Prevalence of diabetes mellitus among patients with oral squamous cell carcinoma and oral potentially malignant disorders - A retrospective study

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Abstract
Oral Squamous Cell Carcinoma (OSCC) is the 12th most common cancer in the world. 90-95% of oral cancer is OSCC and it can be preceded by oral potentially malignant disorder (OPMD). Diabetes mellitus (DM) is a major global health issue and various epidemiological studies have implicated diabetes mellitus as a risk factor for the development of oral squamous cell carcinoma and other oral potentially malignant disorders. The study aimed to evaluate the correlation of diabetes mellitus in OSCC, leukoplakia and oral lichen planus patients and also evaluate age and gender predilection in OSCC and OPMD cases with diabetes mellitus. This retrospective study included a sample size of n=226 [156-OPMD, 70-OSCC]. Data regarding the sample cases were selected after the review and analysis of records of about 86000 patients who visited our institution between June 2019 and March 2020. From n=226, 30% of OSCC cases showed the positive diabetic history and 15% of OLP and 8.3% of leukoplakia were associated with DM. A statistically significant association found between diabetes in OSCC, Leukoplakia, OLP cases with p-value (0.001). 90.48% of OSCC and 75% of leukoplakia cases with a positive diabetic history were males. Among OLP, 77.8% of cases with diabetes mellitus were females. The association of prevalence of diabetes mellitus with gender in Oral squamous cell carcinoma(OSCC), Leukoplakia and Oral lichen planus(OLP) was found to be statistically significant (p=0.001). The most prevalent age range for both OSCC and OPMD patients with a history of diabetes mellitus was found to be 50-60 years, followed by above 60 years. In conclusion, there found to be a significant prevalence of DM in OSCC and OPMD cases. The DM status of oral cancer and OPMD patients may have a significant impact on their disease progression and treatment. DM could be considered as a prognostic factor for OSCC and OPMD.

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INTRODUCTION
Oral squamous cell carcinoma (OSCC) is the most common oral cancer and 12th most common cancer in the world (Misra et al., 2008; Shree et al., 2019). In India, oral squamous cell carcinoma comprises of 90-95% of oral cancer (Sharma, 2015; Gupta and Ramani, 2016). Annual prevalence of oral squamous cell carcinoma is 300,000 cases per year (Markopoulos, 2012; Singh et al., 2016). OSCC can develop in normal mucosa and can be preceded by potentially malignant disorders such as...
Diabetes mellitus is a chronic metabolic disease which is more prevalent in the community (Swathy et al., 2015) and also reported to have an impact on the prognosis and treatment outcomes of malignancies (Wu, 2010). Diabetes Mellitus is a global problem and the number of patients with Diabetes Mellitus increased from 153 million in 1980 to 347 million in 2008 (Danaei et al., 2011). Recent epidemiological studies have incriminated Diabetes Mellitus as a risk factor for the development of OSCC and OPMD (Vairaktaris, 2007; Sridharan et al., 2019). The overlapping risk factors of Diabetes Mellitus suggest a relationship between type 2 Diabetes Mellitus and malignant tumours (Rosta, 2011; Jayaraj, 2015). The pathophysiology of Diabetes Mellitus involves several biological processes in the body (Rosta, 2011).

Several animal research programs were conducted recently to analyze the influence of diabetes in signal transduction pathways in every stage of oral cancer development, from normal epithelium to dysplasia and finally to an aggressive carcinoma (Vairaktaris, 2007; Sherlin et al., 2015). The influence of diabetes mellitus was studied by evaluating the expression of several growth factors, tumor suppressor genes and apoptosis markers and the cell proliferation markers in different stages of oral oncogenesis (Vairaktaris, 2007; Hannah, 2018). Diabetes Mellitus 2 induces erbB2 and erbB3 receptors and which then promotes the activation of Ras/Raf/MAPK signal transduction pathway, leading to increased cell proliferation (Vairaktaris, 2007). In vitro and in vivo animal studies have shown that the relationship between cancer and type 2 DM was influenced by the mitotic effect of hyperinsulinemia (Rosta, 2011).

This study aimed to evaluate the correlation between diabetes mellitus in OSCC, OLP and OLP and to analyse the prevalence of gender, and most affected age range among OPMD and OSCC cases with Diabetes Mellitus.

