Nail disorders in older people, and aspects of their pharmaceutical treatment

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Abstract

The aim of this paper was to explore how aging influences the nail unit, its disorders and its response to treatment, and to identify some of the age-related gaps in the ungual drug delivery literature. Aging causes obvious changes to the nail, some of which are inherently due to old age, while others are due to diseases/conditions which become more prevalent as we age. Alterations in the nail plate's colour, contour, thickness, fragility, surface features, cell size, chemical composition and growth rate are some of the changes, with toenails and fingernails showing different effects. With respect to disease, the incidence of onychomycosis – the most common nail disorder – is considerably higher in older people. Similarly, brittle nails become more common as we age. In contrast, the literature about ageing and the incidence of nail psoriasis is inconclusive, although, it is clear that as one gets older, the negative impact of nail psoriasis on one's quality of life decreases. Pharmaceutical treatment of the diseases comprises local and systemic therapies, sometimes in combination. Systemic therapies have the inherent disadvantages of adverse systemic effects, drug interactions and the need for monitoring, disadvantages which are especially problematic for older people who are more likely to suffer from co-morbidities and be on other medications. Topical therapy avoids such disadvantages. However, the success rates of commercially available preparations are low, and older people may need help with their application. It is also proposed that regular inspection and grooming of nails should become part of routine care of older people, as these would provide opportunities to identify and treat any problems at an earlier stage.

1. The Nail Unit

The nail unit - consisting of the nail plate, the nail bed, the nail folds, the hyponychium and the nail matrix (Fig. 1) - protects the delicate tips of fingers and toes against trauma, enables the sensation of fine touch, is used for scratching, grooming, in self-defence, as a cosmetic organ and a tool [1-13] although ideally it should not be used as a tool to prevent injury. The live nail matrix produces the (dead) nail plate which is firmly held to the nail bed - a very thin epithelium underneath the nail plate. The latter is also supported by the lateral and proximal nail folds which enclose it at its lateral and proximal edges respectively. The dorsal surface of the proximal nail fold is continuous with the cuticle, which adheres strongly to the nail plate surface, creating a physical seal against the entry of exogenous materials. At the distal edge of the nail plate is the hyponychium, which is the region underneath the free edge of the nail plate where the nail plate starts to separate from the nail bed. The whole nail unit is anchored in place by attachment to the distal phalanx, and is well perfused by blood and lymph, and has a rich nerve supply [1-11]. All of these components of the nail unit may be involved in nail disease, although due to the fact that the nail plate is the one that is most associated with the nail unit (and is commonly called the nail) and shows the most obvious changes upon aging and in disease states, it receives the most attention by lay and medical people alike.

The **nail plate** grows throughout life at, on average, 3mm per month (fingernail) and 1.5-1 mm per month (toenail) [2]. Thus, generally fingernails grow out completely in six months and toenails in 12-18 months, rate of growth being influenced by many factors such as gender, age, pregnancy, disease, nutrition, etc. Fingernail plates are also thinner (~0.5mm

at the distal edge) than the big toe (up to 1 mm at the distal edge) [14]. The nail plate is transparent, but usually appears pink which is imparted by the capillary network in the nail bed. It is hard, yet slightly elastic and is curved in both the longitudinal (in the direction of growth) and transverse (perpendicular to the direction of growth) directions. Its size, shape, thickness, surface ridging, curvature, and mechanical properties such as flexibility vary greatly within and among individuals, with site (finger/toe), and other endogenous and exogenous factors such as disease states and seasons. It is made up of three (or two according to some researchers [15]) distinct parallel strata: dorsal, intermediate and ventral [16-18], and consists of 80-90 layers of dead, flattened, keratinised cells and an intercellular 'cement' (thought to consist of proteins and/or mucopolysaccharides [4]) between the cells. Keratin forms the main bulk of the nail plate [19, 20], followed by water (at 5%-30%, [21, 22]), lipids (less than 5% w/w in adults) [20, 23], and small amounts of elements such as calcium, magnesium, sodium, potassium, iron, copper, zinc, aluminium, chlorine, selenium, fluoride [24, 25].

