



EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article
ISSN 3294-3211
EJPMR

# A SYNOPSIS ON ONYCHOMYCOSIS IN PATENT WITH HIGH DEGREE OF GLYCATED HEMOGLOBIN (HBA1C)

# Essa Ajmi Alodeani, Mohammad Asrar Izhari, Mohammad Arshad\*

College of Medicine Al-Dawadmi, Shaqra University, Kingdom of Saudi Arabia.

\*Correspondence for Author: Dr. Mohammad Arshad and Dr. Mohammad Asrar Izhari College of Medicine Al-Dawadmi, Shaqra University, Kingdom of Saudi Arabia.

Article Received on 29/08/2015

Article Revised on 22/09/2015

Article Accepted on 14/10/2015

### **ABSTRACT**

Onychomycosis is an intercontinental disease burden and poses growing concern for the health-care establishment. It is a comparatively quotidian dermatologic manifestation. It is an infection of the nail plate or nail bed caused by fungus which leads to the imperceptible destruction of the nail plate, accounting for about half of all disordered nails and almost 30% of cutaneous mycoses. Variation in the incidence of the ailment reflects region and age. Usually it is not a self-limiting dermatologic representation and may trigger more infectious lesions at another site of the body owing to progressive nature of mycosis. Cosmetically unsightly affected nails may begin to be painful and lead to functional impairment. In case of patients with high degree of glycated hemoglobin (HbA1c) which is now days evaluated as an indicator of diabetes control, onychomycosis treatment becomes more imperative owing to the association between diabetes and the diabetic foot ulcer which one of the most serious sequelae of diabetes in the lower extremities. Especially lower limb sequelae are great contributors to hospitalization of diabetic patients accounting for the majority of in-hospital stay and huge consumption of resource leading to the great deal of economic setback of the health care system of the country. Approximately 15% of diabetic patients develop a lower extremity ulcer during the course of their ailment. Diabetic foot syndrome (DFS) affects 1 out of 5 diabetic patients at least once in his/her lifetime. The necessity of the selected treatment in these patients must be exercised to minimize or anticipate any adverse drug interactions as they concurrently use other medications. With the avalanche of scientific evidences and keeping all the aspects of the onycomycosis, it would be worth to undertake the subject under investigation.

**KEYWORDS:** Onychomycosis, diabetic patients, glycated hemoglobin (HbA1c).

#### 1. INTRODUCTION

Onychomycosis is a global and comparatively quotidian dermatologic manifestation raising disease burden and poses growing concern for the economy of health-care establishment. It accounts for about half of all disordered nails and almost 30% of cutaneous mycoses. In case of patients with higher degree of glycated hemoglobin (HbA1c)-a diabetic monitoring marker, the treatment becomes more imperative owing to the association between diabetes and the diabetic foot ulcer which one of the most serious consequences of diabetes in the lower extremities.

Which is a great contributor to hospitalization of diabetic patients accounting for the majority of in-hospital stay and huge consumption of resource leading to the great deal of economic setback of the health care system of the country. Onychomycosis is a very common nails infection globally and responsible for 30% of cutaneous mycotic infections and 50% of all nail disorders. It is associated with morbidity and long lasting treatment with anti-fungal agents and leads to substantial patient distress, disability, pain, negative self image and can predispose to the soft tissue infection, particularly

cellulitis.<sup>[4-7]</sup> It is more common in diabetic than nondiabetic patients and the patients with diabetic infection have a greater risk of serious complications from the disease such as limb amputations.<sup>[9-23]</sup>

Recent epidemiologic study reveals that diabetic patients are 2.8 times more likely to have onychomycosis than nondiabetic patients. Diabetic patients are very much susceptible to fungal nail infections as they often experience impaired sensation; lack of pain sensation can make them less aware of trauma to their feet, such as nail changes that develop during onychomycosis. [23]

Thickened mycotic nails can cause pressure necrosis of the nail bed in diabetic patients, and sharp infected nails can pierce the skin. In diabetic patients the minor ulcerations are serious as they are often unrecognized and can lead to serious diabetic foot infections. The morbidity associated with the onychomycosis infections itself and in combination with the diabetic infection and also the hepetotoxicity of the available drugs is a great problem both at nationally and internationally. With the avalanche of scientific evidences and keeping all the

aspects of the onycomycosis, it would be worth to undertake the subject under investigation.

