, carried out Surgery, used medications and laboratory data were obtained using a structured review of charts and electronic patient records for patients diagnosed with hyperglycemia. Discharge summaries (if available) confirming diagnosis, and interventions were also documented.

All cases pertaining to hyperglycemia side effects were identified from medical record archive of a random sample of patients admitted to KAMC, Riyadh, Saudi Arabia from January 2015 to December 2015. The association between drugs and hyperglycemia was assessed by the case/non-case method, calculating the reporting odds ratios (ROR) of exposure to each drug. Cases were defined as reports of hyperglycemia in presence of a given drug and non-cases were all reports of other than hyperglycemia in the presence of the same drug. This study was completed over a period of 7 months from December 2015 to June 2016. This study has been approved by institutional review board at King Abdullah international medical research center. Both descriptive and statistical analyses were performed using SPSS (version 20.0) statistical software package.

RESULTS AND DISCUSSION: In the present study, a total of 129 patients with hyperglycemia were identified from a random sample of 1038 patients admitted to KAMC from January 2015 to December 2015. However, 53 patients were excluded since 48 patients have a previous history of diabetes mellitus and 5 patients were less than 2 years old. Thus, only 76 hyperglycemic patients were included in the present study. 36 (47.4%) patients were males and 40 (52.6%) were females. The mean age of included hyperglycemic patients

was 48.8 ± 26.2years (48.1 ± 29.4 for male and 49.5 ± 23.4 for female). A comparable sample of 76 non-hyperglycemic patients were randomly selected from the medical record archive, which served as a non-case. 39 (51.3%) were males and 37 (48.7%) were females. The mean age of those patients was 49.0 ± 24.7 (47.1 ± 24.7 for male and 50.7 ± 24.6 for female). Patients data was reviewed and collected retrospectively from their medical chart and/or medical records.

Peculiarly, there were only 14 patients (18.4%), who were admitted to KAMC primarily due to hyperglycemia. Eight of them were medically free prior to being diagnosed with hyperglycemia. The remaining (62 patients) were admitted for other chief complaints, and their hyperglycemia was revealed during the routine blood testing. The overall average value of random blood glucose levels in selected hyperglycemic patients was 324.3 ± 184.1 mg/dl. Nevertheless, their average HbA1C was 7.70 ± 3.35%. Other lab tests (BUN, sodium, potassium, chloride, pCO_2, cholesterol and serum creatinine) were fairly normal in all patients.

Management of hospitalized patients' hyperglycemia was mostly done after admission using the sliding-scale insulin therapy, where patient blood glucose was measured periodically, and a pre-determined specific short-acting or regular insulin dose was administered based on the patient blood glucose measurement alongside the patient regular medications. On average the patient length of stay in the hospital primarily due to hyperglycemia was only 2.6 ± 2.7 days. **Table 1** shows the prevalence rates of the most common comorbidities in the sample. On the other hand, 67 different drugs had been found in the medical records of hyperglycemic patients. The top 23 medications in those patients are listed in **Table 2**.

TABLE 1: INCIDENCE OF THE MOST COMMON COMORBIDITIES IN THE IDENTIFIED HYPERGLYCEMIC PATIENTS

Most common illnesses	Frequency	Most common illnesses	Frequency
None	8 (10.5%)	Liver Disease	4 (5.3%)
Hypertension	33 (43.4%)	Lung disease	4 (5.3%)
Cataract	17 (22.4%)	Gastroenteritis	4 (5.3%)
Asthma	14 (18.4%)	Stroke	4 (5.3%)
Dyslipidemia	11 (14.5%)	Hypothyroidism	4 (5.3%)
Heart Disease	9 (11.8%)	BPH	2 (2.6%)
Cancer	9 (11.8%)	Osteoarthritis	2 (2.6%)
Pneumonia	6 (7.9%)	Alzheimer's disease	2 (2.6%)
Kidney Disease	4 (5.3%)	Depression	2 (2.6%)

TABLE 2: FREQUENCY OF OCCURRENCE OF TOP DRUGS IN THE IDENTIFIED HYPERGLYCEMIC PATIENTS

Drug name	Frequency	Drug name	Frequency	Drug name	Frequency
Prednisolone	7 (9.2%)	Prednisone	4 (5.3%)	Tacrolimus	2 (2.6%)
Salbutamol	7 (9.2%)	Omeprazole	4 (5.3%)	Atorvastatin	2 (2.6%)
Amlodipine	6 (7.9%)	Aspirin	4 (5.3%)	Dexamethasone	2 (2.6%)
Mycophenolate mofetil	5 (6.6%)	Cyclopentolate	4 (5.3%)	Alfacalcidol	2 (2.6%)
Calcium	5 (6.6%)	Phenylephrine	4 (5.3%)	Furosemide	2 (2.6%)
Acetaminophen	5 (6.6%)	Multivitamin	3 (3.9%)	Ipratropium	2 (2.6%)
Tropicamide	5 (6.6%)	Fluticasone	3 (3.9%)	Lisinopril	2 (2.6%)
Esomeprazole	4 (5.3%)	Metoprolol	3 (3.9%)	Other drugs	23

