CLINICAL DERMATOLOGY: RESEARCH AND THERAPY Open Access

SCIENTIFIC LITERATURE

REVIEW ARTICLE

Diabetes and the Skin

Elisabetta Iacopi*, Nicola Riitano, Alberto Coppelli, Chiara Goretti and Alberto Piaggesi

Diabetic Foot Section, Pisa University Hospital, Italy

ARTICLE INFO

Article history:
Received: 30 May 2018
Accepted: 31 August 2018
Published: 05 September 2018

Keywords:
Diabetic dermopathy;
Diabetic foot ulceration;
Reactive oxygen species;
Advanced glycosylation end products;
Diabetes mellitus;
Insulin-like growth factor 1

Citation this article: Iacopi E, Riitano N, Coppelli A, Goretti C, Piaggesi A. Diabetes and the Skin. Clin Dermatol Res Ther. 2018; 2(1):120.

Correspondence:
Elisabetta Iacopi,
Diabetic Foot Section, Pisa University Hospital, Italy,
Tel: 00393497341970;
Fax: 0039050997468; Email: elisabettaiacopi@gmail.com

ABSTRACT

The prevalence of diabetes mellitus constantly increased during last year's reaching impressive figures and next decades will reserve to us a further escalation. Developing countries, until now almost spared from this pandemia, will become the centre of new disease development and younger groups of population will observe their already reduced life expectancy reduced further. World Health Organization has therefore identified diabetes mellitus, among non-communicable disease, the emergency of the new millennium.

The development of chronic diabetes complications represents today the first cause of death in diabetic patients. The common pathway which led from chronic hyperglycaemia to organic damage both in micro and in macro-vascular districts, acts ubiquitously, damaging thus all body structures. Main targets of this mechanism consisting in heart a cardiovascular system, brain and nerve structures, kidneys and eyes. The developing pathway, as such as the therapeutic options for these complications have been object of diabetological studies during past decades and today had reached a good level of knowledge.

Much less is known today of skin damage mechanisms associated with diabetes. In fact in common clinical practice the knowledge regarding skin disorders diabetes-related is limited to diabetic foot syndrome or, sometimes, to the increased risk of skin cancer which affects diabetic patients. Indeed skin disorders involve one out of three of all diabetic patients often representing one of the first signs of the disease. The skin, representing the largest organ of our body, is an important target for complication development. In this review we will try to investigate the different and less known aspects of skin disorders related to diabetes mellitus.

Introduction

The prevalence of diabetes mellitus constantly increased during last years reaching impressive figures resembling the size of a pandemia [1]. In 2010 the World Health Organization estimated a prevalence of about 12% among adult population but wide recent epidemiological projection studies made by the International Diabetes Federation forecast that in 2040 one adult every 10 will suffer from diabetes [2]. During next decades we will observe also deep changes in the worldwide distribution of the disease that will involve the developing countries and younger age groups [3]. For all these reasons diabetes has been the only non-communicable disease identified by World

Health Organization, alongside to malaria and tuberculosis, as the health emergency of the new millennium [4].

While, until first half of the last century, the major concerns about diabetes were related to the acute complications of the disease, the increase in life expectancy of the diabetic patients put the emphasis on the longer duration of the disease [5]. Diabetes, from an acute illness, became a chronic invalidating disease associated with a huge consumption of resources in economic and human terms [6]. Diabetes represents nowadays the first cause of not-traumatic lower limb amputation and blindness, the second cause of renal failure and is strongly associated to more than half of myocardial infarction and stroke [7]. Epidemiological data derived from disease registers showed how, in Italy, the patients with diabetes suffer from a myocardial infarction every 7 minutes, from a stroke every 30 minutes and undergo to an amputation every 90 minutes. These complications are able to determine an estimate reduction in life expectancy of an average of seven years [8].

This becomes even more alarming considering how about a third of these subjects are not aware of the disease. The lack of consciousness of their real conditions causes diagnostic delays and referral for specific care [9]. This in turn results in a worsening of the chronic complications which are negatively affected by poor metabolic control [10].

Diabetes represents a paradigmatic example of systemic multifactorial disease. Chronic hyperglycemia, through many pathogenic pathways, determines the development of chronic complications ubiquitously, damaging thus all body structures [11]. The skin, representing the largest organ of our body, is also a target for complication development. Damage mechanisms which lead to complications are well known and start from chronic hyperglycemia [3]. It led to not enzymatic glycosylation of skin protein with production of Advanced Glycosylation End Products (AGEs), to an increased production of Reactive Oxygen Species (ROS) and eventually to disturbances in nitric oxide (NO) balances [12]. These same mechanisms acts to develop skin complication, in particular the increased levels of AGEs seems to play a crucial role in this district [13]. In fact structural skin proteins, such as collagen, undergoing to glycosylation, loose their elasticity and become insoluble and resistant to degradation and turnover. In the very same contest also polyneuropathy and macroangiopathy exert their effects on the skin [14]. Neuropathy determines a reduction in sensitive innervation, which is present since the first years after diagnosis of diabetes [15]. Microvascular tree instead shows structural and functional disturbances on the skin [16]. Regarding the structure it determines homogeneous thickening of the basement membrane and of the walls of small-caliber vessels and increased space between endothelial cells and pericytes in post-capillary veins. The action on skin function is focused on increasing capillary permeability and basal pressure values instead [17]. In addition to this, the direct metabolic influences on skin pattern like hypertriglyceridemia, hyperinsulinemia or insulin resistance can create some skin impairment such as xanthomas or acanthosis nigricans [18].

Skin disorders can be diagnosed in one third of all diabetic patients, and they frequently occur before diagnosis and can be useful for the recognition of the underlying disease [19].

The aim of our review was to create an overview of all possible skin disorders reported in diabetic patients and todifferentiate among the different clinical pictures. To do this we searched for all published paper regarding skin in diabetics and selected those referred to skin pathologies. Diabetic foot syndrome represents the most common and disabling disorder regarding skin structure in diabetic patients; therefore a skin review cannot disregard its consideration. Despite this we tried to focus and to deal in depth with skin disease different from diabetic foot, less known and less suspected by clinicians at first approach with patient. To be as systematically as possible we divided skin disorders in six different areas, reported below, according to the amount of published literature and inside each area we searched for published paper and selected among those.

From a systematic point of view, as yet reported, the cutaneous impairment detectable in diabetic patients can be divided in six wide chapters:

1. Skin manifestations of diabetes
2. Cutaneous disorders associated to diabetes
3. Cutaneous infections
4. Complications of anti-diabetic treatment
5. Diabetic foot ulceration
6. Skin cancer [20].

Skin Manifestations of Diabetes

1. Necrobiosis lipoidica

Necrobiosis lipoidica is a chronic granulomatous skin disease. It is relatively uncommon, the prevalence ranges from 0.3 to 1.6% in diabetic patients and it is one of the most disabling skin complication of diabetes [21]. Although it may occur in any type of Diabetes Mellitus (DM), it is more frequent in type 1 diabetes; it has female gender predominance and its onset is usually in the 3rd or 4th decades [22]. The association of necrobiosis lipoidica with diabetes is a double way one. In fact not just diabetic patients presents an higher risk of necrobiosis but also patients suffering from skin disease has an increased risk, estimated of around 22%, to be glucose intolerant yet or to develop DM in the consequent 10 years [23].

The disease is characterized by small erythematous papules which evolve slowly and enlarge into the typical lesions: well-demarcated indurated plaques with yellow-brown atrophic centres and telangiectasia surrounded by narrow red-brown or violaceous borders. The lesions can be located on lower extremities, typically on pretibial areas and bilaterally; less frequent patterns involve the face, trunk and upper extremities [24]. Usually the disease is asymptomatic, sometimes there is pruritus orpain. This secondary ulceration can led to bacterial infection or, very rarely, to the development of squamous cell carcinoma and, however, usually the healing happens through the creation of atrophic scars [25].

