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The Relationship Between Onychomycosis infections and Diabetes: Risks and Management: Review

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Abstract. Diabetes mellitus is a very frequent chronic condition globally, presenting a substantial health issue due to its severe effects on several body processes and its correlation with different consequences. Among these problems, onychomycosis, or fungal nail infections, is a prevalent yet sometimes disregarded illness that can substantially impact patients' quality of life and general health. Onychomycosis is a fungal infection that affects the nail structure, resulting in discoloration, thickness, and occasionally total loss of the nail. The likelihood of getting onychomycosis is significantly increased in diabetic individuals due to weakened immune response, poor circulation, and consistently high blood glucose levels, which provide an optimal environment for fungal proliferation. This review seeks to examine the complex link between diabetes mellitus and onychomycosis, emphasizing the underlying processes, risk factors, and clinical consequences of this interaction. Moreover, it underscores the significance of prompt identification and efficient therapy options to alleviate the effects of this illness and enhance patient outcomes.

Highlights:

1. Diabetics risk infection — 3× higher onychomycosis, ulcers, amputations risk.
2. PAS stain best — 92% sensitivity, superior to culture and KOH.
3. Combo therapy works — Oral terbinafine + topical boosts cure rates.

Keywords: Onychomycosis, Diabetes, Antifungal Treatment, Diagnosis, Complications

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Introduction

Onychomycosis is a highly widespread and severe fungal infection of the nails, impacting a vast worldwide population. This condition manifests in various ways, including alterations in nail plate color to white-yellow, susceptibility to onycholysis and hyperkeratosis, a high prevalence in toenails, the appearance of small, white, dull areas affecting only the superficial layer of the nail plate, a strong association with athlete's foot syndrome or changes in toe posture, initial involvement of the nail matrix followed by subsequent encroachment on the nail plate, the presence of a whitish area on the

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lunula, particularly in fingernails, and extensive invasion of the nail plate without discoloration of the nail bed and lamellar splitting of the affected nails. The concluding phase of all clinical variants of onychomycosis is marked by nail hypertrophy, opacity, and fissuring. The nail plate exhibits fragility, typically resulting from dermatophytes, non-dermatophytes, and yeast. This condition is the most prevalent nail issue encountered in clinical settings and presents considerable challenges, such as localized discomfort, paranesthesia, difficulties in executing everyday tasks, and hindered social relations [2]. Various underlying disorders, including tinea pedis, nail damage, and nail psoriasis, can elevate the risk of onychomycosis, along with variables such as age and weight. Moreover, preexisting comorbidities such as diabetes, cancer, immunodeficiency, or peripheral artery disease may heighten vulnerability to this infection [3].

The Relationship between Diabetes and Nail Changes or Disorders

Diabetes is a disease marked by consistently increased blood glucose levels. If unregulated, this rise may result in various problems, such as retinopathy, nephropathy, and diabetic neuropathy (DN). Neuropathy and peripheral vascular disease are the principal consequences impacting the lower extremities, markedly elevating the incidence of diabetic foot ulcers (DFUs) [4]. In people with normal blood glucose levels, insulin modulates neutrophil activity and serves as an immunomodulator. Chronic hyperglycemia in diabetic individuals negatively impacts cellular immunity and polymorphonuclear leukocytes, diminishing their phagocytic activity and heightening vulnerability to bacterial and fungal infections. persons with diabetes are roughly three times more susceptible to developing onychomycosis than non-diabetic persons [5].

Infections in Diabetic Foot

Diabetic patients experience alterations in the foot and skin that increase their susceptibility to infections and associated complications. Infections generally considered benign in non-diabetic individuals can lead to significant complications in diabetic patients [6]. Diabetic foot infections encompass a spectrum from onychomycosis and tinea pedis to cellulitis, severe necrotizing fasciitis, and potentially life-threatening infections [7].

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Onychomycosis (Fungal Nail Infection)

Onychomycosis can result in nails becoming thick, sharp, and brittle, potentially leading to foot injuries. Nail unit erosion may result from poorly fitting footwear, especially in individuals with sensory loss, thereby heightening the risk of ulcers and secondary infections affecting deeper tissues and bones [8].

Tinea Pedis (Athlete's Foot)

Tinea pedis presents a considerable risk to individuals with diabetes. The condition typically impacts the interdigitated regions, leading to fissures that heighten the risk of secondary infections. Additionally, tinea pedis occurs in about two-thirds of diabetic patients with onychomycosis, complicating both the infection and its management [9].

Complications

Onychomycosis and tinea pedis can lead to skin fissures, thereby undermining the skin's natural barrier function. This can result in diabetic foot ulcers and subsequent infections. In conjunction with complications associated with diabetic foot, these infections may lead to severe consequences, such as non-healing ulcers, deep tissue and bone infections, lower limb amputations, sepsis, and mortality [10].

Diagnosis

Direct Examination: Samples are positioned on a slide and subjected to a potassium hydroxide solution with a concentration of 10–30%. The slide can be heated to improve the visibility of fungal characteristics. A combination of potassium hydroxide and dimethyl sulfoxide is suggested for improved clarity and expedited outcomes. Nail fungus resulting from dermatophytes can be identified by the presence of elongated, regular hyphae. If yeast is the causative agent, budding spores may be present. The appearance of the nail may offer insights into the causative agent; however, it is insufficient for diagnosing the infection independently [11].

