



Potential skin problems of diabetes mellitus patients: a review

Iryani Andamari^{1,2*}, H. Bing Thio¹, Hardyanto Soebono²

¹Department of Dermatology Erasmus University Medical Center, Rotterdam, The Netherlands,

²Department of Dermatology and Venereology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito Hospital, Yogyakarta, Indonesia

ABSTRACT

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Diabetes mellitus (DM) is one of the common metabolic disorders, and a major part of chronic diseases, the prevalence of which tends to increase due to multifactor. Blood vessels, kidneys, lungs, and skin are among the organs that are affected. The first problem that arises, or commonly exists among one-third of diabetics, are problems with their skin, although skin lesions may develop along with the progress of the disease, or can occur during the later phase of DM. The prevalence and symptoms of skin problems in type 1 DM (T1DM) and type 2 DM (T2DM) are often unclear, and at the beginning of the course of the diseases they often go undiagnosed. Several theories regarding the pathophysiology of DM can be used as a logical reference for the early identification and diagnosis of skin problems, aimed at preventing the worsened condition. The use of skin autofluorescence (SAF) and AGEs reader in several cases of skin problems, can also be an important marker as an adjunct to predict the possibility and progressiveness of DM. Skin problems linked to patients with DM can be categorized as strongly related to diabetes, non-specific and related to DM, skin infection in DM, and skin problems due to diabetic medication. With the current COVID-19 pandemic, there are additional demands for more critical investigation of skin problems in patients with DM. The skin problems that occur in DM may need to be examined from the early stage and it is necessary to inhibit the progression of skin problems, as well as to consider the need for multidisciplinary DM therapy.

ABSTRAK

Diabetes mellitus (DM) merupakan salah satu gangguan metabolisme yang sering terjadi, dan merupakan penyakit kronis dengan prevalensi yang cenderung meningkat, dengan penyebab multifaktorial. Pembuluh darah, ginjal, paru-paru, dan kulit termasuk di antara organ-organ yang dapat terpengaruh. Masalah pertama yang muncul, atau yang biasa dialami oleh sepertiga penderita diabetes, adalah permasalahan pada kulit, lesi kulit yang terjadi dapat berkembang seiring dengan perkembangan penyakit, atau bahkan dapat terjadi pada fase lanjut dari DM. Prevalensi dan gejala gangguan kulit pada DM tipe 1 (DMT1) dan DM tipe 2 (DMT2) seringkali tidak jelas, bahkan sering tidak terdiagnosis. Beberapa teori mengenai patofisiologi DM dapat dijadikan sebagai acuan logis untuk identifikasi dini dan diagnosis masalah kulit, yang bertujuan untuk mencegah terjadinya kondisi yang semakin memburuk. Penggunaan *skin autofluorescence* (SAF) dan AGEs reader pada beberapa kasus masalah kulit, dapat menjadi penanda penting untuk memprediksi kemungkinan dan progresivitas DM. Masalah kulit yang berhubungan dengan penderita DM dapat dikategorikan berhubungan erat dengan diabetes, non-spesifik dan berhubungan dengan DM, infeksi kulit pada DM, dan masalah kulit akibat pengobatan diabetes. Dengan adanya pandemi COVID-19 saat ini, diperlukan investigasi yang lebih kritis terhadap pemeriksaan permasalahan kulit pada pasien DM. Permasalahan kulit yang terjadi pada DM perlu diperiksa sejak dini, untuk menghambat progresivitas, serta mempertimbangkan perlunya terapi DM secara multidisiplin.