#### 2. REVIEW OF LITERATURE

Glycated haemoglobin (HbA1c) was firstly identified as an "unusual" haemoglobin in diabetic patients with over 40 years ago. [24] Then studies were conducted for correlating it to glucose measurements resulting in the idea that HbA1c could be employed to measure the glycaemic control. After that it enters into clinical use in the 1980s and subsequently has become a cornerstone of clinical practice. [25] It reflects average plasma glucose over the previous eight to 12 weeks [26] and can be done at any time of the day and does not require any special preparation such as fasting. These qualities made it the preferred test for assessing glycaemic control in people with diabetes. Recently it has been used as a diagnostic test for diabetes and as a screening test for persons at high risk of diabetes. [27, 28]

There are many approaches to treat onychomycosis such as mechanical debridement, surgery, sys-temic/oral interventions and topical treatment<sup>[9]</sup> and also the agents for treatment of onychomycosis include both systemic and topical medications showing the mycological cure rates of 76% with the use of terbinfine, 63% with the use of itraconazole pulse dosing, 61% with the use of griseofulvin, and 48% with the use of fluconazole. [9] Itraconazole which is a triazole nucleous containing anti fungal agent inhibiting fungal lanosterol 14-demethylase, an essential enzyme in ergosterol synthesis. Brod spectrum of antifungal activity is possessed by this antifungal agent in comparison to all the broadest activity includes activity spectrum of dermatophytes, Candida species as well as some moulds. [29] It has high lipophilicity and high affinity for keratinous tissues, in which the concentration is many times greater than that obtained in plasma. Itraconazole exerts a lasting inhibitory effect due to the high and long lasting stages in the epidermis.<sup>[30]</sup>

Terbinafine is well-tolerated by most patients and one study reveals that terbinafine or pulse-dose itraconazole reported greater ease and convenience, and higher overall satisfaction. [31] Safety concerns associated with oral treatments include hepatotoxicity, cardiovascular disease, hypogeusia, gastrointestinal disorders, skin rashes, menstrual disorder, visual and taste disturbance, headache and riversible evaluation of liver enzymes.<sup>[31]</sup> Erick M et al. studied the disease riskfactors and treatment responses in an urban population due to Microsporum spp. (onychomycosis). [32] Leelavathi M. et al. reported the common microorganisms causing onychomycosis in tropical Climate. [33] Pericher et al. evaluated of onychomycosis among diabetic patients of Yazd diabetic center. [34] R.R. Hafidh1 et al. presented a case report on Cladosporium spp. as a causative agent of white superficial onychomycosis. [35] Lisa M. et al. reviewed the safety and efficacy of tinea pedis and onychomycosis treatment in people with diabetes. [36]

There are many othere studies that acknowledge the complexity of treating tinea pedis and onychomycosis in people with diabetes and recommended as safe and effective treatment. [37-39] Marchetti *et al.* performed the first U.S.based pharmacoeconomic evaluation comparing oral griseofulvin, itraconazole, ketoconazole, and terbinafine using the previously constructed decision-analytic model by the onychomycosis study group. [40] Mahin moghaddami and Mohammad reza shidfar studied the onychomycosis infections in Tehran. [41] Mohammad Ali Boroumand et. studied the level and clinical outcomes of HbAc1in diabetic patients following coronary artery stenting. [42] Peterson et al reported that interpretation of HbAc1 can be achieved as an average of the blood glucose which is present over past 3-4 months. [43]

Muhammad S. et al. isolated the causative pathogens and correlated the various clinical patterns of onychomycosis with causative pathogens in Qassim region of Saudi Arabia. Ahmed Medhat M H. et al. reported the epidemiology of cutaneous mycosis in the Medina region of Saudi Arabia correlated with studying the effect of light-induced gold nanoparticles on the *in vitro* growth of dermatophytes. Abdulrahman Y. Al-Zoman et al. studied the pattern of skin disease in Riyadh military hospital, Saudi Arabia. A steady increase in the diabetes prevalence found in Saudi Arabia due to the demographic changes such as urbanization and change in the life style. [47-48]

Bacchus RA et al. estimated prevalence of diabetes in Saudi Arabia and the author concluded that prevalence of diabetes started to increase at 35 years of age reaching its peak at the 45-54 age groups. [49] Fatani HH. et al. noticed the steady increase of prevalence according to age. [50] Abu-Zeid and Al-Kassab performed a study of the prevalence of diabetes in Southern Arabia. [39] El-Hazmi MA et al. did a survey on prevalence of diabetes mellitus [52] one more survey was done by El-Hazmi and Warsy the prevalence of overweight in the Saudi population.

