Gender of the Human Host to Fungal Infection

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Host sex or gender influences the incidence of some fungal infections in humans such as aspergillosis, cryptococcosis, paracoccidioidomycosis, dermatophytosis, and candidiasis due to differences in immune response, behavior, and awareness for early detection and treatment. The dimensions of sex and gender are important determinants throughout the fungal infection process and in approaches to prevent or treat these infections, as well as in development of antifungal drugs. Failure to consider sex and gender may be detrimental to the holistic understanding of the processes involved in fungal infection.

Keywords: fungal diseases ; fungal infection ; Candida albicans ; Aspergillus fumigatus ; Cryprococcus neoformans ; Paracoccidioides brasiliensis ; dermatophytosis ; sex ; gender

1. Introduction

Fungi have a tremendous impact on people's daily lives, much more than most people realize. The fungal kingdom consists of 1.5 million species, while some estimates put the number of fungal species at 6 million, of which only about 5% have been described [1][2]. Fungi first appeared about 1.5 billion years ago and were among the earliest organisms domesticated by humans [3]. They serve as important biofactories for humans, although the vast possibilities offered by the compounds produced by fungi remain largely unexplored. Fungal biotechnology can facilitate the transition from a petroleum-based to a bio-based circular economy. Fungi can be used in the production of food, feed, chemicals, fuels, textiles, and materials for construction, transportation, furniture, and more in an efficient and sustainable manner [1][2].

However, fungi also produce toxins that can spoil food, and cause disease, especially in immunocompromised patients, but also in healthy people, driving up food safety and public health costs [1][2]. Only about 100 to 200 of all fungal species have been associated with human disease [3]. Invasion of the human body is a major challenge for fungal pathogens because they must be able to grow at high (human) body temperatures (i), reach target tissues by penetrating host tissue barriers (ii), digest and absorb components of human tissues (iii), and resist the human immune system (iv) [4]. Fungi that infect healthy humans devote a large part of their physiology to morphogenesis, the variability of cell shapes and the ability to switch between them, resisting or evading the immune system, and establishing a complex network of sensing and signaling systems to produce various proteins and compounds [5]. These proteins include digestive enzymes or lipid-binding pore-forming proteins or steroid-converting cytochromes P450 and other converting enzymes. During sexual development, various secondary metabolites are produced to protect the fungus from predators or hosts [6]. Understanding the pathophysiology of fungi in humans is particularly important for predicting the possible emergence of novel fungal pathogens that may result from global changes in the environment.

2. Difference of Sex and Gender of the Human Host in Susceptibility to Fungal Infection

Depending on biological characteristics, organisms can generally be classified as female, male, intersex, and hermaphrodite. Biological sex describes sexual distinction that goes beyond mere reproductive function and includes appearance, physiology, or neuroendocrine, behavioral, and metabolic systems [7]. Sex differences in humans are the result of a complex interplay of sex hormones, genetic variability, and the environment against a background of intrinsic effects of sex chromosome differences. Indeed, each adult human somatic cell exhibits sex-specific differences in gene expression and epigenetic profile to varying degrees. The long-recognized differences between men and women in health, longevity, disease risk and progression, and response to therapies have a genetic and epigenetic basis [8].

Gender refers to psychological, social, and cultural factors that shape attitudes, behaviors, stereotypes, technologies, and knowledge. It refers to spoken and unspoken rules regarding gender in society and how people in different cultures perceive themselves [7]. It is important to note that sex and gender are related in various unexpected ways. For example, perception of pain shows biological differences in signaling physiology, but also includes sociocultural components of how

women, men, or people of different genders report pain, and how physicians understand and treat pain depending on the patient's perception of gender [9]. Pain perception is an important factor in early detection and timely initiation of treatment for fungal infections.

The Gender and Gender Equality in Research guidelines (SAGER) emphasize the correct distinction between sex and gender to avoid confusion [10].

2.1. Is Awareness of Invasive Fungal Diseases Independent of Gender?

Because invasive fungal diseases cause significant morbidity and mortality, awareness is critical for early diagnosis and treatment. Public awareness of invasive fungal diseases was low in the 2019 U.S. study, with approximately two-thirds of respondents having never heard of any of the fungal diseases included in the study [11]. The least known fungal disease was blastomycosis (4.1% of participants), followed by aspergillosis, histoplasmosis, coccidioidomycosis, and cryptococcosis, and the best known was candidiasis (24.6%) [11]. Individuals who knew one fungal disease were more likely to recognize the others. Male sex, higher educational level, and higher number of prescribed medications were associated with higher knowledge of fungal diseases overall. Women were more than three times as likely as men to recognize candidiasis [11]. Further educational efforts are needed to increase people's awareness of fungal infections.

