UNIVERSITY OF BABYLON

COLLEGE OF MEDICINE

A STUDY OF THE OCCURRENCE OF ORAL CANDIDIASIS IN DIABETIC PATIENTS IN NAJAF PROVINCE

A Thesis

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بِسْمِ اللهِ الرَّحْمَنِ الرَّحِيمِ

((وَعِندَهُ مَفَاتِحُ الْغَيْبِ لاَ يَعْلَمُهَا إِلاَّ هُوَ وَيَعْلَمُ مَا فِي الْبَرِّ وَالْبَحْرِ وَمَا تَسْقُطُ مِن وَرَقَةٍ إِلاَّ يَعْلَمُهَا وَلاَ حَبَّةٍ فِي ظُلُمَاتِ الأَرْضِ وَلاَ رَطْبٍ وَلاَ يَابِسٍ إِلاَّ فِي كِتَابٍ مُّبِينٍ))

صدق الله العلي العظيم

سورة الأنعام

)٥٩ (الآية

Dedication

To*:*

Our Martyrs, the Memory of my friend: Martyr Hussein, and all those who have provided the facilities to complete this research.

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جا معة با بل

كلية الطب

درا سة حدوث ا لمبيضات ا لفموية عند مرضى السكري في محافظة ا لنجف

رسالة مقدمة إلى مجلس كلية الطب –جامعة بابل كجزء من متطلبات نيل درجة الماجستير في الأحياء المجهرية

من قبل الطالب

عدي حسين كاظم

٢٠٠٦

الخلاصة

تعد المبيضات البيضاء السبب الرئيس للإصابة بالفطر يا ت الفموية على مستوىا لعالم .يهدف هذا البحث إلى دراسة المبيضات البيضاء عند مرضى السكري في المنطقة.لقد أجريت الدراسة على مرضى السكري الذين يتلقون العلاج في اكبر اثنين من المستشفيات في مدينة النجف حيث تمت دراسة سلوك المبيضات الفموية وانتشارها بين مرضى السكري وتحديد تأثير عوامل العمر,الجنس,داء السكر من حيث النوع ومدة الإصابة إضافة إلى بيئة المريض واستخدام المضادات الحياتية.

لقد تمت دراسة مدى الإصابة بالمبيضات الفموية في عينة مكونة من مئة مريض مصاب بداء السكري وقورنت النتائج مع مجموعة سيطرة مكونة من مئة شخص معافى خلال فترة الدراسة الممتدة بين تشرين الأول ٢٠٠٤ إلى كانون الثاني ٢٠٠٥ وان الأشخاص الذين شملتهم الدراسة كانوا جميعا معافين باستثناء داء السكري ومن غير المتعاطين للكورتيزونات أو الأدوية السمية ومن لم يحملوا اسنانا" أصطناعية ومن غير المدخنين.

أظهرت الدراسة نسبا" عالية" للحمل الفموي للمبيضات البيضاء بين مرضى داء السكري (٣٩%) بالمقارنة مع مجموعة السيطرة (١٨ %) و كذلك كثافة نمو الفطر. نسبة الحمل الفموي للمبيضات البيضاء أعلى عند مرضى السكري- النوع الأول (٤٦%) مقارنة" بالنوع الثاني (٣٢%) وبفارق ذي دلالة معنوية ولكن لم يكن هنالك تأثير واضح لمدة الإصابة بداء السكري أو عمر المريض. فيما يتعلق بالجنس اظهرت الدراسة وجود فرق معنوي في نسبة الحمل الفموي بين الإناث(٥٤%) مقارنة" بالذكور(٢٤%) .

كما لوحظ وجود فرق ليس معنوياً بين سكان المدينة(٣٦%) مقارنة بسكان القرى والأرياف (٤٢%). مجموعة مرضى السكري الذين يتعاطون المضادات الحياتية لأسباب مرضية اخرى اظهرت نسبة حمل فموي اكبر (٥١%) مقارنة بمجموعة مرضى السكري الذين لم يتعاطون المضادات الحيوية ولكن الفرق لم يكن معنوياً.

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Abbreviations

(+): Carry *C .albicans* in mouth.

(-): Do not carry *C. albicans* in mouth.

A.G. Antibiotic Treated Diabetic Patients Group

C.G. Control Group Involved Healthy Subjects.

D.G. Diabetic Patients Group not treated with antibiotic.

IDDM Insulin Dependent Diabetes Mellitus

mg milligram

mmol millimole

NIDDM Non Insulin Dependent Diabetes Mellitus

No. Number

O.C. Oral Candidiasis

Spp. Species

Abstract

Candida is consider as the major cause of oral candidiasis (O.C.) in people worldwide. This work has been designed to study oral candidiasis in diabetic patients in Najaf. Where patients attended the two main hospitals in this city. The occurrence of oral candidiasis has been studied according to age, sex, type of D.M. ,disease duration , residence of patients, and antibiotics usage. One hundred diabetic patients group (D.G.) , One hundred antibiotics treated patients group (A.G.) and One hundred healthy subjects as control group (C.G) have been studied .All subjects included in this study were free from systemic disease apart from diabetes, not on corticosteroids or cytotoxic drugs, not wearing artificial denture and non smokers. The study started in November ٢٠٠٤ till January ٢٠٠٥.The frequency of oral candidiasis was significantly higher among (D.G.)(٣٩ %) than among (C.G.)(١٨ %).

The use of antibiotics increased the intensity and occurrence of infection (٥١٪Versus ٣٩٪) in diabetic patients taking antibiotic. Type ١ diabetes mellitus has been associated with higher oral carriage rate of *C. albicans* (٤٦٪) than type ٢ (٣٢٪).The patients were categorized into four age groups at ٢٠ years intervals ,the highest percentage of oral carriage (٤٣.٧٥٪)was among age group who were (٤١-٦٠ years),the next were those over ٦٠ years of age (٤٠٪), (٣٨.٣٨٪)was in those less than ٢٠ years and the least (٣٦.٣٧٪)was among those (٢١-٤٠ years) but the differences were not significant (P>٠.٠٥).In addition, the duration of D.M. was categorized into four groups: the result of each group was ٣٥٪ in less than ١ year ,٤٠.٦٢٪in (١-٤)years ,٣٩.١٣٪ in (٥-١٠)years and ٤٠٪ in ١٠ years and more. The effect of the

duration of D.M. on the oral carriage rate was not significant. There were significant differences (P< ٠. ٠٥) in oral carriage rate of *C. albicans* between female (٥٤٪) and male (٢٤٪).There was a difference in carriage rate but not significant (P> ٠. ٠٥) between the rural (٤٢٪) and the urban (٣٦٪) diabetic patients with regared to oral candidiasis.

Introduction

Candidiasis, also known as candidosis or moniliasis refers to the presence of the yeast like fungi (*Candida*) at the site in or on the body such as mouth or vagina (Yas, ١٩٨٩). In normal healthy individuals, there is a balance between the presence of *Candida* species as normal flora and the normal defense mechanism of the body and in the presence of any predisposing factor like: diabetes mellitus, mal-nutrition, humidity, burn, HIV infection, renal failure, endocrine disturbance, pregnancy,oral

contraception, cancer, indiscriminate usage of antibiotics, glucocorticoids and cytotoxic drugs will cause opportunistic infection (Holmes *et al*,٢٠٠٢; Alkhaffaji *et al*.,٢٠٠٢).Other predisposing factors suggested by Akpan and Morgan (٢٠٠٢) include Cushing's syndrome, impaired salivary gland function, dentures, high carbohydrate diet, extremes of life, smoking and malignancies. Darouche *et al.* (١٩٩٦) and Loeb *et al.* (١٩٩٩) mentioned that *Candida albicans* was the most prevalent fungal pathogen of human, this yeast would

cause superficial and systemic infection in immunocompromized individuals in addtion to that oral thrush was an acute form of oral candidaisis and was one of the most common infections in diabetic patients (Dedic and Masic, ١٩٩٩).

Thrush appears as a whitish, creamy plaque in the mouth and on the tongue.Underneath the whitish material there is redness that may bleed and the lesions can slowly increase in number and size (Akpan and Morgan, ٢٠٠٢). Manfredil *et al.* (٢٠٠٢) have suggested that candidal density has also been reported higher in diabetes mellitus than in non-diabetic subjects.

Although angular stomatitis due to *Candida* is a classic complication in diabetic children and an occasional complication in diabetic adults , increased concentrations of salivary glucose reportedly account for its occurrence (Huntely,٢٠٠٥).Cases of clinical candidiasis are common in diabetic patients and involvement of the glans penis and the vulva appears common in type-٢-diabetes (Manfredil *et al.* ,٢٠٠٢) vaginal candidiasis is almost universal among women with long-term diabetes, and yeast infections may even be the presenting manifestation of diabetes (Huntely,٢٠٠٥).

Aims of the study

١-Determining the occurrence of oral candidiasis in diabetic patients attending local hospitals in Najaf.

٢-Knowing the effect of the duration and type of diabetes mellitus on the occurrence of oral candidiasis in diabetic patients.

٣- Knowing the effect of age on the occurrence of oral candidiasis in diabetic patients.

٤-Estimating the occurrence of oral candidiasis in diabetic patients with regard to sex and residence of patients as well as socioeconomic status.

٥-Assessment of the use of antibiotics that inhibit microflora and flourish the oral candidiasis in diabetic patients.

٦-Up to date reports on occurrence of oral candidiasis in diabetic patients attending diabetic clinic in our local hospitals are very few

.This study has been planned to assess the rate in diabetic patients followed up in two major hospitals in the region (Najaf).