The pathogenic mechanisms are still quite unknown although several theories have been suggested. Collagen matrix could be destroyed by synergistic actions of micro-angiopathy, neuropathy and impaired immune mechanisms [26]. The resulted cytokines cascade creates and maintains a chronic inflammatory environment resulting in sclerosis and granuloma formation. The yellow aspect could be related to an excess of lipid deposition [27]. The final diagnosis can be made during histologic exam, in differential diagnosis with anular granuloma: necrobiosis is in fact characterized by presence of poorly differentiated histiocytes in both medium and deep dermis together with PAS positive coloration and vascular impairment such as endothelial oedema, fibrosis and hyalinization [28].

2. Annular granuloma

Annular granuloma represents a relatively bening, self limiting condition consisting in red or flesh-coloured papules roundish and usually located on the dorsal surface of the feet, hands or joints [29]. In the natural history of the disease the lesions, usually asymptomatic, expand and centrally involute, creating rings with raised borders. The lesions may frequently recur [30].

Although several authors identify many different pattern of disease: the most frequent are a localized form and a generalized form respectively. The first one, interesting the lower part of the body, usually starts before the age of 30 and resolves in two or three years. The generalized form starts usually later and the spontaneous healing is unfrequent [31].

The disease has an immunologic origin, generally associated to a type IV hypersensitivity reaction. The histological findings show in fact lympho-histiocytic palisades with mucin deposition and altered collagen in the centre of the granuloma [32].

The association between annular granuloma and diabetes is still controversial. While the generalized form appears to be strongly related to diabetes, the evidence remains poor for the localized pattern of disease [33]. Other possible risk factors are hepatitis, HIV and neoplasia [34]. Despite this, exactly as said for Necrobiosilipoidica, subjects presenting this cutaneous complication have a very high prevalence of diabetes. ThereforeAnnular granuloma represents a real alarm

bell that should suggest to perform a glycometabolic profile assessment [35].

3. Bullosis diabeticorum

The disease is represented by the acute and abrupt onset of tense, painless, serous blisters on lower extremity, typically on feet. The blisters size ranges from few millimetres to many centimetres and the inner fluid is usually serum, while only rarely the blisters can be complicated by infection or bleeding thus becoming haemorrhagic [36]. It usually onsets during the sleep and evolves to complete healing in 2-3 weeks. In rare cases, especially when located on the foot, the blisters may present secondary ulceration and infection [37].

By definition, all patients suffering from bullosis diabeticorum are affected by diabetes. The prevalence is higher in type 1 male patients, especially if affected by evaluated complications, and the mean onset age ranges from 50 to 70 years [38].

The pathogenic mechanism are still not completely clarified although many mechanisms have been proposed such as minor trauma, high variability in plasma glucose concentration, alteration in calcium or magnesium metabolism, and UV exposure. None of the proposed mechanisms explain independently the pathogenic cascade [39].

The microscopic findings distinguish the disease into two great groups related to different localization of cleavage. The first group is composed by the intraepidermal lesions, where the cleavage takes place at lamina lucida, without acantholysis [40]. This lesion solve spontaneously and rapidly, without creation of a scar. The second group is composed by dermis-epidermal junction lesions, related to destruction of anchoring fibrils and healing by a scar [41].

4. Scleredema diabeticorum

Scleredema diabeticorum has to been considered in the context of scleredema adultorum. It is a rare connective tissue disorders, characterize by hardened, non-pitting oedema, localized on upper back, neck and shoulders, extended just occasionally on face, arms, chest and abdomen [42]. The skin involved is hard, thick and sometimes can take and aspect similar to cellulitis. It is usually asymptomatic although the increased thickness can determine reduced joint mobility or pain [43].

The origin seems to be associated to the elevated plasma glucose levels; the generalized form can be associated to other disease such as cancer, paraproteinemias or infections. The prevalence ranges from 2.5 to 14% of diabetic patients and affects especially men – prevalence in male is about 10 times prevalence estimated in female – with long duration of disease [44].

The pathogenic mechanism consists in impairment in collagen metabolism with increased production by fibroblasts and reduced degradation. Diagnosis can be done with full thickness biopsy which reveals thickened reticular dermis and collagen bundles and mucin infiltrate in dermis, without oedema or sclerosis [45].

5. Acanthosis nigricans

Acanthosis nigricans is characterized by the presence of velvety to verrucous thickening of the skin, mainly located in axilla, groin and nape. The plaques appear diffuse, hyperpigmented and the colour ranges from light brown to black. The lesions are usually asymptomatic despite sometimes they might be painful or macerated [46].

Two different forms of the disease have been identified: a benign one, which is the one associated to diabetes, and a malignant form, which occurs as a paraneoplastic syndrome, related to underlying carcinoma, typically adenocarcinoma of the stomach [47]. The benign form, which accounts for 97% of the total, is considered a marker of insulin resistance [48]. It originates from a complex interaction between hyperinsulinemia and insulin resistance which acts through the Insulin-Like Growth Factor 1 (IGF-1) [49]. Its receptor is in fact exposed on the cell membrane of keratinocytes and fibroblasts and the binding with IGF-1 stimulates epidermal cell proliferation. In presence of a very high concentration of insulin, like in many forms of insuline-resistance, the hormone, whose structure is similar to IGF-1, binds with the receptor (Spillover effect) stimulating the proliferation of the basal strata of the epidermis (Keratinocytes) and of the dermis (Fibroblasts). The same abnormality is present also in other endocrine conditions

associated to insulin resistance such as polycystic ovarian syndrome, Cushing or Addison disease and Acromegaly [50]. Occasionally the disease can be located on multiple insulin injection sites. The association with diabetes is such that the occurrence of acanthosis should drive physicians to perform screening to correctly diagnose diabetes [51].

Hystologically acanthosis appears as a lesion characterized by hyperkeratosis, epidermal papillomatosis and acanthosis. The hyperpigmentation is related to a thickening keratin-containing epithelium and is not due to an increased in melanin content [52].

6. Eruptive xanthomas

Eruptive Xanthomas consists in 1-4 mm yellow-red papules with an erythematous halo mainly located on eyelids, extensor surfaces of arms and legs and buttocks. Xanthomas are real skin deposits of very-low density lipoproteins and chylomicrons due to hypertriglyceridemia [53]. Histological analysis shows the presence of foam cells filled of triglycerides mixed with lymphocytes and neutrophils infiltrate in the dermis [54].

In normal condition, the normal clearance of triglycerides is warranted by the activity of Lipoprotein lipase [55]. During a chronic glycometabolic impairment, a double mechanism of blockage acts on the enzyme level: from one side the reduced level of insulin does not exert the normal stimulus on lipoprotein lipase activity; on the other side the increased blood glucose levels promote very low density lipoprotein liver production [56].

Recognizing xanthomas can allows to diagnose hypertriglyceridemia, thus avoiding the serious complication of this condition, such as pancreatitis [57]. But the identification of this skin condition may be essential also to allow diagnosis of diabetes [58].

7. Diabetic dermopathy

Diabetic Dermopathy (DDP) is a dynamic process in which multiple lesions co-exist at different stages of evolution: the disease origins with the occurrence of red or pink papules or plaques typically on pretibial region but also on forearms, thighs and lateral malleoli. Initial stage can be misdiagnosed as a dermatophytosis. Two weeks after occurrence the lesions change and become a well defined atrophic brown macule. Different lesions can be contemporarily present at different stages of evolution. The lesions solve spontaneously, usually leaving a slightly depressed area [59].