**MATERIALS AND METHODS**

The present study was conducted with approval from the Scientific review board, Saveetha dental college and hospitals, Chennai. The ethical approval number for the present study was SDC/SIHEC/2020/DIASDATA/0619-0320. This retrospective study included n=226 samples which include 70 OSCC cases, 96 Oral leukoplakia cases and 60 OLP cases. Data regarding the sample cases were selected after the review and analysis of records of about 86000 patients who visited our institution between June 2019 and March 2020. All the retrieved case sheets were verified by an external reviewer in order to reduce errors in data recording.

OPMD and OSCC cases with a specific diagnosis, proper clinical and past medical history were included. The cases with non-specific diagnosis and improperly recorded case sheets were eliminated from the present study. Cross verification of retrieved data was done by photographs and by desired communications.

The data collected from n=226 were tabulated according to age, gender, presence of absence of Diabetes Mellitus, and the site of the lesion in MS excel software. This tabulated data then transported to IBM SPSS-Statistics 23 software and frequency analysis were done for age range, gender, history of diabetes mellitus, site of the lesion and diagnosis. For analysing the correlation between diabetes in OSCC, leukoplakia and oral lichen planus correlation analysis were performed using chi-square test and p-value <0.05 was considered as statistically significant.

**RESULTS AND DISCUSSION**

70 OSCC cases and 156 OPMD cases were analysed statistically in the present study. Frequency of diabetes mellitus and non-diabetics in individuals with OSCC and OPMD were studied and it was found that 30 % of OSCC cases and 10.9% of OPMD cases have diabetes mellitus history (Figure 1). Among OPMD cases, the percentage of OLP with diabetic history was found to be 15 % (Figure 2), which is more when compared to that of leukoplakia with diabetes mellitus history (8.3%) (Figure 3).

Chi-square test showed a relatively higher preva-
Figure 1: Pie graph depicting the percentage prevalence of diabetes mellitus (DM) among oral squamous cell carcinoma cases.

Figure 2: Pie graph depicting the percentage prevalence of diabetes mellitus (DM) among oral lichen planus cases.

Figure 3: Pie graph depicting the percentage prevalence of diabetes mellitus (DM) among leukoplakia cases.

Figure 4: Bar graph depicting the association of Diabetes mellitus with Oral lichen planus, Leukoplakia and oral squamous cell carcinoma.

The prevalence of Diabetes mellitus among OSCC patients was greater than that of Leukoplakia and Lichen Planus patients. This was found to be statistically significant, with a p-value of 0.001 (Figure 4).

On analysis of OSCC, leukoplakia and OLP cases with diabetes mellitus, 90.48% of the OSCC cases were males and the rest were females. Among leukoplakia cases with diabetes mellitus, 75% were found to be males and 25% were females. But in contrast to this, 77.8% of the OLP cases with diabetes mellitus were females and only 22.22% were males. The association of prevalence of diabetes mellitus with gender in Oral squamous cell carcinoma (OSCC), Leukoplakia and Oral lichen planus (OLP) was found to be statistically significant (p=0.001) (Figure 5).

Among the OSCC cases with diabetes mellitus, 42.85% of the cases were within the age range of 50-60 years, followed by 38.09% above 60 years of age (Figure 6). Similarly, 52.94% and 41.18% of OPMD cases with positive diabetes mellitus history were found to be in the range of 50-60 years and above 60 years, respectively (Figure 7). The association of diabetes mellitus with age group in oral squamous cell carcinoma (OSCC) and oral potentially malignant disorders (OPMD) was found to be non-significant.
with P value=0.481. Figure 8 shows that X-axis representing the age group and Y-axis the percentage of cases with diabetes mellitus. There is an increase in the percentage of diabetes cases in 50-60 years of age belonging to both OSCC and OPMD. However, there was a marginal increase in the percentage of cases belonging to OPMD than OSCC in the 50-60 age group. Chi-square test (Chi-square value=1.462), was not found to be statistically significant with p=0.481 (p>0.05).

Type 2 DM and malignant tumours are frequent diseases worldwide (Rosta, 2011). The coexistence of type 2 diabetes and malignant tumours are more frequent than expected age correlated incidence and prevalence of each disease (Rosta, 2011). The involvement of various biological pathways in the pathophysiology of diabetes may explain the higher cancer risk in type 2 diabetes (Rosta, 2011).

