Relationship Between Glycemic Control and Candida Count in Type 2 Diabetes Mellitus Patient

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Abstract

Poor glycemic control in diabetes mellitus patients is a major risk factor for complications even though complications can develop despite relatively good glycemic control. Candidiasis caused by Candida species is frequent, severe, and difficult to treat especially with poorly controlled diabetes mellitus patients. This study aimed to determine the relationship between glycemic control and Candida count in type 2 diabetes mellitus patients.

This study was an analytical study. Forty type 2 diabetes mellitus patients were included. Demographic data were obtained from a direct question and medical record. Diabetes mellitus diagnosis and glycemic control levels were obtained from medical records and the last blood glucose test result. Candida sampling was done with a concentrated oral rinse method using 10 mL Phosphate-buffered saline solution and cultured on Saboraud's Dextrose Agar. The data were then analyzed with Chi-Square Test.

The results showed a Candida count of >100 CFU/mL was found in 20 (50%) subjects with poor glycemic control. The relationship between glycemic control and Candida count in type 2 diabetes mellitus patients indicated a significant relationship (p=0.0002). Glycemic control predisposes the increase in Candida count. This study showed a relationship between glycemic control and Candida count in type 2 diabetes mellitus patients, and poor glycemic control was associated with high Candida count. Dentists should educate patients about the impact of poor glycemic control on oral health.

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Introduction

Type 2 diabetes mellitus, formerly termed "non–insulin-dependent diabetes mellitus," is characterized by insulin resistance in the peripheral tissue and/or defective insulin secretion by the pancreatic beta cells.[1] Type 2 diabetes mellitus is the most common form of diabetes mellitus.[2] Type 2 diabetes mellitus results from a complex interplay between multiple genetic factors and a huge variety of environmental and lifestyle risk factors, which include physical inactivity, obesity, excessive sugar intake, and low socioeconomic status. The global prevalence of diabetes mellitus among adults rose from 4.7% to 8.5% between1980 and 2014.[3] Diabetes mellitus was the eighth leading cause of death among both males and females.[2] The International Diabetes Federation stated that in 2019, diabetes mellitus caused 4.2 million deaths, and 463 million adults aged between 20 and 79 years old were living with diabetes mellitus and estimated will likely rise to 700 million by 2045. Over 90% of diabetes mellitus cases are type 2 diabetes mellitus.[4] In 2015 about 340-536 million people aged 20-79 years.[5] Previously, type 2 diabetes mellitus was considered to be a disease of older adults. However, in recent decades the age of onset has been falling, and type 2 diabetes mellitus has been reported in younger adults and children, and adolescents as well.[3]

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Diabetes mellitus has adverse effects on general health and leads to severe complications.[5] It is characterized by an increased susceptibility to infection, poor wound healing, and increased morbidity and mortality associated with disease progression.[6] Although poor glycemic control is a significant risk factor for complications, not all poorly controlled diabetes mellitus patients developed complications. Conversely, some people develop complications despite relatively good glycemic control. Oral manifestations and complications of diabetes mellitus are related to the impaired immune response. Candidiasis and bacterial infections are frequent, severe, and difficult to treat, especially in poorly controlled diabetes mellitus.[1] Candida species are notorious opportunistic pathogens whenever the balance between the host and the organism is disturbed.[7] Candida species are commensal organisms in the mouth of about 40% of the population, and carriage rates are increased in the presence of systemic diseases, such as diabetes mellitus.[7,8] Of all Candida species, Candida albicans are the most common and crucial causative agent of oral candidiasis.[8] Other candida species such as Candida glabrata, Candida guilliermondii, Candida parapsilosis, Candida krusei, Candida inconspicua, Candida dubliniensis, and Candida tropicalis can accommodate different environmental conditions and attach to several surfaces.[9]

This study aimed to determine the relationship between glycemic control and Candida count in type 2 diabetes mellitus patients.

Materials and methods

Research Design and Sample

This study was an analytical study to examine the relationship between a risk factor (glycemic control of type 2 diabetes mellitus patient) and Candida count. The study was conducted in Internal Medicine Clinic, Pirngadi Hospital, Medan and Microbiology Laboratory, Medical Faculty, Universitas Sumatera Utara, Medan.

The study involved 40 type 2 diabetes mellitus patients. The inclusion criteria were type 2 diabetes mellitus patients, less than 60 years old, non-smokers who did not wear complete/partially removable dentures, and did not have other diseases that affect Candida count such as HIV/AIDS.