Although many drugs have shown noticeable frequencies in the identified hyperglycemic patients, only prednisolone, and mycophenolate mofetil showed a significant association for hyperglycemia with reporting odds ratios (ROR) of 2.63 (95% CI 1.26-5.51) and 10.85 (95% CI 1.24-24.92), respectively. The difficulty in finding a significant relationship for other drugs from the present data could be due to the small sample size of identified hyperglycemic patients included in the study, which confined our ability to detect any significance due to exposure to individual drug.

However, data of hyperglycemia in the present study was presented and assessed owing to a drug group rather than a particular drug in the selected patient cases. This could give more realistic overview about the adverse effect of these drugs,

taking in consideration differences in the dispensing preference among physician and patients. **Table 3** displays the occurrence of drug groups in the identified hyperglycemic patients.

TABLE 3: DRUG MEMBERS IDENTIFIED IN THE HYPERGLYCEMIA PATIENTS INCLUDED IN THE PRESENT STUDY

Drug group	Drug names
Corticosteroid drugs	budesonide, dexamethasone, fluticasone, hydrocortisone, mometasone, prednisolone, and prednisone
Immunosuppressant agents	azathioprine, cyclosporine, mercaptopurine, mycophenolate mofetil, and tacrolimus
Anticholinergic agents	cyclopentolate, ipratropium and tropicamide
Analgesics	acetaminophen, aspirin, ibuprofen and meloxicam
Adrenergic agonist	phenylephrine and salbutamol
Vitamin D analogue	alfacalcidol and cholecalciferol
Proton-pump inhibitors	esomeprazole and omeprazole
Calcium channel blocker	Amlodipine
Beta-blockers	metoprolol, propranolol, and Timolol
Statins	atorvastatin, rosuvastatin and simvastatin
Sulfonamide diuretics	furosemide and thiazide
Angiotensin converting enzyme inhibitors	fosinopril and Lisinopril

When drugs were combined in groups, a significant association for hyperglycemia was revealed with corticosteroids, with ROR = 2.63; 95% CI (1.26-5.51), (**Table 4**). This significant risk associated with corticosteroid drugs is consistent with most reported cases [17]. The estimated rate of corticosteroids-induced hyperglycemia was more than half of the treated patients (57.6%), which was even higher than other studies, which reported hyperglycemia in about one third of non-diabetic users [18]. However, in a recent study, Katsuyama *et al.*, (2015) reported more than 65% incidence of hyperglycemia in patients receiving corticosteroids treatment[19]. Such high incidence of corticosteroids-induced hyperglycemia could be due to the elderly age of enrolled patients, which was identified as independent risk factor for induced hyperglycemia.

Moreover, hyperglycemia a significant association for hyperglycemia was also found with immunosuppressants, with ROR = 8.38; 95% CI (2.33-30.16), (**Table 4**). Hyperglycemia and new-onset diabetes have been always recognized as expected complications following organ transplantation [20]. Immunosuppressant therapies used in those patients have been reported in several studies to be associated with a markedly increased risk for hyperglycemia [21-23]. Although, several studies have claimed that mycophenolate mofetil was not been associated with metabolic disorders including diabetogenic effects [23, 24], other studies reported noteworthy inconsistent results, where mycophenolate mofetil was associated with either emerging of new-onset hyperglycemia or deterioration of pre-existing diabetes [25, 26]. This perhaps could be due to the variations in study samples or design. On the other hand, tacrolimus was always blamed to disturb the glucose metabolism in organ transplant recipients as a result of insulin resistance and diminished insulin secretion [27, 28].

However, the present study shows a significant increase in the risk of hyperglycemia in the presence of both immunosuppressants, particularly mycophenolate mofetil, with highest hyperglycemia incidence of 81.3% and a significant ROR value of 8.38 (95% CI 2.33-30.16). The combined use of corticosteroids with immunosuppressant therapies may contribute to the high metabolic and hyperglycemic adverse effects occurred in organ transplant recipients. However, other predisposing factors, such genetic susceptibility [29], patient age [30], obesity [31], and infections [32] may also participate in increasing the risk of hyperglycemia in those immune-compromised patients. Therefore, post-transplant screening for identifying hyperglycemia in patients at high risk for such imminent consequence is crucial for adopting an appropriate preventive strategy.