In the present study, the prevalence of diabetes mellitus in OSCC cases was found to be higher and the prevalence of diabetes mellitus in OLP was found to be more compared to that in LP. The increased prevalence of diabetes mellitus among OSCC cases was in concordance with various previous studies. But the decreased prevalence of diabetes mellitus in oral leukoplakia compared to oral lichen planus was not in accordance with some of the previous studies. Dietitian et al. and Albech et al. concluded
in their studies that the prevalence of oral leukoplakia was higher in diabetic persons (Albrecht et al., 1992; Dietrich et al., 2004). Two different studies also compared the prevalence of LP and OLP in diabetic patients, and in both the studies the prevalence of leukoplakia was found to be higher when compared to OLP in diabetic patients (Mohsin, 2014). The deviation is a result of the present study from previous studies can be due to the errors in sampling, small sample size and improper recording of a history of systemic diseases in patients.

The prevalence of diabetes mellitus in OSCC, leukoplakia and oral lichen planus cases was found to be statistically significant in the present study. Compared to OPMD cases, OSCC cases showed a higher prevalence of diabetes mellitus occurrence. This was found to be in concordance with the study by Pablos Ramos-Garcia et al. in 2020 (Ramos-Garcia, 2020). Ramos-Garcia et al. stated that diabetes patients have a high prevalence and greater chance for oral cancer and OPMD development when compared to non-diabetic patients (Ramos-Garcia, 2020). A systematic review and meta-analysis by Gong et al. in 2015 from 10 studies stated that the type 2 DM patients had a significantly elevated incidence of oral cancer with SRR=1.15 (Gong, 2015). Ujpal et al. in 2004 also found a higher prevalence of tumours and precancerous lesions in diabetic patients than non-diabetic patients (Ujpal et al., 2004).

In the present study, among OSCC and leukoplakia cases with positive diabetic history, males were found to be more affected than the females. Chi-square analysis of the gender predilection of cases with positive diabetic history among OSCC and OPMD was found to be statistically significant with p=0.001 (p<0.05). Hence, there is a significant prevalence of diabetes mellitus among Males in OSCC and leukoplakia and among Females in OLP.

This could be explained by the increased predilection of males in both OSCC and leukoplakia cases. The other parameters which can influence the male predominance in OSCC and leukoplakia cases with positive diabetes history were Increased prevalence of various habits among males, small sample size and small duration of sample collection. A study by Rodriguez-Archilla et al. in 2018 found a 1.84 fold higher risk in males for leukoplakia (Rodriguez-Archilla and Garcia-Gamez, 2018). But in the case of lichen planus, females were found to be more affected than males. This could be due to the influence of hormonal factors in females. A study by Rajesh K Dikshit et al. also found that there is a significant association between diabetes and pre-malignant oral lesions among women other than men, but they couldn’t explain the underlying mechanism (Dikshit et al., 2006).

When the age range of OSCC with a positive history of diabetes was analysed, the prevalence of OSCC cases was found to be more in 50-60 years of age, followed by greater than 60 years. This observation was supported by (Kuriki et al., 2007; Bosetti, 2012). OPMD cases with a history of diabetes showed more prevalence in 50-60 years of age, followed by greater than 60 years. This was in concordance with study results of (Dietrich et al., 2004; Ujpal et al., 2004). However, the association of diabetes mellitus with age groups in oral squamous cell carcinoma(OSCC) and oral potentially malignant disorders(OPMD) was not statistically significant. The predilection of OSCC and OPMD cases with a history of diabetes mellitus in the range of 5th to 6th decade of life in the present study could be due to the increased habit history among the elderly population. Small sample size and small duration of sample selection can also influence this observation in the present study.

Since the association between diabetes mellitus in OSCC and OPMD is significant, the recording of past medical history and systemic conditions should be given more weightage in case of OSCC and OPMD patients. Limitations of this present study were small sample size, the inclusion of only leukoplakia and lichen planus cases under OPMD category, geographical limitations of sample collection and errors in data recording.

CONCLUSIONS

In conclusion, the present study analysed the association of diabetes mellitus with OSCC, leukoplakia and OLP (p-value =0.001) and also the association of gender predilection of cases with positive diabetic history among OSCC and OPMD (p=0.001). Analysis of age and gender predilection showed that the prevalence of males was more among OSCC and leukoplakia with diabetes history in contrast to increased female prevalence in OLP with diabetic history. The results for the study prompts the importance of taking a detailed medical history for OSCC and OPMD patients and DM status of oral cancer and OPMD patients may have a significant impact on their disease progression and treatment.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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