DDP is typically present in diabetic men with long duration of disease and poor glycaemic control. The mean age at onset is about 50 years. If the association with diabetes is well known, during recent years the clustering with other diabetes chronic complications have been demonstrated. The incidences range therefore from 7% in general population, to 52% in diabetics without microangiopathy, to 82% in patients suffering from multiple chronic microvascular complications [60].

Histological analysis is varied, from the first stages in which we observe epidermis oedema and perivascular lymphohistiocytic infiltrate, to the later stages, characterized by thickened dermis blood vessels and hemosiderin deposits [61].

The etiopathogenetic mechanism, not well defined, focused on micro-angiopathy associated to unrecognized trauma [62].

8. Rubeosis faciei

This condition has been described for long time as one of the most common skin disorders related to diabetes. It consists in chronic flushing on face and neck. Several studies investigated the real prevalence of the impairment, not reaching conclusive data though, while the reported prevalence ranges across values quite different [63].

Although the condition represent a benign alteration, usually asymptomatic, its detection is extremely relevant because it is usually associated with chronic microvascular complication of the disease related to sub-optimal diabetes control, typically retinopathy [64].

9. Carotenemia: Yellow skin and nails

Carotenemia is a condition characterized by discoloration of skin and nails with a strong increased prevalence in diabetic patients [65]. The patients develop a yellow diffuse hue on skin, particularly on palms and soles, and nails. Also mucous membranes can be involved but the differential diagnosis with jaundice is allowed by the sclera, which is spared. The condition is benign and asymptomatic [65].

There are two main compounds probably responsible of the yellow colour: Beta-carotene and 2-fluoro-1-imidazole, an advanced glycosylation product which is known to have a typical yellow hue [66]. In the first one the accumulation coulderived from diabetic diet rich in fruit and vegetables. In this case the excess of Beta-carotene is quite difficult to detect because it is sequestered in skin or nails and therefore not evaluable in blood [67].

10. Acquired perforating dermatoses

Under the name of acquired perforating dermatoses are classified a number of skin lesions related to trans-epidermal elimination of a connective tissue component [68]. According to the different microscopic pattern related to the main component loss it can be identified four different types of disease: *elastosis perforansserpiginosa, reactive perforating* **4.10.1. Collagenosis, Kyrle's disease and perforating folliculitis [69]:** The skin lesions are hyperkeratotic nodules or papules with a central depressed plug and an adherent crust typically located on extremities, trunk and sometimes head [70]. The patient can complain pruritus. Histologically the pattern shows hyperkeratosis, spongiosis, elastic fibers and extruded collagen [71]. The disorder is almost exclusively found in diabetes or renal failure. Just sporadic findings have been reported in malignancies, hepatic disorders, AIDS and hypothyroidism [72].

Regarding the causative pathway, it is still unknown if the impairment is primarily in dermis or in epidermis [73]. There are several proposed theories regarding the pathogenic mechanisms: metabolic derangement leading to dermis-epidermal alterations, deposition of waste products of various metabolic processes and eventually microtrauma associated to micro-angiopathy or to scratching [74].

11. Acrochordons

Acrochordons or skin tags are soft fibromas, exophytic growths which range from 1 to 6 mm in diameter and form small papules and pedunculated polyps. They can be flesh-colored or hyper pigmented and can be observed on eyelids, neck, axilla or other location such as infra-mammary or inguinal regions [75]. They are usually asymptomatic but they can create discomfort because they containing nerve cells. Histological findings show papillary-like dermis with collagen fibers and vasculature [76].

The lesions are more prevalent in females and the association with diabetes is demonstrated, although in recent studies it seems that the only location really strongly associated with diabetes is represented by infra-mammary region in women [77].

Cutaneous Disorders Associated to Diabetes

1. Psoriasis

Psoriasis consists in a relatively common chronic inflammatory disease. It is primarily located on skin but often presents systemic associated manifestation, such as arthritis [78]. The disease shows in the form of patches or red plaques, covered by whitish scales and located mainly in the knees, sacral region, elbows, hands, feet and scalp [79].

The worldwide prevalence of the disease has been estimated around 2% and wide epidemiological studies have demonstrated an increased risk of psoriasis in autoimmune diseases [80]. On the other side, psoriasis represents itself a strong risk factor for developing diabetes, doubling the likelyhood [81]. This is not surprising, considering that inflammatory pathways can be the root of both disease and that psoriasis and diabetes recognize some common risk factors: obesity, hypertension, smoking habits and insulin resistance [82]. Basic science research has provided some explanatory mechanisms for this association in immune-mediated inflammatory cytokines pattern or in leptin and adiponectin production [83]. Eventually some human major histocompatibility candidate genes have been associated with both diseases, although their exact role in the pathogenic cascade is still unknown [84].

2. Vitiligo

Vitiligo consists in a well delineated loss of skin pigmentation, usually in a spotted manner and with a symmetrical distribution. It is a chronic, acquired disease and is generally quite easy to diagnose involving extremities, face and neck, but also trunk [85]. The disease origin from a selective destruction of

melanocytes, despite the primum movens of the disease is still quite debated. Reduction in amount of skin melanocytes and loss of their function are both involved phenomena and are both associated to cell-mediated autoimmunity [86]. It affects about 0.1-1.5% of people worldwide. This incidence increases rapidly in type 1 diabetic patients reaching 8-10%, such as in other autoimmunity endocrine disorders, like thyroiditis [87]. Although the disease does not create severe physical impairment, it can be associated with mental impairment and heavy reduction in quality of life of such patients, due to defacing appearance [88].

3. Lichen planus

Lichen planus is an immune-mediated disorder associated to T-cells impairment [89]. The clinical typical finding is represented by polygonal pruritic violaceous papulae located generally on ankles and wrists [90]. Mucosae involvement is optional and if present it usually consists in white patchy plaques on oral mucosa or on tongue [91]. It has been associated with C hepatitis infection and, according to an increasing number of authors, to type 1 diabetes. Currently the prevalence of association between the two disease ranges from 10 to 37% in different studies [92].

Cutaneous Infections

Diabetes represents one of the most important condition of immunodeficiency [93]. The normal reactions of immune system are deanged thus making the organism unable to defend itself from the external insults [94]. Moreover skin pH is higher in diabetic patients with a consequent further reduction in ability of defence [95]. Diabetic neuropathy and angiopathy further increase the subject's susceptibility to external agents [96]. And the possibilities of patient to fight against infection are still reduced in case of poor glycaemic control [97]. If the association of all these cutaneous infection with diabetes is well known, recent evidences have demonstrated how their incidence both evaluated in general population and in diabetics, was directly related to mean blood glucose levels [98].

Skin infections, among all skin manifestations, represents the most important diagnostic markers for the presence of diabetes. Their presence allows diagnosing diabetes in a high percentage of patients suggesting this possible link to general practitioner [99].

1. Bacterial infections

The most frequently responsible bacterial agent in skin infection in diabetic patients are surely *Staphylococcus Aureus*, often resistant to Methicillin, and *Streptococcus species*, tipicallyβ-Hemolyzing of Group A. Those are Gram positive micro-organisms [100]. The first one is generally responsible of *folliculitis*, *abscesses* or *impetigo*. Folliculitis consists in small pustules located on the root of hair follicles and generally can be controlled through systemic antibiotic therapy. *Abscess* is a localized purulent material collection which requires, besides to antibiotic treatment, a surgical drainage to avoid further spreading [101]. *Impetigo* is eventually a superficial infection, which can be also associated to Streptococci and can be localized to a body region or diffuse. The lesions are characterized by yellow-crusted erosion with blistering [102]. In case of diffuse impetigo it will be necessary in most cases the use of parenteral antibiotic treatment [103]. Streptococci infections are instead usually responsible of *ecthyma*, *erysipelas* or *cellulitis*. *Ecthyma*, typical of warm countries, is composed by a small ulcer clearly defined by healthy tissue through an erythematous border [104]. *Erysipelas* and *cellulitis* represent instead a local-systemic disease: warm erythema well defined associated to systemic infection signs such as fever, leucocytosis and compromised general state [105]. Eventually both Staphylococcus and Streptococci can be responsible for *Necrotizing fasciitis*. This life-threatening condition starts in a subtle way with erythema, hardening and cyanosis and fastly progress towards necrosis and blisters [106]. This condition, if not promptly surgically treated, is associated with mortality rates higher than 90% [107].

