UNIVERSIDADE SÃO FRANCISCO DE ASSIS
Programa de Pós-Graduação *Stricto Sensu* em Ciências da Saúde

JEANNE MARIE QUEIROZ BORGES BERSANO

TERBINAFINA EM POLÍMERO ACRÍLICO PARA O TRATAMENTO DA ONICOMICOSE EM PACIENTES EM HEMODIÁLISE:
UM ESTUDO CLÍNICO DE FASE II

Bragança Paulista
2024

JEANNE MARIE QUEIROZ BORGES BERSANO – R.A.: 202127425

TERBINAFINA EM POLÍMERO ACRÍLICO PARA O TRATAMENTO DA ONICOMICOSE EM PACIENTES EM HEMODIÁLISE:
UM ESTUDO CLÍNICO DE FASE II

Dissertação apresentada ao Programa de Pós-Graduação *Stricto Sensu* em Ciências da Saúde da Universidade São Francisco, como requisito parcial para obtenção do Título de Mestre em Ciências da Saúde.

Área de Concentração: Ciências da Saúde

Orientador: Prof. Dr. Fernando Augusto de Lima Marson

Bragança Paulista
2024

QV 252
B454t

Bersano, Jeanne Marie Queiroz Borges
Terbinafina em polímero acrílico para o tratamento da onicomicose em pacientes em hemodiálise: um estudo clínico de fase II / Jeanne Marie Queiroz Borges Bersano. -- Bragança Paulista, 2024.
57 p.

Dissertação (Mestrado) – Programa de Pós-Graduação *Stricto Sensu* em Ciências da Saúde da Universidade São Francisco.
Orientação de: Fernando Augusto Lima Marson

1. Antifúngico. 2. Desbridamento ungueal. 3. Diálise renal. 4. Onicomicose. 5. Terbinafina. I. Marson, Fernando Augusto Lima. II. Título.

Sistema de Bibliotecas da Universidade São Francisco – SIBUSF
Ficha catalográfica elaborada por: Maria Clara Reginato P. Duarte - CRB-8/040

BERSANO, Jeanne Marie Queiroz Borges. "Terbinafina em polímero acrílico para o tratamento da onicomicose em pacientes em hemodiálise: um estudo clínico de fase II". Dissertação defendida e aprovada no programa de Pós-Graduação *Stricto Sensu* em Ciências da Saúde da Universidade São Francisco em 18 de junho de 2024 pela Banca examinadora constituída pelos(as) professores(as):

Prof(a). Dr(a). Fernando Augusto de Lima Marson - Orientador(a) e Presidente
Universidade São Francisco

Prof(a). Dr(a). Diba Maria Sebba Tosta de Souza
(por videoconferência)
Universidade do Vale do Sapucaí

Prof(a). Dr(a). Thais Parisotto Ulmer
Universidade São Francisco

AGRADECIMENTO

Aos pacientes (voluntários), profissionais do Centro de Hemodiálise do Hospital Universitário São Francisco de Assis de Bragança Paulista, ao meu orientador, Prof. Dr. Fernando Augusto de Lima Marson, e a todos que contribuíram de alguma forma com este estudo, minha gratidão.

RESUMO

Onicomicoses são infecções das unhas causadas por fungos dermatófitos, fungos não-dermatófitose leveduras. Pacientes com doença renal crônica dialítica apresentam índices mais elevados dessa doença devido, principalmente, a imunodepressão. Seu tratamento encontra limitações impostas pela doença de base e pelas comorbidades. Este estudo, desenvolvido com pacientes do Centro deHemodiálise do Hospital Universitário São Francisco, Bragança Paulista, São Paulo, Brasil,originou dois artigos. O primeiro, intitulado "*Prevalence and Risk Predictors of Onychomycosis inPatients on Hemodialysis: An Observation, Prospective and Unicenter Study in Brazil*" teve por objetivo traçar um perfil epidemiológico das onicomicoses em pacientes dialíticos, e investigar osprincipais fatores de risco relacionados à doença. O estudo incluiu 151 pacientes, sendo que 70 (46,4%) deles apresentaram alterações morfológicas ungueais e 31 (44,3%) apresentaram positividade no exame micológico direto, e os agentes etiológicos forma identificados pela culturafúngica. Como conclusão, os microrganismos mais prevalentes nessa população foramdermatófitos do gênero *Trichophyton*. O escore de gravidade do envolvimento ungueal para a maioria dos pacientes foi grave, e os tipos clínicos subungueal distal e a onicomicose de padrão misto foram os mais prevalentes. Os principais fatores de risco para desenvolver onicomicose foram o sexo masculino, idade avançada e presença de obesidade. O segundo artigo, intitulado "*Terbinafine in Acrylic Polymer for the Treatment of Onychomycosis in Hemodialysis Patients: APhase II Clinical Trial*", avaliou a segurança e o potencial de eficácia de um tratamento que combina desbridamento ungueal com o uso de unhas de gel acrílico carreando terbinafina na concentração de 2%. Foram incluídos pacientes que apresentavam onicomicose em hálux com formas clínicas cujo tratamento envolvia a necessidade de desbridamento ungueal. Após o qual foiaplicada uma prótese ungueal confeccionada com gel de reconstrução acrílico e terbinafina na concentração de 2%. O procedimento foi renovado a cada duas semanas durante 11 meses. A evolução foi acompanhada com medidas da lâmina ungueal e fotografias. O exame micológico direto e a cultura fúngica foram realizados no início do estudo e 30 dias após a interrupção das aplicações. A avaliação da resposta clínica, cura clínica, cura micológica e cura completa foi realizada ao final do estudo e os participantes responderam a um questionário sobre a percepção do tratamento. Dentre um total de 155 pacientes, 64 (41,3%) apresentaram quadro sugestivo de onicomicose em háluces após a análise clínica. Entre eles, 35 (54,7%) indivíduos apresentaram exame micológico direto positivo e realizaram cultura fúngica para identificar o agente etiológico. Desse grupo, 24 (68,6%) indivíduos apresentavam formas clínicas cujo tratamento envolvia a necessidade de desbridamento ungueal. Apenas 15 indivíduos completaram o estudo. Em relação a cura, 5/15 participantes apresentaram resposta clínica, 4/15 cura clínica e 3/15 cura completa. Em conclusão, o método testado apresentou baixa eficácia como tratamento isolado em pacientes comdoença renal crônica dialítica. Por outro lado, a maioria dos pacientes tiveram uma boa percepçãosobre a aparência de suas unhas durante o tratamento, mesmo quando este não resultou em melhora clínica aparente ou cura completa.

Palavras chaves: Antifúngicos.Diálise.Onicomicose.Terbinafina.Unhas.

ABSTRACT

Onychomycoses are nail infections caused by dermatophyte fungi, non-dermatophyte fungi and yeasts. Patients with chronic kidney disease on dialysis have higher rates of this disease, mainly due to immunodepression. Treatment is limited by the underlying disease and comorbidities. Thisstudy, carried out with patients at the Hemodialysis Center of the Hospital Universitário São Francisco, Bragança Paulista, São Paulo, Brazil, resulted in two articles. The first, entitled "Prevalence and Risk Predictors of Onychomycosis in Patients on Hemodialysis: An Observation,Prospective and Unicenter Study in Brazil", aimed to draw up an epidemiological profile of onychomycosis in dialysis patients and to investigate the main risk factors related to the disease. The study included 151 patients, 70 (46.4%) of whom presented morphological nail alterations and 31 (44.3%) were positive in the direct mycological examination, and the etiological agents were identified by fungal culture. In conclusion, the most prevalent microorganisms in this population were dermatophytes of the Trichophyton genus. The severity score of nail involvement for most patients was severe, and distal subungual and mixed pattern onychomycosis were the mostprevalent clinical types. The main risk factors for developing onychomycosis were male gender, advanced age, and the presence of obesity. The second article, entitled "Terbinafine in Acrylic Polymer for the Treatment of Onychomycosis in Hemodialysis Patients: A Phase II Clinical Trial",evaluated the safety and potential efficacy of a treatment combining nail debridement with the useof acrylic gel nails carrying terbinafine at a concentration of 2%. The study included patients withclinical forms of hallux onychomycosis whose treatment involved the need for nail debridement. After this, a nail prosthesis made with acrylic reconstruction gel and terbinafine at a concentrationof 2% was applied. The procedure was renewed every two weeks for 11 months. Progress was monitored with measurements of the nail plate and photographs. Direct mycological examination and fungal culture were carried out at the beginning of the study and 30 days after the applicationswere stopped. The evaluation of clinical response, clinical cure, mycological cure, and complete cure was carried out at the end of the study and the participants answered a questionnaire about their perception of the treatment. Out of a total of 155 patients, 64 (41.3%) presented symptoms suggestive of onychomycosis on the halo after clinical analysis. Among them, 35 (54.7%) had a positive direct mycological examination and fungal culture was carried out to identify the etiologicagent. Of this group, 24 (68.6%) had clinical forms whose treatment involved the need for nail debridement. Only 15 individuals completed the study. Regarding cure, 5/15 participants showed a clinical response, 4/15 a clinical cure and 3/15 a complete cure. In conclusion, the method testedshowed low efficacy as a stand-alone treatment in patients with chronic dialysis kidney disease. On the other hand, most patients had a good perception of the appearance of their nails during treatment, even when it did not result in apparent clinical improvement or complete cure.

Keywords: *Antifungal Agents.Dialysis.Nails.Onychomycosis.Terbinafine.*

LISTA DE SÍMBOLOS E ABREVIATURAS

% – porcentagem

˜ – aproximadamente

IgA – Imunoglobulina A

IgG – Imunoglobulina G

IgM – Imunoglobulina M

FDA – Administração de Alimentos e Medicamentos do inglês “Food and Drug Investigation”

OSI – índice de gravidade da onicomicose do inglês “onychomycosis Severity Index”

PCR – reação em cadeia da polimerase do inglês “polymerase chain reaction”

LISTA DE FIGURAS

SUMÁRIO

1. Introdução

1.1. Onicomicoses

1.1.1. Generalidades

Onicomicose é um termo que descreve todos os tipos de infecções fúngicas das unhas; e que apresenta sinais e sintomas comuns a outras entidades nosológicas, necessitando, por esse motivo, de um exame complementar para identificar o fungo e assim estabelecer o diagnóstico. Como a lâmina ungueal tem um crescimento lento, o tratamento se prolonga por vários meses, sendo necessário manter a medicação até a cura clínica com a presença de recomposição total da unha acometida. Isso torna o tratamento demorado e dispendioso. E além do desconforto que pode causar, a onicomicose representa ainda, um problema estético que pode causar constrangimento (FDA, 2016).

1.1.2. Etiologia

Dentre as onicomicoses, 60 a 70% são causadas por dermatófitos, sendo o *Trichophyton rubrum* o principal responsável (50%), seguido pelo *T. mentagrophites* (20%), e o restante das onicomicoses por dermatófitos são causadas por *Microsporum* spp, *T. violaceum*, *T. verrucosum*, *T. krajdenii* e *Arthroderma* spp. Os fungos filamentosos não dermatófitos são responsáveis por aproximadamente 10% das onicomicoses sendo os agentes mais comuns *Scopulariopsis brevicaulis*, *Aspergillus* spp, *Acremonium* spp, *Fusarium* spp, *Alternaria alternate* e o *Neoscytalidium* spp. Finalmente, leveduras (*Candida* spp) são responsáveis por aproximadamente 10-20% dos casos de onicomicoses (AUGUSTIN et al., 2013). Recentemente evidências apontam que os fungos podem formar um biofilme e, dessa forma, desenvolver resistência a antifúngicos e, dessa forma, resistir ao sistema imunológico (GUPTA; FOLEY, 2019).

1.1.3. Fatores de risco para as onicomicoses

Os principais fatores de risco para ocorrência de onicomicoses incluem: hiperidrose, uso de chuveiros públicos, uso de calçados fechados, unhas morfologicamente alteradas, diabetes mellitus, doença vascular periférica, deficiência imunológica (síndrome da imunodeficiência humana adquirida, uso de imunossupressores, diálise, quimioterapia), obesidade, idade avançada,

micro traumas pelo calçado, tinea pedis, psoríase e malignidades (LIPNER; SCHER, 2019). As unhas dos pés são de quatro a dezenove vezes mais frequentemente acometidas que as unhas das mãos (LECHA et al., 2005).

1.1.4. Onicomicoses e hemodiálise

As taxas de prevalência de onicomicose em pacientes em hemodiálise giram em torno de 23,4% contra 10% de prevalência na população geral (SANTOS FILHO et al., 2017). A doença renal crônica em estádio terminal se associa a ativação imune marcada por inflamação sistêmica e, simultaneamente, à imunodeficiência caracterizada por resposta fraca a vacinação e aumento da incidência e da gravidade de infecções microbianas. A imunodeficiência relacionada a uremia é causada por várias alterações nos leucócitos. A doença renal crônica em estádio terminal é marcada por inflamação sistêmica e estresse oxidativo. As infecções bacterianas são a causa mais comum de hospitalização e a segunda causa mais comum de óbito nesses pacientes. Essa alteração da resposta imune pode ser observada quando verificamos que somente 50 a 75% dos pacientes em diálise que são vacinados desenvolvem anticorpos protetores contra o antígeno de superfície do vírus B da hepatite, comparados a mais de 90% na população geral.

Foram também relatadas altas taxas de falha de vacinação contra o vírus da Influenza, *Clostridium tetani* e *Corynebacterium diphtheriae*. Como os antígenos em todas essas vacinas são proteínas, a resposta imune é dependente de linfócitos T. Por outro lado, a produção de anticorpos após a vacinação contra pneumococo, que usa antígenos polissacarídeos, é normal em pacientes em diálise. Portanto, o distúrbio de imunidade adquirida em pacientes urêmicos envolve principalmente o linfócito T e não o linfócito B. Isso tem apoio no fato de que os isótopos de imunoglobulina G (IgG) sérica tanto a produção de imunoglobulina M (IgM) quanto a de imunoglobulina (IgA) são normais em pacientes com doença renal crônica em estádio terminal. Apesar disso, a ativação de linfócitos B não específicos pode ser responsável pelo aumento de produção de autoanticorpos observado nessa população.

O envelhecimento prematuro do sistema imune em pacientes com doença renal crônica em estádio terminal pode estar relacionado a uma distorção permanente da população de células-tronco hematopoiéticas em direção a linhagem mieloide, similar àquela observada em indivíduos idosos saudáveis. Na uremia, a diminuição da resposta imune contribui para a alta taxa de infecções,

enquanto a pré-ativação e a ativação persistente de células imunes levam a inflamação e, consequentemente, a doenças venosas crônicas. Enquanto a remoção coordenada via apoptose de células imunes ativadas é crucial para a resolução de inflamação, taxas de apoptose inapropriadamente elevadas levam a uma diminuição da resposta imune.

Na uremia ocorre uma perturbação no equilíbrio entre fatores pró-inflamatórios e anti-inflamatórios e entre os fatores pró-apoptóticos e anti-apoptóticos. As doenças venosas crônicas e as infecções se associam a uma alteração da resposta imune e contribuem para a elevada incidência de morbidade e mortalidade em pacientes com disfunção renal. Além do acúmulo de toxinas urêmicas nos pacientes com doença renal crônica, como consequência da redução da filtração glomerular, o desarranjo das atividades metabólicas na doença renal crônica em estádio terminal interfere na defesa imune na uremia. Uma série de fatores adicionais como a deficiência de ferro, sobrecarga de ferro ou deficiência de vitamina D também podem contribuir para as complicações cardiovasculares e infecciosas nos pacientes com doença renal crônica em estádio terminal.

1.1.5. Apresentações clínicas das onicomicoses

As onicomicoses podem se apresentar sob diferentes formas clínicas, conforme o padrão de invasão das unhas: branca superficial, subungueal distal e lateral, subungueal proximal, endonyx, padrão misto, distrófica total e secundária (invasão fúngica sobreposta a outra alteração ungueal prévia (como psoríase ou trauma) (GUPTA et al., 2018).

1.1.6. Medidas de gravidade

Com o intuito de determinar a gravidade da infecção ungueal, em 2011, Carney e colaboradores propuseram o escore denominado de "*Onychomycosis Severity Index"* (OSI). Este escore utiliza uma pontuação para o tamanho da área acometida (intervalo de 0 a 5), multiplicado pela pontuação relativa à proximidade da doença à matriz (intervalo de 1 a 5). Além disso, a pontuação acrescenta dez pontos pela presença de um dermatofitoma ou por mais de 2 mm de hiperqueratose subungueal. A gravidade é descrita de acordo com o número de pontos, sendo: (leve) 1 a 5 pontos, (moderada) 6 a 15 pontos e (grave) 16 a 35 pontos (Figura 1) (CARNEY et al., 2011).

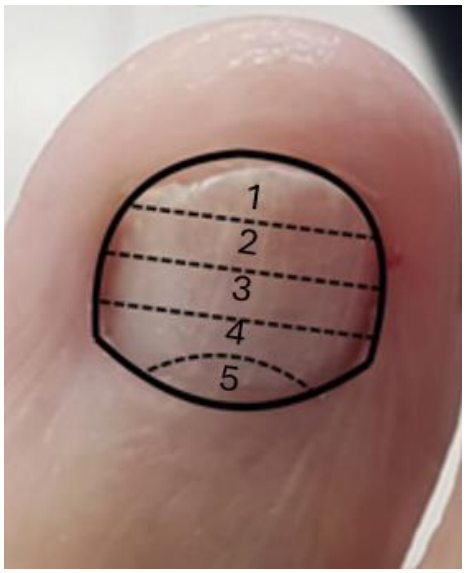


FIGURA 1. Pontuação do escore "*Onychomycosis Severity Index"* conforme a proximidade da matriz ungueal. A unha é dividida transversalmente em quatro partes e recebe pontuação crescente de 1 a 4 conforme se aproxima da lúnula. O envolvimento da lúnula e da prega ungueal proximal representa o envolvimento da matriz e recebe uma pontuação de 5. O escore foi publicado por CARNEY et al., 2011. Fonte: Próprio autor.

1.1.7. Diagnóstico das onicomicoses

A onicomicose tem sinais e sintomas comuns a numerosas outras doenças e seu tratamento é prolongado e oneroso, às vezes envolvendo drogas de uso sistêmico. Esses fatores justificam a necessidade da confirmação diagnóstica pela evidência do agente causal antes de iniciar o tratamento. Os principais exames laboratoriais para realizar o diagnóstico das onicomicoses são (HASHE; PODA, 2018):

i-) Exame micológico direto: O material é coletado do local suspeito, clarificado com potassa e colocado em lâmina para visualizar as estruturas fúngicas por microscópio óptico, podendo ser adicionada tinta azul de Parker, à critério do examinador;

ii-) Microscopia de fluorescência: exame direto no qual o calco flúor branco é utilizado para coraras estruturas fúngicas. A microscopia de fluorescência é mais cara e tem menor disponibilidade doque a microscopia óptica e, aparentemente, não possui vantagens substanciais;

iii-) Cultura fúngica: identifica o fungo e avalia sua viabilidade pelo crescimento de uma colônia fúngica, sendo considerado o padrão ouro para o diagnóstico de onicomicose;

iv-) Histopatologia: O método possui elevada sensibilidade, porém é caro se comparado ao examemicológico direto e a cultura para fungos. Adicionalmente, não permite identificar o agente patogênico e verificar sua viabilidade;

v-) Reação em cadeia da polimerase (PCR): permite identificar o fungo pelo sequenciamento do ADN (ácido desoxirribonucleico, do inglês "*deoxyribonucleic acid*"). Apesar de mais sensível quea cultura para fungos, o método não permite saber se o fungo é viável ou mesmo se é o causador da sintomatologia. A disponibilidade do exame ainda é baixa, principalmente, em países subdesenvolvidos ou emergentes – como é o caso do Brasil;

vi-) Microscopia confocal: utiliza um laser diiodo para visualizar, *in vivo*, seções horizontais entrea placa ungueal e a superfície do leito ungueal, possibilitando identificar estruturas fúngicas. O exame não requer a coleta de amostras, porém, não identifica o organismo e exige treinamento especializado, tem elevado custo e baixa disponibilidade.

1.1.8. Tratamento das onicomicoses

O tratamento das onicomicoses é dificultado pela natureza impermeável da unha, característica atribuída às fortes ligações dissulfeto e ligações de hidrogênio na rede de queratina, tornando a lâmina ungueal uma das barreiras biológicas mais difíceis de transpor. As opções terapêuticas incluem drogas de administração oral e tópica. A terapia antifúngica oral geralmente é longa e traz consigo o risco de efeitos adversos e interações medicamentosas. A terapia tópica, por sua vez, raramente tem efeitos colaterais, e não apresenta absorção sistêmica significativa, sendo adequada para pacientes da geriatria e da pediatria e para mulheres grávidas, mas, sua ação é limitada pela rígida estrutura da unha, difícil de ser permeada. Por este motivo, a terapia tópica é prescrita apenas em casos leves, em que não há acometimento da matriz ungueal. A entrega de medicamentos tópicos pode ser aprimorada por métodos mecânicos, físicos e químicos (TABARA et al., 2015). A escolha do tratamento deve ser individualizada de acordo com o grau de envolvimento das unhas, organismo infectante, comorbidades e uso concomitante de outros medicamentos (AMEEN et al., 2014).

1.1.8.1 Medicamentos de uso tópico nas onicomicoses

A placa ungueal dorsal atua como uma barreira que dificulta a difusão de medicamentos aplicados topicamente, podendo levar a uma redução da concentração da droga em até 1.000 vezes. Além disso, a unha tem natureza hidrofílica, o que impede a penetração da maioria das moléculas lipofílicas de elevados pesos moleculares (GUPTA et al., 2018). Cremes ou pomadas, não são considerados veículos adequados para depositar os antifúngicos na lâmina ungueal. Os esmaltes (ou lacas) foram formulados de forma a melhorar a penetração das substâncias ativas através da lâmina ungueal, mantendo sua concentração adequada, aumentando assim a sua eficácia. A penetração adequada da droga através da superfície da placa ungueal é fornecida por sistemas de liberação transungueal de drogas, que geralmente contêm polímeros insolúveis em água removidos com solventes orgânicos (EL-SALAM et al., 2020). Os medicamentos produzidos pela indústria farmacêutica no Brasil sob a apresentação de esmalte são a Amorolfina com índices de cura clínica de 46% e cura micológica de 52% e Ciclopirox Olamina, com índices de cura clínica de 12% e cura micológica de 36%. Tioconazol é comercializado no Brasil em forma de solução. Eficonazole e Tavaborole são antifúngicos tópicos citados na literatura mundial para tratamento das onicomicoses, porém, ainda não disponíveis no Brasil. O papel da monoterapia com antifúngicos tópicos é limitado a onicomicose superficial branca (exceto em infecções transversais ou estriadas), onicomicose latero-distal precoce (exceto na presença de estrias longitudinais) quando <80% da placa ungueal é afetada pela falta de envolvimento da lúnula ou quando antifúngicos sistêmicos são contraindicados (GUPTA et al., 2018).

1.1.8.2. Medicamentos sistêmicos nas onicomicoses

Os medicamentos sistêmicos aprovados pelo *Food and Drug Administration* são a Terbinafina, com índices de cura micológica em torno de 75% e o Itraconazol, com índice de cura micológica de 61%. No entanto, por possuir maior índice de cura e menor potencial de interações medicamentosas, a Terbinafina, tem sido a escolha preferencial. O Fluconazol, com índice de cura micológica de 31%, é aprovado para tratar onicomicose na Europa, mas nos Estados Unidos da América, seu uso é *off-label* (LIPNER et al., 2019).