٢-١ *Candida albicans*

Candida albicans is a dimorphic fungus, i.e. it can take two forms and most of the time it exists as oval, single yeast cell, produced by budding as well as most yeasts do not produce mycelia (a mass of branching, threadlike hyphal filaments), but *Candida* has a trick up its sleeve (Hull *et al*.,٢٠٠٠). Normal room temperatures favour the yeast form of the organism, but under physiological conditions: the body temperature, the pH (the pH of blood and saliva is ٧.٤ in healthy individuals) and the presence of serum it may develop into a hyphal

form and pseudohyphae, composed of chains of cells, are also common, each cell of *C. albicans* can produce (١٠٠) cells in one hour when its requirements are available in the host. The term "yeast" and "yeastlike" were vernacular terms for unicellular fungal organisms that would reproduce by budding. (Akpan and Morgan, ٢٠٠٢; Mandell *et al*., ١٩٩٤). This is an inadequate definition mainly because:

A-Some yeasts reproduce by fission.

B-Many yeasts can produce mycelium or pseudohyphae under some nutritional and environmental conditions.

C-Many filamentous fungi may exist in a unicellular yeast-like form that reproduces by budding. (Akpan and Morgan, ٢٠٠٢; Mandell *et al*., ١٩٩٤).

The term "yeast" is of no taxonomic significance, it is useful only to describe a morphological form of a fungus. Most yeast have affinities to Ascomycota, but a small percentage have affinities to Basidiomycota and in the strictest sense of the word, there are no inherently pathogenic yeasts (Akpan and Morgan, ٢٠٠٢; Mandell *et al*., ١٩٩٤).

٢- ٢ Candidiasis or moniliasis:

It is called thrush when it grows in the mouth, especially in infants and it shows up on skin as a red, inflamed, and sometimes scaly rash, such as diaper rash, causes vaginal moniliasis, commonly known as a yeast infection, in the vagina and does candidal onchomycosis in the nails or parenchyma next to the nails as well as it can also affect the esophagus and the digestive tract in addtion to that candidal infection of the penis is more common among uncircumcised than circumcised men and may result from sexual intercourse with an infected partner (Koop,٢٠٠١).

٢-٣ Predisposing Factors for Oral Candidiasis

It has been suggested by Mandell *et al.* (١٩٩٤) that risk factors for oropharyngeal candidiasis are related to:

٢-٣-١ Pathogen

Candida as a pathogen has peculiar properties that increase its infectivity rate in the right environment. *Candida* is a fungus, first isolated in ١٨٤٤ from the sputum of a tuberculous patient (Mandell, ١٩٩٤).Like other fungi, they are non-photosynthetic, eukaryotic organisms with cell walls that lie external to the plasma membrane (Magee,٢٠٠٠).There is a nuclear pore complex within the nuclear membrane and the plasma membrane contains large quantities of sterols, usually ergosterol; apart from a few exceptions, the macroscopic and microscopic cultural characteristics of the different *Candida* species are similar (Reasner *et al*.,٢٠٠٣).They can metabolize glucose under both aerobic and anaerobic conditions, temperature influences their growth with higher temperatures such as ٣٧°C that are present in their potential host, promoting the growth of pseudohyphae (Akpan and Morgan, ٢٠٠٢; Manfredil *et al.*, ٢٠٠٢).

٢-٣-٢ Host factors

Akpan and Morgan (٢٠٠٢) have mentioned that predisposing factors for oral candidiasis may have local effect like smoking and dentures or systemic effect such as diabetes mellitus or antibiotics usage .

٢-٣-٢-١ Diabetes mellitus

Yeast infections play an important role in diabetics and therefore, poorly controlled diabetics and diabetics who have high levels of serum glucose carry a high risk,where in poorly controlled diabetics, the rate of *Candida* growth is found high and *Candida* growth rate increases as well as serum glucose level (Reasner *et al*.,٢٠٠٣).Inherited or acquired immune system deficiency, which may be due to a nutritional deficiency, increases demands on the immune system to combat environmental pollution, or damage to

the immune system (e.g., metabolic causes such as diabetes mellitus due to an increase in blood sugar)(Goins *et al*.,٢٠٠٠). Diabetes mellitus is a group of metabolic disorders with one common manifestation: Hyperglycemia ,in addtion to that chronic hyperglycemia causes damage to the eyes, kidneys, nerves, heart and blood vessels, the etiology and pathophysiology leading to the hyperglycemia, however, are markedly different among patients with diabetes mellitus, dictating different prevention strategies, diagnostic screening methods and treatments (Ozturkcan *et al.* ,١٩٩٣; Mandell *et al.*, ١٩٩٤).

Glucose is a simple sugar found in food. It is an essential nutrient that provides energy for the proper functioning of the body cells, where after meals, food is digested in the stomach and the intestine into glucose and other nutrients and the glucose in digested food is absorbed by the intestinal cells into the bloodstream and is carried by blood to all the cells in the body however, glucose cannot enter the cells alone but it needs assistance from insulin in order to penetrate the cell membrane; therefore, insulin acts as a regulator of glucose metabolism in

the Body and it is called the "hunger hormone" and as the blood sugar level increases following a carbohydrate rich meal, the corresponding insulin level rises with the eventual lowering of the blood sugar level and glucose is transported from the blood into the cell for energy (Wang *et al*.,١٩٩٨). When the blood glucose levels are lowered, the insulin release from the pancreas is turned off and when the blood sugar level drops below a certain level, hunger is felt and this often occurs a few hours after the meal (Alae *et al*.,١٩٩٣). In normal individuals, such a regulatory system helps to keep blood glucose levels in a tightly controlled range (William *et al*.,٢٠٠١). Cravings for sweets frequently form part of this cycle, which can lead to snacking, often for more carbohydrates and if the cravings are not fulfilled, sensations such as hunger, dizziness, moodiness, and a state of "collapse" can result (Ozturkcan *et al*, ١٩٩٣; Manfredil *et al*., ٢٠٠٢).

This system of auto-regulation and homeostasis is the function of the pancreas and it works around the clock and dysfunction of this auto- regulation system due to either to the inability of the pancreas to secrete any or insufficient insulin, or the pancreas overload from too much sugar ingested over a long period of time, or over compensatory mechanism, or a combination of these, results in the lack of insulin, and hence high blood sugar, and this is the hallmark of diabetes mellitus commonly called diabetes (Fisher *et al*.,١٩٨٧).According to Ozturkcan *et al*. (١٩٩٣), there are two main types of diabetes mellitus (and third type called Gestational Diabetes occur during pregnancy):

A-Type-١- diabetes mellitus

Is also called insulin dependent diabetes mellitus (IDDM), or juvenile onset diabetes mellitus.

B- Type-٢- diabetes mellitus

It is also referred to as non-insulin dependent diabetes mellitus (NIDDM), or adult onset diabetes mellitus (AODM).

٢-٣-٢-٢ Antibiotics

Repeated courses on antibiotics given therapeutically, for instance for acne, cystitis or upper respiratory tract infections, disrupt the normal competition between separate members of the resident flora of the gut; in other words, the normal balance of organisms in the bowel is upset (Wang *et al*.,١٩٩٨).*Candida* is thus allowed to proliferate (Dodds *et al*.,٢٠٠٠). Drugs which exert an immuno-suppressive affect such as steroids (including hormone residues in meat), oral contraceptives (the Pill), and immuno-suppressive drugs (such as those used to treat cancer) can also contribute to *Candida* (Reasner *et al*.,٢٠٠٣).The progesterone component of the Pill appears to encourage *Candida* growth, which is particularly noticeable in the second half of the menstrual cycle (Kelm and Schauer ,١٩٩٧).Candidiasis can also follow the onset of allergies and will resolve after the allergy has been treated (Ninane,١٩٩٤ ;Akpan

and Morgan,٢٠٠٢). They reduce the number of "friendly bacteria" (flora) in the intestinal tract and in mouth which normally keeps the *Candida albicans* under control (Wang *et al*.,١٩٩٨). Potential causes of *Candida albicans* overgrowth and *Candida* yeast infections, some antibiotics have local irritable effect as well as systemic effect by decreasing the activity of cellular immunity (decreasing the activity of macrophages and leukocytes)(Ninane,١٩٩٤;Akpan and Morgan,٢٠٠٢;Jose *et al*.,١٩٩٨).

٢-٣-٢-٣ **Immunosuppression**

As an opportunist, *Candida* is dependent on conditions which favour its steady growth. An immune system already undermined by other factors such as poor nutrition or exposure to environmental pollutants will be unable effectively to deter this relentless growth (Magee,٢٠٠٠). Thus *Candida* will in turn effectively weaken and disturb the immune system so that further damage may occur due to the invasion of viral agents such as Epstein-Barr virus, cytomegalovirus, herpes simplex virus, HIV and so on (Wang *et al*.,١٩٩٨). Disturbance of the ongoing process of 'self recognition' by the immune system is likely to lead further to the possibility of a range of auto-immune diseases (Ninane, ١٩٩٤; Akpan and Morgan, ٢٠٠٢).

٢-٣-٢-٤ Extremes of age:

It has been reported by Chung and Bennett (١٩٩٢) that the incidence of oral candidiasis occurs at early age and extreme of life, most probably due to immature immune system in infants and decreased defense system with old people.

٢-٣-٢-٥ Smoking

Smoking has been associated with an increased prevalence of the yeast in diabetes mellitus and it interacts with diabetes mellitus in promoting candidal colonization of the mouth and it has irritable

local effect and attention to these predisposing factors could reduce the incidence of thrush in diabetics (Tapper-Jones,١٩٨١).

٢-٣-٢-٦ Malignancies.

