Chapter 2
Predisposing Factors for Onychomycosis

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Key Features

- Onychomycosis is the most prevalent nail disease with a significant burden on quality of life.
- Age is the principal non-modifiable risk factor for onychomycosis development.
- Medical conditions such as diabetes, HIV infection, immunosuppressed states, concurrent tinea pedis, and peripheral artery disease increase the risk for onychomycosis.
- Physical and environmental factors that increase risk include obesity, certain athletic activities, and possibly smoking.

Introduction

Onychomycosis is the most prevalent nail disease, representing up to 50 % of all nail problems and 30 % of all dermatophytoses [1]. It is estimated that over 10 million individuals suffer from onychomycosis in the United States [2], affecting between 2 and 26 % of the general population [2–6]. In Europe, tinea pedis and onychomycosis are estimated to affect a quarter of individuals [7]. Onychomycosis causes a significant burden on quality of life, causing high rates of embarrassment and other psychological sequelae [8–10], in addition to physical costs including pain and loss of dexterity [11].

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Onychomycosis is caused most commonly by dermatophytes followed by yeasts, then non-dermatophytic molds [12]. The predisposing factors, as well as the factors for relapse and reinfection, are important for clinicians to understand to optimize management strategies for at-risk individuals. Predisposing factors include genetic and non-modifiable risk factors, medical conditions, and physical and environmental influences (Table 2.1).

State of Art

Genetic and Non-modifiable Risk Factors

Age is the principal non-modifiable risk factor for the development of onychomycosis. The prevalence of onychomycosis increases significantly with age [13].

Estimates range from 15 to 47.7 % [8, 14, 15] in the elderly, compared to 0.44–0.6 % [8, 16] of children and 10–20 % [8] of adults. Poor peripheral circulation, repetitive nail trauma, diminished immune response, slower nail growth, and duration of exposure to fungi have been suggested as reasons for this age disparity [8]. However, while children experience the lowest prevalence, it is more often

Clinical Pearls (Table 2.1)

Table 2.1 Predisposing factors for onychomycosis

Category	Factors cited in the literature
Genetic and non-modifiable risk factors	Older age [8, 13–15] Male sex [13] Parent or child with onychomycosis [13] Autosomal dominant pattern of inheritance in distal subungual onychomycosis [18–21]. HLA-DR53 [22] and HLA-DR6 [23] may confer protection ICAM-1 deficiency in chronic nail candidiasis [25] Single nucleotide polymorphism in the Dectin-1 gene [26]
Medical conditions	Diabetes [27–31] Immunosuppression [13, 18, 33, 35] HIV infection [18, 33, 34] Concurrent tinea pedis infection [13, 36] Psoriasis [13, 37, 38] Peripheral arterial disease [40–42] Venous insufficiency [41, 43]
Physical and environmental factors	Athletic activity, especially swimming [2, 13, 44, 45] Nail trauma [8] Obesity [8, 46] Smoking [40] Increased prevalence of opportunistic fungal pathogens in the environment [47]

misdiagnosed in them [2]. Lastly, gender also plays a role; most studies have found a higher prevalence in males [13].

Genetic factors, such as inheritance patterns, the role of human leukocyte antigens (HLA), and intensity of immune response [17], have also been studied as potential predisposing factors. Distal subungual onychomycosis caused by *T. rubrum* shows an autosomal dominant pattern of inheritance (Fig. 2.1) [18–21]. Having a parent or child with onychomycosis has also been shown to be a predisposing factor [13].

Several studies have identified a possible role of HLA in the immune response of T cells to fungal peptides; HLA-DR53 [22] and HLA-DR6 [23] may confer protection. However, studies of the role of HLA are inconsistent as another study suggested HLA-controlled immunity is unlikely [24]. Other genetic risk factors may include ICAM-1 deficiency in familial chronic nail candidiasis [25]. Additionally, an allele of the Dectin-1 gene with a single nucleotide polymorphism was identified in a family with a propensity for onychomycosis and vulvovaginal candidiasis [26].

Medical Factors

Acquired medical conditions are significant predisposing factors for onychomycosis. Comorbid cutaneous, vascular, endocrine, infectious, and oncologic conditions have all been implicated [8]. For example, diabetics have a significantly higher

