Prevalence of Anti Hyperglycemic Agents -Associated Oral Lichenoid Lesions in Type 2 Diabetes Mellitus Patients

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Abstract

Objective: This study aimed to estimate the prevalence of lichenoid reactions to Anti Hyperglycemic Agents.

Materials and Methods: In this cross-sectional descriptive and analytic study, we examined the oral mucosa of 411 patients at the age of 29 to 85 in 3 groups who consumed various antihyperglycemic agents.

Results: In overall, 31 patients had lichenoid reactions (12 patients taking glibenclamide, 1 patient taking metformin and 18 patients taking glibenclamide with metformin) and there was a significant difference between the groups ($P = 0.013$). The most of the lesions were at the age's upper than 60 years. From 31 patients with lichenoid reactions, 14 subjects (45%) were male and 17 subjects (55%) were female.

Conclusion: Prevalence of lichenoid reactions in this study was 7.5% approximately. By considering the significant difference among the groups in the incidence of lesions, the significant effect of glibenclamide in inducing lichenoid reactions can be considered.

Keywords: Diabetes mellitus; Lichenoid reactions; Glibenclamide; Metformin

Introduction

Diabetes mellitus is a complex disease with vascular and metabolic components which is induced by sustained hyperglycemia. One of it's major complications include microvascular disorders and a variety of clinical neuropathies (1). Generally, the most common oral complications of diabetes mellitus type 2 are gingivitis, periodontitis, xerostomia, candidiasis, oral lichen planus, leukoplakia, oral cancer, mouth burn, and taste changes (2,3). Type 2 diabetes is usually treated by anti-hyperglycemic agents. Presently, the most common blood sugar lowering agents prescribed in the center of diabetic patients include glibenclamide and metformin. Glibenclamide (glyburide), is an antidiabeticagent of Sulfonylureas classification (4). Sulfonylurea class have been introduced in 1950s by provoking insulin secretion from β cells decrease blood sugar level (5). Biguanids are another category of agents and the most common of which is metformin (6). According to the algorithm provided by ADA (American Diabetes Association) in 2006, metformin is recommended as the first line of diabetes type 2 diabetes (7). Oral lichen planus (OLP) is a

chronic mucocutaneous disease which involves skin, mucosal membrane, nails and scalp with an unknown mechanism (8). Oral lichenoid reactions (OLRs) are caused by different etiological causes by drug consumption, dental restorative materials, foods and artificial flavors and essences. The treatment approach of lichenoid reactions includes remove of the underlying factors such as the drug or amalgam fillings which are in contact with the mucosa. The main treatment of OLP includes topical corticosteroids and other anti-inflammatory agents (9,10,11). The clinical manifestation of these lesions varies from the keratotic to ulcerative types. Due controversial probability of dysplasia in oral lichen planus, biopsy is recommended when the lesion appears with unusual feature (8,12).

While a histopathological assessment is not sufficient for the differentiation between OLP and OLR, there has been some progress in finding Immunohistological markers assisting the discrimination between these two conditions. However, no exact marker has been found for this purpose (9). It has been suggested that OLRs are predominantly unilateral. , this characteristic is not useful to discriminate between OLP and OLRs. Till now these two conditions should be considered clinically indistinguishable and the diagnosis is related to the presence of the underlying factor. Sulfonylurea and metformin as blood sugar lowering agents are capable of producing OLR in the oral mucosa (10). The present study made an attempt to estimate the incidence rate of oral lichenoid reactions in three groups of patients with type 2 diabetes (the glibenclamide group, the metformin group, and the simultaneous glibenclamide-meformin group) and lesion incident comparison among the three study groups.

Materials and Methods

This study assessed the patients with type 2 diabetes who were in the follow-up of Diabetes Research Center of Shahid Sadoughi University of medical science. Medical Ethics Committee of Shaheid Sadoughi University approval was obtained for the study. This study was done on type 2 diabetic patients who had medical files in the center of diabetic patients. Inclusion criterion was consumption of one or both of aforementioned agents. Exclusion criterion was consumption of other agents can cause oral linchenoid reactions according to the list of agents (10). Eventually, oral mucosa examination of 411 eligible patients was done. In this historical cohort a total of 411 subjects participated in a descriptive-analytic study conducted on three groups during 2009. Group 1 included 143 patients (100 females and 43 males) who had taken only glibenclamide for at least 6 months. Group 2 included 100 patients (72 females and 28 males) who had taken only metformin for at least 6 months. Group 3 included 168 patients (119 females and 49 males) who had taken both glibenclamide and metformin simultaneously for at least 6 months. The other exclusion criterion was the presence of lichenoid contact lesions in the patient's oral mucosa. The patients' demographic information as age, gender, duration of affliction with diabetes, duration and type of anti hyperglycemic agents consumption were extracted from the patients' files in the treatment center. The examination performed by means of dental mirror, tongue blade, and gauze. The oral examinations were performed by the dentist specially trained for this purpose. The study assessed the presence of the oral lichenoid lesions. If necessary, the patient was referred to the oral medicine department of dental school for the treatment of mucosal lesions.