An aggressive treatment for malignant disease may produce unavoidable toxicities to normal cells and the mucosal lining of the gastrointestinal tract, including the oral mucosa, is a prime target for treatment-related toxicity by virtue of its rapid cell turnover rate and the oral cavity is highly susceptible to direct and indirect toxic effects of cancer chemotherapy and ionizing radiation ;this risk is due to multiple factors including high cellular turnover rates for the lining mucosa, a diverse and complex microflora (Cohen *et al.*, ١٩٩٨).

٢-٣-٢-٧ Nutritional deficiencies

Dietary foliate or iron deficiencies predispose to Candidiasis development, reports indicate that iron-deficient subjects with candidal infections have a decreasing in the number of lymphocytes(Cohen *et al.*, ١٩٩٨). Other studies show that the immune response can be restored when iron levels are normalized and most of these predisposing conditions cause decreased salivary flow and/or decreased excretion of immunoglobulins in the saliva(S-IgA) in addtion to that the latter decrease lowers the efficiency of the B-lymphocyte immunologic defense mechanism that should help control *Candida* infections; in addition, *Candida* growth in saliva is enhanced and the adhesive property of the yeast to oral tissue is increased by a high carbohydrate diet (Akpan & Morgan,٢٠٠٢; Ueta *et al.*,٢٠٠٠).

٢-٣-٢-٨ Cushing's syndrome

It is a hormonal disorder caused by a prolonged exposure of the body's tissues to high levels of the hormone cortisol and sometimes called "hypercortisolism",or prolonged exposure to exogenous glucocorticoids in addtion to that cortisol performs vital tasks in the body and it helps maintain blood pressure and cardiovascular

function, reduces the immune system's inflammatory response, balances the effects of insulin in breaking down sugar for energy, and regulates the metabolism of proteins, carbohydrates, and fats (Akpan and Morgan, ٢٠٠٢).

٢-٣-٢-٩ Saliva

Impaired salivary gland function can predispose to oral candidiasis (Epstein,١٩٩٠; Peterson ,١٩٩٠)**.**Secretion of saliva causes a dilutional effect and removes organisms from the mucosa and antimicrobial proteins in the saliva such as lactoferrin, sialoperoxidase, lysozyme, histidine-rich polypeptides, and specific anti -*Candida* antibodies, interact with the oral mucosa and prevent overgrowth of *Candida*, therefore conditions such as Sjögren's syndrome, radiotherapy of the head and neck, or drugs that reduce salivary secretions can lead to an increased risk of oral candidiasis (Akpan and Morgan, ٢٠٠٢).Ueta *et al*. (٢٠٠٠) indicate that the decreases in secretion of antimicrobial proteins in saliva and salivary PMN (Polymorphonuclear cells) activity are risk factors for oral candidiasis associated with aging and systemic diseases.

٢-٣-٢-١٠ Inhaled Steroids:

They have been shown to increase the risk of oral candidiasis by possibly suppressing cellular immunity and phagocytosis,the local mucosal immunity reverts to normal on discontinuation of the inhaled steroids (Akpan and Morgan,٢٠٠٢; Epstein,١٩٩٠).

٢-٣-٢-١١ Dentures

Predispose to infection with *Candida* in as many as ٦٥٪ of elderly people wearing full upper dentures and wearing of dentures produces a microenvironment conducive to the growth of *Candida* with low oxygen, low pH, and an anaerobic environment, this may be due to enhanced adherence of *Candida* spp. to acrylic, reduced saliva

flow under the surfaces of the denture fittings, improperly fitted dentures, or poor oral hygiene (Epstein,١٩٩٠; Ueta *et al*.,٢٠٠٠).

٢-٤ Etiology

Oral candidiasis is a common opportunistic infection of the oral cavity caused by an overgrowth of *Candida* species, the commonest being *Candida albicans* (Akpan and Morgan,٢٠٠٢). *Candida* organisms are fungi that normally inhabit the oral cavity, gastrointestinal tract, other mucous membranes, and skin (Epstein,١٩٩٠; Ueta *et al*.,٢٠٠٠).In most humans, this is a commensal relationship; and only a few *Candida* carriers actually go on to develops clinical signs of Candidiasis because yeast growth and colonization are impaired by the resistance of the host (Cannon *et al*.,١٩٩٥). When changes occur in the host environment causing imbalance of the flora or a decrease in resistance, *Candida* becomes an opportunistic pathogen, clinical problems range from relatively mild candidiasis to chronic recurrent candidiasis and life-threatening disseminated infections, these problems are growing, and *Candida* has been called the most important fungal pathogen in humans (Odds, ١٩٨٨).

Candida has been listed as the fourth most common isolate recovered from blood cultures in the United States (Jarvis and Marton,١٩٩٢). Among patients with severe infection acquired while in the hospital, the clinical characteristics of oral infection, local and systemic factors that predispose to infection and treatment in addtion to that though dentists commonly treat the oropharyngeal signs of *Candida* infection and colonization such as denture stomatitis, angular cheilitis, and thrush, they must realize that when dissemination and invasion of internal organs occur, *Candida* becomes life-threatening (Odds, ١٩٨٨). This has become exceedingly important in recent years as the dental patient pool has expanded to include more of the elderly, with an additional increase in organ transplant, immunocompromized, AIDS, chemotherapeutic, and antibiotic- or steroid-laden patients. *Candida* is a human fungal

pathogen that grows as a round yeast and replicates by budding of the ١٥٠ fungal species of *Candida,* about seven are known to be medically important pathogens: *C. albicans, C. tropicalis, C. parapsilosis, C. krusei, C. kefyr, C. glabrata, and C. guilliermondii* (Cannon *et al*.,١٩٩٥).

Other species have been isolated from humans but are considered opportunistic in immunocompromized patients, *C. albicans* is by far the most prevalent pathogenic fungal species found in the human body, yet *C. dubliniensis* has been found primarily in the oral cavities of immune-suppressed individuals (Sullivan and Westerneng ,١٩٩٥; Sullivan and Colleman ,١٩٩٨). Although it is a low-level constituent of the human oral flora, it has the potential to cause oral candidiasis (Coleman *et al*.١٩٩٧*;* Kurazi *et al.,*١٩٩٩). *C. albicans* and *C. dubliniensis* as well as other *Candida* species can be differentiated from one another by polymerase chain reaction techniques (PCR) that are being developed to aid in diagnosis (Kurazi *et al.,*١٩٩٩). Though *C. albicans* can exist in several forms, from the yeast to the hyphal, the yeast form is commensal and relatively harmless, where as the hyphal form is invasive, pathogenic, and the cause of clinical candidiasis. Hyphae are not always seen in lesions, but this could reflect a sampling error(Kerridge,١٩٩٣ ;Odds,١٩٩٣ ;Cannon *et al*.,١٩٩٥). Studies indicate that when the yeast forms grow hyphae, they then act like adherent filaments to spread across, attach, and burrow between and into epithelial cells, this is commonly seen in the more serious tissue invasion and especially in immunocompromized hosts (Stabb *et al*.,١٩٩٩).

٢-٥ Clinical Manifestations of Oral Candidiasis

Five specific clinical oral manifestations of candidiasis have been described: pseudomembranous, acute atrophic/erythematous, chronic atrophic, angular cheilitis and chronic hypertrophic/hyperplastic and the clinical presentation may include more than one of these manifestations but usually one is predominant (Wenzel, ١٩٩٥).

Acute pseudomembranous candidiasis is the one in which the lesions are superficial curd-like white patches that wipe off, leaving an erythematous base and they are located on any or all mucosal surfaces, particularly the buccal mucosa, mucobuccal folds, oropharynx, and dorsal tongue, infants and the elderly are predilected (Pittel *et al*.,١٩٩٣). Predisposing factors include a history of broad-spectrum antibiotics, steroids, nutritional deficiency, diabetes, malignancy, chemotherapy, radiation therapy, and cell-mediated immunity dysfunction including HIV infection (Kobayshi *et al*.,١٩٩٤).

Acute atrophic candidiasis: Loss of the *Candida* organism pseudomembrane causes small to generalized large red lesions with inflammation of surrounding tissues and the tongue typically shows depapillation and dekeratinization in addtion to that atrophic lesions are most often seen on the tongue and palate (Pittel *et al*.,١٩٩٣).Predisposing factors include broad-spectrum antibiotics and corticosteroid aerosols as may be used by asthmatics (Shibata *et al.,*١٩٩٦).Chronic atrophic candidiasis : The lesions are chronic showing erythema and edema with a slight velvety/pebbly surface and small erosion may also be seen as well as the lesions are located on the palate and upper and lower edentulous ridges and are frequently encountered under dentures and predisposing factors include ill-fitting or poorly cleaned dentures, as well as those enumerated for the other forms of candidiasis (Kapteyn *et al.,*٢٠٠٠;Uchiyama *et al*. ٢٠٠٠).

Angular cheilitis (perleche): Angular cheilitis is the same as intraoral chronic atrophic candidiasis, just in a different location;clinically, there are fissures at the commissural angles that allow pooling of saliva and incubation of yeast forms, crusting with underlying erythema and the lesions are localized to the corners of mouth and predisposing factors include ill-fitting dentures with over closure, drooling at corners of mouth, lip-licking habits, and thumb/digit-sucking habits (Regezi and Sciubba, ١٩٨٩).