Another typical bacterial infection in diabetic patients is represented by *Erythrasma*. This is caused by *Corynebacterium minutissimum* [108]. It consists in a superficial skin infection characterized by well defined red or brown scaly patches located in inguinal and crural area, or in inner thighs. It is usually asymptomatic,

sometimes associates to pruritus, and its incidence is strongly associated not only with diabetes, but also with obesity or smoke habits [109].

Eventually a great number of skin infections in diabetics are associated to *Pseudomonas aeruginosa* [110]. While commonly skin and nails infections due to Pseudomonas are usually of poor clinical relevance, it determines a rare malignant otitis externa that starts as a normal otitis may develope as chondritis, osteomyelitis and encephalitis [111]. It is more common in elderly patients with high levels of comorbidity and is associated to extremely high mortality levels [112].

2. Fungal infections

The most common fungal infection in diabetic patients is represented by *Candida* infections. This infection can be a marker of undiagnosed diabetes or the first clinical presentation of the disease [113]. Its incidence is directly related to glycometabolic control, considering that poor level of cell-immunity and a worst microcirculation increase the patient susceptibility to this kind of infection [114]. Furthermore the microorganism is particular dependent to glucose consumption, thus that higher glucose levels create an environment particularly favourable for its development [115]. The typical clinical pictures are represented by angular stomatitis, more common in younger patients, paronychia, intertrigo and inter-digital erosion known as *erosion interdigitalisblastomycetica* [116]. Some clinical presentations of Candidias are tipicaly associated to new diagnosis of diabetes, male or female specific. Male specific infections, typically balanitis, phimosis or balanoposthitis, are typically associated to *Candida Albicans* or *Candida Parapsilosis* [117]. In female diabetic patients it can be observed an increased prevalence of vulvo-vaginitis [118].

In addition to *Candida species*, diabetic patients can complain an increased risk of other fungal infection, first of all Dermatophytes [119]. This condition is associated to a group of 3 strains of fungi (*Tricophyton, Microsporum and Epidermophyton)* and can cause hair, skin and nail infection. While in Candida the association with diabetes has been strongly demonstrated, in this case the data are less clear [120]. Despite this skin infection, due typically to *Trochophytonrubrum* and Tinea Pedis, better known as *Dermatophytosis of the foot* have however a double prevalence in diabetic patients versus not diabetics [121].

Onychomycosis, associated both to Candida and to Dermatophytes, have been reported in slightly less than half of all diabetic patients and in epidemiological studies the prevalence is about four times the prevalence in healthy subjects, and increases with age and male sex. It includes sub-ungueal hyperkeratosis, distal onycholysis, and yellow discoloration and nail dystrophy [122]. Nail infection can be controlled by correct and regular toenails and their danger is associated to the possibility to provide a *locus minorisresistentiae* for the entry of bacterial strains, hazard to be absolutely avoided in diabetic patients [123].

Fungal infections are eventually able, especially in elderly diabetic patients suffering from high levels of comorbidities, to generate opportunistic infection, usually due to *Mucor species* or *Blastomyces* [124]. At skin level infection shows usually small pustules or little non-healing abscesses. The non cutaneous symptoms are generally characterized by ocular pain, nasal congestion, more rarely fever. They mayrepresents sometimes the fatal infection in severely compromised patients. Aggressive treatment is necessary to avoid blood dissemination of the infection [125].

Complications of Anti-Diabetic Treatment

1. Skin reactions due to insulin

Subcutaneous prolonged administration of insulin treatment can be associated with a number of skin reactions: *lipohypertrophy*, *lipoatrophy* and *insulin allergy*. *Lipohypertrophy* is the most common reaction to treatment in insulin treated diabetic patients. It affects around 2% of diabetics and its prevalence and severity are strongly associated with number of daily injections and can be reduced by the use of subcutaneous insulin pumps or by rotation rules of insulin administration which teach to the patients to frequently change the site of puncture [126]. The disease is characterized by dermal nodules quite similar to lipomas due to the lipogenic action of insulin which activated adipocytes [127]. The

problem is not just aesthetical, because the hypertrophic areas do not allow a normal absorption of insulin, thus confounding the efficacy of treatment and increasing hypoglycaemic risk [128].

On the other hand, *lipoatrophy* is characterised by a block in adipocytes function which leads to atrophy in subcutaneous tissue around the insulin injection site [129]. The pathophysiologic mechanisms are still unknown, but probably associated to an inflammatory mechanisms activated by vascular deposits of immune globulins [130]. Also in this case the incidence has been reduced by the introduction of insulin analogues and can be further reduced by using continuous subcutaneous insulin injection pumps [131]. However recently there have been reported cases of lipoatrophy in patients using insulin pumps with *lispro* analogue [132].

Eventually the most dangerous reaction observable after insulin injection is the *insulin allergy*. It may range from local to systemic reaction [133]. After the introduction of insulin analogue, less allergenic, the prevalence of such reaction has collapsed reaching the level of 1% [134]. The reactions are usually based on an immunologic mechanism and can be immediate, due to Ig-E released, or delayed [135]. A local reaction usually consists in hives or erythema with papules or vesicles and pruritus at injection site; systemic manifestations can involve urticaria, angioedema, palmar or plantar pruritus and generalized flushing. Luckily life-threatening systemic reactions with dyspnoea and hypotension are very rare [136].

2. Skin reactions induced by oral antidiabetic drugs

Sulfonylureas have been associated with systemic cutaneous reactions with a prevalence ranging from 2 to 5% [137]. Those reactions occur more frequently and more severely in first generation sulfonylureas users and are usually characterized by erythema multiforme, vasculitis, flush or photosensitivity reactions [138]. Milder erythematous reactions have been reported, although extremely rarely, also after administration of metformin [139] or acarbose [140].

Diabetic Foot Ulceration

Diabetic Foot Ulceration (DFU) represents the most important skin and soft tissue manifestation related to diabetes [141]. The disease is the final result of a long process which starts from chronic hyperglycemia and that progress to functional and anatomic involvement of different systems [142]: nervous, vascular and immune systems are all co-interested and create the conditions for the development of the ulcerative lesion with the causative role of unaverted trivial traumas [143].

The risk for a diabetic patient to develop a foot ulcer throughout life ranges from 15 to 25% according to different studies [144]; about one out of three of these lesions will not reach healing [145], the ulcer will became a chronic, worsening disease, especially in case of concomitant infection or ischemia [146]. 85% of lower limb amputation in diabetics is preceding by an ulcer and diabetics present an overall relative risk of amputation approximately 30 times that of the general population. This means that diabetes causes on planet Earth one amputation every 20 seconds and 4000 amputation per day [147].

But diabetic foot does not consist just in such dangerous disease; it represents furthermore a severity index for other chronic complications of diabetes [148]. It should be considered, moreover, as a cardiovascular risk factor itself. Death risk at 5 years in a diabetic foot patient is 2.5 times that of diabetic patients which had never suffered from foot complications [149]. And this discrepancy remains also if we consider a longer follow up: at ten years the death risk is double in diabetic foot patients. Considering that about one out of five of these lesions will require a surgical intervention the risk increases again: death risk at five years in subjects which undergo to major amputation is 70%, if the patient presents also end stage renal disease the risk reaches 75% [150].

