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Most Reported ADR in Past 15 Year Associated with Diabetic Patient and Antidiabetic Drug.

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Abstract:

Diabetes affects several organ systems throughout the body and is a prevalent and complicated illness. People with diabetes all over the world are now taking drug regimens that target glucose stability from a number of pathophysiologic mechanisms, thanks to a consensus in treatment recommendations that emphasizes the significance of glycemic control in defining the development of the illness. Each of these drugs has a unique risk for negative side effects. In addition to more well-known eruptions like insulin-induced lip hypertrophy and contact dermatitis after subcutaneous injections, there have been more reports of skin responses to diabetes drugs in recent years. This article is a summary of the most common side effects involving diabetic patients and antidiabetic medications that have been recorded in the last 15 years.

Keywords: *"antidiabetic drugs", "skin reactions", "adverse drug reactions", "allergic reactions", "diabetes", "metformin", "insulin", "DPP4 inhibitors", "thiazolindineones", "sulfonylureas", "SGLT2 inhibitors", "GLP-1 agonists", "diabetic medication".*

Introduction: Diabetes already affects 463 million people worldwide, and it's expected to affect 700 million by 2045 [1]. This noncommunicable illness, which ranks ninth among the top causes of mortality worldwide according to the World Health Organisation (WHO), can seriously impair a person's ability to operate [2]. Diabetes sufferers discovered a way to combat the then-universally deadly condition with the invention of insulin 100 years ago. The relevance of glycemic management in lowering the microvascular complications of diabetes has been demonstrated in significant studies from the 20th century, including the United Kingdom Prospective Diabetes Study (UKPDS) [3] and Action in Diabetes and Vascular Disease (ADVANCE), Ref [4]. Reduced blood glucose saturation controls the rate of intracellular glucose absorption, which reduces the formation of advanced glycation end products (AGEs) and the subsequent consequences. Generally speaking, a treatment goal of HbA1c less than 7% is advised, but it's also crucial to keep blood sugar levels steady. Data show that every 1% reduction in A1C leads to better long-term results, regardless of whether glycemic control is moderate or strict [5]. A more multifaceted strategy is required to address the macrovascular sequelae.Pharmacological therapy has been a mainstay of antidiabetic treatment regimens due to the effectiveness of antidiabetic drugs and the increased incidence of diabetes over the past 20 years. From 2008 to 2018, there was an increase in global pharmaceutical spending of almost USD 52 billion on only this medicine class [6]. The selection of an anti-diabetic drug should be made with the patient in mind, taking into account efficacy, side effects, cost, comorbidities, and risk of hypoglycemia. Oral antidiabetic drugs may be divided into seven broad types, each of which has a unique set of adverse effects. A somewhat new appearance of cutaneous responses is being seen across many of the main antidiabetic classes, in addition to the usual gastrointestinal SE.

The case reports in the extant literature that describe cutaneous responses to ic drugs are briefly summarised in this study.From May 2014 to June 2015, a tertiary care hospital in New Delhi, India, conducted the current prospective observational research to document adverse drug reactions (ADRs) in patients with type 2 diabetes mellitus (T2DM) on antidiabetic medications. 220 individuals in all (121 men and 99 women) were enrolled. ADRs were documented using the required form. Using the modified Hartwig and Siegel severity scale for severity evaluation and Naranjo's probability scale for causality, respectively. The medications biguanides, peptide hormone, and sulphonylurea were often administered. There were a total of 26 ADRs (16 in men and 10 in female). Degludec, a 42-hour ultra-long-acting insulin, was rejected by the American Food and Drug Administration (FDA) in 2013. However, this substance is accessible in Europe and is most likely to be resubmitted for approval in the US.The development of several new insulin delivery methods and devices, including improved syringes, pulmonary insulin, insulin pumps, and closed-loop insulin delivery systems, has taken place in addition to the formulation improvements mentioned above. Insulin is undoubtedly the most efficient and predictable (in most, but not all situations) of all the current antihyperglycemic medications and is currently used frequently in patients with type 1 or type 2 diabetes. A cross-sectional research in a tertiary diabetic care facility in Yaoundé, Cameroon, served as the methodology. A pre-structured data collecting form was used to conduct interviews with adult T2DM clinic patients. Patients self-reported adverse drug reactions (ADRs).350 patients were included in the trial, and of them, 61.1% were just taking oral hypoglycemic medications, 24.9% were taking them together with insulin, and 13.4% were using insulin exclusively. A whopping 96.3% of the patients used metformin. 101 putative ADRs were reported by 90 patients.

