The association of yeast infections with diabetic foot ulcer

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Abstract

Recently, fungal infections have increased, and it has been shown that microbial infections are associated with diabetic foot ulcers. In general, diabetic patients were considered immunocompromised patients with insufficient immune defense and would therefore be at risk of developing a microbial infection, such as bacterial, yeast or filamentous infections. Previous works were designed to investigate the implication of yeast species as etiological agents for developing diabetic foot infections. The results suggested that *Candida albicans* is the most common species followed by *C. dubliniensis*, *C. tropical* and parapsilosis and other pathogenic species. Pathogens are resistant to inconvenient and harsh conditions; to overcome these unwanted conditions, they synthesize a variety of elements that enhance the ability of the pathogen to survive and infect the host. These elements are called virulence factors. Yeast possesses the potential ability to produce these necessary elements, for example, biofilm formation, and hydrolytic enzymes. Two hydrolytic enzymes were selected in this review, phospholipase and aspartyl proteinases (*SAP*) and h. Each enzyme has a particular function that involves the mechanism of adhesion, penetration, and invasion of pathogenic yeast into the host tissues. The hydrolytic enzyme activities were analyzed at a phenotypic and genotypic level.

Keywords: Yeast, Candida, diabetic foot ulcer, virulence factors

Introduction

Fungal infections, often known as mycoses, are responsible for a large spectrum of diseases in living organisms, including humans. Few superficial infections are disseminated to other organs, such as the brain, causing a hazard or lethal infections (1). Fungal germs are prevalent colonizers on a variety of human mucosal surfaces, where they can survive by evading host defenses (2). Disruption of physical barriers or weaknesses in immune defenses can enhance the ability of microbiota to invade the host deeply Disturbance of the physical barriers or weaknesses of immune defenses enhances the ability of the microbiota to evade the host deeply. Consequently, life threatening infections will develop leading to economic loss (2). Previous studies indicated that invasive fungal infections (IFIs) were frequent in clinical practice, with *Candida* spp. and *Aspergillus* spp. being by far the most common offenders (3). It was estimated that *Candida* species cause up to 400,000 cases of systemic fungal infection annually, with mortality rates of up to 40% (4).

Diabetes mellitus is the most common endocrine metabolic disorder that disturbs

the immune balance (5) leading to serious conditions, such as the diabetic foot. With the modern lifestyle, the prevalence of diabetic foot has recently increased, with various causative agents including fungal infections. Serious fungal foot infections have been reported to lead to morbidity, mortality, and disability (6). Diabetes-related foot ulcers (DFUs) are a complex combination of neuropathy, peripheral arterial disease, foot deformities, and infections (7)**.**

Many factors contribute to the pathophysiology of the diabetic foot, including peripheral vascular disease, which causes poor circulation to the legs and feet, and neuropathy, a condition in which nerve damage from diabetes causes an impaired sensation in the lower extremities, which can lead to minor abrasions and ulcerations on a diabetic patient's foot going unnoticed until it is too late. In diabetics, these situations can quickly lead to a dangerous microbial infection (8). In these ulcers, secondary infections such as bacterial, fungal, and viral infections are common. Poorly treated diabetic foot ulcers showed significantly higher fungal infection and require particular attention and management (5).

Filamentous fungi and yeasts have been identified as etiological agents of diabetic foot infection (9). *Candida* spp. is the most common fungus found in diabetic foot ulcers (9).

Pathogens produce elements that are known as the virulence factor that contributes to enhancing pathogenicity and adaptation against inconvenient surrounding conditions (10). The production of extracellular hydrolytic enzymes, such as phospholipase and proteinase, facilitates microbe adherence and escape from the host immune system leading to tissue damage (11). Haemolysin was suggested as another virulence factor that facilitates disseminated infection (12). Both *C. albicans* and Non-*Candida albicans* (NCA) species can produce these virulence factors (11).

The aim of this review is to investigate the association of yeast infections with diabetic foot ulcer and to focus on the hydrolytic enzymes as a virulence factor.