Results

A total of 411 subjects (291 females and 120 males) participated in the present study. One hundred and forty threepatients including 100 females (69.9%) and 43males (30.1%) have taken glibenclamide, among 100 patients who have taken metformin, 72 (72%) were female and 28 (28%) were male and of 168 patients who have taken both agents simultaneously

119 (70.8%) were female and 49 (29.2%) were male. SPSS (version 17) was performed.

Chi-square test for OLR prevalence, age and gender distribution and drug taking duration regarding the lichenoid lesions was performed ANOVA for the difference in mean of drug taking duration regarding the type of drug taken. There was no statistically difference between the two genders regarding the type of drug taken (*P*-value=0.941). The patients' age ranged from 29 to 85 years and they were studied in four age groups. There were 15 subjects in the age of 29-39, 81 in the age of 40-49, 156 in the age of 50-59, and 158 in the age group of 60 years and more. The duration of drug consumption ranged from 6 months to 25 years and the patients were divided into four different groups. According to the ANOVA analysis, the mean of drug taking duration had a statistically significant difference between the group of metformin consumption and the two other groups (*P*-value=0.0001). Of the total patients studied, 31 subjects (7.5%) showed oral lichenoid lesions. Twelve patients of group 1 (8.4%), 1 (1%) patient of group 2, and 18 (10%) patients of group 3 had oral lichenoid lesions. There was a statistically significant difference between metformin group and the others (*P*-value=0.013). Table 1 shows the lesion and gender distribution of each group. Among 31 patients with oral mucosal lesions studied here, 4 subjects belonged to the age group of 40-49, 10 subjects belonged to 50-59, and 17 subjects belonged to the 60 years and more. Table 2 shows that there was no significant difference between different age groups regarding the incidence of mucosal lesions (*P*-value=0.2). In Table 3 the distribution of patients with and without the lesions in the category of drug taking duration, is demonstrated and there is a statistically significant difference between them (*P*-value=0.017). Five patients with oral lesions had some complaints in the present time and they were referred to the department of oral medicine for further assessment. The duration of the lesions was unknown, and most of subjects were unaware of the presence.

Discussion

The aim of present study was to investigate the prevalence of oral lichenoid lesions in patients with type 2 diabetes who took oral antihyperglycemic agents and to determine the effect of type of drug taken on the incidence of these lesions. Oral lichen planus is a chronic mucosal disease with unknown etiology while oral lichenoid reactions are a group of oral lesions with clinical and histopathological characteristics similar to oral lichen planus though they have different etiology and

Table1. Prevalence of lichenoid reactions and sex distribution considering the type of consumed agents

Anti hyperglycemic agent	With lichenoid reaction n(%)		Without lichenoid reaction n(%)		Total n(%)	
	f	M	F	M	f	m
Glibenclamide	6(4.1)	6(4.1)	94(65.7)	37(25.8)	100(69.9)	43(30.1)
Metformin	6(1)	0(0)	71(71)	28(28)	72(72)	28(28)
Glibenclamid+Metformin	10(5.9)	8(4.7)	109(64.8)	41(24.4)	119(70.8)	49(29.1)

(*P*-Value=0.013 via chi-square test)

Table 2. Age distribution of patients with and without lichenoid reactions

age group (years)	With lichenoid reaction (n = 31) n(%)	Without lichenoid reaction (n = 379) n(%)	Total (n = 410) n(%)
29 – 39	0(0)	15(4)	15(3.7)
40 – 49	4(12.9)	77(20.3)	81(19.8)
50 – 59	10(32.3)	146(38.5)	156(38)
60	17(54.8)	141(37.2)	158(38.5)

