



Review Article

## Cutaneous Adverse Effects of Oral Hypoglycaemic Agents: A Narrative Dermatological Perspective

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### ABSTRACT

With the rising global prevalence of type 2 diabetes mellitus, oral hypoglycaemic agents (OHAs) are increasingly used for glycaemic control. While their systemic side effects are well-documented, dermatological adverse reactions remain under-recognised. This narrative review compiles and analyses published evidence on the cutaneous manifestations associated with various classes of OHAs. Reported adverse events range from benign rashes to severe reactions such as Stevens–Johnson syndrome and bullous pemphigoid. Given the spectrum of dermatologic presentations, dermatologists must remain vigilant, especially in patients presenting with unexplained eruptions while on antidiabetic therapy. Early recognition and prompt management can mitigate morbidity and guide safer drug selection.

**Keywords:** Bullous pemphigoid, Cutaneous adverse drug eruption, Diabetes

### INTRODUCTION

Diabetes mellitus (DM) is a globally concerning metabolic disorder of varied aetiology as described by the World Health Organization. It is defined by long-term hyperglycaemia and abnormalities in the metabolism of fat, protein and carbohydrates brought on by either decreased insulin secretion or action. The estimated global prevalence at present is 6.1%. Around 96% of diabetics have type 2 DM (T2DM), making it the most common type of DM.<sup>[1]</sup>

DM, if not controlled, can cause irreversible harm such as organ malfunction and organ failure. To avoid such complications, DM should be managed properly. The first line of treatment for DM is having proper glycaemic control, which can be achieved by a strict diet and exercise combined with oral hypoglycaemic medications. This integrated approach helps in avoiding microvascular and macrovascular complications.

Oral hypoglycaemic agents (OHAs).

The OHA, along with its mechanism of action, is summarised in Table 1.<sup>[2]</sup>

### OHAS AND SKIN

While OHAs are largely considered safe, their dermatologic side effects are often overlooked. Cutaneous adverse drug reactions (CADRs) can range from mild erythema and pruritus to severe, life-threatening conditions such as toxic epidermal necrolysis [TEN].<sup>[3]</sup> Despite growing

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**Table 1:** Classification of OHAs.