Diabetes mellitus and glycemic control levels were diagnosed from the patient's medical record. The glycemic control was assessed with a 2-hour postprandial blood glucose level and classified into good glycemic control with a blood glucose level of 80-144 mg/dL, moderate level glycemic control with a blood glucose level of 145-179 mg/dL, and poor glycemic control with a blood glucose level of more than 180 mg/dL.

Candida sampling was done by instructing the patient to rinse for 1 minute with 10 mL Phosphate-buffered saline solution and spitting it back into a sterile container. The sample was then taken from the container using a ten μL inoculating loop and spread four times to Sabouraud's Dextrose Agar. The sample was cultured for 24-48 hours at 37° C. Candida colony was counted manually. Candida count was calculated by multiplying the number of visually formed Candida colonies with 25 to generate Candida count in Colony Forming Unit/mL (CFU/mL). The detection limit was 100 CFU/mL or less.

Data Analysis

The univariate data were including the distribution of patients based on age, gender, and glycemic control. The bivariate data were analyzed with a Chi-square test to determine the relationship between two variables (glycemic control and Candida count) with a significance level of $p<0.05$. Data analysis was done with a computer program.

Ethical Clearance

This study followed national and international ethics guidance and was approved by the Health Research Ethical Committee of Medical Faculty, Universitas Sumatera Utara/H. Adam Malik General Hospital No. 631/TGL/KEPK FK USU-RSUP HAM/2019. All patients were also given informed consent.

Results

Forty type 2 diabetes mellitus patients were included in this research. The results showed patients were mainly in the age group of 50-59 years old with 28 (70%) patients and the age group of 30-39 years was the least with 4 (10%) patients (Figure 1).

The patients of this study were primarily female, with 24 (60%) patients. The distribution of patients based on gender can be seen in Figure 2.

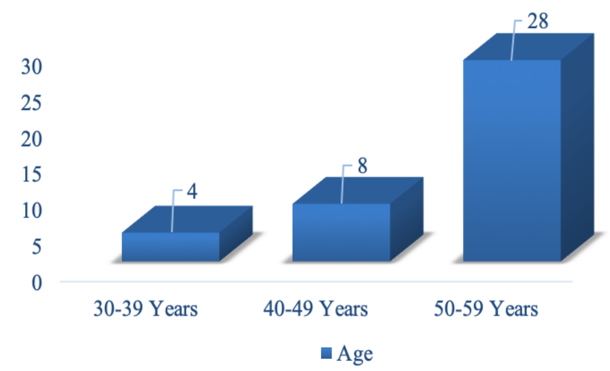

Figure 1. Distribution of patients based on age.

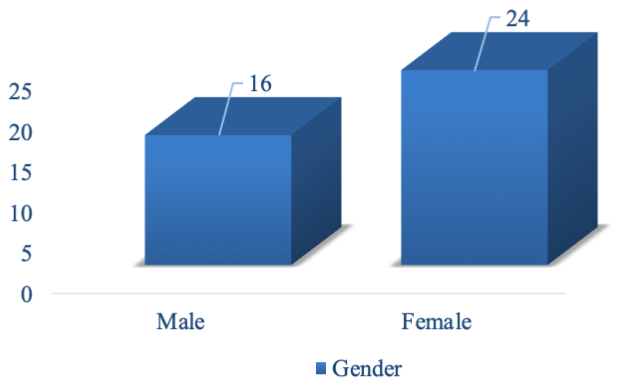

Figure 2. Distribution of patients based on gender.

Figure 3 showed the distribution of patients based on glycemic control. The highest percentage of patients' glycemic control was poor glycemic control with 22 (55%) patients.

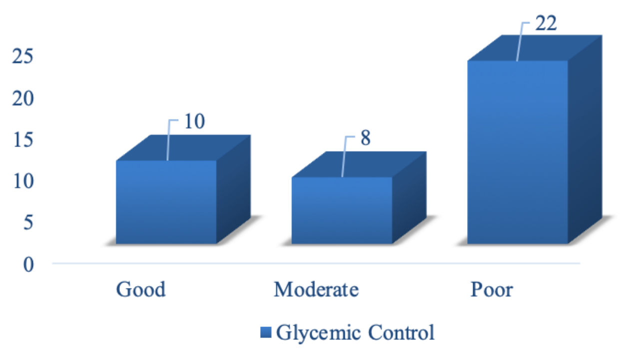

Figure 3. Distribution of patients based on glycemic control.

Table 1 showed the distribution of Candida count based on glycemic control. Patients with Candida count >100 CFU/mL mainly were in poor glycemic control with 20 (50%) patients. There was a significant relationship between glycemic control and Candida count in type 2 diabetes mellitus patients with a p-value of 0.0002 (p<0.05).

