



Subclinical Onychomycosis in Patients with Type II Diabetes

Submitted For Partial Fulfillment of Master Degree in Dermatology

By

Amira Mohammed Hosam EL-Din Elbendary

M.B.B.Ch

Supervised by

Prof. Dr. Amr Abdel Hakim Rateb

Professor of Dermatology

Faculty of medicine

Cairo University

Dr. Naglaa Mohammed Sameh Zaki

Assistant professor of Dermatology

Faculty of medicine

Cairo University

Dr. Amira Mohammed Eltawdy

Assistant professor of Dermatology

Faculty of medicine

Cairo University

Faculty of medicine

Cairo University

2014

LIST OF CONTENTS

	Page
Acknowledgment	ii
Abstract	iv
List of abbreviations	V
List of figures	vi
List of tables	ix
Introduction	1
Review of literature	3
Chapter 1: Overview of nail disorders	3
and onychomycosis	
Chapter 2: Laboratory diagnosis of	43
onychomycosis	
Chapter 3: Subclinical onychomycosis	66
and its association with tinea pedis	
Chapter 4: The prevalence and	70
management of onychomycosis in	
diabetic patients.	
Patients and Methods	80
Results	85
Discussion	100
Summary	107
References	110
Arabic summary	128

Acknowledgment

First and foremost, thanks to Allah for all the blessings he gave me all through my whole life.

I would like to express my gratitude and deepest appreciation to **Dr. Amr Abdel Hakim Rateb**, Professor of Dermatology, Faculty of Medicine, Cairo University, for inspiring me with the idea of this work. His patience, precious advice and guidance enlightened my way throughout this work.

Many thanks to **Dr. Naglaa Mohammed Sameh Zaki,** Assistant professor of Dermatology, Faculty of medicine, Cairo University, for her guidance and great support through this work and for her continuous help and kind supervision.

I am greateful to **Dr. Amíra Mohammed Eltawdy**, Assistant Professor of Dermatology, Faculty of Medicine, Cairo University for her encouragement, motivation and sincere advice through this work.

Special thanks go to **Dr. Inas Elattar** Professor of Biostatistics, Department of Biostatistics & Cancer Epidemiology, National Cancer Institute, Cairo University, for her help in statistical analysis and help in achievement of this work.

My deepest gratitude to my beloved parents, and my husband for their encouragement and support all through my life.

ABSTRACT

Background: Onychomycosis is a common cause of nail dystrophy and may be associated with tinea pedis. Its prevalence among diabetic patients is three times that in healthy individuals. The presence of fungal infection in clinically normal nails in patients with type II diabetes is unknown.

Objective: Assessment of the efficacy of nail clipping in diagnosing both clinical and subclinical onychomycosis, besides, the assessment of possibility of presence of subclinical onychomycosis in patients with type II diabetes that might suggest early therapeutic intervention in such patients.

Patients and methods: 106 patients with type II diabetes with and without vasculopathy, neuropathy, and clinical tinea pedis with normal big toe nail are included, in addition to control groups that include 30 non diabetic subjects with normal toe nails and 10 non diabetic patients with apparent onychomycosis. All were subjected to nail clipping of the big toe nail followed by staining with H&E and PAS stains.

Results: Fungal infection (PAS +ve) were identified in eight specimens of the diabetic group. All patients were uncontrolled diabetes, six patients had neuropathy, five patients had clinically diagnosed tinea pedis, and no one had vasculopathy.

Conclusions: Nail clipping could be a useful diagnostic tool for onychomycosis in addition that subclinical onychomycosis is an existing real condition that can be associated with tinea pedis and it was found in patients with type II diabetes especially the uncontrolled ones.

Key words: nail disease, diabetes mellitus type II, onychomycosis, subclinical disease, tinea pedis, nail clipping.