Diabetic foot

Uncontrolled blood sugar in the diabetic patients is implicated with diabetic foot, which develops several conditions including diabetic foot ulcers, diabetic foot neuropathy, peripheral vascular disease, foot deformities, and amputation (13).

Diabetes-related foot ulcers (DFUs) are a significant condition that affects around 25% of patients with diabetes. (14). It has been described as poorly healing full-thickness dermis wounds below the ankle in diabetic patients, who have had the condition for more than three months.

Neuropathic, ischemic, and neuroischaemic ulcers are the three forms of DFUs (15). In the majority of cases, defects in immunity, peripheral vascular dysfunction, and slower wound healing are further potential contributors and increase the frequency of infections (16). Additionally, high glucose levels are associated with enhanced microbe virulent (9).

Three different forms of infections can affect diabetic patients: mild, moderate, and severe (17). Also, there are three main classes of diabetic foot wound based on the University of Texas wound classification system of diabetic foot ulcers, which is the most famous system. Diabetic foot wounds were classified

according to the University of Texas's system of grades as follows: Grade 0 refers to a pre- or post-ulcerative site that has healed. Grade 1 refers to a superficial wound that does not involve a tendon, capsule, or bone. Grade 2 refers to a wound that penetrates a tendon or capsule (wound penetrating bone or joint). Within each wound grade, there are four stages: clean wounds (stage A), non-ischemic infected wounds (stage B), ischemic non-infected wounds (stage C), and ischemic infected wounds (stage D)(18).

The prevalence of diabetic foot among diabetics increased from 0.7% in 1980 to 2.7% in 1999 (18). The most common reason for hospital admission for patients with diabetes is diabetic foot. According to estimates, 15% of diabetics who have big toes develop foot ulcers across age, and 14–24% of them require amputation preventable (18). Although one leg is amputated every 30 seconds throughout the world due to diabetes, 80% of these cases are preventable (5). Diabetic foot is the most common reason for non-traumatic lower limb amputation, accounting for 40% to 60% of cases. (18). The lesions on the feet are frequently persistent and difficult to treat. These ulcers are exposed to bacterial, fungal, and viral secondary infections (19). Diabetic foot ulcers that were poorly treated had noticeably more fungal infections and needed careful treatment. (5).

Yeast infections

Patients with weak immune defence are prone to microbial infections; meanwhile yeast is one of the prominent microorganisms implicated with diabetic foot infections. (8). It was reported that nearly 56% of diabetic foot ulcers were infected, and 20% of them were amputated in some way (20). The majority of cases of diabetic foot infections, which have been reported, are polymicrobial, while mycotic infections are more likely to result in the development of diabetic foot syndrome (8,20). When fungi isolated from diabetic foot are identified in skin or nail scrapings, they are usually invariably superficially pathogenic. Such infections are most commonly caused by *Trichophyton rubrum* or *Trichophyton metagrophytes* (8).

In Thailand, *Scytalidium dimidiatum* is the main culprit behind tinea pedis and onychomycosis in patients with fungal diabetic foot infections (8,21). Additionally, it has been suggested that *Candida* species is the most common fungal species that were isolated from diabetic foot infections (22).

Furthermore, EL-Nagar *et al*. revealed that 51.7% of diabetic patients suffering from fungal infections and *C. albicans* was the most predominant isolated organism (47.2%) among candida species in deep tissues of DFU(24).

Virulence factors

Microbes have a potential ability to overcome the inconvenient conditions by producing certain elements that enhance their ability to survive. These elements are called virulence factors. Biofilm, pigments, and extracellular hydrolytic enzymes are examples of the virulence factors found in yeast cells that increase pathogenicity.

Many enzymes, which considered as a virulence factors, involve the mechanism of adhesion, penetration, and invasion of pathogenic yeast into the host tissues. The ability to acquire extracellular nutrients is also thought to be enhanced by these enzymes (25,26).

Extracellular hydrolytic enzyme synthesis can facilitate adhesion and escape from the host immune system, as well as damage tissue (11). Examples of these enzymes are phospholipase and proteinase. Another virulence factor that aids in the spread of infection is hemolysin (11).