Keywords:

diabetes mellitus;
skin problems;
pathophysiology;
multidisciplinary therapy;
dermopathy

INTRODUCTION

Diabetes mellitus (DM) is related to several physiological symptoms, including skin symptoms. The main symptoms of DM include increased blood sugar level and insulin resistance, more importantly, changes in glucose level.¹⁻³ Type 1 DM (T1DM) is indicated by the existence of autoantibodies circulating within the cytoplasmic protein in β cell, which causes gradual damage of β -islet immune-mediated in the pancreas, while patients with type 2 DM (T2DM) have chronic hyperglycemia, with defects in glucose, protein, and fat metabolism that are normally accompanied by an increase in insulin resistance, which is age-related, genetically predisposed, and linked to obesity.^{1,4}

The T2DM is the most common form of DM disease accounting for around 90% of all diabetes cases worldwide. It was predicted by the World Health Organization (WHO) within thirty years (2000-2030), and could be one of the highest-ranking causes of death worldwide. The WHO further predicts that DM will affect more than 21 million people of Indonesia's population in 2030. Result of an investigation on DM prevalence in Indonesia in 2018, conducted by Basic Health Research (*Riset Kesehatan Dasar/Riskesda*), there are 8.5% or around 20.4 million people suffered from DM.⁵ The International Diabetes Federation (IDF) explained that T2DM prevalence will rise from 10.3 million in 2010-2017 to become 16.7 million in 2045.⁵ According to data from the United States National Health Interview Survey, the age and sex-adjusted prevalence of T2DM in Caucasians ranges between 3.8% to 6.0%, which is lower than Asian Americans (4.35% to 8.2%) in the United States from 1997 to 2008. Asian Indians, in particular, have the highest diabetes risk. Adult DM was found in 17 percent of Asian Indians, 15% of Native Americans/Alaska natives,

8% of non-Hispanic whites, 13% of non-Hispanic blacks, and 10% of Hispanic Latinos.^{6,7} The occurrence of the pattern and the types of DM are various, with around 32% of diabetic symptoms associated with cutaneous problems.⁸ In different regions worldwide, the cutaneous involvement prevalence in T1DM and T2DM varies between 51.1% - 97%.⁹

The data are very limited regarding the correlation between the two types of diabetes in the initial conditions of skin problems without skin damage. The skin problems of people who suffer from T1DM and T2DM are often not properly or underdiagnosed, e.g. dry skin and pruritus.⁹ Possibly, there is a limited number of well-conducted investigations that have been published on this topic linking DM with skin problems.

As our body's most identifiable organ, the skin often displays the first signs of a metabolic disorder. It can also be used as an effective marker to indicate the risk of DM, as well as to determine the effectiveness of the therapy. As a non-invasive method, the use of skin autofluorescence (SAF) and AGEs reader in several cases of skin problems, can be an important marker that can be used to predict the possibility of DM and the progressiveness of the DM disease.¹⁰

Skin problems linked to patients with DM can be categorized according to the following descriptions: (1) skin problems strongly related to DM; (2) skin problems non-specific and related to DM; (3) skin infection in DM; and (4) skin problems due to diabetic medication.^{9,10} Although there are few criteria with little or limited specificity. One study evaluated 100 patients with T1DM and T2DM in Egypt, with one skin lesion at least, in a one-center cohort study, and the most common cases were cutaneous infection, followed by pruritus.⁹ Another study showed a higher rate of skin disease in T2DM vs T1DM (75.6 vs 41%), for which the differences in

lesions between diabetes types are still unknown. A similar study found further results indicating that the prevalence of skin problems was higher in patients with T2DM,⁹ and should be observed in the initial stage, without regard to the manifestations of the disease and the diabetes type.^{9,10}

This review has several purposes: (a) to remind clinicians about the DM pathology process in a concise manner, (b) to comprehend the effects of diabetes on cutaneous indicators associated with T1DM and T2DM, and (c) to demonstrate the importance to perform early-stage surveillance using a multidisciplinary method in order to prevent unintended consequences with poor avoidable outcomes.