LIST OF ABBREVIATIONS

CYP	Cytochrome P450
DSLO	Distal and lateral subungual onychomycosis
E.	Epidermophyton
H&E	Hematoxyline and Eosine
HbA1c	HeamoglobineA1c
HIV	Human Immunodeficiency Virus
КОН	Potassium Hydroxide
MALDI-TOF MS	Matrix-Assisted Laser Desorption/Ionization Time-of-Flight
	Mass Spectrometry
NPV	Negative predictive value
OCT	Optical coherence tomography
OM	Onychomycosis
OSI	Onychomycosis Severity Index
PAS	Periodic acid-Schiff
PCR	Polymerase chain reaction
PPV	Positive predictive value
RFLP	Restriction fragment length polymorphism
spp	Species pluralis
SWO	Superficial white onychomycosis
TDO	Total dystrophic onychomycosis
T.	Trichophyton
TP	Tinea pedis
WHO	World health organization

LIST OF FIGURES

FIGURE	NAME OF FIGURE	PAGE
NO		NO
	Review of literature	
1	Anatomy of the nail	5
2	Onychomadesis	8
<u>3</u>	Longitudinal groove in Darier disease	8
4	Pitting	10
<u>5</u>	Trachyonychia	10
<u>6</u>	Longitudinal melanonychia	14
7	Onychogryphosis	14
<u>8</u>	Subungual hyperkeratosis	15
9	Onycholysis with secondary infection	15
<u>10</u>	koilonychia	16
<u>11</u>	Muehrcke's Lines.	16
<u>12</u>	Half-and-half nails	17
<u>13</u>	Terry's nails.	17
<u>14</u>	Clubbing	17
<u>15</u>	Distal and lateral subungual onychomycosis	22
<u>16</u>	Superficial white onychomycosis	22
<u>17</u>	Four types of onychomycosis showing different	24
	entry points by infecting organism	
<u>18</u>	Proximal subungual onychomycosis	24
<u>19</u>	Totally dystrophic onychomycosis	25
<u>20</u>	Endonyx onychomycosis caused by Trichophyton	25
	soudanense	
<u>21</u>	Candidal onychomycosis	28

<u>22</u>	Proximity to matrix scoring	32
<u>23</u>	Nail biopsies	46
<u>24</u>	Non uniform hyphae in nail plate (PAS x400)	52
<u>25</u>	Uniform septated hyphae (PAS X 400)	52
	Long uniform septated hyphae (PAS X 400)	
<u>26</u>	Distal subungual onychomycosis	56
	microscopically(H&E and PAS stains)	
<u>27</u>	Onychomycosis (H&E)	56
<u>28</u>	Potassium hydroxide stain shows dermatophytes	57
	and hyphae with arthrospores (original	
	magnification ×40).	
<u>29</u>	Fluorescence microscopy using Calcofluor white	57
<u>30</u>	Dermoscopy of DSO: 'Spikes' of the proximal	65
	margin of the onycholytic area, which acquires a	
	jagged edge (20 x)	
<u>31</u>	Dermoscopy of DSO: 'Longitudinal striae' of	65
	different colours in the onycholytic nail plate (40x).	
	Results	
<u>32</u>	Percentage of patients with neuropathy,	86
	vasculopathy and TP	
<u>33</u>	Percentage of patients with PAS +ve stain	87
<u>34</u>	Fungal infection using PAS and its relation to the	90
<u>35</u>	control of diabetes Fungal infection using PAS and its relation to	91
	neuropathy in diabetes mellitus type II patients	
<u>36</u>	Fungal infection using PAS and its relation to tinea	91
<u>37</u>	pedis H&E for nail clipping showing no parakeratosis in	95
	normal non-diabetic subject (x100)	
38	H&E showing parakeratosis in nail clipping of a	96

List of figures

	diabetic patient with subclinical onychomycosis	
	(x200)	
<u>39</u>	PAS positive stain for nail clipping of a diabetic	97
	patient with subclinical onychomycosis (x400)	
<u>40</u>	PAS positive stain for another diabetic patient with	98
	subclinical onychomycosis (x400)	
<u>41</u>	H&E showing parakeratosis in nail clipping of a	99
	patient with subclinical onychomycosis (x400)	