No Brasil, o Fluconazol é o medicamento sistêmico mais frequentemente prescrito para o tratamento sistêmico das onicomicoses (BELDA; CHIACCHIO; CRIADO, 2018), sendo fornecido

pelo Sistema Único de Saúde para uso ambulatorial. O tratamento sistêmico pode ser indicado em todas as apresentações clínicas, mas deve ser considerado como primeira opção se a matriz ungueal está envolvida, se ocorre acometimento simultâneo de três ou mais unhas, na presença de dermatofitoma, hiperceratose subungueal (>2 mm) e na forma distrófica total (DI CHIACCHIO et al, 2013). No entanto, na literatura, existem registros de casos de insuficiência hepática aguda desencadeada após o uso de antifúngicos orais (TUCCORI et al., 2008; SREBRNIK et al., 2005; PANDHI; VERMA, 2012).

1.1.8.3. Avulsão e desbridamento das unhas nas onicomicoses

A avulsão parcial da placa ungueal danificada tem como objetivo reduzir a massa fúngica e colaborar para que as drogas atinjam as camadas mais profundas do leito ungueal. A avulsão química é feita com produtos de aplicação tópica à base de ureia a 40%. A abrasão mecânica da placa ungueal pode ser realizada utilizando lixas d'água ou a unha pode ser cortada. A avulsão cirúrgica total da unha tem sido evitada por deixar o leito ungueal desprotegido e pelo risco de lesar a matriz ungueal levando a distrofia ungueal permanente. Na retirada completa da unha, ocorre a perda de contrapressão no leito ungueal, podendo levar ao aumento do crescimento lateral da lâmina ungueal, sendo recomendado o uso de uma unha protética para evitar esse problema (BARAN; GARDUNO, 2008; GUPTA; PAQUET; SIMPSON, 2013).

1.1.8.4. Tratamento combinado

As modalidades terapêuticas podem ser associadas conforme as necessidades de cada caso, potencializando assim os resultados (SCHER et al., 2007).

1.1.9. Critérios de cura das onicomicoses

Os critérios de cura tomam por base a evolução clínica e os exames laboratoriais. O crescimento de 5 mm de unha saudável é chamado de resposta clínica. A cura micológica é definida pelo exame micológico direto e cultura negativos e, a cura clínica, pela aparência completamente normal da unha. A cura completa seria definida pela presença de ambos os critérios. Entretanto, nem sempre a cura clínica é alcançável, como em alguns casos de onicomicose grave, trauma prévio

com danos permanentes à matriz ungueal, doença secundária das unhas e imunossupressão (BOLOGNIA; JORIZZO; SHAFFER, 2015).

1.2. Justificativa

A prevalência de onicomicoses na população geral é em torno de 1 a 8% (Bodman; Krishnamurthy, 2024), mas é bem maior em doentes renais crônicos dialíticos, variando de 19 a 51,9% (Gupta; Daigle; Foley, 2015). Frequentemente esse grupo de pacientes apresenta formas graves de onicomicose, para as quais seria indicado o tratamento sistêmico (Maskan Bermudez et al., 2023). Ao mesmo tempo, esses pacientes possuem várias comorbidades e fazem uso de múltiplos fármacos, o que aumenta os riscos de efeitos adversos e interações medicamentosas (Gupta; Hass-Neil; Talukder, 2023), além de ser escassa a literatura que versa sobre os efeitos do uso prolongado de antifúngicos sistêmicos em doentes renais dialíticos. Um dos desafios do tratamento tópico das onicomicoses é fazer com que os medicamentos alcancem concentrações terapêuticas no local onde o fungo encontra-se instalado. As moléculas hidrofílicas e aquelas de menor peso molecular permeiam com mais facilidade a lâmina ungueal, mesmo assim, os ativos podem ter sua concentração muito reduzida ao atravessá-la (Baswan et al.,2017). Os fungos, por sua vez, são produtores de proteases (entre elas a queratinase), lipases e colagenases, o que os torna aptos a invadir e destruir estruturas do aparato ungueal (Peres et al., 2010). Uma vez instalados, os fungos são capazes de formar biofilme, tornando-os ainda mais resistentes ao tratamento e fora do alcance das células do sistema imune (Gupta; Foley, 2019). Outro fator que favorece sua permanência no hospedeiro é a lentidão do crescimento da lâmina ungueal, cerca de 1 mm por mês nas unhas dos pés e 3 mm por mês nas unhas das mãos (Bolognia;Jorizzo; Schaffer, 2015). A avulsão parcial da unha por meios químicos, mecânicos ou cirúrgicos pode fazer parte da estratégia terapêutica e tem como objetivo reduzir a massa fúngica a ser combatida pelos medicamentos e facilitar a chegada da droga ao sítio da infecção. A terbinafina é a droga que, administrada pela via sistêmica, apresenta maiores índices de cura total no tratamento contra dermatófitos (Maxfield; Preuss; Bermudez, 2024). Nesse contexto,no intuito de obter um recurso que ao mesmo tempo trate a onicomicose, proteja o leito ungueal e melhore o aspecto da unha até que a lâmina se recomponha, foi testada a aplicação de terbinafinausando como veículo o polímero acrílico de reconstrução utilizado na confecção de unhas postiças.

2. Objetivos

2.1. Objetivo geral

Verificar a segurança e a eficácia da aplicação tópica de Terbinafina em pacientes em hemodiálise usando como veículo um polímero acrílico que mantenha a droga em contato com os tecidos afetados pela onicomicose, por tempo prolongado.

2.2. Objetivos específicos

i-) descrever a prevalência e os preditores de risco para onicomicose em pacientes em hemodiáliseem um hospital de referência no Brasil.

ii-) realizar um ensaio clínico fase II que propõe limpeza e desbridamento da unha do hálux afetada, seguido da colocação de prótese ungueal moldada com gel acrílico de reconstrução contendo terbinafina na concentração de 2%, para obter exposição prolongada dos tecidos ao agenteantifúngico. Simultaneamente, avaliar se a técnica protege o leito ungueal desbridado e melhorar o aspecto estético da unha.

3. Capítulo 1. Artigo publicado

Título: Prevalência e preditores de risco de onicomicose em pacientes em hemodiálise: estudo observacional, prospectivo e unicêntrico no Brasil

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 23 November 2023
DOI 10.3389/fmed.2023.1268324

Check for updates

OPEN ACCESS

EDITED BY
Devinder Mohan Thappa,
Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), India

REVIEWED BY
Ionela Manole,
Colentina Clinical Hospital, Romania
Indrashis Podder,
College of Medicine & Sagore Dutta Hospital, India

*CORRESPONDENCE
Jeanne Marie Queiroz Borges Bersano
jeanne.marie@usf.edu.br
Matheus Gobbo Cordeiro
matheus.gobbo@mail.usf.edu.br
Fernando Augusto Lima Marson
fernando.marson@usf.edu.br;
fernandolimamarson@hotmail.com

RECEIVED 27 July 2023
ACCEPTED 24 October 2023
PUBLISHED 23 November 2023

CITATION
Bersano JMQB, Cordeiro MG and Marson FAL (2023) Prevalence and risk predictors of onychomycosis in patients on hemodialysis: an observation, prospective, and unicenter study in Brazil.
Front. Med. 10:1268324.
doi: 10.3389/fmed.2023.1268324

COPYRIGHT
© 2023 Bersano, Cordeiro and Marson. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Prevalence and risk predictors of onychomycosis in patients on hemodialysis: an observation, prospective, and unicenter study in Brazil

Jeanne Marie Queiroz Borges Bersano*, Matheus Gobbo Cordeiro* and Fernando Augusto Lima Marson*

Laboratory of Molecular Biology and Genetics, Health Sciences Postgraduate Program, Universidade São Francisco, Bragança Paulista, São Paulo, Brazil

Background: Onychomycoses are fungal infections that can be seen in any component of the nail unit, including the matrix, bed, and plate, and are caused by dermatophyte fungi, non-dermatophyte fungi, and yeasts. This disease affects approximately 1 to 8% of the general population and occurs in approximately 19 to 51.9% of the patients on hemodialysis. The high incidence of onychomycosis in patients on hemodialysis is associated, mainly, with immunologic deficits and histological changes caused by uremia.

Methods: Adult patients of the São Francisco University Hospital Hemodialysis Center were included. The following characteristics were evaluated: age, sex, body mass index, comorbidity, and household location. All patients were clinically evaluated and those with suspected onychomycosis had subungual debris of the affected nail plate collected for the direct mycological examination and fungal culture. The onychomycosis severity for those patients with a positive result in the fungal culture examination was evaluated using the Onychomycosis Severity Index system.

Results: The study included 151 patients, and 70 out of the 151 patients (46.4%) showed nail alteration, and among them, 31 out of the 70 patients (44.3%) had the onychomycosis diagnosis confirmed by direct mycological examination. The pathogens observed in the patients were *Trichophyton rubrum* [8 out of 31 (25.8%)], *Trichophyton mentagrophytes* [7 out of 31 (22.6%)], *Scytalidium* spp. [6 out of 31 (19.4%)], *Candida* spp. [2 out of 31 (6.45%)], *Rhodotorula* spp. [1 out of 31 (3.2%)], *Candida albicans* [1/31 (3.2%)], *Penicillium marneffei* [1 out of 31 (3.22%)], and *T. rubrum* and *Rhodotorula* spp. [1 out of 31 (3.2%)]. Three participants presented negative results in the culture examination, and one did not allow the collection of material for the examination. The nail involvement severity score for the majority of them was severe [23 out of 27 (85.2%)], and only 1 out of the 27 (3.7%) and 3 out of the 27 (1.1%) patients presented moderate and mild scores, respectively. The distal subungual onychomycosis occurred in 12 out of 27 (44.4%) patients, a mixed pattern occurred in 14 out of 27 (51.9%) patients, and, white superficial occurred in only 1 out of 27 (3.7%) patients. In the bivariate analysis, a higher risk of onychomycosis was associated with the male sex [23/31 (74.2%) vs. 56/120 (46.7%); OR = 3.286 (95%CI = 1.362 to 7.928)] and obesity [8/31 (25.8%) vs. 12/120 (10.0%); OR = 3.130 (95%CI = 1.150 to 8.521)]. Patients with diabetes mellitus were more susceptible to onychomycosis attacks (p-value = 0.049; 16

out of 31 (51.6%) vs. 40 out of 120 (33.3%); however, OR was 2.133 (95%CI = 0.959 to 4.648). The patients with onychomycosis were older but without a significant difference between the groups (p-value = 0.073; 66 years old vs. 58 years old). The multivariable model using the logistic regression (backward model) confirmed our results and was able to predict (81.5%) the onychomycosis-positive diagnosis (chi-square = 27.73; p-value <0.001). The age [OR = 1.036; 95%CI = 1.004 to 1.069], male sex [OR = 5.746; 95%CI = 2.057 to 16.046], and presence of obesity [OR = 4.800; 95%CI = 1.435 to 16.055] were positive and significant in predicting the onychomycosis-positive diagnosis.

Conclusion: In our study, onychomycosis in patients on hemodialysis was associated with a great variety of microorganisms, mainly *Trichophyton* species. The nail involvement severity score for the majority of patients was severe, and distal subungual onychomycosis and mixed pattern onychomycosis were the most prevalent clinical types. The main risk factors associated with onychomycosis were male sex, older age, and the presence of obesity.

KEYWORDS

dermatophyte filamentous fungi, gender, microbiology, non-dermatophyte filamentous fungi, obesity, onychomycosis, renal dialysis, yeast

Highlights

1. Onychomycoses affect approximately 1 to 8% of the general population and occur in approximately 19 to 51.9% of the patients on hemodialysis.
2. A total of 70 out of 151 (46.4%) patients on hemodialysis showed nail alteration, and among them, 31 out of 70 (44.3%) had the onychomycosis diagnosis confirmed.
3. The pathogens observed in the patients on hemodialysis were *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Scytalidium* spp., *Candida* spp., *Rhodotorula* spp., *Candida albicans*, *Penicillium marneffei*, and *T. rubrum* and *Rhodotorula* spp.
4. The nail involvement severity score for the majority of them was severe.
5. Distal subungual onychomycosis and mixed pattern onychomycosis were the most prevalent clinical types.
6. A higher risk of onychomycosis in patients on hemodialysis was associated with male sex, older age, and obesity.

1 Introduction

Patients on hemodialysis experience several skin and nail alterations due to the systemic changes caused by the chronic renal disease and its etiologies (e.g., systemic arterial hypertension, diabetes mellitus, glomerulopathy, nephritis, dominant autosomal polycystic renal disease, and obstructive uropathy) (1–4). Among skin alterations, the main occurrences observed are hyperpigmentation, xerosis, pallor, itching, jaundice, plant hyperkeratosis, psoriasis, and viral, bacterial, or fungal infection complications (1–5). Onychomycosis, xerosis, and itching were found to occur simultaneously (1). Moreover, among nail alterations, the most frequent are onychomycosis, half and half nails, absent lunula, subungual hyperkeratosis, onycholysis, subungual hemorrhage, and *tinea pedis* (1–3, 6). Some alterations might occur simultaneously in the same patient such as onychomycosis and onycholysis and onycholysis and subungual hyperkeratosis (6).

Onychomycoses are nail fungal infections that can involve any component of the nail unit, including the matrix, bed, and plate, causing, for example, endonyx onychomycosis, proximal subungual onychomycosis, and total dystrophic onychomycosis (7). Onychomycoses are caused by dermatophyte filamentous fungi (e.g., *Trichophyton rubrum* and *Trichophyton mentagrophytes*—71%), non-dermatophyte fungi (e.g., *Scopulariopsis brevicaulis*, *Acremonium* spp., *Aspergillus* spp., *Fusarium* spp., and *Neoscytalidium* spp.—20.4%), or yeasts (*Candida* spp.—7.6%) (7–9). Dermatophyte filamentous fungi predominate in positive cultures in hemodialysis, followed by non-dermatophyte filamentous fungi, and yeasts (10–13). However, yeasts are more prevalent in older patients with diabetes mellitus and psoriasis (11).

Onychomycosis affects between 1 and 8% of the global population, with higher prevalence among those in hospital treatment (7, 9) and those on hemodialysis—19 to 51.9% (1–6, 10–13), representing 90% of the nail diseases found in toes (8). In patients on hemodialysis, the incidence of onychomycosis increases with older age (10, 11, 13), in men (10, 11, 13), and in the presence of diabetes mellitus or psoriasis (3, 5, 10–13), in renal transplant patients (10, 11), and in those infected by *human immunodeficiency virus* (HIV) (11). On the other hand,

hemodialysis duration as a risk factor for onychomycosis showed divergent results in the literature (6, 10, 12, 13).

In such context, this study aimed to describe the prevalence and risk predictors for onychomycosis in patients on hemodialysis in a referral hospital in Brazil.

2 Methods

The study was carried out at the São Francisco de Assis University Hospital Hemodialysis Center in Bragança Paulista-SP, Brazil. The study included all patients with chronic renal insufficiency who were in regular dialysis treatment in the period from July 2022 to March 2023 and who were over 18 years old. The hemodialysis treatment was carried out in a hospital reference center at a scheduled time so that there was no overcrowding, and the same treatment protocol with similar dialysis days between patients was followed as the referenced unit is associated with severe cases only.

All patients were first clinically evaluated, and those presenting nail dystrophy were subjected to direct mycological examination and fungal culture (Figure 1). The material used in both examinations corresponded to subungual debris of the affected nail plate, obtained from scraping the clinically changed areas after being cleaned with 70% alcohol, using an aluminum spatula and sterile nail pliers to obtain material from the progression region and the confluence of healthy and affected tissue. The material obtained was deposited in sterile bottles and sent to the clinical analysis laboratory.

For the direct mycological examination, the material was cleared with potassium hydroxide to degrade the keratin and placed on a slide to visualize the fungal structures using an optical microscope. The analysis provided information regarding the morphology, but species identification could not be determined by the examination. Fungal culture is considered the gold standard for the diagnosis of onychomycosis since it enables the identification of the fungal species affecting the patient and shows the fungus viability. The examination uses the Sabouraud and Sabouraud cycloheximide agar culture media. The culture is established at 20–25°C, and the waiting time for growth might reach up to 4 weeks. The fungal agent identification is achieved using culture macromorphology and micromorphology analyses. The direct mycological examination and the fungal culture were carried out at the clinical analysis laboratory of the University Hospital, certified by the Brazilian Sanitation Surveillance for this type of examination. In our data, the patients on hemodialysis were considered affected by onychomycosis when the direct mycological examination presented a positive result.

The patients on hemodialysis had the following markers collected: age (years), sex (male and female), race [white, black, mixed race (*pardos*), and yellow (Asian)], schooling (illiterate, elementary school, high school, and higher education), body mass index (kg/m²), household location (rural or urban), presence of comorbidity, hemodialysis duration (classified in ≤1 year or >1 year), and onychomycosis treatment before their inclusion in this study. Schooling was evaluated in our study with the aim of verifying the association of a social marker with the risk of onychomycosis due to accessibility to hemodialysis and onychomycosis treatment since our tertiary hospital is responsible for the care of patients assisted by the public and private healthcare system. For the patient on hemodialysis with a positive result in the fungal culture examination, the following markers were also evaluated: (a) clinical type, (b) nail involvement severity score, and (c) number of dystrophic nails per patient.

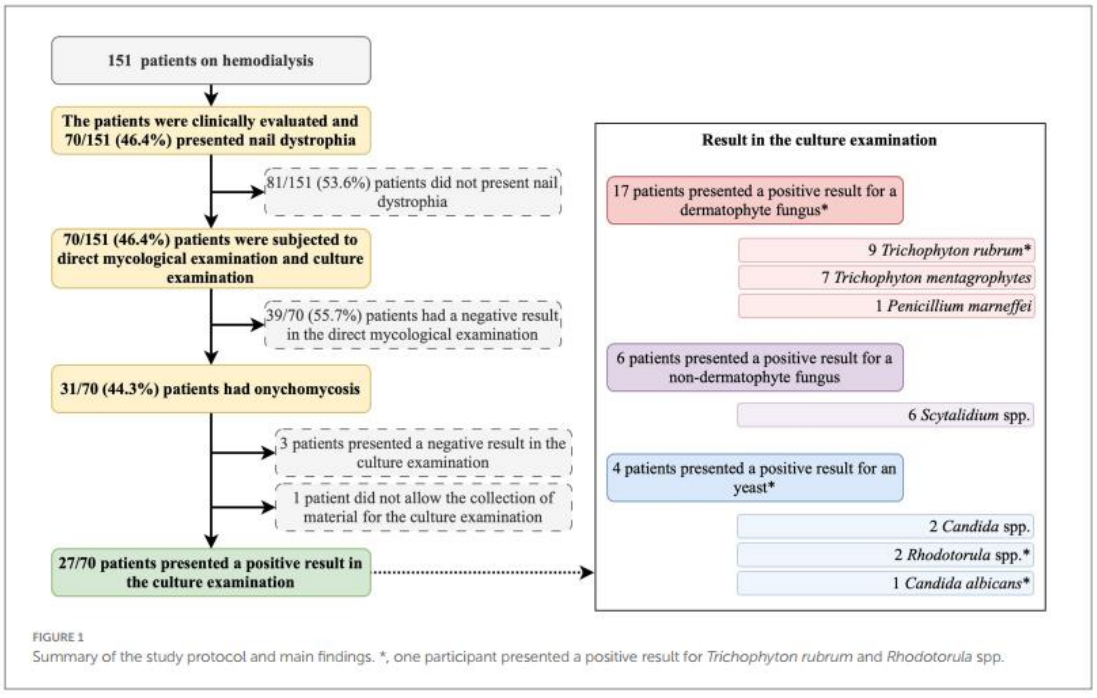


FIGURE 1
Summary of the study protocol and main findings. *, one participant presented a positive result for *Trichophyton rubrum* and *Rhodotorula* spp.

The classification of onychomycosis was performed according to the literature into the following groups: distal and lateral subungual, superficial, endonyx, proximal subungual, mixed, totally dystrophic, and secondary onychomycosis (14).

The onychomycosis severity was evaluated using the Onychomycosis Severity Index system. The score was obtained by multiplying the score for the area of involvement (range, 0 to 5) by the score for the proximity of disease to the matrix (range, 1 to 5). Ten points were added for the presence of a longitudinal streak or a patch (dermatophytoma) or for a patch greater than 2 mm of subungual hyperkeratosis. After measuring the scores, patients on hemodialysis were classified into the following severity groups: (a) mild onychomycosis [score of 1 through 5], (b) moderate onychomycosis [score of 6 through 15], and (c) severe onychomycosis [score of 16 through 35] (15).

The statistical analysis was carried out using the software *Statistical Package for the Social Sciences* (IBM Corp. Released 2021. IBM SPSS Statistics for Macintosh, Version 28.0. Armonk, NY: IBM Corp). In the study, the sample size was not calculated because we enrolled all patients on hemodialysis from our institution (convenience sampling). Categorical data are presented considering absolute frequency (n) and relative frequency (%). The association between categorical markers among those that presented positive ungual alterations and onychomycosis diagnosis and those that did not were obtained employing Pearson's chi-square or Fisher's exact tests. Regarding categorical data, *Odds Ratio* (OR) calculation was performed with a 95% confidence interval (95%CI), and the risk parameter was the group of participants with ungual alterations and onychomycosis-positive diagnosis. Numerical data are presented by the mean ± standard deviation and median (25–75 percentile). The association between markers with numerical distribution among those with and without ungual alterations and onychomycosis-positive diagnosis was carried out using the Mann–Whitney U-test or T-test according to the normality of data. The numerical data normality was evaluated considering three parameters: (i) analysis of the descriptive measure of central tendency, (ii) graphic method (normal Q-Q plot, Q-Q plot without tendency, and boxplot), and (iii) statistical test method (normality tests), Kolmogorov–Smirnov and Shapiro–Wilk tests. The alpha error value adopted was 0.05.

In the multivariable analysis, a binary logistic regression model with the backward stepwise method was used. In the regression model (multivariable analysis), the markers with a p-value of ≤0.25 in the bivariate analysis were included. The inclusion of markers with a p-value of ≤0.25 in the bivariate analysis was based on the Wald test from logistic regression. More traditional levels such as 0.05 can fail in identifying variables known to be important (16–18). The response variable was the onychomycosis-positive diagnosis. The multivariable analysis included eight patients' characteristics. The logistic regression model presented the (i) B coefficient [including the SE (standard error)], which for the constant was called intercept; (ii) the Wald chi-square test and its significance; (iii) degrees of freedom (df) for the Wald chi-square test; and (iv) Exp (B) which represents the exponentiation of the B coefficient (OR) including its 95%CI. Before performing the statistical analysis, the markers were tested for multicollinearity considering cutoffs of <0.1 for tolerance and >10 for variance inflation factor. The alpha error value adopted was 0.05.

3 Results

This study included 151 patients on hemodialysis (Figure 1), predominantly male individuals (n = 79; 52.3%), white (n = 101; 66.9%), residing in the urban area (n = 118; 78.2%), and who had completed elementary school (n = 86; 57.0%) (Table 1). Systemic arterial hypertension (n = 138; 91.4%), diabetes mellitus (n = 56; 37.1%), and obesity (n = 20; 13.2%) were the main comorbidities observed (Table 1).

Hemodialysis was associated, respectively, with secondary chronic renal disease and systemic arterial hypertension (n = 58; 37.9%), systemic arterial hypertension and diabetes mellitus (n = 33; 21.9%), diabetes mellitus (n = 19; 12.6%), glomerulopathy (n = 12; 7.9%), polycystic renal disease (n = 9; 6.0%), nephritis (n = 8; 5.3%), focal segmental glomerulosclerosis (n = 7; 4.6%), obstructive nephropathy (n = 4; 2.6%), and vasculitis (n = 1; 0.7%).