Culture: In the absence of clinical symptoms, culture is the preferred method for diagnosing nail fungus. Samples of the nail plate and subungual debris must be inoculated onto Sabouraud's agar and incubated at 26°C for a duration of 7 to 14 days. The samples may be placed on agar containing or excluding cycloheximide, as cycloheximide inhibits the growth of most non-dermatophytes. Although culture is less sensitive than direct microscopy, particularly post-treatment initiation, it is the sole

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method for identifying the specific pathogen. This identification is crucial for treatment selection, especially in cases where nails do not respond to oral terbinafine [12].

Histopathological Examination: Nail clippings may undergo histopathological evaluation utilising PAS stain, recognised as the most sensitive test available. A study assessed 105 patients with suspected nail fungus through KOH preparation, culture, PAS biopsy, and Calcofluor white biopsy methods. Calcofluor white biopsy is regarded as the gold standard. The research indicated that KOH preparation exhibited a sensitivity of 80% and a specificity of 72%, while PAS biopsy demonstrated a sensitivity of 92% and a specificity of 72%. In contrast, culture showed a sensitivity of 59% and a specificity of 82% [13].

Laboratory Diagnosis: The diagnosis of nail fungus is based on a clinical assessment, which is validated by a laboratory result, including direct microscopic examination using potassium hydroxide, fungal culture, or histological examination with PAS stain. Samples for microscopic analysis, culture, or histological assessment may be obtained from the nail plate or subungual debris. Specimens should be collected from patients with diabetes with caution to prevent injury to the nail bed, as this may elevate the risk of secondary bacterial infections [14].

Treatment

1. Effective Treatment in Diabetic Patients with Onychomycosis
    - Onychomycosis in diabetic patients may result in various complications, including thickened, dystrophic nails that cause pain and impede ambulation, as well as unnoticed injuries to adjacent skin from mycotic nails, which can lead to secondary fungal or bacterial infections, such as paronychia and cellulitis [15].
    - Terbinafine, classified as an allylamine antifungal, serves as the primary treatment for onychomycosis. The administration involves a daily dosage of 250 mg over a period of 3 months. Reports mycological cure rates of 82% for toenail onychomycosis and 71% for fingernail onychomycosis. A study with 89 diabetic patients demonstrated a mycological cure rate of 73% without any episodes of hypoglycemia [16].

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- Itraconazole is demonstrated to be safe and effective at a dosage of 200 mg administered twice daily, with no significant alterations in HbA1c levels noted in diabetic patients [17].
- Topical therapy demonstrates reduced efficacy compared to systemic therapy; however, it is associated with fewer adverse effects. Nail infections are typically inadequately treated due to insufficient penetration, with the exception of superficial white onychomycosis [18].

2. Combination Therapy

   The combination of oral and topical antifungals enhances the probability of achieving a cure. Research indicates enhanced efficacy of terbinafine in conjunction with topical amorolfine. Continuous itraconazole therapy demonstrated improved outcomes when used in conjunction with topical treatments [19].

3. Laser Therapy

   Laser therapy presents a potential treatment for nail fungus; however, it is currently supported by inadequate data. Most laser's function based on the principle of selective photothermolysis, necessitating wavelengths between 750 and 1300 nm for effective penetration of the nail. Commonly utilised laser types comprise long-pulse Nd:YAG lasers, diode lasers, and fractional CO2 lasers. Although laser therapy is effective for cosmetic enhancement, it does not exceed the clinical outcomes of oral or topical antifungal treatments. Laser treatments are deemed safe yet costly and may be considered for patients who are contraindicated for systemic antifungal agents or as an adjunct to other therapies [20].

4. Photodynamic Therapy (PDT)

   Photodynamic therapy (PDT) entails the photoactivation of a photosensitiser using light at designated wavelengths, thereby elevating the energetic state of the photosensitiser. Photosensitisers encompass 5-Aminolevulinic Acid (5-ALA), Methyl Aminolevulinate (MAL), porphyrins, methylene blue, among others. Evidence regarding PDT is restricted to case reports and non-randomized trials [21].

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Prevention

Although nail fungal infections exhibit high cure rates, the possibility of reinfection remains. Recurrence rates of 20–25% have been documented following initial treatment, encompassing both relapse and reinfection. Recurrence is influenced by genetic predisposition, a positive family history of fungal infections, and an impaired immune system [22]. Educating patients on preventive measures is crucial to minimize the risk of reinfection. Maintaining cool and dry feet is important, as warm and moist environments facilitate fungal growth. Patients are advised to refrain from wearing tight or closed shoes and to choose open-toed footwear instead. Shoes that are infected must be either discarded or treated with topical antifungal agents, and nails should be kept short. Prompt intervention for fungal infections can diminish the risk of recurrence, given that infected skin serves as a reservoir for the infection [23]. Experts recommend against walking barefoot in public areas to prevent reinfection and emphasize adherence to prescribed treatment, particularly for long-term therapies. Experts recommend the application of topical antifungals on a weekly or bi-monthly basis for patients at elevated risk of recurrence, extending for a duration of up to two years following the completion of initial treatment [24].