Glycemic Control	Candida Count (CFU/mL) ≤100 CFU/mL N (%)	>100 CFU/mL N (%)	Total	p-value
Good	8 (20)	2 (5)	10	p=0.0002
Moderate	5 (12.5)	3 (7.5)	8	
Poor	2 (5)	20 (50)	22	

Table 1. The relationship of glycemic control and Candida count in type 2 diabetes mellitus patients.

Discussion

Type 2 diabetes mellitus patient in this study was mainly 50-59 years old (Figure 1). More than half of the diabetes mellitus patients are middle-aged, and the incidence rises with increasing ages in both sexes, reaching the highest rates in the older women.[10] The result of this study was similar to the study by Borgharkar in 2019 on real-world evidence of glycemic control among patients with type 2 diabetes mellitus in India: the TIGHT (The Investigation of Glycosylated Hemoglobin on Therapy in Indian diabetics). The study found the subject mainly was <55 years (53.2%) and followed by subjects in the age group of 55-56 years (30.6%), with the mean (±SD) age of patients was 54.31 (±11.11) years.[11] Type 2 diabetes mellitus occurs most commonly in adults at the age of 40 years or older, and the prevalence of the disease increases with advancing age. Indeed, the aging of the population is one reason that type 2 diabetes mellitus is becoming increasingly common.[12] The prevalence of diabetes mellitus in people between the ages of 60-79 years is 18.6% (about 134.6 million people).[1] However, type 2 diabetes mellitus is increasing more rapidly in adolescents and young adults than in other age groups. The disease is increasingly recognized in younger people, particularly in highly susceptible racial and ethnic groups and the obese.[12] The subject's age for this research was limited to 60 years old because patients aged 60 years old and older usually have many other predisposing factors that affect Candida count.

This study showed that the patient was primarily female (Figure 2). Obesity is the primary risk factor for type 2 diabetes mellitus. Obesity is more common in females than males. According to a systematic analysis, females tend to be more obese than males and show a stronger association between increased body mass index and diabetes mellitus risk. Moreover, modifiable social factors, like low educational level, occupation, and income, largely contribute to unhealthy lifestyle behavior and social disparities and thus are related to a higher risk of obesity and type 2 diabetes mellitus, particularly in females.[10]

According to the World Health Organization, diabetes mellitus is a permanent disorder that is treatable but not curable. Primary treatment goals for diabetes mellitus are to achieve blood glucose levels as close to normal as possible and prevent complications.[1] It is well-known that many diabetes mellitus patients had poor glycemic control.[5] As shown in this study were the majority of type 2 diabetes mellitus patients in poor glycemic control (Figure 3). Borgharkar et al., in their study, also found that the Indian population with type 2 diabetes mellitus has a high burden of uncontrolled diabetes mellitus, with three-fourths of 55,639 patients (76.6%) having poor glycemic control (HbA1c ≥7%; 53 mmol/mol). This study also showed obesity, longer duration of diabetes, hypertension, and the number of therapies significantly associated with poor glycemic control.[11] Moreover study by Leung et al. demonstrated that low-income middle-aged to elderly dental patients with type 2 DM had poor diabetic control.[5]

Type 2 diabetes mellitus patients tend to experience increased Candida count and the majority of which were with poor glycemic control (Table 1). Candida species have a predilection for colonizing the oral cavity, particularly in diabetes mellitus patients, with percentages ranging between 60% and 80%.[13] Diabetes mellitus patients have a higher prevalence of Candida than those without diabetes mellitus, and clinical manifestations of Candida infection occur more frequently and severely in diabetes mellitus patients than without diabetes mellitus.[14] The candidal density also has been reported to be higher in diabetes mellitus than without diabetes mellitus.[15] Changing salivary glucose levels in patients with diabetes mellitus can cause an alteration of yeast growth.[14] Moreover, high blood glucose level also aids in Candida colonization and growth.[12] According to a study by Rodríguez-Archilla et al., poor glycemic control increased 2.94 times the risk of Candida species oral infection with a highly significant statistical relationship ($p<0.001$). Several studies have shown that poorly controlled diabetes mellitus or those without metabolic control are significantly more susceptible to having oral candidiasis. In diabetes mellitus patients with poor metabolic control, an oral environment rich in sugars permits high glucose levels in saliva and can contribute to the persistence of aciduric yeasts in the oral cavity. Moreover, carbohydrates in the diet may be a contributing factor, promoting adhesion, biofilm formation, and yeast colonization in the oral environment.[13] Candida albicans can form biofilms on different surfaces and mature biofilm is about 100 folds resistant to antifungals.[9]

