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CLINICAL AND MYCOLOGICAL STUDY OF ONYCHOMYCOSIS IN PATIENTS WITH DIABETES MELLITUS

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LIST OF ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome.
C.albicans	Candida albicans.
C.glabrata	Candida glabrata.
C.guilliermondii	Candida guilliermondii.
C.kefyr	Candida kefyr.
C.krusi	Candida krusi.
C.lusitaniae	Candida lusitaniae.
C.parapsilosis	Candida parapsilosis.
C.tropicalis	Candida tropicalis.
CD	Cluster of differentiation.
DLSO	Distal and lateral subungual onychomycosis.
DM	Diabetes mellitus.
DTM	Dermatophyte test medium.
E.floccosum	Epidermophyton floccosum.
GADA	Glutamic acid decarboxylase autoantibodies.
GDM	Gestational diabetes mellitus.
GSP	Glycated serum protein.
HIV	Human immunodeficiency virus.
HW	House wife.
IAAs	Insulin autoantibodies.
ICAs	Islet cell autoantibodies.
IDDM	Insulin dependent diabetes mellitus.
IFG	Impaired fasting glucose.
IGT	Impaired glucose tolerance.
K1	Keratin 1.
K10	Keratin 10.
K14	Keratin 14.
K16	Keratin 16.
K5	Keratin 5.
K6	Keratin 6.

MW	Manual worker.
NIDDM	Non insulin dependent diabetes mellitus.
OGTT	Oral glucose tolerance test.
P.circulatory impairement	Peripheral circulatory impairement.
PAS	Periodic acid-schiff.
PSO	Proximal subungual onychomycosis.
S.dimidiatum	Scytalidium dimidiatum.
S.hyalinium	Scytalidium hyalinium.
SDA	Sabouraud's dextrose agar.
SIF	Serum inhibitory factor.
Spp.	Species.
SWO	Superficial white onychomycosis.
T.corporis	Tinea corporis.
T.manuum	Tinea manuum.
T.mentagrophytes	Trichophyton mentagrophytes.
T.pedis	Tinea pedis.
T.rubrum	Trichophyton rubrum.
T.soudanense	Trichophyton soudanense.
T.tonsurans	Trichophyton tonsurans.
T.verrucosum	Trichophyton verrucosum.
T.violaceum	Trichophyton violaceum.
TDO	Total dystrophic onychomycosis.

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INTRODUCTION AND AIM OF THE WORK

Introduction:

Diabetes mellitus affects individuals of all ages and all socioeconomic segments of population. There are an estimated 60 million diabetics worldwide. The number of individuals diagnosed with diabetes mellitus increased five folds between 1958 and 1993. The World Health Organization (WHO) estimates that the world population of diabetics will double to over 200 million people by year 2010 *(Dogra et al., 2002).*

It is generally accepted that diabetic patients are more likely to suffer from skin and soft tissue infections than non-diabetics *(Buxton et al., 1996).*

Diabetes mellitus can result in complications affecting all systems of the body, of particular relevance is the lower extremity arterial disease (LEAD). The presence of LEAD in diabetics may be compounded by infections such as onychomycosis and bacterial sepsis *(Gupta et al., 1998).*

Mild early onychomycosis probably possess little threat to the diabetics, while more sever neglected onychomycosis can be more

serious problem. In particular, the high risk diabetic with compromised lower extremities and severe neuropathy is at increased risk of developing complications from onychomycosis *(Rich & Hare, 1999)*.

Onychomycosis is a mycotic infection of the nail unit caused by three groups of fungi, namely dermatophytes, yeasts and non dermatopohyte molds. The dermatophyte Trichophyton rubrum and T. mentagrophytes are responsible for most finger and toe nail infections, and these mycotic infections are termed "tinea unguium". Yeasts account for a relatively smaller number of all infections. Nail plate invasion by Candida spp. may occur in the presence of chronic monilial paronychia *(Dogra et al., 2002 and Sehgal & Jain, 2000)*.

Aim of the work:

The aim of this work is to determine the morbidity of onychomycosis in diabetic patients in comparison to non-diabetic patients, and to determine the most common fungal species of onychomycosis in diabetics in comparison to non-diabetic control groups.

NORMAL NAIL UNIT

The nail apparatus is a specialized keratinous appendage whose functions in humans include protection of the terminal phalanx, contribution to fine touch and skilled hand movement, and the ability to pick up small objects *(Melody et al., 2000)*.

The nail plate is formed by the four structures that make up the nail unit: proximal nail fold, nail matrix, nail bed and hyponychium *(Zaias, 1999)*.

The nail plate is roughly rectangular and flat but demonstrates considerable variation. Although it is translucent, it appears pink as a consequence of rich underlying vascular network. A white, crescent-shaped lunula is seen projecting from under the proximal nail fold. It is the most distal portion of the matrix and determines the shape of the free edge of the nail plate. Its color is caused by scattering of light by the nucleated cells of the keratogenous zone of the matrix *(Melody et al., 2000)*.

The nail plate is resting on and firmly attached to the nail bed. It is less adherent proximally, apart from posterolateral corners. Approximately one-quarter of the nail is covered by the proximal nail fold, and a narrow margin of the sides of the nail plate is often occluded by the lateral nail folds *(Cohen, 1996)*.

The definition of nail matrix is controversial. There is a common acceptance that there is a localized region beneath proximal nail which produces the major part of the normal nail plate. For those who consider this the sole source of nail it is termed simply the

matrix, or germinal matrix. However, there is some evidence that other epithelial parts of the nail unit also contribute to the nail plate. Matrix can be subdivided into dorsal (ventral aspect of the proximal nail fold), intermediate (germinal matrix or matrix) and ventral (nail bed) sections. The nail bed is also termed the sterile matrix and its role in the production of nail is unclear *(de Berker et al., 2004)*.

Although it appears that the nail plate may thicken by up to 30% as it passes from the distal margin of the lunula to the end of the nail bed, this is not associated with an increase in cell numbers and may represent compaction of the nail from distal tip trauma rather than nail bed or nail plate production. The situation may change in disease, where the nail bed changes its histological appearance to gain a granular layer and may contribute a false nail of cornifid epithelium to the undersurface of the nail *(de Berker et al., 1996)*.

At the point of separation of the nail plate from the nail bed, the proximal part of the hyponychium may be modified as the solehorn. This is a central thickened structure with a dermal core. It is usually found on the toes of elderly people, where there are often associated vascular abnormalities. Beyond the solehorn region, the hyponychium terminates at the distal nail groove; the tip of the digit beyond this ridge assumes the structure of the epidermis elsewhere *(de Berker et al., 2004)*.

Microscopic anatomy of the nail unit:

Nail folds:

Three potential spaces would become apparent if the nail plate was not present; these are the single proximal and the two lateral nail grooves. Folds of skin known as the proximal and lateral nail folds wrap around the nail plate and form these grooves. The proximal nail fold is an invaginated, wedge-shaped fold of skin on the dorsum of the distal digit. It consists of both a dorsal and a ventral surface epithelium. The keratinization process in both portions is the same as that of the epidermis elsewhere, with a granular layer that is absent in all parts of the nail matrix. The dorsal surface of the proximal nail fold is a continuation of the epidermis and dermis of the digit and contains sweat glands but no follicles or sebaceous glands. The epidermis includes all the layers found in normal skin, including a granular layer and a rete ridge- dermal papilla pattern *(Melody et al., 2000)*.

At the distal tip of the proximal nail fold the skin reflects proximally and ventrally, then extends approximately 5mm toward the distal interphalangeal joint. The skin of the ventral portion is very thin and has all of the layers of normal epidermis, including a granular layer, however, it lacks both a rete ridge-dermal papilla pattern and appendages. The stratum corneum of the dorsal tip and the ventral walls extends onto the dorsal surface of the nail as the cuticle; this provides a protective barrier to the entery of infectious organisms into the germinative matrix. Disruption results in formation of a real space from a potential space, allowing irritants to

enter and produce the inflammation seen in chronic paronychia *(Melody et al., 2000)*.

Deep to the edge of the cuticle and continuous with the ventral wall dorsally is the eponychium. It has been demonstrated that the eponychium results from cuticular desquamation occurring on the nail plate *(Zaias, 1990)*. However, this theory has been the source of some controversy *(de Berker et al., 1995)*.

Diseases that affect the ventral portion of the proximal nail fold may affect the newly formed nail plate and lead to pits and grooves. The lateral nail folds are structurally similar to the adjacent skin but are devoid of and pilosebaceous glands. Acanthosis and papillomatosis of the epithelium as well as a granular layer are present *(Melody et al., 2000)*.

Nail matrix (intermediate matrix):

Nail matrix produces the nail plate in the absence of disease *(de Berker et al., 2004)*. It is bordered proximally by the ventral proximal nail fold and distally by the nail bed *(Zaias, 1990)*.

The basal compartment of the matrix is broader than the same region in normal epithelium or in other parts of the nail unit, such as the nail bed *(de Berker et al., 2004)*.

There is no granular layer, and cells differentiate with the expression of trichocyte "hard" keratin as they become incorporated into the nail plate, along side normal epithelial keratins. During this process, they may retain their nuclei until more distal in the nail plate. These retained nuclei are called pertinax bodies. Apart from

this, the detailed cytological changes seen in the matrix epithelium under the electron microscope are essentially the same as in the epidermis *(de Berker et al., 2000)*.

The nail matrix contains melanocytes in the lowest three cell layers and these donate pigment to the keratinocytes. The presence of 6.5 melanocytes per millimeter of matrix basement membrane can be used as a guide to a normal matrix melanocyte population *(Tosti et al., 1994)*.

The appearance of melanocytes separate from the basement membrane distinguishes them from those found in the nail folds, which are primarily basal. Matrix melanocytes are further distinguished from those elsewhere by their failure to produce melanin in normal circumstances in white people. This can change with melanotic streaks presenting in local inflammatory, naevoid or neoplastic disease. In non white people, brown streaks are common and are almost universal in Afro-Caribbeans by the age of 60 years *(de Berker et al., 2004)*.

Langerhans' cells are detectable in the matrix by CD1a staining, and the matrix appears to contain basement membrane components indistinguishable from normal skin *(Sinclair et al., 1994)*.

Nail bed:

The nail bed begins where the distal matrix or lunula ends, it extends to the hyponychium near the end of the finger, where the free edge of the nail separates. Like the matrix, the nail bed epithelium cornifies without a granular layer. However, unlike the matrix the

nail bed consists of a thin epithelium that lies beneath the nail plate, and it is less active and has a longer turn over time than either the matrix or the skin. There fore, histological differentiation between the metrical epithelium and that of the nail bed is a simple matter. The cornified layer of the nail bed is scant, and few cornified cells are added to the underside of the already formed nail plate. The transition zone from living keratinocytes to dead ventral nail plate cells is abrupt and is very similar to what occurs in the Henle layer of the internal root sheath of the formative hair shaft *(Melody et al., 2000)*.

The nail bed is firmly attached to the underlying dermis by a unique longitudinal, tongue-in-groove spatial arrangement of dermal papillae and epidermal ridges. These ridges are almost parallel to one another and are readily demonstrated after avulsion of the nail plate or in transverse histological sections. Fine capillaries traverse the parallel dermal ridges, and disruption results in the splinter hemorrhages commonly seen in normal and disease states *(Zaias, 1990)*.

The nail bed dermal collagen is mainly oriented vertically, being directly attached to the phalangeal periosteum and the epidermal basal lamina. Within the connective tissue network lie blood vessels, lymphatics, a fine network of elastic fibers and scattered fat cells; at the distal margin, eccrine sweat glands have been seen *(de Berker et al., 2004)*.

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Nail plate:

Microscopically, the nail plate consists of closely packed cornified cells that lack nuclei and organelles. The onychocytes of the dorsal nail plate are normally irregular, polyhedral, and unucleated. There are many intercellular links between cells, including tight, intermediate, and desmosomal junctions. The cells on the surface of the nail plate overlap, slanting from proximal-dorsal to distal-volar. As a result, the dorsal aspect of the nail plate reveals a smooth surface while the palmer aspect is irregular, as seen by scanning electron microscopy. The lunula is composed of epithelial cells with flattened nuclei and eosinophilic cytoplasm with retained keratohyaline granules. This corresponds to the keratogenous zone of the nail matrix. These cells eventually lose their nuclei and from the nail plate cells, or onychocytes, which are devoid of keratohyaline granules *(Melody et al., 2000)*.

The nail plate contains significant amounts of phospholipids, which contribute to its flexibility. The detectable free fats and long-chain fatty acids may be of extrinsic origin. The nail plate is rich in calcium, found as the phosphate in hydroxyapatite crystals, it is pound to phospholipids intracellularly. The relevance of other metals (copper, manganese, zinc, iron and others), which are present in smaller amounts is not known. Calcium does not significantly contribute to the hardness of the nail *(de Barker et al., 2004)*. The hardness of the nail is caused by the high concentration of sulfur matrix protein *(Conejo, 1992)*.

Hyponychium:

The hyponychium is a narrow zone of epidermis between the nail bed and the distal nail groove beneath the free edge of the plate. The hyponychium cornifies with a granular layer and produces a thick, compact, cornified layer. The epithelium demonstrates marked acanthosis and papillomatosis with the crest orinted horizontally, an architecture that is similar to that seen in normal skin appendages. An important feature of this zone is the accumulation of cornified debris under the distal nail plate, which renders the nail bed impermeable to external insults. The hyponychium is the initial site of invasion by dermatophytes in the most common type of onychomycosis, distal subungual onychomycosis. The intermediate zone between the nail bed and hyponychium has been termed the onychodermal band. It varies in width from 0.5 to 1.5mm and has a paler color than the pink nail bed because it has a different blood supply than the remainder of the nail bed has *(Melody et al., 2000)*.

Nail keratin:

Nail keratine analysis shows essentially the same fractions as in hair:

1- Fibrillar, low-sulphur protein;

2- Globular, high-sulphur matrix protein;

3- High glycine-tyrosine-rich matrix protein.

Amino acid analysis shows higher cysteine, glutamic acid and serine and less tyrosin in nail compared with hair *(Westgate et al., 1997)*.

An alternative classification of keratins defines them as soft epithelial keratins or hard trichocyte keratins. The latter are characteristic of hair and nail differentation, where their high sulphur content is probably responsible for their rugged physical qualities. This is matched by the resistance of trichocyte keratins to dissolution in strong solven. Immunohistochemistry of the epithelial structures of normal nail demonstrates that the suprabasal keratin pair K_1/K_{10} is found in both aspects of the proximal nail fold and to a lesser degree in the matrix. However, it is absent from the nail bed. This is reversed when there is nail bed disease, such as onychomycosis or psoriasis, where a granular layer develops and K_1/K_{10} becomes expressed at corresponding sites. The nail bed contains keratin synthesized in normal basal layer epithelium, K_5/K_{14}, which is also found in nail matrix. Recent examination of the bed using monospecific monoclonal antibodies to the keratin pair K_6/K_{16} demonstrates these proteins in the nail bed but not the germinal matrix *(de Berker et al., 2004)*.

Nail morphology:

Several factors probably combine to produce a relatively flat nail plate: the orientation of the matrix rete ridges and papillae; moulding of the direction of nail growth between the proximal nail fold and distal phalanx containment laterally within the lateral nail folds assists this orientation, and adherent nature of the nail bed is likely to be important. In diseases such as psoriasis, the nail bed can loose its adherent properties, exhibiting onycholysis. In addition there may be subungual hyperkeratosis *(de Berker et al., 2004)*.

The predominant orientation of the longer axis of the plate (longitudinal or transverse) will determine the shape of the plate. This characteristic is influenced by the breadth of the matrix and the length of the bed *(Sonnex et al., 1986)*.

Nail growth:

Nails grow on the average at 0.1mm/day, although there is considerable variation between individuals. Finger nails grow faster than toe nails. Seasonal and moderate temperature variations do not have much effect. Declining growth rate with aging has been well documented. Serious systemic illness seems to slow or temporarily stop growth *(Howard, 1987)*.

Sex makes a small difference in early adulthood with men faster than women. This gradually diminishes with age till age of 69 where women's nails grow faster than men's *(Dawber et al., 1994)*.

DIABETES MELLITUS

Diabetes mellitus (DM) is a complex multisystemic disorder characterized by a relative or absolute insufficiency of insulin secretion and/or concomitant resistance to the metabolic action of insulin on target tissues. Hyperglycaemia is the immediate metabolic consequence of DM but, ultimately, there is widespread multisystem damage. In particular microvascular disease (microangiopathy) with capillary basement membrane thickening, macrovascular disease (macroangiopathy) with accelerated arteriosclerosis, neuropathy involving both the somatic and autonomic nervous system, neuromuscular dysfunction, embryopathy, and decreased resistance to infection *(Garber, 1998)*.