DISCUSSION

Pathophysiology of DM on skin

Changes in skin function and clinical skin changes in patients with DM are very complex.¹¹ Briefly, some of DM mechanisms that cause skin lesions are directly from the hyperglycemia state (pathologic glucose level)/direct increase of glucose level and indirect mechanism via glycation of lipid, protein, nucleic acid, which induce the development of advanced glucose end products (AGEs) that are linked to the skin manifestations of DM.^{10,12} Formation of AGEs via several pathways further induce among others: formation of reactive oxygen species (ROS), harmful ROS clearance, which upsets the function of the intracellular matrix (ICM) and extracellular matrix (ECM) protein.¹⁰ AGEs also transform the collagen,^{10,11} usually type I and type IV which are susceptible to glycation,¹⁰ and cause the impairment of skin elasticity that can contribute to skin problems, e.g. skin aging extrinsically.^{10,11} Even though, non-enzymatic glycosylation is a normal process of aging,³ the skin of patients with DM often has signs of premature skin

aging.¹⁰ When such condition persists, it can lead to the development of a micro and macroangiopathy diabetic condition, which can cause tissue hypoxia, and ultimately will be followed by nerve damage, also neuropathy, retinopathy, and nephropathy.^{1,12}

Skin problems in DM

Generally, the cause of diabetes-related skin problems is unknown, it is most likely due to the direct effects of hyperglycemia and hyperlipidemia. However, as the disease progresses, it can cause damage to the vascular, neurologic, and immune systems, which can lead to skin problems.^{4,8,13} Skin symptoms may appear before a DM diagnosis and be due to the disease, or they can appear during the course of diabetes as a result of diabetes complications or antidiabetic treatment side effects.^{10,13} The most common skin problems in 100 patients with T2DM diabetes aged 34 to 76 years, according to one study in 2020, were fungal infections (55%).¹³ The following is a list of the most common skin problems that patients with DM face, regardless of whether they have T1DM or T2DM.

Skin problem strongly associated with diabetes

Diabetic dermopathy

Diabetic dermopathy (DD) is an asymptomatic condition, which affects a significant proportion of males, with a mean age of 50 years, also known as “shin spots”. While DD affects between 7-70% of all DM patients, actually it is not a particular lesion of the DM disease, since non-diabetic patients as many as 20% have similar lesions.¹⁴ Atrophic skin lesions as a clinical sign, involve irregular red papules or plaques that are pink to brown within 0.5-1 cm in diameter, numerous, bilateral, asymmetrical of the lower extremity, extensor surface of the

lower legs, and forearms.^{4,15} In several studies, microvascular complications have been discovered to be serious in patients with DM,¹⁴ including retinopathy, nephropathy, and neuropathy.^{4,12,15} This

disorder typically does not need any treatment and will recover on its own in around 1-2 years.¹⁶ FIGURE 1A shows a diabetic dermopathy lesion in a male patient.



A B
FIGURE 1. A. Diabetic dermopathy on right lower leg (Source: Photography Unit, Dermatovenereology Outpatient Care Clinic, Dr. Sardjito General Hospital) and B. Necrobiosis lipoidica (Source: authors)

Necrobiosis lipoidica

The pathogenesis of necrobiosis lipoidica (NL) is unknown, but changes in microangiopathy and hypoxia may be to blame. Necrobiosis lipoidica affects 0.3% of patients with DM, and women tend to develop the disease. The history of a family with DM is seen in 43% of patients with NL.⁷ The yellow appearance of the lesions in the central region is most likely due to dermal thinning, which makes subcutaneous fat more noticeable.^{14,17} Necrobiosis lipoidica is characterized by a sharply developed atrophic in the center,¹⁹ and telangiectatic plaque with a glazed appearance containing yellow-brown color, with NL that resembles granuloma annulare (GA).^{17,19} A few cases reported the risks of the change into squamous cell carcinoma.²⁰ FIGURE 1B shows the lesion of NL (before biopsy).

Acanthosis nigricans

Acanthosis nigricans (AN) is frequent in the general population, but darker-skinned people tend to have a higher prevalence, and it is higher among females than males. In some cases, increased androgen production may contribute as has been shown in other etiologies of malignancy, and is most often seen in prediabetic,¹⁵ and obese T2DM patients.^{4,15,17} Lesions appear as smooth, hyperkeratotic, velvety plaques, and hyperpigmented skin, chiefly involving folds in the body, i.e. neck, axillae, and flexures,^{4,14,15} meanwhile there is a rare case also found on acral area,¹⁸ most of the cases are linked to obesity and insulin resistance. FIGURE 2 shows AN in the neck and right axillae of a woman.



