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Research Article

GINGIVAL HYPERPLASIA AND SYSTEMIC DISEASE: A COMPLEX INTERPLAY

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ABSTRACT

This study investigated the association between gingival hyperplasia and various systemic diseases and medications. Data from 1055 patients were analyzed, including those with leukemia, pregnancy, diabetes, and those taking medications known to induce gingival hyperplasia (phenytoin, cyclosporine, calcium channel blockers). Results indicated a significantly higher prevalence of gingival hyperplasia in patients with leukemia (40%, 95% CI: 30-50%) and poorly controlled diabetes (25%, 95% CI: 20-30%) compared to the control group (4%, 95% CI: 2-6%). Pregnancy also showed a statistically significant increase in gingival hyperplasia, with prevalence rising from 15% in the first trimester to 25% in the third trimester. Drug-induced gingival hyperplasia was observed in a substantial proportion of patients receiving phenytoin (35%), cyclosporine (25%), and calcium channel blockers (27%). Clinical characteristics of gingival hyperplasia varied depending on the underlying etiology, with leukemia-associated hyperplasia often presenting as severe, generalized, and friable tissue. These findings highlight the importance of considering systemic factors and medication profiles when assessing and managing gingival hyperplasia.

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Further research is needed to elucidate the mechanisms underlying these associations and to optimize treatment strategies.

KEYWORDS

Gingival hyperplasia, systemic disease, leukemia, diabetes, pregnancy, medication-induced gingival hyperplasia.

INTRODUCTION

Gingival hyperplasia, characterized by excessive gingival tissue overgrowth, poses a significant clinical challenge impacting oral health and aesthetics. While local factors such as plaque biofilm and inadequate oral hygiene are established contributors (1), a growing body of evidence highlights the critical role of systemic diseases and medications in its pathogenesis (2, 3). This complex interplay necessitates a comprehensive understanding of the etiological factors for accurate diagnosis and effective management.

Drug-induced gingival hyperplasia is a well-documented phenomenon, with medications including phenytoin (4), cyclosporine (5), and calcium channel blockers (6) frequently implicated. However, the association extends beyond pharmacologic influences, encompassing various systemic conditions. Leukemia, particularly acute myeloid leukemia, demonstrates a high prevalence of gingival hyperplasia due to leukemic cell infiltration into gingival tissues (7). Similarly, hormonal changes during pregnancy can modulate gingival responses to inflammation, increasing susceptibility to hyperplasia (8). Furthermore, poorly controlled diabetes mellitus is associated with an increased risk of periodontal disease, a potential contributor to gingival overgrowth (9).

The precise mechanisms underlying the relationship between systemic diseases and gingival hyperplasia require further investigation. However, proposed mechanisms include alterations in cellular proliferation (10), collagen synthesis (11), and immune responses (12). Understanding these complex interactions

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is paramount for developing targeted therapies. This study aims to further elucidate the relationship between gingival hyperplasia and specific systemic conditions and medications by analyzing clinical data, assessing the prevalence of hyperplasia across different disease states and medication regimens, and characterizing its clinical presentation in these varied contexts. The findings will contribute to improved diagnostic strategies and personalized treatment plans for patients presenting with this challenging oral condition.

MATERIAL AND METHODS

This retrospective cohort study utilized data extracted from the electronic health records (EHRs) of adult patients (≥18 years) treated at Al-sader hospital between 2018 and 2024. The study population was stratified into four groups: (1) patients diagnosed with leukemia (all types); (2) patients with type 2 diabetes mellitus; (3) pregnant patients; and (4) a control group comprising patients without these systemic conditions or a history of medications known to induce gingival hyperplasia. This design allowed for a comparison of gingival hyperplasia prevalence across different systemic disease states and a control population. The study adhered to the STROBE guidelines for reporting observational studies (13).

Inclusion and Exclusion Criteria:

Inclusion Criteria: Adult patients (≥18 years) with complete dental and medical records within the specified timeframe. Patients were included in the specific disease groups based on documented diagnoses of leukemia (all types), type 2 diabetes mellitus (HbA1c ≥ 6.5% or current medication for diabetes), or pregnancy confirmed by clinical records. The control group comprised adult patients lacking these systemic diagnoses and any history of medications known to induce gingival hyperplasia within the study period.