Classification and pathogenesis of diabetes mellitus:

The American Diabetes Association has recently developed a classification system based upon disease aetiology. The classification scheme includes two major forms of DM: type 1 (previously insulin dependent diabetes mellitus or IDDM) and type 2 (previously non-insulin-dependent diabetes mellitus or NIDDM). Type 1 disease includes a type A immune-mediated, and a type B idiopathic DM. Type 2 includes the most common form of diabetes, which combines insulin resistance with an insulin secretory defect. In addition to these types of DM there are other specific forms of disease such as diabetes secondary to autoimmune endocrinopathies, infection (e.g. congenital rubella, cytomegalovirus, coxsackie virus), genetic disease or DM induced by drugs or pregnancy. All types of DM are

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biochemically characterized by hyperglycaemia tested during an oral glucose tolerance test (OGTT). Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are used to indicate a metabolic stage intermediate between normal glucose homeostasis and DM, this stage includes individuals who have IGT and individuals with fasting glucose levels > or = 110mg/dl but < 126mg/dl. *(Manfredi et al., 2004).*

General signs and symptoms of diabetes mellitus:

The initial clinical features of type 1 DM include the typical triad of polyuria, polydypsia and polyphagia. Irritability, malaise, apathy and pruritus can also be early features of type 1 DM *(Teuscher et al., 1989).* Patients with undiagnosed type 1 DM are prone to ketoacidosis *(Bell and Hockaday, 1996).* The features of type 1 DM are reversible with effective insulin therapy. The features of type 2 DM are of slower onset and less specific than those in type 1, sometimes only being detected when patients are being investigated for disease unrelated to DM. Patients with type 2 disease are often obese and although the relevant biochemical defect is not profound, complications of long-standing DM still arise. Both type 1 and 2 of DM have equal risk of developing vascular complications *(Manfredi et al., 2004).*

Complications of diabetes mellitus:

While good glycaemic control can prevent or reduce the likelihood of the possible complications of DM, approximately 50% of patients with DM develop vascular chronic complications following years of DM *(Rees, 1994).*

The eyes and kidneys are particularly liable to disease. Diabetic retinopathy is one of the most common causes of loss of vision in the USA *(Little et al., 1997)*. Proliferative retinopathy is particularly problematic and is more common in type 1 than type 2 DM. Cataract occurs at an earlier age and with a higher frequency in patients with DM than those without DM *(Kannel and McGee, 1979)*.

Progressive renal disease can arise in 30-40% of patients with DM, especially those with type 1 disease. The majority of these patients will develop end-stage renal disease and require haemodialysis or combined renal-pancreas transplantation *(Manfredi et al., 2004)*.

Accelerated arteriosclerosis, with resultant cerebrovascular, cardiovascular and other vascular disease occurs in long-standing DM. Myopathy can produce progressive weakness and exercise intolerance. Peripheral neuropathies cause paraesthesia and anaesthesia, reduced motor function, while autonomic neuropathy can cause orthostatic hypotension *(Bell and Hockaday, 1996)* and may reduce salivary flow rate *(Marchetti et al., 1989)*. Recently, it has been reported that peripheral diabetic neuropathy may be a risk factor for severe temporomandibular joint dysfunction *(Collin et al., 2000)*.

Type 1 diabetes mellitus:

Type 1 DM immune-mediated (A) (previously termed juvenile-type onset diabetes or insulin dependent) constitutes 5-15% of all cases of diabetes. Although having a worldwide distribution, this condition affects North Americans and Europeans more frequently than other ethnic groups. This type of DM is due to cell-mediated autoimmune destruction of the [beta]- cells of the islet of Langerhans of the pancreas leading to a complete inability of the cells to secrete insulin *(Atkinson and Maclaren, 1994)*.

Recently, the [beta]-cell damage has been suggested to be due to islet cell autoantibodies (ICAs), autoantibodies to insulin (IAAs), autoantibodies to glutamic acid decarboxylase (GADA65) and autoantibodies to the tyrosine phosphatase IA-2. Individuals (85-90%) with initial hyperglycaemia have one or more of these autoantibodies, which can be considered as markers of this type of DM. It has been reported that genes for type 1 DM can provide both susceptibility and protection in relation to the disease *(Bingley et al., 2001)*.

Type 1 DM usually develops before 30 years of age, although can occur at any age. It is suggested that pancreatic destruction occurs when genetically predisposed individuals are subjected to a triggering event, such as viral infection, that induces the destructive autoimmune response *(Rees, 1994)*.

The rate of [beta]- cell destruction is variable being rapid in some individuals (usually infants and children) and slow in others

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(typically adults). There are two age-associated peaks of incidence most commonly in the middle of the first decade, and in adolescence *(Zimmet et al., 1994)*.

The idiopathic form of type 1 DM (B) is of unknown aetiology. Most affected patients have a permanent insulinopenia and are prone to ketoacidosis. A minority of patients with type B disease, most of whom are Asian or African, suffer episodic ketoacidosis and have varying degrees of insulin deficiency between these episodes. This form of diabetes is strongly inherited, but lacks immunological evidence for [beta]-cell autoimmunity and it is not human leucocyte antigen associated *(Banerji and Lebovitz, 1989)*.

Type 2 diabetes mellitus:

Type 2 DM previously termed NIDDM, often arises in middle to late life and is the more common form of DM, representing between 80 and 93% of all affected patients *(Manfredi et al., 2004)*. Type 2 DM is characterized by a [beta]-cells dysfunction to secrete adequate amounts of insulin, particularly after meals, and/or peripheral insulin resistance. Patients with type 2 DM have some endogenous insulin secretory capability, but have overt abnormalities of glucose homeostasis, including fasting hyperglycaemia *(Garber,1998)*. Depending upon the degree of accompanying hyperglycaemia, patients with type 2 DM are managed by dietary control of sugars and/or with oral hypoglycaemic agents, although sometime insulin therapy becomes necessary if their disease can not be managed adequately with oral agents and diet *(Manfredi et al., 2004)*.

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Type 2 DM frequently remains undiagnosed for many years as in the early stages of disease the hyperglycaemia develops gradually and is often not severe enough to give rise to polyuria, polydypsia nor weight loss *(Fujimoto et al., 1987).*

Unlike patients with type 1 disease, those with type 2 DM are relatively resistant to the development of ketoacidosis, as a consequence of the retention of endogenous insulin secretion. Type 2 DM often has a familial basis, although does not clinically manifest until middle to late life. As a consequence of an accompanying insulin resistance, obesity is a major risk factor for the development of this type of DM, indeed up to 80% of patients with type 2 DM have mild to marked overweight *(Harris et al., 1995).* Women with prior gestational diabetes mellitus (GDM) may also be liable to type 2 DM as can individuals with hypertension or hyperlipidaemia *(Newman et al., 1987).*

Diagnostic criteria for diabetes mellitus:

The diagnostic criteria for DM as recommended by National Diabetes Data Group or World Health Organization have been recently modified by an Expert Committee. The primary methods to diagnose DM and monitor blood glucose levels have traditionally been fasting blood glucose, ($\geq$ 7mmol/L or 126mg/dl) a combination of fasting blood glucose plus a 2h test after glucose loading (2h postprandial), ($\geq$ 11.1mmol/L or 200mg/dl) during an OGTTs. The revised criteria suggest the diagnosis of DM by one of three methods, each requiring confirmation by repeat testing *(Manfredi et al., 2004).*

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Assessment of glycaemic control in patients affected by diabetes mellitus:

According to *Manfredi et al., (2004)*, different methodologies are available to assess glycaemic control, these depending exactly upon the severity of the disease and the clinical setting:-

Blood glucose monitoring: Levels of blood glucose can be self-monitored by patients, using blood glucose test strips. This approach allows ketoacidosis to be avoided and encourages good compliance with dietary sugar intake.

Glycosylated haemoglobin: The estimation of blood level of glycosylated haemoglobin (HbA1) provides an accurate and objective measure of glycaemic control over past weeks to months. Several minor components of adult haemoglobin (HbA1) can be separated from unmodified haemoglobin (HbA0) by ion-exchange chromatography, and these haemoglobin moieties are increased in DM by the slow non-enzymatic covalent attachment of glucose and other sugars (glycation). The rate of formation of this glycosylated haemoglobin is directly proportional to these ambient blood glucose concentrations.

Glycosylated haemoglobin is expressed as a percentage of the normal haemoglobin. Non-diabetic subjects have HbA1c values of less than 6%, while levels in poorly controlled patients may reach 10-12%, and can be as great as 20%.

Glycosylated haemoglobin estimates may be incorrectly reduced with anaemia or during pregnancy, and some assay methods

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are complicated by uraemia or haemoglobinopathy. In clinical practice glycosylated haemoglobin is usually measured periodically (at least twice yearly) to assess glycaemic control, permit appropriate changes to treatment and to determine the degree of inconsistency with a patient's records of home blood glucose monitoring.

Plasma fructosamine: in situations where the HbA1c cannot be measured (e.g. haemolytic anaemias), glycated serum protein (GSP) may also be measured by means of the fructosamine assay as an index of glucose control. A single measurement of GSP provides an index of glycaemic status over the preceding 1-2 weeks, while a single HbA1c test provides an index of glycaemic status over a considerably longer period of time, 2-3 months. Other than in diabetic pregnancy, this is generally too short a time period to allow appropriate clinical decisions of therapy to be made.

Urine testing: Testing of urine for glucose has been used a method of diabetic monitoring for over 50 years. However, the introduction of new and more efficient methods of blood glucose has permitted much closer good glycaemic control. Negative urine tests fail to distinguish between normal and low blood glucose levels, which is a particular disadvantage since the aim of treatment is to obtain normal blood glucose level avoiding hypoglycaemia. Urine tests are routinely performed to monitor the levels of urinary proteins and ketones to confirm prior diagnosis of renal-insufficiency in patients with DM. However, long-term follow-up studies suggested that raised urinary albumin secretion is a predictive parameter for overt diabetic nephropathy in DM patients, particularly in type 1

DM. It has been reported that achievement of a satisfactory metabolic control, in the early stage renal dysfunction, reduces or normalizes the increased glomerular capillary permeability to albumin, which is the cause of the so-called microalbuminuria.

Management of diabetes mellitus:

The aims of management of DM are to maintain a normal blood glucose levels without episodes of hypoglycaemia, and to prevent or lessen, the complications of long-standing disease. These aims cannot be achieved without good patient compliance. Type 2 DM can usually be managed with control of dietary carbohydrates, control of body weight and increased physical activity. If this fails to adequately reduce blood glucose levels, oral hypoglycaemic agents are required in addition to diet control *(Little et al., 1997)*.

Oral hypoglycaemic agents and insulin: The drugs commonly used to manage DM are sulphonylureas and biguanides. In particular, sulphonylureas stimulate the secreation of insulin, increase the number of insulin receptors if there is some endogenous insulin production. Metformin is the only available biguanide. This drug acts mainly by decreasing hepatic gluconeogenesis and increasing peripheral utilization of glucose. Metformin is the drug of first choice in grossly obese patients in whom diet has failed to control the DM. The use of metformin is contraindicated in patients with renal-insufficiency (i.e. a serum creatinine concentration exceeds 1.4mg dl in women or 1.5mg dI in men, or abnormal creatinine clearance), acute or chronic metabolic acidosis or in patients with severe hepatic dysfunction. In these patients, metformin

use may contribute to the development of lactic acidosis *(Scheen, 1997)*.

A number of other agents are available to manage DM. [alpha]- glucosidase inhibitors, such as acarobose and miglitol delay the digestion and absorption of complex carbohydrates, and although these agents do not increase the response to insulin in any tissue, their ability to limit postprandial glucose increase can reduce the need for insulin supplements. These drugs are generally safe, but they often cause flatulence, especially when the dosage is increased rapidly *(Manfredi et al., 2004)*.

Repaglinide is a benzoic acid derivative and the first of the non-sulphonylurea meglitinides introduced in 1998. the mechanism of action of this drug is similar to those of the sulphonylureas. Repaglinide is the most rapid and short-acting agent and reduces fasting hyperglycaemia. It is a suitable option for patients with a recent diagnosis of type 2 DM who have high postprandial glucose levels. All types of oral hypoglycaemic agents should be used carefully in elderly patients and in those with renal or hepatic dysfunction *(Riddle, 1999)*.

Pioglitazone, rosiglitazone and troglitazone belong to a new class of oral glucose- lowering drugs (thiazolidinediones) that enhance the response of muscle and adipose tissue to insulin in patients who are otherwise relatively unresponsive, for example the extremely obese. However, troglitazone was withdrawn from the USA in March 2000, following 61 deaths from hepatic failure and

seven liver transplants associated with the drug. This has also been withdrawn in Europe *(Krentz et al., 2000)*.

The newer antidiabetic drugs are usually prescribed in combination with sulphonylureas and biguanides, when the older agents prove inadequate in reducing the high blood glucose levels *(Manfredi et al., 2004)*.

Insulin therapy is required for type 1 DM, and for patients with long-standing type 2 DM when there is a failure of other therapies. Insulin is administered by subcutaneous injection and is available as short-acting, intermediate-acting and long-acting forms *(Mealey, 1998)*. Mixed insulin preparations are also available. Management typically involves a combination of short-acting and intermediate-acting insulin. Continuous subcutaneous insulin infusions or 'insulin pumps' are now available. These deliver a basal dosage of insulin to maintain glucose control without hypoglycaemia *(Varon and Mack-Shipman, 2000)*.

Insulin is available in three different types: human (produced synthetically or by DNA recombinant technology using *Escherichia coli)*, porcine and bovine. Human insulin has a more rapid onset and shorter duration of action than porcine insulin, while bovine insulin has the longest duration of activity, although the non- human forms are now rarely employed *(Mealey, 1998)*.

The absorption of insulin from subcutaneous sites is variable both within and between individuals. Most patients with type 1 DM require three to four injections of insulin daily, but it is clearly necessary to individualize therapy and even then the same dose of

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insulin may have quite different effects on different days in the same patient *(Bell and Hockaday, 1996)*. The main aim of insulin therapy is to reproduce the natural peak levels of insulin during and after meals with basal concentration postprandially *(Garber, 1998)*. The pharmacokinetics of insulin make this difficult and hypoglycaemia is the most common complication of inadequate management *(Bell and Hockaday, 1996)*.

Hypoglycaemia (blood sugar < 60mg dI^{-1}) may give rise to a variety of clinical features that include reactions: irritability, tachycardia, palpitations, confusion and possibly coma *(Varon and Mack-Shipman, 2000)*.

FUNGI

There are more than 50.000 species of fungi, but most are beneficial to human kind. They reside in nature and are essential in breaking down and recycling organic matter. Some fungi greatly enhance our quality of life by contributing to the production of food and spirits. Other fungi have served medicine by providing useful bioactive secondary metabolites such as antibiotics (e.g. penicillin) and immunosuppressive drugs (e.g., cyclosporine) *(Thomas, 2004)*.

Although fungi were once believed to be descended from plants, it was recognized over 20 years ago that they represented a distinct kingdom, and that certain features of their biochemistry were quite different from those found in bacteria and plants. All fungi are heterotrophic and must exist as saprophytes or parasites, fortunately, the vast majority exist purely as saprophytes or plant parasites *(Hay & Moore, 1998)*, while only few hundred species of fungi have been implicated in human disease *(Thomas, 2004)*.

Members of the kingdom fungi show all the typical eukaryotic features, such as the organization of genetic material into chromosomes enclosed within a membrane bound nucleus, mitochondria and ribosomes. Unlike animal cells, their cells are enclosed by a rigid cell wall containing varying amounts of chitin, a polymer of N-acetyl glucosamine, and B-glucans. The wall also contains mannans, glycoproteins and enzymes, some of which are secreted into the surrounding environment and break down complex organic compounds prior to their absorption.

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Fungi have an absorptive mode of nutrition. Within the cell wall, the cytoplasm is bounded by a plasma membrane in which the predominant sterol is not cholesterol, as in humans, but ergosterol *(Hay & Moore, 1998)*.

Fungi grow in two basic forms, as yeasts and molds. The thallus (body) of a mold consists of long filaments of cells joined together, these filaments are called hyphae varying in diameter from $2\mu m$ to $10\mu m$. In most molds, the hyphae contain cross walls called septa which divide them into distinct, uninucleated cell like units. These hyphae are called septate hyphae. In a few classes of fungi, the hyphae contain no septa and appear as long continuous cells with many nuclei. These are called coenocytic hyphae. Hyphae grow by elongations at the tips. Each part of a hypha is capable of growth, and when a fragment breaks off, it can elongate to form a new hypha. The portion of a hypha that obtains nutrients is called the vegetative hypha; the portion concerned with reproduction is the reproductive or aerial hypha, so named because it projects above the surface of the medium on which the fungus is growing, *(Tortora et al., 2004)*.

Under standardized growth conditions in the laboratory, molds produce colonies with characteristic features such as rates of growth, texture and pigmentation. The genus, if not the species, of most clinical molds isolated can be determined by microscopic examination of the ontogeny and morphology of their asexual reproductive spores *(Brooks et al., 2004)*. When environmental conditions are suitable, the hyphae grow to form a filamentous mass

called mycelium, which is visible to the unaided eye *(Tortora et al., 2004)*.

Yeasts are single cells, usually spherical to ellipsoid in shape and varying in diameter from 3μm to 15μm. Most yeasts reproduce by budding, some species produce buds that characteristically fail to detach and become elongated, continuation of the budding process then produces a chain of elongated yeast cells called pseudohyphae. Yeast colonies are soft, opaque, 1-3mm in size, and cream-colored. Because the colonies and microscopic morphology of many yeasts are quite similar, yeast species are identified on the basis of physiologic tests and a few key morphologic differences *(Thomas, 2004)*.