Among the study participants, 70 (46.4%) showed ungual alterations (Figure 1), and only 15 (9.9%) of those evaluated had used some medication to treat onychomycosis, and out of them, only one reported systemic use of the medication (Table 1). In the mycological exam, 31 (44.3%) out of the 70 examined participants had a positive result (Figure 1). According to the microbiological culture result, 8 (25.8%) participants presented *T. rubrum*, 7 (22.6%) presented *T. mentagrophytes*, 6 (19.4%) presented *Scytalidium* spp., 2 (6.5%) presented *Candida* spp., 1 (3.2%) presented *Rhodotorula* spp., 1 (3.2%) presented *Candida albicans*, 1 (3.2%) presented *Penicillium marneffei*, and 1 (3.2%) presented *T. rubrum* and *Rhodotorula* spp. colony growth (Figure 1). Three participants presented negative results in the culture examination, and one did not allow the collection of material for the examination (Figure 1).

For the patients on hemodialysis and with a positive result in the fungal culture examination, the nail involvement severity score for the majority of them was severe [23 out of 27 (85.2%)], and only 1 out of 27 (3.7%) and 3 out of 27 (1.1%) patients presented moderate and mild scores, respectively. In addition, for those patients on hemodialysis, distal subungual onychomycosis occurred in 12 out of 27 (44.4%) patients, mixed pattern in 14 out of 27 (51.9%) patients, and, white superficial onychomycosis in only 1 out of 27 (3.7%) patients (Table 2).

In our data, the male sex was associated with the higher prevalence of ungual alterations [43/70 (61.4%) vs. 36/81 (44.4%); OR = 1.991 (95%CI = 1.038 to 3.817)]; moreover, other markers such as race, schooling, comorbidities, household location, and hemodialysis period were not associated as risk factors (Table 3). Body mass index did not show a statistically significant difference between the groups of participants regarding the ungual alterations (p-value = 0.174; 24.0 Kg/m² vs. 23.0 Kg/m²) (Figure 2B). Patients on hemodialysis with ungual alterations were older (p-value = 0.050; 62.5 years old vs. 56.0 years old) (Figure 2A).

Among the markers evaluated in this study, those associated with higher risk of onychomycosis were male sex [23/31 (74.2%) vs. 56/120 (46.7%); OR = 3.286 (95%CI = 1.362 to 7.928)] and obesity [8/31 (25.8%) vs. 12/120 (10.0%); OR = 3.130 (95%CI = 1.150 to 8.521)]. At the same time, patients with diabetes mellitus were more susceptible to the onychomycosis attack [p-value = 0.049; 16/31 (51.6%) vs. 40/120 (33.3%); however, OR was 2.133 (95%CI = 0.959 to 4.648)] (Table 4; Figure 3). Participants with onychomycosis-positive diagnosis presented higher body mass index (p-value = 0.003; 26.0 Kg/m² vs.

10.3389/fmed.2023.1268324

TABLE 1 Markers evaluated in the study on patients on hemodialysis that were examined for the presence of onychomycosis.

Patients' characteristics	n/N (%) or mean ± standard deviation; median (p25 to p75)
Sex	
Female	72/151 (47.7%)
Male	79/151 (52.3%)
Race	
White	101/151 (66.9%)
Black	20/151 (13.2%)
Pardo (mixed race)	24/151 (15.9%)
Asian	6/151 (4.0%)
Age (years)	57.64 ± 15.36; 60 (46 to 70)
Body mass index (Kg/m²)	24.63 ± 5.21; 24 (22 to 28)
Schooling	
Illiterate	13/151 (8.6%)
Elementary school	86/151 (57.0%)
High school	43/151 (28.5%)
Higher education	9/151 (6.0%)
Household location	
Urban	118/151 (78.2%)
Rural	33/151 (21.8%)
Comorbidity	
Systemic arterial hypertension	138/151 (91.4%)
Diabetes mellitus	56/151 (37.1%)
Obesity	20/151 (13.2%)
Cardiopathy	15/151 (9.9%)
Thyroidopathy	8/151 (5.3%)
Others	20/151 (13.2%)
Hemodialysis duration	
≤1 year	64/151 (42.4%)
>1 year	87/151 (57.6%)
Individuals with ungual alteration	
Yes	70/151 (46.4%)
No	81/151 (53.6%)
Previous medication treatment	
Yes	15/151 (9.9%)
No	136/151 (90.1%)
Mycological exam result	
Positive	31/70 (46.3%)
Negative	36/70 (53.7%)
Culture result*	
Trichophyton rubrum (dermatophyte fungus)	9/31 (29.0%)
Trichophyton mentagrophytes (dermatophyte fungus)	7/31 (22.6%)
Scytalidium spp. (non-dermatophyte fungus)	6/31 (19.4%)
Candida spp. (yeast)	2/31 (6.5%)
Rhodotorula spp. (yeast)	2/31 (6.5%)
Candida albicans (yeast)	1/31 (3.2%)
Penicillium marneffei (dermatophyte fungus)	1/31 (3.2%)
Negative	3/31 (9.7%)
Refused (inconclusive)	1/31 (3.2%)

*One participant presented a positive result for *T. rubrum* and *Rhodotorula* spp. *N*, number of patients; p25, percentile 25%; p75, percentile 75%; %, percentage; ≤, less than or equal to; >, greater than.

TABLE 2 Clinical type, nail involvement severity score, and number of dystrophic nails per patient on hemodialysis with a positive result in the fungal culture examination.

Culture result	Microorganisms' classification	Clinical type (hallux)	Nail involvement severity score*	Dystrophic nails (N)
Candida albicans	Yeast	Distal subungual	Severe	2
Candida spp.	Yeast	Mixed pattern	Severe	6
Candida spp.	Yeast	Mixed pattern	Severe	1
Penicillium marneffei	Non-dermatophyte fungus	Distal subungual	Severe	4
Rhodotorula spp.	Yeast	White superficial	Mild	8
Scytalidium spp.	Non-dermatophyte fungus	Mixed pattern	Severe	10
Scytalidium spp.	Non-dermatophyte fungus	Distal subungual	Severe	10
Scytalidium spp.	Non-dermatophyte fungus	Mixed pattern	Severe	10
Scytalidium spp.	Non-dermatophyte fungus	Distal subungual	Severe	1
Scytalidium spp.	Non-dermatophyte fungus	Mixed pattern	Moderate	2
Scytalidium spp.	Non-dermatophyte fungus	Distal subungual	Severe	9
Trichophyton mentagrophytes	Dermatophyte fungus	Mixed pattern	Mild	3
Trichophyton mentagrophytes	Dermatophyte fungus	Distal subungual	Severe	3
Trichophyton mentagrophytes	Dermatophyte fungus	Distal subungual	Severe	6
Trichophyton mentagrophytes	Dermatophyte fungus	Distal subungual	Severe	4
Trichophyton mentagrophytes	Dermatophyte fungus	Mixed pattern	Severe	2
Trichophyton mentagrophytes	Dermatophyte fungus	Mixed pattern	Severe	10
Trichophyton mentagrophytes	Dermatophyte fungus	Distal subungual	Mild	2
Trichophyton rubrum	Dermatophyte fungus	Distal subungual	Severe	4
Trichophyton rubrum	Dermatophyte fungus	Mixed pattern	Severe	9
Trichophyton rubrum	Dermatophyte fungus	Mixed pattern	Severe	4
Trichophyton rubrum	Dermatophyte fungus	Mixed pattern	Severe	10
Trichophyton rubrum	Dermatophyte fungus	Distal subungual	Severe	5
Trichophyton rubrum	Dermatophyte fungus	Distal subungual	Severe	2
Trichophyton rubrum	Dermatophyte fungus	Mixed pattern	Severe	10
Trichophyton rubrum	Dermatophyte fungus	Mixed pattern	Severe	9
Trichophyton rubrum + *Rhodotorula* spp.	Dermatophyte fungus + Yeast	Mixed pattern	Severe	6

N, number of patients. *The onychomycosis severity was evaluated using the Onychomycosis Severity Index system. The score was obtained by multiplying the score for the area of involvement (range, 0 to 5) by the score for the proximity of disease to the matrix (range, 1 to 5). Ten points were added for the presence of a longitudinal streak or a patch (dermatophytoma) or for greater than 2 mm of subungual hyperkeratosis. Mild onychomycosis corresponds to a score of 1 through 5; moderate, 6 through 15; and severe, 16 through 35 (15).

23.0 Kg/m^2) (Figure 4B). Age did not show a statistically significant difference between the groups of participants regarding the onychomycosis diagnosis (p-value = 0.073; 66 years old vs. 58 years old) (Figure 4A).

The multivariable model using the logistic regression (backward model) was able to predict (81.5%) the onychomycosis-positive diagnosis (chi-square = 27.73; degrees of freedom = 5; p-value <0.001; R^2 Nagelkerke = 0.263) (Table 5). The older age [OR = 1.036; 95% CI = 1.004 to 1.069], male sex [OR = 5.746; 95%CI = 2.057 to 16.046], and presence of obesity [OR = 4.800; 95% CI = 1.435 to 16.055] were positive and significant in predicting the onychomycosis-positive diagnosis (Table 5).

Some clinical phenotypes of onychomycosis in the patients on hemodialysis included in the study are presented below (Figure 5); in addition, an overview of our study protocol and main findings are presented in Figure 6.

4 Discussion

Patients with chronic renal disease on hemodialysis presented a high risk of developing onychomycosis when compared to the general population. Most of the patients evaluated in this study were male individuals, and the comorbidities frequently associated with these patients on hemodialysis were systemic arterial hypertension, diabetes mellitus, obesity, cardiopathy, and tyroidopathy, while male sex and the presence of obesity and diabetes mellitus were risk factors for onychomycosis. Among the 151 patients evaluated, 70 out of 151 (46.4%) showed ungual alterations and, among them, 27 out of 70 (38.5%) obtained positive direct mycological examination and culture. When investigating the positive cultures, a predominance of dermatophyte fungi was observed, followed by non-dermatophyte fungi and yeasts, and the etiological agents were, respectively,

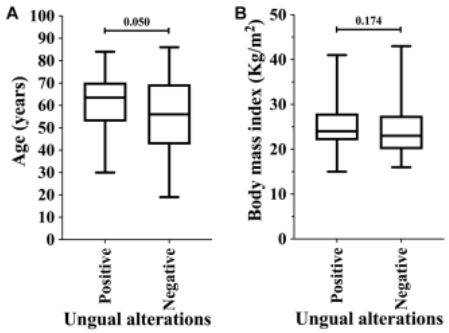


FIGURE 2
Association of ungual alterations in patients on hemodialysis in relation to age (years) **(A)** and body mass index **(B)**. An alpha error of 0.05 was adopted in both analyses. The statistical analysis was carried out using the Mann–Whitney U-test or T-test according to the normality of data.

T. rubrum, *T. mentagrophytes*, *P. marneffei*, *Scytadilium* spp., *Candida* spp., *Rhodotorula* spp., and *C. albicans*.

In the literature, a review was carried out aiming at determining the prevalence of onychomycosis in high-risk patients, that is, children, older individuals, patients with diabetes mellitus, individuals with psoriasis, HIV+, individuals with renal transplant, and those on hemodialysis. Out of the patients evaluated, 109 patients were on hemodialysis and the most common onychomycosis presentation was the distal-lateral subungual, while the most prevalent etiological agents were filamentous and dermatophyte fungi, while yeast prevailed in the elderly, patients with diabetes mellitus, and individuals with psoriasis. Older patients with diabetes mellitus, psoriasis, HIV+, on hemodialysis, and with renal transplants showed high onychomycosis prevalence. Reports were found describing that the factors that might influence these results are damaged immunity, reduced peripheral circulation, and ungual dystrophy (11).

In our data, we identified *P. marneffei* in one patient on hemodialysis, which is an opportunistic fungal species mainly for immunocompromised patients, such as HIV+ patients, and can

TABLE 3 Association between markers evaluated in the study and risk of ungual alterations in patients on hemodialysis of a tertiary hospital.

Marker	Group	Positive	Negative	Total	*P*-value	OR	95%CI
Sex	Male	43 (61.4%)	36 (44.4%)	79 (52.3%)	**0.050[a]**	**1.991**	**1.038 to 3.817**
	Female	27 (38.6%)	45 (55.6%)	72 (47.7%)		1	Reference
Race	White	48 (68.6%)	53 (65.4%)	101 (66.9%)	0.543[b]	1.153	0.583 to 2.278
	Pardo (mixed race)	12 (17.1%)	12 (14.8%)	24 (15.9%)		1.190	0.497 to 2.848
	Black	9 (12.9%)	11 (13.6%)	20 (13.2%)		0.939	0.365 to 2.417
	Asian	1 (1.4%)	5 (6.2%)	6 (4.0%)		0.222	0.005 to 2.056
Schooling	Illiterate	7 (10.0%)	6 (7.4%)	13 (8.6%)	0.270[b]	1.389	0.444 to 4.346
	Elementary school	44 (62.9%)	42 (51.9%)	86 (57.0%)		1.571	0.819 to 3.016
	High school	17 (24.3%)	26 (32.1%)	43 (28.5%)		0.679	0.331 to 1.392
	Higher education	2 (2.9%)	7 (8.6%)	9 (6.0%)		0.313	0.031 to 1.721
Comorbidities							
Systemic arterial hypertension	Yes	66 (94.3%)	72 (88.9%)	138 (91.4%)	0.263[b]	2.053	0.541 to 9.563
	No	4 (5.7%)	9 (11.1%)	13 (8.6%)		1	Reference
Diabetes mellitus	Yes	28 (40.0%)	28 (34.6%)	56 (37.1%)	0.504[a]	1.262	0.651 to 2.446
	No	42 (60.0%)	53 (65.4%)	95 (62.9%)		1	Reference
Obesity	Yes	10 (14.3%)	10 (12.3%)	20 (13.2%)	0.812[a]	1.183	0.462 to 3.034
	No	60 (85.7%)	71 (87.7%)	131 (86.8%)		1	Reference
Cardiopathy	Yes	7 (10.0%)	8 (9.9%)	15 (9.9%)	1.000[a]	1.014	0.348 to 2.952
	No	63 (90.0%)	73 (90.1%)	136 (90.1%)		1	Reference
Thyroidopathy	Yes	6 (8.6%)	2 (2.5%)	8 (5.3%)	0.145[b]	3.673	0.629 to 38.41
	No	64 (91.4%)	79 (97.5%)	143 (94.7%)		1	Reference
Other comorbidities	Yes	11 (15.7%)	9 (11.1%)	20 (13.2%)	0.474[a]	1.492	0.579 to 3.840
	No	59 (84.3%)	72 (88.9%)	131 (86.8%)		1	Reference
Household location	Urban	57 (81.4%)	61 (75.3%)	118 (78.1%)	0.432[a]	1.438	0.655 to 3.155
	Rural	13 (18.6%)	20 (24.7%)	33 (21.9%)		1	Reference
Hemodialysis period	≤1 year	26 (37.1%)	38 (46.9%)	64 (42.4%)	0.251[a]	0.669	0.348 to 1.284
	>1 year	44 (62.9%)	43 (53.1%)	87 (57.6%)		1	Reference

OR, Odds Ratio; 95%CI, 95% confidence interval; ≤, less than or equal to; >, greater than. [a]Pearson's chi-square test. [b]Fisher's Exact test. Significant data are presented in bold. An alpha error of 0.05 was adopted in all analyses carried out.

TABLE 4 Association between markers evaluated in the study and risk of onychomycosis-positive diagnosis in patients on hemodialysis of a tertiary hospital.

Marker	Group	Positive	Negative	Total	*P*-value	OR	95%CI
Sex	Male	23 (74.2%)	56 (46.7%)	79 (52.3%)	**0.008**[a]	**3.286**	**1.362 to 7.928**
	Female	8 (25.8%)	64 (53.3%)	72 (47.7%)		1	Reference
Race	White	22 (71.0%)	79 (65.8%)	101 (66.9%)	0.825[b]	1.269	0.536 to 3.005
	Pardo (mixed race)	5 (16.1%)	19 (15.8%)	24 (15.9%)		1.022	0.349 to 2.996
	Black	4 (12.9%)	16 (13.3%)	20 (13.2%)		0.963	0.217 to 3.330
	Asian	0 (0.0%)	6 (5.0%)	6 (4.0%)		NA	NA
Schooling	Illiterate	3 (9.7%)	10 (8.3%)	13 (8.6%)	0.795[b]	1.177	0.195 to 4.994
	Elementary school	20 (64.5%)	66 (55.0%)	86 (57.0%)		1.488	0.656 to 3.374
	High school	7 (22.6%)	36 (30.0%)	43 (28.5%)		0.681	0.269 to 1.721
	Higher education	1 (3.2%)	8 (6.7%)	9 (6.0%)		0.469	0.010 to 3.732
Comorbidities							
Systemic arterial hypertension	Yes	30 (96.8%)	108 (90.0%)	138 (91.4%)	0.306[b]	3.314	0.455 to 147.2
	No	1 (3.2%)	12 (10.0%)	13 (8.6%)		1	Reference
Diabetes mellitus	Yes	16 (51.6%)	40 (33.3%)	56 (37.1%)	**0.049**[a]	2.133	0.959 to 4.748
	No	15 (48.4%)	80 (66.7%)	95 (62.9%)		1	Reference
Obesity	Yes	8 (25.8%)	12 (10.0%)	20 (13.2%)	**0.027**[a]	**3.130**	**1.150 to 8.521**
	No	23 (74.2%)	108 (90.0%)	131 (86.8%)		1	Reference
Cardiopathy	Yes	1 (3.2%)	14 (11.7%)	15 (9.9%)	0.141[b]	0.254	0.006 to 1.803
	No	30 (96.8%)	106 (88.3%)	136 (90.1%)		1	Reference
Thyroidopathy	Yes	4 (12.9%)	4 (3.3%)	8 (5.3%)	0.056[b]	4.241	0.741 to 24.32
	No	27 (87.1%)	116 (96.7%)	143 (94.7%)		1	Reference
Other comorbidities	Yes	7 (22.6%)	13 (10.8%)	20 (13.2%)	0.082[a]	2.401	0.866 to 6.657
	No	24 (77.4%)	107 (89.2%)	131 (86.8%)		1	Reference
Household location	Urban	26 (83.9%)	92 (76.6%)	118 (78.1%)	0.387[a]	1.583	0.556 to 4.506
	Rural	5 (16.1%)	28 (23.3%)	33 (21.9%)		1	Reference
Hemodialysis period	≤1 year	9 (29.0%)	55 (45.8%)	64 (42.4%)	0.068[a]	0.484	0.206 to 1.136
	>1 year	22 (71.0%)	65 (54.2%)	87 (57.6%)		1	Reference

NA, not applicable; OR, Odds Ratio; 95%CI, 95% confidence interval; ≤, less than or equal to; >, greater than. [a]Pearson's chi-square test. [b]Fisher's exact test. Significant data are presented in bold. An alpha error of 0.05 was adopted in all analyses carried out.

cause the penicilliosis disease (19, 20). This disease was first identified in Thailand and Southeast Asia, and it affects the skin, mucosa, lungs, pleura, lymph nodes, central nervous system, and bone marrow, and the risk increases with exposure to soil (21, 22). This disseminated fungal infection causes high morbidity and mortality (19). This fungus is uncommon in onychomycosis and immunocompetent patients in the general population, and it was first described by Gupta (23) in a 60-year-old man who had onychomycosis diagnostic in the fingernail, and the only risk factor was gardening. To the best of our knowledge, this infection has never been described in Brazil (24).

The incidence of superficial fungal infections is related to genetic susceptibility, family background (25, 26), and environmental factors such as moist, wearing shoes, excessive sweat, and cross-contamination by other contaminated individuals and contaminated objects and surfaces (27). These factors associated with low immunity predispose the individual to onychomycosis development. Chronic renal disease tends to occur simultaneously with high uremia, which increases oxygen-reactive species, leading to oxidative stress (28). In addition, patients on hemodialysis show a higher pro-inflammatory response occurring with increased expression of polymorphonuclear neutrophils of the TRL2 (*Toll-like Receptor 2*) and TRL4 (*Toll-like Receptor 4*) receptors of monocytes. They also decrease the number and function of dendritic cells reducing the innate immunologic system expression, in addition to harming the adaptive immunologic system with a reduction in the number and function of T CD4+ (cluster of differentiation 4) and CD8+ (cluster of differentiation 8) cells as well as B cells. Thus, renal function loss reduces the effectiveness of the immunologic system and creates a pro-inflammatory environment with important consequences such as endothelial dysfunction, systemic inflammation, and predisposition to infections, including fungal infections (29).

Male sex is considered a risk factor for the development of onychomycosis in patients on hemodialysis (10, 11, 13) and in the general population (30–33); men present approximately 2.99 more chances of acquiring fungal infection when compared to women (34).

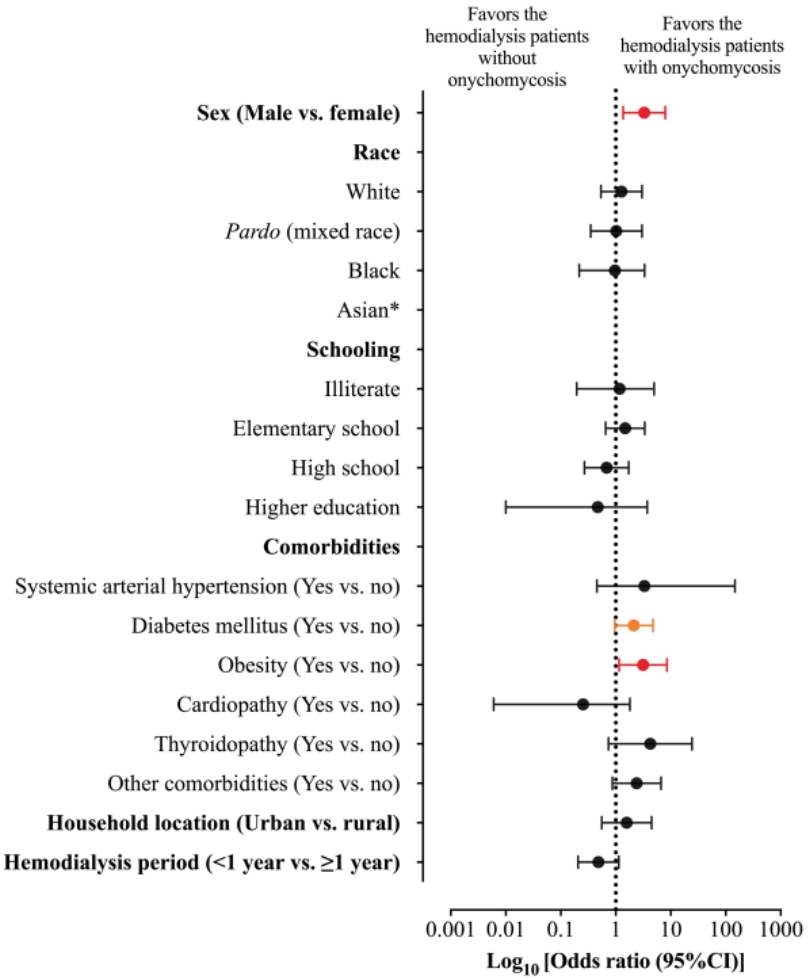


FIGURE 3
Odds ratio (OR) and 95% confidence interval (95%CI) for the association between markers evaluated in the study and risk of onychomycosis-positive diagnosis in patients on hemodialysis of a tertiary hospital. *, the OR was not imputed because no patient was classified as Asiatic in the group of onychomycosis-positive diagnosis. The red color represents the markers (gender and obesity) with a statistical significance difference between groups and with a significant 95%CI which did not include one. The orange color represents the marker (diabetes mellitus) with a statistical significance difference between groups and with a significant 95%CI which included one.

