



Evaluating the oral side effects of immunosuppressive medications: Importance of early lesion detection in dentistry.

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I. INTRODUCTION

The oral cavity is defined as the space extending from the lips anteriorly to facial pillars posteriorly and is bounded laterally by the cheeks, superiorly by the palate and inferiorly by the muscular floor and the tongue.^[1] Our oral cavity frequently serves as initial site where signs and symptoms of various health issues become apparent. Also the side effects of various medications, particularly those that modulate immune and inflammatory responses are often first observed in the oral cavity, this includes a range of adverse effects spanning from heightened

vulnerability to infections, the formation of oral ulcers to gingival overgrowth.^[2]

Immunosuppressive drugs, as their nomenclature implies constitutes a category of chemical compounds designed to selectively act upon the immune system, thereby mitigating diverse facets of its functioning. These drugs are mostly used for treatment of several chronic inflammatory conditions, for reducing rejection in patients undergoing organ transplantation and for specifically modulating the immune system to temper its overactive responses.^[2]

These immunosuppressive drugs can be classified into four broad categories namely :-^[3]

CLASS OF DRUG	EXAMPLES	MECHANISM OF ACTION
Calcineurin inhibitors	<ul style="list-style-type: none"> Cyclosporine analogues Tacrolimus 	Inhibitors of intracellular phosphatase required for interleukin 2 production in T lymphocytes.
Non calcineurin inhibitors	<ul style="list-style-type: none"> Sirolimus 	Inhibitors of mTOR [Mammalian Target Of Rapamycin] activation of lymphocytes, resulting in cell cycle arrest.
Antimetabolites	<ul style="list-style-type: none"> Azathioprine Mycophenolate mofetil 	Inhibitors of de novo purine synthesis in lymphocytes.
Corticosteroids	<ul style="list-style-type: none"> Prednisolone Methyl prednisolone 	Regulators of gene expression.



Immunosuppressive functions by impeding the immune systems ability to harm healthy cells and tissues through inhibition of T cells, a subset of white blood cells responsible for direct elimination of foreign molecules in the body. These drugs are designed to target intracellular signaling pathways activated by T lymphocytes, as well as to inhibit calcineurin, an enzyme crucial for T cell activation, ultimately diminishing T cell activity.^[4] Consequently, they suppress cell mediated immune responses by blocking the genes responsible for coding cytokine IL1 to IL6, 8 an interferon C, resulting in reduced T cell proliferation. Additionally they suppress humoral immunity leading to a reduction in B cells, antibody synthesis and diminished activation of T lymphocytes.^[2]

Although these immunosuppressants have proven to be beneficial in treatment of acute autoimmune rejection and autoimmune diseases, their non specific capacity to broadly dampen the entire immune system has led to increased susceptibility to infections and cancer.^{[3][5][6]}

The adverse effects associated with these medications encompass hepatotoxicity, neurotoxicity, nephrotoxicity, hyperglycemia, hyperlipidemia, susceptibility to immunosuppressant rejection, leukopenia, post transplant lymphoproliferative disorder [PTLD], pulmonary edema and renal dysfunction. In context of oral health, potential side effects include gingival hyperplasia, increased neoplasm risk, impaired wound healing, temporomandibular joint arthritis, altered cementum deposition, mucocutaneous pigmentation including melanosis and development of hairy tongue.^{[5][6][7][8]} Burkets textbook of oral medicine also underscores the importance of considering mucormycosis in differential diagnosis of patients undergoing immunosuppressive therapy and presenting with extensive oral ulcers.^[9] Furthermore disseminated geotrichosis infection may manifest in debilitated patients or those prescribed immunosuppressants.^{[4][5][7][10]}

Patients receiving immunosuppressive treatment may exhibit indications of the reactivation of latent infections including hepatitis B and C, tuberculosis and HIV 1-8. With this cohort various oral manifestation may manifest such as herpes simplex 1 and 2, varicella zoster, hairy leukoplakia, cytomegalovirus, mononucleosis, kaposissarcoma, gingivostomatitis and herpes labialis.^{[5][6][11]} Incases where the facial nerve is impacted as in instance of

varicella zoster, this can lead to unilateral facial and oral tissue paralysis.^{[5][11]}