Chronic Hypertrophic/hyperplastic candidiasis (*Candida* leukoplakia) Chronic nodular hard lesions appear white, cream-coloured, or red (Shibata *et al.,*١٩٩٦).These hypertrophic lesions are located on the surface of tongue, buccal mucosa, palate, denture-bearing areas, central dorsum of tongue (median rhomboid glossitis), as papillary nodules on palate usually under dentures (papillary hyperplasia), and in areas of epithelial hyperplasia (pre-existing leukoplakias and keratotic papillomas) (Jones *et al*.,١٩٩٥).Predisposing factors include cellular hyperplasia, oral precancerous lesions, smoking, and denture wearing (Soares *et al*.,٢٠٠٠). There is a generalized mucocutaneous form of candidiasis that presents as chronic infection of the oral mucosa, nails, skin, and vaginal mucosa. Resistance to therapy is common which is usually initiated by pseudomembranous candidiasis and then proceeds to a chronic form (Jones *et al*.,١٩٩٥). A familial form, possibly autosomal recessive, also exists, with about half of the patients presenting with associated endocrinopathy (hypoparathyroidism, Addison's disease, hypothyroidism, or diabetes mellitus) (Wadsworth *et al*., ١٩٩٣). Other familial forms are associated with abnormalities of iron metabolism or cell-mediated immunity (Regezi and Sciubba,١٩٨٩).

٢-٦ General Symptoms of *Candida albicans* infection

Thrush appears as creamy-white or bluish-white patches on the tongue which is inflamed and sometimes beefy red and on the lining of the mouth, or in the throat (Jones *et al*.,١٩٩٥). Diaper caused by *Candida* is an inflammation of the skin, usually red and sometimes scaly as well as vaginitis is characterized by a white or yellow discharge. Inflammation of the walls of the vagina and of the vulva (external genital area) causes burning and itching. Infections of the fingernails and toenails appear as red, painful swelling around the nail. Later, pus may develop and infection of the penis often results in balanitis (inflammation of the head of the penis (Wadsworth *et al*., ١٩٩٣).

An infection in the bloodstream can affect the kidneys, heart, lungs, eyes, or other organs causing high fever, chills, anemia, and sometimes a rash or shock however *Candida* can cause the following problems depending upon the organ infected:

A-In the kidneys: it can cause blood in the urine.

B-In the heart: it can cause murmurs and valve damage.

C-In the lungs: it can cause bloody sputum (mucus discharge) .

D-In the eyes: it can cause pain and blurred vision.

E-In the brain: it can cause seizures and acute changes in mental function or behaviour (Koop, ٢٠٠١).

Both men and women can have candidiasis. However, it does occur more frequently in women (especially young women) with more severe effects (Wadsworth *et al*., ١٩٩٣).

٢-٧ Epidemiology of *Candida*

Candida organisms live on the skin and mucous membranes of up to ٧٥ % of the population, they can live commensally without causing harm or can change to an aggressive form and invade tissue, causing both acute and chronic disease in the host (Dixon,١٩٩٦). Oropharyngeal candidiasis manifests clinically as acute pseudomembranous, acute atrophic, chronic atrophic, chronic hypertrophic/hyperplastic, and angular cheilitis. Systemic infection leading to candidemia can be devastating and cause up to a ٦٠ % mortality rate in medical or post-surgical intensive care wards (Cannon *et.al*.,١٩٩٩). Infections by pathogenic fungi, particularly *Candida* species, are both widespread and increasing in frequency (Dixon,١٩٩٦). Oral colonization by *Candida albicans* has been reported at ١٧.٧٪ in the healthy population (Cannon *et al*.,١٩٩٩).

Among hospitalized patients, oral carriage of *Candida albicans* rises to ٤٠.٦٪ ,healthy, asymptomatic women demonstrate an incidence of vaginal colonization by *Candida* of ١٥% to ٢٠٪, this percentage rises to ٢٠ - ٤٠٪ in healthy pregnant women and to ٤٠% to ٦٠٪ in human immunodeficiency virus-infected pregnant women (Sobel,١٩٨٥; Odds,١٩٨٨;Burnus *et al*.,١٩٩٧; Schuman *et al*.,١٩٩٨). Hospitals in the United States participating in the National Nosocomial Infection Survey System reported a nosocomial fungal infection frequency of ٣.٨ per ١,٠٠٠ discharges in ١٩٩٠, indicating an increase from ٢.٠ per ١,٠٠٠ discharges in ١٩٨٠ (Beck-Sauge and Jarvis, ١٩٩٣). *Candida* species accounted for ٧٨.٣٪ of all such nosocomial fungal infections, followed by *Torulopsis* (now *Candida*) *glabrata* and *Aspergillus* species,*C. albicans* were the most frequently isolated of all the *Candida* species (Beck-sauge *et al*.,١٩٩٣; Pfaller and Diekema,٢٠٠٢). Furthermore, a European study reported that fungal species in general accounted for ١٧.١٪ of intensive care unit-acquired infections (Vincent *et al*.,١٩٩٥).Using the National Nosocomial Infection Survey (١٩٨٠ to ١٩٩٠) data, Jarvis and Marton (١٩٩٢) reported that *Candida* species accounted for ٩.٤٪ of nosocomial urinary tract infections, ١٠.١٪ of nosocomial infections in adults and pediatric intensive care units, and ٧.٨٪ of nosocomial bloodstream infections (Vincent *et al*.,١٩٩٥).In ١٩٩٠, fungi as a whole accounted for ١٠٪ of all nosocomial bloodstream infections(Beck-sauge and Jarvis, ١٩٩٣).

Ten years later, the rates of bloodstream infections due to *Candida* are still rising, with half of these candidemias due to *C. albicans* (Rangel *et al.,*١٩٩٩). More recently, other *Candida* species such as *C. glabrata*, *C. tropicalis*, and *C. dubliniensis* have been isolated with increasing frequency (Pfuller *et al.,* ١٩٩٨). A study carried out by five university hospitals in the Netherlands also reported increased fungemia rates and Between ١٩٨٧ and ١٩٩٥, episodes of fungal bloodstream infections rose from ٠.٣٧ to ٠.٧٦ per ١٠,٠٠٠ patients of these infections, ٩٣٪ were due to *Candida* species whereas ٧٪ were due to *Cryptococcus* species (Voss *et al.* ,١٩٩٦). In addition to the observed increases in incidence, fungal infections continue to be

a serious clinical problem with respect to increased morbidity and mortality (Miller *et al*.,١٩٩٤ ;Wenzel,١٩٩٥). An analysis of records from the National Center of Health Statistics indicated that mycoses ranked ١٠th among the underlying causes of death in the United States in ١٩٨٠, but that by ١٩٩٧ this rank had risen to ٧th (Wang *et al*.,١٩٩٨). Increased morbidity due to nosocomial fungal infections also has taken a heavy toll, resulting in longer hospital stays (Wenzel,١٩٩٥; Chapuis *et al*.,٢٠٠١; Leleu *et.al.*٢٠٠٢) and higher patient care costs (Goff *et al*.,١٩٩٦;Tambyah,٢٠٠٢). The increasing incidence of fungal infections has, to a certain degree, coincided with the incredible medical advances of the last few years in addtion to that life-prolonging technologies, although welcomed by medicine and those it cares for, have unfortunately created numerous opportunities for emerging fungal infections (Vincent *et al*.,١٩٩٥).The rising number of immunocompromized patients, whether through immunosuppressive therapy, AIDS, or other ailments, the prophylactic use of antimicrobics, and the increasing number of indwelling catheters and prosthetic devices seen among patients all unwittingly subject patients to the threat of invasive disease (Dixon *et al*.,١٩٩٦;Xing and Ning,٢٠٠٣).

Patients with central intravenous (IV) catheters were over three times more likely to have bloodstream infections than patients without such catheters (Beck-sague and Jarvis, ١٩٩٣). Patients undergoing orthotropic liver transplantation demonstrated an incidence of invasive fungal infection of ٥% to ٤٢٪, with *Candida* species being the most commonly isolated organism, followed by *Aspergillus* species (Collins *et al*.,١٩٩٤*).* A study of heart transplant patients reported that fungal infections accounted for only ٧٪ of all infections, they were associated with the highest (٣٦٪) mortality (Miller *et al*.,١٩٩٤). Taken together, these clinical observations strongly reinforced the necessity for understanding the relationship between fungus and host and the interaction between fungus and patient occurs first at the level of the cell wall (Calderon,١٩٩٣).The cell wall of most fungi is composed of glycoproteins embedded within a polysaccharide matrix or scaffolding. (Vincent *et*

al.,١٩٩٥).Additionally, some fungal species produce a polysaccharide capsule that surrounds the cell wall (e.g. the glucuronoxylomannan) (Beck-sague and Jarvis, ١٩٩٣).

٢-٩ *Candida* Pathogenesis

C. albicans can exist in several forms, from the yeast to the hyphal and the yeast form is commensal and relatively harmless, where as the hyphal form is invasive, pathogenic, and the cause of clinical candidiasis and hyphae are not always seen in lesions, but this could reflect a sampling error (Kerridge ,١٩٩٣;Odds,١٩٩٤;Cannon *et al.*,١٩٩٩).

Studies indicate that when the yeast forms grow hyphae, they act like adherent filaments to spread across, attach, and burrow between and into epithelial cells and this is commonly seen in the more serious tissue invasion and especially in immunocompromized hosts (Staab *et al*.,١٩٩٩).