2.2. Who Can Get a Fungal Infection?

Fungi are common in the environment, and every day people breathe spores in or are exposed to fungi without getting sick. Anyone can get a fungal infection, even otherwise healthy people, but many of the fungal infections are classified as opportunistic. Some people are born with a weakened immune system; others suffer from a disease that impairs their immune function. In addition, some medications can interfere with the ability to fight infections [12]. Most fungal infections occur in people who are already seriously ill, and often jeopardize even the success of recent medical advances in cancer treatment, organ and hematopoietic stem cell transplantation, neonatal medicine, autoimmune disease treatment, trauma and critical care, and sophisticated surgery [4].

Although *Candida* and *Aspergillus* species remain the most common causative agents of invasive fungal diseases, there has been a worrying increase in regional fungal diseases and infections with invasive fungi of the genera *Blastomyces*, *Coccidioides*, *Histoplasma*, *Cryptococcus*, *Pneumocystis*, and *Sporothrix* [13]. New fungal diseases caused by fungi from different taxonomic groups are constantly emerging. The human fungal pathogens affecting healthy or immunocompromised individuals have been identified in several taxonomic groups: phylum Ascomycota, e.g., Chaetothyriales, Eurotiales, Hypocreales, Microascales, Mycosphaerellales, Onygenales, Ophiostomatales, Pleosporales, Pneumocystidales, Saccharomycetales, and Venturiales; phylum Basidiomycota, e.g., Malasseziales, Tremellales, and Trichosporonales; subphylum Entomophthoromycota, e.g., Entomophthorales; and phylum Mucoromycota, e.g., Mucorales [4][14][15]. Not much is known about the relationship between mating type and infection in some of these species.

2.3. Is There a Sex-Dependent Difference in the Human Immune Response?

The sex of the human host influences the immune response to various antigens, e.g., fungi, viruses, bacteria, parasites, and allergens, and shows differences in innate and adaptive immune responses. Differences in immune response can be influenced by both sex and gender, with sex contributing to physiological and anatomical differences that affect fungal exposure, recognition, clearance, or transmission [16]. Some immunological differences between sexes persist throughout life, while others become apparent only after puberty and before reproductive aging, suggesting the involvement of genes and hormones. Conversely, gender may reflect behaviors that affect fungal exposure, access to healthcare, or mode of seeking medical help, which in turn influences the course of infection. In addition, early microbiome exposure also affects infections [16]. Female cyclic immunity should be considered to understand the phenotypic diversity of female behavioral immunity and reproductive behavior, male immunity, and the evolution of sex-specific pathogen virulence [17]. The resulting immunological differences contribute not only to differences in susceptibility to infectious diseases caused by fungi and other pathogens and response to vaccines in men and women, but also to the greater incidence of cancers or autoimmune diseases associated with fungal infections than in healthy individuals.

In general, sex and age influence: susceptibility to infection (i), modulation of immune response (ii), immunosenescence (iii), and response to vaccination (iv) [18]. For many infectious diseases, the rate of infection or mortality is higher in men than in women, with some exceptions, such as sexually transmitted diseases. Some infectious diseases are equally prevalent but more severe in women, e.g., measles, toxoplasmosis, dengue, or hantavirus. Aging alters the sex difference in part through the contribution of hormones (i) [18]. Estrogens significantly strengthen the immune system. Androgens and

progesterone have mainly immunosuppressive effects. The effects of sex steroid hormones are observed on both adaptive cells, e.g., CD4 + and B cells, and innate cells, e.g., natural killer cells, macrophages, and dendritic cells. Sex hormones affect cytokine secretion and the balance of cytokine profiles of T helper lymphocytes. Estrogens also increase the production of high-affinity immunoglobulins (ii) [18]. The immune and endocrine systems change with age, but the aging of the immune system in women and men is different. Menopause has a particularly strong effect on the immune system in women. Hormone replacement therapy partially reverses the effects of aging on the immune system and returns it to premenopausal levels, confirming the effect of hormones (iii) [18]. The immune response to some vaccines differs between women and men. Women often have a stronger humoral response, for example, to influenza and hepatitis B. Men may also have a stronger response, e.g., to pneumococcal polysaccharide vaccines. With age, the sex difference changes to some degree, suggesting a contribution from hormones. Animal models suggest that hormone replacement therapy may reverse vaccine efficacy in premenopausal levels (iv) [18].