However, despite the several reports in the literature addressing its predominance in male patients, there is no consensus about the explanation for this fact. It might be associated with immunity reduction and genetic and environmental factors, as previously mentioned. Moreover, women seek medical assistance to solve skin problems more often than men, which might modulate the onychomycosis prevalence according to gender (35). There are reports about *Trichophyton* spp. and *Microsporum* spp. presenting cytosolic proteins specifically and with great affinity to progesterone, which in turn inhibits the growth of dermatophyte fungi in a dose-dependent manner since anthropophilic species respond better to steroids than geophilic species (36).

Diabetes mellitus is considered one of the main risk factors for onychomycosis among patients on hemodialysis (3, 10, 12, 13) and among the general population (7, 37–40). As described by Lamb et al. (13), patients with diabetes mellitus show 88% more risk of acquiring onychomycosis than those without that disease, and these data confirm the findings reported by Gupta et al. (34), who reported that the risk of a diabetes mellitus patient acquiring onychomycosis is 2.77 higher than that of the general population. This value is even higher in male patients with diabetes mellitus (~2.99 times). In this study, the onychomycosis severity was also related to the time of duration of the diabetes mellitus (34). Gupta et al. (34) reported other factors related to onychomycosis, the presence of this disease in the family

background is among them along with the use of immunosuppressive therapy, reduction or absence of the foot dorsal artery and the posterior tibial artery pulse, and capillary filling and ankle-brachial pressure index reduction (34). The neuropathy associated with diabetes mellitus reduces skin sensitivity; thus, small traumas might remain unnoticed and when not cured, they might remain a point of entry for infections. This is associated with immunity reduction and microangiopathy results among other complications in the development of onychomycosis (41). Moreover, a neuroischemic foot increases the prevalence of onychomycosis (42).

Obesity is a risk factor for onychomycosis (37, 38, 43, 44) representing one of the most predominant factors for this disease (45); moreover, the increases in body mass index and the persistent overweight has increased the incidence of onychomycosis (46). According to Gulcan et al. (47), the association of excess fat tissue accumulation, which alters the local microvasculature and causes more sweating, also creates favorable conditions for fungal infections (47). Moreover, some authors reported an association between the presence of onychomycosis in adult patients with the coexistence of risk factors such as obesity and diabetes mellitus (43, 45).

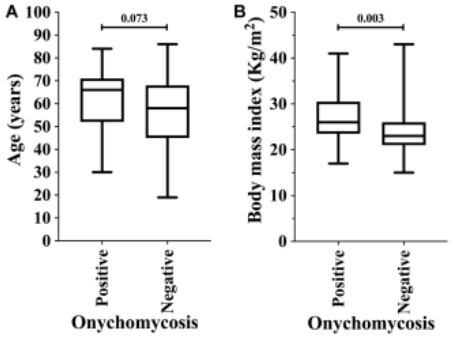


FIGURE 4
Association of onychomycosis-positive diagnosis in patients on hemodialysis in relation to age (years) **(A)** and body mass index **(B)**. An alpha error of 0.05 was adopted in both analyses. The statistical analysis was carried out using the Mann–Whitney U-test or T-test according to the normality of data.

Hemodialysis duration as a risk factor for onychomycosis is not well established in the literature, and our study revealed that it is not a risk factor, which agrees with some previous studies (10, 13); however, other studies do not agree with these data (12).

According to the etiological agents found in this study and other reports in the literary review, dermatophyte fungi were the most prevalent, followed by non-dermatophyte fungi and yeasts (8, 9). Lamb et al. (13) reported dermatophyte fungi (69.2%) as the main cause, followed by non-dermatophyte fungi (15.4%) and yeast (15.4%), and the main fungi found in the cultures were *T. interdigitale* ($n = 12$), *Candida* spp. ($n = 6$), and *T. rubrum* ($n = 4$). Filho et al. (10) reported dermatophyte fungi (80.3%) as the main cause, while yeast (18%) appeared as the second main cause, and the minority of cases was associated with non-dermatophyte fungi (1.6%). The main etiological agents found in the culture were *T. rubrum* (39.1%), *C. parapsilosis* (30.4%), and *T. mentagrophytes* (21.7%) in patients on hemodialysis. Kuvandik et al. (12) also found dermatophyte fungi (86.7%) as the main cause associated with onychomycosis, followed by non-dermatophyte fungi (13.3%). However, yeast was not identified, and the positive cultures presented mainly *T. rubrum* (9.2%) and *T. mentagrophytes* (1.8%) species (12). The positive culture result in this study included dermatophyte fungi *T. rubrum* (29%), *T. mentagrophytes* (22.6%), and *P. marneffei* (3.2%), the non-dermatophyte fungi *Scytalidium* spp. (19.4%), and the yeasts *Candida* spp. (6.5%), *Rhodotorula* spp. (6.5%), and *C. albicans* (3.2%), and these values agree with other studies that reported fungi *T. rubrum* and *T. mentagrophytes* as the main dermatophyte fungi and *Candida* spp. as the main cause among yeasts (8, 10, 12).

This study has some limitations, for example, the low number of participants, the inclusion of only one research center, the identification of the agents causing onychomycosis restricted to the direct microbiological and culture exams, and patient data collected using interviews and medical records. In our study, it was not possible to assess the presence of onychomycosis before hemodialysis. The population that was included belonged to the low-income class, and all participants were evaluated, free of charge, upon inclusion in the study. After inclusion, all patients with nail alterations, mainly with onychomycosis, are being followed up and, with the results of the study, we intend to implement routine follow-up of these patients by a dermatologist. In addition, the literature presents few studies on this theme, which hampers the comparative analysis of the epidemiological

TABLE 5 **Multivariable analysis to determine the association between markers evaluated in the study and risk of onychomycosis-positive diagnosis in patients on hemodialysis of a tertiary hospital.[*,*]**

Markers	B	SE	Wald	df	*P*-value	*Odds ratio*	95%CI
Age (years)	0.035	0.016	4.854	1	**0.028**	**1.036**	**1.004 to 1.069**
Sex (male)	1.748	0.524	11.135	1	**0.001**	**5.746**	**2.057 to 16.046**
Comorbidities (yes)							
Obesity	1.569	0.616	6.483	1	**0.011**	**4.800**	**1.435 to 16.055**
Cardiopathy	−1.941	1.118	3.017	1	0.082	0.144	0.016 to 1.283
Thyroidopathy	1.633	0.887	3.391	1	0.066	5.121	0.900 to 29.132
Constant	−4.757	1.112	18.314	1	<0.001	0.009	

SE, standard error; 95%CI, 95% confidence interval; df, degrees of freedom. In the multivariable analysis, it was used the binary logistic regression model with the backward stepwise method. Significant data are presented in bold. An alpha error of 0.05 was adopted in all analyses carried out. *Markers included in step one: age, gender, comorbidities (obesity, cardiopathy, thyroidopathy, and other comorbidities), and hemodialysis period. *It was included in the regression model (multivariable analysis) the markers with a *p*-value of ≤0.25 in the bivariate analysis (Table 4).

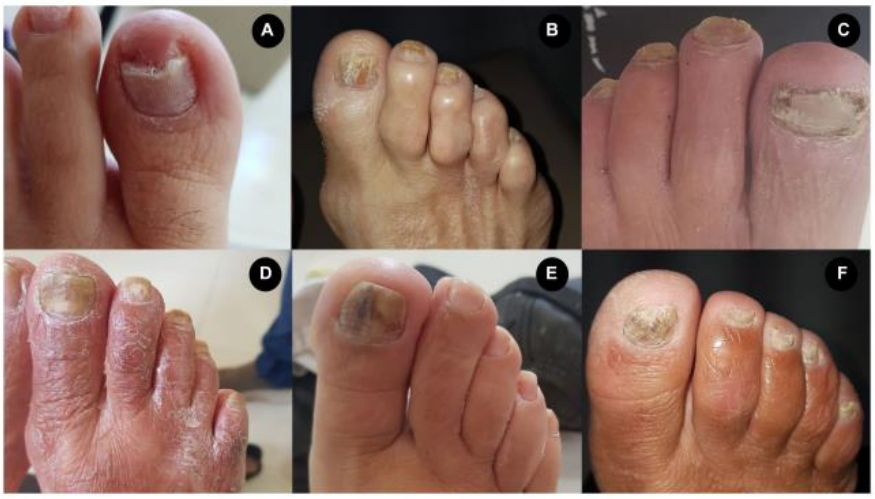


FIGURE 5
Presentation of different phenotypes associated with onychomycosis in patients on hemodialysis. **(A)** *Candida albicans* (yeast). **(B)** *Trichophyton rubrum* (dermatophyte fungus). **(C)** *Scytalidium* spp. (non-dermatophyte fungus). **(D)** *T. rubrum* (dermatophyte fungus) and *Rhodotorula* spp. (yeast). **(E)** *Candida* spp. (yeast). **(F)** *Trichophyton mentagrophytes* (dermatophyte fungus).

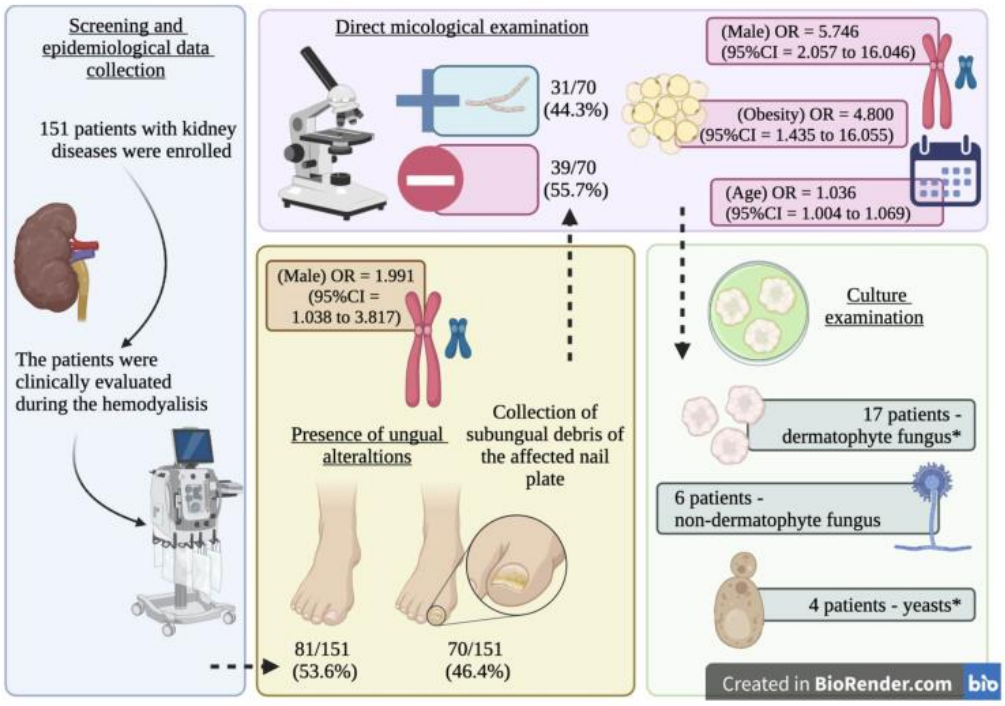


FIGURE 6
Graph summary. Scheme of the study protocol and main findings including the *Odds ratio* (OR) and 95% confidence intervals for the risk factors of ungual alterations (gender) and onychomycosis (age, gender, and obesity) in patients on hemodialysis. *, one participant presented a positive result for *Trichophyton rubrum* and *Rhodotorula* spp.

profile associated with onychomycosis in patients on hemodialysis with other studies.

5 Conclusion

In our study, onychomycosis in patients on hemodialysis was associated with a great variety of microorganisms, mainly *Trichophyton* species, and the main risk factors associated with this infection are male sex, older age, and the presence of obesity. The main fungi associated with onychomycosis in patients on hemodialysis were the dermatophyte fungi (*T. rubrum* and *T. mentagrophytes*), followed by non-dermatophyte fungi (*Scytalidium* spp.), and yeast. The nail involvement severity score for the majority of patients was severe, and distal subungual onychomycosis and mixed pattern onychomycosis were the most prevalent clinical types. Since this fungal infection can provoke drastic consequences such as amputation in patients on hemodialysis and a social constraint factor, it is important to evaluate the treatment of this condition to improve their quality of life.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Comitê de Ética da Universidade São Francisco. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JB: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. MC: Conceptualization, Investigation, Methodology, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. FM: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Funding

The authors declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Anees M, Butt G, Gull S, Nazeer A, Hussain I, Ibrahim M. Factors affecting dermatological manifestations in patients with end stage renal disease. *J Coll Physicians Surg*. (2018) 28:98–102. doi: 10.29271/jcpsp.2018.02.98

2. Onelmis H, Sener S, Sasmaz S, Ozer A. Cutaneous changes in patients with chronic renal failure on hemodialysis. *Cutan Ocul Toxicol*. (2012) 31:286–91. doi: 10.3109/15569527.2012.657726

3. Picó MR, Lugo-Somolinos A, Sánchez JL, Burgos-Calderón R. Cutaneous alterations in patients with chronic renal failure. *Int J Dermatol*. (1992) 31:860–3. doi: 10.1111/j.1365-4362.1992.tb03543.x

4. Udayakumar P, Balasubramanian S, Ramalingam KS, Lakshmi C, Srinivas CR, Mathew AC. Cutaneous manifestations in patients with chronic renal failure on hemodialysis. *Indian J Dermatol Venereol Leprol*. (2006) 72:119–25. doi: 10.4103/0378-6323.25636

5. Schwade MJ, Tien L, Waller JL, Davis LS, Baer SL, Mohammed A, et al. Treatment of psoriasis in end-stage renal disease patients is associated with decreased mortality: a retrospective cohort study. *Am J Med Sci*. (2021) 362:24–33. doi: 10.1016/j.amjms.2021.03.009

6. Salem A, Al Mokadem S, Attwa E, Abd El Raoof S, Ebrahim HM, Faheem KT. Nail changes in chronic renal failure patients under haemodialysis. *J Eur Acad Dermatol Venereol*. (2008) 22:1326–31. doi: 10.1111/j.1468-3083.2008.02826.x

7. Bodman MA, Krishnamurthy K. Onychomycosis In: *StatPearlsPl*. Eds. Bodman, MA, Krishnamurthy K. Treasure Island (FL): StatPearls Publishing (2023).

8. Gupta AK, Stec N, Summerbell RC, Shear NH, Piguet V, Tosti A, et al. Onychomycosis: a review. *J Eur Acad Dermatol Venereol*. (2020) 34:1972–90. doi: 10.1111/jdv.16394

9. Gupta AK, Versteeg SG, Shear NH. Onychomycosis in the 21st century: an update on diagnosis, epidemiology, and treatment. *J Cutan Med Surg*. (2017) 21:525–39. doi: 10.1177/1203475417716362

10. Filho AMS, Ventura CG, Criado PR, Del Negro GB, Freitas RS, Luiz OC, et al. Hemodialysis and kidney transplantation as predisposing conditions to onychomycosis. *Nephron*. (2017) 137:38–46. doi: 10.1159/000475674

11. Gupta AK, Daigle D, Foley KA. The prevalence of culture-confirmed toenail onychomycosis in at-risk patient populations. *J Eur Acad Dermatol Venereol*. (2015) 29:1039–44. doi: 10.1111/jdv.12873

12. Kuvandik G, Cetin M, Genctoy G, Horoz M, Duru M, Akcali C, et al. The prevalance, epidemiology and risk factors for onychomycosis in hemodialysis patients. *BMC Infect Dis*. (2007) 7:102. doi: 10.1186/1471-2334-7-102

13. Lamb FM, Ottonelli Stopiglia CD, Vetoratto G, Goldani JC, Scroferneker ML. Frequency of onychomycoses in chronic renal failure patients undergoing hemodialysis in Porto Alegre, Brazil. *Acta dermatovenerologica Iugoslavica*. (2013) 21:19–23.

14. Hay RJ, Baran R. Onychomycosis: a proposed revision of the clinical classification. *J Am Acad Dermatol*. (2011) 65:1219–27. doi: 10.1016/j.jaad.2010.09.730

15. Carney C, Tosti A, Daniel R, Scher R, Rich P, DeCoster J, et al. A new classification system for grading the severity of onychomycosis: onychomycosis severity index. *Arch Dermatol*. (2011) 147:1277–82. doi: 10.1001/archdermatol.2011.267

16. Bendel RB, Afifi AA. Comparison of stopping rules in forward "stepwise" regression. *J Am Stat Assoc*. (1977) 72:46–53. doi: 10.2307/2286904

17. Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. *Source Code Biol Med*. (2008) 3:17. doi: 10.1186/1751-0473-3-17

18. Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation. *Am J Epidemiol*. (1989) 129:125–37. doi: 10.1093/oxfordjournals.aje.a115101

19. Conant MA. The AIDS epidemic. *J Am Acad Dermatol*. (1994) 31:S47–50. doi: 10.1016/s0190-9622(08)81267-4

20. Ungpakorn R. Mycoses in Thailand: current concerns. Nihon Ishinkin Gakkai Zasshi Jpn. *J Med Mycol.* (2005) 46:81–6. doi: 10.3314/jjmm.46.81

21. Marques SA, Robles AM, Tortorano AM, Tuculet MA, Negroni R, Mendes RP. Mycoses associated with AIDS in the third world. *Med Mycol.* (2000) 38:269–79. doi: 10.1080/mmy.38.s1.269.279

22. Vithayasai P, Vithayasai V. Clinical manifestations of 174 AIDS cases in Maharaj Nakorn Chiang Mai hospital. *J Dermatol.* (1993) 20:389–93. doi: 10.1111/j.1346-8138.1993.tb01305.x

23. Gupta M, Sharma NL, Kanga AK, Mahajan VK, Tegta GR. Onychomycosis: Clinico-mycologic study of 130 patients from Himachal Pradesh, India. *Indian J Dermatol Venereol Leprol.* (2007) 73:389–92. doi: 10.4103/0378-6323.37055

24. Søndergaard J, Weismann K, Vithayasai P, Srisuwan S, Manela-Azulay M. Ethnic and geographic differences and similarities of HIV/AIDS-related mucocutaneous diseases. *Danida Study Groups Int J Dermatol.* (1995) 34:416–9. doi: 10.1111/j.1365-4362.1995.tb04443.x

25. Dubljanin E, Džamić A, Vujčić I, Grujičić SŠ, Arsenijević VA, Mitrović S, et al. Epidemiology of onychomycosis in Serbia: a laboratory-based survey and risk factor identification. *Mycoses.* (2017) 60:25–32. doi: 10.1111/myc.12537

26. Papini M, Piraccini BM, Difonzo E, Brunoro A. Epidemiology of onychomycosis in Italy: prevalence data and risk factor identification. *Mycoses.* (2015) 58:659–64. doi: 10.1111/myc.12396

27. García-Romero MT, Arenas R. New insights into genes, immunity, and the occurrence of dermatophytosis. *J Invest Dermatol.* (2015) 135:655–7. doi: 10.1038/jid.2014.498

28. Vaziri ND. Oxidative stress in uremia: nature, mechanisms, and potential consequences. *Semin Nephrol.* (2004) 24:469–73. doi: 10.1016/j.semnephrol.2004.06.026

29. Betjes MGH. Immune cell dysfunction and inflammation in end-stage renal disease. *Nat Rev Nephrol.* (2013) 9:255–65. doi: 10.1038/nrneph.2013.44

30. Ghannoum M, Isham N. Fungal nail infections (onychomycosis): a never-ending story? *PLoS Pathog.* (2014) 10:e1004105. doi: 10.1371/journal.ppat.1004105

31. Gregoriou S, Mpali N, Vrioni G, Hatzidimitriou E, Chryssou S-E, Rigopoulos D. Epidemiology of onychomycosis in an academic nail unit in South Greece during a three-year period. *Skin Appendage Disord.* (2020) 6:102–7. doi: 10.1159/000504812

32. Gupta AK, Gupta G, Jain HC, Lynde CW, Foley KA, Daigle D, et al. The prevalence of unsuspected onychomycosis and its causative organisms in a multicentre Canadian sample of 30 000 patients visiting physicians' offices. *J Eur Acad Dermatol Venereol.* (2016) 30:1567–72. doi: 10.1111/jdv.13677

33. Gupta AK, Jain HC, Lynde CW, Macdonald P, Cooper EA, Summerbell RC. Prevalence and epidemiology of onychomycosis in patients visiting physicians' offices: a multicenter Canadian survey of 15,000 patients. *J Am Acad Dermatol.* (2000) 43:244–8. doi: 10.1067/mjd.2000.104794

34. Gupta AK, Konnikov N, MacDonald P, Rich P, Rodger NW, Edmonds MW, et al. Prevalence and epidemiology of toenail onychomycosis in diabetic subjects: a multicentre survey. *Br J Dermatol.* (1998) 139:665–71. doi: 10.1046/j.1365-2133.1998.02464.x

35. Sigurgeirsson B, Baran R. The prevalence of onychomycosis in the global population – a literature study. *J Eur Acad Dermatol Venereol.* (2014) 28:1480–91. doi: 10.1111/jdv.12323

36. Peres NTDA, Maranhão FCA, Rossi A, Martinez-Rossi NM. Dermatófitos: interação patógeno-hospedeiro e resistência a antifúngicos. *An Bras Dermatol.* (2010) 85:657–67. doi: 10.1590/S0365-05962010000500009

37. Frazier WT, Santiago-Delgado ZM, Stupka KC. Onychomycosis: rapid evidence review. *Am Fam Physician.* (2021) 104:359–67.

38. Lipner SR, Scher RK. Onychomycosis: clinical overview and diagnosis. *J Am Acad Dermatol.* (2019) 80:835–51. doi: 10.1016/j.jaad.2018.03.062

39. Oz Y, Qoraan I, Oz A, Balta I. Prevalence and epidemiology of tinea pedis and toenail onychomycosis and antifungal susceptibility of the causative agents in patients with type 2 diabetes in Turkey. *Int J Dermatol.* (2017) 56:68–74. doi: 10.1111/ijd.13402

40. Trovato L, Calvo M, De Pasquale R, Scalia G, Oliveri S. Prevalence of onychomycosis in diabetic patients: a case-control study performed at university hospital Policlinico in Catania. *J Fungi Basel Switz.* (2022) 8:922. doi: 10.3390/jof8090922

41. Rich P, Hare A. Onychomycosis in a special patient population: focus on the diabetic. *Int J Dermatol.* (1999) 38:17–9. doi: 10.1046/j.1365-4362.1999.00009.x

42. Aragón-Sánchez J, López-Valverde ME, Víquez-Molina G, Milagro-Beamonte A, Torres-Sopena L. Onychomycosis and tinea Pedis in the feet of patients with diabetes. *Int J Low Extrem Wounds.* (2023) 22:321–7. doi: 10.1177/15347346211009409

43. Chang S-J, Hsu S-C, Tien K-J, Hsiao J-Y, Lin S-R, Chen H-C, et al. Metabolic syndrome associated with toenail onychomycosis in Taiwanese with diabetes mellitus. *Int J Dermatol.* (2008) 47:467–72. doi: 10.1111/j.1365-4632.2008.03606.x

44. Elewski BE, Tosti A. Risk factors and comorbidities for onychomycosis. *J Clin Aesthetic Dermatol.* (2015) 8:38–42.

45. Chan MKT, Chong L-YAchilles Project Working Group in Hong Kong. A prospective epidemiologic survey on the prevalence of foot disease in Hong Kong. *J Am Podiatr Med Assoc.* (2002) 92:450–6. doi: 10.7547/87507315-92-8-450

46. Ha SJ, Han KD, Song Y, Lee JH. Weight change and risk of onychomycosis: a nationwide cohort study in Korea. *J Am Acad Dermatol.* (2018) 78:613–4. doi: 10.1016/j.jaad.2017.09.030

47. Gulcan A, Gulcan E, Oksuz S, Sahin I, Kaya D. Prevalence of toenail onychomycosis in patients with type 2 diabetes mellitus and evaluation of risk factors. *J Am Podiatr Med Assoc.* (2011) 101:49–54. doi: 10.7547/1010049

4. Capítulo 2. Artigo submetido

Título: Terbinafina em polímero acrílico para o tratamento de onicomicose em pacientes em hemodiálise: um ensaio clínico de fase II

Title: Terbinafine in Acrylic Polymer for the Treatment of Onychomycosis in Hemodialysis Patients: A Phase II Clinical Trial

Jeanne Marie Queiroz Borges Bersano [1,*]; Matheus Gobbo Cordeiro [1,*]; Juliana Mozer Sciani [2]; Iara Lúcia Tescarollo [3]; Fernando Augusto Lima Marson [1,*]

[1] Molecular Biology and Genetics Laboratory, Health Sciences Postgraduate Program, São FranciscoUniversity, Bragança Paulista 12916-900, SP, Brazil.