FIGURE 2. Acanthosis nigricans (Source: Photography Unit, Dermatovenereology Outpatient Care Clinic, Dr. Sardjito General Hospital).

Diabetic thick skin and stiff skin

Usually asymptomatic, this type of lesion affects the fingers and hands, as well as the back of the neck and upper back. There are three types: asymptomatic lesions, where we can calculate the thickness of the skin, clinically evident thickening on fingers and hands, and diabetic scleroderma, where we can see thickening on the fingers and hands. In a common syndrome, the skin of the upper back and posterior neck thickens noticeably, spreading to the lumbar and deltoid regions. The progression of this disorder began with stiffness in the metacarpophalangeal and proximal joints of the interphalangeal joints, as well as progressivity and reduced joint motion.¹⁴ The diabetic hand syndrome affects anywhere from 8 to 50% of diabetics, which commonly affects people more than 60 years old.²¹ Pathogenesis requires biochemical changes in dermal collagen and mucopolysaccharides. Receptors for AGE products (RAGEs) activate protein kinase C, which stimulates many inflammatory and fibrogenic growth factors and cytokines,¹⁵ while increased deposition and improper degradation of these constituents cause clinical syndromes, which are possibly linked to the formation of AGEs.^{4,21}

Diabetic bullae

These lesions usually affect older patients with DM, with more males than females, while the etiology of bullae is unclear.²¹ The lower legs and feet, as well as the hands and fingers, can be affected by non-scarring subepidermal bullae up to several centimeters in diameter on a noninflamed base, particularly on the acral area. These lesions are rare, but they are considered to be a distinct diabetes marker, which may take several weeks to recover without scarring.²¹

Skin problem non-specific and related to DM

Skin tags

According to one report, skin tags or acrochordon were related to an atherogenic lipid profile, including in cases where low levels of high-density lipoprotein (HDL) cholesterol were found. In a study of a large quantity of patients with acrochordon, 8% of them had reduced glucose tolerance, > 25% suffered from DM,¹⁴ while in another study, 57 (26%) of 216 patients with skin tags had noninsulin-dependent DM. These skin tags usually affect the face, neck, axilla, back, armpit, and trunk.^{15,17} Skin tags, which are also known as

acrochordon, appear soft, small, skin-colored or hyperpigmented and pedunculated lesions, to be a marker for diabetes, independent of obesity, women, and acanthosis nigricans.^{17,21}

Granuloma annulare

The connection between granuloma annulare (GA) and DM is weaker than the one between NL and diabetes,⁴ around 50% of NL patients have DM,¹⁹ although single lesion can resolve spontaneously.²¹ The skin lesions of GA are usually symmetrically distributed along the distal region of the extremities and sun-exposed skin, with skin-colored or red borders,¹⁶ usually with an annular lesion.^{19,21} The lesion may be generalized or localized; in diabetics, the generalized distribution appears to be more common and thought to be associated with diabetes.²¹ While a correlation between GA and DM has been proposed, no definitive evidence of such a link has been found.^{14,19,21} However, recent studies identified patients with DM account for 9.7% of patients with localized GA and 21% of patients with generalized GA. The cause of the disease is unknown.^{4,21}

Eruptive xanthoma

In patients with DM, this form of skin lesion, eruptive xanthoma (EX) is linked to high triglyceride levels,⁴ eruptive xanthomas form a crop of yellow papules with erythematous halo, and typically appear on the buttocks and extensors.^{14,21} Controlling carbohydrate and lipid metabolism have the potential to overcome these lesions.^{4,14,21}