The sexes differ in the intensity (i.e., pathogen load), prevalence (i.e., proportion of the population with disease), incidence (i.e., new cases), and severity (i.e., hospitalization or progression) of diseases caused by fungi, viruses, bacteria, and parasites. Men are generally more susceptible to these infections than women, but the reasons for the higher susceptibility in men are diverse [19][20]. Five types of fungal infections are considered here: aspergillosis, cryptococcosis, paracoccidioidomycosis, dermatophytosis, and candidiasis.

2.4. Susceptibility to Infection with the Fungus *Aspergillus fumigatus* by Sex/Gender

Sex differences in the anatomy and physiology of the respiratory system have been widely reported. These intrinsic sex differences have also been shown to influence the pathophysiology, incidence, morbidity, and mortality of various pulmonary diseases across the lifespan [21].

One study examined the incidence and development of invasive pulmonary aspergillosis and galactomannan testing in patients with aspergillosis infections [22]. For the incidence of invasive pulmonary aspergillosis, a male-to-female ratio of 1.85:1.15 was obtained. An increasing trend of invasive pulmonary aspergillosis was observed over time in both men and women. Galactomannan testing is recommended for early diagnosis of patients with suspected aspergillosis. The increase in the incidence of invasive pulmonary aspergillosis may be positively related to the increase in galactomannan testing over the past decade, with these tests being performed more frequently in men than in women [22].

In invasive pulmonary aspergillosis of patients with viral SARS-CoV-2 infection, the possibility of colonization is the most important confounder rather than invasive disease [23]. The vast majority of patients did not have any of the classic host risk factors, such as immunosuppression due to organ transplantation or neutropenia, although a significant proportion (half) had received corticosteroids. Male sex, age, and pulmonary comorbidities were associated with higher mortality. Mortality was generally lower in patients treated with voriconazole. In critically ill patients with coronavirus disease 2019 (COVID-19) who do not improve, clinical surveillance for associated pulmonary aspergillosis is advisable, even in patients who do not meet classic host criteria for invasive mycoses, especially if they are receiving corticosteroids [23].

Another study aimed to determine the frequency of invasive pulmonary aspergillosis in patients with COVID-19 admitted to the intensive care unit, to describe the characteristics of patients with invasive pulmonary aspergillosis, and to evaluate its impact on prognosis [24]. Invasive pulmonary aspergillosis is a relatively common complication in severe patients with COVID-19 and is responsible for increased mortality. Probable invasive pulmonary aspergillosis was diagnosed in 5.7% of patients with COVID-19 admitted to the intensive care unit and in 19.4% who had a respiratory sample taken due to an exacerbation. No significant differences were observed between patients with and without invasive pulmonary aspergillosis in terms of age, sex, medical history, and severity on admission and during hospitalization. Azithromycin, which is known to have immunomodulatory properties, may contribute to increasing the susceptibility of patients with COVID-19 to invasive pulmonary aspergillosis. The propensity for invasive pulmonary aspergillosis and its occurrence were observed at high doses of dexamethasone. All-cause mortality was higher in patients with invasive pulmonary aspergillosis [24].

Given the increasing incidence and mortality of influenza-related aspergillosis, a study summarized risk factors, clinical features, and prognostic factors for the development of aspergillosis in immunocompetent influenza hosts to further investigate the high-risk population and improve outcomes [25]. The study showed that coinfection with aspergillosis increased all-cause mortality in severe influenza from one-quarter to one-half of cases, along with higher white blood cell, neutrophil granulocyte, procalcitonin, and lower CD4 + T-cell counts in the death group. Sex, age, underlying disease, use of immunosuppressant and steroids, and CD4+ T-cell count did not affect the incidence of influenza-associated aspergillosis. However, cases of influenza-associated aspergillosis are usually more likely to have H1N1 subtypes and higher levels of C-reactive protein and interleukin-6 than cases without aspergillosis. Concurrent aspergillosis infection in

patients with severe influenza can lead to markedly increased mortality associated with severe respiratory failure due to mixed infection and immunosuppression. Excessive inflammatory response in the lungs has been associated with coinfection with invasive pulmonary aspergillosis [25].

Male sex, advanced age, low body mass index, chronic obstructive pulmonary disease, systemic steroids, *Mycobacterium* abscesses complex as the etiologic organism, and the fibrocavitary form of nontuberculous mycobacterial lung disease remained significant predictors for the development of chronic pulmonary aspergillosis in patients with nontuberculous mycobacterial lung disease [26].