[2] São Francisco University Multidisciplinary Research Laboratory, Health Sciences Postgraduate Program, São Francisco University, Bragança Paulista 12916-900, SP, Brazil.

[3] Health Sciences Postgraduate Program, São Francisco University, Bragança Paulista 12916-900, SP, Brasil.

*** Corresponding Author:**
Fernando Augusto Lima Marson, Molecular Biology and Genetics Laboratory, Health Sciences Postgraduate Program, São Francisco University, Bragança Paulista 12916-900, SP, Brazil.
Phone: +55 19 9 99752911.
E-mail: fernando.marson@usf.edu.br and fernandolimamarson@hotmail.com.

E-mail and ORCIDs:
JMB: jeanne.marie@usf.edu.brORCID: 0000-0001-8144-2967
MGC: matheus.gobbo@mail.usf.edu.brORCID: 0009-0008-2102-8746
JMS: juliana.sciani@usf.edu.brORCID: 0000-0001-7213-206X
ILT: iara.dias@usf.edu.br ORCID: 0000-0002-8110-8771
FALM: fernando.marson@usf.edu.br and fernandolimamarson@hotmail.com
ORCID: 0000-0003-4955-4234

Statements
Funding: The study was supported by the National Council for Scientific and Technological Development (CNPq, n° 126410/2022-4).
Conflict of Interests: The authors declare that they have no conflicts of interest.
Ethical approval: The study was approved by the research ethics committee of the São Francisco University (no 59763022.8.0000.5514 – Opinion n° 064544/2022).
Participants' Consent: The research participants or their legal guardians signed the free and informed consente form before the participants' inclusion in the study.
Consent for publication: All authors approved and agreed with the study publication.

Abstract

Introduction: Onychomycoses are nail infections caused by dermatophyte fungi, non-dermatophyte fungi and yeast.Patients with chronic kidney disease on dialysis are part of the population that presents higher rates of this disease, mainly due to immunosuppression. Among patients with chronic kidney disease on dialysis, the treatment ofonychomycosis is complex, mainly due to the limitations imposed by comorbidities. In this context, the study evaluatedthe safety and potential efficacy of a treatment that combines nail debridement with the use of acrylic gel nails carryingterbinafine at a concentration of 2%. **Methods:** Patients from the Hemodialysis Center of the São Francisco de Assis University Hospital in BragançaPaulista, São Paulo, Brazil were included. Those had hallux onychomycosis with clinical forms whose treatmentinvolved the need for nail debridement. After the debridement procedure, a nail prosthesis made with acrylicreconstruction gel and 2% terbinafine was applied. The procedure was renewed every two weeks (~14 days) for 11months. The evolution was monitored with measurements of the normal-appearing nail plate and photographs. Directmycological examination and fungal culture were performed at the beginning of the study and 30 days afterapplications were interrupted. Assessment of clinical response, clinical cure, mycological cure, and complete cure wasperformed at the end of the study. All participants answered a questionnaire about their perception of the treatment. **Results:** Out of the 155 patients, 64/155 (41.3%) individuals were identified with symptoms suggestive ofonychomycosis in the halluces after clinical analysis. Among them, 35/64 (54.7%) individuals presented a positivedirect mycological examination and underwent fungal culture to identify the etiological agent. In this group of patients,24/35 (68.6%) individuals who presented clinical forms whose treatment involved the need for nail debridement wereselected. Only 15/24 (62.5%) individuals completed the study. Among the study participants, 5/15 (33.3%) stillpresented positive fungal culture in the presence of a negative direct mycological examination and 1/15 (6.7%)presented a positive direct mycological examination, but with a negative culture. Among those with a positive fungalculture, 3/15 (20.0%) participants presented microorganisms different from those isolated in the initial exams.Regarding cure, 5/15 (33.3%) participants showed a clinical response, 4/15 (26.7%) clinical cure and 3/15 (20.0%)complete cure. No patient presented an allergic reaction or local irritation caused by the material used in the treatment.There were accidental superficial ulcerations caused by the electric sandpaper; however, no wound developedsecondary infection. No participant reported discomfort due to the nail prosthesis use, 3/15 (20.0%) reported a feelingof discomfort caused by the vibration of the electric file and 12/15 (80.0%) reported the perception that their nails had a better appearance during treatment. **Conclusion:** The application of 2% terbinafine in acrylic reconstruction gel for the manufacture of nail prostheses applied after debridement of moderate and severe forms of onychomycosis showed low efficacy as an isolated treatment in patients on dialysis due to chronic kidney disease. On the other hand, most patients had a good perceptionof the appearance of their nails during treatment, even when it did not result in apparent clinical improvement or complete cure.

Keywords: Antifungal. Nail plate debridement. Kidney dialysis. Clinical trial. Microbiology. Onychomycoses. Terbinafine.

1. Introduction

Onychomycosis is a term that encompasses all forms of fungal infections in the nails and presents signs and symptoms similar to other pathological conditions, requiring, for this reason, a complementary examination to detect the fungus presence and establish a definitive diagnosis [1,2]. Due to the slow growth of the nail plate, the treatment is long lasting and expensive [1,2]. The most common etiological agents are dermatophyte fungi (~70% of cases), mainly from the genus *Trichophyton*, which has two species of greater epidemiological importance – *T. rubrum* and *T. mentagrophytes* [3–6]. Non-dermatophyte filamentous fungi are responsible for ~20% of the cases, and the most common species are *Scopulariopsis brevicaulis*, *Aspergillus* spp., *Acremonium* spp., *Fusarium* spp., *Alternaria alternate* and *Neoscytalidium* spp. [3–6]. Also, yeast of the genus *Candida* are responsible for 10-20% of this diseasecases [3–6]. The clinical forms of onychomycosis are classified according to the pattern of nail invasion, as white superficial, distal/lateral subungual, proximal subungual and endonyx [1,2,5]. There is also a mixed pattern, when more than one clinical type is found in the same nail [1–3,5,7]. Finally, the total dystrophic pattern occurs when the nail plate is seen to be extensively and seriously destroyed and dystrophic, corresponding to the advanced state of theother clinical forms [1–3,5,7]. Commonly, toe nails are more frequently affected than finger nails [8].

The onychomycosis treatment is hampered by the impermeable nature of the nail, a characteristic ascribed todisulfide bonds and hydrogen bonds within the keratin network, making the nail plate a difficult biological barrier to overcome [9,10]. Fungi have the ability to form a biofilm on the nail plate, leading to the development of resistance against antifungal agents and providing protection against the immune system [11,12]. Therefore, personalized treatment should be administered based on the nail involvement extent, infecting organism, presence of comorbiditiesand the simultaneous use of other medications, due to the risk of drug interactions and adverse effects [1,13–15].

Systemic treatment of onychomycosis is recommended as an initial approach when the nail matrix is involved, if three or more nails are simultaneously affected, in the presence of dermatophytoma, subungual hyperkeratosis greaterthan 2 mm and in the total dystrophic form [2,13,14]. Terbinafine is widely known as the most efficient systemic medication to treat onychomycosis [16]. This medication inhibits the cytochrome P450 (CYP450) 2D6 (CYP2D6) system pathways, with relatively low risks of drug interactions and generally negligible adverse effects [16–18]. On the other hand, itraconazole, the second most effective systemic drug, inhibits the CYP450 P3A4 (CYP3A4) system and has the potential to interfere with the metabolism of several other medications, such as statins, immunosuppressants, anticonvulsants, coumarins and antiretrovirals [19–21]. Moreover, itraconazole has the potential to cause QT prolongation, torsade de pointes, heart failure and rhabdomyolysis, [17,22,23]. In Brazil, fluconazole is the most commonly prescribed medication for the treatment of onychomycosis, however, its use is considered off- label in the United States of America [24,25]. Fluconazole inhibits the CYP3A4 and P2C9 (CYP2C9) systems of CYP450, thus interacting with other drugs that are metabolized through these pathways [26]. The most frequently reported adverse reactions include nauseas, vomiting, diarrhea, headache, and skin rash [27]. The occurrence of hepatotoxicity, QT prolongation, and the

Stevens-Johnson syndrome is sometimes reported [27,28].

Topical antifungals rarely exhibit adverse effects and have negligible systemic absorption [13,24,29,30]. However, its use as monotherapy is limited to superficial white onychomycosis and less severe clinical manifestations, in which less than 80% of the nail plate is affected, in clinical forms in which there is no involvement of the lunula, orwhen systemic antifungals are contraindicated [17,24]. This is the most recommended presentation to treat older patients, children, pregnant women and patients with chronic kidney disease undergoing renal replacement therapy, even though its effectiveness is associated with low rates of complete cure [17].

The most recommended topical antifungal agents for the treatment of onychomycosis are ciclopirox olamineand amorolfine in the form of lacquer and, to a lesser extent, tioconazole solution [13,14,24,30,31]. Drugs such as efinaconazole, tavaborole and luliconazole are alternative medicines in the form of solutions, but they are still not available in many countries, including Brazil [13,14,24,30,31]. Nail debridement is considered an adjuvant form of topical therapy that aims to reduce the fungal mass and favor the penetration of medications into the deeper layers of the nail bed [32–34]. Nail debridement is mainly indicated in the presence of dermatophytoma or nail plate hyperkeratosis [33,35]. Such procedure is carried out through several mechanisms, including: a) cutting part of the nailthat is detached from the nail bed; b) mechanical abrasion of the nail plate using water sandpaper, and c) chemical debridement applying urea-based formulations followed by occlusion [36,37]. Total nail avulsion is avoided due to thepotential damage to the nail matrix, which can result in permanent dystrophy. In cases where nail debridement is necessary, the nail bed is unprotected and the aesthetic problem remains, in addition, there is a loss of counterpressurein the nail bed, which can lead to increased lateral growth of the nail plate, thus the use of prosthetic nail is recommended [36,37]. Different types of therapy can be associated according to the needs of each case, aiming to improve the treatment effectiveness, especially in cases that are not responsive to monotherapy or with severe clinicalphenotypes [38].

The main risk factors for the occurrence of onychomycosis include hyperhidrosis, use of public showers, use of closed shoes, micro trauma caused by footwear, tinea pedis, morphologically altered nails, psoriasis, peripheral vascular disease, obesity and situations involving some immunological deficiency such as diabetes mellitus, advancedage, malignancies, chemotherapy, acquired human immunodeficiency syndrome, transplants and hemodialysis [1,6,34,39–45]. Dialysis chronic kidney disease is associated with an immune deficiency related to uremia and increased oxidative stress that affects the innate and adaptive immune systems in ways similar to premature aging [46–48]. The biological age of the T cell system of patients with chronic kidney disease on dialysis is approximately 20 years ahead of their chronological age, with a reduction in the production of naïve T cells, an increase in the number of memory T cells and changes in the compartment of regulatory T cells [49–51]. In the same context, there is a reduction in the proliferative response to antigenic stimuli and the expression of cell surface markers that favor apoptosis [51]. The patient develops a pro-inflammatory state with the increase and activation of innate immune systemcells, such as monocytes and granulocytes, however, with compromised functionality [52]. On the other hand, a reduction in the quantity and functionality of dendritic cells present in the skin and circulation is observed [53]. Therefore, the decline in renal function decreases the effectiveness of the immune system and generates a pro- inflammatory milieu with notable consequences such as endothelial dysfunction, systemic inflammation and susceptibility to infections, including fungal infections [6,41,45].

In view of the challenges encountered in the treatment of onychomycosis in patients with chronic kidney disease on dialysis, we carried out a phase II clinical trial that proposes cleaning and debridement of the affected hallux nail, followed by the placement of a nail prosthesis molded with acrylic reconstruction gel containing terbinafine at a 2% concentration, to obtain prolonged exposure of the tissues to the antifungal agent. Simultaneously, this technique aims to protect the debrided nail bed and improve the nail aesthetic appearance.

2. Methods

2.1. Inclusion and Exclusion Criteria

Chronic renal dialysis patients undergoing treatment at the Hemodialysis Center of the São Francisco de Assis University Hospital in Bragança Paulista, São Paulo, Brazil were selected to participate in the study. The participants were over 18 years old and had hallux onychomycosis whose treatment involved debridement of the nail plate (dermatophytoma, subungual keratosis with a thickness of +2 mm or extensive onycholysis).

All patients at the Hemodialysis Center were initially evaluated through a clinical examination carried out by a medical professional. Those who presented nail morphological abnormalities suggestive of onychomycosis in the hallux underwent collection of nail fragments to perform a direct mycological examination and, subsequently, an additional sample was obtained to perform fungal culture to identify the etiological agent.

The exclusion criteria included clinical forms of onychomycosis that did not require debridement, namely white superficial onychomycosis, endonyx and mild distal subungual onychomycosis. Patients with secondary onychomycosis, chronic mucocutaneous candidosis, individuals infected with the human immunodeficiency virus and patients with psychiatric illness or reduced level of consciousness were also excluded. The criterion for discontinuation was the appearance of allergic or irritative contact dermatitis triggered by the material used in the intervention. Participants were volunteers and signed an informed consent form before the start of the study. The study was approved by the São Francisco University research ethics committee (n° 59763022.8.0000.5514 – Opinion n°064544/2022).

2.2. Study Protocol

Patients presenting dermatophytoma, subungual hyperkeratosis with a thickness of +2 mm or extensive distal/lateral onycholysis underwent debridement of the affected nail plate by cutting with sterile nail pliers or sanding with an electric file with a disposable water sandpaper tip and /or sterile scissors/pliers, to reduce the extent of the fungal mass to be treated. Next, a small disposable brush with plastic bristles was used to eliminate keratin residue from the nail folds and, subsequently, the nail was cleaned using a 90% alcohol solution. Then, a layer of acrylic gel containing 2% terbinafine was administered and molded into the desired shape using a brush dipped in a mixture of acrylic monomers (Monomer) (Acrylic Liquid Honey Girl®, Lagoa Santa, Minas Gerais, Brazil) to reconstitute the nail plate that was debrided, spreading a thin layer of acrylic gel over the remaining nail plate. After

molding the nailprosthesis, the gel was exposed to an ultraviolet light-emitting diode (UV/LED) source at 48 W for two minutes to solidify and polymerize the gel and the nail containing the nail prosthesis was cleaned with 90% alcohol again. Finally,the nail prosthesis was polished with an electric file to obtain a uniform relief.

Participants were re-evaluated every two weeks (~14 days), with a new cleaning and filing of the nail apparatus and a new application of the acrylic polymer containing 2% terbinafine. The process was carried out thoroughly to avoid damaging the healthy nail plate. In cases where the growth of a thickened nail plate was observed, with changes in color, or that was not adhered to the nail bed, the altered portion was again filed and/or trimmed before a new prosthetic nail was applied.

All participants were monitored and underwent intervention for 11 months until the final evaluation. The evolution was monitored through photographic records and measurement of healthy nail growth. At the end of the proposed treatment period, a direct mycological examination and fungal culture were performed, and the images werecompared.

The terbinafine used in the study was supplied by the Alquimia compounding pharmacy of Bragança Paulista,São Paulo, Brazil and was mixed with acrylic gel at the São Francisco University Molecular Biology and Genetics Laboratory, in São Paulo, Brazil to obtain a concentration of 2% of the drug in the polymer.

The study complete protocol is shown in **Figure 1**.

2.3. Terbinafine availability Assessment

Terbinafine at a concentration of 2% was added to polymerized acrylic gel and applied to healthy human nails. After seven days, the nails were cut and sent for laboratory analysis to evaluate the bioavailability of the drug. The terbinafine was extracted from the nail by immersion in 100% acetonitrile, subjected to an ultrasound bath for 10min. The solvent was removed by nitrogen flow and the compound was resuspended in a solution containing 50% acetonitrile in water. The samples were quantified by mass spectrometry (triple quadrupole Xevo TQ-S, Waters Co., Barueri, São Paulo, Brazil) monitoring of the terbinafine corresponding ion (292.4 m/z), in positive mode, using a method previously validated by the research center to confirm the presence of the compound in the treated nail.

2.4. Onychomycosis Patients' Demographic Markers and Clinical Data

The study participants who were undergoing hemodialysis had data regarding age (years) and sex (male and female) collected. Furthermore, due to the presence of a positive result in the fungal culture exam, the following markers were also evaluated: a) clinical type, b) nail involvement severity score, and c) measurement of the nail area.

The onychomycosis severity was assessed using the Onychomycosis Severity Index (OSI) system. The finalscore was obtained by multiplying the area of involvement score (range 0 to 5) by the proximity of the disease to the matrix score (range 1 to 5). Ten points were added for the presence of dermatophytoma, subungual hyperkeratosis witha thickness of +2 mm or a longitudinal stripe. After measuring the scores, the hemodialysis patients were classified into the following severity groups: a) mild onychomycosis [score from 1 to 5], b) moderate onychomycosis [score from 6 to 15] and c) severe onychomycosis [score from 16 to 35] [54].

The nail plate area measurement was performed using the Image J, 1.47v image analysis software (NHI Bethesda, MD, USA). Measurements were taken immediately after the first debridement and repeated monthly and were used to evaluate the disease evolution. It seems relevant to observe that although debridement does not reduce the affected area, the elimination of subungual hyperkeratosis and dermatophytomas results in an immediate decreasein OSI.

2.5. Onychomycosis Patients' Laboratory Markers

Before starting the treatment, the nail containing morphological changes was cleaned with 70% alcohol. After the cleaning procedure, nail fragments and subungual debris were obtained by scraping the region of progression andconfluence of healthy and affected tissue and of clinically altered areas, using an aluminum spatula and sterile nail scissors/pliers. The material obtained was deposited in sterile vials and sent to the clinical analysis laboratory.

For direct mycological examination, the material was bleached with potassium hydroxide to degrade the keratin and placed on a slide to visualize the fungal structures under an optical microscope. Analysis provided information on morphology, but species identification could not be determined by the examination. Fungal culture is considered the gold standard in onychomycosis diagnosis, as it allows the identification of the fungal species that affect the patient and shows the fungus viability. This examination employs Sabouraud and Sabouraud cycloheximide agar culture media. The culture is established between 20 and 25°C and the waiting time for growth might reach four weeks.The identification of the fungal agent is carried out through macromorphology and culture micromorphology analyses.

Direct mycological examination and fungal culture were carried out at the São Francisco de Assis UniversityHospital clinical analysis laboratory in Bragança Paulista, São Paulo, Brazil, which is accredited by the Brazilian Health Surveillance Agency for this type of examination. In our data, patients on hemodialysis were considered to beaffected by onychomycosis when direct mycological examination and fungal culture showed positive results.

2.6. Clinical Response Criteria

Cure criteria were established based on clinical progression and laboratory tests and were outlined as follows:(clinical response) growth of 5 mm healthy nail, (mycological cure) negative direct mycological examination andfungal culture, (clinical cure) completely normal appearance of the nail and (complete cure) presence of clinical and mycological cure [55].

The participants' perception of nail involvement was assessed using an open questionnaire. At the beginningof the treatment, the participants were asked about their foot care and nail hygiene habits. During the biweekly procedures, the participants were asked whether they felt pain or discomfort during debridement and placement of nailprostheses, as well as in the subsequent days. Additionally, they were asked if they noticed any improvement in the appearance of their nails after starting treatment.

3. Results

A total of 155 patients who were undergoing dialysis treatment during the study inclusion period were screened through clinical examination carried out by a medical doctor. Among the individuals, 64/155 (41.3%) patientspresented nail changes that were indicative of onychomycosis of the halluces. Then, fragments of the affected nail were collected, and a direct mycological examination was performed with positive results in 35/64 (54.7%) of the individuals. All individuals with a positive direct mycological examination underwent a new collection of material forfungal culture and the etiological agent was identified. Out of this group, 24/35 (68.6%) individuals were indicated fordebridement according to the inclusion criteria (**Figure 1**). During the study period, 9/24 (37.5%) participants discontinued the follow-up for the following reasons: a) four participants died due to the kidney disease complications,

b) three participants were transplanted and stopped attending the dialysis service, and c) two participants decided not to continue in the study for personal reasons. Thus, 15 individuals completed the study protocol.

In the study, 5/15 (33.3%) participants were female and 10/15 (66.6%) were male. The mean age ± SD

(standard deviation) of the participants was 66.6 ± 12.3 years, ranging between 39 and 78 years. Initially, the clinical type of hallux involvement was assessed, with the presence of a distal subungual pattern and a mixed pattern observedin 9/15 (60.0%) and 6/15 (40.0%) study participants, respectively. All participants had a positive direct mycological test and only three participants had a negative culture test. Among the participants with a mixed pattern, the followingmycological profile was evidenced at the time of inclusion: i) *Candida* spp (1 case), ii) *T. rubrum* (2 cases), iii) *Trichophyton mentagrophytes* (2 cases), and iv) *Scytalidium* spp (1 case). Regarding participants who presented a distalsubungual pattern, the following mycological profile was observed at the time of inclusion: *Candida* spp (1 case), ii)

T. rubrum (1 case), iii) *T. mentagrophytes* (2 cases), iv) *Scytalidium* spp (1 case), v) *Penicillium marneffei* (1 case), and vi) negative exam (3 cases). Demographic data and microbiological profile at the time of inclusion are summarizedin **Table 1**.

At the time of inclusion, 14/15 (93.3%) participants had an OSI system classified as severe and only 1/15 (6.7%) participant had a score classified as moderate (**Table 1**). After the intervention, there was a change in the severity profile associated with the OSI system, with the participant initially classified as moderate OSI remaining in that classification and, among those classified as severe, 4/14 kept the OSI classification as severe, 6/14 started to be classified as moderate OSI, 1/14 were classified as mild OSI (with a degree of involvement below 10%) and 3/14 wereclassified as zero in the OSI system (clinical cure) (**Table 1**).

After the intervention period, the participants' direct mycological examination result was negative in 14/15 (93.3%), and in one case there was the presence of yeast. The participant who presented the yeast had initially been diagnosed as infected with *Scytalidium* spp. Regarding fungal culture, after the intervention, participants with an initially negative result maintained the outcome profile. However, the remaining participants changed their microbiological profile, except in two cases in which the presence of *Candida* spp and *T. rubrum* was observed in bothmoments evaluated. Furthermore, in 7/15 cases the culture became negative (1 case of *Candida* spp, 1 case of *Scytalidium* spp, 1 case of *P. marneffei*, 1 case of *T. rubrum*, and 3 cases of *T. mentagrophytes*), while in 3/15 cases

there was a change in the etiological agent. The change occurred for participants who were initially classified as infected by *T. rubrum*, *Scytalidium* spp and *T. mentagrophytes* and started to present *Candida* spp, *P. marneffei* and *Candida* spp in their fungal cultures, respectively. The result of the microbiological profile after the intervention is presented in **Table 1**.