LIST OF TABLES

Table	Title	Page number
number		
1	Onychomycosis severity index	31
2	Descriptive data of the diabetic patients included in the study.	85
3	Correlation between results of PAS staining in the study and the control group No(1)	88
4	Descriptive data of patients with fungal infection (+ve PAS stain)	89
5	Relation of patients with fungal infection to TP, neuropathy, and vasculopathy.	86
6	All data related to the patients with type II diabetes included in the study	92-94

INTRODUCTION

Onychomycosis (OM) is a common problem, accounting for up to half of all diseases of the nail, with an estimated prevalence of 10% of the general population and approaching 60% in the elderly (*Elewski*, 1998).

Among diabetic patients, onychomycosis is 2.8 times more prevalent than it is in patients without diabetes (*Gupta et al.*, 1998). Nails that are thickened with fungus can develop serious bacterial infections and ulcerations. Patients with diabetes related disorders are at increased risk for morbidity in onychomycosis. Diabetic patients suffering from decreased foot sensation are more prone to trauma which damages the nail and the nail matrix, opening portals of entry for the fungus to infect the nails, and the presence of this infection increases the risk of other infections of the foot and leg (*Boyko et al.*, 1999).

Approach to diagnose onychomycosis can be painful and it may also be prolonged and complicated. Nail clipping is an easy doing exam, free from pain, cheap and sensible, examining the histopathology of the nail keratin. In dermatology, clippings are fragments cut from the distal portion of nail plate used for histopathological assessment (*Fillus Neto.*, 2009).

Clippings appeared from the need to have a quick, low cost and non-painful histological response to identify nail plate abnormalities that could express any nail system pathology. One of the most frequent indications is observed when there are clinical abnormalities compatible with onychomycosis, but with repetitive negative mycological tests. Other situations may also be assessed by histological analysis of ungueal keratin, such as psoriasis, lichen planus, trauma, dyschromia, melanonychia and even tumors (*Lawry et al.*, 2000).

It is a non-painful test to the patient, has no sequels and high sensitivity (*Lawry et al.*, 2000).

While onychomycosis is a common problem among patients with diabetes, there are no clear, hard and fast solutions as to how to treat it. It affects quality of life and it can lead to more serious conditions such as ulcers and subsequent amputations. The presence of fungal infection in clinically normal nails in these diabetic patients is not known, and knowing about it will give us much benefit as regard early diagnosis and treatment and early prevention of serious complications.

Review

Of

Literature

CHAPTER 1

OVERVIEW OF NAIL DISORDERS AND ONYCHOMYCOSIS

OVERVIEW OF NAIL DISORDERS

INTRODUCTION:

The human nail shields the distal digit from harm, assists in the picking-up of small objects, improves fine touch, and enhances the aesthetic appearance of the hand. Aesthetically displeasing nails and nail-associated symptoms such as pain or throbbing are common factors that contribute to a patient's decision to seek medical attention (*Baran et al.*, 2006).

ANATOMY AND PHYSIOLOGY OF THE NAIL UNIT:

The nail unit is composed of the nail matrix, the nail bed, the proximal and lateral nail folds, and the hyponychium (**figure 1**).

The nail matrix is the germinative epithelium from which nail matrix keratinocytes differentiate to ultimately form the nail plate. Most of the nail matrix is hidden beneath the proximal nail fold, but the distal third is sometimes visible through the proximal portion of the nail plate as a half-moon shaped structure called the lunula (*Haneke*, 2006).

Maturation and differentiation of the nail matrix occurs along a diagonal axis oriented distally. Thus, the keratinization of the distal matrix cells forms the ventral portion of the nail plate whereas the keratinization of the proximal matrix cells forms the dorsal portion of the nail plate (*De berker et al.*, 1996)

Nail plate abnormalities typically result from pathological processes involving the nail matrix or space-occupying lesions involving the overlying nail fold (*Rich*, 2006).