S. No.	OHA class	Drugs	Mechanism of action	Systemic adverse effects	Contraindications
1	Sulphonylureas	Glipizide, glyburide, gliclazide, glimepiride	Inhibits adenosine triphosphate-sensitive potassium channels (K-ATP channels) in the pancreas, causing an influx of calcium and the stimulation of insulin secretion.	Diaphoresis, pruritus, headache, hypoglycaemia, diarrhoea, flatulence, dyspepsia, vomiting, syncope, dizziness, anxiety, depression, hypoesthesia, insomnia, pain, paraesthesia, drowsiness and headache	Hypersensitivity to the drug or sulphonamide derivatives. Diabetic ketoacidosis
2	Meglitinides	Repaglinide and nateglinide	Regulates adenosine triphosphate-sensitive potassium channels in pancreatic beta cells, thereby causing an increase in insulin secretion	Upper respiratory tract infection, headache, hypoglycaemia, weight gain and cardiovascular ischaemia	1. Type 1 diabetes, 2. Diabetic ketoacidosis 3. Known hypersensitivity to the drug
3	Biguanides	Metformin	Increases hepatic adenosine monophosphate-activated protein kinase activity, thus reducing hepatic gluconeogenesis and lipogenesis and increasing insulin-mediated uptake of glucose in muscles	Digestive disturbances including diarrhoea, vomiting, flatulence, flushing, palpitation, headaches, chills, dizziness, nail illness, diaphoresis, skin rash and vitamin B12 insufficiency	1. Hypersensitivity to the drug 2. Severe renal dysfunction 3. Metabolic acidosis
4	Thiazolidinediones	Rosiglitazone, pioglitazone	Activate PPAR- $\gamma$ , a nuclear receptor, which increases insulin sensitivity and resultant peripheral uptake of glucose, and increases the level of adiponectin	Sinusitis, pharyngitis, headaches, bone fractures, oedema, hypoglycaemia and heart failure	1. Hypersensitivity to the drug 2. Severe hepatic impairment 3. Heart failure (NYHA class III or IV) 4. Pregnancy
5	$\alpha$ -Glucosidase inhibitors	Acarbose, miglitol, voglibose	Competitively inhibit alpha-glucosidase enzymes in the intestinal brush border cells that digest the dietary starch, thus inhibiting the polysaccharide reabsorption and the metabolism of sucrose to glucose and fructose	Stomach pain, diarrhoea, flatulence and elevated serum transaminases.	1. Hypersensitivity to acarbose 2. Diabetic ketoacidosis 3. Cirrhosis 4. Inflammatory bowel disease
6	DPP-4 inhibitors	Sitagliptin, saxagliptin, vildagliptin, linagliptin, alogliptin	Influence glucose control through multiple effects, such as decreasing glucagon release and increasing glucose-dependent insulin release, decreasing gastric emptying and increasing satiety.	Hypoglycaemia, nasopharyngitis, acute pancreatitis, peripheral oedema, urinary tract infection	patients on haemodialysis or peritoneal dialysis
7	SGLT2 inhibitors	Dapagliflozin and canagliflozin	Inhibit SGLT-2 in proximal tubules of renal glomeruli, causing inhibition of 90% glucose reabsorption and resulting in glycosuria	Respiratory tract infection, fungal vaginosis, dysuria, dyslipidaemia, hyperphosphatemia, hypovolaemia, nausea, bone fracture and renal impairment.	1. Hypersensitivity to the drug 2. End-stage renal disease 3. Patients on dialysis.
8	Dopamine D2 agonist	Bromocriptine	Resets the hypothalamic circadian rhythm, which might have been altered by obesity	Weakness, rhinitis, constipation, headache, exhaustion and dizziness	Allergy to the drug, breastfeeding and syncopal migraine

(Contd...)

**Table 1: (Continued).**

S. No.	OHA class	Drugs	Mechanism of action	Systemic adverse effects	Contraindications
9	GLP-1 agonists	Semaglutide Liraglutide Exenatide Dulaglutide	Activates GLP-1 receptors located in the pancreas and intestine, thus enhancing glucose-dependent insulin secretion.	Nausea, vomiting, diarrhoea, dizziness, mild tachycardia, dyspepsia.	Hypersensitivity to the drug Pregnancy.

K-ATP: Adenosine triphosphate-sensitive potassium channel, OHAs: Oral hypoglycaemic agents, PPAR-γ: Peroxisome proliferator-activated receptor gamma, SGLT-2: Sodium-glucose co-transporter 2, GLP-1: Glucagon-like peptide-1

**Table 2: Summary of cutaneous adverse effects with various classes of OHA.**

Antidiabetic agent	Adverse effects
Biguanide (Metformin)	Erythema multiforme, Lichen Planus, Bullous pemphigoid, Photosensitivity, leucocytoclastic vasculitis, psoriasiform and lichenoid drug eruptions, Fixed drug eruptions
Sulphonylureas • First generation- (tolbutamide and chlorpropamide) • Second Generation- (gliclazide, gliquidone, glipizide, glibenclamide and glimepiride)	Lyell's syndrome, erythema nodosum, fixed erythema, erythema multiforme, pruritus, urticaria, phototoxic and photoallergic reactions and maculopapular exanthema Stevens–Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Acute generalised exanthematous pustulosis (AGEP), lichenoid drug eruptions, leucocytoclastic vasculitis, psoriasiform rash, erythroderma, exanthematous pustulosis, pigmented purpuric dermatosis, Erythema multiforme and lichen planus pemphigoid
DPP-IV inhibitors (gliptin)	Bullous pemphigoid and Stevens–Johnson syndrome, angioedema, polymorphic erythema, leucocytoclastic vasculitis, photosensitivity
Alpha-glucosidase inhibitor (Acarbose)	Erythema multiforme and generalised exanthematous pustulosis
SGLT-2 inhibitors (canagliflozin, dapagliflozin and empagliflozin)	Urticaria, drug eruptions, severe generalised rash, eczema and erythema Bullous pemphigoid Angioedema, Diabetic foot increased risk of genital fungal infections and Fournier's gangrene
GLP-1 agonists	Injection site erythema and pruritus Bullous pemphigoid Morbilliform drug eruptions Eosinophilic panniculitis Cutaneous hypersensitivity reactions.