Effectiveness of Topical Antifungal Prophylaxis:

In comparison to the absence of prophylaxis, the application of a topical antifungal biweekly following terbinafine treatment has demonstrated efficacy in decreasing the recurrence rate.

- The recurrence rate with prophylaxis is 33%.
- The recurrence rate in the absence of prophylaxis is 76% [25].

Discussion

The initial study conducted among diabetics in Cameroon indicated that distal subungual onychomycosis was the predominant clinical presentation, aligning with findings from other studies [26]. The significant prevalence of this subtype may indicate extended exposure to dermatophytes in tropical regions, exacerbated by inadequate foot hygiene practices in resource-constrained environments [27].

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Research indicates that onychomycosis in diabetic patients correlates with subclinical atherosclerosis, which is the primary cause of mortality in this population [28]. Chronic inflammation resulting from fungal infections can worsen endothelial dysfunction, thereby accelerating the formation of atherosclerotic plaques. This mechanism is evidenced by increased inflammatory markers in diabetic patients with onychomycosis [29]. The thickened, brittle nails characteristic of this infection were observed to inflict damage on the adjacent skin, which may remain undetected due to concurrent neuropathy. Enlarged, dystrophic toenails exert increased pressure on the underlying toe, compromising its vascular supply and resulting in pressure ulcers [30]. The mechanical stress is notably problematic in individuals with diabetes, as compromised wound healing heightens the likelihood of ulcer advancement to gangrene [31]. The pressure necessary for clipping thickened toenails has been recognised as a possible factor contributing to unintentional injury of the adjacent skin. In cases where patients could not maintain adequate foot hygiene, the overgrowth of thickened toenails was observed to exacerbate skin damage [32]. Podiatric interventions, including regular nail debridement, have demonstrated a 58% reduction in complications among neuropathic patients [33]. Subungual debris characteristic of distal subungual onychomycosis has been identified as a reservoir for moulds and bacteria, potentially invading compromised skin barriers [34]. Coinfections involving Staphylococcus aureus and Pseudomonas aeruginosa in these instances are associated with increased incidences of cellulitis and osteomyelitis [35].

Systemic treatment is indicated for patients with three or more affected nail plates or involvement of the nail matrix [36]. Recent guidelines highlight the importance of combining oral antifungals with topical ciclopirox to enhance cure rates, especially in patients with more than 50% nail involvement [37]. Treatment adjustments were necessary for patients with chronic renal disease (creatinine clearance <50 mL/min), as terbinafine was contraindicated in these cases. In these instances, itraconazole was advised; however, the presence of polypharmacy in diabetic populations complicated management due to potential drug interactions [38]. Itraconazole's inhibition of CYP3A4 significantly increases risks when co-prescribed with common diabetic medications such as sulfonylureas, thereby necessitating dose reductions [39]. Baseline and follow-up liver function tests are essential for patients receiving itraconazole, as studies indicate

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that 3.7% of users experience asymptomatic transaminase elevations. Emerging therapies such as fosravuconazole demonstrate potential for patients with hepatic comorbidities, attributed to their lower hepatotoxicity profile [42].

The Achilles Foot Screening Project identified fungal infections as the predominant foot diseases in diabetic patients consulting dermatologists, with onychomycosis at 23% and tinea pedis at 22%, accounting for 35% of cases overall [43]. The elevated incidence may be associated with immune dysfunction linked to diabetes, which hinders Th17-mediated antifungal responses [44]. A 14-year retrospective study on mold-related onychomycosis conducted at the Hospital General de México found that lateral and distal subungual presentations occurred in 69% of cases, with Scopulariopsis brevicaulis and Aspergillus niger identified as common pathogens [45]. These moulds demonstrate intrinsic resistance to terbinafine, highlighting the necessity for species-specific treatment [46].

Mixed infections and non-dermatophyte moulds are observed to be more common in warmer climates, with humidity levels exceeding 80% enhancing the viability of mould spores on nails. Regional variations in antifungal susceptibility patterns complicate treatment; for instance, Aspergillus species in tropical zones exhibit 32% resistance to itraconazole [49].

The direct examination using KOH is characterized as operator-dependent, yet it shows correlation with culture and histopathological findings [50]. False negatives are a significant issue, as KOH sensitivity decreases to 61% in early infections when compared to PCR-based methods [51]. Calcofluor white staining has been shown to improve both sensitivity and specificity in the detection of fungi, especially in distinguishing arthroconidia from keratin granules. The study's limitations comprised the absence of molecular confirmation and difficulties in differentiating pathogens from contaminants or secondary invaders [54]. The integration of MALDI-TOF mass spectrometry has the potential to enhance the accuracy of pathogen identification, as evidenced by recent mycological studies [55]. Clinical scoring systems, such as the Onychomycosis Severity Index, may assist in standardizing diagnostic criteria across various populations [56].

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