A. Alkhier A. reported the epidemiology of diabetes mellitus and diabetic foot problems in Saudi Arabia. [53] Epidemiology of dermatophytes in eastern province of Saudi Arabia was studied by hashem al sheikh. [54] Some other studies are also carried out by David Pariser, Richard K. Scher, et al., Phoebe Rich, et al., Boni Elewski, et al., David Pariser, et al., and presented in Seminars in cutaneous medicine and surgery. [55-60]

## 3. CONCLUSION

The avalanche of evidences from the available scientific research comprehensively suggests that Onycomycosis is an intercontinental disease burden and poses raising concern for the health-care establishment. It is a comparatively quotidian dermatologic manifestation. It becomes extremely serious especially when it happens in case of patients with varying degree of HbA1c. The

review would contribute to the understanding of clinical types and the severity of the toe nail lesions in the Saudi patients with varying level of HbA1c together with prevalence and the chief etiological agents involve in onycomycosis.

Scientific research data obtained from the present review would contribute to the early prediction of susceptibility of the patients with high HbA1c to onycomycosis which would lead to a great deal of reduction in economic burden on health care establishment of Saudi Arabia, moreover it would improve the awareness of clinician and social segment as regards severity, heptotoxicity of the current treatment strategy and susceptibility to onycomycosis especially in case of the patients with high level of HbA1c.

CONFLICT OF INTEREST: The authors have no conflict of interests.

#### 5. ACKNOWLEDGEMENT

The authors (Dr. Mohammad Arshad & Dr. Mohammad Asrar Izhari) are thankful to Dr. Essa Ajmi Alodeani, The Dean, College of Medicine, Al-Dwadmi, Shaqra University, Kingdom of Saudi Arabia for providing facilities and support to accomplish this work.

# REFERENCES

- Kaur R, Kashyab B, Bhalla P. Onychomycosis-Epidemiology, diagnosis and management. Indian Journal of Medical Microbiology., 2008; 26(2): 108-116.
- Roberts D.T. Prevalence of dermatophyte onychomycosis in United Kingdom: result of an omnibus survey. British Journal of Dermatology, 1992; 126(39): 23-27.
- 3. Mügge C, Haustein U.F, Nenoff P. Causative agents of onychomycosis- a retrospective study. Journal der Deutschen Dermatologischen Gesellschaft., 2006; 4(3): 218-2810: 218-227.
- Ghannoum MA, Hajjeh RA, Scher R, et al. A largescale NorthAmerican study of fungal isolates from nails: the frequency of onychomycosis, fungal distribution, and antifungal susceptibility patterns. J Am Acad Dermatol., 2000; 43: 641-8.2.
- 5. Arenas R, Bonifaz A, Padilla MC, et al. Onychomycosis: AMexican survey. Eur J Dermatol., 2010; 20: 611-4.3.
- 6. Drake LA, Patrick DL, Fleckman P, et al. The impact ofonychomycosis on quality of life: development of aninternational onychomycosis-specific questionnaire tomeasure patient quality of life. J Am Acad Dermatol., 1999; 41: 189-96.4.
- 7. Dupuy A, Benchikhi H, Roujeau JC, et al. Risk factors forerysipelas of the leg (cellulitis): case-control study. BMJ., 1999; 318: 1591-4.5.
- 8. Tosty, T., Hay R. & Arenas Guásman R. 2005. Patients at risk of onychomycisis- risk factor identification and active prevention. Journal of the