OHA: Oral hypoglycaemic agents, SGLT-2: Sodium-glucose co-transporter 2, GLP-1: Glucagon-like peptide-1

case reports, a comprehensive dermatological perspective on these adverse effects remains limited in the literature. This review aims to address that gap.

Table 2 summarises the cutaneous reactions to different classes of OHAs.<sup>[4]</sup>

### Sulphonylureas

This class of OHAs is derived from sulphonamides and is divided into two generations. They increase insulin release by stimulating the beta cells in the pancreas. Although they are typically used in conjunction with metformin, patients who are hypersensitive or unable to take metformin as a first-line therapy may consider using this alone. At present, the first-generation sulphonylureas-tolbutamide

and chlorpropamide are not in use. On the other hand, the most widely used oral antidiabetic medications are the second-generation sulphonylureas, which consist of gliclazide, gliquidone, glipizide, glibenclamide (glyburide) and glimepiride.<sup>[5]</sup>

About 1% of people on sulphonylureas experience CADR.<sup>[6]</sup> Skin reactions caused by the first-generation drugs are Lyell's syndrome, erythema nodosum, fixed erythema, erythema multiforme, pruritus, urticaria, phototoxic and photoallergic reactions and maculopapular exanthema.<sup>[7]</sup> Furthermore, 10–15% of patients have reported experiencing chlorpropamide-alcohol flushing (CPAF).<sup>[8]</sup> It presents as facial erythema that appears after a small amount of alcohol intake. Patients who test positive for CPAF are at a lower risk of having vascular problems, suggesting that CPAF is an

autosomal dominant hereditary characteristic with prognostic value.

CADRs caused by second-generation sulphonylureas include lichenoid drug eruptions, leucocytoclastic vasculitis, psoriasiform rash, erythroderma, exanthematous pustulosis, pigmented purpuric dermatosis, erythema multiforme and lichen planus pemphigoid. It has also been reported that this drug class can cause serious adverse reactions in the form of Stevens–Johnson syndrome (SJS), TEN and acute generalised exanthematous pustulosis (AGEP).<sup>[9]</sup> In addition, glipizide, glibenclamide and gliquidone have demonstrated phototoxic potential in both *in vitro* and *in vivo* studies.

Furthermore, interaction with other sulphonamide analogues may also cause CADRs to sulphonylureas. There is a significant risk of allergic responses while using sulphonamides. T cells are exposed to sulphonamide metabolites when they bind to proteins and function as haptens. These complexes are then presented to major histocompatibility complex (MHC) class I or II molecules. Because of their structural similarities, sulphonylureas and sulphonamides can both cause allergic reactions.<sup>[10]</sup> The existing literature reports a few instances of this cross-reactivity where a patient presented with TEN after sulphamethoxazole-trimethoprim hypersensitivity, likely related to glimepiride.<sup>[9]</sup>

According to recent databases, the administration of second-generation sulphonylureas has been linked to 4073 reports of cutaneous reactions, in which 24 cases involved gliquidone, 816 cases involved gliclazide, 929 cases involved glimepiride, 995 cases involved glipizide and 1309 cases involved glyburide (glibenclamide). Rash, pruritus and dermatitis are the most frequently reported CADRs. In the EudraVigilance database, 1923 cases of cutaneous adverse effects are listed: 21 cases were associated with gliquidone, 162 with glipizide, 380 with glyburide (glibenclamide), 659 with gliclazide and 701 with glimepiride.<sup>[11]</sup>