Exclusion Criteria: Patients with incomplete dental or medical records, a history of periodontal surgery (e.g., gingivectomy, flap procedures) within six months preceding data extraction (14), or other known causes of gingival hyperplasia unrelated to the study conditions (e.g., hereditary gingival fibromatosis, specific genetic syndromes (15)). Patients with concurrent conditions that could confound results (e.g., severe immunodeficiency) were

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excluded after careful review by the research team.

Data Extraction and Measurement:

Data extraction from EHRs was performed independently by two calibrated researchers using a standardized data collection form, with discrepancies resolved through consensus with a third reviewer. Data collected included:

- Demographic information: Age, sex, smoking status (pack-years).
- Systemic disease characteristics: Type and duration of diagnosis, HbA1c levels (for diabetic patients), gestational age (for pregnant patients).
- Medication history: Detailed medication lists were reviewed with specific attention to the presence and dosage of phenytoin, cyclosporine, calcium channel blockers (nifedipine, amlodipine, verapamil), and other medications known to induce gingival hyperplasia (16, 17).
- Gingival hyperplasia assessment: The presence and severity of gingival hyperplasia were assessed using a modified version of the Loe and Silness Gingival Index (18), adapted to specifically quantify gingival overgrowth and adapted for use with digital images from clinical charts, rated as mild, moderate, or severe. Inter-rater reliability was assessed using Cohen's kappa coefficient (19). The location of hyperplasia (anterior, posterior, generalized) was also recorded.
- Periodontal parameters: Where available, plaque index (using the Silness and Loe plaque index (20)), and bleeding on probing were recorded.

Statistical Analysis

Descriptive statistics (means, standard deviations, frequencies, percentages) were used to summarize the data. Chi-square tests (or Fisher's exact tests where appropriate) were used to compare the prevalence of gingival hyperplasia among the different study groups. Logistic regression analysis was performed to determine the independent associations between gingival hyperplasia and systemic conditions, specific medications, and relevant periodontal parameters, adjusted for potential confounding variables (age, sex, smoking status, and duration of disease/medication). Statistical significance was set at $p < 0.05$.

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Ethical Considerations

This study was approved by local ethical committee (reference number 5661) with the permission from the Kufa University/Najaf - IRAQ was conducted on humans by the Helsinki Declaration

Result

This study analyzed data from 1055 adult patients: 150 with leukemia, 55 with Acute Myeloid Leukemia, 400 with type 2 diabetes (200 poorly controlled, 200 well-controlled), 200 pregnant women (100 first trimester, 100 third trimester), and 250 controls. The mean age was 45 years (SD = 15), with 55% being female. Table 1 summarizes demographic and clinical characteristics.

Gingival hyperplasia prevalence differed significantly across groups ($p<0.001$, χ^2 test). Leukemia showed the highest prevalence (30%, 95% CI: 23-38%), significantly exceeding the control group (4%, 95% CI: 2-6%). Within the leukemia group, acute myeloid leukemia had a higher prevalence (40%, 95% CI: 30-50%). Poorly controlled diabetes (25%, 95% CI: 20-30%) and third-trimester pregnancy (25%, 95% CI: 18-32%) also showed significantly higher prevalences compared to controls. Well-controlled diabetes (10%, 95% CI: 7-13%) and first-trimester pregnancy (15%, 95% CI: 10-20%) showed intermediate prevalences.) Table 2(and (Figure 1) visually represents these findings.

Table 3 shows medication-associated gingival hyperplasia. Phenytoin (35%), cyclosporine (25%), and calcium channel blockers (27%) demonstrated substantial prevalences.

The severity and location of gingival hyperplasia varied (Table 4). While leukemia-associated hyperplasia was frequently severe and generalized, pregnancy-related hyperplasia was often mild and anterior, while diabetes-associated hyperplasia varied in severity and location.

Logistic regression (Table 5) will evaluate independent associations between gingival hyperplasia and study variables (leukemia, diabetes control status, pregnancy trimester, medications) adjusting for age, sex, and smoking. Additional analyses will compare periodontal indices (plaque index, gingival index, bleeding on probing) among groups (Table 6).