2. Nail changes and diseases/disorders in older people

Nail disorders can affect all ages, from totally or partially absent nail plates in newborns to severely distorted nailplates in older people. Nail disorders can be benign, such as change in colour, to extremely serious, such as tumours which require surgical removal, and others which may not seem so severe, but are long-term, recalcitrant to treatment and affect patients physically and emotionally. Symptoms include swollen and inflamed nail folds and nail plates that are over- or under- curved, excessively thickened/hard/soft/friable/ridged longitudinally or transversely, covered in pits (shallow depressions in the nail plate) and

detached from the nail bed. These symptoms may be caused by a variety of factors, such as chemicals (including medicinal drugs), infections, trauma, and congenital, hereditary, systemic and local diseases, and can affect all or only some of the components of the nail unit.

Aging causes obvious changes to the nail, some of which are inherently due to old age, while others are due to other diseases/conditions which become more prevalent as we age, such as diabetes, reduced immunity, impaired peripheral blood circulation, trauma and abnormal biomechanics [26-28].

An obvious change upon aging is the nail plate's colour, from pale pink to yellow, grey or white, with a dull, opaque appearance. Some older individuals present 'Neapolitan' nail plates which show no lunulae, a white proximal portion, a normal pink central band and an opaque distal free edge [29]. Nail plates with multiple transverse white bands or longitundinal dark bands have also been reported [30, 31]. Histological examination has revealed an increase in the size (area) of nail plate keratinocytes [32, 33], and an increase in the number of pertinax bodies (remnants of keratinocyte nuclei) [34]. The nail plate's chemical composition is also altered, with increase in carbon and decrease in nitrogen contents with aging [35]. While there is no significant change in the total lipid content, the proportions of the different lipid fractions making up the total lipid content become more variable with advancing age [23]. In the nail bed, there is thickening of the blood vessels and degeneration of elastic tissue [34].

Upon aging, nail plates also grow at a slower rate [14, 36], which may be an excellent evolutionary response as some older individuals experience problems cutting their finger- and toe- nails due to poorer eyesight and reduced manual dexterity and flexibility needed to groom one's nails, especially the toenails. The problems with cutting one's toenails may be compounded by the fact that toenails thicken with age [37]. The toenail may also curve sideways as it thickens, appearing as a ram's horn dystrophy (called onychogryphosis) [38]. Ingrowing toenails are also a common problem in older people [38]. Trauma to the toes or poorly fitting shoes can also result in subungual hematoma in elderly patients, especially those on anticoagulant therapy [38].

In contrast to the toenail, the fingernails, in general, become thinner with age [37], and less curved in both the longitudinal [27, 28] and transverse directions [39]. There is increased longitudinal ridging in the nail plate, which may lead to splitting at the distal ends, and subsequently interfere with daily activities [34]. Horizontal peeling of layers of the fingernail plate at the distal end is also common. The incidence of brittle nails, characterized by increased fragility of the nail plate, also increases with aging, with 19% of people under 60 years old versus 35% of those aged 60 or over reporting brittle nails [40]. There is a considerable influence of sex however, with the influence of age being more marked in males; 12% of younger males (< 60 years old) reported brittle nails compared to 31% of those aged ≥ 60 years, while, 29% of younger females (< 60 years old) reported brittle nails compared to 36% of those aged ≥ 60 years [40]. It is not known exactly what causes brittle

nails, although they are associated with repeated exposure to water and certain chemicals, excessive use of nail cosmetics and cosmetic removers and aggressive manicuring [41].

In the general population, the most common nail disease is onychomycosis (fungal infections of the nail plate and/or nail bed) which accounts for up to 50% of all nail disorders [38]. Onychomycosis affects both finger and toe nails, although toenail infection is more common and more recalcitrant to treatment, and males are more commonly affected than females [42]. The great majority of toenail infections are caused by dermatophytes, especially *Trichophyton rubrum*, followed by non-dermatophyte moulds and Candida, while fingernail infections are mainly caused by yeast [42, 43]. Aging has a profound effect on the incidence of onychomycosis, affecting 10% of the general population, 20% of people aged over 60 years and up to 50% of people aged over 70 years [44]. The causative organism in a population of old people in a nursing home in Turkey was found to be the same as that in the general population i.e. the dermatophyte *T. rubrum* [45]. The increasing incidence of fungal infections with aging is likely due to immunosenescence [46] , as well as other factors such as a higher incidence of co-morbidities such as diabetes [47] and peripheral vascular disease, which are also predisposing factors for onychomycosis, repeated nail trauma, slower nail growth [48], a favourable environment at the anatomic site and higher incidence of fungal infections of the foot [49], which could be acting as a fungal reservoir for onychomycosis.

