

Non-ulcerative skin pathologies of the diabetic foot

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Summary

Many of the complications of the diabetes are well studied but robust research documenting the cutaneous effects of the disease remains sparse. Various studies have suggested that the majority of patients with diabetes will suffer a skin disorder during the course of their disease and for some, the skin changes may even precede the diagnosis of diabetes.

Cutaneous pathology of the diabetic foot and lower leg can arise as a result of the direct or indirect effects of diabetic complications. The most common manifestations include fungal and bacterial skin infection, nail disease and diabetic dermopathy. Other less commonly observed conditions include diabetic bullae, necrobiosis lipoidica diabetorum (NLD), granuloma annulare and reddening of the soles. For many of the less common disorders, there is little in the way of effective treatment. However, much can be done in the clinical setting in the management of the more common manifestations such as bacterial and fungal infection. Fungal infection, in particular, although relatively inconspicuous, is a very common foot problem and if left untreated can threaten tissue viability in the diabetic foot leading to secondary bacterial infection and cellulitis. Management of fungal disease is often considered difficult due to high relapse and re-infection rates, although by introducing a combination of therapies including mechanical and pharmacological the success in treating this stubborn condition can be greatly improved. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords diabetes; skin; cutaneous; complications

Introduction

There are many ways in which the body's systems can be affected by diabetes and its complications. Much research has been devoted to understanding some of these pathological processes such as retinopathy, nephropathy and neuropathy but very little has been investigated on non-ulcerative skin disorders in the patient with diabetes. Elucidating reliable data on this subject is difficult. Most of the available data is derived from older studies. Moreover, the epidemiological data offered are of variable quality. Much of the work has focussed on small or selected populations with various methodologies and diagnostic criteria. Even fewer have attempted to explain the pathology behind these dermatoses. This article will begin to review some of the more common skin lesions thought to be associated with the disease.

How does diabetes affect the skin?

With all types of diabetes the key feature of the disease is hyperglycaemia and as a result a number of changes in the cellular biochemistry. This includes the increased formation of glycation end products and sorbitol [1]. The extent and effects of these changes may vary between individuals but ultimately the skin may suffer by alterations in collagen synthesis and structure, abnormal

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blood flow from microangiopathy and become vulnerable to infection due to a suppressed immune response. Alone, or in combination, each of these may contribute to the pathology of skin disease.

The epidemiology of skin disease

In the general population, skin disease is said to affect around one in three people during the course of their lifetime [2]. Literature pertaining to the prevalence of non-ulcerative skin disorders in the patient with diabetes is sparse. Generally, it is accepted that it is common in this group of patients. However, little data is available to substantiate this claim. Literature suggests the figure lies between 30% and 100% [3–6] reflecting the paucity of knowledge. The vast majority of these cases arise during the course of the disease; however, it is not unusual for the skin disorder to precede the diagnosis or to exist in patients in a pre-diabetic state.

In 2006, Wang and Margolis [7] published a study drawing data from previously conducted medical surveys and compared the frequency of skin complaints with two control populations (those with hypertension and those with gastric reflux). They concluded that patients with diabetes were more prone to skin infections but data on non-infective conditions were not conclusive, possibly due to under-reporting in the initial survey.

Specific to the foot, few studies have been carried out. A two-phase study of nearly 90 000 patients was conducted across Europe by Burzykowski and colleagues [8] who reported that 57% of their subjects had foot pathology: about 9% of this population had diabetes, although data specifically pertaining to this sub-group were not ascertainable. However, diabetes as a risk factor nearly doubled an individual's risk of developing a foot problem. Obesity and vascular disease similarly increased the risk. Kanjee and colleagues [4] surveyed 100 diabetic patients for cutaneous lesions and found 30% of their cohort had skin lesions occurring on the foot. Diabetic disorders can be classified as:

- (1) Non-infective
- (2) Infective
- (3) Complications related to treatment.

This article will focus on the most common conditions which occur on the foot. Clinically, when confronted with a patient presenting with a skin disorder on the lower leg, it is often difficult to discern if it represents a condition purely associated with diabetes or if it is part of a more generalized, unrelated disease. Careful and meticulous assessment is required.

