SYSTEMIC ETIOLOGY OF GINGIVAL OVERGROWTH: CLINICAL AND THERAPEUTIC ASPECTS. LITERATURE REVIEW

Anca Mihaela Predescu[1], Dan Alexandru Popescu[2], Gabriela Boldeanu[3], Cristina Maria Munteanu[4†], Anda-Elena Crișan[5], Elena Cristina Andrei[1], Ilona Mihaela Liliac[1†], Ciprian Laurențiu Pătru[6]

[1] Department of Histology, University of Medicine and Pharmacy Craiova
[2] Department of Endodontics, University of Medicine and Pharmacy Craiova
[3] Medical Resident, Internal Medicine Specialty, Emergency County Clinical Hospital Craiova
[4] Department of Oral and Maxillofacial Surgery, University of Medicine and Pharmacy Craiova
[5] Department of Oncology, University of Medicine and Pharmacy of Craiova, Romania
[6] Department of Obstetrics and Gynecology, University of Medicine and Pharmacy Craiova

Corresponding author; Andrei Elena Cristina *e-mail:* andreicristina2201@gmail.com
†These authors contributed equally to this work.

ABSTRACT

Introduction Drug-induced gingival overgrowth is a condition characterized by a series of modifications in the gingival mucosa, including tumefaction, changes in color, and gingival bleeding. This condition can involve a variety of drugs, such as anticonvulsants and calcium channel blockers. **Aim of the study** To present the clinical modifications of hypertrophic gingival overgrowth of systemic and drug etiology, as well as to highlight therapeutic alternatives. **Results** Key aspects of drug-induced gingival overgrowth include the risk of recurrence, the importance of eliminating predisposing factors such as poor oral hygiene and bacterial plaque, as well as treatment options, such as surgical excision, which can be performed with diode dental laser or traditional techniques. **Conclusions** A personalized therapeutic approach, considering clinical and morphological aspects, is essential for achieving an optimal outcome in managing this condition.

Key words: gingival overgrowth; diabetes; leukemia; phenythoin; cyclosporines.

INTRODUCTION

Gingival overgrowth of systemic etiology is a common condition of the periodontium characterized by an increase in gingival volume [1], resulting from the excessive accumulation of the extracellular matrix in the chorion of the gingival mucosa, especially collagen fibers produced by gingival fibroblasts, associated with varying degrees of inflammation [1, 2]. This leads to local speech problems, issues with proper nutrition, lack of aesthetics, and can eventually cause various cardiovascular conditions [1].

Based on the etiopathogenesis [3], gingival overgrowth can be inflammatory, drug-induced [4-6], associated with systemic conditions or diseases [7, 8], tumoral or pseudotumoral gingival overgrowth.

There are two types of gingival overgrowth: gingival hypertrophy or gingival hyperplasia. This differentiation can only be made based on histopathological examination. Gingival hyperplasia is characterized by an increase in the number of cells [9868421], while gingival hypertrophy is characterized by an increase in cell volume and constituent elements of the gingival mucosa [3, 7].

GINGIVAL OVERGROWTH ASSOCIATED WITH SYSTEMIC CONDITIONS

There are numerous systemic pathological conditions that can lead to gingival overgrowth. Most commonly,

we encounter gingival overgrowth in diabetic patients [9, 10], those with cardiac [11] or neurological [12] conditions, as well as in immunocompromised patients who have undergone organ transplant procedures [5, 13-15], and patients diagnosed with leukemia [16, 17].

Gingival overgrowth in leukemia

Generalized gingival overgrowth associated with leukemia, is a condition we encounter due to the massive infiltration of leukocytes in the gingival chorion[18]. Clinically, gingival overgrowth may mimic an inflammatory origin. Other oral cavity characteristics determined by leukemia include: oral ulceration [19], spontaneous gingival bleeding [18, 20, 21], petechiae [22], mucosal pallor [18, 22], herpetic infections [23], and candidiasis [18, 24]. The most severe condition associated with gingival overgrowth [25] in this category is represented by acute myeloid leukemia [18]. This may be associated with signs and symptoms of marrow failure [26], such as bruising, night sweats, recent infections, and lethargy. A presumptive diagnosis can be made based on the interpretation of the complete blood count.

Gingival overgrowth in patients diagnosed with leukemia: this condition worsens directly proportional with the amount of existing bacterial plaque on dental surfaces [18, 27]. Even with good oral hygiene, gingivitis may be present, but its intensity is usually mild to moderate [18].