Some fungi exhibit dimorphism (two forms of growth). Such fungi can grow either as a mold or as a yeast. The mold-like form produce vegetative and aerial hyphae; the yeast like forms reproduce by budding. Dimorphism in pathogenic fungi is temperature dependent: At 37°C, the fungus is yeast like, and at 25°C, it is mold like *(Tortora et al., 2004)*.

In addition to their vegetative growth as yeasts or molds, fungi can produce spores to enhance their survival. Spores are more resistant to adverse conditions and can germinate when conditions for growth are favorable. Spores can be derived from sexual or asexual reproduction *(Thomas, 2004)*. The sexual phase is termed the teleomorph and the asexual phase is termed the anomorph, when both are present the growth is termed the holomorph *(Hay & Moore, 1998)*.

Asexual spores are formed by the hyphae of one organism. When these spores germinate, they become organisms that are genetically identical to the parent. Sexual spores result from the fusion of nuclei from two opposite mating strains of the same species of fungus. Fungi produce sexual spores less frequently than asexual spores. Several types of asexual spores are produced by fungi, including: conidiospore (unicellular or multicellular spore that is not enclosed in a sac), chlamydospore (thick walled spore that formed by roundening and enlargement within a hyphal segment), sporangiospore (spore formed within a sac at the end of an aerial hypha). In laboratory settings, most fungi exhibit only asexual spores, consequently clinical identification is based on microscopic examination of asexual spores *(Tortora et al., 2004)*.

On the other hand, according to *Brooks et al., (2004),* the classification of fungi is based on the spores that result from sexual reproduction. Accordingly, the major groups are:

A. **Zygomycetes:** Sexual reproduction results in a zyygspore, asexual reproduction occurs via sporangia, vegetative hyphae are sparsely septate. Examples: Rhizopus.

B. **Ascomycetes:** Sexual reproduction involves a sac or ascus in which karyogamy and meiosis occurs, producing ascospores. Asexual reproduction is via conidia, molds have septate hyphae. Examples: Ajellomyces (anamorphic genera, blastomyces histoplasma), Arthroderma (anamorphic genera, Microsporum,

Trichophyton), and yeast genera such as Saccharomyces.

C. **Basidiomycetes:** Sexual reproduction results in four progeny basidiospores supported by a club shaped basidium. Hyphae have complex septa. Examples: Muschrooms, Filobasidiella nefomans (anamorph, Cryptococcus neoformans).

D. **Deuteromycetes:** This is an artificial grouping of the imperfect fungi for which a teleomorph or sexual reproduction has not been discovered. The anamorphic state is characterized by asexual condia. Examples: Coccidioides immitis, Candida albicans.

All fungi have an essential rigid cell wall that determines their shape. Cell walls are composed largely of carbohydrate layers, long chains of polysaccharides, as well as glycoproteins and lipids. During infection, fungal cell walls have important pathobiologic properties. The surface components of the cell wall mediate attachment of the fungus to host cells. Cell wall polysaccharides may activate the complement cascade and provoke an inflammatory reaction; they are poorly degraded by the host and can be detected with special stains. Cell walls release immunodominant antigens that may elicit cellular immune responses and diagnostic antibodies. Some yeasts and molds have melanized cell walls, imparting a brown or black pigment. Such fungi are dematiaceous. In several studies, melanin has been associated with virulence *(Thomas, 2004)*.

Growth and isolation of fungi:

Most fungi occur in nature and grow readily on simple sources of nitrogen and carbohydrate. Traditionally, Sabouraud's agar, which contains glucose and modified peptone (PH 7.0), has been used because it does not readily support the growth of bacteria.The morphologic characteristics of fungi used for identification from the growth on Sobouraud's agar. However, other media, such as inhibitory mold agar, have facilitated the recovery of fungi from clinical specimens. To culture medical fungi from nonsterile specimens, antibacterial antibiotics (e.g chloramphenicol) and cyclohexamide are added to the media to inhibit bacteria and saprophytic molds, respectively *(Brooks et al., 2004)*.

Fungal diseases:

Any fungal infection is called a mycosis. Mycoses are classified according to the degree of tissue involvement and mode of entry into the host into systemic, subcutaneous, cutaneous and superficial *(Tortora et al., 2004)*.

According to *Hay & Moore (1998),* the superficial mycosis are fungal infections of hairs, skin and nails that generally do not provoke a significant histopathological inflammatory response in the host, such as: pityriasis versicolor, tinea nigra, and black and white piedra.While the cutaneous mycoses, are fungal infections of hairs, skin and nails where, although the fungus is localized to the non-living layers of the stratum corneum, pathological changes do occur in the host tissue. The cutaneous infections include dermatophytosis, candidosis and a range of non dermatophyte infections of the skin

and nails, such as dermatomycoses caused by Scytalidium species and onychomycosis caused by other non- dermatophyte molds:

Dermatophytosis:

Dermatophytosis are infections of keratinized tissue caused by organisms of three genera of fungi known as the dermatophytes. The dermatophytes represent more than 40 closely related species classified in three genera: Microsporum, Trichophyton, and Epidermophyton *(Wagner & Sohnle, 1995)*.

It has been traditional for clinical and epidemiological reasons to group dermatophytes that infect humans according to their ecological niche: geophilic species originating in soil, zoophilic species having animal origins and anthropophilic species, which are largely restricted to human skin *(Martin &Kobayashi, 1999)*.

Geophilic organisms sporadically infect humans; when they do, the resulting disease is usually inflammatory. M. gypseum is the most common geophile isolate in human infections *(Greer, 1994)*.

Zoophilic species may be transmitted to human through direct contact with specific animal species or indirectly by infected animal hair carried on clothing or present in contaminated stalls, barns or feed. Although human infections with zoophiles are often suppurative, animal infection may be clinically silent *(Aly, 1994)*. Zoophilic species (and their natural hosts) include Microsporum canis (dogs and cats), Microsporum gallinate (Fowl), Microsporum nanum (pigs), Trichophyton equinum (horses), and Trichophyton verrucosum (cattle) *(Thomas, 2004)*.

Anthropophilic species have adapted to infect humans. They are transmitted from person to person either by direct contact or indirectly through fomites. Host differences and intercurrent diseases play a role in the epidemiology of anthropophilic infections, dermatophytosis may be severe or recalcitrant to therapy in patients with diabetes mellitus, immunologic compromise or Cushing's syndrome *(Odom, 1993)*.

Some anthropophilic species are geographically restricted, but others, such as Epidermophyton floccosum, Trichophyton mentagrophytes var interdigitale, T. rubrum, and T. tonsurans, are globally distributed *(Thomas, 2004)*.

Age, sex and race differences define populations at risk for these infections. For example, tinea capitis due to anthropophilic organisms is more common in African-American children, when it occurs in adults it is far more common in women. In contrast, tinea pedis, tinea unguium and tinea cruris are more common in adults, with the latter occurring predominantly in males. Certain strains of dermatohytes are endemic to specific geographic areas. Because of patterns of travel to and from these areas, resident dermatophytes may remain restricted geographically or become more cosmopolitan *(Aly, 1994)*.

The location of the dermatophytosis is partially dependent on climatic conditions of the area and the customs of the resident population. Tinea pedis for example, is more common in areas where occlusive footwear is used. In extremely hot humid climates, tinea corporis may occur readily under occlusive garments. There is some

evidence to suggest that certain human populations may be genetically more susceptible to particular dermatophyte infection *(Odom, 1993)*.

In addition to host and geographic factors, the virulence of the infecting organism must be considered. T. mentagrophytes var. mentagrophytes is a zoophilic organism that produces a marked inflammatory infection in the human host, whereas the variant interdigitale does not *(Martin & Kobayashi, 1999)*.

Pathogenesis:

The presence of a suitable environment on host skin is of critical importance in the development of clinical dermatophytosis. In addition to trauma, increased hydration of the skin with maceration is important. Occlusion with a non porous material increases the temperature and hydration of the skin and interferes with the barrier function of the stratum corneum *(Wagner& Sohnle, 1995)*.

If the host skin is inoculated under suitable conditions, there follow several stages through which the dermatophyte infections progress, including periods of incubation, enlargement followed by a refractory period, and a stage of involution. During the incubation period, a dermatophyte grows in the stratum corneum, sometimes with minimal clinical signs of infection. A carrier state has been postulated when the presence of a dermatophyte is detected on seemingly normal skin by KOH examination or culture *(Martin & Kobayashi, 1999)*.

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Once infection is established in the stratum corneum, two factors are important in determining the size and duration of the lesion: (1) The rate of growth of the organism, and (2) The epidermal turnover rate. The fungal growth rate must equal or exceed the epidermal turnover rate or the organism will be shed quickly *(Odom, 1993)*.

Keratinases and other proteolytic enzymes are produced by dermatophytes. The role of these enzymes in the pathogenesis of clinical infection relates to skin colonization and invasion as well as organism virulence. Host immunologic response and also enzymes or toxins produced by the organism account for the clinical findings in dermatophytoses *(Dahl, 1994)*.

Immunology:

Resistance to dermatophyte infections may involve nonimmunologic as well as immunologic mechanisms *(Dahl, 1987)*. From the increase in saturated fatty acids on the skin that occurs after puberty to the presence of a serum inhibitory factor (SIF) that appears to limit the growth of dermatophytes. Unsaturated transferrin is a likely SIF candidate, because it binds the iron that dermatophytes need for continued growth. An $alpha_2$- macroglobulin keratinase inhibitor has also been identified in serum and may modify the growth of the organisms *(Martin & Kobayashi, 1999)*.

The humoral limb of the immune system has a minor role in the development of acquired resistance to dermatophyte infections. While the major immunologic defense mechanism is the type IV delayed- hypersensitivity response *(Dahl, 1994)*.

Dermatophytid reactions are secondary inflammatory reactions of the skin at a site distant from the associated fungal infection, occurring in 4 to 5 percent of patients. In contrast to material obtained from the dermatophytosis, cultures and KOH examinations of the "id" lesions are negative. The mechanism responsible for the id response is unknown but may involve a local immunologic response to systemically absorbed fungal antigen. Disappearance of the dermatophytid reaction occurs when the dermatophyte infection is successfully treated *(Martin & Kobayashi, 1999)*.

Clinical findings:

Dermatophyte infections were termed ring warm because of the raised circular lesions. The clinical forms are based on the site of involvement as follows:

- *Tinea corporis (dermatophytosis of the glabrous skin),*
- *Tinea capitis (dermatophytosis of the scalp),*
- *Tinea barbae (dermatophytosis of the beard),*
- *Tinea faciei (dermatophytosis of the face),*
- *Tinea pedis (dermatophytosis of the foot),*
- *Tinea mnuum (dermatophytosis the hand),*
- *Tinea cruris (dermatophytosis of the groins),*
- *Tinea unguium (dermatophytosis of the nails) (Hay & Moore, 1998).*

Wood's Light:

Only some dermatophytes capable of invading hair will induce

fluorescence with a Wood's light, these include members of the genus microsporum, for example M. audouinii and M. canis. Hairs infected by these species produce a brilliant green fluorescence *(Hay & Moore, 1998)*.

Laboratory diagnosis:

Specimens:

Specimens consist of scrapings from both the skin and the nails plus hairs plucked from involved areas *(Thomas, 2004)*.

Microscopic examination:

specimens are placed on a slide in a drop of 10-20% potassium hydroxide, with or without calcoflour white, which is a nonspecific fungal cell wall stain viewed with a flourescent microscope. A cover slip is added, and the specimen is examined immediately and again after 20 minutes. In skin or nails regardless of the infecting species a branching hyphae or chains of arthroconidia (arthrospores) are seen. In hairs, most microsporum species form dense sheaths of spores around the hair (ectothrix). T. tonsurans and T. violaceum are noted for producing arthroconidia inside the hair shaft (endothrix) *(Thomas, 2004)*.

Culture:

Culture is a definitive diagnostic measure for dermatophyte infections. Specimens must be cultured on media suitable for growth of these fungi. Sabouraud's dextrose agar is the most commonly used medium in medical mycology. Specimens are inoculated onto Sabouraud's agar slants containing cyclohexamide and

chloramphenicol to suppress mold and bacterial growth respectively, incubated for up to 4 weeks before they are discarded as showing no growth *(Martin & Kobayashi, 1999)*.

Species are identified on the basis of colonial morphology (growth rate, surface texture, and any pigmentation), microscopic morphology (macroconidia, microconidia), and in some cases, nutritional requirements or other tests such as growth at 37°C, as, with the exception of T. verrucosum, dermatophytes grow poorly at 37°C *(Hay & Moore, 1998)*.

The out standing features of the commonest dermatophytes are described by *Thomas (2004)* as follows:

The typical colony of T.rubrum has a white, cottony surface and a deep red, non diffusible pigment when viewed from reverse side of the colony. The microconidia are small and piriform.

T. mentagrophytes colonies may be cottony to granular, both types display abundant grape-like clusters of spherical microconidia on terminal branches. Coiled or spiral hyphae are commonly found in primary isolates, and macroconidia may be seen.

Epidermophyton floccosum colonies are usually flat and velvety with a tan to olive-green tinge. It produces only macroconidia, which are smooth-walled, clavate, 2 – to 4 – called and formed in groups of two or three.

T. tonsurans produces a flat powdery to velvety colony on the obverse surface that becomes reddish brown on reverse. The microconidia are mostly elongated.

T. violaceum colonies are slowly growing creased and swollen with intense diffusible violet color. Rarely some strains from the tropics remain white and unpigmented. Microscopically, conidia are absent but chlamydospores are numerous.

T. verrucosum growth is slow and cannot be observed well for at least 3 weeks. The colony is compact, glassy, velvety, heaped or furrowed, and usually white, but may be yellow or gray. Chlamydospores are present in early cultures, and microconidia may be seen.

Candidiasis:

Candidiasis or (candidosis) is an infection with clinical manifestations caused by candida albicans or, on occasion, by other yeasts of genus Candida. These are members of the normal flora of the skin, mucous membranes and gastrointestinal tract *(Thomas, 2004)*.

C. albicans is the most common cause of superficial and systemic candidiasis being the causative agent in 85 to 90 percent of yeast infection. Other species classified in this genus can also be responsible for clinical disease under certain circumstances (e.g. host immunosuppression, indwelling catheters, intravenous drug

delivery), the most common of these agents (in descending degree of pathogenicity): C. stellatoidea, C. tropicalis, C. parapsilosis, C. kefyr, C. guilliermondii and C. krusei *(Martin & Kobayashi, 1999)*. The development of disease due to Candida species is dependent on the complex interaction between the innate pathogenicity of the organism and the defense mechanisms in the host. Important factors in the initiation of candidal infections include differences in virulence among the species of Candida, adherence of the organism to epithelial cells and subsequent invasion by elaboration of keratinolytic enzymes, phospholipases, or strain specific proteolytic enzymes *(Dupont, 1995)*.

Multiple host factors predispose to candidal infectious including local occlusion, moisture and or maceration, trauma, nutritional factors (e.g. avitaminosis, iron deficiency, malnutrition), physiologic alterations (e.g. extreme of age, pregnancy), systemic illnesses (e.g. diabetes mellitus, malignancy, immunodeficiency states, AIDS), iatrogenic causes (e.g. immunosuppressive agents, broad spectrum antibiotics, oral contraceptives) *(Martin & Kobayashi, 1999)*.

The mechanisms of host defense during candidal infections include non immune and immune factors. The non immune factors include: (1) interaction with other members of the microbial flora,

(2) The functional integrity of the stratum corneum, (3) The desquamation process induced by inflammation induced epidermal proliferation, (4) Opsonization and phagocytosis. The host microbial flora are protective in that they compete with Candida for nutrients

and epithelial adherence sites, and produce by- products toxic to the yeast. Like wise, normal intact skin with its constant sloughing and regeneration, provides an effective barrier against Candida. Skin surface lipids are partially inhibitory as well *(Odds, 1994)*.

Some serum factors may be important in defense mechanisms against candidal infections include controversial serum "clumping" factor. Transferrin and lactoferrin may inhibit candidal proliferation by binding iron necessary for fungal growth *(Boxer, 1982)*.

The immune mechanisms responsible for protection against candida infections include both humoral and cell-mediated responses. The latter are considered to be more important. Proof for this comes form experience with chronic mucocutaneous candidiasis and human immunodeficiency virus (HIV) infection, where a defect in cell-mediated immunity leads to extensive superficial candidiasis despite normal or even exagerated humoral defenses *(Dupont, 1995)*.

Clinical manifestations:

The cutaneous and mucosal manifestations of candidiasis are varied but characteristic in most cases and include:

Oral candidiasis, vaginal and vulvovaginal candidiasis, balanitis or balanoposthitis, cutaneous candidiasis and chronic mucocutaneous candidiasis *(Zegrelli, 1993)*.

Laboratory diagnosis:

In superficial candidal infections the diagnosis can be made by performing an examination of skin scrapings and observing typical budding yeasts with hyphae or pseudohyphae *(Martin & Kobayashi, 1999)*.

Candida albicans grows readily on bacterial media, but Saboraud's agar with added antibiotics is usually recommended for isolation *(Anaissie & Pinczowski, 1993)*.