(*P*-Value=0.2 via chi-square test)

treatment. Lichenoid lesions are treatable with the removal of predisposing factor. Medications are the contributing factors of these reactions (9). Presently, second generation of sulfonylurea (glibenclamide was considered in this study) and metformin are among the oral antihyperglycemic agents most commonly used by diabetics. Some case reports have highlighted the possible involvement of sulfonylurea agents in inducing OLR such as Byrd & Ahmad (13), Zein & Nor (14), Barnette et al. (15), Fox Gn et al. (16), Nokes R et al. (17), and Franz CB et al. (18). Prevalence studies of oral complications due to metformin are rare. Nonetheless, both of the mentioned dugs are assumed to induce lichenoid reactions (10). Generally, the significance of these groups of oral lesions is their probable contribution to the manifestation of symptoms as burning, making erosions or ulcers and dysplastic changes, the latter being still controversial (8,12). Regarding the worldwide incidence of diabetes and the high consumption of the above-mentioned agents, and also with respect to the fact that no satisfactory study has been conducted on the incidence of oral lesions related to taking of these agents, the present study focused on the effect of consumption of these oral antihyperglycemic agents by diabetics on the incidence of oral complications. The study by Torpet et al. on drug lichenoid lesions demonstrated that 6 to 16 months of drug consumption by diabetic patients led to the creation of lesions and the time required for the healing of the lesions after discontinuing the use of agents was 5 months (19). Hence, the agents taken by the patients for at least 6 month are considered in this study. Since the differential diagnosis of OLP lesions from the OLR ones is merely a clinical issue, and there is no necessity for obtaining biopsies, so the mere clinical examination of oral lesions sufficed for our purposes (20). In this study, of the 411 subjects participating, 31 (7.5%) had oral lichenoids. In a study by Vandis ML et al. the incidence of the lesions among 273 diabetic patients studied was 4% (21). Furthermore, in a study by Petro Americanou et al, the prevalence of lichen planus among the patients with types 1 and 2 diabetes was 5.7% and 2.83%, respectively (22). Also, Zarei et al conducted their study on 101 diabetic patients, and reported an incidence rate of 4.96% for lichen planus (23). In Ahmed et al's results of 86 patiets with type 2 diabetes mellitus, 8 patients (6.9 %) had histopathologically oral lichen planus (24). Tahrir and Aldelaimi, also studied 112 diabetic patients that from the study population 11 patients (9.8%) had lesions fitted the criteria of lichen planus (25). The slight difference between our findings and those of similar studies may be attributed to the characteristics of the populations under study and the presence or absence of intervening variables which were accounted for as far as possible in our study. By considering the history of taking predisposing agents as the only clinical criterion for differentiation between oral lichen planus and drug lichenoid lesions, the lesions in the aforementioned studies can be ascribed to drug lichenoid reactions based on the type of the drug used. In our study, the absolute frequency of the lichenoid lesions in females was higher than males. This finding is similar to those of other articles and textbooks. In reviewing the related literature to find the probable cause of the lichenoid lesions due to sulfonylurea,

Table 3. Frequency distribution of patients with and without lichenoid reactions, in a category of drug taking duration

Duration of drug consumption (years)	With lichenoid reaction n= 31 (n%)	Without lichenoid reaction n = 380(n%)	Total n = 411(n%)
< 3	1(3.2)	88(23.2)	89(21.7)
3 – 5	13(41.9)	173(45.5)	186(45.3)
6 – 10	11(35.5)	78(20.5)	89(21.7)
> 10	6(19.4)	41(10.8)	47(11.4)

(*P*-Value = 0.017 via chi-square test)

which is a kind of delayed hypersensitivity reaction related to T-cells, we came across a category of drug allergies called sulfa allergy in which the main agents involved are belonging to the group of sulfonamide antibiotics (26, 27). Sulfonylurea agents are among the non-antibiotic agents for which the presence of this allergy can be considered (26, 27, 28). In this way, we can consider the presence of sulfur as a possible cause for the significant rate of lichenoid lesions induced by the chemical structure of sulfonylurea agents.

Conclusion

In this study, 7.5% of the diabetic subjects showed drug-induced lichenoid reactions. The type of drug taken affected the incidence of these reactions. Future studies should focus on the investigation of the correlation between the dominant pattern of lichenoid lesions and the agents used. Furthermore, future studies should investigate the definitive role of duration of drug consumption on the incidence rate of the lichenoid reactions using larger populations and matching the subjects regarding the duration. The studies may also deal with drug allergies among the patients with lichenoid lesions who take sulfonylurea agents. They may also find allergies to the consumption of agents with similar chemical structures. Finally, it is advised that the diabetic patients under treatment have periodic regular examinations of the oral mucosa.

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