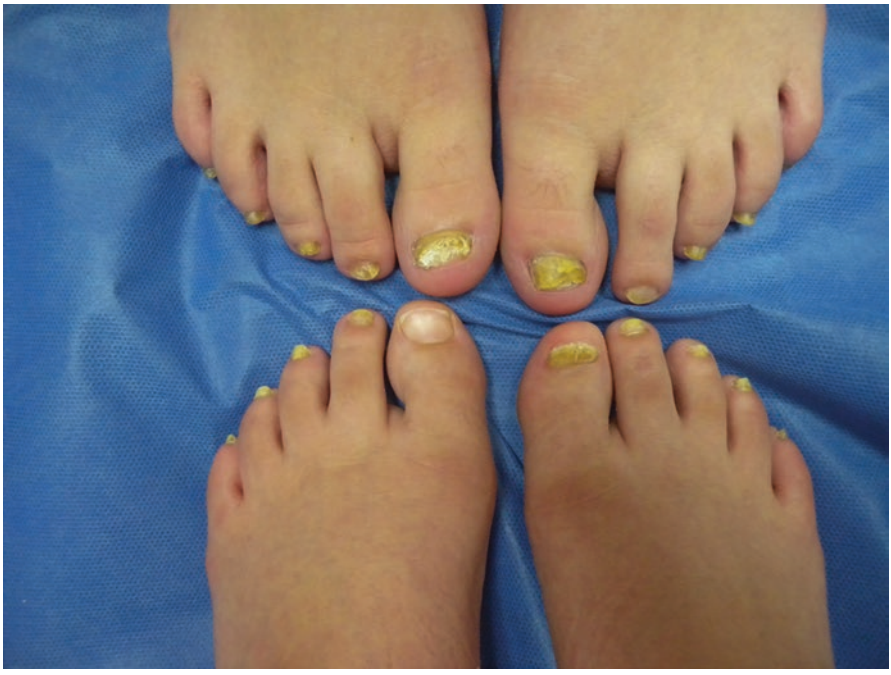

Fig. 2.1 Distal lateral subungual onychomycosis due to T. rubrum in two sisters

likelihood of developing onychomycosis [27, 28], with an estimated one third of diabetics affected (Fig. 2.2) [27, 29]. In patients with diabetic foot complications, the prevalence is even higher, with 53.3 % of patients affected in one study [30]. Additionally, onychomycosis in diabetics can lead to serious complications including limb-threatening infections due to the micro- and macrovascular and neurologic sequelae of diabetes [29]. Diabetics are also prone to less common fungal organisms including Aspergillus [31]. Lastly, there is some evidence that onychomycosis in diabetics may be resistant to treatment, but studies are conflicting [8, 32].

Immunosuppressed patients such as those with HIV [18, 33] or cancer [13] are also at increased risk of developing onychomycosis. Studies of HIV-infected individuals have estimated a prevalence of a quarter [33] to 30.3% [18, 34] compared to 6.9 [33] to 12.6 % [34] of immunocompetent controls (Fig. 2.3). Associated factors in HIV-positive individuals include a CD4 count of 370 or less, family history, history of tinea pedis, use of swimming pools, and walking barefoot [33]. Proximal subungual onychomycosis is also more prevalent in immunosuppressed patients [33, 35]. Recurrent proximal subungual onychomycosis was identified in a patient with a defect in defect of polymorphonuclear chemotaxis [35]. There is also a risk of systemic dissemination in immunocompromised patients, particularly of Fusarium species [18]. Importantly, in patients with a compromised immune system, the usual dose and treatment length may not be appropriate and drug interactions may be an issue [18].

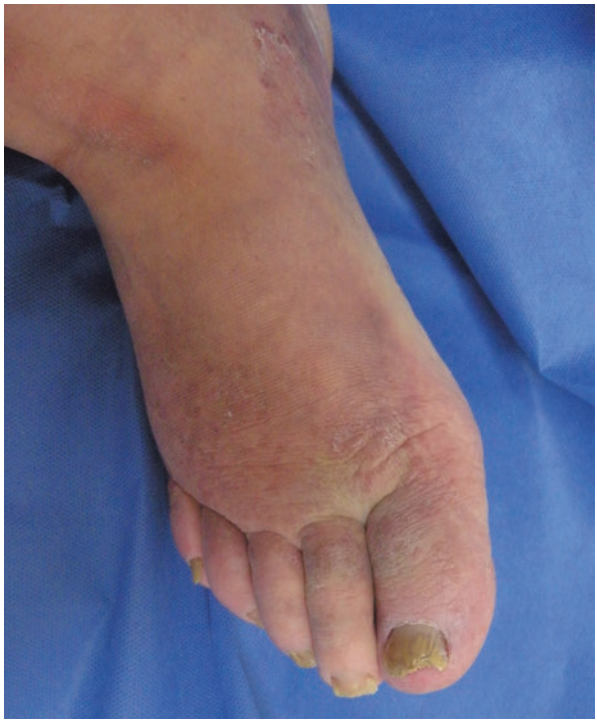

Fig. 2.2 Distal lateral subungual onychomycosis and tinea pedis in a diabetic patient