Gingival overgrowth in diabetes

Recent research indicates a correlation between gingival conditions and diabetes [28]. In addition to the already recognized fact that individuals with diabetes are more prone to developing gingival conditions [28], recent studies suggest that chronic gum involvement may constitute a diabetic risk factor [29]. The primary factor in the etiology of periodontal disease is dental bacterial plaque [29], represented by bacterial aggregation adhering to tooth surfaces, which cannot be removed by water jets or simple rinsing. Bacterial plaque may also be present in other hard-to-reach areas of the oral cavity, such as the surfaces of dental restorations, fixed or removable prostheses, orthodontic appliances, and dental implants [30, 31].

The pathogenesis of periodontal disease is complex, deriving from a combination of initiation and maintenance of the chronic inflammatory process by the rich microbial flora and its numerous bacterial products [30, 32]. The host response to this infection mediates a complex cascade of tissue destruction. Additional factors contributing to the initiation and progression of the disease include certain systemic diseases, especially diabetes mellitus, which can exacerbate the host's response to local microbial factors (e.g., bacterial endotoxin), leading to intense and unusual periodontal destruction. Aggressive periodontitis is recognized by periodontology specialists as the sixth most frequent complication of diabetes mellitus [33].

Patients with type 1 diabetes mellitus are more predisposed to gingivitis [34]. Both children [34] and adults with poor metabolic control are highly susceptible to gingivitis [35]. The prevalence of gingivitis in children and adolescents is nearly double compared to children and adolescents without diabetes. The severity and extent of gingivitis are significantly higher in young patients with diabetes [36, 37]. The association of diabetes with gingivitis in children and adolescents is well accepted, with diabetic-associated gingivitis being included as a specific entity in recent classifications of periodontal diseases. In adults with type 2 diabetes mellitus, gingival inflammation

may occur with a much higher incidence and intensity than in adults without diabetes. The degree of metabolic control of diabetes appears to be an important factor in the development and progression of gingivitis [38, 39].

In diabetic patients, concentrations of oral microbial flora are increased due to higher concentrations of glucose in saliva and gingival crevicular fluid. The increase in glucose levels in gingival crevicular fluid and blood of diabetic patients could modify the microflora environment, inducing qualitative changes in bacteria that could contribute to the severity of periodontal disease observed in those with poorly controlled diabetes [40]. Both diabetes and marginal periodontitis are considered chronic conditions. Diabetes has numerous adverse effects on the periodontium, including impairment of neutrophil function and increased periodontal destruction. Periodontitis can alter systemic physiology in diabetic patients. The effect of periodontitis on diabetes mellitus is believed to result from the inflammatory nature of the inflammatory response in periodontal tissues.

Other oral conditions related to diabetes include candidiasis [41] and xerostomia [42], which can cause sensations of pain, ulcerations, infections, and carious processes[43].

Medications most commonly associated with gingival overgrowth are phenytoin, cyclosporine, and calcium channel blockers [6].

Phenytoin is an anticonvulsant medication used for certain types of epileptic seizures. In approximately 50% of cases, phenytoin can cause gingival hyperplasia [6].

Cyclosporines are immunosuppressive drugs commonly used in organ transplant cases. The prevalence of gingival hyperplasia in this case is 25-30% in adults and up to 70% in children [44].

Calcium channel blockers are a class of medications prescribed for cardiovascular conditions such as hypertension, angina pectoris, or cardiac rhythm disorders. The prevalence of gingival hyperplasia with this medication depends on the type of drug administered; nifedipine carries the highest risk of inducing gingival hyperplasia, occurring in approximately 6-15% of cases [45].

Gingival overgrowth induced by phenytoin

Gingival overgrowth induced by phenytoin typically begins at the interdental gingival papillae, often within one month of initiating medication administration [46]. The volume of gingival overgrowth is influenced by the dose, duration, and plasma levels of the drug [47, 48]. Numerous studies have demonstrated a direct correlation between plaque and tartar accumulation and the severity of gingival overgrowth [49]. As gingival changes gradually become more pronounced, marginal tissues often extend to cover portions of the clinical crowns of teeth. This involvement tends to be more pronounced on the vestibular surface than on the lingual surface of the teeth [49, 50].

Histologically, phenytoin-induced gingival overgrowth is characterized by increased thickness of the squamous epithelium, with a reduced layer of keratin on the surface. Additionally, acanthosis is present in varying degrees, determined by hyperplasia of the spinous layer of the gingival mucosa epithelium. Acantholysis of different degrees is encountered in the spinous layer. The lamina propria is thickened, showing an increased number of fibroblasts, which also explains the well-represented collagen fibrillar component, leading to a fibrous transformation of the gingival lamina propria. Collagen fibers have different thicknesses, arranged compactly

or in bundles that intersect, delimiting areas of different sizes, where the intercellular matrix is found with numerous fibrocytes and moderate vascularity [51].