CSA, an immunosuppressant is a cyclo polypeptide medication which originates from fungal metabolite known as Beaveria Nivea. It is often associated with occurrence of drug induced gingival enlargement which is hypersensitive response to cyclosporine therapy.^[7] Intake of CSA also exhibit presence of extensive and multilobulated fibrous polyps on the lateral border of tongue, lip and buccal mucosa.^[12] Patients on tacrolimus, a macrolide immunosuppressant may experience changes in taste perception, development of fibrous growth in oral cavity and increased susceptibility to fungal infections like mucormycosis.^{[2][8][13][14][15]} Sirolimus [Rapamycin] due to its direct toxic and antiproliferative affect on parenchymal and stromal elements of submandibular salivary secretion and xerostomia thereby leading to detrimental oral health.^[16]

Azathioprine, an antimetabolite immunosuppressant is associated with a noteworthy elevation in the likelihood of neoplasia and infections, particularly varicella and herpes simplex.^{[17][18]} Moreover, it heightens vulnerability to dental caries and exerts a substantial influence on the production and secretion of tertiary dentin.^[19] Mycophenolate mofetil which is an antimetabolite, an ester mycophenolic acid is administered in conjunction with tacrolimus shows several adverse effects one of them being multiple oral ulcers.^[20] It also causes immunosuppressant rejection leukopenia, gingival enlargement, destruction of PDL support ultimately resulting in severe tooth loss.^[21] Corticosteroids are non specific type of immunosuppressant causing several secondary effects on oral cavity.^{[22][23]} Oral candidiasis and gingival hyperplasia are frequently encountered adverse effects of corticosteroid.^{[5][7][11]}

The primary aim of this survey is to emphasize the significance of understanding the adverse effects of immunosuppressants on oral cavity. This survey aims to highlight the importance of knowledge in both dental and medical field and collaboration among both dental and medical professionals while prescribing these medications to ensure comprehensive patient care.

ABSTRACT

This survey explores immunosuppressants' adverse effects on the oral cavity, highlighting its crucial role as an early health indicator. Despite efficacy, non-specific immunosuppression presents challenges, increasing susceptibility to infections



and cancers. Adverse effects extend to hepatotoxicity, neurotoxicity, nephrotoxicity, and various oral manifestations. Insights into specific drugs shed light on their impacts. The primary aim is to underscore the need for interdisciplinary collaboration in prescribing, ensuring comprehensive patient care.

Methodology: Conducted in Pune, this survey assesses dentists' knowledge on immunosuppressant effects through a reliable questionnaire developed over six months. Voluntarily distributed online, responses from a calculated sample size of dentists were collected, ensuring confidentiality. Demographic data and perspectives on immunosuppressants' significance in dentistry were analyzed using statistical software.

Result: Among 108 dentists, 50 prescribed immunosuppressants, primarily for oral ulcers, lichen planus, pemphigus, and other lesions. Most practitioners (81.5%) had over 5 years of experience. Notably, 78.7% were aware of immunosuppressants during academic training. Collaboration challenges included a lack of awareness among physicians (32.4%) and dentists (14.8%).

Conclusion: The survey highlights dentists' awareness in Pune regarding immunosuppressive medication effects on the oral cavity, emphasizing ongoing education and interdisciplinary collaboration for improved patient care.

KEYWORDS

Adverse effects, dentistry, gingival enlargement, immunosuppressants, immunosuppressive medications, oral cavity, transplant.

II. Methodology

A study was carried out among dentists in Pune city to gauge their knowledge, awareness, and attitudes concerning the adverse effects of immunosuppressive medications on the oral cavity. The research involved a review of multiple articles, the development of an online questionnaire, and spanned a six-month duration to evaluate

knowledge, awareness, and practice related to immunosuppressants. The study, comprising 20 multiple-choice questions, was distributed to participants through various social media platforms. Participation in the study was entirely voluntary, and all responses were treated as confidential, used exclusively for research purposes. The questionnaire was assessed for validity and reliability. The questionnaire demonstrated a satisfactory level of validity and the questionnaire's reliability was assessed using Cronbach's alpha value, which was 0.603 indicating either a "satisfactory" or "good" level. The calculated sample size was determined to be 107. The study questionnaire underwent revision and was conducted in the English language. A total of 107 dentists actively participated in the survey, representing Mumbai and Pune cities. The questionnaire encompassed inquiries concerning participants' demographic information, such as name, gender, age, tenure of practice as well as their knowledge and awareness of immunosuppressive medications. Furthermore, it delved into participants' perspectives on the significance of these medications in dentistry and the need for interdisciplinary communication to mitigate adverse effects by early assessment. Data derived from the study underwent analysis using statistical software, and the results were subsequently presented in an aggregated format while maintaining the anonymity of all participants.