Allergic bronchopulmonary aspergillosis commonly affects patients with cystic fibrosis and asthma; it often occurs at a young age and is not sex-specific [27]. *Aspergillus fumigatus* frequently colonizes the airways of patients with cystic fibrosis and can cause severe disease such as allergic bronchopulmonary aspergillosis, *A. fumigatus* bronchitis, or even *A. fumigatus* pneumonia. Urban living should be considered as a possible new risk factor for *A. fumigatus* colonization of the airways of cystic fibrosis patients [28].

Clinically, gender differences were observed in children with asthma and allergic diseases, with a higher prevalence of asthma in males before puberty [29]. Blood was collected each year, and mononuclear cells were stimulated with phytohemagglutinin. The concentrations of interferon-β, interleukin-5, -10, and -13 in the supernatants were determined by immunoassay. Total and allergen-specific IgE were measured. There are gender differences in the expression of the atopic phenotype and in vitro immune responses between boys and girls in the prepubertal school years. Boys aged six to nine years have higher rates of atopy and altered cytokine responses to phytohemagglutinin stimulation compared to girls [29].

2.5. Susceptibility to Infection with the Fungus *Cryprococcus neoformans* by Sex/Gender

Cryptococcosis affects a quarter of a million people each year and results in more than 180,000 deaths [30]. Men are more frequently affected by cryptococcosis than women, a phenomenon observed more than half a century ago. The gender imbalance is also observed in the non-HIV-infected population, where the ratio is about three males to one female, compared to the HIV-positive population, where the ratio is about four males to one female [19][30][31]. Male sex is considered a risk factor for cryptococcosis. Men who have the disease have more severe symptoms and poorer treatment outcomes. There are a number of observational, clinical, and epidemiologic studies documenting greater male involvement in *C. neoformans* infections, but there is no further explanation of the cause or mechanism. The very limited primary research suggests that sex hormones are likely the cause. Given that sex differences are widespread and accepted by many researchers, it is surprising that this is not more widely known [30].

Resistance to the pathogenic fungus *Cryptococcus neoformans* is sex-dependent. The nematode *Caenorhabditis elegans* consists of a population of self-fertilizing hermaphrodites with occasional males that differ anatomically and behaviorally from hermaphrodites. They also differ in their susceptibility to the fungal pathogen *C. neoformans*. Wild-type males exhibit greater resistance to this pathogen than do hermaphrodites, and this resistance may be caused by insufficient activation of the male sex determination pathway in hermaphrodites. Resistance is determined at the molecular level by overlapping pathways that control immunity and longevity, and is not due to behavioral changes or reproductive differences [32].

2.6. Susceptibility to Infection with the Fungus *Paracoccidioides brasiliensis* Is Sex/Gender Dependent

Paracoccidioidomycosis is a tropical lung disease caused by the dimorphic fungus *Paracoccidioides brasiliensis* and is the most common invasive mycosis in Latin America. Pleomorphic disease can be broadly divided into two forms, acute/subacute and chronic, and an asymptomatic form. The diversity of clinical manifestations is attributed to the increased pathogenicity of some strains of *P. brasiliensis* and, more importantly, to host factors that modulate the immune response to the fungus. The incidence is thought to be similar in both sexes and may be related to agricultural work leading to higher exposure to the fungus in the soil [33].

Most patients (three quarters) had the chronic form (adult type) of paracoccidioidomycosis, which presented as chronic lung disease, oropharyngeal and/or upper respiratory tract ulcers with or without regional lymph node enlargement. The chronic form of paracoccidioidomycosis is known to be more common in males, and the clinical disease occurs in adults in an extremely high male-to-female ratio of more than (11–15):1 [34][35][36].

The acute/subacute form (juvenile type) of the disease accounts for a quarter of cases. It is a common disease characterized mainly by generalized nodular enlargement with or without hepatosplenomegaly, skin, bowel, or bone lesions. It is directly related to female sex and inversely related to age. Although females are less likely to develop paracoccidioidomycosis after puberty, they are more susceptible to the acute/subacute form after acquiring the disease. This corresponds to a male-to-female ratio of (2–3):1 [33]. Paracoccidioidomycosis animal models show the same distribution of invasive pulmonary mycosis, however, sex differences in the immune response in humans remain to be studied in detail [35][37][38].

2.7. Incidence of Dermatophytosis Associated with Differences in Lifestyle between Women and Men

Tinea, or dermatophytosis, is a common infection of the skin and nails caused by about 40 different species of fungi from genera such as *Microsporum*, *Trichophyton*, and *Epidermophyton*. The infection can cause an itchy, red, circular rash; the different forms of tinea are usually named after the location of the infection on the body [12].