In this review, two types of hydrolytic enzymes have been taken into account as follows:

Phospholipases

The phospholipases enzymes were identified as one of the virulence factor in the pathogenic yeast. Five hydrolytic enzymes were identified and categorized into five groups: A1, A2, B, C, and D, depending on which ester bond is dissolved (27). However, two genes, *PLB1* and *PLB2*, were identified that encoded Phospholipases in the C albicans.

The primary function of phospholipase is to hydrolyze the phospholipids found in the host cell membrane.In other words, all phospholipases use phospholipids as their substrates, each enzyme can cleave a specific ester bond (28), which is also the primary building block of cell membranes (27).

The two major phospholipases that associated with pathogenicity in fungi are phosphatidylinositol (*PI*)-preferring phospholipase C (*PI-PLC/Plc*) and phospholipase B (*Plb*) (29,27,30). The Previous work evidence demonstrated the implication of phospholipases with the host cell penetration, damage, and lysis in *C. albicans* (28).

The aspartyl proteinases (*SAP*)

The aspartyl proteinases are encoded by ten including *SAP1* to *SAP10* (31). Proteinases enhance the ability of pathogenic cells to adhere to host surfaces. Because of this function, this enzyme is considered a significant virulence factor (32). However, proteinases synthesized by most *Candida* spp., the expression rate varied among species based on host and environmental factors (31)**.** *SAP9* and *SP10* remain bound to the surface of the cell, while *Sap1–Sap8* are secreted and discharged into the environment (32). Previous work found that the *Sap1-Sap3* genes enhance the virulence of pathogens in the mouse model as well as damage reconstituted human epithelium (RHE) in vitro. A variety of hydrolytic enzymes secrete in bacterial species for example *Staphylococci epidermidis* (33). The correlation of proteinases with pathogenic microbes' virulence was demonstrated (34,35). Al-laaiby *et al*. suggested that oral cavity flora possess the potential virulence factors, such as proteinase that make the opportunistic creature explode any disturbance in the host balance(36). Numerous pathogenic *Candida* species, such as *C. dubliniensis*, *C. tropicalis*, and *C. parapsilosis*, were found to contain *SAP* genes, which produce active extracellular proteinases in vitro. *C. tropicalis* have four *SAP* genes, whereas only two genes were determined in the *C. parapsilosis* (30). Generally, the significance of *SAP* proteinase in C. *dubliniensis* pathogenicity has not been extensively discussed in the previous studies (38,39,30).

Highly proteolytic strains of *C. albicans* were shown to attach to human buccal epithelial cells more readily (39). additionally, *SAP*(s) have been demonstrated to adhere to the cell wall, raising the possibility that these enzymes do play a role in *C. albicans*' adhesion to host surfaces (40). A link has also been discovered between phagocytic resistance and *SAP* synthesis, as *C. albicans* cells

induced for Sap production demonstrated significantly higher phagocytic resistance than uninduced cells (41). Studies with cultured phagocytic human tumor cells (V-937) infected with *Candida* cells provided additional support for a function for Saps in phagocytosis resistance (39). Saps have a diverse spectrum of substrates that can hydrolyze, including both pure and conjugated proteins. The *Candida SAPs* can hydrolyze collagen, keratin, and mucus, unlike other aspartic proteinases (39). A cytotoxic effect was also observed, which greatly reflected the yeast's proteolytic activity, and pepstatin A had a dose-dependent inhibitory effect (39).

Conclusion

Diabetic patients are at risk of developing a diabetic foot ulcer, which are associated with fungal and yeast infections. It has demonstrated that unbalanced blood sugar is related to weakened immune defenses. Different yeast species can cause serious infections in immunocompromised diabetic patients. The most common species identified was *C. albicans*. Pathogenic microorganisms, including yeast, have a potential capacity to produce important elements that enhance the pathogen's ability to overcome harsh circumstances, called virulence factors. The hydrolytic enzymes, such as phospholipase, proteinase and hemolysin were regarded as significant virulence factors. The mechanisms of infections included the adhesion and penetration to the cell, therefore, each enzyme has a particular function. The cell membrane composes of protein and lipids. According to enzyme function, phospholipase hydrolyses lipids, while proteinase hydrolyses proteins.

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