Metformin:

The drug metformin is most frequently used to treat type 2 diabetes.Metformin likely enhances glucose metabolism by activating AMP-activated protein kinase (AMPK), while the precise mechanism is unknown (7). In the bone as well as other parts of the body, AMPK is widely expressed (8). It has been demonstrated that the expression and activation of AMPK subunits differs depending on the tissue (9). In bone marrow progenitor cells (10), primary osteoblasts (11), and primary bone marrow macrophages (12), metformin has been demonstrated to be a powerful activator of AMPK activation. A dimethyl biguanide known as metformin, which is the first-line therapy for type 2 diabetes, works by reducing intestinal glucose absorption, raising insulin sensitivity, and inhibiting hepatic glucose production. The most often observed metformin reaction was leukocytoclastic vasculitis (LCV). The women's ages in all six cases ranged from 33 to 60. Each instance included biopsy evidence of LCV, and all other possible LCV causes were eliminated [13]. Each of their legs first developed the vasculitis, which was described as hemorrhagic papules, vesicles, and bullae, and in some cases, it extended to their trunks and forearms. The eruption was significantly reduced once metformin was withdrawn and prednisone was begun [14]. From isolatederythematous lesions on the patient's palms and soles to a widespread macular eruption with cutaneous hemophagocytosis, FDEs caused by metformin have been documented [15]. The most severe cutaneous reaction to metformin was reported in a 40-year-old DRESS condition patient [16]. The patient's rash, pruritus, lymphadenopathy, and eosinophilia disappeared right away after quitting the metformin. Three people experienced photo-contact dermatitis, which improved once the metformin was stopped. The rash on these people varied from eczematous to erythematous.

Sulfonylureas:

Immunologic-related eruptions are brought on by the majority of sulfonylureas. But unlike metformin, several loosely defined exanthematous reactions—such as instances of TEN [17], psoriasiform rash [18], exanthematous pustulosis [19], pigmented purpuric dermatosis [20], erythroderma [21], and lichenoid reactions—make up the biggest subset within this category.Sulfonylureas Despite being among the most frequently given medications for T2DM and being in use for more than 50 years, there is surprisingly little clinical data on the impact of sulfonylureas on bone health. A local pruritic skin rash that proceeded to generalized erythema with many brown lesions and blisters as well as mucosal involvement appeared one week after a 76-year-old patient started using glimepiride [22]. It should be noted that a study employing hairless mice revealed phototoxicity to sulphonamide-derived oral anti-diabetes drugs such glibenclamide, glipizide,

glymidine, tolazamide, and tolbutamide. Necrosis or edema was discovered at readings 24 and 28 hours after UVA exposure and injection of test chemicals [23].

Meglitinides:

Meglitinides are used to treat diabetes and operate by promoting the release of insulin. In reaction to repaglinide and nateglinide, the FAERS reporting system records 577 cases of skin and subcutaneous tissue diseases. Out of the 577 instances, 96 include hyperhidrosis, with pruritus, rash, and pemphigoid being the next three most frequent responses in this subgroup [24]. One instance describes a 61-year-old man who, after receiving repaglinide medication for five days, manifested a maculopapular rash [25].

Glucagon-like Peptide-1 Receptor Agonists:

An anti-diabetic drug family known as GLP-1 agonists works by turning on GLP-1 receptors in the pancreas, which then increases insulin production and reduces glucagon release. They can be used as monotherapy if a patient is intolerant to metformin, although they are often used as an adjuvant therapy if haemoglobin A1c remains uncontrolled. 9266 reports of skin and subcutaneous tissue problems brought on by GLP-1 treatment are included in the FAERS database. The incidence of skin-related adverse drug events following the administration of diabetic medication is the highest, although only seven case reports describing CADRs have been discovered. All the instances were immune-related, and there were three distinct response patterns mentioned in the literature: two exanthematous [25], one urticarial [26], and one blistering [27].