Pruritus

There are several detailed studies about generalized pruritus,¹⁵ generalized pruritus has been reported in around 3% to 50% of patients with DM, one study observed around 25% of diabetics,^{13,17} another study of pruritus found in around 18.4% to 27.5% can be the initial symptom of DM, although without initial skin lesion.²² There are few comprehensive studies on the association with DM,¹⁷ and a recent study from Japan reported an increased prevalence of truncal,¹⁵ pruritus may be used as a marker for polyneuropathy,^{15,17} and the dysfunction of the sympathetic nerves that causes hypohydrosis and dry skin condition.²² However, there was no correlation with hemoglobin A1c (HbA1c) performance.¹⁷ Instead, uremic pruritic (UP) patients who usually have a poor glycemic control have a correlation with HbA1c.²³

Vitiligo

This pigmentary disorder, an acquired autoimmune disorder, which lacks intact melanocytes has been detected on the skin and has been observed in association with DM and thyroid diseases.^{18,24} The prevalence in the general population is around 1%.²⁴ One study conducted in 2020, among 120 subjects diagnosed with DM, there are 5.8% cases with vitiligo.²⁵ FIGURE 3A shows a case of stable vitiligo on the right hand, especially on the right acral area (right hand) of a 53 years age woman.

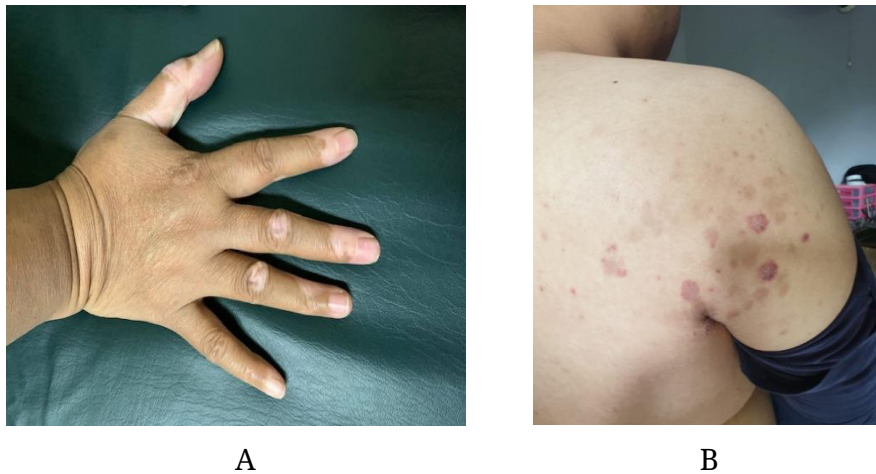


FIGURE 3. A. Acral vitiligo and B. Psoriasis in the right back of the upper arm (Source: authors)

Psoriasis

Psoriasis is a skin disorder, which can be categorized as a chronic inflammatory skin disease,^{24,26} observed in around 125 million of the population, worldwide.²⁶ Various symptoms, such as an erythematous plaque with scaly areas of the skin,²⁴ which is linked to a number of risk factors.^{24, 26} Among individuals with psoriasis, it has been discovered that there is a higher frequency condition of obesity, hypertension, and diabetes in a one cohort study,²⁶ besides the cardiometabolic syndrome it was also found that other diseases were associated with psoriasis, e.g.: bowel disease, cancer, etc.²⁷ Several studies reported that in the population, the obese people with psoriasis are around twice, while one study more specifically discovered that this prevalence was also the case for T2DM.²⁸ A retrospective cohort study in 2018 revealed that children who suffered from psoriasis tend to have a higher chance for comorbidities, have excess body weight and some have a cardiometabolic

syndrome, including DM, hypertension, etc.²⁹ Therefore, children with psoriasis, who are usually obese, have the higher risk of the development of DM in the future. FIGURE 3B shows psoriasis in the right back of the upper arm in an obese man.