Candida cultures are incubated at room temperature and examined periodically for growth of yeast. Whitish mucoid colonies grow within 2-5 days. On Gram stain the yeast shows dense, gram-positive, ovoid bodies. Two simple morphologic tests distinguish C. albicans, the most common pathogen, from other species of Candida: after incubation in serum for abort 90 minutes at 37°C yeast cells of C. albicans will begin to form true hyphae or germ tubes, and on nutritionally deficient media, C. albicans form large chlamydospores. Sugar fermentation and assimilation tests can be used to confirm the identification and speciate the more common candida isolates such as C. tropicalis, C. parapsilosis, C. guilliermondii, C. kefyr, C. krusei and C. lusitaniae. C. glabrata is unique among these pathogens because it produces only yeast cells and no pseudohyphal forms *(Thomas, 2004)*.

On histopathologic examination, superficial candidiasis is characterized by subcorneal pustules. Organisms are seldom seen within the pustule, but can be visualized with the aid of a periodic

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acid-schiff (PAS) stain in the stratum corneum. The pathology of candidal granuloma shows marked papillomatosis, hyperkeratosis, and a dense dermal infiltrate consisting of lymphocytes, granulocytes, plasma cells, and multinucleated giant cells. In systemic candidal infection with skin involvement, biopsies show focal areas within the dermis and within blood vessels, where organisms can be identified using PAS or methenamine silver stains. There may be a surrounding mononuclear cell infiltrate, leukocytoclastic vasculitis, or micro abscesses formation *(Martin & Kobayashi, 1999)*.

Serologic studies using immunodiffusion, counter immunoelectrophoresis, and latex agglutination methods may be some what helpful in the diagnosis of systemic candidiasis *(Penn, 1983)*.

Scytalidium species:

Scytalidium dimidiatum, previously known as Hendersonula toruloidea, is a weak secondary pathogen of higher plants, found mainly in tropical areas, but also in the USA and the Mediterranean region. This grey to black mold is now recognized as the cause of ring worm-like infections of the palms, soles, toe webs and nails *(Greer & Gutierrez, 1987)*.

S. hyalinium, a similar but non-pigmented organism, can also mimic tinea pedis and manuum and invade the nail plate *(Hay & Moore, 1998)*.

Laboratory diagnosis:

Although pigmented, brown hyphae have occasionally been observed in skin and samples infected by S. dimidiatum, in the vast majority of cases the hyphae are hyaline and appear very similar to those of dermatophytes. Typically, however, they are more irregular, varying noticeably in width along the length of a single hypha. Both S. dimidiatum and S. hyalinium are sensitive to cyclohexamide, and this antibiotic must be excluded from the culture medium (*Hay & Moore, 1998)*.

Other non-dermatophyte molds causing onychomycosis:

Dermatophytes are the principle cause of onychomycosis, however, non dermatophytic molds such as scytalidium, Scopulariopsis, Fusarium and Aspergillus species can also cause this disease. Yeasts notably Candida albicans, may also give rise to nail infection *(Elewski, 1998)*.

Until recently, the concept of onychomycosis caused by non-dermatophye molds has been remained controversial. Molds are often found in nail culture, but these have in the past been often dismissed as saprophytes of otherwise damaged nails. Techniques of molecular biology have however, produced new evidence that the non dermatophytes may be the cause of onychomycosis *(Sehgal & Jain, 2000)*.

Laboratory diagnosis:

Before the isolation of a non-dermatophyte mould can be considered significant, a second direct examination will allow any unusual features to be assessed. For instance, some moulds will take up Parker's stain, which immediately excludes the possibility of dermatophytes infection. Atypical morphology such as the presence of a large number of fronding hyphae or the production of characteristic conidia may be present, concurrent culture on medium free of cyclohexamide is also recommended. For example: *Aspergillus* species grow rapidly producing aerial hyphae that bear characteristic conidial structures in the form of long conidiophores with terminal vesicles on which phialides produce basipetal chains of conidia . *(Summerbell et al., 1989).*

ONYCHOMYCOSIS

Onychomycosis refers to involvement of the nail bed by fungal organisms with subsequent invasion of the undersurface of the nail plate and other locations within the nail unit *(Gupta et al., 1997)*.

Epidemiology:

Onychomycosis represents up to 50% of all nail disorders and 30% of all superficial fungal infections diagnosed *(Garg et al., 2004)*. Typically, 2-3% of the adult population are affected but, in some countries, this figure approaches 10% *(Baran and Kaoukhov, 2005)*. It is know to occur at any age, but is more common between 40 and 60 years of age and is unusual prior to puberty *(Garg et al., 2004)*.

Studies from United Kingdom, Spain, Finland and Canada reported the incidence of onychomycosis as 2.7% 2.6%, 8.4%, 6.85% respectively *(Ghannoum et al., 2000)*. However, it has been estimated that the incidence of onychomycosis in United States is 15% to 25% in those persons 40 to 60 years of age and the prevalence of onychomycosis is as many as 14-28% of > 60 years olds *(Gupta et al., 1997)*.

The increased incidence of onychomycosis in older age groups is explained by *Gupta (2000)* by the following reasons:

- Faster rate of outgrowth of the nail plate in children compared with adults.

- Smaller area of nail bed and nail plate available for attack by fungal organisms in children compared with adults.

- Reduced amount of micro- and macro- trauma in children at the hyponychium, in particular. Adults are more prone to wearing ill fitting shoes and taking part in sports and other activities that result in damage or breakage of physiological seal at the hyponychium.

- Older individuals may be more susceptible to eukaryotic pathogens because of changes in immune competence that occur with aging.

- The prevalence rate of tinea pedis is less in children than in older individuals.

- Children may be less likely exposed to frequent areas which may have a high density of fungal spores. The importance of this environmental factor is uncertain.

According to *Piraccini* and *Tosti (2004)* up to 30% of patients with HIV infection have onychomycosis. All varieties of onychomycosis are more frequent in HIV positive individuals than in controls and their frequency is related to the patients degree of immunosuppression. Onychomycosis is most likely to develop when the CD4 cell count drops to approximately 450 μL.

Toe nails are 4-10 times more frequently affected than finger nails, probably because of their slower growth and increased exposure to injury and infecting organisms *(Roberts, 1999)*.

Males are more commonly affected than females, study done by *Garg et al., (2004)*, showed that male, female ratio was 3:1. They suggested that the increased prevalence of onychomycosis in men is the result of more trauma to nails and the more common use of occlusive foot wear.

Aetiology:

The causal agents of onychomycosis include three groups of fungi, dermatophytes, nondermatophyte molds and yeasts *(Midgley and Moore, 1996)*.

Dermatophytes are the principle cause of onychomycosis, accounting for 90% of toenail infections *(Baran & Kaoukhov, 2005)*, and at least 50% of fingernail infections. Trichophyton rubrum and Trichophyton mentagrophytes var. interdigital are the dominant dermatophyte species involved *(Ellis et al., 1997)*. However, non dermatophytic molds such as Scytalidium, Acremonium, Fusarium spp. and Aspergillus spp. can also cause the disease. Yeasts notably Candida albicans, may also give rise to nail infection, although fingernails are more likely to be affected than toenails *(Elewski, 1998)*.

Until recently, the concept of onychomycosis caused by non-dermatophytes has remained controversial. Molds are often found in nail culture, but these have in the past been considered irrelevant, often dismissed as saprophytes of otherwise damaged nails. Techniques of molecular biology have however, produced new evidence that the nondermatophytes may be the cause of some

onychomycosis. Immunohistochemistry, using either immunofluorescence or immunoperoxidase, with the use of specific antibodies, can show the presence of molds inside the nail plate *(Sehgal & Jain, 2000)*.

There are many risk factors associated with getting onychomycosis. It is known that patients with diabetes, psoriasis, atopy and immunosuppression are more prone to onychomycosis *(Sigurgeirsson, 2004; Blake, 2005)*. Even otherwise, healthy individuals engaged in sporting activities, involving shared bathing and changing facilities, are prone to the disease *(Baran & Kaoukhov, 2005)*.

Increasing age, poor peripheral circulation, trauma and tinea pedis are other factors that predispose to onychomycosis *(Ghannoum et al., 2000)*.

<u>Clinical picture and pathogenesis:</u>

The importance of onychomycosis is often underestimated, it is, frequently regarded as an unimportant and trivial disease *(Scher, 1994)*. Several studies have shown that onychomycosis, although not life threatening, does have an important impact on patients quality of life *(Sehgal & Jain, 2000)*. Nail changes from mycotic infections may provide a portal of entery for secondary bacterial infections *(Leib, 1994)*. Also it has been reported that T. rubrum fungal infection may suppress cell- mediated immunity *(McCarthy et al., 1994)*.

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According to *Sehgal & Jain (2000)*, onychomycosis patients harbor a large fungal load and, from an epidemiologic point of view, may be a source of reinfection with tinea manuum and tinea pedis.

Baran et al., (1998), put a scheme for the classification of onychomycosis as follows:

1. Distal and lateral subungual onychomycosis (DLSO).

2. Superficial white onychomycosis (SWO).

3. Proximal subungual onychomycosis (PSO):

    3.1. Without paronychia.

    3.2. With candida paronychia.

    3.3. With non dermatophyte mold paronychia.

4. Endonyx onychomycosis.

5. Total dystrophic onychomycosis (TDO):

    5.1. Secondary total dystrophic onychomycosis.

    5.2. Primary total dystrophic onychomycosis.

1. Distal and lateral subungual onychomycosis (DLSO):

This is the most common type of fungal nail infection *(Baran & Kaoukhov, 2005)*. DLSO most commonly affect big toe nails *(Gupta, 2000)*.

DLSO may be associated with three major clinical features whose contribution may vary with individual cases: subungual hyperkeratosis, onycholysis and paronychia *(Baran et al., 1998)*.

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At the onset, the infection may be entirely confined to the hyponychium and the lateral nail groove. Further extension of the infection occurs from the lateral grooves, underneath the lateral borders of the nail into keratin produced by the nail bed. It may extend into the lower surface of the nail plate. The infection frequently becomes static at this point, resulting in only a white yellow discoloration of the lateral borders of the nail, and minor disorganization of the nail plate *(Sehgal & Jain, 2000)*.

If the fungus extends further into the lower portion, local mild inflammation results in focal subungual hyperkeratosis. As keratotic depris from the infection builds under the nail, the nail plate is lifted off its bed from distal to proximal, thus exposing more nail bed to infection. This leads to onycholysis (detatchement of the nail plate from the nail bed). The resulting subungual space provides a reservoir for super infection by bacteria and molds giving yellowish brown appearance to the nail plate *(Tan & Joseph, 2004)*.

T. rubrum is thought to cause > 90% of DLSO. Several non-dermatophytic molds have also been implicated, including Aspergillus, Scopulariopsis, Scytalidium and Fusarium *(Elewski, 1998)*.

2. Superficial white onychomycosis (SWO):

SWO is a form of onychomycosis characterized by a superficial location of fungi on the dorsal surface of the nail plate *(Piraccini & Tosti, 2004)*. The prevalence of SWO in the general population is estimated to be approximately 1% to 2% *(Gupta & Summerbell, 1999)*.

Classic SWO due to dermatophytes in healthy people was first described by *Zaias in 1966.* SWO typically affects one or more toenails, most commonly the first, second and third. Interdigital tinea pedis (or rarely planter tinea pedis) due to trichophyton interdigitale is often associated. Involvement of finger nails has been rarely described in adults *(Kornblueth & Hsu, 1999).*

Clinically, SWO presents as one or more white opaque plaques with distinct edges localized on the dorsal surface of the nail plate, each plaque corresponding to a dermatophyte colony. Because of the minimal nail plate penetration, the plaques are easily scraped a way with gentle curetting *(Piraccinii & Tosti, 2004).*

This variety is usually caused by Trichophyton mentagrophyte interdigitale (in more than 90% of cases), although in some cases it is due to trichophyton rubrum, and rarely, to other dermatophytes *(Sweren, 1984).*

Dermatophytes cause SWO when they possess keratinolytic enzymes able to metabolize the hard keratin of the superficial nail plate *(Piraccinii and Tosti, 2004).*

Several nondermatophyte molds are known to be able to invade the superficial nail plate *(Zaias, 1990).* The most common are Aspergillus spp., Fusarium spp and Acremonium spp *(Baran et al., 2004).* According to *Zaias (1990)* 5% of all SWOs are due to non dermatophytic molds.

Mold SWO usually affects a single toenail. Clinically, mold SWO may be indistinguishable from dermatophyte SWO or it may

show a diffuse involvement of the nail both in width and depth. This is specially seen in Fusarium and Aspergillus SWO *(Piraccini et al., 2002)*.

Periungual inflammation is commonly associated, usually without pus discharge. Scytalidium dimidiatum may cause a superficial black onychomycosis characterized by small, opaque black patches on the dorsal nail plate that are easily scraped away *(Piraccini & Tosti, 2004)*.

In prepubertal children, dermatophyte SWO can be observed ,in whom it is due to trichophyton rubrum *(Piraccinii et al., 2002)*. However, Diffuse Candida species SWO of several fingernails and toe- nails may be seen in premature infants born to mothers with vaginal candidiasis *(Arbegast et al., 1990)*.

Clinically SWO in children may present as a classic SWO or, more frequently, may show diffuse invasion of the nail plate. In these cases the nail appears with clinical features resembling a PSO extending to the superficial nail plate *(Gupta et al., 2003)*.

The involvement of the entire thickness of the nail plate of children SWO may be explained by *Baran et al., (2004)*, by the their thin nail plate.

A recent study by *Gupta et al., (2000)*, has shown a prevalence of SWO of 9.5% in HIV- infected patients. It is usually due to trichophyton rubrum *(Cribier et al., 1998)*, and is not only seen in the toenails but can also affect the fingernails *(Daniel et al., 1992)*.

Clinically, the affected nail appears diffusely opaque and white, and the pigmentation often reaches the proximal portion of the nail. It is therefore often difficult to discriminate between SWO that has extended deeply and a PSO that has extended superficially *(Penabad et al., 2001)*.

3. Proximal subungual onychomycosis (PSO):

According to *Elewski (1998)*, PSO is the least common subtype seen clinically in the general population. PSO it is commonly seen among AIDS patients and is considered an early marker of HIV infection *(Tan & Joseph, 2004)*. Another combination pattern is seen in AIDS patients where PSO and SWO may develop at the same time and spreads rapidly to involve the nail plate *(Dompmartin et al., 1990)*.

The fungus invades the proximal nail fold through the cuticle area penetrating the newly formed nail plate and migrate distally to all layers of the nail. The first clinical sign is a whitish to whitish-brown area on the proximal part of the nail plate. The patient commonly presents with subungual hyperkeratosis, proximal onycholysis, leuconychia and destruction of the proximal nail plate. The infection spreads gradually to involve the entire nail resulting in total dystrophic onychomycosis *(Elewski, 1998)*. Following infection of the nail matrix, transverse depressions (Beau's lines) may appear in the nail plate, which become convex, irregular and rough, and ultimately dystrophic *(Tan & Joseph, 2004)*. According to *Baran et al., (1998)*, PSO may be associated with paronychia and with different organisms.

In cases without paronychia the usual causative fungus is T. rubrum, but some other dermatophytes have been reported, as well as Candida infection. While other cases paronychia may be followed by secondary nail involvement by C. albicans which produces opaque strips of onycholysis along the lateral edges of the nail plate. Fusarium and scopulariopsis brevicaulis can also cause PSO with paronychia, producing white or buff-colored discoloration of the nail plate. In Aspergillus nail infection, the proximal nail plate shows areas of black or green discoloration.

Study done by *Garg et al., (2004),* showed that PSO without paronychia was seen both in finger nails and toe nails, while PSO with paronychia was seen only in fingernails.

4. Endonyx onychomycosis:

This form of infection involves invasion of the superficial surface as well as deeper penetration of the nail plate. As it produces a characteristic pattern of disease with lamellar splitting of the plate, and the mood of penetration of hyphae is distinct, it is described as a separate entity. This form of invasion caused by organisms which normally produce endothrix scalp infection, notably T. soudanense, T. violaceum may also produce this pattern of nail disease *(Baran et al., 1998).*

5. Total dystrophic onychomycosis (TDO):

TDO is the most advanced or endstage form of all the types of onychomycosis. The entire nail is thickened and dystrophic *(Tan & Joseph, 2004).*

According to *Baran et al., (1998)*, there are 2 main forms of **TDO:**

Secondary TDO: This results from complete progression of any of the different types of destructive nail dystrophy previously mentioned.

Primary TDO: This type occurs in chronic mucocutaneous candidiasis where all the tissues of the nail apparatus may be involved simultaneously, including the nail fold.

Chronic paronychia:

Chronic paronychia is a chronic inflammatory reaction of the proximal nail fold. It most commonly occurs in persons whose hands are repeatedly exposed to wet environment or in those who have prolonged and repeated contact with irritants. Mechanical or chemical traumas damage the cuticle that is generally lost. The condition is then maintained by penetration, of irritant and allergenic enviromental hazards, which cause an inflammatory reaction of the proximal nail fold and nail matrix. Inflammation impairs nail fold keratinization preventing formation of a new cuticle and damage to the nail matrix interferes with the normal nail growth. Secondary colonization with Candida albicans and / or bacteria occurs in most cases causing self-limited episodes of painful acute inflammation *(Tosti, 2004)*.

Nail dystrophy or deformity in so-called Candidal onycomychosis in a purely secondary process, subsequent to chronic paronychia. The fungus is not ordinarily found in the substance of

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the nail plate, but this may occur when its formation has been so facultative as to permit penetration of the organism into the porous interstices *(Sehgal & Jain, 2000)*. In addition to swelling of the nail fold, there's mild pain, tenderness and intermittent pus discharge. The lateral border of the nail may be undermined with onycholysis *(Elewski, 1996)*.