From these considerations it is clear that the treatment of this pathology requires an integrated multidisciplinary approach able to manage not just the local state of the patient but also and especially the systemic conditions of damage [151].

Skin Cancer

Considering the higher prevalence of cancer in diabetics for many years it has been postulated that diabetic patients should be affected by an elevated prevalence also regarding skin cancer.

In particular Skin lymphoma seemed to present a higher incidence in diabetics. The role of diabetes in their emergence has been severely revaluated in recent trials and therefore the question is still controversial [152].

Conclusion

As described above, being the skin the larger organ of the body, its involvement in diabetes complication is particularly extensive.

Despite these conditions are not generally life-threatening, their importance has to been underlined. First of all some of these lesions, occurring in exposed portion of the body, such as face or arms,deeply impact on the quality of life of the patients.

The association of these conditions with diabetes has been strongly validated both from a pathogenic point of view and from an epidemiological one. Therefore health professionals who diagnose skin condition associated to diabetes should perform further diagnostic tests which allow to detect the presence of diabetes. Some of these conditions can be also a marker of reduced glucose tolerance, condition sometimes called as “pre-diabetes”. In these patients, at very higher risk to develop diabetes, must be put in place all the weapons to reduce this risk, especially reducing the body weight.

References

1. Jaacks LM, Sieg el KR, Gujral UP, Narayan KM. (2016). Type 2 diabetes: a 21st century epidemic. Best Pract Res Clin Endocrinol Metab. 30: 331–343.

2. Ogu rtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, et al. (2017). IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract. 128: 40-50.

3. DeFronzo RA, Ferrannini E, Groop L, Henry RR, Herman WH, et al. (2015). Type 2 diabetes mellitus. Nat Rev Dis Primers. 1: 15019.

4. Centers for disease control and prevention. (2014). National diabetes statistics report: estimates of diabetes and its burden in the United States. Atlanta, GA: US Department of Health and Human Services.

5. Chaturvedi N. (2007). The burden of diabetes and its complications: trends and implications for intervention. Diabetes Res Clin Pract. Suppl 1: S3-S12.

6. O'Brien JA, Shomphe LA, Kavanagh PL, Raggio G, Caro JJ. (1998). Direct medical costs of complications resulting from type 2 diabetes in the U.S. Diabetes Care. 21: 1122-1128.

7. DCCT Research Group. (1993). The effect of intensive treatment of diabetes on the development and progression of long --term complications in insulin-dependent diabetes mellitus. N Engl J Med. 977-986.

8. Ward A, Alvarez P, Vo L, Martin S. (2014). Direct medical costs of complications of diabetes in the United States: estimates for event-year and annual state costs (USD 2012). J Med Econ. 17: 176-183.

9. Khalil H. (2017). Diabetes microvascular complications-A clinical update. Diabetes Metab Syndr. Suppl 1: S133-S139.

10. Pozzilli P, Leslie RD, Chan J, De Fronzo R, Monnier L, et al. (2010). The A1C and ABCD of glycaemia management in type 2 diabetes: a physician's personalized approach. Diabetes Metab Res Rev. 26: 239-244.

11. Brownlee M. (2005). The pathobiology of diabetic complications: a unifying mechanism. Diabetes. 54: 1615-1625.

12. Beisswenger PJ, Moore LL, Curphey TJ. (1993). Relationship between glycemic control and collagen-linked advanced glycosilation end-products in type 1 diabetes. Diabetes Care. 16: 689-694.

13. Sell DR, La Polla A, Odetti P, Fogarty J, Monnier VM. (1992). Pentosidine formation in skin correlates with severity of complications in individuals with long-standing IDDM. Diabetes. 41: 1286-1292.

14. Levy DM, Ternghi G, Gu XH, RR AbrahamD, R Springall, et al. (1992). Immunoistochemical measurementof nerves and neuropeptides in diabetic

skin: relationship to tests of neurological function. Diabetologia. 35: 889-897.

15. Braverman IM, Sibley J, Keh-Yen A. (1986). A study of the veil cells around normal, diabetic and aged cutaneous micro-vessels. J Invest Dermatol. 86: 57-62.

16. Khalil H. (2016). Diabetes microvascular complications-A clinical update. Diabetes Metab Syndr. pii: S1871-4021(16)30264-8.

17. Bollinger A, Frey J, Jager K, Furrer J, Seglias J. (1982). Patterns of diffusion through skin capillaries in patients with longterm diabetes. N Engl J Med. 307: 1305-1310.

18. Pecoraro R, Reiber G, Burgess E. Pathways to diabetic limb amputation: basis for prevention. Diabetes care. 1990; 13: 513-521.

19. Lima AL, Illing T, Schliemann S and Elsner P. (2017). Cutaneous manifestations of diabetes mellitus: a review. Am J Clin Dermatol. 18: 541-553.

20. Levy L, Zeichner JA. (2012). Dermatologic manifestations of diabetes. Journal of diabetes. 4: 68-76.

21. Erfurt-Berge C, Dissemond J, Schwede K, Seitz AT, Al Ghazal P, et al. (2015). Updated results of 100 patients on clinical features and therapeutic options in necrobiosis lipoidica in a retrospective multicentre study. Eur J Dermatol. 25: 595-601.

22. Lowitt MH, Dover JS. (1991). Necrobiosis lipoidica. J Am Acad Dermatol. 25: 735–748.

23. Sibbald C, Reid S, Alavi A. (2015). Necrobiosis lipoidica. Dermatol Clin. 33: 343–360.

24. Lepe K, Salazar FJ. (2017). Necrobiosis Lipoidica. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing.

25. Jiquan S, Khalaf AT, Jinquan T, Xiaoming L. (2008). Necrobiosis lipoidica: a case with histopathological findings revealed asteroid bodies and was successfully treated with dipyridamole plus intralesional triamcinolone. J Dermatol Treat. 19: 54–57.

26. Mistry BD, Alavi A, Ali S, Mistry N. (2017). A systematic review of the relationship between glycemic control and necrobiosis lipoidica diabeticorum in patients with diabetes mellitus. Int J Dermatol. 56: 1319-1327.

27. Mitre V, Wang C, Hunt R. (2016). Necrobiosis Lipoidica. J Pediatr. 179: 272-272.

28. Reid SD, Ladizinski B, Lee K, Baibergenova A, Alavi A. (2013). Update on necrobiosis lipoidica: a review of etiology, diagnosis, and treatment options. J Am Acad Dermatol. 69: 783–791.

29. Goucha S, Khaled A, Kharfi M, Fazaa B, Zermani R, et al. (2008). Granuloma annulare. G Ital Dermatol Venereol. 143: 359–363.

30. Piette EW, Rosenbach M. (2016). Granuloma annulare: pathogenesis, disease associations and triggers, and therapeutic options. J Am Acad Dermatol. 75: 467–479.

31. Ma HJ, Zhu WY, Yue XZ. (2006). Generalized granuloma annulare associated with chronic hepatitis B virus infection. J Eur Acad Dermatol Venereol. 20: 186–189.

32. Spicuzza L, Salafia S, Capizzi A, Vitaliti G, Rotolo N, et al. (2012). Granuloma annulare as first clinical manifestation of diabetes mellitus in children: a case report. Diabetes Res Clin Pract. 95: e55-57.

33. Tecilazich F, Kafanas A, Veves A. (2011). Cutaneous alterations in diabetes mellitus. Wounds. 23: 192-203.

34. Li A, Hogan DJ, Sanusi ID, Smoller BR. (2003). Granuloma annulare and malignant neoplasms. Am J Dermatopathol. 25: 113–116.

35. Studer EM, Calza AM, Saurat JH. (1996). Precipitating factors and associated diseases in 84 patients with granuloma annulare: a retrospective study. Dermatology. 193: 364-368.