Remarkably, the present study also found a significant association between the anticholinergic agents, tropicamide, cyclopentolate and ipratropium, and hyperglycemia in the identified patients included in this study with an overall incidence of 68.8%, and ROR of 4.11 (95% CI 1.39-12.20). Tropicamide and cyclopentolate were mainly used for cataracts in those identified hyperglycemic patients, whereas, ipratropium was found as a part of asthma regimens, which typically include corticosteroids. Consequently, the risk of hyperglycemia in case of anticholinergics was

estimated without ipratropium, which again turn to be highly significant with ROR of 8.41 (95% CI 1.78-39.76). Interestingly, the drug groups which showed the remarkable associations with hyperglycemia also displayed large percent ratios of hyperglycemic reports in the identified cases. Corticosteroids, immunosuppressants and anticholinergic agents were responsible for 57.6%, 81.3%, and 68.8% of reports, respectively. Although, remaining drugs or drug groups also exhibit a considerable percent ratio, they did not reveal any significant association with hyperglycemia (**Table 4**).

TABLE 4: ASSOCIATION OF HYPERGLYCEMIA WITH THE IDENTIFIED DRUG OR DRUG GROUP IN THE STUDIED RANDOM SAMPLE

Drug / Drug group	All reports	Hyperglycemia	Hyperglycemic percent ratios of reports	Reporting Odds Ratio(ROR)	95% CI	
All reports	280	103				
Corticosteroid drugs	33	19	57.6%	2.63	1.26	5.51
Immunosuppressant agents	16	13	81.3%	8.38	2.33	30.16
Anticholinergic agents	16	11	68.8%	4.11	1.39	12.20
Analgesics	33	11	33.3%	0.84	0.39	1.82
Adrenergic agonist	21	11	52.4%	2.00	0.82	4.88
Proton-pump inhibitors	77	8	10.4%	0.13	0.06	0.29
Amlodipine	17	6	35.3%	0.93	0.33	2.60
Beta-blockers	14	5	35.7%	0.95	0.31	2.92
Calcium	14	5	35.7%	0.95	0.31	2.92
Statins	15	4	26.7%	0.61	0.19	1.97
Vitamin D analogue	6	4	66.7%	3.54	0.64	19.65
Sulfonamide diuretics	7	3	42.9%	1.30	0.28	5.92
Angiotensin converting enzyme inhibitors	11	3	27.3%	0.63	0.16	2.44

Hyperglycemia was also a well-recognized adverse effect of beta adrenergic blockers and sulfonamide diuretics (*e.g.*, thiazide), which increase the risk of developing hyperglycemia in hypertensive patients using these medications as first-line therapy [33]. This risk was further increased in elderly and obese patients [34]. However, few studies have reported contradictory results, where the use of these drugs in hypertensive patients was not associated with a statistically significant increase in risk of hyperglycemia [35]. Similarly, data in the present study also failed to demonstrate such significant association for either beta-blockers or sulfonamide diuretics.

Additionally, beta-2 receptors have a vital role in regulating hepatic gluconeogenesis and thus plasma glucose levels, therefore, the inhibitory effect of the non-selective beta blocker may contribute to the hypoglycemia occurred in some patients. However, hypoglycemia has been also reported in a patient receiving metoprolol, a selective beta-1 blocker [36]. Nevertheless, there are great inconsistencies in the results of many studies, which assess the risk of hyperglycemia of other antihypertensive agents, such as angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) or calcium channel blockers (CCBs). Where most of the previous studies suggested a potentially hyperglycemic protective effects of ACEIs, ARBs and CCBs [37 - 39], others reported no significant difference [40, 41]. However, the risk for hyperglycemia has been found, in further studies, to increase in patients receiving multiple antihypertensive agent regimens [42]. In the present study, the incidence of hyperglycemia in the presence of ACEIs (fosinopril or Lisinopril) or CCBs (amlodipine) were notable high 27.3% and 35.3%, respectively. However, neither were associated with a statistically significant difference with corresponding ROR values of 0.63 (95% CI 0.16-2.44) and 0.93 (0.33-2.60), respectively.