Non-infective conditions

Diabetic dermopathy

Diabetic dermopathy (shin spots, spotted leg syndrome) is characterized by hyper-pigmented, atrophic macules of

a few millimetres in diameter on the shins. A few patients may recall a preceding traumatic event but for most they appear spontaneously. The condition is considered to be one of the most common lesions associated with diabetes mellitus. Yosipovitch [9] found 7% of young patients with type 1 diabetes had such lesions, while Melin [10] in an earlier study found 55% of older patients with the condition. Romano [11] discovered 12% of a population totalling 457 had the condition. The lesions do occur in patients without diabetes, but when refining the diagnosis to those with four or more lesions the condition is exclusively seen in diabetic patients [12].

The cause of the lesion is unknown, but probably represents a post-inflammatory lesion in poorly vascularized skin or a manifestation of microangiopathy [13]. To reinforce this, observations have been made that the condition often occurs in those patients with accompanying retinopathy, neuropathy and nephropathy [14]. Currently there is no treatment for the condition; so, for the moment the disease remains a clinical marker of internal disease.

Necrobiosis lipidica diabetorum

Necrobiosis lipidica diabetorum (NLD) is a cutaneous disorder almost exclusive to the diabetic patient. Even so, the condition remains relatively rare with an incidence of 0.3% in patients with the disease [15]. The condition typically affects those in their fourth to sixth decades and appears as bilateral red brown papules, which gradually develop on the anterior surface of the shins. Lesions enlarge to form yellow, atrophic plaques with a translucent lustre and stippled with telangiectasia. Subsequent trauma to the area frequently results in ulceration [16].

The aetiology of the condition remains a mystery. Histologically, the lesion is characterized by a disorganized degeneration of collagen with basement membrane thickening and inflammation of the underlying subcutaneous fat. Management of the condition remains challenging with a number of suggested approaches including topical and systemic corticosteroids [17], aspirin and dipyridamole [18] and most recently anti-TNF therapies [19], although no robust studies have demonstrated any particular effective therapy to date.

Diabetic bullae

The spontaneous appearance of painless blisters on the feet of a patient with diabetes is a rare but a significant event. Lesions appear rapidly anywhere on the foot, for most with no precipitating factors such as trauma, friction or infection to form tense blisters which gradually enlarge becoming more flaccid as they develop. Typically these lesions develop most frequently over the toes, heels and occasionally on the anterior surface of the shins ranging in size from a few millimetres to centimetres in diameter (Figure 1).

It is unclear in the literature as to who is most at risk of developing these lesions. Some authors believe



Figure 1. Blistering of the foot

lesions to be more common in type 1 than type 2 diabetic patients [20], while a case series of the condition have suggested the converse is true [21]. There is general consensus, however, that it is most frequently adult males who are afflicted. The aetiology is unclear but it has been suggested that some patients may have a reduced threshold to frictional forces. An association with neuropathy and retinopathy has been found [22].

At a cellular level, blisters appear to be of two types. Most tend to manifest as an intra-epidermal blister, which are filled with clear fluid. This type appears to heal without scarring. The second, less common variety is a sub-epidermal blister. Typically these lesions are haemorrhagic and heal with scarring. Such blistering is normally typical of an immunological process (as typified by some blistering diseases of the skin). However, immunofluorescent studies have failed to demonstrate an immunological cause [23].

Clinically, prevention of such lesions is difficult as most occur spontaneously. However, standard measures should be taken to prevent secondary infection following rupture. Where lesions are likely to rupture by themselves, fluid should be released under clean conditions and should be managed as any other ulcer, with attention paid towards off-loading and careful follow-up to monitor for signs of infection.

Dry skin (anhidrosis, xerosis)

Normal epidermal skin water content is around 15%. When this drops, the skin becomes dry and loses resilience. Anhidrosis is extremely common [24] indeed, to such an extent that it is rarely considered to be a condition in its own right. It is often a symptom of other skin diseases such as psoriasis, eczema and fungal infection which needs to be considered. In the diabetic foot, autonomic neuropathy

is considered to be a significant cause [25]. The condition predisposes an individual to fissuring and cracking of the epidermis which in turn can lead to secondary infections of the foot.