Nail psoriasis – the most common nail disorder associated with cutaneous disease - is also a common problem in the general population, given that 80-90% of patients with skin

psoriasis (which affects 1 and 3% of most populations [50]) develop nail psoriasis at some point in their life [51]. Symptoms include white spots, pitting, transverse furrows, salmon-coloured 'oil drop' discolouration of the nail plate, onycholysis (separation of the nail plate from the nail bed), subungual hyperkeratosis, splinter haemorrhages, paronychia (inflammation of the nail folds), nail fragility, crumbling, and nail loss [38]. There are conflicting reports about aging and the incidence of nail psoriasis, with one paper reporting a greater incidence of nail changes in older people with psoriasis [52], and another showing no influence of age [53]. In contrast to this ambiguity regarding its incidence, it is clear that nail psoriasis has a lower negative impact on one's quality of life as one gets older [54].

3. Treatment of nail diseases in older people

Treatment of nail disease includes: i) removal of the cause, for example replacement of drugs responsible for nail changes, ii) preventive measures, such as wearing of rubber gloves and gentler manicuring for the management of brittle nails, iii) use of supports, such as braces for ingrowing toenails, iv) surgical removal of tumours, v) treatment of systemic diseases causing nail changes (for example finger nail clubbing - a symptom of disorders of the lungs, the cardiovascular system, the gastro-intestinal system, and the liver - is often reversible following successful treatment of the associated condition [55]), vi) dietary supplementation for example biotin for brittle nails [26], vii) local treatment of the nail by devices such as lasers for onychomycosis, and viii) local and systemic treatment of the nail disease using drugs. In the following sections, *pharmaceutical* treatment is discussed, specifically, of onychomycosis, psoriasis and of brittle nails, and specifically with respect to the geriatric population. For more general information on ungual (i.e. of the nail) drug

delivery and the treatment of nail diseases, the reader is referred to the numerous reviews in this field such as [56-66].

3.1 Systemic treatment

Onychomycosis is most commonly treated using oral anti-fungal agents, mainly terbinafine, itraconazole and fluconazole, terbinafine being the drug of choice in the UK, due to its higher efficacy and fewer drug interactions. Following oral administration and absorption into the systemic circulation, the drugs diffuse from the blood vessels into the nail plate via the nail bed. Terbinafine is usually administered at 250mg daily for 6 weeks for fingernails and for 12-16 weeks for toenails. Itraconazole is usually taken intermittently - due to the fact that it accumulates in the nail [67] - at 200mg twice a day for 1 week, followed by 3 weeks off between successive pulses. In general, 2 pulses are administered for fingernails and 3 to 4 pulses for toenails. Fluconazole is also administered in pulses – it is recommended that it is taken once weekly (150 mg) until the diseased nail plate has grown out (6-9 months for fingernails, and 9-18 months for toenails). The success rates of these oral medicines in adults is much less than 100%; pooled mycological cure rates in randomised controlled trials of 76 ±3% for terbinafine, 63% ±7% for itraconazole and 48 ±5% for fluconazole have been reported [68]. The success rates do not seem to be very different in older people, with mycological cure rates of 64% (95% confidence interval, 57%-71%) for terbinafine and 63% (95% confidence interval, 56%-70%) for itraconazole being reported in a single-blind randomised study in a group of patients who were over 60 years old (mean of 68 years) [69]. While it has not been conclusively proven that success rates are lower (or not) in the elderly population, a number of factors predispose to lower success

rates of therapy, such as thicker toe nails (which can present a greater barrier to drug permeation into the nail), slower nail growth (such that it will take longer for diseased nail to grow out which can discourage patients), higher likelihood of peripheral vascular disease (which can influence drug transport to the nail unit) and polypharmacy (which is known reduce adherence to medication [70]). In addition, dermatophytoma (a hyperkeratotic mass containing densely packed thick walled dermatophyte hyphae) and a large load of drug-resistant fungal spores, which are also predictors of poorer response to therapy, may be more common in older people due to a longer duration of disease. Adverse events of terbinafine, itraconazole and fluconazole include headache and gastrointestinal symptoms, taste disturbance, and more rarely, but seriously, liver and kidney disturbances and heart failure. Such adverse effects may be more common in older people who are more likely to have reduced liver and kidney function. Following reports of heart failure with itraconazole, caution is advised when it is prescribed to at-risk patients such as older adults [71] . Drug interactions are also a problem with oral anti-fungal agents. Terbinafine inhibits CYP2D6, while itraconazole and fluconazole inhibit the cytochrome P450 3A4 isoenzyme system. In addition, fluconazole also inhibits CYP2C9. These drugs can thus increase or decrease plasma concentrations of other concomitantly administered drugs that are metabolised by these enzyme systems. Given that older people are more likely to suffer from concomitant diseases and be on multiple medications, some of which may interact with these drugs, systemic therapy of onychomycosis may not always be feasible in this patient population.