## MEGLITINIDES

This class of OHAs consists of repaglinide, mitiglinide and nateglinide. They are insulin secretagogues used to treat DM and are preferred in patients with renal disease (chronic or end-stage). Although reports of any CADRs are rare in this group, few reports have documented itching, rash and pemphigoid. In another case report, a hypersensitivity reaction was seen in a 61-year-old male in the form of a maculopapular rash within 5 days of starting repaglinide.<sup>[12]</sup>

Sixty-eight cases of mitiglinide, 124 cases of nateglinide and 522 cases of repaglinide are amongst the 634 reported cutaneous reactions that the Food and Drug Administration's adverse events reporting system (FAERS) has recorded in conjunction with meglitinides.<sup>[13]</sup> Similarly, EudraVigilance

has reported 425 cases of cutaneous reactions: 14 cases for mitiglinide, 84 cases for nateglinide and 327 cases for repaglinide.<sup>[11]</sup>

## METFORMIN

It is a derivative of biguanide which decreases blood sugar levels by raising insulin sensitivity, decreasing the absorption of glucose in the intestine and suppressing glucose production in the liver. Metformin is commonly used and recommended as a first-line medication in the treatment of T2DM by the American Diabetes Association and the European Association for the Study of Diabetes.<sup>[14]</sup>

The cutaneous reactions due to metformin are immune-mediated. CADRs, such as erythema multiforme, lichen planus, rosacea-like facial rash, bullous pemphigoid and psoriasiform drug eruption, are seen with metformin intake.<sup>[15]</sup> Metformin-induced photosensitivity has also been reported in a few reports with symptoms of erythematous, eczematous or even blistering lesions over the sun-exposed areas.<sup>[16]</sup> Other cutaneous adverse effects include leucocytoclastic vasculitis and fixed-drug eruptions.

Moreover, there are reports of metformin-induced severe CADR in the form of drug rash with eosinophilia and systemic symptoms syndrome. Here, the patients present with a rash, generalised pruritus, eosinophilia and lymphadenopathy.<sup>[17]</sup>

Furthermore, continuous metformin therapy can result in vitamin B12 deficiency, which presents as hyperpigmented lesions over the knees, lateral surfaces of the legs, the dorsum of hands and feet, fingers and skin folds. A cohort study by Yen *et al.* studied the association of metformin with the initiation of urticarial lesions and concluded that the use of metformin had a significantly higher risk of chronic urticaria. Furthermore, a longer average cumulative duration of metformin use was associated with a higher risk of outcomes.<sup>[18]</sup>

Moreover, the recent adverse event databases have encountered about 8712 reports of metformin-associated CADRs. In this, the most commonly reported cutaneous lesions were pruritus (1495), rash (1209), hyperhidrosis (1057) and urticaria (734).<sup>[12]</sup> Whereas EudraVigilance has reported about 3624 cases of cutaneous lesions due to metformin use.<sup>[11]</sup>

## THIAZOLIDINEDIONES

To treat T2DM, rosiglitazone and pioglitazone have been approved, either as monotherapy or in combination with metformin or sulphonylureas. They regulate gene expression by binding to the peroxisome proliferator-activated receptor-gamma, which in turn enhances insulin sensitivity and action.

In thiazolidinedione therapy, hypersensitivity responses are the main cause of CADR. A case study of pioglitazone hypersensitivity has been reported, where the rash and pruritus developed after 2 months of treatment.<sup>[19]</sup> Similarly, another report describes the development of systemic drug-related intertriginous and flexural exanthema in a 72-year-old female within 2 weeks of starting pioglitazone.<sup>[20]</sup> At present, the FAERS accounts for around 183 cases, and EudraVigilance reports 679 events of skin and subcutaneous issues.<sup>[11]</sup>

### ALPHA-GLUCOSIDASE INHIBITORS

They act by inhibiting the enzymes that break down complex non-absorbable carbohydrates to absorbable simple carbohydrates from the small intestine. This delays carbohydrate absorption, hence reducing the increase in post-prandial blood glucose concentrations. This class of drugs includes acarbose, miglitol and voglibose.