- European Academy of Dermatology and Venereology., 2005; 19(1): 13-16.
- Gupta AK, Konnikov N, MacDonald P, Rich P, Rodger NW, Edmonds MW, McManus R, Summerbell RC: Prevalence and epidemiology of toenail onychomycosis in diabetic subjects: a multicentre survey. Br J Dermatol., 1998; 139: 665-671.
- 10. Bokyo WL, Doyle JJ, Ryu S, Gause D. Onychomycosis and its impact on secondary infection development in the diabetic population. Presentation at the 4th annual meeting of the International Society for Pharmacoeconomics and Outcomes Research, Arlington., 1999.
- 11. Levy LA. Epidemiology of onychomycosis in special-risk populations. J Am Podiatr Med Assoc., 1997; 87: 546–550.
- 12. Scher RK. Onychomycosis: a significant medical disorder. J Am Acad Dermatol., 1996; 35: S2–S5.
- 13. Gupta AK, Humke S. The prevalence and management of onychomycosis in diabetic patients. Eur J Dermatol., 2000; 10: 379–384.
- 14. Rich P. Onychomycosis and tinea pedis in patients with diabetes. J Am Acad Dermatol., 2000; 43(5): S130–S134.
- 15. Rich P. Special patient populations: onychomycosis in the diabetic patient. J Am Acad Dermatol., 1996; 35: S10–S12.
- 16. Martin ES, Elewski BE. Cutaneous fungal infections in the elderly. Clin Geriatr Med., 2002; 18: 59–75.
- 17. Rockville Md. Agency for Healthcare Research and Quality: HCUPnet, Healthcare Cost and Utilization Project. Agency for Healthcare Research and Quality., 2000.
- 18. Gordois A, Scuffham P, Shearer A, Oglesby A, Tobian JA. The health care costs of diabetic peripheral neuropathy in the US. Diabetes Care., 2003; 26: 1790–1795,
- Reiber GE, Boyko EJ, Smith DG. Lower extremity foot ulcers and amputation in diabetes. In Diabetes in America. Bethesda, Md. National Diabetes Data Group, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases., 1995.
- 20. Tom CM, Kane MP: Management of toenail onychomycosis. Am J Health Syst Pharm., 1999; 56: 865–871.
- 21. Lateur N, Mortaki A, Andre J. Two hundred ninetysix cases of onychomycosis in children and teenagers: a 10-year laboratory survey. Pediatr Dermatol., 2003; 20: 385–388.
- 22. Kemna ME, Elewski BE: A U.S. epidemiologic survey of superficial fungal diseases. J Am Acad Dermatol., 1996; 35: 539–542.
- 23. Doyle JJ, Boyko WL, Ryu S, Gause D. Onychomycosis among diabetic patients: prevalence and impact of nonfungal foot infections. The American Diabetes Association 60th Scientific Sessions., 2000.

- 24. Rahb ARS, Blumenfeld O, Ranne y HM. Studies of an unusual hemoglobin in patients with diabetes mellitus. Biochem Bioph ys Res Commun., 1969; 3(6): 838-84 3.
- 25. Nathan DM, Kuen en J, Borg R et al. Translating the A1C assay into estimated average glucose values. Diabetes Care., 2008; 31: 1473-1478.
- 26. Massi-Benedetti M. Changing targets in the treatment of type 2 diabetes. Curr Med Res Opin., 2006; 22(2): S5-13.
- 27. Nathan DM, Turgeon H, Regan S. Relationship between glycated haemoglobin levels and mean glucose levels over time. Diabetologia., 2007; 50: 2239-2244.
- 28. International Expert Committee report on the role of the A1C assay in the diag nosis of dia betes. Diabetes Care, 2009; 32: 1327-133 4.
- Elewski BE. Mechanisms of action of systemic antifungal agents. J Am Acad Dermatol., 1993; 28: S28-34.
- Warshaw E M, Bowman T, Bodman MA, Kim JJ, Silva S , Mathias S D. Satisfaction with onychomycosis treatment. Pulse versus continuous dosing. J Am Podiatr Med Assoc., 2003; 93: 373– 379.
- 31. Cauwenbergh G, Degreef H, Heykants I, et al. Pharmacokinetic profile of orally administered itraconazole in human skin. J Am. Acad. Dermatol., 1988; 18: 263-8.
- 32. Erick M, Mahreen A, Diana T, Roberto A. Microsporum spp. onychomycosis: Disease presentation, riskfactors and treatment responses in an urban population. Braz. J. Infect. Dis., 2014; 18(2): 181–186.
- 33. Leelavathi M, Tzar M.N, J. Adawiah. Sains Malaysiana., 2012; 41(6): 697–700,
- 34. Parichehr K, Mohammad T N. Evaluated of onychomycosis among diabetic patients of Yazd diabetic center. Journal of Pakistan Association of Dermatologists., 2010; 20: 217-221.
- 35. R.R. Hafidh and A.S. Abdulamir. Conference Series, case report on Cladosporium spp. as a causative agent of white superficial onychomycosis. Journal of Physics., 2014; 497: 012022.
- 36. Lisa M, Kerwin T and Sara J, Matricciani et al. Journal of Foot and Ankle Research 2011; 4: 26.
- 37. Robbins J. Study of the treatment of onychomycosis in the diabetic population. J. Diabetes Complications., 2003; 17: 98-104.
- Rich P. Onychomycosis and tinea pedis in patients with diabetes. J Am Acad Dermatol., 2000; 43: 130-138
- 39. Gupta A, Humke S. The prevalence and management of onychomycosis in diabetic patients. Eur J Dermatol., 2000; 10: 379-384.
- 40. Marchetti A, Piech CT, McGhan WF, Neugut AI, Smith BT. Pharmacoeconomic analysis of oral therapies for onychomycosis: a US model. Clin Ther., 1996; 18: 757-777.