٢-٩-١ Adherence and local invasion

Colonization of the oral cavity appears to be facilitated by several specific adherence interactions between *C. albicans* and oral surfaces which enable the yeast to resist host clearance mechanisms (Cannon *et al.*,١٩٩٩).Thus, *Candida* has been shown to adhere to complement receptors, various extracellular matrix proteins, and specific sugar residues displayed on host or bacterial surfaces in the oral cavity and oral candidiasis results from yeast overgrowth and penetration of the oral tissues when the host's physical and immunological defenses have been undermined (Cannon *et al.*,١٩٩٩). Adherence by the hyphae to oral keratinocytes may be partially due to a protein called Hwp١, which is present in *Candida* filaments but not in the yeast form and this protein forms a covalent and permanent bond to epithelial cells with the help of the enzyme transglutaminase and without Hwp١, the adherence to human oral mucosal cells is reduced ٨٠ %; mice infected with *Candida* strains

containing Hwp١ develop more severe disease than those infected with Hwp١-free *Candida* (Staab *et al*.,١٩٩٩*).*

٢-٩-٢ Secreted Proteins

A complex assortment of hydrolytic enzymes such as proteinases (secreted aspartyl proteinase), phospholipases, acid phosphatase, chitinases, esterase and glucoamylase can be found in culture filtrates of *C. albicans* cells (Chaffin *et al*.,١٩٩٨). Tavares *et al*. (١٩٩٣) have purified from the supernatants of *C. albicans* cultures an immunosuppressive B-cell mitogenic (ISM) protein that plays an important role in the survival of the microorganism in the host and glycolytic enzymes are abundant immunodominant antigens during *C. albicans* infections and *C. albicans* enolase (٢-phospho-D-glycerate hydrolase; EC ٤.٢.١.١١) phosphoglycerate kinase (PGK; EC ٢.٧.٢.٣), alcohol dehydrogenase (ADH; EC ١.١.١.١), pyruvate kinase (PYK; EC ٢.٧.١.٤٠), aldolase (EC ٤.١.٢.١٣) and glyceraldehyde-٣-phosphate dehydrogenase(GAPDH; EC ١.٢.١.١٢) have been described as major allergens or immunogens during candidiasis(Gil *et al*.,١٩٩٧). All of these enzymes appear to be highly conserved and glycolytic enzymes of *C. albicans* are immunogens during candidiasis (Cannon *et al.*,١٩٩٩).

Enolase seems to be the most immunodominant antigen in humans and anolase stimulates both humoral and cellular immune responses in mice and these responses are indicative of *C. albicans* proliferation in the host (Chaffin *et al*., ١٩٩٨; Zahing *et al*., ١٩٩٨).

C. albicans also has the ability to produce secreted aspartyl proteinase that degrade many human proteins found at lesion sites and the proteins affected include albumin, hemoglobin, keratin, collagen, mucin, and secretory immunoglobulin A(SIg-A) in addtion to that the hyphal forms with increased adherence have been found to express secreted aspartyl proteinase (Naglik *et al.,*١٩٩٩). Louis *et al*.,(٢٠٠٠) suggest that *C.albicans* may both adhere to and enzymatically degrade, mucins by the action of secretory aspertyle

proteinase and that both properties may act to modulate *Candida* populations in the oral cavity and gastrointestinal tract and the surface-attached human C٤ binding proteins(C٤BP) serves multiple functions relevant for immune evasion and likely pathogenicity.It inhibits complement activation at the yeast surface and, in addition ,mediates adhesion of *C. albicans* to host endothelial cells (Meri *et al.,*٢٠٠٤;Yuan *et al*.,١٩٩٨).

٢-٩-٤ Systemic Invasion of *C. albicans*

Candida is present in the mouths of ٢٥ % to ٧٥ % of the population, depending on the study and sampling techniques and current large-scale sampling methods such as saliva sampling or oral rinse procedures may identify the presence of yeast but do not diagnose clinical candidiasis or colonization. Patients who have intra-oral candidiasis have been found to have greater than ٤٠٠ colony-forming units per ml of saliva while carriers of *C. albicans* have less than this amount(Epstein ,١٩٩٠). High levels may thus suggest the possibility of systemic candidiasis, particularly in the immunocompromized patient, but do not prove deep-seated infection (Reasner *et al*.,٢٠٠٣). This is particularly true in the hospital setting in that the problem of candidiasis is clear, but there are difficulties in establishing an early or even specific diagnosis. In hospital-acquired infections, *Candida* isolates from blood have become a common finding in the United States; similarly, instances of candidemia have increased in Europe, usually one-half of these occur in surgical intensive care units, while the other half occur in medical units (Wang *et al*.,١٩٩٨).In these settings, the mortality rates are attributable to candidemia range from ٤٠ % to ٦٠ % (Pittel *et al*., ١٩٩٣; Wenzel, ١٩٩٥).Antibodies against *C. albicans* or *Candida*-derived molecules in the sera of a patient may point to deep-seated infection and investigations to detect *C. albicans* proteins (Walsh *et*

al.,١٩٩١). Metabolites DNA and polysaccharides are being done(Flahaut *et al.,*١٩٩٨ ;Switchenko *et al*.,١٩٩٤) . For example, studies looking at mannans, which are a major component of *C. albicans* cell wall structure, may help determine the presence of *C. albicans* systemically by evaluating the antibody reaction to the organism, thus,enzyme immunoassays for sensitive detection of circulating *C. albicans* mannan and anti-mannan antibodies look promising in the diagnosis of systemic candidiasis (Sendid *et al*.,١٩٩٩).

This single cell fungi multiplies and develops toxins which circulate in the bloodstream which cause an array of maladies, *Candida* produces ethanol producing an intoxicating effect in the blood if the count level is too high and *Candida* grows rapidly when yeast has a food source like white sugar or white floor products and in severe cases, it produces much more than the liver can oxidize and eliminate (Hill *et al*.,١٩٨٧). It can produce a false estrogen and make the body think it has enough, which signals the body to cease production or send messages to the thyroid, making it think it has enough , stopping the production of thyroxin and the cause of this is menstrual problems and hypothyroid problems (Kelm and Schauer ,١٩٩٧). Another by- product is acetaldehyde and it is related to formaldehyde; this disrupts collagen production,fatty acid oxidation and blocks normal nerve functions and basically, it interferes with the normal functions of the entire body and is a severe problem (Sendid *et al*.,١٩٩٩).

One way to get an overdose of *Candida* in the system is by taking antibiotics and birth control pills, and consuming sugar products (Kelm and Schauer ,١٩٩٧). *Candida* feeds on antibiotics ;it is their food source (Sendid *et al*.,١٩٩٩). Yeast cell produces around (٧٥) known toxic substances that poison our body and these toxins contaminate the tissues where it weakens the immune system, the glands, the kidneys, bladder, lungs, liver and especially the brain and nervous system (Walsh *et al*.,١٩٩١). *Candida* yeast can become so strong that it transforms into fungal form where it starts to

penetrate the mucous lining of the gastrointestinal wall (Reasner *et al.*,٢٠٠٣). This penetration breaks down the protective barrier between the intestinal tract and bloodstream, allowing many unhealthy and toxic substances to poison the blood systemically (Shibata *et al.* ,١٩٩٥).

Proteins and other food wastes that are not completely digested or eliminated from the body can assault the immune system and cause strong allergic reactions, fatigue and other health problems and it also allows that *Candida* itself enters our bloodstream, from which it may find its way to other tissues, resulting in far-ranging effects such as soreness of the joints, chest pain, sinus and skin problems, etc as well as it can cause a heart failure because the heart can become encased with *Candida albicanis* (Shibata *et al.* ,١٩٩٥).Vaginal yeast infections are more prevalent today than ever, and they will never completely go away until the yeast has been cleared from the intestinal area. *Candida* can be sexually transmitted from one person to another (Reasner *et al.*,٢٠٠٣). other causes: cortisone, progesterone suppositories, diet, too much meat, weakened immune systems, and high-mercury levels from mercury fillings (William *et al.*,٢٠٠١).

٢-١٠ Diagnosis of *Candida albicans*

The diagnosis of mucocutaneous candidiasis is often made clinically and confirmation can be sought by scraping the lesions and doing either a KOH preparation or a Gram stain to look for budding yeast and pseudohyphae (Hull *et al.*,٢٠٠٠). Pseudohyphae are not always noted and are never seen in infection due to *C. glabrata* and in circumstances in which disease is recurrent or unresponsive to standard therapy, culture should be done to establish whether a more resistant species, such as *C. glabrata* or *C. krusei*, is the causative agent (Goff *et al.*,١٩٩٦). In the case of suspected esophagitis, endoscopy should be performed; biopsy of the plaque like lesions or ulcerations will show mucosal invasion with budding yeasts and pseudohyphae(Hill *et al.*,١٩٨٧). The diagnosis of invasive or disseminated candidiasis is more difficult as well as evidence for

dissemination is usually sought by culturing blood or other sterile body sites (Varki *et al.*,١٩٩٩).

Automated blood culture systems (Bac T/A lert, BACTEC, and ESP) are as sensitive as the lysis-centrifugation system for growing *Candida* from blood; however, no system is sensitive enough for clinicians to rely on blood cultures to always establish the diagnosis of invasive candidiasis or to rule out candidiasis as a diagnostic possibility (Varki *et al.*,١٩٩٩).

In addition, ١ to ٤ days are required for growth to occur; in a desperately ill patient, this is problematic; the tip of intravenous catheters that have been removed should be sent for culture (Reasner *et al.*,٢٠٠٣). No studies have evaluated the numbers of yeast that are indicative of infection and many physicians accept the growth of any yeast as affirming infection that requires treatment and because osteomyelitis and other focal forms of candidiasis are generally indistinguishable from bacterial infection, biopsy should be done for histopathology and culture studies (Carol *et al.*, ٢٠٠٤).

For the seriously ill patient suspected of having candidiasis, the development of pustular skin lesions or typical retinal lesions can be helpful (Hill *et al.*,١٩٨٧).Budding yeasts typical for *Candida* species should be sought by smearing material from a pustule on a slide and staining with Gram stain or by performing a biopsy of a lesion and staining the tissue section with a silver stain in addtion to that all patients who are candidemic or suspected of having disseminated *Candida* infection should have an ophthalmologic examination to look for typical retinal lesions. (Lain *et al.*,٢٠٠٠; Varki *et al.*,١٩٩٩).