Nail psoriasis, like onychomycosis, is a disease which is difficult to treat, and which requires long treatment duration. Systemic therapy is indicated when topical, intralesional or

phototherapy has failed or in patients suffering from moderate-to-severe psoriasis with nail involvement, and may be used in combination with topical therapy [72, 73]. Oral drugs include the immunosuppressant cyclosporine, the dihydrofolate reductase enzyme inhibitor methotrexate, the second-generation retinoid acitretin, and have shown varying success. More recently parenterally administered biological therapies such as infliximab – a tumour necrosis factor alpha (TNF-α) inhibitor which suppresses the immune system - have shown considerable success [73]. These systemic therapies have the inherent disadvantages of adverse systemic effects, drug interactions and the need for monitoring, and as discussed above for onychomycosis, these disadvantages may preclude their use in older people who are more likely to suffer from co-morbidities and be on other medication. In addition, the use of immunosuppressants in the elderly, whose ability to mount a robust or effective immune response is already attenuated by ageing [46] would be questionable.

3.2 Topical drug delivery

Topical therapy avoids the problems associated with the adverse events and drug interactions of systemic drugs mentioned above, and a number of topical drugs and formulations have been developed, as reviewed in, for example, [74-77]. Topical drugs for onychomycosis include amorolfine, ciclopirox, and the more recently-approved efinaconazole and tavaborole. Topical drugs for nail psoriasis include glucocorticosteroids (e.g. betamethasone, clobetasol propionate, flucinolone acetonide, triamcinolone acetonide), vitamin D3 analogs (calcipotriol, tacalcitol, calcitriol), retinoids (e.g. tazarotene), 5-fluorouracil, anthralin, cyclosporine, tacrolimus, and are often used in combination.

In both onychomycosis and nail psoriasis, the drug formulation is applied on the nail plate surface, as well as on the skin surrounding the nail plate, such as the nail folds and the hyponychium. If onycholysis is present, the nail plate is trimmed to the point where it separates from the nail bed. Sometimes, the nail plate is chemically avulsed and the formulation is applied onto the nail bed. Topical drug administrations are of long durations, e.g. daily for 6 months for fingernails and for 9 to 12 months for toenails for the treatment of onychomycosis. Despite such long treatment durations, the success of topical therapy is low for both onychomycosis (Table 1a-b) [78-82] and nail psoriasis, and topical therapies are generally recommended for mild disease states or when systemic therapy is contra-indicated. The response rates to anti-onychomycotic medicines in older patients do not seem to be different to those in the general population, as indicated on the package inserts of Julia (containing efinaconazole), Kerydin (containing tavaborole), Penlac (containing ciclopirox). For both onychomycosis and nail psoriasis, topical therapy can be used in combination with systemic therapy to improve cure rate.

A number of topical formulations have been tested, patented and a few have been marketed. Commercially available topical drug formulations include nail lacquers, solutions, paints, creams, ointments, gels. Lacquers – which form a film on the nail surface following application and solvent evaporation - are attractive as they can remain on the nail plate surface, and have been developed for the treatment of both onychomycosis and psoriasis [62, 83]. As they provide some protection to the nailplate, they have also been marketed for the treatment of brittle nails [84, 85]. The other formulations, including lacquers which

form a water-soluble film following application and solvent evaporation, are easily washed off, and are either applied before bedtime, or need to be re-applied if they are washed off. Loceryl® (containing the drug amorolfine) and Penlac® (containing ciclopirox) are lacquers which, following application, produce a water-insoluble film on the nail plate upon solvent evaporation. Due to the water resistance of the Loceryl film, Loceryl is applied once or twice weekly, rather than daily. Penlac is applied daily, with a fresh lacquer applied over the previous coat, and every seven days, the film is removed with alcohol. Due to the poor efficacy of Penlac, ciclopirox was formulated into another lacquer formulation (Onytec), using hydroxypropyl chitosan as the film-forming agent [86-89]. The hydroxypropyl chitosan film is water-soluble, and therefore has the advantage that alcohol is not needed for its removal from the nail. However, to prevent film (and drug) loss from washing, Onytec is applied every night before bedtime. Although in vitro ungual permeation studies indicated that Onytec could be superior to Penlac, having a shorter lag time (3h vs 12h) [90], clinical trials showed that Onytec was neither inferior nor superior to Penlac, although it was superior to the placebo [80]. Newer topical anti-onychomycotic formulations, Jublia® (containing efinaconazole) and Kerydin® (containing tavaborole), approved in 2014, have been formulated as (non-lacquer) alcohol-based solutions for daily application (for 48 weeks). Jublia was formulated to have a low surface tension to increase drug penetration into the nail unit; it is believed that the low surface tension of the formulation not only helps drug penetration through the nail plate, but also enables the formulation to access the nail bed more easily by spreading under the nail plate and wicking into the space between the nail plate and the nail bed to the site of infection [91].