The management of simple anhidrosis is straightforward. Regular application of an emollient has been shown to reduce dryness on the diabetic foot [26]. The difficulty comes in engaging patient adherence. Incorporation of this into the patient education programme should help. Which brand of emollient is selected, is a matter of individual patient choice. The medicament which is considered cosmetically unsuitable by the patient is unlikely ever to be applied.

Plantar erythema

A minority of patients may suffer with a reddening of the soles of the feet (plantar erythema). Some authors believe it to be a manifestation of microangiopathy resulting in slowing of the microcirculation which leads to engorgement of the superficial venous plexus giving rise to the colouration [27], while others have suggested an autonomic neuropathy [20]. Reddening in diabetes can also be observed in the palms and face (rubeosis faciei). Parallels have been drawn to the condition erythromelalgia, which gives rise to reddening of the extremities accompanied by pain.

There is no treatment for plantar erythema, although tighter blood glucose control has been shown to reverse these changes in a minority of patients. Diagnosis of the condition remains difficult owing to the natural variation of skin complexion, and other causes of plantar erythema such as liver disease and myeloproliferative disorders should be considered.

Yellow nails

Yellow nails have been cited as a condition frequently associated with diabetes mellitus. Lithner [13] observed the discolouration most commonly in this group of patients and those with an increased glucose tolerance. It was suggested that non-enzymatic glycosylation of the tissues leads to the clinical appearance, which is most evident in the distal aspect of the hallux. Although this has been simulated experimentally [28], others have suggested that carotenaemia, also more common in diabetic populations, may lead to this discolouration through deposition of the yellow pigment into the tissues of the skin and nail. From a clinical standpoint, onychomycosis remains the most common cause of toenail discolouration and should therefore be ruled out by microscopy and culture if suspected.

Koilonychia

Also known as spooning, this nail condition is characterized by an abnormal upward convexity of the nail plate giving it a spoon like appearance. Although, not considered to be the main cause, it has been reported in patients with long standing diabetes [29]; however,

primary research establishing this fact is lacking. The condition may be observed in diabetic patients with renal disease as spooning may signify renal failure [30].

Granuloma annulare

When discussing skin conditions related to diabetes, Granuloma annulare (GA) is frequently mentioned. The condition is a benign, self-resolving inflammatory eruption characterized by erythematous plaques and papules. The lesion typically occurs on the dorsa of the hands and feet. There are a number of suggested causes, but to date none have been proven. The link between diabetes and GA has been debated and there have been few robust studies undertaken. Studies have failed to show conclusively any link between GA and type 2 diabetes [31], although a weak link with type 1 diabetes has been demonstrated [32].

Infective conditions

Before the advent of insulin injections, infections were a major cause of morbidity and mortality in the diabetic patient. However, since the introduction there has been a significant reduction in infections – some authors suggesting reduction to the level of their non-diabetic counterparts [27]. However, it is more likely that patients with diabetes still encounter a higher rate of infection [33]. How the disease predisposes an individual is debated, but the effects of the disorder have been shown to reduce the migration and killing ability of neutrophils as well as induce changes in the adaptive immune response and T cell function [34]. The risk of infection in the diabetic foot is also heightened by additional factors such as reduced skin integrity, lack of sensory perception and poor peripheral circulation [35]. Work by Romano suggests that patients with type 2 diabetes are more susceptible to skin infection than type 1 patients [36].

Fungal infections

Fungal foot infection (FFI) represents the most common microbial infection in the form of both tinea pedis (skin infection) and onychomycosis (nail infection). In the general population, FFI affects around 35% of adults, and those with diabetes have a greater risk of developing the condition [8]. Other authors have confirmed this; Yosipovitch [9] found 32% of young diabetic patients compared to just 7% of controls were affected. Gupta and colleagues [37] found that people with diabetes were nearly 3 times more likely to develop onychomycosis than age-matched controls. Co-existing peripheral vascular disease has also been identified as an additional factor [38].