Clinical response was described in 5/15 (33.3%) participants; however, mycological cure, clinical cure and complete cure were described, respectively for 9/15 (60.0%), 4/ 15 (26.7%%) and 3/15 (20.0%) participants (**Table 1**). Regarding the clinical response, although all cases showed healthy nail growth (**Figure 2A**), the growth was higherthan that recommended as a positive response (growth greater than 5 mm) in only five cases, among them, 5, 5.1, 5.2, 5.2- and 8.3-mm nail growth was observed, respectively, for PB, EFL, ER, VAC and ACS cases (**Figure 2B**). Clinicalresponse and cure rates were compared to values observed when using some systemic or topical drugs, as described in**Table 2**.

In **Figure 3** and **Supplementary Material 1**, two clinical cases are presented in which there was complete cure. In the images, the sequence shows the nail affected by onychomycosis, the nail after debridement, the nail containing the polymerized acrylic gel with 2% terbinafine and, finally, complete healing showing the nail without signs of infectious agents through the clinical and laboratory analysis. **Figure 4** summarizes the main findings of the study.

No participant presented an allergic reaction or local irritation caused by the material used in the treatment. There were superficial and accidental ulcerations caused by electric sandpaper. No wound developed secondary infection. Participants responded to a questionnaire about their perception of onychomycosis and the treatment development. At the beginning of the treatment, 7/15 (46.7%) participants reported difficulty in cutting their nails dueto the hardness of the nail plate, even with the help of family members, 5/15 (33.3%) reported that they did not have enough mobility to clean their feet or cut their nails, 4/15 (26.7%) reported that they did not see well enough and weretherefore unable to clean their feet and cut their nails. No participant reported discomfort due to the use of nail prostheses, 3/15 (20.0%) reported a feeling of discomfort caused by the vibration of the electric file, 4/15 (26.7%) reported that they felt embarrassed when wearing sandals due to the appearance of their nails before treatment, 12/15(80.0%) reported the perception that their nails looked better during treatment, and 3/15 (20.0%) claimed that they could not see their nails well enough to give an opinion.

We observed that in the gel in which terbinafine was inserted, the ion corresponding to the drug was detected, both in MS1 mode, with an increase in total ion current (TIC) in the retention time corresponding to the terbinafine standard, and in MS2 mode, in which the parental ion and its respective fragment were detected (291.30 m/z → 140.89 m/z). In the sample of a nail without the addition of terbinafine, used as a negative control, the presence of the ion wasnot detected in any of the modes, and in MS, even with the presence of an 292.18 m/z ion, its fragment was not visualized, therefore not corresponding to terbinafine. In a nail sample after seven days with terbinafine gel, the 292.25ion was detected, as well as its 141.40 m/z fragment, confirming the presence of the drug under these analysis conditions.

4. Discussion

In this study, most participants presented mycological cure; however, clinical response, clinical cure and, mainly, complete cure were infrequent. Furthermore, adverse effects associated with the treatment were not observed,and it was well tolerated by all individuals. The participants also reported that the treatment presented benefits in termsof self-esteem by promoting aesthetic improvements associated with the onychomycosis presence.

In the literature, onychomycosis is described as a prevalent condition among individuals subjected to dialysis[6,25,41,43,44]. The renal function decline reduces the immune system effectiveness and generates a pro-inflammatory milieu with the concomitant evolution to endothelial dysfunction, systemic inflammation and susceptibility to infections, including fungal infections [6]. In immunocompromised individuals, people with diabetes mellitus, as wellas those with peripheral venous or arterial insufficiency, pedal onychomycosis assumes greater importance, as it can act as a gateway for bacterial agents, leading to greater complications [56]. However, this condition may go unnoticedor be underreported as a health problem by these patients, whose attention is mainly focused on issues related to kidneydisease and other serious comorbidities.

The onychomycosis management presents some particularities in chronic kidney disease patients on dialysis,as changes in immunity lead to an increased risk of becoming infected and developing more serious and difficult-to- treat forms of the disease, while the most effective treatments to date are carried out with medications for systemic use, which in the context of dialysis patients may require dose adjustments, present adverse effects and drug interactions [1,4,13,17,25,29,30,34]. Terbinafine is considered the most effective drug. It is metabolized by the liver, and 80% of the dose is excreted in urine and 20% in feces [16,57–59]. However, according to the literature, there are no extensive studies guiding safely the use of oral terbinafine in chronic renal patients on dialysis.

Itraconazole, the second drug with the highest cure rates, undergoes hepatic metabolism and is a strong CYP3A4 inhibitor [19,20,60,61], with ~54% of the dose excreted in feces and 35% in urine [62]. Itraconazole is not eliminated by intermittent dialysis, but rather by continuous hemofiltration [63]. Fluconazole, another systemic use drug, is widely used in Brazil, undergoes glomerular filtration and tubular reabsorption, with 60% to 80% eliminated by the kidneys [27,62]. A single dose of fluconazole can be used in patients on dialysis without adjustments, but for prolonged use, dose adjustments are required since a 4-hour hemodialysis session reduces plasma levels by ~40% [64].

Regarding the use of topical medications, considering the insignificant systemic absorption and the very lowrate of adverse effects, they would represent the ideal therapy for chronic kidney disease patients on dialysis [5,14]. However, despite offering lower risk, they also present lower efficacy since they face the challenge of permeating themail and reaching suitable concentrations in the nail bed [8,65,66]. In the context of chronic renal patients on dialysis,there is also physical limitations such as visual impairment and mobility issues, which might result in difficulties regarding the application of topical medication on toes.

Ointments and creams are easily removed in contact with water and are not suitable vehicles in the onychomycosis treatment. Due to their occlusive properties, varnish, enamel, adhesive and films are able to increase nail hydration and keep the antifungal in the desired site for longer, favoring the medication permeation [10,10,29,66,67]. However, the cure indices using lacquer are still rather low [13,13,29,68,69]. Interestingly, these

efficacy levels Regard the general population when clinical phenotypes of diverse severity are considered. In such context, lower complete cure indices, such as those found in this study, must be evaluated considering the disease etiology, the patient's age, the immunosuppression level, the probability of adverse effects, the possibility of using other medications and, mainly, the cure rates resulting from conventional treatments in the population of kidney diseasepatients subjected to hemodialysis.

Several new strategies to promote nail permeation of drugs have been tested around the world. They are systems of chemical nature, such as nanoparticles, microemulsions, hydrogels and liposomes [70–73]. Physical methods such as iontophoresis, laser, and ultrasound have also been tested [13,74–77]. However, no method was foundthat could tackle the problem in the short term [4,6,13,25,30], including from the aesthetic standpoint. Some studies reported that harm to quality of life associated with onychomycosis affects more women than men, and might in somecases generate embarrassment and social isolation [78–80].

Therefore, aiming to find an alternative for a immunocompromised population affected by severe forms of onychomycosis and with systemic treatment limitations, a new method was designed that combines nail plate debridement (required in these cases), with the application of a device that keeps contact between an antifungal agentand the nail bed for a long period. At the same time, this device also protects the debrided nail bed, thus improving thenail appearance. Subungual hyperkeratosis and prolonged onycholysis areas form a dead space where moist, keratin remains, and external residue tend to accumulate, resulting in an environment that favors fungus growth [81]. When debridement is carried out, the fungal mass decreases and the environment is changed [82].

Terbinafine was selected for this study for being a broad-spectrum antifungal with greater efficacy against dermatophyte fungi, which are the most prevalent in the general population, as well as in the population selected for the intervention [16,83]. Higher terbinafine concentrations in the acrylic gel resulted in a more porous and fragile prosthesis consistency after polymerization, with consequent shorter fixation periods on the skin and nail plate, thus facilitating removal. On the other hand, the addition of 2% terbinafine at to the acrylic reconstruction gel resulted in a resilient nail prosthesis with satisfactory local fixation. We observed that even with a significantly reduced remainingnail plate after extensive debridement, a nail prosthesis could be attached. When applied, the acrylic gel adhered to thenail and nail bed, remaining that way for a variable period, depending on each patient's characteristics and habits. Overtime, the gel detaches, first from the nail bed, remaining attached only to the remaining nail plate. Consequently, a dead space is once again formed between the prosthesis and the nail bed, creating an environment similar to that observed during onycholysis, with the difference that the acrylic gel can be changed periodically and the area corresponding to the dead space can be sanitized, preventing the biofilm formation.

Nail hydration plays a significant role in its permeability. The literature describes that the flow of water in thefully hydrated nail plate is almost 6.5 times greater than in completely dry nails [84,85]. The gel contact with the ungual plate increases its hydration degree, making it more flexible [86,87], and this effect favors the antifungal permeation. However, increased moist also promotes an environment that favor the development of fungi [88]. In addition to hydrophilicity, molecular weight, ionization status, and the ability to bond to the keratin are also factors that affect the ability of the medication topically applied to permeate the nail [10,29,67,89]. This study observed that,despite periodically repeating nail cleaning, most patients continued to present hyperkeratosis in the nail bed, an indicator of fungal activity in the epithelium, despite the terbinafine presence in the reconstruction gel.

The complete cure low efficacy as a result of the adopted treatment strategy can potentially be ascribed to factors such as the low local bioavailability of terbinafine, the absence of substances that facilitate the permeation of the active ingredient in the nail bed and nail plate and the increase in local humidity, which creates an environment favorable to the growth of fungi. Host-related factors include immunodeficiency and limitations in maintaining adequate foot hygiene. It seems relevant to mention that achieving clinical cure is not always possible, particularly incases of severe onychomycosis, previous damage to the nail matrix due to trauma resulting in permanent effects, secondary nail disease and immunosuppression [2,5,8,13].

The occurrence of growth of a microorganism different from that initially isolated in the culture after treatmentwas observed in three patients. According to the literature, this fact can occur in mixed infections, with the culture medium favoring the growth of one of the etiological agents, in this case, dermatophytes [90–92]. Thus, the agent identified in the first culture might be suppressed for being more sensitive to the antifungal used in the treatment, whilein the post-treatment culture, a co-infecting etiological agent can be identified. The use of molecular methods to detect multiple agents is suggested as a solution [91,93]. However, in this study, only the direct mycological examination and the fungal culture were employed. Finally, one cannot completely rule out the possibility of contamination in the clinical analysis laboratory.

The study limitations include the fact that molecular methods were not used to identify the etiological agents.Furthermore, the number of participants was reduced, mainly due to the nature of the cases analyzed. The patients' difficulty to keep suitable hygiene of their feet might have interfered with the evolution and outcomes observed. Despite the low cost of the materials and input used in the interventions, the protocol execution was quite hard and time consuming, which might make the procedure less accessible for routine treatment use. Moreover, the study population involves a complex phenotype to be considered regarding the onychomycosis management, namely, the severity of the kidney disease, commonly associated with countless comorbidities, age group (most patients in the study were older individuals), immunosuppression and genetic and environmental factors.

5. Conclusion

The addition of terbinafine to acrylic reconstruction gel for the manufacture of nail prostheses applied after debridement of moderate and severe forms of onychomycosis showed low efficacy as an isolated treatment in patientswith chronic kidney disease on dialysis. On the other hand, most patients had a good perception of the appearance of their nails during treatment, even when it did not result in a therapeutic response or clinical cure. In future experiments, debridement and occlusion with the nail prosthesis may eventually be associated with formulations that combine antifungal medication with substances that facilitate nail and skin permeation that can be deposited between the prosthesis and the nail bed, and/or substances capable of reducing the local moist, making the nail bed a more hostile environment for fungal growth.

6. References

[1] Bodman MA, Syed HA, Krishnamurthy K. Onychomycosis. StatPearls, Treasure Island (FL): StatPearls Publishing; 2024.
[2] Maskan Bermudez N, Rodríguez-Tamez G, Perez S, Tosti A. Onychomycosis: Old and New. J Fungi (Basel) 2023;9:559. https://doi.org/10.3390/jof9050559.
[3] Lipner SR, Scher RK. Onychomycosis: Clinical overview and diagnosis. J Am Acad Dermatol 2019;80:835–51. https://doi.org/10.1016/j.jaad.2018.03.062.

[4] Gupta AK, Versteeg SG, Shear NH. Onychomycosis in the 21st Century: An Update on Diagnosis, Epidemiology, and Treatment. J Cutan Med Surg 2017;21:525–39. https://doi.org/10.1177/1203475417716362.
[5] Gupta AK, Stec N, Summerbell RC, Shear NH, Piguet V, Tosti A, et al. Onychomycosis: a review. J Eur AcadDermatol Venereol 2020;34:1972–90. https://doi.org/10.1111/jdv.16394.
[6] Bersano JMQB, Cordeiro MG, Marson FAL. Prevalence and risk predictors of onychomycosis in patients on hemodialysis: an observation, prospective, and unicenter study in Brazil. Front Med (Lausanne) 2023;10:1268324. https://doi.org/10.3389/fmed.2023.1268324.
[7] Lee DK, Lipner SR. Optimal diagnosis and management of common nail disorders. Ann Med 2022;54:694–712.https://doi.org/10.1080/07853890.2022.2044511.
[8] Gupta AK, Venkataraman M, Talukder M. Onychomycosis in Older Adults: Prevalence, Diagnosis, and Management. Drugs Aging 2022;39:191–8. https://doi.org/10.1007/s40266-021-00917-8.
[9] Gupta AK, Polla Ravi S, Choi SY, Konda A, Cooper EA. Strategies for the enhancement of nail plate permeation of drugs to treat onychomycosis. J Eur Acad Dermatol Venereol 2023;37:243–55. https://doi.org/10.1111/jdv.18638.
[10] Phan K, Kaur K, Wright K, Tran S, Stewart B, Brown M, et al. The Penetrance of Topical Nail Therapy: Limitations and Current Enhancements. Clin Podiatr Med Surg 2021;38:535–40. https://doi.org/10.1016/j.cpm.2021.06.004.
[11] Gupta AK, Foley KA. Evidence for biofilms in onychomycosis. G Ital Dermatol Venereol 2019;154:50–5. https://doi.org/10.23736/S0392-0488.18.06001-7.
[12] Castillo C, Masi MF, Mishko A, Sheltzer A, Speer A, Tran H, et al. Biofilms and the Nail Unit. Clin Podiatr Med Surg 2021;38:529–33. https://doi.org/10.1016/j.cpm.2021.06.005.
[13] Aggarwal R, Targhotra M, Kumar B, Sahoo PK, Chauhan MK. Treatment and management strategies of onychomycosis. J Mycol Med 2020;30:100949. https://doi.org/10.1016/j.mycmed.2020.100949.
[14] Leung AKC, Lam JM, Leong KF, Hon KL, Barankin B, Leung AAM, et al. Onychomycosis: An Updated Review. Recent Pat Inflamm Allergy Drug Discov 2020;14:32–45.https://doi.org/10.2174/1872213X13666191026090713.
[15] Gupta AK, Haas-Neill S, Talukder M. The safety of oral antifungals for the treatment of onychomycosis. ExpertOpin Drug Saf 2023;22:1169–78. https://doi.org/10.1080/14740338.2023.2280137.
[16] Maxfield L, Preuss CV, Bermudez R. Terbinafine. StatPearls, Treasure Island (FL): StatPearls Publishing; 2024.
[17] Ricardo JW, Lipner SR. Safety of current therapies for onychomycosis. Expert Opin Drug Saf 2020;19:1395–408. https://doi.org/10.1080/14740338.2020.1829592.
[18] Abdel-Rahman SM, Gotschall RR, Kauffman RE, Leeder JS, Kearns GL. Investigation of terbinafine as a CYP2D6 inhibitor in vivo. Clin Pharmacol Ther 1999;65:465–72. https://doi.org/10.1016/S0009-9236(99)70065-2.
[19] Wang Y, Lipner SR. Retrospective analysis of adverse events with systemic onychomycosis medications reported to the United States Food and Drug Administration. J Dermatolog Treat 2021;32:783–7. https://doi.org/10.1080/09546634.2019.1708242.
[20] Xie S-L, Zhu X, Gao N, Lin Q, Chen C, Yang Y-J, et al. Genetic variations of CYP3A4 on the metabolism of itraconazole in vitro. Food Chem Toxicol 2023;181:114101. https://doi.org/10.1016/j.fct.2023.114101.
[21] Etgü F. Retrospective Analysis of Liver Enzyme Abnormalities in Patients Prescribed Terbinafine and Itraconazole for Onychomycosis. Cureus 2023;15:e44914. https://doi.org/10.7759/cureus.44914.
[22] Salem M, Reichlin T, Fasel D, Leuppi-Taegtmeyer A. Torsade de pointes and systemic azole antifungal agents: Analysis of global spontaneous safety reports. Glob Cardiol Sci Pract 2017;2017:11. https://doi.org/10.21542/gcsp.2017.11.
[23] Ezad S, Cheema H, Collins N. Statin-induced rhabdomyolysis: a complication of a commonly overlooked druginteraction. Oxf Med Case Reports 2018;2018:omx104. https://doi.org/10.1093/omcr/omx104.
[24] Falotico JM, Lipner SR. Updated Perspectives on the Diagnosis and Management of Onychomycosis. ClinCosmet Investig Dermatol 2022;15:1933–57. https://doi.org/10.2147/CCID.S362635.
[25] Lipner SR, Scher RK. Onychomycosis: Treatment and prevention of recurrence. J Am Acad Dermatol 2019;80:853–67. https://doi.org/10.1016/j.jaad.2018.05.1260.
[26] Niwa T, Imagawa Y, Yamazaki H. Drug interactions between nine antifungal agents and drugs metabolized byhuman cytochromes P450. Curr Drug Metab 2014;15:651–79.https://doi.org/10.2174/1389200215666141125121511.
[27] Govindarajan A, Bistas KG, Ingold CJ, Aboeed A. Fluconazole. StatPearls, Treasure Island (FL): StatPearls

Publishing; 2024.
[28] Godfrey H, Jedlowski P, Thiede R. Medication Associations With Severe Cutaneous Adverse Reactions: A Case/Non-Case Analysis Using the FDA Adverse Event Reporting System. J Cutan Med Surg 2024;28:51–8. https://doi.org/10.1177/12034754231220931.
[29] Costa P de S, Mendes V, Veiga FF, Negri M, Svidzinski TIE. Relevant insights into onychomycosis' pathogenesis related to the effectiveness topical treatment. Microb Pathog 2022;169:105640. https://doi.org/10.1016/j.micpath.2022.105640.
[30] Beuscher TL, Kelechi TJ. Onychomycosis: Diagnosis, Treatment, and Prevention. J Wound Ostomy ContinenceNurs 2019;46:333–5. https://doi.org/10.1097/WON.0000000000000556.
[31] Geizhals S, Lipner SR. A Timeline of Onychomycosis Therapy and Future Directions. Skinmed 2020;18:367– 71.
[32] Frazier WT, Santiago-Delgado ZM, Stupka KC. Onychomycosis: Rapid Evidence Review. Am Fam Physician2021;104:359–67.
[33] Gupta AK, Wang T, Cooper EA. Dermatophytomas: Clinical Overview and Treatment. J Fungi (Basel) 2022;8:742. https://doi.org/10.3390/jof8070742.
[34] Zaraa I, Dehavay F, Richert B. Onychomycosis. Hand Surg Rehabil 2024:101638.https://doi.org/10.1016/j.hansur.2024.101638.
[35] Hm A. Excellent Response of Dermatophytoma and Nail Splitting to Nail Plate Debridement Plus Topical Ciclopirox Olamine 1% Solution. Skin Appendage Disorders 2021;7. https://doi.org/10.1159/000512037.
[36] Baran R, Hay RJ, Garduno JI. Review of antifungal therapy and the severity index for assessing onychomycosis:part I. J Dermatolog Treat 2008;19:72–81. https://doi.org/10.1080/09546630701243418.
[37] Lin K, Lipner SR. Painless technique for debridement of onychodystrophic nails. J Am Acad Dermatol 2020;82:e39–40. https://doi.org/10.1016/j.jaad.2019.05.069.
[38] Falotico JM, Lapides R, Lipner SR. Combination Therapy Should Be Reserved as Second-Line Treatment of Onychomycosis: A Systematic Review of Onychomycosis Clinical Trials. J Fungi (Basel) 2022;8:279. https://doi.org/10.3390/jof8030279.
[39] Navarro-Pérez D, Tardáguila-García A, García-Oreja S, López-Moral M, García-Madrid M, Lázaro-Martínez JL. Onychomycosis associated with diabetic foot syndrome: A systematic review. Mycoses 2023;66:459–66. https://doi.org/10.1111/myc.13577.
[40] Ogawa T, Matsuda A, Ogawa Y, Tanaka R. Risk factors for the development of tinea pedis and onychomycosis:Real-world evidence from a single-podiatry center, large-scale database in Japan. J Dermatol 2024;51:30–9. https://doi.org/10.1111/1346-8138.16991.
[41] Eftekhari H, Haghdar Saheli Y, Ashoobi MT, Mahjoob M, Kazemnezhad Leyli E, Bagheri Toolaroud P. The prevalence of onychomycosis in patients with chronic renal failure undergoing dialysis: A cross-sectional study.Heliyon 2024;10:e25737. https://doi.org/10.1016/j.heliyon.2024.e25737.
[42] Bunyaratavej S, Srinonprasert V, Kiratiwongwan R, Wongdama S, Leeyaphan C. Onychomycosis in older adults: The age and associated factors affecting the complete cure rate. Australas J Dermatol 2022;63:74–80. https://doi.org/10.1111/ajd.13686.
[43] Filho AMS, Ventura CG, Criado PR, Del Negro GB, Freitas RS, Luiz OC, et al. Hemodialysis and Kidney Transplantation as Predisposing Conditions to Onychomycosis. Nephron 2017;137:38–46. https://doi.org/10.1159/000475674.
[44] Kuvandik G, Cetin M, Genctoy G, Horoz M, Duru M, Akcali C, et al. The prevalance, epidemiology and risk factors for onychomycosis in hemodialysis patients. BMC Infect Dis 2007;7:102. https://doi.org/10.1186/1471-2334-7-102.
[45] Anees M, Butt G, Gull S, Nazeer A, Hussain I, Ibrahim M. Factors Affecting Dermatological Manifestations in Patients with End Stage Renal Disease. J Coll Physicians Surg Pak 2018;28:98–102. https://doi.org/10.29271/jcpsp.2018.02.98.
[46] Betjes MGH. Immune cell dysfunction and inflammation in end-stage renal disease. Nat Rev Nephrol 2013;9:255–65. https://doi.org/10.1038/nrneph.2013.44.
[47] Zoccali C, Mallamaci F. Innate Immunity System in Patients With Cardiovascular and Kidney Disease. Circ Res2023;132:915–32. https://doi.org/10.1161/CIRCRESAHA.122.321749.
[48] Kong L, Andrikopoulos S, MacIsaac RJ, Mackay LK, Nikolic-Paterson DJ, Torkamani N, et al. Role of the adaptive immune system in diabetic kidney disease. J Diabetes Investig 2022;13:213–26. https://doi.org/10.1111/jdi.13725.
[49] Yang TO, Chuang Y-F, Chiu Y-L. T-cell aging in end-stage renal disease: an evolving story with CMV. Med Microbiol Immunol 2019;208:281–7. https://doi.org/10.1007/s00430-019-00596-8.