Since these drugs are poorly absorbed in the intestines, the risk of cutaneous side effects is low. A few reports have been mentioned in the literature where CADR such as generalised erythema multiforme and AGEP have been seen in a few patients within a few days of acarbose therapy.<sup>[21]</sup> Furthermore, a population-based cohort study using the 1999–2013 Taiwanese Longitudinal Cohort of Diabetes Patients Database found that the use and interruption of alpha-glucosidase inhibitors may be linked with an increased psoriatic disease risk in patients with T2DM.<sup>[22]</sup>

541 cases of cutaneous reactions resulting from the use of alpha-glucosidase inhibitors are reported by the FAERS, out of which 396 cases were due to acarbose and 74 cases were due to miglitol. The most common symptoms documented were pruritus and hyperhidrosis. In addition, there have been 11 cases of SJS due to voglibose intake, 508 cases of CADR are listed in EudraVigilance: 393 cases of acarbose, 58 cases of miglitol and 57 cases of voglibose.<sup>[11]</sup>

### DIPEPTIDYLPEPTIDASE-4 INHIBITORS (DPP-4 INHIBITORS)

It consists of vildagliptin, alogliptin, anagliptin, linagliptin, saxagliptin, sitagliptin, teneligliptin and anagliptin. When metformin is unsuitable or in patients without a history of high-risk or confirmed cardiovascular disease, gliptins are advised as a second-line treatment. Gliptins function to stop the breakdown of the incretin hormone (glucagon-like peptide 1), which is involved in regulating glycaemic levels after a meal. This is done by blocking the enzyme dipeptidylpeptidase-4. Incretin inhibits the release of glucagon from  $\alpha$  cells and stimulates insulin production from  $\beta$  cells in a glucose-dependent manner.

It has been stated that gliptins are associated with the highest number of CADR amongst OHAs. The symptoms of gliptin hypersensitivity include angioedema, peripheral oedema, pruritus, rash, widespread rash, urticaria and pemphigoid. There have been cases of spongiotic dermatitis associated with vildagliptin and blistering and ulceration associated with linagliptin.<sup>[23]</sup> On the other hand, patients treated with sitagliptin experienced the following skin reactions: photosensitivity, pemphigus vulgaris, bullous lichenoid dermatitis, maculopapular-type eruption and SJS.<sup>[24]</sup> Psoriasiform dermatitis and lichenoid dermatitis are two more CADR associated with sitagliptin therapy that have been documented.

One of the most documented CADR by this class of drug is dipeptidylpeptidase 4 inhibitor-associated bullous pemphigoid (DPP4i-BP) or gliptin-associated bullous pemphigoid (GABP).<sup>[25]</sup> Vildagliptin has been identified as the most common drug that triggers DPP4i-BP. It has been demonstrated that older individuals and those with dementia have an increased risk of GABP. Studies showed that the latency period of onset of GABP symptoms varied greatly, ranging from 8 days to 6.5 years, from the initiation of gliptin therapy. Numerous Asian trials demonstrated a non-inflammatory phenotype with less eosinophilia infiltration in GABP than seen in usual bullous pemphigoid (BP), which was not supported by the European research.<sup>[26]</sup>

Most of the pathomechanism underlying GABP is still unknown. The fact that DPP-4 is expressed as a cell surface protein by a variety of cells, including fibroblasts, keratinocytes, macrophages and T lymphocytes, and is also present in bodily fluids, appears to be relevant as it is engaged in numerous biological processes. Amongst other things, the conversion of plasminogen into plasmin is carried out by the cell-surface plasminogen receptor DPP-4. Collagen XVII, which is essential for maintaining the firm adherence of the epidermis to the dermis, is cleaved by plasmin. DPP-4 inhibition is thought to alter plasmin's cleavage of collagen XVII and may have an impact on the development of novel BP autoantibody epitopes. Furthermore, it is also believed that DPP-4 inhibition increases the activity of proinflammatory chemokines like CCL11/eotaxin, which promotes the development of bullae and the activation of eosinophils in the skin.<sup>[27]</sup>