36. Larsen K, Jensen T, Karlsmark T, Holstein PE. (2008). Incidence of bullosis diabeticorum--a controversial cause of chronic foot ulceration. Int Wound J. 5: 591-596.

37. Anand KP, Kashyap AS. (2004). Bullosis diabeticorum. Postgrad Med J. 80: 354.

38. Ghosh SK, Bandyopadhyay D, Chatterjee G. (2009). Bullosis diabeticorum: a distinctive blistering eruption in diabetes mellitus. Int J Diabetes Dev Ctries. 29: 41–42.

39. Aye M, Masson EA. (2002). Dermatological care of the diabetic foot. Am J Clin Dermatol. 3: 463–474.

40. Lopez PR, Leicht S, Sigmon JR, Stigall L. (2009). Bullosis diabeticorum associated with a prediabetic state. South Med J. 102: 643-644.

41. Basarab T, Munn SE, McGrath J, Russell Jones R. (1995). Bullosis diabeticorum. A case report and literature review. Clin Exp Dermatol. 20: 218–220.

42. Beers WH, Ince A, Moore TL. (2006). Scleredema adultorum of Buschke: a case report and review of the literature. Semin Arthritis Rheum. 35: 355–359.

43. Dinato SL, Costa GL, Dinato MC, Sementilli A, Romiti N. (2010). Scleredema of Buschke associated with diabetes mellitus type 2: case report and review of the literature. Arq Bras Endocrinol Metabol. 54: 852–855.

44. Shazzad MN, Azad AK, Abdal SJ, Afrose R, Rahman MM, et al. (2015). Scleredema Diabeticorum - A Case Report. Mymensingh Med J. 24: 606-609.

45. Rongioletti F, Kaiser F, Cinotti E, Metze D, Battistella M, et al. (2015). Scleredema. A multicentre study of characteristics, comorbidities, course and therapy in 44 patients. J Eur Acad Dermatol Venereol. 29: 2399-2404.

46. Bustan RS, Wasim D, Yderstræde KB, Bygum A. (2017). Specific skin signs as a cutaneous marker of diabetes mellitus and the prediabetic state - a systematic review. Dan Med J. 64: pii: A5316.

47. Yu Q, Li XL, Ji G, Wang Y, Gong Y, et al. (2017). Malignant acanthosis nigricans: an early diagnostic clue for gastric adenocarcinoma. World J Surg Oncol. 15: 208.

48. Veysey E, Ratnavel R. (2005). Facial acanthosis nigricans associated with obesity. Clin Exp Dermatol. 30: 437–439.

49. Stoddart ML, Blevins KS, Lee ET, Wang W, Blackett PR, et al. (2002). Association of acanthosis nigricans with hyperinsulinemia compared with other selected risk factors for type 2 diabetes in Cherokee Indians: the Cherokee Diabetes Study. Diabetes Care. 25: 1009–1014.

50. Apridonidze T, Essah PA, Iuorno MJ, Nestler JE. (2005). Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 90: 1929–1935.

51. Bhagyanathan M, Dhayanithy D, Parambath VA, Bijayraj R. (2017). Acanthosis nigricans: A screening test for insulin resistance - An important risk factor for diabetes mellitus type-2. J Family Med Prim Care. 6: 43-46.

52. Rodríguez-Gutiérrez R, Salcido-Montenegro A, González-González JG. (2018). Early Clinical Expressions of Insulin Resistance: The Real Enemy to Look For. Diabetes Ther. 9: 435-438.

53. Zak A, Zeman M, Slaby A, Vecka M. (2014). Xanthomas: clinical and pathophysiological relations. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 158: 181-188.

54. Wani AM, Hussain WM, Fatani MI, Qadmani A, Akhtar M, et al. (2009). Eruptive xanthomas with Koebner phenomenon, type 1 diabetes mellitus, hypertriglyceridaemia and hypertension in a 41-year-old man. BMJ Case Rep. 2009. pii: bcr05.2009.1871.

55. Solak B, Kara RO, Acikgoz SB, Kosem M. (2015). First and only symptom of undiagnosed diabetes mellitus: eruptive xanthoma. BMJ Case Rep. 2015.

56. Kala J, Mostow EN. (2012). Images in clinical medicine. Eruptive xanthoma. N Engl J Med. 366: 835.

57. Ravic-Nikolic A, Mladenovic V, Mitrovic S, Milicic V, Djukic A, et al. (2014). Generalized eruptive xanthomas associated with diabetic dyslipidemia. Eur J Dermatol. 24: 394-395.

58. Abdelghany M, Massoud S. (2015). Eruptive xanthoma. Cleve Clin J Med. 82: 209-210.

59. Kiziltan ME, Benbir G. (2008). Clinical and nerve conduction studies in female patients with diabetic dermopathy. Acta Diabetol. 45: 97–105.

60. Ahmed I, Goldstein B. (2006). Diabetes mellitus. Clin Dermatol. 24: 237–246.

61. Morgan AJ, Schwartz RA. (2008). Diabetic dermopathy: a subtle sign with grave implications. J Am Acad Dermatol. 58: 447–451.

62. Abdollahi A, Daneshpazhooh M, Amirchaghmaghi E, Sheikhi S, Eshrati B, et al. (2007).

Dermopathy and retinopathy in diabetes: is there an association? Dermatology. 214: 133-136.

63. Namazi MR, Jorizzo JL, Fallahzadeh MK. (2010). Rubeosis faciei diabeticorum: a common, but often unnoticed, clinical manifestation of diabetes mellitus. ScientificWorldJournal. 10: 70-71.

64. Pavlovic MD, Milenkovic T, Dinic M, Misovic M, Dakovic D, et al. (2007). The prevalence of cutaneous manifestations in young patients with type 1 diabetes. Diabetes Care. 30: 1964-1967.

65. Nikoleishvili LR, Kurashvili RB, Virsaladze DK, Khachapuridze NG, Kurashvili LR. (2006). [Characteristic changes of skin and its accessories in type 2 diabetes mellitus]. Georgian Med News. 131: 43-46.

66. Julka S, Jamdagni N, Verma S, Goyal R. (2013). Yellow palms and soles: A rare skin manifestation in diabetes mellitus. Indian J Endocrinol Metab. 17(Suppl 1): S299-300.

67. Suzuki K, Ito Y, Nakamura S, Ochiai J, Aoki K. (2002). Relationship between serum carotenoids and hyperglycemia: a population-based cross-sectional study. J Epidemiol. 12: 357–366.

68. Yancovitz M, Johnson H, Wang N, Pomeranz MK. (2008). Perforating collagenosis. Dermatol Online J. 14: 14.

69. Tsuboi H, Katsuoka K. (2007). Characteristics of acquired reactive perforating collagenosis. J Dermatol. 34: 640–644.

70. Saray Y, Seçkin D, Bilezikçi B. (2006). Acquired perforating dermatosis: clinicopathological features in twenty-two cases. J Eur Acad Dermatol Venereol. 20: 679-688.

71. Nebel R, Fiedler E, Danz B, Marsch WC, Kreft B. (2007). Acquired reactive perforating collagenosis associated with diabetes mellitus and renal insufficiency requiring dialysis. Dtsch Med Wochenschr. 132: 2624–2626.

72. Ataseven A, Kayacetin S. (2012). Acquired reactive perforating collagenosis. Eurasian J Med. 44: 51–53.

73. Lynde CB, Pratt MD. (2009). Clinical Images: Acquired perforating dermatosis: association with diabetes and renal failure. CMAJ. 181: 615.