Beau's lines (transverse superficial depressions of the nail plait) and onychomadesis (a transverse whole thickness sulcus that splits the nail plate into two parts) may occur as a consequence of nail matrix damage. The nail plate may some times presents a green discoloration of its lateral margins due to pseudomonas colonization *(Tosti, 2004)*.

According to *Sehgal & Jain (2000)*, nail plate invasion due to Candida may occur in chronic mucocutaneous candidiasis. In addition, some patients may develop genuine nail plate invasion and destruction, particularly if there is underlying Raynaud's disease or Cushing's syndrome Here, the nail plate is seldom grossly thickened, but onycholysis and terminal erosion may occur together.

Diagnosis of onychomycosis:

Diagnosis of fungal infections of the nail involve the use of KOH preparations and fungal cultures. Unfortunately, microscopy is often negative in nails that appear to be infected clinically. Furthermore, nails that are positive by microscopic examination often yield negative cultures. The reason for this discrepancy is that fungi seen on KOH examination may not be viable and hence do not grow as expected *(Midgley & Moore, 1996))*.

On histopathologic examination, hyphae are seen lying between the laminae of nail parallel to the surface. The ventral nail and the stratum corneum of the nail bed are preferentially affected. The epidermis may show spongiosis and focal Parakeratosis the inflammatory response in the dermis is minimal *(Danie et al., 1992)*.

Onychomycosis and diabetes mellitus:

It is generally accepted that diabetic patients are more likely to suffer from skin and soft tissue infections than non-diabetics *(Buxton et al., 1996)*. The prevalence of fungal nail infections is elevated in patients with diabetes compared with non-diabetics *(Rich et al., 2003)*. Study done by *Gupta et al. (1998)* showed that the prevalence of onychomycosis was nearly three times higher than in a comparison group of non diabetic dermatology patients.

While mild early onychomycosis probably poses little threat to the diabetic, more severe, neglected oncychomycosis can be a more serious problem. In particular, the high-risk diabetic with compromised lower extremities and severe neuropathy is at increased risk of developing complications from onychomycosis. Onychomycosis results in thick, brittle nails that can be sharp, pointed and result in injury to the surrounding skin. The diabetic with neuropathy does not notice small cuts and breaks in the skin which can become a portal of entery for bacteria resulting in serious limb threatening bacterial infections *(Rich & Hare, 1999)*.

Thickened dystrophic mycotic nails can cause pressure erosions of the nail bed and hyponychium, and because of the proximity of the nail bed to underlying bone, osteomyelitis can

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develop as a consequence of neglected nail bed erosion *(Rich et al., 2003).*

In a retrospective study done by *Boykoto et al. (1999),* onychomycosis was associated with a threefold increase in gangrene and foot ulcers among patients with diabetes.

Onychomycosis is often associated with tinea pedis, which can lead to cracks and fissures that become secondarily infected, resulting in serious deep space infection *(Rich et al., 2003).*

Onychomycosis can contribute to the difficulties of maintaining nail hygiene in elderly diabetic patients. Onychomycosis can contribute also to lowering of self-esteem and restriction of social activities in younger diabetic individuals *(Rich, 1996).*

While it is possible to treated onychomycosis presumptively based on the clinical appearance of the nails, in the diabetic patients the diagnosis should be confirmed by culture to avoid treating conditions different form onychomycosis that can also produce abnormal appearing nails *(Elewski, 1996).*

Treatment of onychomycosis in diabetic patients requires a three pronged approach. Mechanical, topical and or oral measures and patient education *(Rich & Hare, 1999).*

Mechanical measures:

Physical debridement of the infected nail, by decreasing fungal load, may enhance the efficacy of topical or systemic treatment, and by reducing hyponychial pressure, problems such as ulceration of the

nail bed are less likely to be encountered in patients with diabetic neuropathy *(Tan & Joseph, 2004).*

Topical therapy:

Topical antifungals can be used for treatment of patients with mild to moderate infection. In elderly patients receiving polypharmacy, topical agents generally have the advantage of a reduced potential for drug-drug interactions relative to oral agents nail lacquers such as amorolfine 8% or ciclopirox, in one study, are effective in almost 50% of cases *(Tan & Joseph, 2004),* and in another study, ciclopirox was as effective in diabetic patients (efficacy was good or satisfactory in 86% of patients) as it was in the general population *(Seebacher et al., 2001).* Some studies in patients with severe onychomycosis and nail matrix involvement indicated that combined therapy with nail lacquers and oral antifungals might enhance efficacy and cost-per-cure rates. Combination of antifungal with nail softeners (bifonazale plus urea; 2% tolnaftate plus an occlusive 20% urea dressing) have been used successfully specially in Europe *(Tan & Joseph, 2004).*

Oral antifungals:

The cornerstone of the management of fungal skin and nail diseases in diabetics is oral antifungal therapy *(Rich & Hare, 1999).*

The traditional oral agent griseofulvin, while effective against tinea pedis, has clinical cure rates of only 12-16% in patients with pedal onychomycosis; such low cure rates can probably be attributed to poor drug penetration into nails. Conversely, in numerous randomized, double-blind studies, oral allylamines or triazoles

demonstrated markedly superior cure rates to griseofulvin after relatively short-term treatment schedules (12-24 weeks) and long-term follow up *(Gupta et al., 2004)*.

According to *Farkas et al. (2002),* Terbinafine has demonstrated high mycological cure rates in both type 1 and type 2 diabetic patients with pedal onychomycosis, and both terbinafine and itraconazole are effective and well tolerated in the treatment of dermatophytic infections in diabetic patients.

Because of hepatotoxicity, oral ketoconazole is no longer advocated for the treatment of onychomycosis. In diabetic patients with Candida onychomycosis, with or without mucocutaneous candidiasis, oral fluconazole, itraconazole or terbinafine may be used *(Tan & Joseph, 2004).* The same applies for onychomycosis due to non-dermatophytic molds such as scopulariopsis brevicalis, although organisms such as scytalidium dimidiatum may not respond well to any of these three oral antifungal agents *(Gupta et al., 2004).*

In pedal onychomycosis, itraconazole pulse or intermittent therapy(200 mg twice daily for one week per month for 2 months in fingernails, 3 to4 months in toenails) is equally effective as continuous therapy (100 mg daily for 6 months) *(Tan & Joseph, 2004).* In a study in elderly patients, itraconazole pulse therapy and continuous terbinafine treatment(250 mg once daily for 6 weeks in fingernail, 12 weeks in toenails) were equally effective *(Gupta et al., 2001),* whereas another study suggested that continuous trbinafine treatment was significantly more effective than intermittent itraconazole *(Evans & Sigurgeirsson, 1999).*

A study done by *Havu et al. (2000)* documented that fluconazole in a dose of 150 to 300 mg once weekly for 6 to 12 months, was significantly less effective than continuous trbinafine therapy.

Itraconazole causes potent inhibition of cytochrome p450 iso enzyme 3A4. This may be of particular concern in patients receiving sulphonylureas. Hence, blood glucose concentrations in patients receiving an azole, especially itraconazole and oral antidiabetic agents should be monitored closely, and dosage of antidiabetic agents adjusted accordingly as this combination potentiate the hypoglycaemic effect of antidiabetic drugs. Metformine has not been shown to have interaction with azoles *(Verspeelt et al., 1999)*. Griseofulvin and terbinafine do not have interactions with oral antidiabetic agents. However, patients who are taking a sulphonylurea and griseofulvin may have additive photosensitization *(Ljunggren & Bjellerup, 1986)*.

Patients with diabetes have a high propensity to cardiovascular disease. Co-administration of an azole with a calcium channel antagonist results in decreased clearance of the latter. In patients who are on warfarine, co-administration of an azole should be closely monitored by checking the prothrombin time, because azoles increase the activity of warfarin *(Albengres et al., 1998)*. Terbinafine has less drug-drug interactions compared with azoles *(Tan & Joseph, 2004)*.

Patient education:

The high-risk diabetic patient should be educated about the importance of proper foot care, and should be instructed to examine his or her feet daily. Self-examination should include careful inspection of the web spaces, heels and perionychium *(Rich & Hare, 1999)*.

MATERIALS AND METHODS

This study included one hundred patients who had attended the Dermatology out patient clinic and Diabetes out patient clinic of Mansoura University Hospital in the period from April 2005 to February 2006. Patients included sixty diabetic subjects and forty, age and sex matched, non diabetic subjects.

All the patients were clinically diagnosed as having onychomycosis and classified into one or more of the described clinical types. Patients on systemic antifungal therapy within the last 4 weeks or topical antifungal therapy within the last 1 week were not included in this study. All patients gave their consent.

The patients were subjected to the following:

(1) Thorough history taking with special stress on:

- Personal history: age, sex, residence and occupation.
- History of onychomycosis: onset, course, duration, family history of onychomycosis, history of contact with animals, history of previous treatment and history of recurrence.
- Diabetic history (for diabetic patients): type of diabetes, duration, treatment, control, complications, blood sugar level in last 6 months whether controlled or not, family history of diabetes, medications including immunosuppressive therapies, associated medical illnesses were also recorded.

(2) Examination including:

a. **General examination:** evaluation of dorsalis pedis, posterior tibial and radial pulses. Fundus examination for retinopathy and neurologic examination were carried out in the diabetic patients.

Dermatological examination:

- Skin examination: for other fungal infection at other sites, other skin disease.
- Nail examination: for site, number of nails affected, signs detected in nails.
- The severity of onychomycosis was evaluated globally for all nails as mild (< 25% of the nail plate involvement or < 4 nails involved), moderate (26-74% of the nail plate involvement or 5-8 nails involved), or severe ($\geq$ 75% of the nail plate involvement or $\geq$ 9 nails involved).

(3) Mycological examination:

Specimen collection:

- A severely affected nail was selected as the target nail, where more than one nail was affected. When both finger nails and toenails were involved simultaneously, specimens were collected from both sites after selecting target nails. Separate samples were also obtained if different clinical types were seen in the same patient.
- The selected nail and surrounding skin were first cleaned with 70% alcohol to remove contaminants. The nails were

clipped short using nail clippers. The initial clippings and their depris were discarded. Scrapings were collected from the nail bed as proximal as possible and from the underside of the nail plate, with a no. 23 sterile scalpel blade.

- Specimens transported to the laboratory in a folded paper. The time taken to transport the sample to the laboratory does not seem to affect the success of microscopy or cultures as the fungi remain viable in keratin material for months *(Sehgal & Jain, 2000)*.

Direct microscopic examination:

- Direct microscopy using KOH preparation, beside confirming if the sample is positive or negative for the fungus, an experienced observer may be able to distinguish dermatophytes from yeasts, and often it may be possible to identify non dermatophyte infection *(Sehgal & Jain, 2000)*.

- Debris was put onto a slide and covered with a cover slip. From the edge 20% potassium hydroxide is trickled from a dropper under the cover slip. The solution should flow evenly beneath the cover slip by surface tension. The preparations were allowed to remain at room temperature for 15-20 minutes, in this way keratin will be dissolved or become transparent, while elements of the fungus consisting of cellulose or chitin well remain. Light pressure on the cover slip makes the keratin cells move a part, so that the fungus is seen more easily. The preparations were examined

at low and high power unstained, under a microscopy with reduced light.

- Dermatophytes were identified by presence of translucent, non pigmented, septate mycelium and arthrospores. Yeasts were identified by the presence of pseudohyphae and budding. Molds show hyaline, colored hyphae and conidia.

Culture:

- Two types of growth media should be used, one with cyclohexamide (dermatophyte test medium [DTM] or Mycosel) for dermatophytes and one without cyclohexamide (sebouraud glucose agar, Litman ox inhibitory mold agar) to isolate yeasts and nondermatophyte molds *(Blumberg, 2005)*.

In this study specimens were cultured in duplicate on sabouraud's dextrose agar (SDA) and dermatophyte test medium (DTM).

- DTM contains combination of three antimicrobial agents: cyclohexamide, chloramphenicol and gentamycin to inhibit the growth of bacteria and saprophytic yeasts and molds, and phenol red (indicator). Dermatophytes produce alkaline metabolites which raise the PH causing the phenol red indicator to change the color of the medium from yellow to pink to red. *(Blumberg, 2005)*.

Sabouraud's dextrose agar consists of dextrose (40gm) pepton (10gm), agar (20gm) and distilled water (1000ml) adjusted to pH 5.5 *(Rippon, 1982)*.

Specimens for culture collected as before put on a sterile small Petri dishes labeled by the name and code number of the patient for subsequent culture.

The specimens obtained in the small Petri dishes were cultivated on the previously described media in slopes labeled by the name, code number of the patient, the date of inoculation.

The culture bottle after inoculation of the specimens should be loosely capped and incubated at room temperature and observed daily for fungal growth. Culture is considered negative after 8 weeks of inoculation.

Dermatophyte and mold growth was identified by gross colony morphology, microscopic examination with lactophenol blue preparation, yeast colonies were confirmed microscopically by gram stain.

RESULTS

The Age distribution of the studied cases of onychomycosis in both non diabetic and diabetic cases is shown in table (1).

It was observed that onychomycosis is more common in older age group, as 21% of cases were below 45 years, and 79% of cases were above 45 years.

In non diabetic patients, 11 cases (27.5%) were below 45 years, and 29 cases (72.5%) were above 45 years, with the mean age 48.58 ± 8.6.

On the other hand, 10 cases (16.7%) of diabetic patients were below 45 years, and 50 patients (83.3%) were above 45 years, with mean age 51.85 ± 9.8.

There is no significant difference regarding the age in both groups. $X^2 = 1.7$ $P = 0.193$.

Table (1) : Age distribution of cases with onychomycosis.

Age	Non diabetic	Diabetic	Total
<45 years	11 27.5%	10 16.7%	21 21.0%
≥ 45 years	29 72.5%	50 83.3%	79 79.0%
Total	40 100.0%	60 100.0%	100 100.0%

$X^2 = 1.7$ $P = 0.193$

Table (2) shows sex distribution of the studied cases of onychomycosis in both non diabetic and diabetic groups.

It was noted that 23 cases (23%) were males and 77 cases (77%) were females.

In non diabetic patients, 8 cases (20%) were males, and 32 (80%) were females. In diabetic patients, 15 cases (25%) were males, and 45 cases (75%) were females. With no significant difference between the 2 groups.

$X^2 = 0.339$ $P = 0.561$.

Table (2) : Sex distribution of cases with onychomycosis.

Sex		Non diabetic	Diabetic	Total
Male	count %	8 20.0%	15 25.0%	23 23.0%
Female	count %	32 80.0%	45 75.0%	77 77.0%
Total	count %	40	60	100 100.0%

$X^2 = 0.339$ $P = 0.561$

Different Occupations of the studied cases are shown in table (3).

65% of cases were housewives followed by employees (12%) of cases, and then came farmers (11%) of cases, manual workers (7%) of cases, and lastly students (5%).

In non diabetic patients, 57.5% of cases were housewives, 15% of cases were employees, 12.5% were students, and both farmers and manual workers were represented by 7.5% of cases for each.

In diabetic patients, 70% of cases were housewives, 13.3% were farmers, 10% were employees, and 6.7% were manual workers.

Table (3) : Different occupations of cases with onychomycosis

Occupation		Non diabetic	Diabetic	Total
HW	count %	23 57.5%	42 70.0%	65 65.0%
Student	count %	5 12.5%	—	5 5.0%
Employee	count %	6 15.0%	6 10.0%	12 12.0%
MW	count %	3 7.5%	4 6.7%	7 7.0%
Farmer	count %	3 7.5%	8 13.3%	11 11.0%
Total	count %	40 100.0%	60 100.0%	100 100.0%

The residence of the studied cases is shown in table (4). 71% of cases were from rural areas, while 29% of cases were from urban areas.

In non diabetic cases, 65% of cases were from rural areas, and 35% of cases were from urban areas. On the other hand, 75% of diabetic cases were from rural areas, and 25% were from urban areas. With no significant difference between the 2 groups.

$P = 0.280$.

Table (4) : The residence of cases with onychomycosis.

Residence		Non diabetic	Diabetic	Total
Rural	count	26	45	71
	%	65.0%	75.0%	71.0%
Urban	count	14	15	29
	%	35.0%	25.0%	29.0%
Total	count	40	60	100
	%	100.0%	100.0%	100.0%

$P = 0.280$.

Table (5) shows types of fungal skin infections other than onychomycosis in the studied cases. It was noticed that T.pedis was the commonest associated fungal skin infection, it was detected in 73% of studied cases.

T.pedis in diabetic cases (91.7%), in comparison with non diabetic cases (45%). The difference was statistically significant.

$$X^2 = 26.52 \qquad\qquad P = 0.001.$$

T.corporis that was noticed only in 3 patients of the studied cases. 3.3% of diabetic patients vs. 2.5% of non diabetic patients had T.corporis. With no significant difference between the 2 groups. P = 1.00.

Table (5) : Types of fungal skin infections other than onychomycosis in the studied cases.