A total of 32 cases of anagliptin, 41 cases of teneligliptin, 66 cases of saxagliptin, 97 cases of alogliptin, 302 cases of sitagliptin, 703 cases of vildagliptin and 1707 cases of linagliptin are reported by the FAERS as resulting from DPP-4 inhibitors. Furthermore, pemphigoid accounts for 970 of all documented cases of CADR. 6419 cases of cutaneous reactions are listed in EudraVigilance: 283 cases for saxagliptin, 342 cases for alogliptin, 1603 cases for linagliptin, 1720 cases for vildagliptin and 2471 cases for sitagliptin.<sup>[11]</sup>

## SODIUM-GLUCOSE COTRANSPORTER 2 (SGLT-2) INHIBITORS

SGLT-2 inhibitors aim at the SGLT-2 proteins present in the proximal convoluted tubules. They act by inhibiting the reabsorption of tubular lumen's filtered glucose. Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, bexagliflozin, ipragliflozin and sotagliflozin are amongst the SGLT-2 inhibitors. For T2DM patients with heart failure, chronic renal disease or atherosclerotic cardiovascular disease, they are advised as a second-line treatment following metformin.

CADRs due to SGLT-2 inhibitors are commonly seen within 2 weeks of their intake in the form of urticaria, drug eruptions, severe generalised rash, eczema and erythema. In addition, there have been reports of a fixed drug eruption after dapagliflozin therapy, generalised severe pruritus brought on by canagliflozin and a case of bullous pemphigoid after ipragliflozin treatment.<sup>[28]</sup> According to the research by Sakaeda *et al.* and Yabe *et al.*, ipragliflozin was linked to the highest occurrence of cutaneous dermatoses.<sup>[29]</sup> The drug's interaction with the melanin pigment may result in a substantial risk of ipragliflozin-induced CADRs. According to research by Maegawa *et al.*, females older than 65 years are more likely to experience skin problems when taking ipragliflozin.<sup>[30]</sup>

Since SGLT-2 inhibitors cause glucosuria, an elevated urine glucose concentrations provide a nutrient-rich environment for microorganisms like bacteria and fungi, leading to an increase in the prevalence of urinary tract infections such as *Candida* balanoposthitis and monilial vulvovaginitis.<sup>[31]</sup> It is anticipated that vaginal fungal infections affect 5–10% of women with T2DM who are taking this class of OHAs. Furthermore, research has demonstrated an association between SGLT2 inhibitors and Fournier's gangrene, or necrotising fasciitis affecting the external genitalia and/or perineum, which has been known to be fatal in certain circumstances.<sup>[32]</sup>

At present, 6123 cases of cutaneous reactions are connected with SGLT-2 inhibitors as reported by the FAERS: 1 case associated with bexagliflozin, 2 with ipragliflozin, 4 with sotagliflozin, 1203 with dapagliflozin, 1956 with empagliflozin and 2957 with canagliflozin. Angioedema, skin ulcers, rashes, pruritus and diabetic foot are some of the CADRs that are most frequently reported. 5638 reports of cutaneous reactions are preserved in the EudraVigilance database: 19 for ertugliflozin, 1677 for dapagliflozin, 1884 for empagliflozin and 2058 for canagliflozin.<sup>[11,13]</sup>

## GLUCAGON-LIKE PEPTIDE-1 (GLP-1) AGONISTS

They activate GLP-1 receptors located in the pancreas and intestine, thus enhancing glucose-dependent insulin

secretion. It simultaneously decreases the glucagon secretion, slows stomach emptying and boosts pancreatic  $\beta$ -cell proliferation, which helps to reduce hunger.