74. Wagner G, Sachse MM. (2013). Acquired reactive perforating dermatosis. J Dtsch Dermatol Ges. 11: 723-730.

75. Ragunatha S, Anitha B, Inamadar AC, Palit A, Devarmani SS. (2011). Cutaneous disorders in 500 diabetic patients attending diabetic clinic. Indian J Dermatol. 56: 160-164.

76. Demir S, Demir Y. (2002). Acrochordon and impaired carbohydrate metabolism. Acta diabetol. 39: 57-59.

77. Akpinar F, Dervis E. (2012). Association between acrochordons and the components of metabolic syndrome. Eur J Dermatol. 22: 106-110.

78. Wan MT, Shin DB, Hubbard RA, Noe MH, Mehta NN, et al. (2018). Psoriasis and the Risk of Diabetes: A Prospective Population-Based Cohort Study. J Am Acad Dermatol. 78: 315-322.

79. Cohen AD, Gilutz H, Henkin Y, Zahger D, Shapiro J, et al. Psoriasis and the metabolic syndrome. Acta Derm Venereol. 87: 506-509.

80. Li W, Han J, Hu FB, Curhan GC, Qureshi AA. (2012). Psoriasis and risk of type 2 diabetes among women and men in the United States: a population-based cohort study. J Invest Dermatol. 132: 291-298.

81. Cheng J, Kuai D, Zhang L, Yang X, Qiu B. (2012). Psoriasis increased the risk of diabetes: a meta-analysis. Arch Dermatol Res. 304: 119-125.

82. Barreda-Zaleta L, Pérez-Rojas DO, Espinoza-Hernández CJ, Ramírez-Terán AL, Vega-Memije ME. (2017). Psoriasis and diabetes mellitus in the dermatological consultation. Gac Med Mex. 153: 524-525.

83. Gisondi P, Cazzaniga S, Chimenti S, Giannetti A, Maccarone M, et al. (2013). Metabolic abnormalities associated with initiation of systemic treatment for psoriasis: evidence from the Italian Psocare Registry. J Eur Acad Dermatol Venereol. 27: e30-41.

84. Shiina T, Inoko H, Kulski JK. (2004). An update of the HLA genomic region, locus information and disease associations: 2004. Tissue Antigens. 64: 631-649.

85. Richetta A, D'Epiro S, Salvi M, Campoli M, Giancristoforo S, et al. (2013). Serum levels of

functional T-regs in vitiligo: our experience and mini-review of the literature. Eur J Dermatol. 23: 154-159.

86. Raveendra L, Hemavathi RN, Rajgopal S. (2017). A Study of Vitiligo in Type 2 Diabetic Patients. Indian J Dermatol. 62: 168-170.

87. Forschner T, Buchholtz S, Stockfleth E. (2007). Current state of vitiligo therapy--evidence-based analysis of the literature. J Dtsch Dermatol Ges. 5: 467-475.

88. Amer AA, Gao XH. (2016). Quality of life in patients with vitiligo: an analysis of the dermatology life quality index outcome over the past two decades. Int J Dermatol. 55: 608-614.

89. Lehman JS, Tollefson MM, Gibson LE. (2009). Lichen planus. Int J Dermatol. 48: 682-694.

90. Seyhan M, Ozcan H, Sahin I, Bayram N, Karincaoğlu Y. (2007). High prevalence of glucose metabolism disturbance in patients with lichen planus. Diabetes Res Clin Pract. 77: 198-202.

91. Trentin MS, Verardi G, De C Ferreira M, de Carli JP, da Silva SO, et al. (2017). Most Frequent Oral Lesions in Patients with Type 2 Diabetes Mellitus. J Contemp Dent Pract. 18: 107-111.

92. Mozaffari HR, Sharifi R, Sadeghi M. (2016). Prevalence of Oral Lichen Planus in Diabetes Mellitus: a Meta-Analysis Study. Acta Inform Med. 24: 390-393.

93. Pozzilli P, Leslie RD. (1994). Infections and diabetes: mechanisms and prospects for prevention. Diabet Med. 11: 935-941.

94. Dryden M, Baguneid M, Eckmann C, Corman S, Stephens J, et al. (2015). Pathophysiology and burden of infection in patients with diabetes mellitus and peripheral vascular disease: focus on skin and soft-tissue infections. Clin Microbiol Infect. 21 Suppl 2: S27-32.

95. Yosipovitch G, Tur E, Cohen O, Rusecki Y. (1993). Skin surface pH in intertriginous areas in NIDDM patients. Possible correlation to candidal intertrigo. Diabetes Care. 16: 560-563.

96. Yosipovitch G, Hodak E, Vardi P, Shraga I, Karp M, et al. (1998). The prevalence of cutaneous manifestations in IDDM patients and their association with diabetes risk factors and microvascular complications. Diabetes Care. 21: 506-509.

97. Wu C, Chen X, Shu J, Lee CT. (2017). Whole-genome expression analyses of type 2 diabetes in human skin reveal altered immune function and burden of infection. Oncotarget. 8: 34601-34609.

98. Murphree RW. (2017). Impairments in Skin Integrity. Nurs Clin North Am. 52: 405-417.

99. de Macedo GM, Nunes S, Barreto T. (2016). Skin disorders in diabetes mellitus: an epidemiology and physiopathology review. Diabetol Metab Syndr. 8: 63.

100. Suaya JA, Eisenberg DF, Fang C, Miller LG. (2013). Skin and soft tissue infections and associated complications among commercially insured patients aged 0-64 years with and without diabetes in the US. PLoS One. 8: e60057.

101. Sunderkotter C, Becker K. (2015). Frequent bacterial skin and soft tissue infections: diagnostic signs and treatment. J Dtsch Dermatol Ges. 13: 501–524; quiz 525-526.

102. Koning S, van der Sande R, Verhagen AP, van Suijlekom-Smit LW, Morris AD, et al. (2012). Interventions for impetigo. Cochrane Database Syst Rev. 1: CD003261.

103. Yeoh DK, Bowen AC, Carapetis JR. (2016). Impetigo and scabies—disease burden and modern treatment strategies. J Infect. 72: S61–67.

104. Tschachler E, Brockmeyer N, Effendy I, Geiss HK, Harder S, et al. (2007). Streptococcal infections of the skin and mucous membranes. J Dtsch Dermatol Ges. 5: 527–532.

105. Kilburn SA, Featherstone P, Higgins B, Brindle R. (2010). Interventions for cellulitis and erysipelas. Cochrane Database Syst Rev. (6): CD004299.

106. Iacopi E, Coppelli A, Goretti C, Piaggesi A. (2015). Necrotizing Fasciitis and The Diabetic Foot. Int J Low Extrem Wounds. 14: 316-327.

107. Chen KJ, Klingel M, McLeod S, Mindra S, Ng VK. (2017). Presentation and outcomes of necrotizing soft tissue infections. Int J Gen Med. 10: 215-220.

108. Holdiness MR. (2002). Management of cutaneous erythrasma. Drugs. 62: 1131-1141.

109. Sariguzel FM, Koc AN, Yagmur G, Berk E. (2014). Interdigital foot infections: Corynebacterium minutissimum and agents of superficial mycoses. Braz J Microbiol. 45: 781-784.

110. Oumeish OY. (2008). Skin disorders in patients with diabetes. Clin Dermatol. 26: 235-242.

111. Rubin Grandis J, Branstetter BF 4th, Yu VL. (2004). The changing face of malignant (necrotising) external otitis: clinical, radiological, and anatomic correlations. Lancet Infect Dis. 4: 34-39.

112. Ali T, Meade K, Anari S, ElBadawey MR, Zammit-Maempel I. (2010). Malignant otitis externa: case series. J Laryngol Otol. 124: 846-851.

113. Nern K. (2002). Dermatologic conditions associated with diabetes. Curr Diab Rep. 2: 53-59.

114. Murphy-Chutorian B, Han G, Cohen SR. (2013). Dermatologic manifestations of diabetes mellitus: a review. Endocrinol Metab Clin N Am. 42: 869-898.