	Non diabetic no = 40	Diabetic no = 60	Total no = 100	Sig.
T.Pedis	18 45.0%	55 91.7%	73 73.0%	$X^2 = 26.5$ P < 0.0001
T.corporis	1 2.5%	2 3.3%	3 3%	P = 1.00

Table (6) shows the duration of onychomycosis in the studied cases. In non diabetic patients duration of onychomycosis was < 1 year in 22.5% of cases, and 1-5 years in 65% of cases, and the remaining 12.5% had onychomycosis for > 5 years.

On the other hand, 13.3% of diabetic patients had onychomycosis for < 1 year, 70% had onychomycosis for 1-5 years, and the remaining 16.7% of diabetic cases had onychomycosis for > 5 years.

There was no significant difference between both diabetic and non diabetic groups regarding the duration of onychomycosis. P = 0.460.

Table (6) : The duration of onychomycosis in diabetic and non-diabetic cases.

Duration		Non diabetic	Diabetic	Total
<1Years	count	9	8	17
	%	22.5%	13.3%	17.0%
1-5Years	count	26	42	68
	%	65.0%	70.0%	68.0%
>5Y	count	5	10	15
	%	12.5%	16.7%	15.0%
Total	count	40	60	100
	%	100.0%	100.0%	100.0%

P = 0.460.

Table (7) compares different clinical presentations of onychomycosis in cases of diabetic and non diabetic groups.

DLSO was the most common presentation of onychomycosis in this study, it was detected in 62 cases out of 100 cases (62%), followed by PSO which was detected in 21 cases out of 100 cases (21%). In the third place came combined presentation of both DLSO and TDO which was noticed in 16 cases out of 100 cases (16%), and lastly TDO was detected only one case.

In non diabetic group, 32 cases (80%) had DLSO alone, while 7 cases (17.5%) had PSO, and the remaining 1 case (2.5%) had both DLSO and TDO.

In the diabetic group, 30 cases (50%) showed DLSO alone, and 14 cases (23.3%) had PSO, while 15 cases (25%) had both DLSO and TDO. TDO alone was detected in only 1 case (1.7%).

This shows that the clinical presentation of combined DLSO and TDO was significantly increased in the diabetic group.

$X^2 = 9.9$ $\qquad\qquad$ $P = 0.002$.

While the clinical presentation of PSO was increased in the diabetic group, but with no statistical significance

Table (7) : The clinical presentations of onychomycosis in the studied cases.

Clinical type	Non diabetic	Diabetic	Total	Significance
DLSO	32 (80%)	30 (50%)	62	X^2 = .043 P = .97
DLSO+TDO	1 (2.5%)	15 (25%)	16	X^2 = 9.9 P = 0.002
TDO		1 (1.7%)	1	
PSO	7 (17.5%)	14 (23.3%)	21	X^2 = .026 P = 0.610
Total	40 (100.0%)	60 (100.0%)	100	

Table (8) shows the site of nail affection in relation to different clinical presentations of onychomycosis.

It was noticed that 16 cases (28.07%) of patients with DLSO had finger nail affection, 19 cases (33.33%) had toe nail affection, and 22 cases (38.6%) had both toe- and finger nail involvement.

In patients with combined DLSO and TDO 1 patient (8.3%) had finger nail affection, 5 patients (41.7%) had toe nail affection, and 6 patients (50%) had both finger- and toe nail involvement.

PSO with paronychia was detected only in finger nails, while in patients with PSO with out paronychia, 3 cases (60.0%) had finger nail affection, one patient (20%) had toe nail affection and another patient had both finger- and toe nail affection.

The only patient with TDO was found to have toe nail affection.

Table (8) : The relation between site of nail affection and the clinical presentations of onychomycosis.

	Finger	Toe	Both	Total
DLSO	16 (28.07%)	19 (33.33%)	22 (38.6%)	57 (100.0%)
TDO	–	1 (100.0%)	–	1 (100.0%)
DLSO+TDO	1 (8.3%)	5 (41.7%)	6 (50%)	12 (100.0%)
PSO with paronychia	13 (100%)	–	–	13 (100.0%)
with out paronychia	3 (60.0%)	1 (20.0%)	1 (20.0%)	5 (100.0%)

Table (9) shows severity of onychomycosis in both diabetic and non diabetic patients. 75% of non diabetic cases had mild to moderate onychomycosis, while 25% of cases had severe onychomycosis. In diabetic group, 56.7% of cases had mild to moderate onychomycosis, and 43.3% had severe onychomycosis.

This shows that, severe onychomycosis is more common in the diabetic group, but does not reach statistical significance.

$$X^2 = 3.5 \qquad P = 0.061$$

Table (9) : The severity of onychomycosis in diabetic and non-diabetic cases.

Severity		Non diabetic	Diabetic	Total
mild/moderate	count %	30 75.0%	34 56.7%	64 64.0%
Severe	count %	10 25.0%	26 43.3%	36 36.0%
Total	count %	40 100.0%	60 100.0%	100 100.0%

$$X^2 = 3.5 \qquad P = 0.061$$

Table (10) shows the relation between sex of the studied cases and the severity of onychomycosis.

In diabetic patients, 11 cases (73.3%) of male patients had severe onychomycosis, while 15 cases (33.3%) of female patients had severe onychomycosis, and the remaining cases had mild to moderate onychomycosis. This indicates significant increase in the severity of onychomycosis in male diabetic patients.

$X^2 = 7.33$ $P = 0.007$.

On the other hand in non diabetic patients, onychomycosis was severe in 4 male cases (50.0%), and 6 female cases(18.8%),while the remaining cases had mild to moderate onychomycosis , showing some increase in the severity of onychomycosis in males that did not reach statistical significance.

$P = 0.089$.

Table (10) : The relation between the sex of the studied cases and the severity of onychomycosis.

Sex		Severity		Total	Sig.
		mild/moderate	severe		
DM	male	4 26.7%	11 73.3%	15 100.0%	X^2 = 7.330
	female	30 66.7%	15 33.3%	45 100.0%	P = 0.007
Total		34	26	60	
NDM	male	4 50.0%	4 50.0%	8 100.0%	P = 0.089
	female	26 81.3%	6 18.8%	32 100.0%	
Total		30	10	40	

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Table (11) shows the relation between severity of onychomycosis and type of diabetes mellitus (DM) in the diabetic group.

In this study from 60 diabetic cases, 11 patients had type I DM and 49 cases had type II DM. It was noticed that there was a significant increase in the severity of onychomycosis in cases with typeI DM, two cases only (18.2%) showed mild to moderate onychomycosis, while 9 cases (81.8%) showed severe onychomycosis. On the other hand, 32 cases with type II DM (65.3%) had mild to moderate onychomycosis, and 17 cases (34.7%) had severe onychomycosis. P = 0.006.

Table (11) : The relation between the severity of onychomycosis and the type of DM.

DM type		Severity		Total
		mild/moderate	severe	
Type I	Count %	2 18.2%	9 81.1%	11 100.0%
Type II	Count %	32 65.3%	17 34.7%	49 100.0%
Total	Count %	34 56.7%	26 43.3%	60 100.0%

P = 0.006

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The relation between duration of diabetes mellitus (DM) and the severity of onychomycosis in diabetic cases is shown in table (12). It was noticed that severity progressively increased with increased duration of DM.

In cases with DM for less than 5 years, 12 cases (80%) had mild to moderate onychomycosis, and 3 cases (20%) had severe onychomycosis.

In cases with DM for 5-10 years, 16 cases (66.7%) had mild to moderate onychomycosis, and 8 cases (33.3%) had severe onychomycosis.

In cases with DM for > 10 years, 6 cases (28.6%) had mild to moderate onychomycosis, while 15 cases (71.4%) had severe onychomycosis.This shows that the difference in severity of onychomycosis in relation to the duration of DM is highly significant.

$$X^2 = 11.054 \qquad P = 0.004.$$

Table (12) : The relation between the duration of DM and the severity of onychomycosis.

Duration of DM		Severity		Total
		mild/moderate	severe	
<5Y	Count %	12 80.0%	3 20.0%	15 100.0%
5-10Y	Count %	16 66.7%	8 33.3%	24 100.0%
>10Y	Count %	6 28.6%	15 71.4%	21 100.0%
Total		34	26	60

$X^2 = 11.054$ P = 0.004.

Table (13) shows the state of control of DM whether controlled or not (in the previous 6 months) in relation to the severity of onychomycosis .

All cases with controlled blood sugar in the previous six months had only mild to moderate onychomycosis .

On the other hand, cases with uncontrolled blood sugar in the previous six months were divided equally between mild to moderate and severe nail involvement indicating significant increase in the severity of onychomycosis in cases with uncontrolled DM. $P = 0.008$

Table (13) : The relation between the state of control of DM and the severity of onychomycosis.

State of control of DM		Severity		Total
		mild/ moderate	severe	
Uncontrolled	Count %	26 50.0%	26 50.0%	52 100.0%
Controlled	Count %	8 100.0%	—	8 100.0%
Total	Count %	34 56.7%	26 43.3%	60 100.0%

$P = 0.008$.

Table (14) shows the relation between complications of DM and the severity of onychomycosis.

It was noticed that out of the 60 diabetic cases in this study 55 patients had peripheral neuropathy and it was associated in 43 of them with impaired peripheral circulation, while 13 patients had retinopathy and only 3 patients had nephropathy.

23 cases out of 43 diabetic patients with combined peripheral neuropathy and impaired peripheral circulation had severe onychomycosis, while only 3 cases (17.6%) out of 17 diabetic patients with out this combination had severe onychomycosis, and the remaining patients had mild to moderate onychomycosis. This indicates significant increase in the severity of onychomycosis in cases with these two complications.

P = 0.012 X^2 = 6.37.

On the other hand, onychomycosis was severe in 10 cases (76.9%) of diabetic patients with retinopathy, and in 16 cases (34.%) of diabetic patients with out retinopathy, while the remaining cases had mild to moderate onychomycosis. This indicates significant increases in the severity of onychomycosis in patients with retinopathy.

P = 0.006 X^2 = 7.62.

Table (14) : The relation between complications of DM and the severity of onychomycosis.

DM complication		Severity		Total	Sig.
		mild/ moderate	severe		
Neuropathy + P.circulatory impairment	detected	20 46.5%	23 53.5%	43 100%	X^2 =6.37
	not detected	14 82.4%	3 17.6%	17 100%	P =0.012
Total		34	26	60	
Retinopathy	not detected	31 66.0%	16 34.0%	47 100%	X^2 =7.62
	detected	3 23.1%	10 76.9%	13 100%	
Total		34	26	60	P =0.006

Table (15) shows that the direct microscopic examinations of samples obtained from the nails diagnosed clinically to have onychomycosis were positive in 24 cases out of 100 cases (24%), and cultures were positive in 89 cases out of 100 cases (89%). 5 cases (20%) were positive only by direct microscopic examinations but negative by cultures, meanwhile 70 cases (70%) were positive only by cultures and negative by direct microscopic examination s. Moreover 6 cases (6%) were negative by both cultures and direct microscopic examinations, and 19 cases (19%) were positive by both cultures and direct microscopic examinations. So both cultures and direct microscopic examinations agreed in 25 cases (19 positive and 6 negative), and disagreed in 75 cases. The measure of agreement (Kappa) is poor = 0.067.

Table (15) : Direct microscopic examination and fungal culture from the affected nails of the studied cases.

			Culture		Total
			-ve	+ve	
KOH	-ve	count %	6 6.0%	70 70.0%	76 76.0%
KOH	+ve	count %	5 5.0%	19 19.0%	24 24.0%
Total		count %	11 11.0%	89 89.0%	100 100.0%

Kappa = 0.067

Table (16): As regard the fungal organisms isolated from cases clinically diagnosed as onychomycosis and had culture positive results: most cases were caused by dermatophytes (68.5%), followed by molds (Aspergillus), which were detected in 16.9% of cases and lastly came yeasts (Candida), which were isolated from 14.6% of cases.

The strains were more or less similar in their percentage in both diabetic and non-diabetic cases except yeasts which were isolated from 10 diabetic cases(18.9%) vs. 3 non-diabetic cases (8.3%).

The commonest dermatophyte isolated was T.rubrum that was isolated from 22 cases (24.7%), followed by T.mentagrophytes that was isolated from 13 cases (14.6%). In the third place came E.floccosum that was isolated from 10 cases (11.2%), T.tonsurans was isolated from 9 cases (10.1%).

T.violaceum was isolated from 5 cases (5.6%), and lastly came T.verrucosum that was isolated from 2 cases (2.2%). The previous order of frequency was similar in both diabetic and non diabetic cases.

Table (16) : Fungal organisms isolated from cases diagnosed clinically as onychomycosis and had culture positive results

Fungal pathogen		Non diabetic	Diabetic	Total
Dermatophytes	T. rubrum	9 25.0%	13 24.5%	22 24.7%
	T.mentagrophytes	6 16.7%	7 13.2%	13 14.6%
	E.Floccosum	4 11.1%	6 11.3%	10 11.2%
	T.tonsurans	4 11.1%	5 9.4%	9 10.1%
	T.violaceum	3 8.3%	2 3.8%	5 5.6%
	T.verrucosum	1 2.8%	1 1.9%	2 2.2%
Molds	Aspergillus	6 16.7%	9 17.0%	15 16.9%
Yeasts	Candida	3 8.3%	10 18.9%	13 14.6%
Total	count %	36 100.0%	53 100.0%	89 100.0%

The relation between different clinical presentations of onychomycosis and the fungal pathogens in culture positive cases is shown in table (17).

It was noticed that in cases with DLSO only, 16 cases (28.07%) showed T.rubrum in cultured samples, while T.mentagrophytes was isolated from 11 cases (19.3%), and E.floccosum was isolated from 8 cases (14.03%), followed by T.tonsurans that was isolated from 7 cases (12.3%). T.violaceum was detected in 3 cases (5.3%), and T.verrucosum was detected in 2 cases (3.5%). Aspergillus was isolated from 10 cases (17.5%).

In cases with combined DLSO and TDO, 6 cases (50%) showed T.rubrum in culture. Both T.violaceum and E.floccosum were detected in 2 cases (16.7%) for each. The remaining 2 cases were divided equally between T.mentagrophytes and Aspergillus.

In cases with PSO, most of the cases, 13 cases (72.2%), showed Candida on samples taken from nails. 4 cases (22.2%) showed Aspergillus, while T.tosurans was detected in only 1 case (5.6%).

The one case with TDO only, showed T.tonsurans in culture.

Table(17) : The relation between the clinical presentations and the fungal pathogens in culture positive cases

Fungal pathogen	DLSO	TDO	DLSO + TDO	PSO	Total
Dermatophytes					
T.rubrum	16 (28.07%)		6 (50%)		22
T.mentagrophytes	11 (19.3%)		1 (8.3%)		13
E.floccosum	8 (14.03%)		2 (16.7%)		10
T.tonsurans	7 (12.3%)	1		1 (5.6%)	9
T.violaceum	3 (5.3%)		2 (16.7%)		5
T.verrucosum	2 (3.5%)				2
Mold Aspergillus	10 (17.5%)		1 (8.3%)	4 (22.2%)	15
Yeast Candida				13 (72.2%)	13
Total	57 (100%)	1 (100%)	12 (100%)	18 (100%)	89

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Figure (1): Toe nail of a patient with distal and lateral subungual onychomycosis.

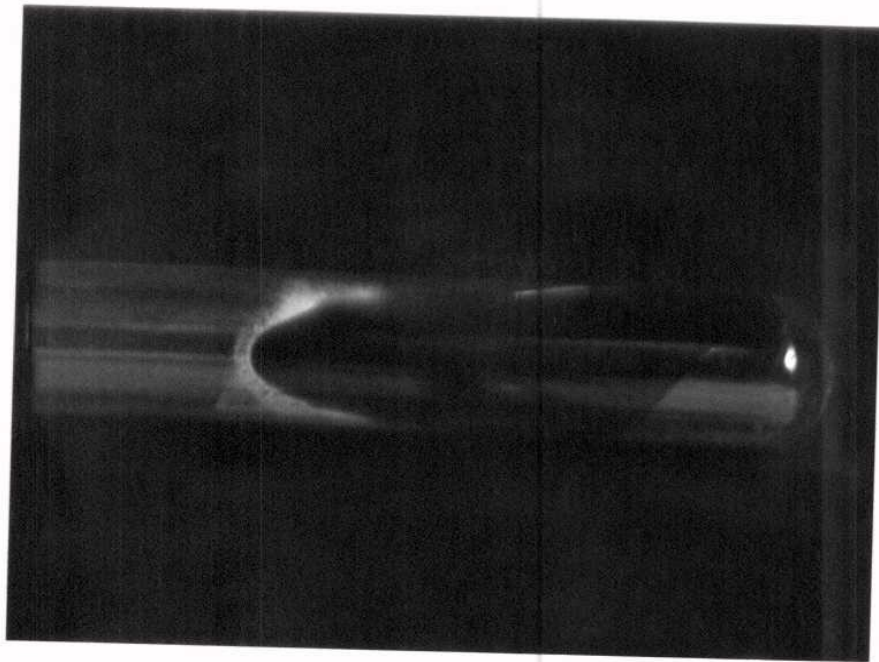**Figure (2): Toe nails of a patient with distal and lateral subungual onychomycosis.**
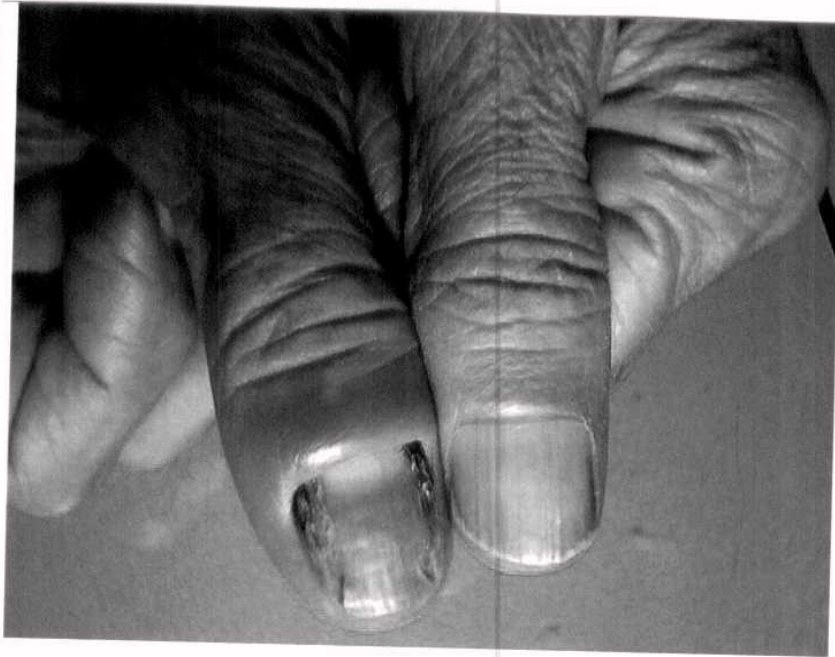
Figure (3): Finger nail of a patient with proximal subungual onycomycosis with paronychia.