The most common infecting fungi are the dermatophytes [39] responsible of 90% of FFI, particularly *T. rubrum*. Infection virtually always begins on the skin on the plantar surface and then spreads to other parts of the foot (Figure 2). Typically, this type of infection produces little in the way of symptoms and often goes unnoticed,



Figure 2. Tinea pedis presenting as a dry, plantar infection

mistaken for dry skin. From the plantar area dermatophytes may spread to the hands, nails and groin. FFI in itself is little more than a nuisance. However, the infection has the ability to reduce skin integrity and leave it vulnerable to secondary infection through fissures and splits. The presence of a portal of entry hugely increases the risk of cellulitis in the affected limb [40,41].

FFI is easy to prevent but more difficult to treat. For patients with skin infection the application of a topical anti-fungal agent is effective, although allylamines such as terbinafine have been found to be more rapid in their action than the older imidazoles such as clotrimazole and miconazole [42]. Minor onychomycosis can be managed with topical agents such as amorolfine which has been shown to be up to 66% successful [43]. When the lunula is infected, topical agents alone are insufficient. Oral preparations are the drugs of choice. Agents such as oral terbinafine have been shown to be safe and effective in the treatment of onychomycosis in diabetic patients [44]. By combining topical nail lacquers with concurrent oral medications as a combination can improve cure rates further [45], particularly if the affected toe nails are mechanically reduced prior to therapy [46]. Reoccurrence rates for FFI are high through skin re-infection and therefore prophylactic use of topical agents should be encouraged to prevent further spread to the nails.

Bacterial infections

Bacterial skin infections, according to available data, are a less common event than fungal invasion. Despite this



Figure 3. Paronychia of the hallux due to *Staphylococcus aureus*

people with diabetes still have a greater predisposition than other patients [7].

On the foot, bacterial infections usually begin due to a breach in the epidermis as a result of physical trauma or pre-existing fungal infections. The most common organisms to take advantage are *Staphylococcus aureus* and Beta Haemolytic Group A *Streptococcus*. *S. aureus* typically causes problems such as paronychia (Figure 3) and ecthyma while *Streptococcus* causes cellulitis of the foot and leg. Patients with diabetes have an increased risk of developing cellulitis [47] and are likely to require longer hospitalizations than their non-diabetic counterparts [48]. Recurrent streptococcal infections of the lower limb can lead to inflammation and scarring of the lymphatics. In turn, this can lead to a permanently swollen limb; therefore patients with recurrent bouts may require prophylaxis with long-term penicillin. In addition, precipitating factors such as blood glucose control and pre-existing fungal infections should be managed appropriately.

The inter-digital areas of the foot can also harbour infections. Firstly, erythrasma, which is an overgrowth of resident flora, particularly *Corynebacterium minutissimum*, appears as inter-digital maceration, often with a brownish stain. The condition has been shown to be common in patients with diabetes [9]. It is easily diagnosed, as the bacterium responsible fluoresces pink under ultra-violet (or Woods) light. Microbiological reports can help discern this from fungal infection. Treatment for this minor problem is straightforward, with topical antiseptics and advice on proper hygiene and drying between the toes. Rarely, systemic antibiotics, such as erythromycin are indicated.

Pseudomonas aeruginosa, a gram-negative organism, can also be observed on the foot. The infection commonly invades compromised tissues; therefore on the foot common locations include wounds and inter-digital

spaces, superimposed over active fungal infection. Its presence is marked by a blue/green pigment produced by the bacteria (pyocyanin). For uncomplicated infection, simple measures such as vinegar soaks or topical silver sulphadiazine are effective. Deeper infection requires careful selection of an appropriate systemic antibiotic.

Non-ulcerative skin pathology is a common occurrence in diabetes and frequently may involve the foot. Although there is no skin disorder exclusive to diabetes, many conditions occur more frequently in this patient group and thus, their appearance should alert the clinician to the diagnosis. For non-infective skin conditions there is little effective treatment available. However, skin infection still remains a major threat to the diabetic foot and therefore early recognition and management of the minor infections could ultimately prevent the occurrence of more major infections.

Conflict of interest

The author has no conflicts of interest.

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