115. Man A, Ciurea CN, Pasaroiu D, Savin AI, Toma F, et al. (2017). New perspectives on the nutritional factors influencing growth rate of Candida albicans in diabetics. An in vitro study. Mem Inst Oswaldo Cruz. 112: 587-592.

116. Raiesi O, Siavash M, Mohammadi F, Chabavizadeh J, Mahaki B, et al. (2017). Frequency of Cutaneous Fungal Infections and Azole Resistance of the Isolates in Patients with Diabetes Mellitus. Adv Biomed Res. 6: 71.

117. Dockerty WG, Sonnex C. (1995). Candidal balano-posthitis: a study of diagnostic methods. Genitourin Med. 71: 407-409.

118. de Leon EM, Jacober SJ, Sobel JD, Foxman B. (2002). Prevalence and risk factors for vaginal Candida colonization in women with type 1 and type 2 diabetes. BMC Infect Dis. 2: 1.

119. Lugo-Somolinos A, Sánchez JL. (1992). Prevalence of dermatophytosis in patients with diabetes. J Am Acad Dermatol. 26: 408-410.

120. Eckhard M, Lengler A, Liersch J, Bretzel RG, Mayser P. (2007). Fungal foot infections in patients with diabetes mellitus--results of two independent investigations. Mycoses. 2: 14-19.

121. Takehara K, Amemiya A, Mugita Y, Tsunemi Y, Seko Y, et al. (2017). The Association between Tinea Pedis and Feet-Washing Behavior in Patients with Diabetes: A Cross-sectional Study. Adv Skin Wound Care. 30: 510-516.

122. Gupta AK, Konnikov N, MacDonald P, Rich P, Rodger NW, et al. (1998). Prevalence and epidemiology of toenail onychomycosis in diabetic subjects: a multicentre survey. Br J Dermatol. 139: 665-671.

123. Gulcan A, Gulcan E, Oksuz S, Sahin I, Kaya D. (2011). Prevalence of toenail onychomycosis in patients with type 2 diabetes mellitus and evaluation of risk factors. J Am Podiatr Med Assoc. 101: 49-54.

124. Petrikkos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, et al. (2012). Epidemiology and clinical manifestations of mucormycosis. Clin Infect Dis. 1: S23-34.

125. Casqueiro J, Casqueiro J, Alves C. (2012). Infections in patients with diabetes mellitus: A review of pathogenesis. Indian J Endocrinol Metab. 1: S27-36.

126. Deng N, Zhang X, Zhao F, Wang Y, He H. (2017). Prevalence of lipohypertrophy in insulin-treated diabetes patients: A systematic review and meta-analysis. J Diabetes Investig.

127. Verma R. (2017). Insulin-Mediated Lipohypertrophy. N Engl J Med. 377: 573.

128. Young RJ, Hannan WJ, Frier BM, Steel JM, Duncan LJ. (1984). Diabetic lipohypertrophy delays insulin absorption. Diabetes Care. 7: 479-480.

129. Katzman BD, Traum P, Medline PB. (2018). New Histologic Finding of Amyloid Insulin Bodies at an Insulin Injection Site in a Patient With Diabetes. Am J Dermatopathol. 40: 527-530.

130. Havel PJ. (2004). Update on adipocyte hormones: regulation of energy balance and carbohydrate/lipid metabolism. Diabetes. 1: S143-151.

131. Sahasrabudhe RA, Limaye TY, Gokhale VS. (2017). Insulin Injection Site Adverse Effect in a Type 1 Diabetes Patient: An Unusual Presentation. J Clin Diagn Res. 11: OD10-OD11.

132. Radermecker RP, Piérard GE, Scheen AJ. (2007). Lipodystrophy reactions to insulin: effects of

continuous insulin infusion and new insulin analogs. Am J Clin Dermatol. 8: 21-28.

133. Heinzerling L, Raile K, Rochlitz H, Zuberbier T, Worm M. (2008). Insulin allergy: clinical manifestations and management strategies. Allergy. 63: 148-155.

134. Yuan T, Zhao W, Wang L, Dong Y, Li N. (2016). Continuous Subcutaneous Insulin Infusion as an Effective Method of Desensitization Therapy for Diabetic Patients with Insulin Allergy: A 4-year Single-center Experience. Clin Ther. 38: 2489-2494.

135. Bavbek S, Lee MJ. (2017). Subcutaneous Injectable Drugs Hypersensitivity and Desensitization: Insulin and Monoclonal Antibodies. Immunol Allergy Clin North Am. 37: 761-771.

136. Murray BR, Jewell JR, Jackson KJ, Agboola O, Alexander BR, et al. (2017). Type III Hypersensitivity Reaction to Subcutaneous Insulin Preparations in a Type 1 Diabetic. J Gen Intern Med. 32: 841-845.

137. Noakes R. (2003). Lichenoid drug eruption as a result of the recently released sulfonylurea glimepiride. Australas J Dermatol. 44: 302-303.

138. Goldberg I, Sasson A, Gat A, Srebrnik A, Brenner S. (2005). Pemphigus vulgaris triggered by glibenclamide and cilazapril. Acta Dermatovenerol Croat. 13: 153-155.

139. Koca R, Altinyazar HC, Yenidünya S, Tekin NS. (2003). Psoriasiform drug eruption associated with metformin hydrochloride: a case report. Dermatol Online J. 9: 11.

140. Kono T, Hayami M, Kobayashi H, Ishii M, Taniguchi S. (1999). Acarbose-induced generalised erythema multiforme. Lancet. 354: 396-397.

141. Boulton AJ. (1988). The diabetic foot. Med Clin North Am. 72: 1513-1530.

142. Urbancic-Rovan V. (2005). Causes of diabetic foot lesions. Lancet. 366: 1675-1676.

143. Pecoraro RE, Reiber GE, Burgess EM. (1990). Pathways to diabetic limb amputation. Basis for prevention. Diabetes Care. 13: 513-521.

144. Apelqvist J. (2012). Diagnostics and treatment of the diabetic foot. Endocrine. 41: 384-397.

145. Mauricio D, Jude E, Piaggesi A, Frykberg R. (2016). Diabetic Foot: Current Status and Future Prospects. J Diabetes Res. 2016: 5691305.

146. Lavery LA, Armstrong DG, Wunderlich RP, Tredwell J, Boulton AJ. (2003). Diabetic foot syndrome: evaluating the prevalence and incidence of foot pathology in Mexican Americans and non-Hispanic whites from a diabetes disease management cohort. Diabetes Care. 26: 1435-1438.

147. Ziegler-Graham K, MacKenzie EJ, Ephraim PL, Travison TG, Brookmeyer R. (2008). Estimating the prevalence of limb loss in the United States: 2005 to 2050. Arch Phys Med Rehabil. 89: 422-429.

148. Schaper NC. (2012). Lessons from Eurodiale. Diabetes Metab Res Rev. 1: 21-26.

149. Walsh JW, Hoffstad OJ, Sullivan MO, Margolis DJ. (2016). Association of diabetic foot ulcer and death in a population-based cohort from the United Kingdom. Diabet Med. 33: 1493-1498.

150. Lavery LA, Hunt NA, Ndip A, Lavery DC, Van Houtum W, et al. (2010). Impact of chronic kidney disease on survival after amputation in individuals with diabetes. Diabetes Care. 33: 2365-2369.

151. Edmonds ME, Foster AV. (2006). Diabetic foot ulcers. BMJ. 332: 407-410.

152. Lenz G. (2015). Insights into the molecular pathogenesis of activated B-cell like diffuse large B-cell lymphoma and its therapeutic implications. Cancers. 7: 811–822.