Figure (4): Toe nail of a patient with total dystrophic onychomycosis.

Figure (5): Macroscopic appearance of T.rubrum isolated from onychomycosis patient (slope).

Figure (6): The reverse view of T.rubrum slope.

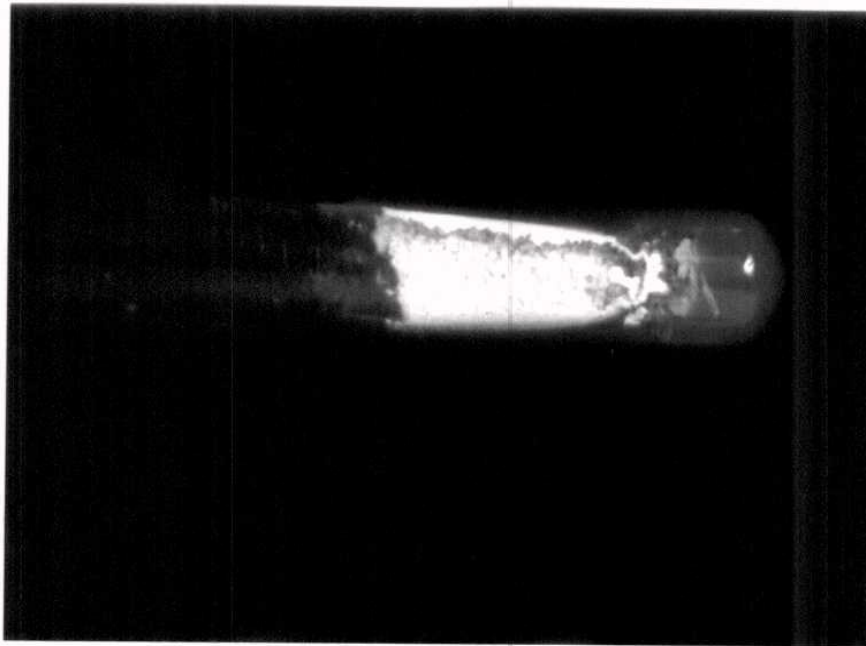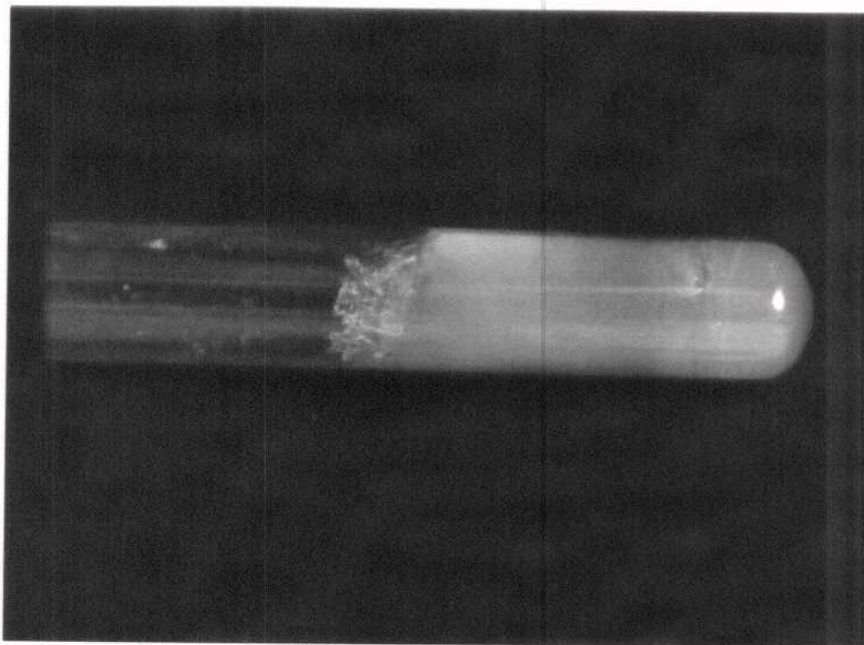**Figure (7): Macroscopic appearance of T.mentagrophyte isolated from onychomycosis patient (slope).**
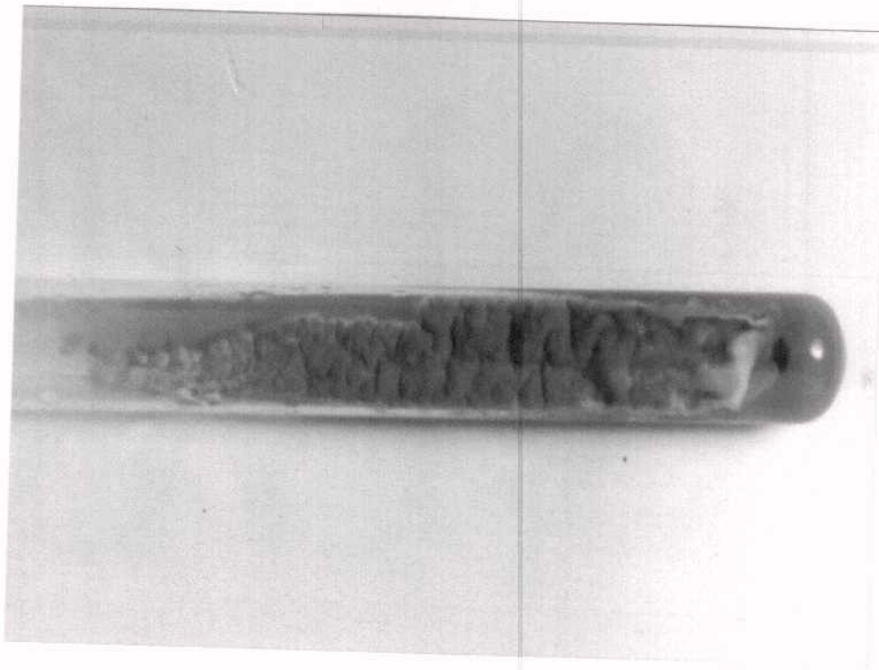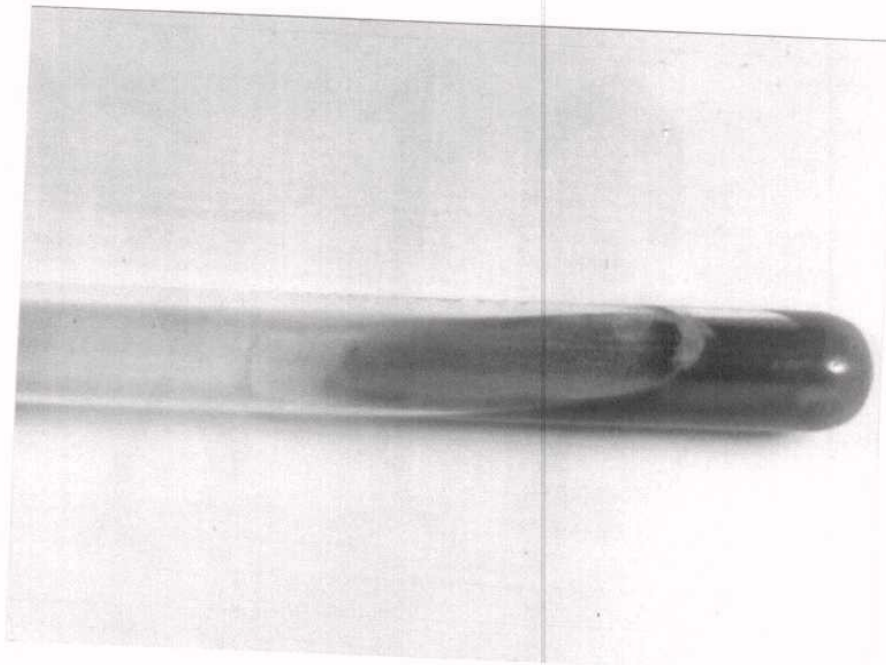

Figure (8): The reverse view of T.mentagrophyte slope.

Figure (9): Macroscopic appearance of E.floccosum isolated from onychomycosis patient (slope).

Figure (10): The reverse view of E.floccosum slope.

Figure (11): Macroscopic appearance of Aspergillus isolated from onychomycosis patient (slope).

Figure (12): Macroscopic appearance of Candida isolated from onychomycosis patient (slope).

DISCUSSION

Fungal nail infections, termed onychomycosis, are a relatively common disorder. The importance of onychomycosis is often under estimated. It 's frequently regarded as an unimportant and trivial disease, causing only aesthetic problems and of cosmetic nuisance *(Scher, 1994)*. Several studies have shown that onychomycosis, although not life threatening, does have an important impact on the patient's quality of life, in terms of embarrassment, reduced self-esteem, and impaired social interactions, thus leading to psychological trauma. Finger and toenail onychomycosis may cause significant discomfort and pain, which may limit physical activity, thus interfering with professional activities and becoming a major occupational hazard *(Lubeck, 1998)*.

Onychomycosis may pose a greater risk for diabetics rather than general population because of the possible sequelae. Onychomycosis may aggravate pre-existing problems, such as diabetic foot and neuropathic ulcers. Impaired sensation may make many diabetics less aware of minor abrasions and ulcerations on the feet that may be caused by trauma from poor nail grooming or by the nail changes characteristic of onychomycosis.

These lesions, in turn, may develop into serious bacterial infections and contribute to the severity of diabetic foot *(Sehgal & Jain, 2000)*. *Doyle et al. (2000)* have shown that there is a higher incidence of both foot ulceration and gangrene in patients with onychomycosis who have diabetes compared with those who do not.

Our study was carried on 100 patients with onychomycosis, 60 diabetic and 40 age and sex matched non-diabetics.

As regard the age distribution of the studied cases, our study showed that onychomycosis was more common in older age group. This is in agreement with the results from each of the studies done by *Roberts (1992), Heikkila and Stubb (1995) and Ghannoum et al. (2000)*. This may be explained by slower linear nail growth, poor peripheral circulation and traumatized nails in elderly *(Hay & Moore, 1998)*. Also by the greater tendency of younger patients to seek medical treatment at an earlier stage *(Ghannoum et al. , 2000)*.

Our study revealed that females were more commonly affected than males. This is in agreement with *Sias et al. (1995) and Gupta et al. (2000)*. On the contrary, studies done by *Banrjee et al. (1989), Khosarvi et al. (1994) and Garg et al. (2004)* showed that onychomycosis affected males more commonly than females.

Vasenova et al. (2004) explained this by that although onychomycosis affect males more often than females, but females more often address the doctor.

This statement together with that of Garg et al. , that nails of males are more liable to trauma and the more common use of occlusive foot wears, may also account for another finding in our study , that severity of onychomycosis was significantly increased with male sex (P = 0.007).

Housewives constitute the major group of cases in this study. This may be explained by the fact that their hands and feet are immersed in water for longer duration than other categories. This humid environment favors fungal infections in finger- and toenails.

Most of our cases (71%) were from rural areas , this may be due to more negligence for hygienic measures and underestimating onychomycosis regarding it as just a cosmetic problem rather than a disease process.

Our study showed that 95% of cases were mycologically confirmed for onychomycosis. Culture was +ve in 89% of cases, while KOH examination was +ve in 24% of cases, indicating that culture is better than KOH test for the diagnosis of onychomycosis.

These figures are close to those found by _Garg et al. (2004),_ who found that culture was +ve in 81.1%, while KOH test was +ve in 28% of cases of onychomycosis.

On the other hand, study done by _Dogra et al. (2002)_ showed that culture was +ve in 39.7% of cases, while KOH test was +ve in 19.1% of cases of onychomycosis.

This variability is referred, by *Sehgal and Jain (2000)*, to the technique of sampling.

Onychomycosis in our patients was more severe in diabetic cases in comparison to non-diabetics. This is in agreement with the study done by *Pierard (2005)* who showed higher morbidity of onychomycosis in diabetics vs. non-diabetic cases.

Our study revealed high association between onychomycosis and T.pedis. This is in agreement with the results of the studies done by *English and Atkinson (1973), Zaias et al. (1996), Tan and Joseph (2004)*, that all showed that onychomycosis is associated with T.pedis in the great majority of cases, and that T.pedis may precede the onset of onychomycosis in many instances. This explains the predominance of the dermatophytes: T.rubrum, T.mentagrophyte, and E.floccosum as etiologic agents for onychomycosis, as theses three agents are responsible for the vast majority of cases of T.pedis throughout the world.

This association is shown in our study to be increased significantly in diabetics vs. Non-diabetics (P = 0.001).This is in agreement with *Rich (1996) and Dogra et al (2002)*, who found significant increase in the incidence of T.pedis in diabetic subjects when compared with age and sex matched non-diabetics. This indicates increased susceptibility of diabetic patients to different types of fungal infections.

In our study, dermatophytes were the most common isolated pathogen in both diabetics and non diabetics. This is in agreement with the reports of *Gupta et al. (1998), Pierrard (2005), Hilmioglu et al. (2005), and Ilkit (2005).* They all emphasized that the dermatophytes largely predominate over yeasts and non-dermatophyte molds as a cause of onchomycosis.

Of the dermatophytes, T.rubrum was the most common organism found, followed by T.mentagrophyte, then in the third place came E.floccosum. The predominance of these three dermatophytes in cases of onychomycosis is in agreement with many reports from many countries , for example: UK *(Williams,1993),* Finland *(Heikkila & Stubb, 1995),* Spain *(Sias et al., 1995),* USA *(Kemna & Elewski, 1996),* Australia *(Ellis et al, 1997),* Canada *(Gupta et al., 1998),* and Turkey *(Ilkit, 2005).*

This predominance of these dermatophytes in tinea unguium may be explained, according to *Hay and Moore (1998),* by the relative ease by which these dermatophytes invade the nail plate hard keratin, also by the observation that in the great majority of cases T.unguium is associated with T.pedis or T.manuum, for both of which, these three agents are the cause for the vast majority of cases.

In the forth and the fifth place came T.tonsurans and T.violaceum respectively. This is in agreement with Saray et al. (2004) who found that these two organisms followed T.rubrum,

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T.mentagrophytes and E.floccosum as causative agents of tinea unguium. According to *Hay and Moore (1998)*, these organisms not infrequently infect nails and they even are likely to predominate as a cause of tinea unguium in regions or populations where T.capitis due to these fungi Is frequent and T.pedis is uncommon.

The dermatophyte T.verrucosum causes various lesions in cattle and humans, and according to *Larone (1993)*, it has rarely been reported as a causative agent of onychomycosis. However, T.verrucosum was isolated from 2.2% of cases in our study. This is in agreement with recent study carried by *Garg et al. (2004)* in central India who detected T.verrucosum in 2.2% of cases of onychomycosis. Theses cases were accounted for by the incidental exposure of some patients to cattle.

There was no marked difference in the frequency of dermatophytic organisms between diabetic and non-diabetic cases, with similar order of frequency.

Our study revealed that non-dermatophyte molds (Aspergillus species) were the second most common isolate (16.9%) following dermatophytes. This percentage is lower than that found in reports from Lahore, Pakistan *(Bokhari et al.,1999)* that showed that non-dermatophyte molds represented 30% of isolates, and from central India *(Garg et al., 2004)* where 39.58% of cases of onychomycosis were caused by non-dermatophyte molds.

This high frequency is explained by the researchers that it may be due to the hot humid climate in these areas.

On the other hand, frequency of molds in our study is higher than other reports for example: from Australia where molds were found in 2.5% of cases *(Ellis et al. 1997)*, from Canada (7.8% of cases) *(Gupta et al., 2000)*, and from Izmir, Turkey (9% of cases) *(Hilmioglu et al., 2005)*.

Frequency of molds in this study may be explained by that the climate in Egypt is midway between areas with higher frequencies and those with lower frequencies, concerning humidity and temperature.