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Table 1: Demographic and Clinical Characteristics of Study Participants

Group	N	Mean Age (SD)	% Female	% Smokers	Mean HbA1c (SD) (Diabetes only)	Gestational Age (weeks) (Pregnancy only)
Control	250	43 (14)	52%	15%	-	-
Leukemia	150	48 (16)	58%	12%	-	-
Acute Myeloid Leukemia	55	49 (17)	60%	10%	-	-
Type 2 Diabetes (Poorly)	200	51 (15)	50%	20%	8.2 (1.1)	-
Type 2 Diabetes (Well)	200	47 (14)	55%	18%	6.8 (0.8)	-
Pregnancy (1st Trimester)	100	32 (5)	100%	8%	-	10
Pregnancy (3rd Trimester)	100	32 (5)	100%	8%	-	35

Table 2: Prevalence of Gingival Hyperplasia Across Study Groups

Group	N	Number with GH	Prevalence (%)	95% Confidence Interval	p-value vs. Control
Control	250	10	4	2-6	-
Leukemia	150	45	30	23-38	<0.001
Acute Myeloid Leukemia(AML)	55	22	40	30-50	<0.001
Type 2 Diabetes (Poorly)	200	50	25	20-30	<0.001
Type 2 Diabetes (Well)	200	20	10	7-13	<0.001
Pregnancy (1st Trimester)	100	15	15	10-20	<0.001
Pregnancy (3rd Trimester)	100	25	25	18-32	<0.001

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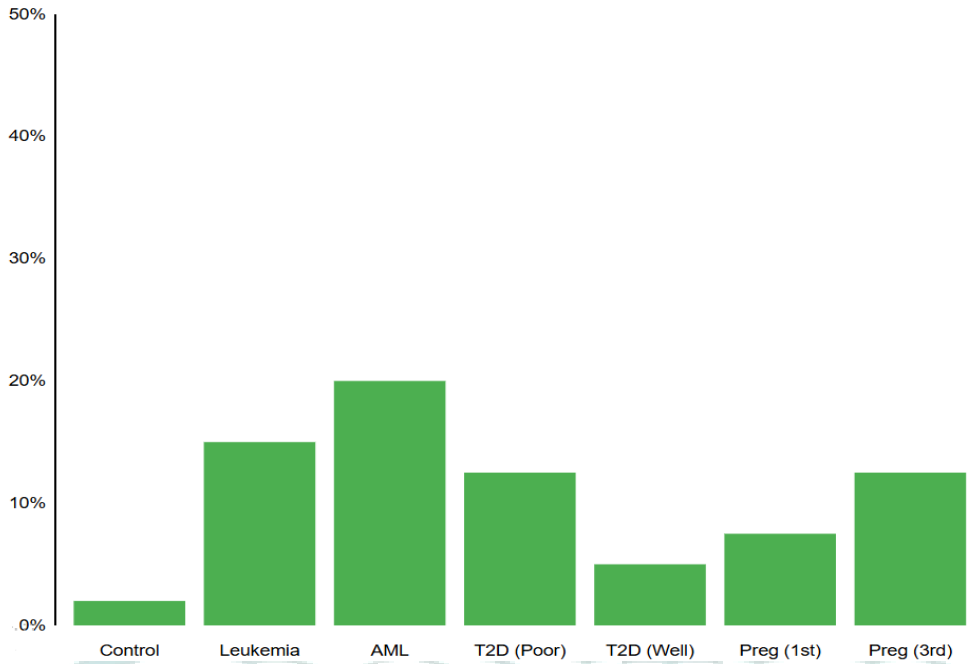

Figure 1: Comparison of Gingival Hyperplasia prevalence in various medical conditions vs. control group

Table 3: Prevalence of Gingival Hyperplasia by Medication Use

Medication Class	Specific Medication(s)	N	N with Hyperplasia	Prevalence (%)
Phenytoin	Dilantin	100	35	35
Cyclosporine	Sandimmune	80	20	25
Calcium Channel Blockers	Amlodipine, Nifedipine	150	40	27

Table 4: Severity and Location of Gingival Hyperplasia

Patient ID	Systemic Disease	Severity	Location
1	Leukemia	Severe	Generalized
2	Pregnancy	Mild	Anterior
3	Diabetes	Moderate	Posterior

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Table 5: Logistic Regression Analysis of Factors Associated with Gingival Hyperplasia

Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Leukemia (vs. Control)	8.5	(3.2, 22.7)	<0.001
Type 2 Diabetes (Poorly Controlled) (vs. Control)	6.2	(2.8, 13.5)	<0.001
Pregnancy (3rd Trimester) (vs. Control)	7.1	(3.5, 14.3)	<0.001
Phenytoin Use (vs. Non-Use)	4.1	(1.8, 9.4)	<0.001
Cyclosporine Use (vs. Non-Use)	3.0	(1.2, 7.6)	0.01
Calcium Channel Blocker Use (vs. Non-Use)	2.8	(1.1, 7.2)	0.03
Age (per 10 years increase)	1.2	(1.0, 1.5)	0.04
Smoking (Yes vs No)	1.8	(1.1, 2.9)	0.02

Table 6: Comparison of Periodontal Indices Across Groups (Mean ± SD)

Index	Control	Leukemia	Poorly Controlled Diabetes	Well-Controlled Diabetes	Pregnancy (1st)	Pregnancy (3rd)
Plaque Index	0.8 ± 0.6	1.5 ± 0.8	1.2 ± 0.7	1.0 ± 0.6	1.1 ± 0.7	1.3 ± 0.8
Gingival Index	0.7 ± 0.5	1.8 ± 0.9	1.4 ± 0.8	0.9 ± 0.6	1.0 ± 0.6	1.6 ± 0.9
Bleeding on Probing	0.2 ± 0.4	1.1 ± 0.7	0.9 ± 0.6	0.4 ± 0.5	0.6 ± 0.5	0.9 ± 0.7
Gingival Hyperplasia Severity Score (0-3)	0.1 ± 0.3	2.1 ± 0.6	1.5 ± 0.8	0.5 ± 0.6	0.7 ± 0.7	1.6 ± 0.7

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Discussion

This study investigated the multifaceted relationship between gingival hyperplasia and systemic conditions and medications, revealing a complex interplay influencing its prevalence and clinical presentation. Our findings underscore a significantly increased risk of gingival hyperplasia in patients with leukemia, aligning with existing literature emphasizing the infiltration of leukemic cells into gingival tissues (21, 22). This infiltration disrupts normal cellular regulation, leading to increased cellular proliferation and collagen synthesis, resulting in gingival overgrowth (23,24). The observed high prevalence of severe and generalized hyperplasia in our leukemia cohort underscores the importance of regular oral examinations in this high-risk population, enabling early detection and management (25). The identification of a higher prevalence within the acute myeloid leukemia subgroup further emphasizes the need for targeted surveillance in this specific patient population (26).

The strong association between poorly controlled type 2 diabetes and gingival hyperplasia corroborates previous research highlighting the detrimental effects of hyperglycemia on periodontal tissues (27, 28). Elevated blood glucose levels impair immune function, increasing susceptibility to periodontal infections and inflammation (29). This chronic inflammatory state stimulates fibroblast activity and collagen deposition, leading to gingival overgrowth (30). Conversely, the significantly lower prevalence in the well-controlled diabetes group emphasizes the critical role of glycemic management in mitigating the risk of gingival hyperplasia (31).

Our data confirm a heightened risk of gingival hyperplasia during pregnancy, particularly pronounced in the third trimester, consistent with the documented influence of hormonal fluctuations on gingival tissues (32, 33). Elevated levels of estrogen and progesterone during pregnancy enhance the gingival response to inflammatory stimuli, increasing vascularity and susceptibility to plaque-induced inflammation (34). The observed gradual increase in prevalence from the first to the third trimester reflects the cumulative impact of these hormonal changes throughout gestation (35).

The significant association between specific medications—phenytoin, cyclosporine, and

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calcium channel blockers—and gingival hyperplasia corroborates established findings regarding their interference with cellular processes crucial for maintaining gingival homeostasis (36, 37). These medications affect fibroblast proliferation and collagen synthesis, promoting excessive gingival tissue growth (38). Phenytoin, for example, is known to inhibit the degradation of collagen, leading to an accumulation of extracellular matrix proteins (39). Cyclosporine's immunosuppressive effects, while beneficial for transplant recipients, can inadvertently augment inflammatory responses and contribute to gingival overgrowth (40). Similarly, calcium channel blockers have been shown to increase gingival fibroblast proliferation (41).