Candida antibody tests have proved to be neither sensitive nor specific and are of no benefit in the diagnosis of *Candida* infections and cell wall or cytoplasmic antigen tests and metabolite detection systems also have not been proved useful in the clinical setting and although it is hoped that a polymerase chain reaction-based assay for *Candida* species will prove to be both sensitive and specific, this has not yet occurred; for current assays, the sensitivity is similar to that of standard blood culture methods (Carol *et al.*,٢٠٠٤). Oral candidiasis

should be differentiated from other diseases or conditions such as Herpes simplex virus**,** the human periodontal diseases, drug induced oral lesions and others(Lain *et al*.,٢٠٠٠).

٢-١١ Treatment

The first line of treatment in most cases of *Candida* infection is the use of frequent normal saline rinses, which can be found in all hospitals for bedside use or can be mixed at home using ١/٢ teaspoon of salt in ١ quart of water (Wang *et al*.,١٩٩٨).This helps to decrease the fungal counts and is soothing to the mucous membranes and the temperature of the rinse should be adjusted for comfort, if the epithelium is intact and not sloughing, the patient should gently swab or brush the mouth and use a tongue scraper (Varki and Diaz ١٩٨٤). Medication therapy falls into three basic categories; however, fungal resistance is a growing problem, and a new generation of drugs is needed, the polyenes, which include amphotericin -B and nystatin, help destroy the protein gradient in the cell due to leakage of cellular components(Goff *et al*.,١٩٩٦).Resistance to amphotericin-B is rare except for *C. lusitaniae, C. guilliermondii* and *Trichosporon beigelli* (White and Marr,١٩٩٨).

It is highly effective when given intravenously but toxicities and renal dysfunction are problematic.Nystatin is easy to use but some dislike the taste and the azoles which include ketoconazole, clotrimazole, fluconazole and itraconazole inhibit ergosterol biosynthesis in addtion to that fluconazole has been the drug of choice for AIDS-associated fungal infections, but resistance is rapidly becoming a problem, particularly among the non-*albicans* species (e.g.: *C. krusei, C. glabrata, C. lusitaniae* and *C. dubliniensis*) (Wingard *et al.,*١٩٩١; Sullivan and Haynes ,١٩٩٧ ; Sullivan and Coleman,١٩٩٨ ; Kirkpatrick *et al*.,١٩٩٨). The third category, ٥-Flucytosine, disrupts the DNA and protein synthesis of the cell. It is used in connection with amphotericin -B, fluconazole, and itraconazole (Dodds *et al*.,٢٠٠٠). For most cases seen in the general

dental arena, various forms of nystatin or clotrimazole are sufficient (Wingard *et al*.,١٩٩١). The recommended treatments also vary widely and include the elimination of specific foods, detoxification, herbal cleansing, multiple vitamins, special diets, colonics, and high enemas (Rees and Scott,١٩٧١). Keeping skin clean, dry, and free from abbreviations or cuts can help prevent skin *Candida* infections (Koop,٢٠٠١). The prognosis is good for oral candidiasis with appropriate and effective treatment. Relapse when it occurs is more often than not due to poor compliance with therapy, failure to remove and clean dentures appropriately, or inability to resolve the underlying/predisposing factors to the infection (Akpan and Morgan,٢٠٠٢; Wingard *et al*.,١٩٩١).

٣-١ Materials

Table (٣-١) showed the instruments and Cultures Media which were used in this study and their company:

Cultures Media	**Company**
Sabouraud's Dextrose Agar	Oxoid

Corn Meal Agar	Mast laboratories
Instrument	**Company**
Light Microscope	Olympus-Japan
Inoculating Loop	Oxford-Japan
Benson burner	Germany
pH Meter	Germany

٣-١-١ Cultures Media

The following types of culture media were used for the isolation and identification of *Candida albicans*. They were prepared and sterilized according to the instructions by the manufactures.

A-Sabouraud's Dextrose Agar Medium

Sixty five grams of this media was dissolved in one liter of distilled water and mixed well by exposing it to heat, it was sterilized by autoclave ,the pH of this medium is (٥.٦).To this medium, the following antibiotics: Penicillin, Streptomycin and

Chloramphenicol were added after sterilization and cooling to ٥٠ ˚c (Collee *et al*. ,١٩٩٦; Hill *et al*.,١٩٨٧).

B-Corn Meal Agar Medium

Sixty five grams of this medium was dissolved in one liter of distilled water and mixed well by exposing it to heat, it was sterilized by autoclave ,the pH of this medium is (٦.٠) .To this medium, the same antibiotics were added after sterilization and cooling to ٥٠ ˚c (Chaffin *et al*.,١٩٩٨).

٣-١-٢ Solutions

A- Normal Saline (٠.٨٥٪ Nacl)

This was used for direct microscopical examination.

D- KOH (Merk-Darmstadt)(٢٠٪)

It was also used for direct microscopical examination.

E- Stain

Gram stain was used for staining of the prepared smears**.**

٣-١-٣ Human Serum

It was used to identify the organism through its ability to form germ tubes when it was inoculated in the serum. It was prepared by centrifugation of clotted human blood at ٣٠٠٠ rpm/١٥min and aspirated by pipette (Chaffin *et al.*,١٩٩٨).

٣-١-٤ The Samples

Three hundred saliva samples were collected from the study subjects who were divided into three groups:(١٠٠) subjects healthy control group , (١٠٠) subjects diabetic patients group who were not on antibiotics treatment and (١٠٠) subjects antibiotic received diabetic patients group, attending to the main two hospitals in Najaf city named: AL Forat Hospital and AL Sadder Hospital**)**.During the period of the study which started in November ٢٠٠٤ till January ٢٠٠٥.

٣-٢ Clinical Evaluation For The Patients.

Clinical evaluation for the patients were performed according to the following formula and all results were reported:

-No:

-Name:

-Age:

-Sex:

- Residence:

-Occupation:

-Type of diabetes mellitus:

-Type ١ :

-Type ٢ :

-Duration of the disease:

-Health status:

-Debilitating illnesses:

-Diarrhea more than ٦ weeks, cancer or leukemia and other

diseases:

-Any antibiotic or chemotherapy for other disease was used:

-Signs of oro-esophageal candidiasis (sore mouth or disphagea, etc):

-Results of examination:*C. albicans+*or *C. albicans* -

٣-٣ Diagnosis of Diabetes Mellitus

Diabetic patients included in this study were diagnosed in hospitals based on World Health Organization (WHO) criteria.

Diagnosis of type of D.M. :to ovoid over lap between the two types of D.M. the following criteria were adopted:

Type -١- D.M. :any patient who was under the age of ٤٠ year and who required insulin since the diagnosis for metabolic control. Type -٢- D.M. : any patient who was above ٤٠ year and did not require insulin therapy since the diagnosis for metabolic control. Patients who required a change of treatment to insulin were excluded from the study.

٣-٤ Methods

For control group of healthy individuals oral swabs were taken

during attendance to the lab in the hospitals for checking ,using sterile swabs. Then oral swabs were obtained from diabetic patients also during attendance to the hospital. Saliva samples were taken from different sites of mouth and especially the dorsum of the tongue.

A-The Inoculation on Sabouraud's Dextrose Agar

All swabs were inoculated on sabouraud's dextrose agar plates to which Pencillin,chloramphenicol and streptomycin were added to prevent bacterial growth and the inoculated sabouraud's agar plates were then incubated at ٣٧˚c for ٢٤-٧٢ hour(Hill *et al*.,١٩٨٧).

B- Stain :

According to Collee *et al*. (١٩٩٦) Gram-staining is a four part procedure which uses certain dyes to make a fungal cell stand out against its background. The specimen should be mounted and fixed on a slide stained it. The reagents we will need to successfully perform this operation are:

١-Crystal Violet (The Primary Stain) .

٢-Iodine Solution (The Mordant).

٣-Decolorizer (Ethanol ٩٥٪) Fluka Chemika-Switzerland

٤-Safranin (The Counter Stain) .

٥-Distelled Water .

C-KOH

It was added one or two drops to the oral sample which contained oral epithelial cells, where KOH dissolved these cells making *C . albicans* clear.

٣-٥ Statistical Analysis:

The data were recorded and **s**tatistical analysis was performed using Chi square (X^2) and standard normal distribution (Z) test (Daniel ,١٩٩٩).

Results

٤-١ Detection of *C. albicans*

Several methods, which were previously mentioned, were used for the detection of *C. albicans*.

A-Cultivation on sabouraud's agar:

Were shown in Figure (٤-١).The colonies were oval and smooth in shape and had white creamy colour.

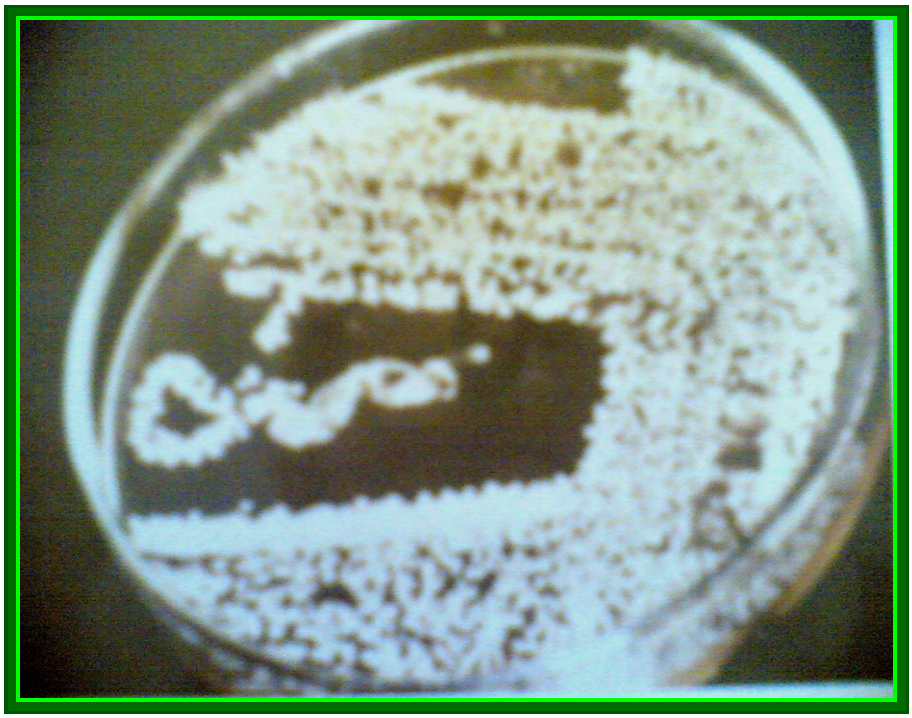

Figure (٤-١)

***C. albicans* grown on sabouraud's dextrose agar.**

B-Gram stain methods:

The cell of *C.albicans* stained with gram stain was shown in Figure (٤-٢).