Yeasts (Candida species) were isolated as the sole etiologic agent from 14.5% of our cases. Frequency of Candida species in onychomycosis was variable in different reports. It was 3% in the study done by *Gupta et al. (1998)* in Canada, 4.5% in the study done by *Maleszka et al.(2004)* in Poland, 24.17% in the study done by *Garg et al.(2004)* in India, and 41% in the study done by *Hilmioglu et al. (2005)* in Turkey.

This variability is explained by *Garg et al.(2004)* that it may be due to variability in the working environment (e.g. kitchen or laundry work), the local climate or other environmental factors.

Our study revealed marked difference in frequency of Candida species in diabetics (18.9%) vs. non-diabetics (8.3%). This is in agreement with *Dogra et al. (2002)* who found that yeasts were isolated more often in the diabetic group. This may be explained by the statement of *Ellis et al.(1997)* that Candida usually found as saprophyte in nail tissue, but directly invade the nail plate only when host defenses are disturbed.

The role of non-dermatophyte molds and yeasts remains controversial. Traditionally they have been regarded as secondary pathogens of nails which are already diseased, but recently methods such as immunochemistry, which employs antibodies to certain fungi to help positive identification, and flow cytometry, which differentiates fungi on the basis of molecular differences, such methods provide new evidences that non-dermatophyte molds and yeasts can actively invade nail tissue *(Aly, 2001)*.

Our study revealed that different fungi were isolated from both finger- and toenails with no marked difference except in Candida species which were isolated only from finger nails. This is in agreement with the study done by *Gupta et al. (2000)* that showed marked difference in frequency of Candida in fingernails (29.2%) than toenails (1.6%). This can be explained by *Tosti (2004)* as the chronic paronychia most often occurs in persons whose hands are repeatedly exposed to wet environment or irritants, and then the condition us maintained by penetration of irritants allergenic

environmental hazards followed by secondary colonization with Candida and / or bacteria.

DLSO was the most common presentation of onychomycosis encountered in our study, followed by PSO, then combined presentation of DLSO and TDO.

TDO alone was rare , detected only in 1% of cases, while no cases with SWO were detected in our study. Similar observations for this order of frequency were reported by *Banerjee et al. (1989), Williams (1993), Velez et al. (1997), and Baran et al. (1998).*

The similar clinical presentations were represented both in fingernails and toenails except PSO with paronychia that was seen only in fingernails. This finding is in accordance with reports by *Velez et al. (1997), and Bokhari et al. (1999).*

There was no significant difference regarding the clinical presentation of both DLSO or TDO between diabetic and non diabetic cases. PSO showed some increase in frequency in diabetic cases (23.3%) than non-diabetic cases (17.5%). This may be attributed to more susceptibility of the diabetic patients, due to more immune disturbance, to invasion of the nails by molds and Candida both of which were the main causes of PSO in our study.

Combined presentation of both DLSO and TDO showed significant increase in frequency in diabetic patients (25%) vs.

non-diabetic patients (2.5%), this indicates more aggressive nature of onychomycosis in diabetic subjects rather than non diabetics.

This may be explained by more immune disturbance in diabetic patients, poor circulation and poor blood perfusion to extremities , and negligence of onychomycosis considering it just a cosmetic problem or a minor one compared with other systemic complications of diabetes mellitus, or even lack of notice of nail lesions caused by retinopathy and poor vision.

The clinicoetiologic correlation revealed that a single pathogen could give rise to more than one clinical type. DLSO, TDO, or combined presentation of both were the usual presentations of dermatophyte infection, however PSO was caused by dermatophytes only in 5.6% of cases.

Molds were isolated from nails with DLSO, TDO, and PSO. Candida species were presented only as PSO. This is in agreement with *Garg et al. (2004)*.

Our study revealed that the severity of onychomycosis significantly increased in cases with type I diabetes mellitus vs. type II diabetes mellitus (P = 0.006). This may be explained by earlier onset of type I diabetes resulting in more liability to develop complications if the diabetic condition is not controlled and the longer duration of exposure to these complications, helping more aggressive nature of onychomycosis.

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This claim is supported by the observation that the severity of onychomycosis was significantly increased in our study with the increase in the duration of diabetes mellitus. Onychomycosis was severe in 20% of cases that had diabetes mellitus for less than 5 years, 33.3% in cases with diabetes mellitus for 5-10 years, while it was 71.4% in cases who had diabetes mellitus for more than 10 years (P = 0.004). This is in agreement with *Gupta et al. (1998),* who showed similar progressive increase in the severity of onychomycosis with the duration of diabetes mellitus.

Degree of control of diabetes in the previous 6 months seems to have significant impact on morbidity of onychomycosis in the diabetic subjects. Our study revealed that 50% of diabetic cases with uncontrolled blood glucose level in the previous 6 months, had severe onychomycosis. On the other hand, none of the diabetic cases with controlled blood glucose level in the previous 6 months had severe onychomycosis, but only mild to moderate forms (P = 0.008). This is in agreement with the study done by *Pierard (2005),* that showed increase in the morbidity of onychomycosis with the lower degree of diabetic control, and also the study done by *Jolly et al. (1969)* who showed that the higher the level of blood glucose, the more likely dermatophyte infection is to occur. This may be explained by the effect of control of diabetes on the immunity of the patients.

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Lunt (1996) also suggested that the improved glycaemic control in diabetic subjects, particularly those with IDDM, reduces the risk for developing microangiopathy and diminishes the rate of progression of established microvascular disease.

Both peripheral circulatory impairment and peripheral neuropathy were shown in our study to have significant effect on the morbidity of onychomycosis in diabetic cases.

Severe onychomycosis were observed in 53.5% of patients with these complications, however only 17.6% of cases with out these complications had severe onychomycosis.

This is in agreement with the study done by *Gupta et al. (1998)* who found that the peripheral vascular disease is an important predictor of onychomycosis. Also the study done by *Vasenova et al. (2004)*, which involved the assessment of the capillary network of the skin using duplex scanning, showed an increase in the morbidity of onychomycosis in cases with microcirculatory disturbance which plays a certain role in decreasing the resistibility of skin and nails for fungal infections.

Rich (1996) explained the role of microangiopathy in onychomycosis by that it causes compromised perfusion to the extremities leading to poor tissue oxygenation causing their resistance to infection to decrease.

Ghannoum et al. (2000) found that circulatory disease is a significant predisposing factor for onychomycosis. This also agrees with *Haneke (1989)* who suggested that slower nail growth due to poor circulation may be responsible.

According to *Tan and Joseph (2004),* the potential for serious sequelea is increased in diabetics wit peripheral neuropathy, vascular disease of the extremity, and those with poorly fitting shoes, as onychomycosis causes thickening of the nail, this thickening in combination with the a nail bed that has been rendered insensitive from diabetic sensory neuropathy and tight shoe wear, combined with impaired wound healing, may lead to subungual ulceration, gangrene, osteomyelitis and possible amputation.

Our study revealed that diabetic cases with retinopathy showed significant increase in the severity of onychomycosis. 76.9% of cases with retinopathy had severe onychomycosis vs. 34% of cases with out retinopathy (P = 0.006). This is in agreement with *Dogra et al. (2002)* who found that retinopathy is one of the significant predictors for the development of onychomycosis in diabetics.

This may be explained by that the visual impairment which increases the possibility for onychomycosis not to be noticed by the patient resulting in delayed seeking for medical advice, allowing more progression of onychomycosis.

SUMMARY AND CONCLUSION

Onychomycosis is the most common nail disorder, it is a mycotic infection of the nail unit caused by three groups of fungi, namely dermatophytes, yeasts and non-dermatophyte molds. Although no life threatening, onychomycosis does have an important impact on patients' quality of life, and it may pose a greater risk for diabetic rather than general population because of the possible sequalae. The potential for serious sequalae is increased in diabetic patients with peripheral vascular impairment and peripheral neuropathy and lastly may result in limb loss.

The aim of this work is to determine the morbidity of onychomycosis in diabetics in comparison to non-diabetics, and to determine the most common fungal species of onychomycosis in diabetic in comparison to non-diabetic patients.

In this study 100 patients, 60 diabetic and 40 age- and sex-matched non diabetics, diagnosed clinically as having onychomycosis were selected from Dermatology out patient clinic and Diabetes out patient clinic of Mansoura University Hospital. They were 23 males and 77 females. Their ages ranged from 20 to 75 years.

The patients were subjected to thorough history taking especially for age, sex residence, occupation, history of contact with

animals, the clinical history of onychomycosis, diabetic history, general and dermatological examination.

The nails were clipped short and scrapings were collected from the nail bed as proximal as possible and from the underside of the nail plate and subjected to direct microscopic examination using potassium hydroxide and culture in duplicate on sabouraud's dextrose agar (SDA) and dermatophyte test medium (DTM), then incubated at room temperature, observed daily for growth up to 8 weeks. The growth was identified by macroscopic and microscopic characteristics.

Onychomycosis was observed to be more common in older age group and in female patients.71% of cases were from rural areas.

High association between onychomycosis and tinea pedis was noticed in our study (73.0%), this association significantly increased in diabetic patients($P < 0.001$).

DLSO was the most common presentation of onychomycosis in our study, followed by PSO, then the combined presentation of both DLSO and TDO. TDO alone was detected only in one case. The combined presentation of both DLSO and TDO was significantly increased in diabetic subjects ($P= 0.002$). All these presentations were detected in both finger- and toe nails with no much difference except PSO with paronychia that was seen only in finger nails.

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The severity of onychomycosis showed some increase in diabetic subjects more than non-diabetics. In the diabetic group, the severity of onychomycosis was significantly increased in patients with longer duration of DM (P = 0.004), with type I DM (P = 0.006), in patients with uncontrolled diabetic condition (P = 0.008), and in diabetic patients complicated with peripheral vascular impairment and peripheral neuropathy (P = 0.012) and those with retinopathy (0.006).

94% of our cases were mycologically confirmed for onychomycosis, 70% by culture alone, 5% by KOH alone, and 19% by both culture and KOH. Dermatophytes were the most common isolated pathogen in both diabetic and non diabetic subjects, followed by non-dermatophytic molds then yeasts in non-diabetics , while yeasts preceded molds in diabetics. Of the dermatophytes, T.rubrum and T.mentagrophytes were the commonest organisms followed by E.floccosum, T. tonsurans, T.violaceum and T.verrucosum.

Different fungi were isolated from both finger- and toe nails with no much difference except Candida species which were isolated only from finger nails.

From the previous we can conclude that :

- Onychomycosis is caused, in both diabetics and non-diabetics, mainly by dermatophytes , specially T.rubrum

and T.mentagrophyte , to lesser extent by molds and yeasts, in both diabetics and non-diabetics.

- DLSO is the most common presentation of onychomycosis followed by PSO then combined presentation of DLSO and TDO while TDO and SWO are rare presentations.
- A single pathogen can give rise to more than one clinical pattern of onychomycosis with the exception of Candida species which were presented only as PSO .
- Onychomycosis is usually associated with T.pedis and this association is more marked in diabetic patients.
- Onychomycosis is more common in older age group, and females, while the severity of onychomycosis is significantly related to male gender, type I DM, duration of DM, uncontrolled diabetic condition , peripheral circulatory impairment, peripheral neuropathy and retinopathy.

From the previous we recommend that the recognition and early intervention before the development of nail infections or when onychomycosis is less severe is advisable because of the potential progressive nature of fungal infections and the potential serious sequelae associated with the persistence of untreated mycotic nails,

and that the education of the diabetic patient about the importance of foot and nail care should be an essential component of diabetic management.

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Arabic
Summary

الملخص العربي

يعد مرض الأظافر الفطري أكثر الأمراض التي تصيب الأظافر شيوعا ويسبب هذا المرض ٣ أنواع من الفطريات وهى فطريات الجلد و الخميره والفطريات الصغيرة .وعلى الرغم من أن مرض الأظافر الفطري لا يشكل تهديدا لحياه المريض المصاب به ولكن له تأثيرا مهما على طبيعة حياه المريض ويسبب تأثيرا اكبر لمريض البول السكري مقارنه بغير المصاب بمرض البول السكري و هذا نتيجة للعواقب الخطيرة التي قد تنتج في مرضي البول السكري و خاصة عند وجود اعتلال في الأوعية الدموية الطرفية أو اعتلال في الأعصاب الطرفية أو اعتلال الشبكية مما قد ينتج عنه في نهاية الأمر فقدان المريض لأحد أطرافه.

الهدف من هذه الدراسة هو تحديد شدة مرض فطريات الأظافر في مرضى البول السكري مقارنة بمرضى فطريات الأظافر غير المصابين بمرض البول السكري و معرفة أنواع الفطريات الأكثر شيوعا في مرضى الأظافر الفطري في كل من المصابين بمرض البول السكري و غير المصابين به .

أجريت هذه الدراسة على عدد منة مريض تم تشخيصهم إكلينيكيا كمصابين بمرض الأظافر الفطري منهم ستون مريضا مصابون بمرض البول السكري و أربعون مريضا غير مصابين بمرض البول السكري و روعي أن يكون مرضى كلا المجموعتين متناسبين من حيث السن و الجنس ، و قد تم اختيار المرضى من المترددين على العيادة الخارجية للأمراض الجلدية بمستشفى المنصورة الجامعي و العيادة الخارجية لمرضى البول السكري بمستشفى الباطنة التخصصي التابعة لمستشفى المنصورة الجامعي.

و قد تضمنت هذه الدراسة عدد ٢٣ من الذكور و عدد ٧٧ من الإناث تتراوح أعمارهم بين ٢٠ عاما و ٧٥ عاما ولكل مريض قد أخذ تاريخ مرضي كامل خاصة العمر ،الجنس ، محل الإقامة ،الوظيفة ،مخالطه الحيوانات والتاريخ المرضى الكامل لكل من مرض الأظافر الفطري ومرض البول السكري،كما تم فحص كل مريض فحصا إكلينيكيا و جلديا شاملا.

تم اخذ العينات من أجزاء صغيره من الأظافر المصابة و من كحت لمهد الظفر و تم

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فحصها مجهريا باستخدام محلول هيدروكسيد البوتاسيوم وزراعه جزء من كل عينه على كل من مزارع سبارود دكستروز أجار و مزارع ديرماتوفيت تست مديم وتم وضع المزارع في درجه حرارة الغرفة و ملاحظتها يوميا لمده ٨ أسابيع ثم التعرف على نتيجة الزرع بفحصها بالعين المجردة و مجهريا.

وقد وجد أن مرض الأظافر الفطري كان أكثر شيوعا في المرضى الأكبر سنا و في الإناث و قد كان ٧١% من المرضى من مناطق ريفية.

و قد لوحظ وجود ارتباط ملحوظ بين مرضى الأظافر الفطري و سعفة القدم (٧٣%) وقد ازداد هذا الارتباط بشكل كبير في مرض البول السكري.

و قد لوحظ أن شده مرض الأظافر الفطري ازدادت إلى حد ما في مرض البول السكري عن غير المصابين بهذا المرض. و في مرض البول السكري ازدادت شده مرض الأظافر الفطري يشكل ملحوظ مع ازدياد مده الإصابة بمرض البول السكري و مع النوع الأول من مرض البول السكري و مع المرضى المصابين بمضاعفات اعتلال الدورة الدموية الطرفية واعتلال الأعصاب الطرفية و اعتلال الشبكية.

من السابق يمكن استنتاج الآتي :

- في كل من مرضى البول السكري و غير المصابين بهذا المرض تمثل فطريات الجلد السبب الرئيسي في مرض الأظافر الفطري، خاصة كل من تريكو فيتون ربرم و تريكو فيتون منتجروفيت، يليها الفطريات الصغيرة و الخميرة.

- يمكن لنوع الفطر الواحد أن يسبب أكثر من شكل إكلينيكي من أشكال مرض الأظافر الفطري فيما عدا المبيضات.

- يقترن مرض الأظافر الفطري في معظم المرضى مع سعفة القدم و يزداد هذا الارتباط بشكل ملحوظ في مرضى البول السكري .

- يعد مرض الأظافر الفطري أكثر شيوعا بين المرضى الأكبر سنا و الإناث بينما تزداد شدة هذا المرض بشكل ملحوظ في المرضى الذكور و في النوع الأول من مرض البول السكري و مع ازدياد مدة الإصابة بمرض البول السكري و مع اعتلال الدورة الدموية الطرفية و اعتلال الأعصاب الطرفي و اعتلال الشبكية في مرضى البول السكري.

وبنـاء علـي الـسابق نوصـي بـضرورة التشخيص و العـلاج المبكـر لمـرض الأظـافر الفطري تجنبا لعواقب هذا المرض وبضرورة أن يكون تعليم مريض البول السكري كيفيـة العناية بالقدم و بالأظافر جزء رئيسي من علاج مرض البول السكري.

جامعــة المنصورة
كليــة الطــب
قسم الأمراض الجلدية والتناسلية والذكورة

دراسة إكلينيكية وميكولوجية لمرض الأظافر الفطري في مرضي البول السكري

رسالة مقدمة من

الطبيبة: فاتن عبد اللطيف محمود ابراهيم

بكالوريوس الطب والجراحة

طبيب مقيم بقسم الأمراض الجلدية والتناسلية والذكورة

توطئة للحصول على درجة الماجستير في الأمراض الجلدية والتناسلية والذكورة

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