III. RESULTS

In the surveyed group of 108 participating dentists, 50 reported prescribing immunosuppressants to their patients. A majority of them have been practicing dentistry for more than 5 years which accounts for 81.5 % of the total survey population, 12 % have been practicing since 5 to 10 years, 2.7% of them have been practicing since 10-15 years, 0.9% have been practicing since 15-20 years and 2.7 % of them have been practicing for 20 years and above.

Table 1 :- Are you made aware about immunosuppressants in your academic training period (BDS, MDS) ?

	Frequency (n)	Percentage (%)
Yes	85	78.7
No	23	21.3

Respondents were asked about their awareness of immunosuppressants during their academic training period (BDS, MDS). A significant majority, comprising 78.7% (n=85) of participants, indicated that they were made aware of immunosuppressants. Conversely, 21.3% (n=23)

reported not receiving such awareness during their academic training. [Table 1]

The respondents were queried regarding the frequency of encountering patients who have undergone transplantation and are on immunosuppressive medications. The majority of



participants, 51.9% (n=56), reported encountering such patients rarely. A smaller percentage reported encountering them very often (9.3%, n=10), often (26.8%, n=29), while 12% (n=13) indicated that they never encountered patients who had undergone transplantation and were on immunosuppressive medications.

Respondents were asked about their practices in providing information and guidance to patients on immunosuppressants regarding maintaining oral health and addressing potential side effects. The majority, 32.4% (n=35), reported always providing such information, while 30.5% (n=33) indicated that they often offer guidance. A portion of respondents reported providing

information sometimes (19.4%, n=21), rarely (7.4%, n=8), and never (10.2%, n=11) in respective frequencies.

Respondents were queried about their experiences with patient compliance regarding recommended oral health practices among those on immunosuppressants. The distribution of responses indicates that 10.2% (n=11) reported patients as 'Very Compliant,' 27.8% (n=30) as 'Compliant,' and 42.6% (n=46) as 'Somewhat Compliant.' A smaller percentage reported patients as 'Not very Compliant' (16.7%, n=18), while only 2.8% (n=3) characterized patients as 'Not Compliant at all.' These findings shed light on the varied degrees of compliance observed in the surveyed population

Table 2 :- What is the first line of treatment prescribed to patient with lesion in oral cavity who are on immunosuppressants?

	Frequency (n)	Percentage (%)
Change in drug dosage	25	23.1
Change in drug	26	24
Combination with other drugs	38	35.2
Suspension of medicines	6	5.6
Others	13	12

In Table 2 the study explored the first line of treatment prescribed for patients with oral cavity lesions who are on immunosuppressants. The findings indicate that 35.2% (n=38) of respondents preferred a 'Combination with other drugs' as the initial approach, while 'Change in drug dosage' and

'Change in drug' were reported by 23.1% (n=25) and 24% (n=26) respectively. A smaller proportion, 5.6% (n=6), mentioned 'Suspension of medicines' as the first line of treatment, and 12% (n=13) opted for 'Others.'

Table 3:- Did you ask the physician to discontinue or change the drugs that effects the immune system

	Frequency (n)	Percentage (%)
Yes	80	74
No	28	26
No	38	35.2

Table 3 delves into the practice of asking physicians to discontinue or change drugs affecting the immune system. A notable 74% (n=80) of respondents confirmed that they had requested such changes, while 26% (n=28) indicated otherwise.

Respondents were asked whether they encountered complications while performing dental procedures on patients with immunosuppressants. A significant majority, 57.4% (n=62), reported experiencing complications, while 42.6% (n=38) indicated otherwise.

Table 4 :- If yes , What kind of complications are observed?