One of the possible reasons for the low efficacy of topical formulations could be low patient adherence. To the author's knowledge, patient's level of adherence to topical nail medicines is not known, although a clinical trial is currently recruiting patients to determine patient adherence and satisfaction [92]. Although topical formulations are theoretically easy to apply, they are not practical for the elderly [93]. Older patients may find it difficult to reach their toes and to perform the medicine application procedure. For example, to apply Loceryl, patients have to file the nail plates as much as possible, clean the nail surface with a swab, apply the lacquer using an applicator and wait for about three minutes for the lacquer to dry [94]. This procedure could be difficult in older people suffering from poor flexibility, dexterity and vision. Older people may therefore need help with medicine application. Longer-lasting formulations, such as UV-cured gels [95] which need less frequent applications may be advantageous to increase patient adherence, as long as a healthcare profession (or a manicurist) is available/accessible to the patient.

4. Gaps in the knowledge

Most of the work in the ungual drug delivery field has been conducted with the general population in mind, and there are many unknowns about whether the findings relate equally to the geriatric population. A few of the gaps in the knowledge base are outlined below.

While it is known that the incidence of onychomycosis is considerably higher in older people, the reasons for this - which can be speculated on (as above) - are not known.

Greater knowledge of the causes of the increased incidence of onychomycosis would enable more effective preventive measures as well as treatment. For nail psoriasis, the influence of aging on its incidence is not clear-cut. This needs further investigation. It is possible that, psoriasis being an immune disorder, immune senescence in the elderly leads to reduced incidence and/or reduced severity of disease. There is also a lack of information on the response to anti-psoriatic treatment in the elderly, compared to that in the general adult population.

Commercial formulations have also been developed for the general population. However, aging might influence the in vivo residence of topical nail medicines, and the ungual drug permeation following topical application, which will influence the success of topical therapy. On the one hand, the increased nail plate ridging in the elderly could reduce the adhesion between the nail plate and the medicine, while on the other hand reduced activity by older people might mean reduced hand/feet washing, such that formulations, especially water-sensitive ones, have a longer in vivo residence. Ungual drug permeation is also likely to be affected by aging-associated nail plate changes, such as thickness, and the effects could be different for fingernails (which become thinner) and for toenails (which become thicker) upon aging.

It was mentioned above that the negative impact of nail psoriasis on one's quality of life decreases as one gets older. It is possible that the same holds for other nail diseases. For example, compared to a retired older person, a working-age adult is more likely to be concerned about the nail's appearance, especially if the hand is affected and if the hand is

routinely used in interactions with other people, and about taking time off work for treatment. It has also been said that as 'not all elderly patients with onychomycosis need to be treated, and not all patients want to be treated' [93]. What the elderly population wants, in terms of treatment options such as type of formulation, frequency of application, preference for treatment administered by oneself or by a health-care practitioner does not seem to have been investigated. Given that the elderly are the main users of medicines, this needs to be known, to improve compliance and the success of therapy.

5. Conclusions

While the elderly suffer more than the general population from nail diseases such as onychomycosis, there are many gaps in the ungual literature regarding the impact of aging. Systemic treatment is more challenging due to a higher incidence of co-morbidities, and related polypharmacy and the consequently higher possibility of drug interactions. Topical treatment may not be an option if the person cannot reach their toes and perform the procedure of drug application, although this can be more easily remedied by help from healthcare practitioners and/or carers. Topical drug formulations which need less frequent application and which are more effective are needed. It is also important to ascertain if an older person wants treatment, needs help with drug application, and organize help if necessary. Even if older people do not suffer from any obvious nail disease, regular inspection and grooming of nails should be part of their care, as these would provide occasions to identify any problems.

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