Furthermore, it has been reported that cholinergic system has a crucial role in regulating glucose blood levels. Cholinergic agonists can significantly reduce blood glucose levels through enhancing the release of insulin form the pancreatic islet, while muscarinic blockade by atropine could improve insulin sensitivity [43]. It has been also demonstrated that hyperglycemia could be induced in the rat model by activation of ganglionic nicotinic

receptors which in turn stimulate the release of catecholamines that increase blood glucose level via activating adrenergic receptors [44]. However, most of these results were demonstrated in animal model, whereas, very little is known about such mechanism in human. However, recently a study has suggested that the cholinergic signalling responsible for regulating insulin secretion in human is predominantly a paracrine system, where local endogenous acetylcholine release from α-cells rather than a neural signal [45]. Yet, acetylcholine also stimulates somatostatin secretion from δ-cell, which is a strong inhibitor of insulin secretion. However, the glucose-induced insulin response was not affected. This complex regulation of insulin secretion from the pancreatic islets by cholinergic signalling in the human is still poorly understood. The well-known hyperglycemic adverse effect of atypical antipsychotics, e.g., olanzapine, has been also attributed to their selective impairment of cholinergic-stimulated insulin secretion as being potent muscarinic M3 antagonists [46]. However, the present data does not identify any hyperglycemic cases related to those antipsychotic agents, since KAMC does not include psychiatric clinic or ward.

On the other hand, the present data indicates that omeprazole and esomeprazole, the proton-pump inhibitors, were associated with a substantial reduction in risk of hyperglycemia, with ROR of 0.13 (95% CI 0.06-0.29); ROR for Esomeprazole alone was 0.21 (95% CI 0.07-0.63) and for Omeprazole 0.16 (95% CI 0.05-0.47). Our result is very consistent with recent studies that reported a significant dose-dependent decrease in the risk of diabetes with Proton-pump inhibitors use [47, 48]. Proton-pump inhibitors were also accompanied by reduction of HbA1C levels in the previous studies.

It has been shown earlier that the long-term inhibition of gastric acid secretion by proton-pump inhibitors resulted in increasing levels of gastrin hormone [49]. Both *in vitro* and animal model studies have demonstrate that high levels of gastrin hormone enhanced pancreatic β-cells generation and thus insulin secretion was increased [50, 51]. These results indicate that proton-pump inhibitors seem to have a potential advantage in diabetic patients or in those who are at high risk to develop hyperglycemia. However, further studies may be required to confirm the established findings.

Salbutamol (also called albuterol), on the other hand, has shown a high frequency of incidence in the included hyperglycemic patients. However, the present data failed to demonstrate a significant association with the risk of hyperglycemia (ROR 1.46 (95% CI 0.53-4.04)). β2 - receptors agonists are known to influence glucose metabolism via hepatic glycogenolysis and gluconeogenesis, however, there are no reports to support hyperglycemia due to β2 - receptors agonists. Though, there are several incidences of hyperglycemia, which were attributed to salbutamol intoxication in young children [52, 53]. Similarly, other medications identified in the present study, with fair frequencies do not show any association. Nevertheless, the involvement of any drug in the induced-hyperglycemia hazard should be always assessed before excluding such risk.

Can Drug Induced Hyperglycemia be Prevented? There are several studies that have tried to reverse glucose impairments and eventually prevent the imminent development of diabetes [54, 55]. Potassium supplement, for example, was suggested to be used to treat thiazide-induced hypokalemia, which ultimately may prevent hyperglycemia attributed to thiazide diuretics [56]. Other drugs were also endorsed to improve control of hyperglycemia. The angiotensin II receptor blocker telmisartan was reported to improve insulin resistance in hypertensive patients [57]. Induced-hyperglycemia was also prohibited by pre-treatment with phentolamine or yohimbine [44].

Hyperglycemia has been a major concern for both patients and health care provider, as it is always associated with deleterious consequences. Therefore, it is always necessary to be vigilant about unrecognized cases of diabetes, and to recognize drugs associated with the risk of hyperglycemia to evade the increase risk of new onset diabetes mellitus. Due to the scarcity or inadequacies of available alternative drugs, patient should be cautious about the possibility of drug-induced hyperglycemia. Thereby, it may be plausible to reduce risk of hyperglycemia, ketoacidosis, and even diabetes by increasing population awareness about such potentially harmful effect of drugs, especially patients with a family history of diabetes or glucose intolerance.

Early diagnosis of drug-induced hyperglycemia is pivotal to provide the optimal effective treatment and to reduce the likelihood of diabetes-related complications to ensure a healthy lifestyle of patients.

Finally, the limited number of identified hyperglycemic patients in the present study restricted our ability to perform adequate subgroup analyses to establish the risk association with individual drugs. The small sample size of the included patients also does not permit confident generalization about new drug entities. Further, investigational studies may be required to confirm the hyperglycemic risk of these new drugs. This necessitates the conduction of multinational population-based surveys of drug-induced hyperglycemia.

CONCLUSION: In conclusion, the results of the present study show a consistent hyperglycemic risk for both corticosteroids and immunosuppressants. Anticholinergic agents were recognized to be significantly associated with hyperglycemia. It is worth noting that further investigations are required before drawing a definite conclusion on the associated risk of hyperglycemia of other drugs. This study also highlight the importance of routine screening for hyperglycemia in patients who are at a greater risk of developing hyperglycemia due to their medications.

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