	Frequency (n)	Percentage (%)
Abscess	15	13.9
Cellulitis	5	4.7
Dry socket	28	25.9
Ostitis	6	5.6
Delayed mucosal healing	50	46.3
Implant osteointegration failure	1	0.9
Jaw bone osteonecrosis	3	2.8



For those who reported complications (Table 4), the types observed varied, with ‘Delayed mucosal healing’ being the most prevalent at 46.3% (n=50). Other complications included

‘Abscess’ (13.9%, n=15), ‘Dry socket’ (25.9%, n=28), ‘Ostitis’ (5.6%, n=6), ‘Jaw bone osteonecrosis’ (2.8%, n=3), and ‘Implant osteointegration failure’ (0.9%, n=1).

Table 5 :- What kind of dental treatment contributed to these complications?

	Frequency (n)	Percentage (%)
RCT	22	20.4
Extraction	39	36.1
Scaling	18	16.7
Surgeries with open flap access and bone cutting	29	26.8

The dental treatments contributing to these complications. ‘Extraction’ was the most frequently cited, accounting for 36.1% (n=39), followed by ‘Surgeries with open flap access and bone cutting’ at 26.8% (n=29), ‘RCT’ at 20.4% (n=22), and ‘Scaling’ at 16.7% (n=18).[Table 5]

Table 6 :- Do you think most of the physicians do not consult the dentist prior to transplant or prescribing immunosuppressants?

	Frequency (n)	Percentage (%)
Strongly agree	33	30.6
Agree	62	57.4
Disagree	10	9.3
Strongly disagree	3	2.8

Regarding collaboration with physicians, it was observed that 87.8% of respondents either ‘Agree’ or ‘Strongly agree’ that most physicians do not consult dentists prior to transplantation or prescribing immunosuppressants. This perception underscores potential gaps in interdisciplinary communication.[Table 6]

Table 7 :- How often do you collaborate with general physicians or specialists in managing patients on immunosuppressant therapy

	Frequency (n)	Percentage (%)
Always	20	18.5
Often	37	34.3
Sometimes	34	31.5
Rarely	8	7.4
Never	9	8.3

Table 7 explores the frequency of collaboration between dentists and physicians in managing patients on immunosuppressant therapy. While 34.3% (n=37) reported collaborating ‘Often,’ 18.5% (n=20) mentioned ‘Always,’ indicating room for improvement in collaborative practices.

Table 8 :- Why do you think oral cavity is the most neglected aspect while prescribing immunosuppressants?

	Frequency (n)	Percentage (%)
Focus on chief complaint of the patient	42	38.9
Lack of awareness among physician	40	37
Lack of communication between dentist and physician	26	24.1

Examining the reasons for the neglect of the oral cavity in immunosuppressant prescriptions (Table 8), 38.9% (n=42) cited a ‘Focus on chief complaint of the patient,’ while 37% (n=40) attributed it to ‘Lack of awareness among physicians’ and 24.1% (n=26) to ‘Lack of communication between dentist and physician.’



Table 9 :- In your opinion, how important is interdisciplinary collaboration between physicians and dentists in managing patients on immunosuppressant therapy?

	Frequency (n)	Percentage (%)
Very important	46	42.6
Important	34	31.5
Somewhat important	22	20.4
Not very important	3	2.8
Not important at all	3	2.8