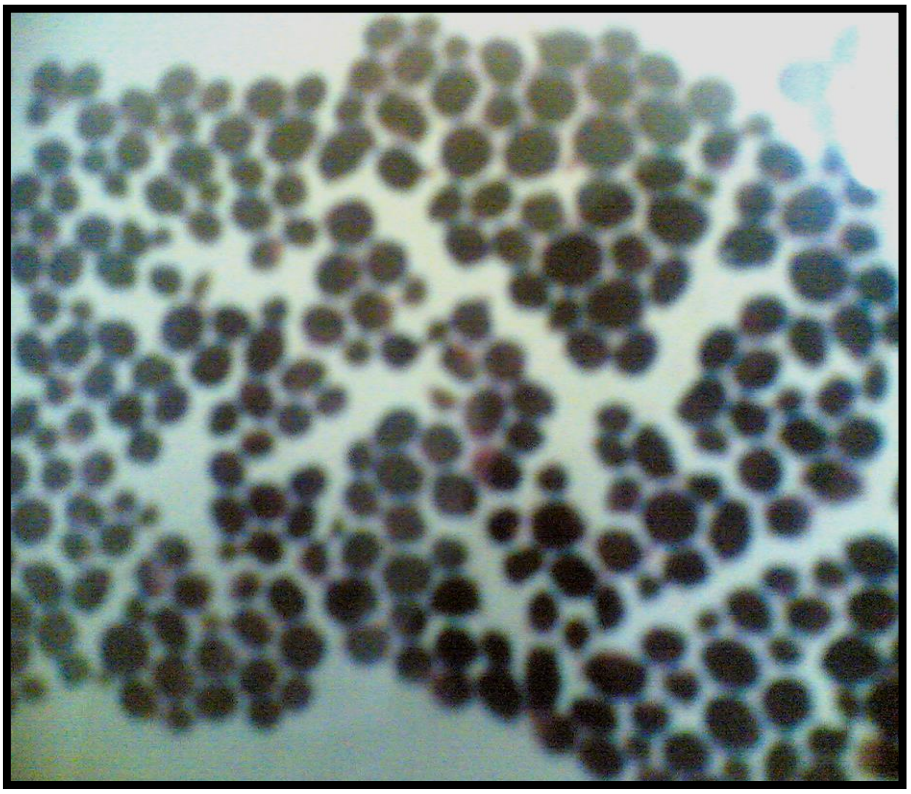

Figure (٤-٢)

Blastospores of *C. albicans* Gram stain on the slide(x ٤٠٠).

C-Germ tube detection:

Figure (٤-٣) showed germ tube production by *C . albicans* on corn meal agar.

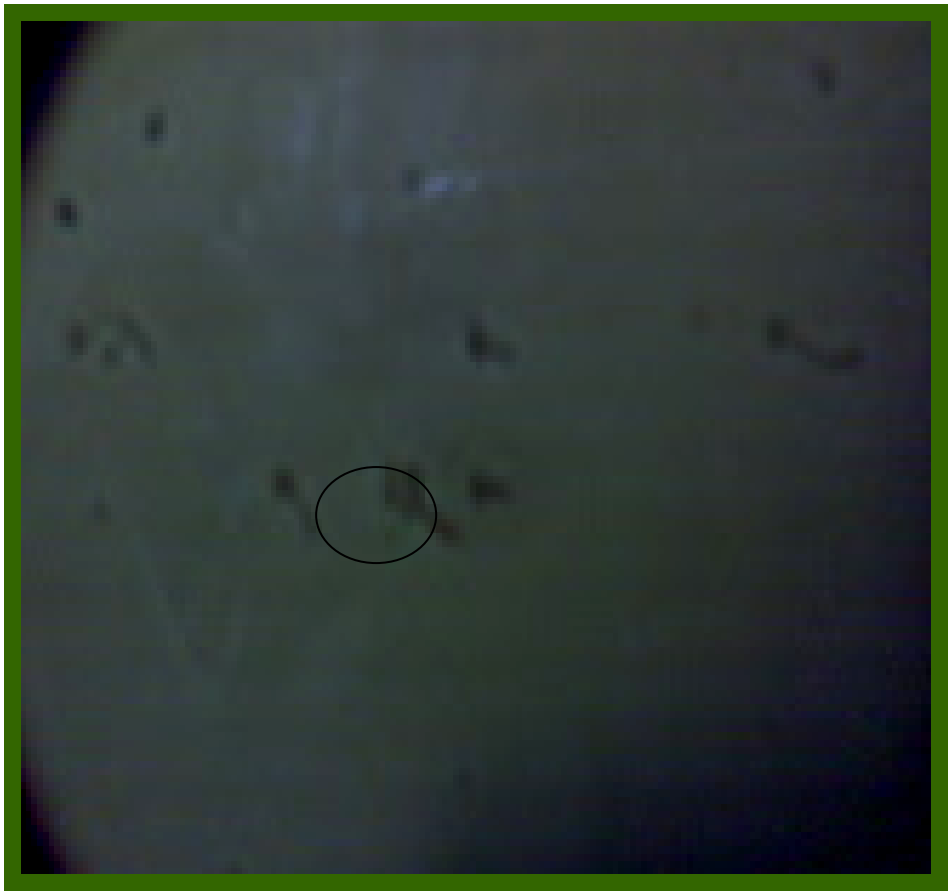

Figure (٤-٣)

Germ tube production by *C.albicans* on corn meal agar

Figure (٤-٤)

Chlamydcondia formation by *C. albicans* on the slide (X ١٠٠٠).

During the period of this study ٣٠٠ saliva samples were collected from the oral cavity of ٣٠٠ individuals, divided into three groups:١٠٠ oral samples from healthy subjects as control group C.G ,١٠٠ oral samples from diabetic patients D.G and ١٠٠ oral samples from antibiotics treated diabetic patients A.G. .The number of individuals and the percentage of oral candidiasis (carried *C. albicans* in their mouth) were showed in Table (٤-١) ,Table (٤-٢)

Table (٤-١) Distribution of Oral Candidiasis in Control Group and Diabetic Group.

Group of supjects	No. of cases	(+)	%	P value	(-)	%
C.G	١٠٠	١٨	١٨٪	P<٠.٠٥ significance	٨٢	٨٢٪
D. G	١٠٠	٣٩	٣٩٪		٦١	٦١٪

C.G. Control Group Involved Healthy Subjects.

D.G. Diabetic Patients Group not treated with other antibiotic.

(+): Carry *C. albicans* in mouth

(-): Do not carry *C. albicans* in mouth

Table (٤-٢) Distribution of Oral Candidiasis in Diabetic Group and Antibiotics Group

Group of patients	No. of cases	(+)	%	P value	(-)	%
D. G	١٠٠	٣٩	٣٩٪	P>٠.٠٥ Not significance	٦١	٦١٪
A.G.	١٠٠	٥١	٥١٪		٤٩	٤٩٪

A.G. Antibiotic Treated Diabetic Patients Group)

Sex of patients of D.G.	Total No.	(+) No.	%	(-) No.	%	P value

Male	٥٠	١٢	٢٤٪	٣٨	٧٦٪	**P< ٠.٠٥ significance**
Female	٥٠	٢٧	٥٤٪	٢٣	٤٦٪	

Table (٤-٣) Distribution of Oral Candidiasis according to sex

Patients of	**Age(Year)**	**P value**

Table (٤-٣) illustrates the difference between male and female in oral carriage rate.

	< ٢٠	٢٠-٤٠	٤١-٦٠	> ٦٠	
(+) No.	١٤	١٢	٧	٦	
%	٣٨.٨٨٪	٣٦.٣٧٪	٤٣.٧٥ %	٤٠٪	**P>٠.٠٥** **Not significance**
(-) No.	٢٢	٢١	٩	٩	
%	٦١.١١ %	٦٣.٦٣٪	٥٦.٢٥ %	٦٠٪	
Total No.	٣٦	٣٣	١٦	١٥	

The groups of age showed different values of oral carriage rate as in Table (٤-٤).

Table (٤-٤) Distribution of oral candidiasis according to the age

The duration had no recognizable effect on the oral carriage rate but the categories showed different rates, the highest rate of occurrence was in patients with ١-٤ years of Duration of his disease (١-٤) years of D.M.as in Table (٤-٥).