Skin infection in diabetes

TABLE 1 shows the more common and serious skin infections in diabetic patients, indicating that skin infection disorders are linked to impaired glycemic control in patients with DM,^{4,14,15,21} affecting 20% to 50% of patients and are more frequent in T2DM patients,¹⁴ but both T1DM and T2DM have the risk of skin infection.³⁰ Infection is thought to be caused by a connection between hyperglycemia, neutrophil chemotaxis, phagocytes, and killer T-cells, which act abnormally,¹⁸ and can be identified as generalized immunologic defects in diabetics.³⁰ Bacteria, fungi, and yeast cause the majority of infections,⁴ which typically affect patients with uncontrolled DM.^{19,21,30}

TABLE 1. Bacterial and Fungal Infections in DM

Bacteria	Fungal and Yeast
<ul style="list-style-type: none"> • Eritrasma caused by: <i>Corynebacterium minutissimum</i> • <i>Staphylococcus aureus</i> or β-hemolytic streptococci cause condition of erisipelas, impetigo, folliculitis & others • Invasive group B streptococcus • Invasive group A streptococcus • Malignant external otitis most frequent caused by <i>Pseudomonas aeruginosa</i>, can be fatal 	<ul style="list-style-type: none"> • Caused by Candida, dermatophyte <p>The rare infections include:</p> <ul style="list-style-type: none"> • Infection by Phycomycetes cause Mucormycosis • Clostridium species cause anaerobic cellulitis • Caused by Dermatophyte: <i>Trichopyton rubrum</i>, <i>Trichopyton mentagrophytes</i>, <i>Epidermophyton flocosum</i>

One study on helminth infection and DM was undertaken in Indonesia, which took place in a semi-urban coastal area of Nangapanda, a sub-district of Ende District of Flores Island, Indonesia. This region has been found to be endemic for soil-transmitted helminth (STH) infections in previous studies. The research looked at how helminthiasis affects insulin resistance. The study examined the relationship between worm infection status, immune condition of the people, and metabolic factors, with the connectivity of whole-body metabolic condition and inflammation to be established.³¹

Another study revealed that Helminth-derived antigens present, therefore possible novel therapies to treat obese people and obesity with the connection of the metabolic diseases i.e.: insulin resistance and T2DM through the induction of several protective mechanisms. In the conclusion, filarial infection and antigens would protect against the onset of T1DM and reduce diet-induced insulin resistance. Identification of those regulatory mechanisms, as well as helminth-derived products that cause them, may provide a powerful tool for combating autoimmune and metabolic diseases, which are becoming a growing public health concern.³²

Skin problems in DM in connection with COVID-19 infection

Corona virus disease-2019 (COVID-19) pandemic that has occurred since the beginning of 2020, has drawn more attention to the need for more serious treatment of patients with DM, which is possibly linked to skin problems. COVID-19 is a viral infection that causes severe acute respiratory syndrome (SARS-CoV-2). It is important to consider that there are strong associations between acute and chronic inflammation, the receptors, and the pathogenic association between DM and COVID-19. One example of association is that chronic hyperglycemia causes chronic complications of diabetes.³³

The COVID-19 infection exacerbates the stress of DM by releasing glucocorticoids and catecholamines into the bloodstream, causing glycemic regulation to deteriorate also there is an increase in the formation of AGEs in many tissues, as well as a worsening prognosis.³³ According to recent research, aging patients who have DM, are at higher risk to contract COVID-19, and have a higher mortality rate.^{33,34}

In order to understand the pathomechanism of SARS-CoV-2 on diabetic skin comorbidity, it is crucial to

prevent and treat the difficult conditions of the skin and soft tissue problems in COVID-19 in patients with DM.^{33,34} Among aging patients with DM, chronic ulcers and diabetic foot are two examples of complications of skin problems and soft tissue which are frequently found. The possible pathomechanism of SARS-CoV-2 is currently unknown, despite some research findings. Researchers have speculated that the pathomechanisms can be: a lack of blood glucose control, which SARS-CoV-2 causes blood glucose instability; increases an angiotensin-converting enzyme-2 (ACE2). Expression of ACE2 (found in skin, tissues, lungs, and other organs), which can predispose people with diabetes to become infected with SARS-CoV-2, possibly influencing tissue that expresses an ACE2, such as skin; then, impaired angiogenesis: the occurrence of leukopenia and thrombocytopenia, as well as an increase in D-dimer levels in DM patients with ischemia and hypoxia condition; and SARS-inflammatory CoV-2's response, and cytokine storm can distress the response of inflammation in patients with DM, intruding the normal skin and soft tissue microenvironment.³⁴