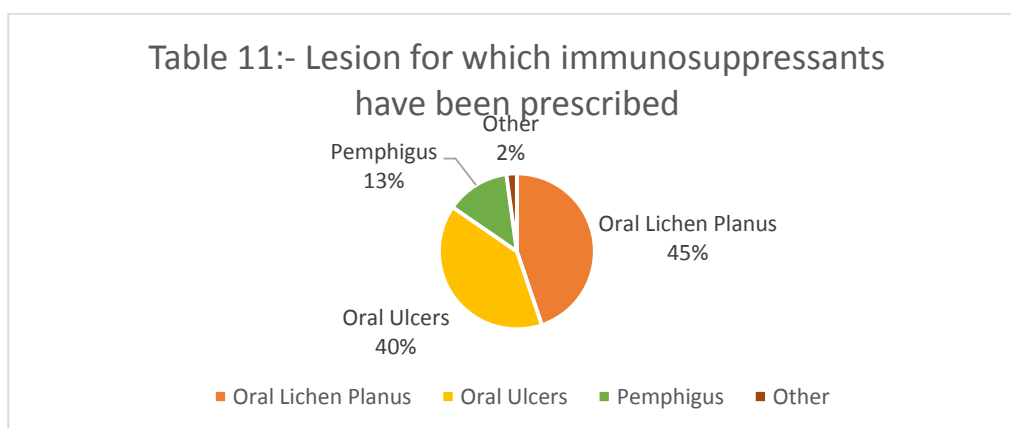
Table 9 gauges the perceived importance of interdisciplinary collaboration, revealing that 74.1% (n=80) view it as either ‘Very important’ or ‘Important’ in managing patients on immunosuppressant therapy. While according to 26% dentist it is of not importance to establish interdisciplinary collaboration with physicians while managing patients on immunosuppressants.

Table 10 :- What do you perceive as the main barriers to interdisciplinary collaboration between dentists and physicians in managing patients on immunosuppressant therapy?

	Frequency (n)	Percentage (%)
Lack of awareness among dentist	16	14.8
Lack of awareness among physician	35	32.4
Time constraints	19	17.6
Patient preference	15	13.9
Lack of established guidelines	15	13.9
Communication challenges	4	3.7
Others	4	3.7

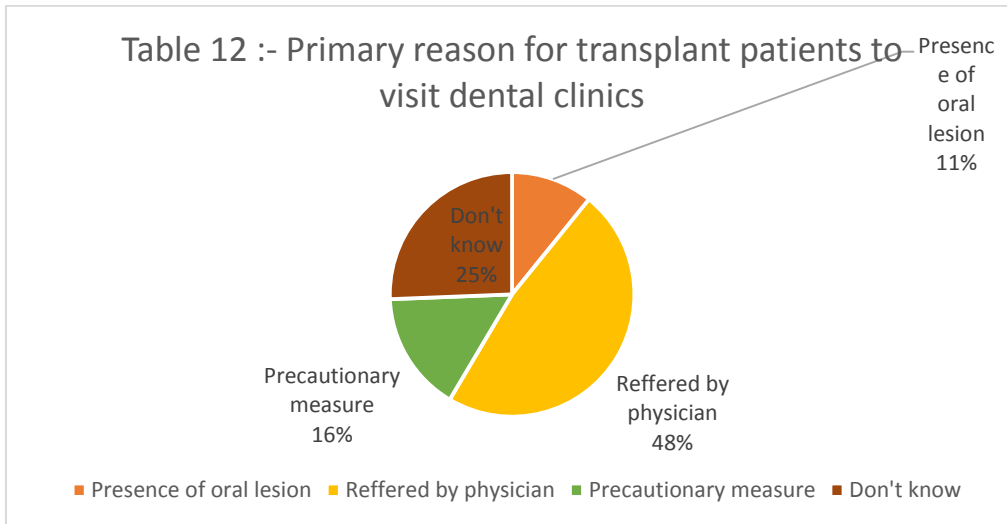
Lastly, Table 10 explores perceived barriers to interdisciplinary collaboration. Respondents identified ‘Lack of awareness among physicians’ (32.4%, n=35) and ‘Lack of awareness among dentists’ (14.8%, n=16) as significant barriers, along with ‘Time constraints’ (17.6%, n=19) and ‘Patient preference’ (13.9%, n=15). Communication challenges, lack of established guidelines, and other factors were also mentioned.

Table 11 illustrates the distribution of lesions for which dentists prescribed immunosuppressants. Among the surveyed dentists, 22.2% recommended immunosuppressants for patients with oral ulcers, 25% for those with oral lichen planus, 7.4% for pemphigus cases, and 45.3% for lesions falling outside these categories.