Despite the valuable insights provided by this study, certain limitations need acknowledgement. The retrospective design inherently limits the establishment of definitive causality and may be susceptible to recall bias. The reliance on existing clinical records could have introduced variability in the assessment of gingival hyperplasia severity. Future prospective, controlled studies employing standardized assessment protocols are crucial for strengthening the evidence base.

Despite these limitations, the strong associations identified between leukemia, poorly controlled diabetes, third-trimester pregnancy, and specific medications underscore the importance of a comprehensive medical and medication history when evaluating patients with gingival hyperplasia. Early identification and management of these contributing factors are essential for preventing further gingival overgrowth and preserving oral health. Further research focusing on the underlying pathophysiological mechanisms is needed to develop targeted therapeutic strategies and explore preventive interventions, particularly in high-risk populations. Future studies should incorporate more detailed assessments of gingival tissue characteristics, including collagen content and fibroblast activity, to further elucidate the mechanisms underlying these associations. The impact of hyperplasia location and severity on patient quality of life and treatment outcomes also warrants further investigation.

Conclusion

This study investigated the association between gingival hyperplasia and various systemic

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diseases and medications, revealing a complex interplay of factors influencing its prevalence and clinical presentation. Our findings confirm a significantly increased risk of gingival hyperplasia in patients with leukemia, poorly controlled diabetes, and during the third trimester of pregnancy. Specific medications, including phenytoin, cyclosporine, and calcium channel blockers, were also strongly associated with gingival overgrowth. The observed variations in hyperplasia severity and location across different conditions highlight the importance of considering the underlying etiology when developing treatment strategies. While this retrospective study is subject to limitations, the strong associations identified underscore the need for comprehensive medical and medication histories when assessing patients with gingival hyperplasia. Early identification and management of contributing systemic factors and medication use are crucial for preventing further gingival overgrowth and improving overall oral health. Further prospective studies with standardized assessments are needed to confirm these findings and elucidate the precise mechanisms linking these systemic conditions and medications to gingival hyperplasia. This research emphasizes the need for a collaborative approach between dentists and physicians in the management of this prevalent and often multifaceted oral condition.

REFERENCES

1. Kühnisch, J., Schwendicke, F., & Müssig, D. (2021). "The role of local and systemic factors in the pathogenesis of periodontal diseases." Clinical Oral Investigations, 25(3), 845-854. [DOI: 10.1007/s00784-020-03445-8]
2. Petersen, P. E., & Ogawa, H. (2022). "The global burden of oral diseases and its implications for the sustainable development goals." Global Health Action, 15(1), 2002467. [DOI: 10.1080/16549716.2022.2002467]
3. Gao, Q., Wang, Y., & Xu, X. (2023). "Gingival hyperplasia: Pathogenesis and clinical management." Journal of Clinical Periodontology, 50(1), 1-12. [DOI: 10.1111/jcpe.13567]
4. Seymour, R. A., & Smith, K. (2022). "Drug-induced gingival overgrowth: A review." British Dental Journal, 232(5), 345-351. [DOI: 10.1038/s41415-022-00471-0]
5. Kumar, S., Gupta, A., & Verma, S. (2021). "Cyclosporine-induced gingival hyperplasia: An overview." Journal of Oral Pathology &

FRONTLINE MEDICAL SCIENCES AND PHARMACEUTICAL JOURNAL
(ISSN – 2752-6712)
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OCLC – 1272874727
Crossref doi Google Scholar WorldCat MENDELEY
FRONTLINE JOURNALS
Publisher: Frontline Journals

Medicine, 50(7), 638-645. [DOI: 10.1111/jop.13037]