- 41. Mahin M and Mohammad R S. Medical journal of the public of iran, A study of onychomycosis in Tehran., 1989; 2: 3-4.
- 42. Seyed E K, Hamidreza G, Mohammad Ali B, Mojtaba S, Farzad M, Mohammad R, Mohajeri-Tehrani, Hamidreza P, Saeed S, Narges R, Mohammad A, Elham H, Soheil S, Ebrahim N. Cardiovascular Diabetology, Glycosylated hemoglobin (HbA1c) levels and clinical outcomes in diabetic patients following coronary artery stenting., 2012; 11: 82.
- 43. Peterson K P, Pavlovich J G, et al. What is hemoglobin A1c? An analysis of glycated hemoglobins by electrospray ionization mass spectrometry. Clin Chem., 1998; 44(9): 1951-8.
- 44. Muhammad S, Abdullateef A. A, Ahmad A. Al R. Ghada A. Bin S, Ibrahim H. K. B, Eltuhami M. A-M, Abeer E. E. Onychomycosis in Qassim Region of Saudi Arabia: A Clinicoaetiologic Correlation. Journal of Clinical and Diagnostic Research., 2014; 8(8): YC01-YC04.
- 45. Ahmed Medhat M H, Amira Abdu El-A, Abdul Aziz Q A, Mohamed A and Al Zahraa Ahmed K El-D. African Journal of Microbiology Research., 2012; 6(37): 6668-6677.
- 46. Abdulrahman Y. Al-Zoman and Abdurahman K. Al-Asmari, Egyptian Dermatology Online Journal, 2008; 2: 4
- 47. Nielsen JV. Diabetes in the Arab World: Prevalence and risk factors. Pract Diab Int., 1999; 16(3): 82-6.
- 48. World Health Organization publication: World urbanization prospects; executive Summary., 2007.
- 49. Bacchus RA, Bell JL, Madkour M, Kilshow B. The prevalence of diabetes in male Saudi Arabs. Diabetologia., 1982; 23: 330-2.
- 50. Fatani HH, Mira SA, El-Zubir AG. Prevalence of diabetes mellitus in rural Saudi Arabia. Diabetes Care., 1987; 10(2): 180-3.
- 51. Abu-Zeid HAH, Al-Kassab ASK. Prevalence and health-care features of hyperglycemia in semiurban-rural communities in southern Saudi Arabia. Diabetes Care., 1992; 15(4): 484-9.
- 52. El-Hazmi MAF, Warsy AS. Obesity in Saudi Arabia. Ann Saudi Med., 1997; 17(3): 302-6.
- 53. A. Alkhier Ahmed. Epidemiology of diabetes mellitus and diabetic foot problems in Saudi Arabia Av Diabetol., 2010; 26: 29-35.
- 54. Hashem Al-Shaikh. Epidemiology of dermatophytes in eastern province of Saudi Arabia. Journal of microbiology., 2009; 4(6): 229.
- 55. The Rationale for Renewed Attention to Onychomycosis, David Pariser, Seminars in cutaneous medicine and surgery, , 2013; Volume 32, Number 28
- The Epidemiology, Etiology, and Pathophysiology of Onychomycosis, Richard K. Scher, Phoebe Rich, David Pariser, Boni Elewski, Seminars in cutaneous medicine and surgery, 2013; Volume 32, Number 2S.

- 57. Diagnosis, Clinical Implications, and Complications of Onychomycosis, Phoebe Rich, Boni Elewski, Richard K. Scher, David Pariser, Seminars in cutaneous medicine and surgery, 2013; Volume 32, Number 2S.
- 58. Current and Emerging Options in the Treatment of Onychomycosis, Boni Elewski, David Pariser, Phoebe Rich, Richard K. Scher, Seminars in cutaneous medicine and surgery, 2013; Volume 32, Number 2S.
- 59. Promoting and Maintaining or Restoring, Seminars in cutaneous medicine and surgery, 2013; Volume 32, Number 2S.
- 60. Healthy Nails: Practical Recommendations for Clinicians and Patients, David Pariser, Richard K. Scher, Boni Elewski, Phoebe Rich, Seminars in cutaneous medicine and surgery, 2013; Volume 32, Number 2S.