Table (٤-٥) Distribution of oral candidiasis according to the Duration of Diabetes Mellitus

Patients	**Duration(Years)**	

of D.G.	<١	١-٤	٥-٩	>١٠	P value
(+) No. %	٧ ٣٥٪	١٣ ٤٠.٦٢٪	٩ ٣٩.١٣٪	١٠ ٤٠٪	P>٠.٠٥
(-) No. %	١٣ ٦٥٪	١٩ ٥٩.٣٨٪	١٤ ٦٠.٨٧٪	١٥ ٦٠٪	Not significance
Total No.	٢٠	٣٢	٢٣	٢٥	

Table (٤-٦) Distribution of oral candidiasis in type (١&٢) diabetes mellitus

Patients of D.G.	Total No.	(+)	%	(-)	%	P value
Type-١-	٥٠	٢٣	٤٦٪	٢٧	٥٤٪	P>٠.٠٥ Non significance
Type-٢-	٥٠	١٦	٣٢٪	٣٤	٦٨٪	

Table (٤-٦) showed the difference in oral carriage rate of *C. albicans* between type-١- and type-٢- diabetes mellitus which was higher in type -١-than type-٢-but with non Significance difference P> ٠.٠٥

Table (٤-٧) illustrated the oral carriage rate in rural and urban patients as follows:

Table (٤-٧) Distribution of Oral Candidiasis according to the residence

Patients of D.G.	**Residence**		**P value**
	Rural	**Urban**	
(+) No.	٢١	١٨	**P>٠.٠٥**
%	٤٢٪	٣٦٪	
(-) No.	٢٩	٣٢	**Not Significance**
%	٥٨٪	٦٤٪	
Total No.	٥٠	٥٠	

٥-١ The rate of oral candidiasis

The percentage of oral carriage rate of *Candida albicans* in this study was (٣٩٪) in (D.G.) compared to (١٨٪) in (C.G.) and the difference was significant (Table ٤-١). These findings were in agreement with other studies. In Spain , Negroni *et al*. (٢٠٠٢) found in a study of individuals all in healthy oral conditions that ٢١.٤٢٪ were positive with *Candida* in their oral cavity. Kumar *et al.* (٢٠٠١) found in a study of healthy population that ٢٧٪ of them were positive with *Candida* species oral carriage.

AL-khaffaji (٢٠٠٥) found in a study of healthy population in Iraq that the rate of oral carriage with *C. albicans* was ٥٤.٨ %. Whereas Mohammed (٢٠٠٢) found that ٣٧٪ of diabetic patients carried *Candida* spp. in their oral cavity
and ٢٦٪were positive with *C. albicans*.

Up to ٦٠٪ of the population carry *Candida albicans* as part of the oral flora without having evidence of candidiasis. (Ramanathan *et al*.,١٩٨٥). Fongsmut *et al*.(١٩٩٨) studied the oral candidal prevalence and identified that the most frequent candidal species in diabetics patients was *C. albicans* (٨١.٣٪) . Kumar *et al.* (٢٠٠١) suggested that the disparity in results might be due to a difference in sampling

techniques. Hill *et al*. (١٩٨٩) mentioned that the prevalence of oral yeast infection in diabetics was (٤٩)%. It had been suggested by Cannon *et al*.

(١٩٩٥) that (٧٧٪) of diabetic patients carried *Candida* species in their oral cavity, with *C. albicans* being the species most frequently isolated. It had been suggested by Gloria *et al. (*٢٠٠٥) that when the blood sugar increases, two things happen. One, all the body secretions will have an increased amount of glucose. Two, all of the tissues of the body stop functioning normally, and therefore the normal defenses that the body has against intrusion by outside substances such as yeast will be abnormal.

٥-٢ The influence of antibiotic therapy on the oral carriage rate of *C. albicans*

Treatment with antibiotic was known to predispose to infection of gastrointestinal tract with *C. albicans* an important opportunistic pathogen (Gloria *et al*.,٢٠٠٥).The antibiotic therapy in diabetic patient seemed to have an additive influence in predisposing to oral carriage of *C. albicans* as shown in this study in Table(٤-٢) where detected in (٥١٪) of A.G. compared to (٣٩٪) of diabetic patients who were not taking antibiotic during sampling and the differences were not significant. Ninane (١٩٩٤) ;Akpan and Morgan (٢٠٠٢**)** mentioned that the antibiotics reduce the number of "friendly bacteria" (flora) in the intestinal tract and in mouth which normally keeps the *Candida albicans* under control. *Candida* feeds on antibiotics ;it is their food source. Potential causes of *Candida albicans* overgrowth and *Candida* yeast infections, some antibiotics have local irritable effect as well as systemic effect by decreasing the activity of cellular immune (decreasing the activity of macrophages and leukocytes) (Gloria *et al*.,٢٠٠٥).

٥-٣ The occurrence of oral candidiasis according to the sex

In this study we noticed that the rate of O.C. in females (٥٤٪) was higher than it was in males (٢٤٪) and the difference was significant (Table ٤-٣) in addtion to that the result was in agreement a previous study by Mohammed (٢٠٠٢) who found ٤٦٪ in female and ٢١٪ in male . This difference might be correlated with physiological factors affecting the rate of the infection. Increased level of progesterone in the last half of menstruation period could be a factor. However, some investigation failed to fined gender differences.

٥-٤ The occurrence of oral candidiasis according to the age of the patients

The highest percentage of oral carriage (٤٣.٧٥ %) was among age group (٤١-٦٠ year),the next were those over ٦٠ year of age (٤٠٪), (٣٨.٣٨٪)was in those less than ٢٠ year and the least(٣٦.٣٧٪) was among those who were (٢١-٤٠ year) (Table ٤-٤). The statistical analysis indicated that the differences were not significant among all age groups (P>٠.٠٥).This result also detected by Tapper-Jones *et al.* (١٩٨١) where they found that no differences in candidal status could be detected according to the patient's age. Lamey *et al*. (١٩٨٨) did not observe significant differences in relation to the age of the patient. Willis *et al.* (١٩٩٩) found that candidal load was not associated with age.Mohammed (٢٠٠٢) also mentioned that the differences were not significant (P>٠.٠٥).

٥-٥ The occurrence of oral candidiasis according to the duration of diabetes mellitus

The occurrence of oral candidiasis and the frequency of isolation of *Candida albicans* and its density and distribution were studied (Table ٤-٥) and the differences statisticaly were not significant . There are no significant differences in candidal status detected according to the duration of diabetes (Tapper-Jones *et al.*,١٩٨١). Lamey *et al.* (١٩٨٨) did not observe significant differences in relation to the number of microorganisms with the duration of the disease. The exact cause for lack of effect of the duration on the rate of oral carriage rate of

O.C.was unknown .However, the type of treatment and degree of control of diabetes that affect salivary glucose concentration might be related factors.

٥-٦ The occurrence of oral candidiasis according to type of diabetes mellitus

It was found that (٤٦٪) in type -١- carried *C. albicans* in their mouth (Table ٤-٦)and the rate was higher but there were not significant differences than type-٢-(٣٢٪).Other previous studies by Ozturkcan *et al.* (١٩٩٣) observed that the rate of oral *Candida albicans* carriage was higher in type-١- than type-٢-. Kumar *et al.* (٢٠٠١) found in that (٨٣.٦٧٪) were in type-١- and is higher than type-٢- (٦٨.٥٢٪) .While Mohammed (٢٠٠٢) found that ٢٤٪ in type-١- D.M. and ٢٧٪ in type -٢-. Richard *et al.* (٢٠٠٣) found that the high level of *Candida* carriage was seen in ٤٤٪ of the type-١- diabetic subjects .Bartholomew *et al.* (١٩٩٩) found that (٧٥٪)of patients with insulin-dependent diabetes mellitus (IDDM) showed high frequency and severity of oral *Candida* colonization . Bai *et al.* (١٩٩٥) found in a study of oral candidal carriage state that ٩٢٪ of patients with insulin-dependent diabetes mellitus showed *Candida* carrier state. In this study type -٢- showed (٣٢٪) oral carriage rate . Mohammad (٢٠٠٢) found that ٢٧٪ of Type -٢- D.M. showed oral carriage of *Candida albicans* . Dodds *et al.* (٢٠٠٠) found that ٣٠٪ of type ٢ diabetes mellitus subjects had high oral yeast counts Kumar *et al.* (٢٠٠١) found that (٦٨.٥٢٪) of type -٢- diabetes mellitus subjects carried *Candida* in their oral cavity. The exact cause of the difference between type -١-and type-٢- was not exactly known. However, type -١- D.M. was severer than type -٢- and type-١- being insulin requiring and of a younger ages were at greater risk of poorer glycaemic control and microbial including *Candida albicans.*

٥-٧ The occurrence of oral candidiasis according to the residence

Rate of carriage of O.C. was higher (٤٢٪) in rural patients but the difference was not significant compared to (٣٢٪) in urban (Table ٤-٧).This mild difference might be related to low socioeconomic status

in rural areas. Shibata *et al*. (١٩٩٢) revealed that *Candida* species were most predominantly found in persons with poor oral cleanliness .Moreover, low educational standard was associated with lower glycemic control and higher rate of occurrence of O.C. in diabetics patients.

Conclusions

١-The fungus was detected in ٣٩٪ of ١٠٠ patients with D.M., ٥١٪ of ١٠٠ patients with antibiotics treatment and in ١٨٪ of ١٠٠ healthy individuals C.G.

٢-There were significant differences in the oral candidal carriage rate by *C. albicans* between female (٥٤٪) and male (٢٤ %)**.**

٣-There is no significant effect of age and duration of D.M. on the percentage of occurrence of O.C.

Recommendations

١- Diabetic patients need to be routinely screened for oral carriage of *C. albicans* regardless of symptoms.

٢-Antimicrobial therapy should not be freely offered to diabetic patients in the absence of clear indication.

٣-Oral candidiasis in diabetic patients especially those receiving antibiotics probably requires prompt eradication by antifungal therapy if risk of invasive candidiasis is to be prevented.

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