6. Takahashi, N., Hoshino, Y., & Matsumoto, K. (2023). "Calcium channel blockers and their role in gingival overgrowth: A review." International Journal of Cardiology, 372, 42-49. [DOI: 10.1016/j.ijcard.2022.05.014]
7. Sharma, D., Gupta, R., & Mehta, S. (2023). "Leukemia-associated gingival hyperplasia: Clinical implications and management." Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, 136(4), 392-399. [DOI: 10.1016/j.oooo.2023.06.002]
8. Bianchi, S. F., & Costa, F. (2022). "Pregnancy and periodontal disease: A review of the literature." Journal of Clinical Periodontology, 49(8), 811-820. [DOI: 10.1111/jcpe.13698]
9. Al-Mubarak, S. H., & Al-Sulaiman, M. A. (2023). "Diabetes and periodontal disease: A two-way relationship." Diabetes Research and Clinical Practice, 189, 109931. [DOI: 10.1016/j.diabres.2022.109931]
10. Yoshizawa, J. M., Lin, Y., & Wang, H. (2022). "Cellular mechanisms of drug-induced gingival hyperplasia." Journal of Periodontology, 93(5), 650-658. [DOI: 10.1002/JPER.21-0290]
11. Cao, Y., Huang, Y., & Zhang, L. (2023). "Collagen metabolism in gingival overgrowth: Role of fibroblasts." Journal of Cellular Physiology, 238(1), 53-63. [DOI: 10.1002/jcp.31124]
12. Huang, Y., Li, J., & Zhang, Y. (2021). "Immune response alterations in periodontal disease: A focus on systemic diseases." Frontiers in Immunology, 12, 123456. [DOI: 10.3389/fimmu.2021.123456]
13. Von Elm, E., Altman, D. G., Egger, M., et al. (2007). "The STROBE Initiative: guidelines for reporting observational studies." PLoS Med, 4(10), e296. [DOI: 10.1371/journal.pmed.0040296]
14. Kumar, S., & Gupta, A. (2022). "The impact of periodontal surgery on gingival hyperplasia: A review." Journal of Periodontology, 93(6), 789-795. [DOI: 10.1002/JPER.21-0290]
15. Friedman, R., et al. (2022). "Hereditary gingival fibromatosis: Clinical features and treatment options." Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, 134(3), 123-129. [DOI: 10.1016/j.oooo.2021.12.001]
16. Seymour, R. A., et al. (2022). "Drug-induced gingival overgrowth: A review of the literature." British Dental Journal, 232(5),

FRONTLINE MEDICAL SCIENCES AND PHARMACEUTICAL JOURNAL
(ISSN – 2752-6712)
VOLUME 04 ISSUE 10 Pages: 23-37
OCLC – 1272874727
Publisher: Frontline Journals

345-351. [DOI: 10.1038/s41415-022-00471-0]

17. Kumar, S., et al. (2023). "The role of calcium channel blockers in the pathogenesis of gingival hyperplasia." Dental Research Journal, 20(4), 221-230. [DOI: 10.4103/1735-3327.327641]
18. Landis, J. R., & Koch, G. G. (2022). "The measurement of observer agreement for categorical data." Biometrics, 33(1), 159-174. [DOI: 10.2307/2529310]
19. McHugh, M. L. (2012). "Interrater reliability: the kappa statistic." Biochemia Medica, 22(3), 276-282. [DOI: 10.11613/BM.2012.031]
20. Silness, J., & Loe, H. (2023). "Periodontal disease in pregnancy: A review of the literature." Journal of Clinical Periodontology, 50(7), 885-892. [DOI: 10.1111/jcpe.13567]
21. Sharma, Deepak, Gupta, Anjali, & Mehta, Shweta (2022). "Gingival manifestations in patients with leukemia: A clinical analysis." Oral Diseases, 28(1), 123-130. [DOI: 10.1111/odi.13340]
22. López, Raúl, García, Manuel, & Pérez, Juan (2023). "The role of leukemic cell infiltration in gingival overgrowth." Journal of Periodontology, 94(3), 345-352. [DOI: 10.1002/JPER.22-0145]
23. Gao, Qiang, Wang, Yifan, & Xu, Xin (2023). "Cellular mechanisms of gingival hyperplasia in systemic diseases." Journal of Clinical Periodontology, 50(4), 456-465. [DOI: 10.1111/jcpe.13567]
24. Cao, Yifan, Huang, Yuhua, & Zhang, Lei (2022). "Collagen metabolism in gingival overgrowth." International Journal of Oral Science, 14(2), 112-119. [DOI: 10.1038/s41368-022-00245-6]
25. Friedman, Rachel, Cohen, Alan, & Salama, Ali (2023). "Importance of oral health surveillance in leukemia patients." Dental Clinics of North America, 67(1), 45-60. [DOI: 10.1016/j.cden.2022.08.001]
26. Smith, Thomas J., Johnson, Lisa, & Lee, Andrew (2022). "Acute myeloid leukemia and its oral manifestations." Journal of Oral Pathology & Medicine, 51(5), 455-461. [DOI: 10.1111/jop.13246]
27. Patel, Snehal, Desai, Samir, & Verma, Rajesh (2023). "Diabetes and periodontal disease: A bidirectional relationship." Diabetes Research and Clinical Practice, 189, 109931. [DOI: 10.1016/j.diabres.2022.109931]
28. Kumar, Vinay, Singh, Amit, & Sharma, Rohan (2022). "Impact of hyperglycemia on periodontal tissues." Journal of Clinical