The skin signs of SARS-CoV-2 infection according to one study with 375 sample cases, are in the form of vesicular eruption that appears in the initial stage of the disease, and tend to be a specific sign.³⁵ Covid-19 presents many aspects in the skin, of which the specific manifestations have connections with the severity of the disease.³⁶ The manifestations can be classified into: vesicular eruption as described above; urticarial lesions, maculopapular eruption, livedo or necrosis,³⁵ exanthematous eruptions, and acral purpuric nodule resemble to idiopathic perniosis (chilblains), which can also be a specific symptom in the later stages.³⁶ A study about skin manifestation of Covid-19 explains that there are differences in morphology

and prevalence of skin manifestations in COVID-19. Among Europeans, pseudo-chilblains were the most common skin manifestations of COVID-19, but only once reported in Asia. However, understanding the scientific skin manifestations in patients with COVID-19 is still evolving.³⁷

Skin problems due to diabetic medication

Insulin injection

Insulin injections under the skin are linked to a variety of localized changes. Lipohypertrophy is the most typical case of the local adverse effect of insulin injection, affecting approximately 30% of diabetic patients who use insulin injection, in the injection site,²⁴ liposuctions on this site may have a satisfactory cosmetic result.³⁸ However, lipotrophy is less common in DM patients with regular insulin injection,³⁸ but more common in young women who suffered from diabetes.²¹ Skin lesions are mostly found where insulin is injected. The reaction can be quick (a few hours) or delayed (within a day), and appear as a local allergic reaction e.g.: erythema, induration and pruritus, as well as a systemic reaction.^{21,24,38} Such subcutaneous allergic reaction to insulin is quite rare with only 1% of DM patients with insulin medication,²⁴ and with the introduction of new insulins, cutaneous adverse reactions tend to decrease.³⁸

Oral medications

Several oral diabetic medications can cause cutaneous adverse drug reactions in particular patients, even though this is a rare case.^{24,39} There are first and second generations of sulfonilurea. The first-generation sulfonilurea has brought more cutaneous reactions and photosensitivity reactions. Possible cutaneous reactions are linked to sulfoniluria treatment,

including: urticarial, generalized erythematous reactions, photosensitive reactions, and a lichenoid eruption.^{21,24} It is also reported some cases of pemphigus vulgaris and psoriasiform are related to drug eruption,²¹ as well as erythema multiforme, and exfoliative dermatitis, specifically due to the therapy of sulfonyleurea, such as glibenclamide.^{21,39} Even though, in another study almost 83% of patients who used metformin alone have mild to moderate eruption without severe adverse drug reactions.⁴⁰

CONCLUSION

The prevalence and symptoms of skin problems between T1DM and T2DM remain unclear, and at the beginning of the course of the disease, they often go undiagnosed. Several theories regarding the pathophysiology of DM can be used as a logical reference for the occurrence of skin problems. The differences in DM prevalence among ethnicities are linked to dietary habits and other factors, including lifestyle. Skin lesions found in diabetics are directly from pathologic glucose levels and indirectly via glycation of lipid, protein, and nucleic acid that induced the development of AGEs. The stability of those conditions demands proper control, when the skin elasticity is reduced and appears some signs of premature aging. If the symptom persists, then several damage signs will appear in the form of micro and macroangiopathy, even worse organ damage. The skin problems that occur in patients with DM may need to be examined from the early stage and it is necessary to inhibit the progression of skin problems. In addition, the benefit and importance of multidisciplinary DM therapy are worth considering in order to prevent a worsening condition. Due to the COVID-19 pandemic, serious attention should be given to DM patients' skin conditions. Skin symptoms may appear prior to the diagnosis of DM, and

persist along with the progression of the disease, or they can appear during the course of diabetes as a result of diabetes complications or antidiabetic treatment side effects. Therefore, future studies will be necessary to involve multi and interdisciplinary approaches.

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