Candida count >100 CFU/mL is most commonly found in poor glycemic control with 20 (50%) patients, and there was a significant relationship between glycemic control and Candida count in type 2 diabetes mellitus patients ($p=0.0002$) (Table 1). Diabetes mellitus patients are predisposed to higher candidal carriage in the oral cavity due to poor glycemic control.[15] Study by Rodríguez-Archilla et al. suggests that uncontrolled or poorly controlled diabetes mellitus increases susceptibility to oral opportunistic infections, such as oral candidiasis.[13] The study by Lingaiah et al. in 2018 also showed diabetes mellitus patients with candidiasis were found more with poor glycemic control.[16] High blood glucose levels in diabetes mellitus patients with poor glycemic control can increase Candida count because glucose is a suitable medium for microorganisms growth, including Candida.[17] Research by Man et al. in 2017 on nutritional factors affecting Candida growth showed a positive correlation between Candida count and high blood glucose level and proved the high incidence of Candida infections in diabetes mellitus patients with poor glycemic control.[18]

Diabetes mellitus patients are more prone to fungal infections, probably due to immune disturbance and salivary composition changes.[13] Study suggested that diabetes mellitus results in changes in the function of immune cells, including neutrophils, monocytes, and macrophages.[2] Immunosuppression can occur with diabetes mellitus, which could increase the susceptibility to oral infections caused by Candida.[14] The overgrowth of a hyphal form of Candida albicans may be harmful in immunocompromised people due to mucosal or cutaneous barrier damage thus causing the development of lesions in the oral cavity or oral candidiasis.[19] Meanwhile, High blood glucose levels in diabetes mellitus result in low salivary flow rate and cause high saliva viscosity and increased saliva glucose level.[17]

Recent theory suggests that the glycosylation of immunoglobulins in uncontrolled diabetes mellitus patients renders the patient to be more susceptible to infection.[15] Salivary glucose forms chemically reversible glycosylation products with proteins in tissues during hyperglycemic episodes, and this leads to the accumulation of glycosylation products in oral epithelial cells, which may increase the number of receptors available for Candida.[13] The enzymatic activity of Candida albicans isolates obtained from type 2 diabetes mellitus patients is much higher than normal patients.[15] Moreover, glucose supports Candida virulence by stimulating the blastospores' transition into hyphae.[18] Adherence of Candida to host tissue is the first step, and the enzymes facilitate the adherence by damaging cell membranes. The accumulation of sugar in tissues also favors the growth and proliferation of Candida. The high salivary glucose level can increase candidal adherence to the buccal epithelial cells, which form glycosylation products with the proteins in tissues. Thus, hyperglycemic episodes in uncontrolled diabetes mellitus patients can lead to the accumulation of glycosylation products which, in turn, increase the receptor for Candida.[15] Furthermore, many common infections in diabetes mellitus patients tend to be more frequent and severe because of their associated abnormalities of cell-mediated immunity and impaired polymorphonuclear leucocyte (neutrophil) function. Neutrophil chemotaxis and phagocytosis are diminished because at high blood glucose concentration, neutrophil superoxide generation is impaired, reducing tissue vascularity. Reduced tissue vascularity results in hypoxia and ischemia, which limit neutrophil access.[12]

Hyposalivation in diabetes mellitus patients can be related to polyuria and the substitution of normal functioning gland tissue by adipose tissue in major salivary glands.[15] Diabetes mellitus affects the composition and amount of saliva, which influences the microorganism population in the oral cavity.[14] Thereby, the growth of Candida species in the oral cavity is favored due to decreased saliva production and the consequential reduced immunological activity of saliva.[15] Previous studies showed a higher percentage of decreased salivary flow rate in diabetes mellitus patients with poor glycemic control than in good and moderate glycemic control.[20] Moreover, diabetes mellitus patients usually have systemic medications that favor the reduction of salivary flow, facilitating the proliferation of microorganisms in oral biofilms.[13]

Conclusions

In summary, glycemic control in diabetes mellitus can predispose patients to opportunistic oral infections such as oral candidiasis, which is caused by Candida. As shown in this study, there was a relationship between glycemic control and Candida count in type 2 diabetes mellitus patients. Moreover, poor glycemic control was associated with a high Candida count. Therefore, dentists and physicians should educate diabetes mellitus patients about the impact of poor glycemic control on oral health. In future research, it is recommended to use media that can identify Candida species that are commonly found associated with glycemic control levels in diabetes mellitus patients.

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Declaration of Interest

The authors report no conflict of interest.

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