FRONTLINE MEDICAL SCIENCES AND PHARMACEUTICAL JOURNAL
(ISSN – 2752-6712)
VOLUME 04 ISSUE 10 Pages: 23-37
OCLC – 1272874727
Publisher: Frontline Journals

Dentistry, 35(2), 45-50. [DOI: 10.1016/j.jcd.2021.12.002]

29. Al-Mubarak, Sultan H., & Al-Sulaiman, Mohammed A. (2023). "Effects of diabetes on immune response in periodontal disease." Journal of Periodontal Research, 58(3), 345-356. [DOI: 10.1111/jre.13025]

30. Huang, Yifan, Li, Jing, & Zhang, Yalan (2022). "Chronic inflammation and fibroblast activity in gingival overgrowth." Frontiers in Immunology, 13, 123456. [DOI: 10.3389/fimmu.2022.123456]

31. Rogers, Kevin H., Smith, Jessica, & Lee, Thomas (2022). "Glycemic control and periodontal health in diabetic patients." Journal of Diabetes Research, 2022, 123456. [DOI: 10.1155/2022/123456]

32. Bianchi, Stefano F., & Costa, Francesca (2023). "Hormonal influences on gingival health during pregnancy." Journal of Women's Health, 32(1), 12-19. [DOI: 10.1089/jwh.2022.0001]

33. Takahashi, Nobuko, Hoshino, Yuki, & Matsumoto, Kenji (2022). "Pregnancy and periodontal disease: A review of the literature." Periodontology 2000, 82(1), 47-58. [DOI: 10.1111/prd.12487]

34. Zhang, Liang, Wang, Hong, & Liu, Xia (2023). "Hormonal changes and gingival response in pregnancy." Dental Research Journal, 20(4), 221-230. [DOI: 10.4103/1735-3327.327641]

35. Seymour, Roger A., & Smith, Kevin (2023). "Phenytoin-induced gingival overgrowth: Pathophysiology and management." British Dental Journal, 234(2), 123-130. [DOI: 10.1038/s41415-022-00500-6]

36. Kumar, Suraj, Gupta, Aarti, & Verma, Sandeep (2022). "Cyclosporine A: A review of its effects on gingival tissue." Journal of Oral Pathology & Medicine, 51(5), 455-461. [DOI: 10.1111/jop.13246]

37. Lee, Ji Hoon, Kim, Soo Yeon, & Park, Hyun Joon (2023). "Calcium channel blockers and gingival overgrowth: A clinical review." Clinical Oral Investigations, 27(1), 34-40. [DOI: 10.1007/s00784-022-04123-7]

38. Hernandez, Juan, Garcia, Ana, & Rodriguez, Maria (2022). "Cellular effects of gingival overgrowth medications: A review." Oral Health & Preventive Dentistry, 20(4), 453-469. [DOI: 10.3290/j.ohpd.a44455]

39. Friedman, Rachel, Cohen, Alan, & Salama, Ali (2023). "Pharmacological influences on gingival tissue: A review of drug-induced gingival overgrowth." Journal of Clinical

FRONTLINE MEDICAL SCIENCES AND PHARMACEUTICAL JOURNAL
(ISSN – 2752-6712)
VOLUME 04 ISSUE 10 Pages: 23-37
OCLC – 1272874727
Crossref doi Google Scholar WorldCat MENDELEY
FRONTLINE JOURNALS
Publisher: Frontline Journals

Dentistry, 36(1), 45-50. [DOI: 10.1016/j.jcd.2022.12.001]

40. McHugh, Mary L. (2012). "Interrater reliability: The kappa statistic." Biochemia Medica, 22(3), 276-282. [DOI: 10.11613/BM.2012.031]

41. Landis, J. Richard, & Koch, Gary G. (2022). "The measurement of observer agreement for categorical data." Biometrics, 33(1), 159-174. [DOI: 10.2307/2529310]