[50] Sampani E, Vagiotas L, Daikidou D-V, Nikolaidou V, Xochelli A, Kasimatis E, et al. End stage renal disease has an early and continuous detrimental effect on regulatory T cells. Nephrology (Carlton) 2022;27:281–7. https://doi.org/10.1111/nep.13996.
[51] Zakaria MM, Derbala SA, Salem AE, El-Agroudy AE, El-Tantawy FM. Inflammatory markers in chronic kidney disease and end stage renal disease patients. Mol Biol Rep 2021;48:6857–62. https://doi.org/10.1007/s11033- 021-06684-4.
[52] Gusev E, Solomatina L, Zhuravleva Y, Sarapultsev A. The Pathogenesis of End-Stage Renal Disease from the Standpoint of the Theory of General Pathological Processes of Inflammation. Int J Mol Sci 2021;22:11453. https://doi.org/10.3390/ijms222111453.
[53] Kim JU, Kim M, Kim S, Nguyen TT, Kim E, Lee S, et al. Dendritic Cell Dysfunction in Patients with End-stageRenal Disease. Immune Netw 2017;17:152–62. https://doi.org/10.4110/in.2017.17.3.152.
[54] Carney C, Tosti A, Daniel R, Scher R, Rich P, DeCoster J, et al. A new classification system for grading the severity of onychomycosis: Onychomycosis Severity Index. Arch Dermatol 2011;147:1277–82. https://doi.org/10.1001/archdermatol.2011.267.
[55] Gupta AK, Studholme C. How do we measure efficacy of therapy in onychomycosis: Patient, physician, and regulatory perspectives. J Dermatolog Treat 2016;27:498–504.https://doi.org/10.3109/09546634.2016.1161156.
[56] Matricciani L, Talbot K, Jones S. Safety and efficacy of tinea pedis and onychomycosis treatment in people withdiabetes: a systematic review. J Foot Ankle Res 2011;4:26. https://doi.org/10.1186/1757-1146-4-26.
[57] Humbert H, Cabiac MD, Denouël J, Kirkesseli S. Pharmacokinetics of terbinafine and of its five mainmetabolites in plasma and urine, following a single oral dose in healthy subjects. Biopharm Drug Dispos 1995;16:685–94. https://doi.org/10.1002/bdd.2510160807.
[58] Kovarik JM, Mueller EA, Zehender H, Denouël J, Caplain H, Millerioux L. Multiple-dose pharmacokinetics and distribution in tissue of terbinafine and metabolites. Antimicrob Agents Chemother 1995;39:2738–41. https://doi.org/10.1128/AAC.39.12.2738.
[59] Gupta AK, Polla Ravi S, Talukder M, Mann A. Effectiveness and safety of oral terbinafine for dermatophyte distal subungual onychomycosis. Expert Opin Pharmacother 2024;25:15–23. https://doi.org/10.1080/14656566.2024.2305304.
[60] Piérard GE, Arrese JE, Piérard-Franchimont C. Itraconazole. Expert Opin Pharmacother 2000;1:287–304. https://doi.org/10.1517/14656566.1.2.287.
[61] Gupta AK, Foley KA, Mays RR, Shear NH, Piguet V. Monotherapy for toenail onychomycosis: a systematic review and network meta-analysis. Br J Dermatol 2020;182:287–99. https://doi.org/10.1111/bjd.18155.
[62] Bellmann R, Smuszkiewicz P. Pharmacokinetics of antifungal drugs: practical implications for optimized treatment of patients. Infection 2017;45:737–79. https://doi.org/10.1007/s15010-017-1042-z.
[63] Willems L, van der Geest R, de Beule K. Itraconazole oral solution and intravenous formulations: a review of pharmacokinetics and pharmacodynamics. J Clin Pharm Ther 2001;26:159–69. https://doi.org/10.1046/j.1365- 2710.2001.00338.x.
[64] Oono S, Tabei K, Tetsuka T, Asano Y. The pharmacokinetics of fluconazole during haemodialysis in uraemic patients. Eur J Clin Pharmacol 1992;42:667–9. https://doi.org/10.1007/BF00265934.
[65] Thomas J, Peterson GM, Christenson JK, Kosari S, Baby KE. Antifungal Drug Use for Onychomycosis. Am J Ther 2019;26:e388–96. https://doi.org/10.1097/MJT.0000000000000696.
[66] Issa NT, Kircik L. Individual Article: Updated Review of Topical Pharmaceuticals and Complementary and Alternative Medications for the Treatment of Onychomycosis in Both General and Special Populations in the United States. J Drugs Dermatol 2023;22:SF378719-SF378719s10. https://doi.org/10.36849/JDD.8719.
[67] Murdan S. Drug delivery to the nail following topical application. Int J Pharm 2002;236:1–26. https://doi.org/10.1016/s0378-5173(01)00989-9.
[68] Gupta AK, Mays RR, Versteeg SG, Shear NH, Piguet V. Update on current approaches to diagnosis and treatment of onychomycosis. Expert Rev Anti Infect Ther 2018;16:929–38. https://doi.org/10.1080/14787210.2018.1544891.
[69] Lipner SR, Joseph WS, Vlahovic TC, Scher RK, Rich P, Ghannoum M, et al. Therapeutic Recommendations for the Treatment of Toenail Onychomycosis in the US. J Drugs Dermatol 2021;20:1076–84. https://doi.org/10.36849/JDD.6291.
[70] Valdez AF, Zamith-Miranda D, Nimrichter L, Nosanchuk JD. Micro- and nanoparticles as platforms for the treatment of fungal infections: present and future perspectives. Future Microbiol 2023;18:1007–11. https://doi.org/10.2217/fmb-2023-0079.

[71] Barot BS, Parejiya PB, Patel HK, Mehta DM, Shelat PK. Microemulsion-based antifungal gel delivery to nail for the treatment of onychomycosis: formulation, optimization, and efficacy studies. Drug Deliv Transl Res 2012;2:463–76. https://doi.org/10.1007/s13346-012-0109-8.
[72] Kesharwani P, Fatima M, Singh V, Sheikh A, Almalki WH, Gajbhiye V, et al. Itraconazole and Difluorinated-Curcumin Containing Chitosan Nanoparticle Loaded Hydrogel for Amelioration of Onychomycosis. Biomimetics (Basel) 2022;7:206. https://doi.org/10.3390/biomimetics7040206.
[73] Tanrıverdi ST, Hilmioğlu Polat S, Yeşim Metin D, Kandiloğlu G, Özer Ö. Terbinafine hydrochloride loaded liposome film formulation for treatment of onychomycosis: in vitro and in vivo evaluation. J Liposome Res 2016;26:163–73. https://doi.org/10.3109/08982104.2015.1067892.
[74] Dhamoon RK, Popli H, Gupta M. Novel Drug Delivery Strategies for the Treatment of Onychomycosis. PharmNanotechnol 2019;7:24–38. https://doi.org/10.2174/2211738507666190228104031.
[75] Kline-Schoder A, Le Z, Zderic V. Ultrasound-Enhanced Ciclopirox Delivery for Treatment of Onychomycosis. Annu Int Conf IEEE Eng Med Biol Soc 2018;2018:5717–20. https://doi.org/10.1109/EMBC.2018.8513552.
[76] Zhang J, Lin P, Li J, Guo C, Zhai J, Zhang Y. Efficacy of laser therapy combined with topical antifungal agentsfor onychomycosis: a systematic review and meta-analysis of randomised controlled trials. Lasers Med Sci 2022;37:2557–69. https://doi.org/10.1007/s10103-022-03561-9.
[77] Martins Andrade JF, da Cunha Miranda T, Cunha-Filho M, Taveira SF, Gelfuso GM, Gratieri T. Iontophoresisapplication for drug delivery in high resistivity membranes: nails and teeth. Drug Deliv Transl Res 2023;13:1272–87. https://doi.org/10.1007/s13346-022-01244-0.
[78] Debbagh F, Babokh F, Sbai M, El Mezouari EM, Moutaj R. Impact of onychomycosis on the quality of life of patients. Curr Med Mycol 2023;9:39–44. https://doi.org/10.18502/cmm.2023.345062.1430.
[79] Lipner SR, Falotico JM, Konda A. On the Basis of Sex: Impact and Treatment of Toenail Onychomycosis in Female Patients. J Clin Aesthet Dermatol 2023;16:52–7.
[80] Stewart CR, Algu L, Kamran R, Leveille CF, Abid K, Rae C, et al. Effect of onychomycosis and treatment on patient-reported quality-of-life outcomes: A systematic review. J Am Acad Dermatol 2021;85:1227–39. https://doi.org/10.1016/j.jaad.2020.05.143.
[81] Nagar R, Nayak CS, Deshpande S, Gadkari RP, Shastri J. Subungual hyperkeratosis nail biopsy: a better diagnostic tool for onychomycosis. Indian J Dermatol Venereol Leprol 2012;78:620–4. https://doi.org/10.4103/0378-6323.100579.
[82] Grover C, Bansal S, Nanda S, Reddy BSN, Kumar V. Combination of surgical avulsion and topical therapy for single nail onychomycosis: a randomized controlled trial. Br J Dermatol 2007;157:364–8. https://doi.org/10.1111/j.1365-2133.2007.08014.x.
[83] Arca E, Taştan HB, Akar A, Kurumlu Z, Gür AR. An open, randomized, comparative study of oral fluconazole, itraconazole and terbinafine therapy in onychomycosis. J Dermatolog Treat 2002;13:3–9. https://doi.org/10.1080/09546630252775171.
[84] Walters KA, Flynn GL, Marvel JR. Physicochemical characterization of the human nail: permeation pattern for water and the homologous alcohols and differences with respect to the stratum corneum. J Pharm Pharmacol 1983;35:28–33. https://doi.org/10.1111/j.2042-7158.1983.tb04258.x.
[85] Walters KA, Abdalghafor HM, Lane ME. The human nail--barrier characterisation and permeation enhancement. Int J Pharm 2012;435:10–21. https://doi.org/10.1016/j.ijpharm.2012.04.024.
[86] Bhuptani RS, Deshpande KM, Patravale VB. Transungual permeation: current insights. Drug Deliv Transl Res2016;6:426–39. https://doi.org/10.1007/s13346-015-0259-6.
[87] Shivakumar HN, Juluri A, Desai BG, Murthy SN. Ungual and transungual drug delivery. Drug Dev Ind Pharm 2012;38:901–11. https://doi.org/10.3109/03639045.2011.637931.
[88] Zaias N, Escovar SX, Zaiac MN. Finger and toenail onycholysis. J Eur Acad Dermatol Venereol 2015;29:848–53. https://doi.org/10.1111/jdv.12862.
[89] Chouhan P, Saini TR. Hydroxypropyl- β -cyclodextrin: A Novel Transungual Permeation Enhancer for Development of Topical Drug Delivery System for Onychomycosis. J Drug Deliv 2014;2014:950358. https://doi.org/10.1155/2014/950358.
[90] Gupta AK, Summerbell RC, Venkataraman M, Quinlan EM. Nondermatophyte mould onychomycosis. J Eur Acad Dermatol Venereol 2021;35:1628–41. https://doi.org/10.1111/jdv.17240.
[91] Gupta AK, Nakrieko K-A. Trichophyton rubrum DNA Strains in Patients with Onychomycosis with Persistent Mixed Infections Involving a Nondermatophyte Mold. J Am Podiatr Med Assoc 2020;110:Article_3. https://doi.org/10.7547/17-201.
[92] Gupta AK, Renaud HJ, Quinlan EM, Shear NH, Piguet V. The Growing Problem of Antifungal Resistance

in Onychomycosis and Other Superficial Mycoses. Am J Clin Dermatol 2021;22:149–57. https://doi.org/10.1007/s40257-020-00580-6.

[93] Lim SS, Ohn J, Mun J-H. Diagnosis of Onychomycosis: From Conventional Techniques and Dermoscopy to Artificial Intelligence. Front Med (Lausanne) 2021;8:637216. https://doi.org/10.3389/fmed.2021.637216.

[94] Tabara K, Szewczyk AE, Bienias W, Wojciechowska A, Pastuszka M, Oszukowska M, et al. Amorolfine vs. ciclopirox - lacquers for the treatment of onychomycosis. Postepy Dermatol Alergol 2015;32:40–5. https://doi.org/10.5114/pdia.2014.40968.

[95] Iozumi K, Abe M, Ito Y, Uesugi T, Onoduka T, Kato I, et al. Efficacy of long-term treatment with efinaconazole 10% solution in patients with onychomycosis, including severe cases: A multicenter, single-arm study. J Dermatol 2019;46:641–51. https://doi.org/10.1111/1346-8138.14935.

[96] Gupta AK, Versteeg SG. Tavaborole - a treatment for onychomycosis of the toenails. Expert Rev Clin Pharmacol2016;9:1145–52. https://doi.org/10.1080/17512433.2016.1206467.

[97] Kawai M. Characteristics and Efficacy of Two Topical Therapeutic Agents for Onychomycosis. Med Mycol J 2019;60:71–4. https://doi.org/10.3314/mmj.19.006.

Table 1. Description of the onychomycosis characteristis in chronic kidney patients on dialysis and outcomes observed in relation to the treatment of onychomycosis of hallux after debridement and application of acrylic polymer with 2% terbinafine.

Participant	Sex	Age (years)	Inclusão no estudo			Após intervenção – conclusão do estudo					
			Fungal culture[a]	Clinical Type	OSI (points)	OSI (points)	Direct Mycological[a]	Fungal culture[b]	Clinical response[c]	Clinical cure[c]	Complete cure[c]
ABS	M	67	*Trichophyton rubrum*	Distal sunbungual	Severe (35)	Moderate (9)	Negative	*Trichophyton rubrum*	No	No	No
ACS	M	68	*Trichophyton rubrum*	Mixed pattern	Severe (35)	0	Negative	*Candida* spp	Yes	Yes	No
DPZ	M	40	Negative	Distal sunbungual	Severe (26)	Moderate (16)	Negative	Negative	No	No	No
EFL	M	67	*Trichophyton rubrum*	Mixed pattern	Severe (19)	0	Negative	Negative	Yes	Yes	Yes
EAG	M	64	*Scytalidium* spp	Mixed pattern	Severe (35)	Moderate (9)	Negative	*Penicillium manarffei*	No	No	No
ER	M	69	*Trichophyton mentagrophytes*	Distal sunbungual	Severe (35)	0	Negative	Negative	Yes	Yes	Yes
JPM	M	71	*Trichophyton mentagrophytes*	Distal sunbungual	Severe (19)	Moderate (6)	Negative	Negative	No	No	No
JAR	F	70	*Candida* spp	Distal sunbungual	Severe (25)	Moderate (14)	Negative	Negative	No	No	No
LS	M	71	*Trichophyton mentagrophytes*	Mixed pattern	Severe (35)	Moderate (15)	Negative	*Candida* spp	No	No	No
MR	F	47	Negative	Distal sunbungual	Severe (26)	Severe (19)	Negative	Negative	No	No	No
NB	M	78	Negative	Distal sunbungual	Moderate (14)	Moderate (6)	Negative	Negative	No	No	No
PB	M	45	*Trichophyton mentagrophytes*	Mixed pattern	Severe (35)	Moderate (12)	Negative	Negative	Yes	No	No
REA	F	62	*Scytalidium* spp	Distal sunbungual	Severe (35)	Severe (35)	Yeast	Negative	No	No	No
SAN	F	45	*Candida* spp non albicans	Mixed pattern	Severe (35)	Severe (25)	Negative	*Candida* spp	No	No	No
VAC	F	47	*Penicillium marneffei*	Distal sunbungual	Severe (35)	Leve (4)*	Negative	Negative	Yes	Yes	Yes

M, male; F, female; [a], all participants in this study presented positive direct mycological exam at the time of inclusion. The direct mycological and fungal culture exams were carried out at the São Francisco de Assis University Hospital clinical analysis laboratory in Bragança Paulista, São Paulo, Brazil, which is accredited by the Agência Vigilância Sanitária Brasileira (Brazilian Sanitation Surveillance Agency). [b], the onychomycosis severity was assessed using the Onychomycosis Severity Index (OSI) system. The final score was obtained by multiplying the involvement area score (ranging from 0 to 5) by the disease proximity with the matrix score (ranging from 1 to 5). Ten points were added in the presence of subungual hyperkeratosis dermatophytoma +2 mm thick or longitudinal band. After having the scores measured, the patients subjected to hemodialysis were classified in the following severity groups: mild onychomycosis [score from 1 to 5], moderate onychomycosis [score from 6 to 15], and severe onychomycosis [score from 16 to 35] [54]. [c], Cure criteria were set based on the clinical progression and laboratory exam results, and were designed as follows: (clinical response) healthy nail 5 mm growth, (mycological cure) negative direct mycological and culture, (clinical cure) completely normal nail appearance, and (complete cure) presence of clinical and mycological cure. *, the patient presented less than 10% of the nail affected (clinical success).

Table 2. Cure indices in the systemic and topic treatments of onychomycosis according to some of the drugs available in the market, and the treatment proposed in which debridement and application of acrylic polymer with 2% terbinafine was used in patients on hemodialysis due to the presence of chronic kidney disease.*

Systemic Drug	**Mycological cure**	**Clinical cure**	**Complete cure**	**Reference**
Terbinafine	75%	81.3%	62.5%	[83]
Itraconazole	61.1%	77.8%	61.1%	[83]
Fluconazole	31.2%	37.5%	31.2%	[83]
Topical Use Drug	**Mycological cure**	**Clinical cure**	**Complete cure**	**Reference**
Amorolfine	51.8	46%	44.6%	[94]
Ciclopirox	36%	Unavailable	12%	[94]
Efinaconazole	61.6%	56.6%	31.1%	[95]
Tavaborole	35.9%	Unavailable	unavailable	[96]
Luliconazole	45.4%	32.8%	14.9%	[97]
Proposed treatment	**Mycological cure**	**Clinical cure**	**Complete cure**	**Reference**
Desbridement followed by the application of acrylic polymer with terbinafine	60.0%	26.7%	20.0%	ND

* The cure indices described in the studies are associated with the treatment, mainly of onychomycosis patients in thegeneral population. However, in our study, only patients with severe onychomycosis phenotype and debridement indication for the disease management were included. ND, nothing to declare; %, percentage.

List of Figures

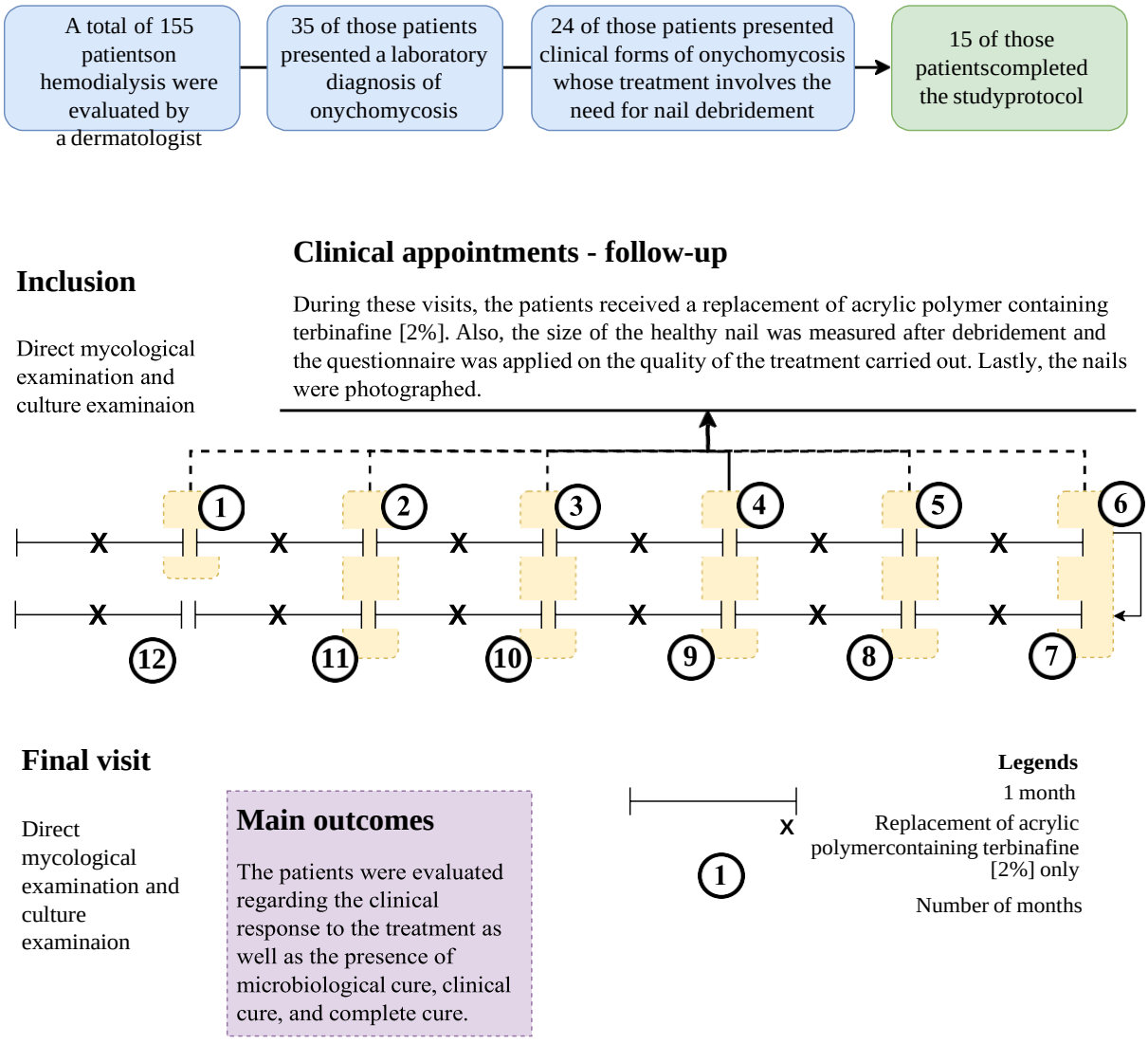


Figure 1. Study protocol showing the participants' inclusion and their follow-up during the intervention period. Intervention was carried out with debridement of the nail followed by the application of acrylic polymer with 2% terbinafine. Participants were over 18 years old and presented onychomycosis of hallux, whose treatment involved debridement of the ungual plate (dermatophytoma, +2 mm thick subungual keratosis, or prolonged onycholysis). During the study period, nine participants discontinued the follow-up, as follows: a) four participants died due to complications of the kidney disease, b) three participants received a transplant and stopped to use the dialysis service, and c) two participants decided not to continue in the study for personal reasons.