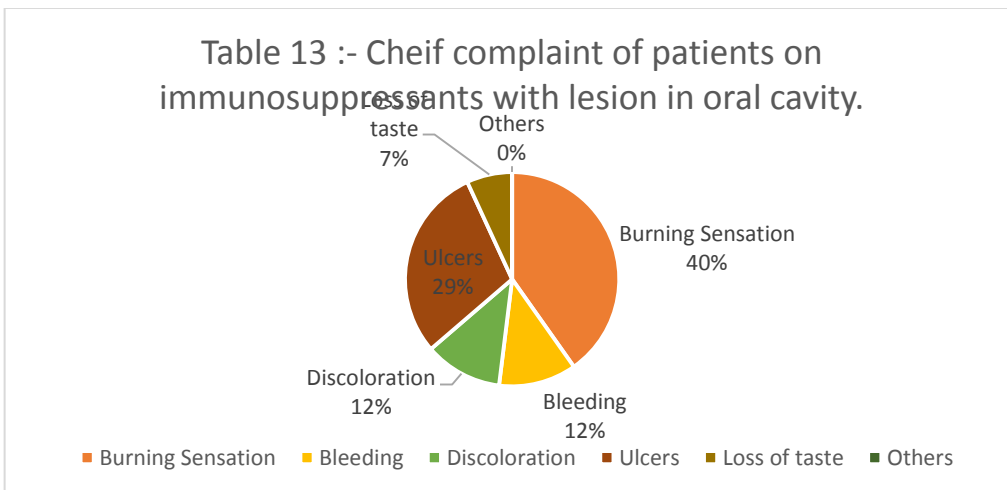


“In Table 12, respondents were asked about the primary reasons for transplant patients to visit dental clinics. The data reveals diverse motivations, with 32.4% (n=35) citing the presence of oral lesions as the prime reason, followed closely by 36.1% (n=39) who reported referrals from

physicians. Additionally, 12% (n=13) of respondents indicated precautionary measures as a significant factor, while 19.4% (n=21) mentioned uncertainty, stating ‘Don’t know,’ highlighting the various factors influencing transplant patients’ visits to dental clinics.”



In Table 13, respondents were surveyed on the chief complaints of patients on immunosuppressants presenting with lesions in the oral cavity. The data highlights that a significant percentage, 38% (n=41), reported a 'Burning Sensation' as the chief complaint, followed by 'Ulcers' at 27.8% (n=30). 'Bleeding' and 'Discoloration' were each reported by 11.1% (n=12) of respondents, while 'Loss of taste' accounted for 6.5% (n=7). A small proportion, 5.6% (n=6), cited 'Others' as the chief complaint. This diversity in chief complaints underscores the multifaceted nature of oral lesions in patients on immunosuppressants.



Moving to Table 14, the survey investigated the most common oral side effects observed in patients taking immunosuppressants. The majority, 39.8% (n=43), reported 'Oral ulcers' as a prevalent side effect, followed by 'Dry mouth' at 27.8% (n=30). 'Gum inflammation' constituted

17.6% (n=19), 'Infection' was observed in 10.2% (n=11), and 'Others' were noted by 4.7% (n=5) of respondents. These findings provide valuable insights into the clinical considerations and challenges associated with managing oral health in patients on immunosuppressants..



These findings underscore the complex landscape of managing patients on immunosuppressant therapy, highlighting both challenges and opportunities for enhanced interdisciplinary collaboration between dentists and physicians.

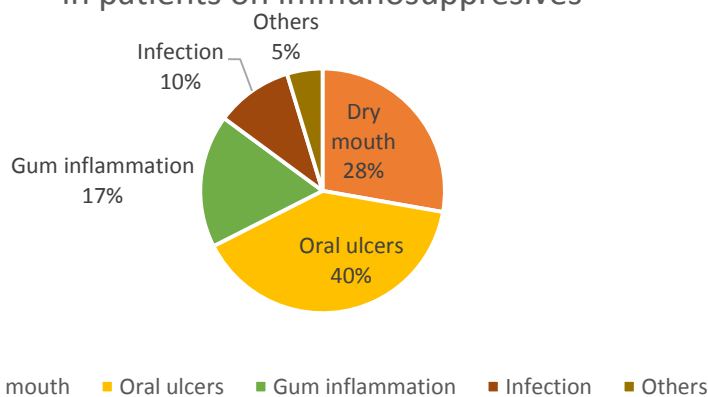
IV. DISCUSSION

In the realm of dental care, heightened awareness of immunosuppressant-induced side effects is imperative, particularly given their frequent prescription in transplant patients. The oral cavity serves as an early indicator of these adverse effects, necessitating a keen understanding among dental professionals. As far as our knowledge extends, this study represents the first systematic attempt to explore the awareness landscape within the dental community concerning the implications of immunosuppressive therapies, particularly in the context of oral health. The study underscores the unprecedented significance of collaborative consultations with physicians, ensuring a synergistic approach to patient care.