Onychomycosis (tinea unguium) can occur in both sexes, but most studies have shown that onychomycosis is more common in men [39]. Nail lesions and thickened nails are more common in men than in women. Women seem to be more conscious about their nails; however, because they wear tight shoes more often than men, deformity of the fifth nail is more common in women. In addition, due to oxidation caused by the use of nail polish products that darken the nails, treatment in women appears less favorable than it actually is. Although there are insufficient data on the actual effect of nail polish use on drug penetration, some physicians advise their patients not to use nail polish during topical treatment. One study showed better results with the use of the topical antifungal drug efinaconazole in women [40]. The incidence of tinea pedis increases with age and is higher in men than in women [39]. Men are affected about three times more frequently than women. This is probably due to different habits of wearing shoes (sports shoes or open shoes), foot hygiene, and occupational differences between the genders [39]. The fungus *T. rubrum* is the most common cause of tinea cruris, which is almost exclusively a male disease due to the moist environment created by contact between the scrotum and the skin of the groin [39]. Tinea cruris has also been found in female sex workers [39]. Tinea capitis: there is no difference in infection with the fungus *T. tonsurans*, as men are affected in a similar manner to women [39]. When infected with the fungus *M. canis*, males are more frequently affected than females [39]. If tinea capitis is caused by the fungus *T. schoenleinii*, it can occur in children and adults and affect males and females equally [39]. Adults who have had close contact with infected children are more likely to transmit the disease; shorter scalp hairs are more contagious, so the carrier stage and infection are more likely to be transmitted in men than in women. The prevalence of tinea manuum is less common and occurs slightly more frequently in men than in women [39]. This gender difference can be explained by occupational differences. Tinea manuum is observed in occupations where the palms are used intensively, and these occupations are common in men [39].

2.8. Incidence of Candidiasis in Relation to Life Circumstances

Factors that favor colonization with *C. albicans* include various life circumstances (advanced age, high-carbohydrate diet, newborns, pregnancy, smoking, stress, and urban lifestyle), diseases (AIDS, *Clostridium difficile* infection, dental caries, dentures, inflammatory bowel disease, and primary sclerosing cholangitis), and xenobiotics (antibiotics, cancer treatment, H2 receptor blockers, immunosuppression, proton pump inhibitors, and oral contraception). After menopause, the likelihood of *C. albicans* colonization decreases [41]. Diabetes mellitus, immunosuppression, malignancy, pregnancy, renal insufficiency, and xerostomia are factors that promote oral candidiasis [39]. Some studies have shown that women with denture stomatitis, another form of chronic oral candidiasis, are more commonly affected than men [39]. Candida folliculitis is an infection of the hair follicles of the beard and mustache in men [39]. Frequent contact of hands with water is associated with paronychia and candida onychomycosis, which is more common in women [39]. Fungal infections of the mucous membranes associated with an inflammatory host response are very common and can severely affect the quality of life for many people. The second most common cause of vaginitis is candida vulvovaginitis, which affects three quarters of women of childbearing age at least once in their lifetime, while almost one in ten of them suffers from a recurrent event [39][42]. Risk factors for candida vulvovaginitis are associated with elevated estrogen levels due to oral contraceptive use and pregnancy [39][41][43]. The vaginal bacterial microbiota also correlates with the menstrual cycle and sexual activity [44]. Candida balanitis is thought to be acquired through sexual contact with a partner who has candida vulvovaginitis [39]. Uncircumcised men have a higher incidence of balanitis. The risk factor for recurrent vulvovaginal candidiasis or onychomycosis may also be in genetics; the poorly expressed early-stop codon mutant in the β-glucan receptor dectin-1 did not mediate β-glucan binding and resulted in defective production of cytokines (interleukin-17, tumor necrosis factor, and interleukin-6) after stimulation with β-glucan or *C. albicans* [45].

The fungus *C. albicans* contains an estrogen-binding protein with a high affinity for estradiol, which may act as a potential receptor for estrogen and promote a number of different processes [46]. Estrogen promotes the morphological transition to a hyphal form, which may increase the virulence of the fungus via NADPH oxidoreductase- or heat shock protein-90-related pathways. Estrogen enhances fungal drug resistance by upregulating the expression of *C. albicans* drug resistance genes or the transcription of phosphatidylinositol transfer protein 16 [47]. Estrogen also affects the intravaginally infected female host: On the one hand, estrogen affects the vaginal epithelium by causing increased glycogen production, epithelial remodeling, and increased adhesiveness (focal adhesion kinase is involved). On the other hand, estrogen affects the transepithelial migration of neutrophils (CD44, CD47, and Cxcl1 are involved) and the ability to kill neutrophils (heparan sulfate is involved). As a result, *C. albicans* can survive and attach to the vaginal mucosa much more easily [47] [48].

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