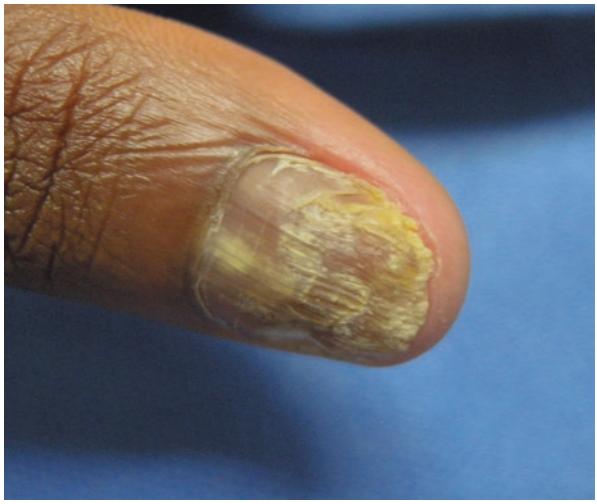

Fig. 2.3 Proximal subungual onychomycosis in a patient with HIV infection

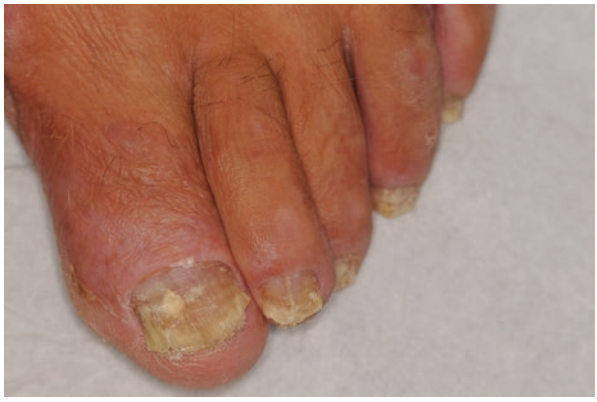

Fig. 2.4 Distal lateral subungual onychomycosis and psoriasis

Concurrent tinea pedis infection increases the risk of onychomycosis [13, 36]. Both the moccasin and interdigitalis form are implicated [13]. Tinea pedis is also associated with subclinical onychomycosis in which fungal organisms are isolated from the nails without any clinical manifestations. In a study of 35 patients with tinea pedis, 6 cases (17 %) had subclinical onychomycosis compared to 1 case (1.5 %) in the 66 control subjects [36]. Subclinical onychomycosis is also common in diabetics and is associated with neuropathy and poor glycemic control [29].

Dermatophytic invasion of involved psoriatic nails is more common than previously thought (Fig. 2.4) [37]. The organisms isolated from patients with psoriasis are similar to those of the normal population, although the odds of having onychomycosis are greater than those of the same age and sex [13, 38]. However, in an in-patient setting, the prevalence of onychomycosis among patients with psoriasis may not be different from those with other skin disorders [39].

Peripheral arterial disease and venous insufficiency are also thought to confer a greater risk for onychomycosis [40–42]. However, studies are conflicting. Ozkan et al. found a significant increase in onychomycosis in patients with venous insufficiency but not in peripheral arterial disease [41]. This contrasts with a study by Fukunaga et al. who found a significantly higher proportion of onychomycosis in patients with peripheral arterial disease than those without [43].

Other medical conditions that may show an increased risk include angioedema, urticaria, and asthma [13]. However, these connections were not strong and are not confirmed by any additional studies.

Physical and Environmental Risk Factors

Physical and environmental factors also play a role in the development of onychomycosis. For example, frequent athletic activity appears to increase the risk of onychomycosis [2, 44]. Athletes are more susceptible to developing toenail problems in general and onychomycosis is a common observance. However, the association between activity level and development onychomycosis is stronger in children and young adults than in older adults [2]. Swimming in particular has been associated with higher risk in several studies [13]; one study estimated the risk for toenail onychomycosis was three times higher for swimmers than the general population [45]. Further, wearing airtight shoes for sports like running and cycling is often associated with onychomycosis [2, 8].

Other physical and environmental factors that may increase the risk of onychomycosis include obesity [8, 46], nail damage [8], smoking [40], and prevalence of opportunistic fungal pathogens in a given environment [47]. Obesity may also negatively affect treatment outcomes; in two studies, topical 10 % efinaconazole was less effective in overweight or obese patients [8]. The evidence for smoking is less clear as studies are conflicting. One study found no correlation, but had too few heavy smokers to make any significant conclusions [13]. Another study by Gupta et al. found an association in smokers who attended a vascular clinic. However, the risk odds ratio was much higher for those with peripheral arterial disease (4.8) compared to those who smoked (1.9) [40].

Outlook: Future Developments

The risk factors for relapse and reinfection are the same as the predisposing factors for onychomycosis [18]. However, the risk factors for dermatophytic infections are not the same as for mold onychomycosis. Moreover, no systemic or local predisposing factors for mold onychomycosis have been identified [48]. Important future directions will include recognizing any predisposing factors for

mold onychomycosis, if they exist, as well as optimizing or personalizing treatment plans based on what underlying conditions and predisposing conditions patients have.

Summary for the Clinician

Predisposing factors for onychomycosis include genetic, medical, physical, and environmental factors. Certain comorbid medical conditions such as diabetes or an immunosuppressed state are especially associated with a higher prevalence of onychomycosis. Further, treatment for patients with certain diseases or physical characteristics, like diabetes and obesity, may be less effective. Identification and management of these underlying conditions is important.

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