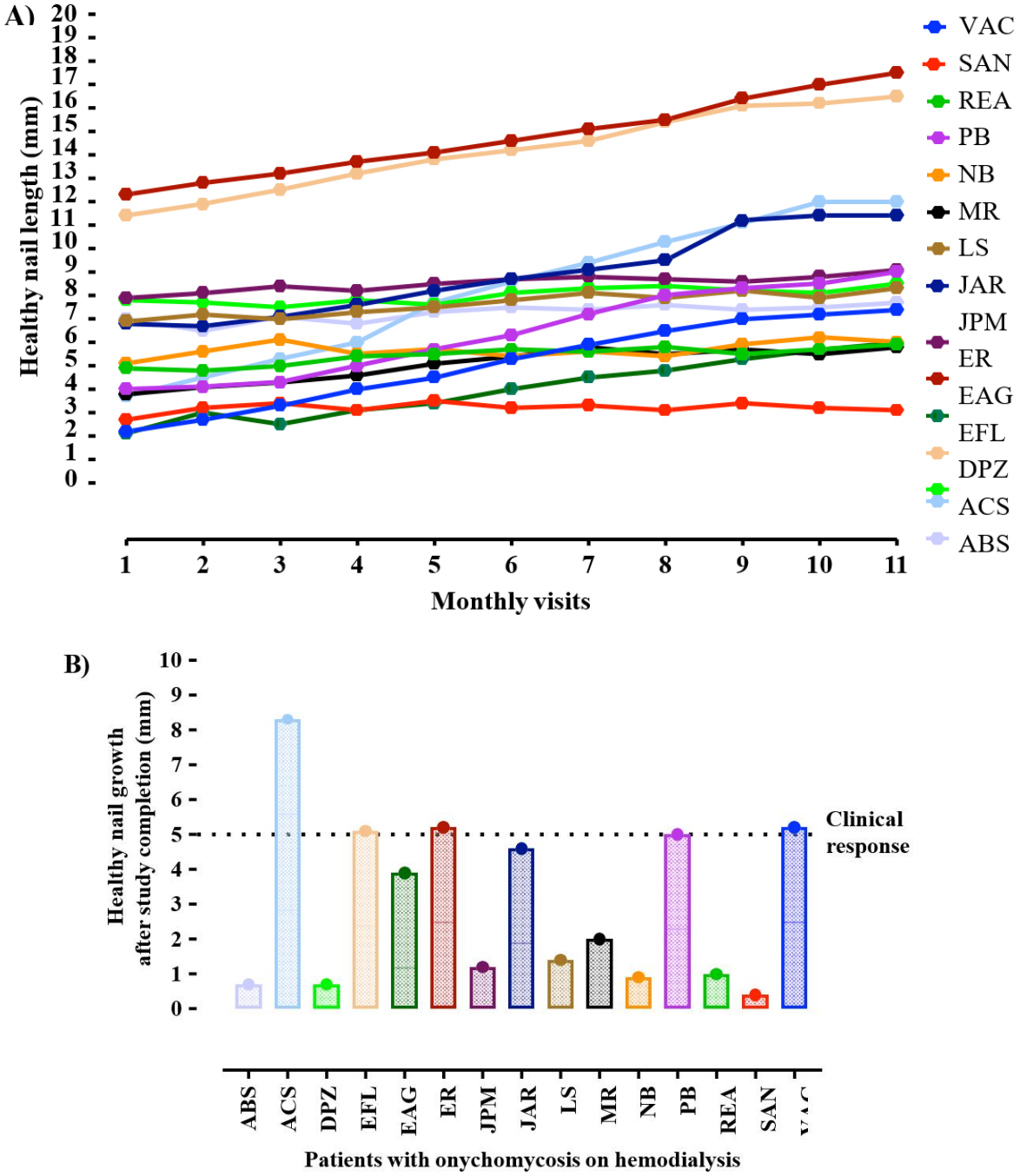


Figure 2. Evolution of the nail growth during the intervention period. The intervention was carried out with the nail debridement followed by the application of acrylic polymer with 2% terbinafine. The clinical response was positive in the presence of at least 5mm healthy nail during the follow-up period. A). All participants showed healthy nail growth. **B)** The healthy nail growth was higher than that set as positive response in only five cases, who showed 5, 5.1, 5.2, 5.2, and 8.3mm nail growth, respectively, in the PB, EFL, ER, VAC, and ACS cases.

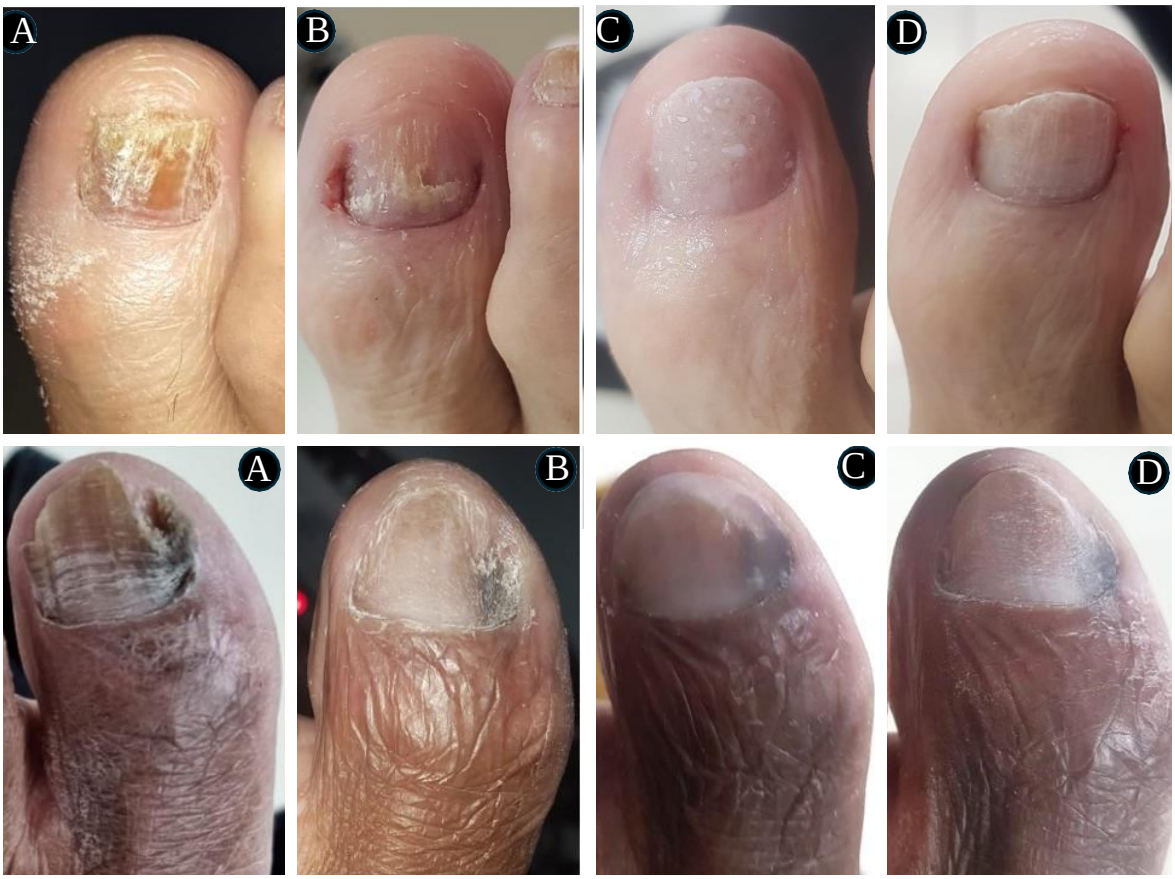


Figure 3. The images show two severe onychomycosis cases in which complete cure was observed after the intervention period carried out with nail debridement followed by the application of acrylic polymer with 2% terbinafine. In both cases, we can see as follows: A) appearance of the hallux nail at the time of the initial evaluation – study inclusion period, when the direct mycological and fungal culture exams were carried out; B) appearance of thehallux nail after the first debridement and cleaning. The ungual plate debridement was carried out only in the cases indicated such as the presence of dermatophytoma, +2mm thick subungual keratosis, or prolonged onycholysis. C) Nail appearance during the intervention period. It seems relevant to observe that the polymerized acrylic gel with 2%terbinafine guaranteed the nail healthy appearance. D) Nail appearance after 11 months of treatment with the polymerized acrylic gel with 2% terbinafine. Both cases resulted in complete cure and absence of infectious agents according to the clinical and laboratory analyses.

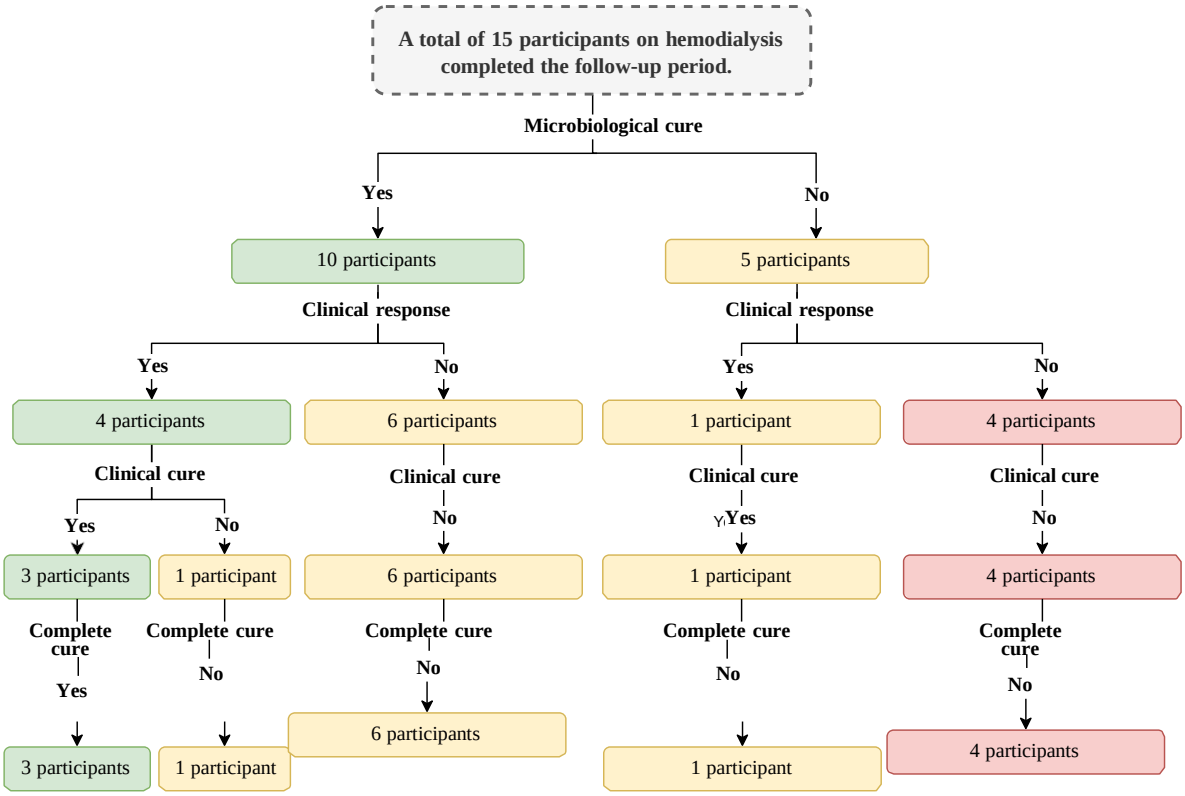
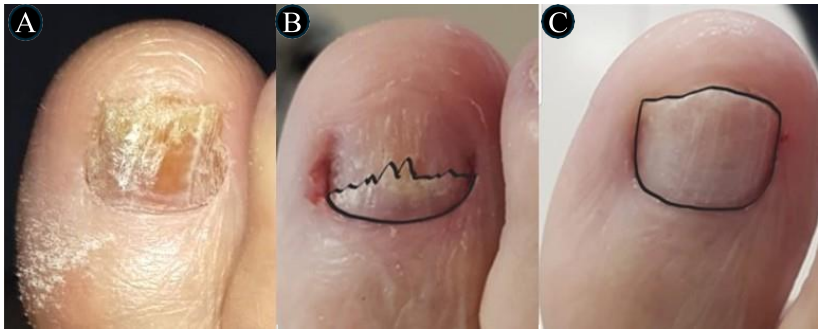


Figure 4. Summary of the main findings of the study with the outcomes observed. The outcomes were evaluated afterthe intervention period. The intervention was carried out with the nail debridement followed by the application of acrylic polymer with 2% terbinafine. Cure criteria were set based on the clinical progression and the laboratory examsand were designed as follows: (clinical response) healthy nail 5 mm growth, (mycological cure) negative direct mycological and fungal culture exams, (clinical cure) nail with a completely normal appearance, and (complete cure)presence of clinical and mycological cure. *, the patient showed less than 10% of the nail affected (clinical success).

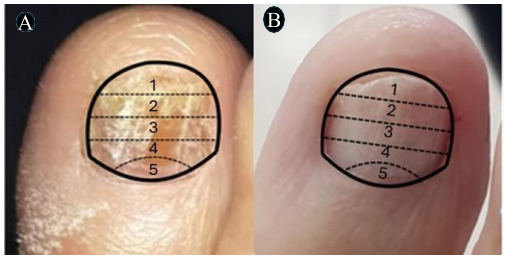
Title: Terbinafine in Acrylic Polymer for the Treatment of Onychomycosis in Hemodialysis Patients: A Phase IIClinical Trial

Jeanne Marie Queiroz Borges Bersano; Matheus Gobbo Cordeiro; Juliana Mozer Sciani; Iara Lúcia Tescarollo;Fernando Augusto Lima Marson

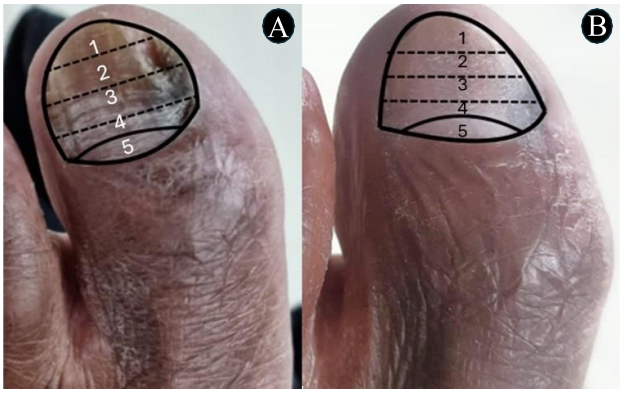
Supplementary Material



A) Appearance of the nail with onychomycosis before debridement in the presence of a 35-point Onychomycosis Severity Index (OSI). B) Nail appearance immediately after the first debridement. The OSI value reduced from 35 (time of inclusion in the study) to 25 points, due to the removal of the subungual hyperkeratosis. Thus, to evaluate thetherapeutical response, the remaining ungual plate area was measured aided by the Image J, 1,47v software (NHI Bethesda, MD, EUA). During the maintenance, whenever there was healthy nail growth, the increased area was added,but when dystrophic nail growth was observed, it was debrided again and, consequently the increased area removed was not recorded. C) Nail appearance after the intervention period with a 0-point OSI.



A) Nail appearance with mixed pattern onychomycosis, involvement of the ungual plate in the whole extension, in thepresence of over 2 mm subungual hyperkeratosis. The Onychomycosis Severity Index (OSI) score was 35 points at the time of inclusion in the study. B) Ungual plate appearance without clinical alteration after the intervention period with a 0-point OSI.



A) Mixed pattern onychomycosis with 26 to 50% involvement of the ungual plate, reaching segment 3. Presence of over 2 mm subungual hyperkeratosis. The Onychomycosis Severity Index (OSI) score was 19 points at the time of inclusion in the study. B) After the intervention period, the ungual plate did not show clinical alterations and a 0-pointOSI was recorded.

5. Conclusões

A onicomicose em pacientes em hemodiálise esteve associada a uma grande variedade de microrganismos, principalmente espécies de *Trichophyton*. O escore de gravidade do envolvimentoungueal para a maioria dos pacientes foi grave, e a onicomicose subungueal distal e a onicomicosede padrão misto foram os tipos clínicos mais prevalentes. Os principais fatores de risco associados à onicomicose foram sexo masculino, idade avançada e presença de obesidade.

A aplicação de terbinafina na concentração de 2% veiculada em gel de reconstrução acrílico para a confecção de próteses de unhas aplicadas após o desbridamento de formas moderadas e graves de onicomicose apresentou baixa eficácia como tratamento isolado em pacientes com doença renal crônica dialítica. Por outro lado, a maioria dos pacientes tiveram uma boa percepçãosobre a aparência de suas unhas durante o tratamento, mesmo quando este não resultou em melhoraclínica aparente ou cura completa.

REFERÊNCIAS

AMEEN, M.; LEAR, J.T.; MADAN, V.; MUSTAPA, M.F.; RICHARDSON, M. British Association of Dermatologists' guidelines for the management of onychomycosis 2014. **Br J Dermatol.**, vol. 171, n. 5, p. 937–58, 2014.

AUGUSTIN, M.; RADTKE, M.A.; HERBERGER, K.; KORNEK, T.; HEIGEL, H.; SCHAEFER, I. Prevalence and Disease Burden of Hyperhidrosis in the Adult Population. **Dermatology**, vol. 227, n. 1, p. 10–3, 2013.

BARAN, R.; HAY, R.J.; GARDUNO, J.I. Review of antifungal therapy and the severity index for assessing onychomycosis: Part I. **J. Dermatolog. Treat.**, vol. 19, n. 2, p. 72–81, 2008.

BELDA, W.J.; CHIACCHIO, N.; CRIADO, P.R. Tratado de Dermatologia. 3ªth ed. Rio de Janeiro: Atheneu, 2018. p. 3360.

BODMAN, M. A.; KRISHNAMURTHY, K. Onychomycosis. Disponível em: <https://www.ncbi.nlm.nih.gov/books/NBK441853/>.

BOLOGNIA, J.L.; JORIZZO, J.L.; SCHAFFER, J.V. **Dermatologia**. 3ªth ed. Rio de Janeiro: GEN Guanabara Koogan, 2015. p. 2792.

CARNEY, C.; TOSTI, A.; DANIEL, R.; SCHER, R.; RICH, P.; DECOSTER, J; ELEWSKI, B. A new classification system for grading the severity of onychomycosis: Onychomycosis Severity Index. **Arch Dermatol.**, vol. 47, n. 11, p. 1277–82, 2011.

DI CHIACCHIO, N.; SUAREZ, M.V.; MADEIRA, C.L.; LOUREIRO, W.R. An observational and descriptive study of the epidemiology of and therapeutic approach to onychomycosis in dermatology offices in Brazil. **An. Bras. Dermatol.**, vol. 88, n. 1, p. 3–11, 2013.

EL-SALAM, S.S.A.; OMAR, G.A.; MAHMOUD, M.T.; SAID, M. Comparative study between the effect of topical tazarotene 0.1 gel alone vs its combination with tioconazole nail paint in treatment of onychomycosis. **Dermatol Ther.**, vol. 33, n. 6, p. e14333, 2020.

FILHO, A.M.S.; VENTURA, C.G.; CRIADO, P.R.; DEL NEGRO, G.B.; FREITAS, R.S.; LUIZ, O.C. GIUDICE, M.C.; NETO, E.D.; BENARD, G. Hemodialysis and Kidney Transplantation as Predisposing Conditions to Onychomycosis. **Nephron.**, vol. 137, n. 1, p. 38–46, 2017

GUPTA, A. K.; DAIGLE, D.; FOLEY, K. A. The prevalence of culture-confirmed toenail onychomycosis in at-risk patient populations. **Journal of the European Academy of Dermatology and Venereology: JEADV**, v. 29, n. 6, p. 1039–1044, 1 jun. 2015.

GUPTA, A.K.; FOLEY, K.A. Evidence for biofilms in onychomycosis. **Giornale Italiano Di Dermatologia E Venereologia: Organo Ufficiale, Societa Italiana Di Dermatologia E Sifilografia**, v. 154, n. 1, p. 50–55, 1 fev. 2019.

GUPTA, A.K.; MAYS, R.R.; VERSTEEG, S.G.; SHEAR, N.H.; PIGUET, V. Update on current approaches to diagnosis and treatment of onychomycosis. **Expert Rev Anti Infect Ther.**, vol. 16, n. 12, 929–38, 2018.

GUPTA, A.K.; PAQUET, M.; SIMPSON, F.C. Therapies for the treatment of onychomycosis. **Clin. Dermatol.**, vol. 31, n. 5, p. 544–54, 2013.

GUPTA, A. K.; SANDOR HAAS-NEILL; TALUKDER, M. The safety of oral antifungals for the treatment of onychomycosis. **Expert Opinion on Drug Safety**, v. 22, n. 12, p. 1169–1178,

15 nov. 2023.

GUPTA, A.K.; VERSTEEG, S.G.; SHEAR, N.H.; PIGUET, V.; TOSTI, A.; PIRACCINI, B.M. A Practical Guide to Curing Onychomycosis: How to Maximize Cure at the Patient, Organism, Treatment, and Environmental Level. **Am J Clin Dermatol.**, vol. 20, n. 1, p. 123–33, 2019.

HASCHE, E.G.; PODDA, M. [Onychomykose: Konzepte für die Praxis]. **Der. Hautarzt.**, vol. 69, n. 9, p. 718–25, 2018.

KREIJAMP-KASPERS, S.; HAUWKE, K.; GUO, L.; KERIN, G.; BELL-SYER, S.E.; MAGIN, P.; BELL-SYER, S.B.; DRIEL M.L. Oral antifungal medication for toenail onychomycosis. **Cochrane Database of Systematic Reviews**, 14 jul. 2017.

BERMUDEZ, N.M.; TAMEZ, G.R.; PEREZ S.; TOSTI A. Onychomycosis: Old and New. **Journal of Fungi**, v. 9, n. 5, p. 559–559, 12 maio 2023.

LECHA, M.; EFFENDY, I.; FEUILHADE DE CHAUVIN, M.; DI CHIACCHIO, N.; BARAN, R. Taskforce on Onychomycosis Education. Treatment options--development of consensus guidelines. **J. Eur. Acad Dermatol. Venereol.**, vol. 19, n. 1, p. 25–33, 2005.

LIPNER, S.R.; SCHER, R.K. Onychomycosis: Treatment and prevention of recurrence. **J. Am. Acad. Dermatol.**, vol. 80, n. 4, p. 853–67, 2019.

Medical devices and clinical trial design for the treatment or improvement in the appearance of fungally-infected nails: Guidance for Industry and Food and Drug Administration Staff [Internet]. Rockville, MD: U.S. Department of Health and Human Services Food and Drug Administration. Updated FDA guidelines on the treatment of onychomycosis. Disponível em "https://www.fda.gov/regulatory-information/search-fda-guidance-documents/medical-devices-and-clinical-trial-design-treatment-or-improvement-appearance-fungally-infected". Acesso em 20 de março de 2024.

PANDHI, D.; VERMA, P. Nail avulsion: indications and methods (surgical nail avulsion). **Indian J. Dermatol. Venereol. Leprol.**, vol. 78, n. 3, p. 299–308, 2012.

PERES, N. T. A.; MARANHÃO, F. C. A.; ROSSI, A.; ROSSI, N. M. M. Dermatófitos: interação patógeno-hospedeiro e resistência a antifúngicos. **Anais Brasileiros de Dermatologia**, v. 85, n. 5, p. 657–667, out. 2010.

SCHER, R.K.; TAVAKKOL, A.; SIGURGEIRSSON, B.; HAY, R.J.; JOSEPH, W.S.; TOSTI, A.; FLECKMAN, P.; GHANNOUM, M.; ARMSTRONG, D.G.; MARKINSON, B.C.; ELEWSKI, B.E. Onychomycosis: diagnosis and definition of cure. **J. Am. Acad. Dermatol.**, vol. 56, n. 6, p. 939–44, 2007.

SREBRNIK, A.; LEVTOV, S.; BEN-AMI, R.; BRENNER, S. Liver failure and transplantation after itraconazole treatment for toenail onychomycosis. **J. Eur. Acad. Dermatol. Venereol.**, vol. 19, n. 2, p. 205–7, 2005.

TABARA, K.; SZEWCZYK, A.E.; BIENIAS, W.; WOJCIECHOWSKA, A.; PASTUSZKA, M.; OSZUKOWSKA, M.; KASZUBA, A. Amorolfine vs. ciclopirox - lacquers for the treatment of onychomycosis. **Postepy Dermatol. Alergol.**, vol. 32, n. 1, p. 40–5, 2015.

TUCCORI, M.; BRESCI, F.; GUIDI, B.; BLANDIZZI, C.; DEL TACCA, M.; DI PAOLO, M. Fatal hepatitis after long-term pulse itraconazole treatment for onychomycosis. **Ann. Pharmacother.**, vol. 42, n. 7, p. 1112–7, 2008.