In this study a total of 109 structured questionnaire were distributed among dental

professionals in Pune, India. The questionnaire was distributed among practicing dental professionals to ensure unbiased responses, as their extensive knowledge and experience with clinical cases in the field make them well-suited to provide informed insights on the topic. 32.5% of dental professionals reported that transplant patients visited the dental clinic because of lesions in their oral cavity, this is similar to a study conducted in Iran by Mahnaz sahebamee^[24] et al on transplant patients which reported that 24% of transplant patients on immunosuppressants showed oral lesions. A similar study was conducted by Rosa Gracia^[25] and colleagues which reported a 60% prevalence rate of oral lesions in transplant patients. A study conducted by Lopez Pintor RM^[26] reported that 40% of renal transplant patients showed oral lesions. According to the survey most common adverse effects observed in transplant patients on immunosuppressants were oral ulcers (39.8%), gingival enlargement (17.6%) and dry mouth (27.8%), this is in line with the study conducted by Mahnaz sahebamee et al which reports the most common oral lesions in transplant patients on immunosuppressants to be oral candidiasis (16%),

Table 14:- Most common side effects observed in oral cavity in patients on immunosuppressives



gingival enlargement (7%) and coated tongue (2%). Lopez Pintor RM^[26] reports xerostomia prevalence to be significantly greater in renal transplant patients on immunosuppressants. A study conducted by Kaswansumita et al reported that 21.8% of kidney transplant patients showed gingival overgrowth. Al-Mohaya^[28] et al reported a higher prevalence of gingival enlargement (74.1%), coated tongue (22.4%) and erythematous candidiasis (15.5%) in transplant patients. In our survey, 38% of transplant patients on immunosuppressants reported to the clinic with a chief complaint of a burning sensation in the oral cavity. This condition is attributed to oral

candidiasis and aphthous ulcers, known adverse effects of immunosuppressive medications. This observation aligns with findings by Rosa Gracia et al^[25], and Mahnaz Sahebamee et al^[24] research which identifies oral candidiasis as the most common oral lesion in this context. 11.1% of patients in our survey reported bleeding as their chief complaint, which aligns with gingival inflammation which is a major adverse effect of immunosuppressant medications. King^[29] and colleagues found that 22% of their kidney transplant recipients had gingival enlargement, similar to present study, in which grade 1 Gingival



enlargement was the most prevalent type. 23.1 % dental practitioners changed the drug dosage as the first line of treatment similar to the case study by Asare K^[30] et al wherein the drug dose of MMF was changed which showed significant impact on patients oral health. 74% dental practitioners asked the physicians to discontinue the drug as in case study of Asare K^[30] et al where Tacrolimus was discontinued. 46.3 % dentists reported that poor wound healing was the most common complication observed after performing a dental treatment on these patients and that flap surgery and extractions were the two major treatments which contributed to this. Approximately 38.9% of surveyed dentists expressed the belief that the oral cavity tends to be overlooked in transplant patients, as the primary focus often centers around addressing their chief complaints. This insight underscores the importance of raising awareness and prioritizing oral health within the broader healthcare context for transplant recipients. 42.6 % dentists believed that an interdisciplinary collaboration between medical and dental fraternity is very important for treating these patients effectively. This survey was conducted on a limited scale, emphasizing the necessity for further comprehensive investigations on the subject. Further research and tailored interventions are essential to mitigate these challenges and enhance the overall well-being of transplant recipients.

V. CONCLUSION

In conclusion, this survey among dentists underscores the imperative for heightened awareness and meticulous detection of oral lesions in transplant patients undergoing immunosuppressive therapy. Collaboration between the medical and dental fraternities is crucial for effective patient care. The prevalence of oral candidiasis and gingival inflammation highlights the need for proactive management, emphasizing the pivotal role of patients in maintaining optimal oral health to mitigate potential side effects.

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