Despite being licensed for the treatment of diabetes, semaglutide has become very popular on social media because of its impact on weight loss. It diminishes food cravings and amplifies the feeling of satiety, thus facilitating weight loss. This frequently causes a discernible decrease in facial volume and gauntness, which is known as 'semaglutide face'. The face appears 'sunken-in' as a result of subcutaneous fat loss.<sup>[33]</sup>

Although most GLP-1 agonists are administered subcutaneously, the Food and Drug Administration has recently approved oral semaglutide. Literature has a few reports of cutaneous drug reactions from this class of drugs, which include hyperesthesia, burning sensation, bullous pemphigoid, morbilliform drug eruptions, eosinophilic panniculitis and cutaneous hypersensitivity reactions.<sup>[34]</sup> Given the wide spectrum of GLP-1-induced cutaneous responses, a complete history, clinical suspicion, and, if available, supportive histological findings are necessary for diagnosis. The proper management of such cases entails stopping the offending drug use with a customised regimen.

## CONCLUSION

The overall cutaneous adverse effects of any OHA are diverse, ranging from mild pruritus to life-threatening cutaneous reactions. As the use of OHAs continues to rise with the growing burden of T2DM, awareness of their dermatologic manifestations becomes imperative. Hence, before prescribing any antidiabetic medication, one should obtain a detailed history from the patient to minimise the risk of any possible adverse reaction. Furthermore, the patient should be followed up at regular intervals to check for any adverse effects caused by OHAs. Dermatologists should be well-versed with the CADRs caused by OHAs for prompt diagnosis, timely treatment and cessation of the offending drug.

### Multiple choice questions

- Which class of OHAs is most strongly associated with Bullous pemphigoid?
  - Sulphonylureas
  - DPP-4 inhibitors
  - SGLT-2 inhibitors
  - Biguanides
- Chlorpropamide-alcohol flushing (CPAF) is a classic cutaneous adverse reaction of which OHA?
  - Metformin
  - Chlorpropamide
  - Pioglitazone

- d) Acarbose
3. Which cutaneous reaction has been most frequently linked to metformin use?
  - a) Photosensitivity
  - b) Chronic urticaria
  - c) Psoriasiform rash
  - d) Lichen planus
4. Ipragliflozin, an SGLT-2 inhibitor, has been particularly associated with:
  - a) Drug-induced lupus
  - b) Fixed drug eruption
  - c) Bullous pemphigoid
  - d) Photosensitivity
5. Which drug class shows a potential cross-reactivity with sulphonamide antibiotics leading to TEN?
  - a) Meglitinides
  - b) Sulphonylureas
  - c) Thiazolidinediones
  - d) DPP-4 inhibitors
6. Alpha-glucosidase inhibitors like acarbose are most often implicated in which cutaneous adverse event?
  - a) AGEP and erythema multiforme
  - b) Urticaria and angioedema
  - c) Rosacea-like eruption
  - d) Hyperpigmentation
7. Which rare but life-threatening infection is associated with SGLT-2 inhibitors?
  - a) Necrotising fasciitis of perineum (Fournier's gangrene)
  - b) Toxic epidermal necrolysis
  - c) DRESS syndrome
  - d) Kaposi's sarcoma
8. Which OHA class has been shown to induce cutaneous adverse reactions even years after therapy initiation, with a latency period up to 6.5 years?
  - a) SGLT-2 inhibitors
  - b) DPP-4 inhibitors
  - c) Meglitinides
  - d) Thiazolidinediones
9. Which of the following cutaneous effects has been linked to vitamin B12 deficiency induced by prolonged metformin therapy?
  - a) Acneiform eruptions
  - b) Hyperpigmentation over extremities and folds
  - c) Photosensitivity rashes
  - d) Morbilliform eruptions
10. Which cutaneous adverse reaction is most characteristic of GLP-1 receptor agonists?
  - a) Injection site erythema and pruritus
  - b) Stevens-Johnson Syndrome
  - c) Pigmented purpuric dermatosis
  - d) Psoriasiform rash

Answer Key

1-b, 2-b, 3-b, 4-c, 5-b, 6-a, 7-a, 8-b, 9-b, 10-a

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