Sodium-Glucose Cotransporter-2 Inhibitors:

SGLT-2 inhibitors are medications that reduce blood sugar by preventing the kidneys from reabsorbing filtered glucose. These are the most recent oral diabetic medications, all of which should be taken once day. Diabetic foot, rash, and skin ulcers are the top three adverse effects, accounting for 811, 765, and 617 of the total instances of skin and subcutaneous tissue diseases reported by the FAERS following usage of SGLT2-I, respectively. Research to ascertain the prevalence and characteristics of hypersensitive adverse events brought on by dapagliflozin was finished in 2016. The most frequent events caused by hypersensitivity included rash, eczema, dermatitis, and urticaria, and overall, adverse events of hypersensitivity were minor and not significantly different from placebo [28] Due to a compromised immune system, persons with diabetes mellitus are more susceptible to this illness. Prior urinary tract infections and morbid obesity are thought to be predisposing factors when the infection is linked to SGLT2-I, with the illness being documented to develop anywhere between five days and 49 months [29].

Thiazolidinediones:

This group of drugs, sometimes referred to as "glitazones," aims to treat type 2 diabetes by increasing the sensitivity of tissues to insulin and functioning as a nuclear transcription regulator. Episodes of urticaria are responsible for 17% of skin responses, with hyperhidrosis and erythema making up the next two most common subcategories. The database also lists pruritis, alopecia, rash, blistering, angioedema, hyperkeratosis, palmar-plantar erythrodysesthesia syndrome, dry skin, and other skin eruptions with numerous occurrences. All responses indicated below these have less than four documented cases.DPP-4 Inhibitors, often known as "gliptin" medicines, work by blocking the incretin pathway. They boost endogenous secretion similarly to GLP-1RA, but they do so by inhibiting the enzyme that breaks down GLP-1. The FAERS system has received 248 reports of adverse skin and subcutaneous problems caused by these drugs. The most prevalent adverse event, which is responsible for 76 of the cases, is pemphigoid responses. Exanthematous (generalized skin eruption [30], maculopapular eruption [31], and DRESS syndrome [32]) and blistering (pemphigoid [33], SJS, TEN, fixed drug eruption, hypersensitivity vasculitis, and photosensitivity [34]) drug reaction patterns are the subcategories of cutaneous reactions discussed in the literature. One patient on linagliptin, aged 70, showed signs of non-bullous pemphigoid. When sitagliptin was prescribed in place of linagliptin, the patient's oral mucous membrane erosion and a few blisters on his upper chest and back disappeared [35].

Insulin:

The cutaneous responses to insulin have received the greatest research attention among the anti-diabetic drugs. Formulations have changed throughout time to lessen the body's sensitivity to chemicals or kinds of particular insulins. Insulin Aspart, Insulin Degludec, Insulin Detemir, Insulin Glargine, and Insulin Glulisine together have been the subject of 8158 responses reported by the FAERS system, with the majority of these reactions indicating to a type 1 hypersensitivity picture of pruritis, urticaria, and erythema. Insulin can trigger a variety of immunologic reactions in the skin, the majority of which follow the urticarial reaction pattern, as widely described in the literature. These include pruritus, urticaria, edema, and induration on both a local and systemic level that proceed to anaphylaxis. Lipodystrophies, which are more common in medium- and long-acting insulin formulations, are other skin-related responses that have been widely studied. The anabolic actions of insulin are known to cause lipohypertrophy, which often manifests as soft, dermal nodules of various sizes within the skin. Since its introduction in 1983, there have been more than 75 occurrences of insulin injection sites growing a hard, single subcutaneous nodule. While diagnosed, diabetics who are more vulnerable typically have poor glycemic control even while using insulin [36].

E. Pramlintide:

Amylin is a member of the same family of peptides as calcitonin, peptides linked to the calcitonin gene, adrenomedullin, and intermedin. The calcitonin receptor, a particular G protein-coupled receptor, and a receptor activity-modifying protein (RAMP1 or RAMP3) are how amylin works. Amylin and insulin are cosecreted by pancreatic cells. Both peripheral and central systems are involved in how food intake and amylinon glucose metabolism have an impact. Amylin is completely or almost completely absented in T1DM, but early in T2DM, amylin is present in excess and declines to low concentrations towards the end of the illness. Additionally, in individuals with severe T2DM, amylin concentrations do not appear to vary in response to meals. Amylin has been connected to bone physiology, just as calcitonin.

Conclusion:

Patients with type 2 diabetes whose treatment regimen does not follow local therapeutic recommendations in Cameroon may experience adverse medication responses often. Therefore, in the future, improving the treatment of diabetes and lowering the incidence of preventable ADRs might be achieved in Cameroon by promoting active pharmacovigilance and designing educational initiatives to encourage the right use of medications at hospital level.

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