Gingival overgrowth induced by calcium channel blockers

Gingival overgrowth induced by calcium channel blockers, most commonly associated with nifedipine, is a well-recognized side effect. Other agents associated with this gingival condition include diltiazem, verapamil [52, 53], and amlodipine [54]. Case studies have indicated that gingival overgrowth may also occur with the use of felodipine and nitrendipine [45, 55, 56].

Clinically, gingival overgrowth induced by calcium channel blockers closely resembles that induced by phenytoin. It typically becomes evident between 1 and 3 months after initiating medication administration. Specific dosage or plasma levels have been associated with this type of gingival overgrowth in laboratory animals but have not been demonstrated in humans. One theory is that plaque accumulation due to poor oral hygiene may contribute to the severity of this form of gingival involvement [53]. Histologically, gingival overgrowth induced by calcium channel blockers is characterized by increased extracellular matrix and an increased number of fibroblasts [45, 55, 56].

Gingival overgrowth induced by cyclosporine

Cyclosporine is a selective immunosuppressant with various applications in medical practice. Similar to phenytoin and calcium channel blockers, this medication is associated with gingival overgrowth [51]. The mechanism of cyclosporine-induced gingival overgrowth is not fully understood. Studies on cell cultures have shown that both cyclosporine and its metabolites have direct effects on the proliferation of gingival fibroblasts [57], protein synthesis, and collagen production [1, 57]. The results of clinical studies suggest that the incidence and severity of gingival growths in patients treated with cyclosporine depend on the interaction of multiple factors [57]. These include plaque control, level of gingival inflammation, degree of periodontal destruction, dosage and duration of cyclosporine treatment, plasma and tissue concentrations of the drug and its metabolites, patient age, and likely underlying medical condition [57].

Cyclosporine-induced gingival overgrowth begins with swelling of the interdental papilla, which is more pronounced at the vestibular papilla. This gives the gingival tissues a lobulated appearance. Excessive gingival tissue induced by cyclosporine has not been reported in edentulous subjects. Hyperplastic gingival tissues [44] often exhibit marked inflammatory changes, bleed easily on probing, and show accentuated hyperemia compared to phenytoin-induced gingival overgrowth [58, 59].

Gingival overgrowth induced by oral contraceptives

Oral contraceptives have become a widely used form of contraception over the past two decades [60, 61]. These medications involve the use of gestational hormones at concentrations that mimic pregnancy to prevent ovulation. All oral contraceptives act by artificially altering the levels of sex hormones [62].

Oral contraceptives can promote periodontal degradation [63] by reducing resistance to dental plaque and can induce gingival overgrowth in healthy women [64]. Oral contraceptives accentuate the immune response of the

gingival mucosa to local irritants similar to that observed during pregnancy. The incidence and severity of gingival diseases are positively correlated with plasma concentrations of sex hormones and the duration of use. Long-term use of oral contraceptives can lead to increased gingival inflammation, loss of gingival attachment, and gingival overgrowth. The gingival mucosa contains estrogen and progesterone receptors. The latter influence periodontal tissues to act as a target organ for sex hormones. In most cases, gingival overgrowth was reduced or absent when oral contraceptives were discontinued or the dosage was reduced [65].

The therapeutic approach to gingival overgrowth is complex and challenging. In cases where drug-induced gingival overgrowth is present, there is a risk of recurrence [66, 67]. It is particularly important that predisposing factors such as poor oral hygiene, bacterial plaque, and tartar be addressed [3]. For the treatment of gingival overgrowth, regardless of the etiology, surgical excision of the lesion is a common practice. Surgical excision can be performed using traditional techniques or with the assistance of diode dental laser. Recent studies have shown that excising the lesion with a laser presents a higher recurrence rate [66].

THERAPEUTIC ISSUES

CONCLUSIONS

Managing gingival overgrowths requires a personalized approach, taking into consideration both clinical and morphological aspects that indicate a definitive diagnosis, with the aim of providing the patient with an optimal outcome in the treatment of this condition.

REFERENCES

1. 1. Trackman PC, Kantarci A. Molecular and clinical aspects of drug-induced gingival overgrowth. J Dent Res, 2015, 94(4):540-546.
2. 2. Samudrala P, Chava VK, Chandana TS, Suresh R. Drug-induced gingival overgrowth: A critical insight into case reports from over two decades. J Indian Soc Periodontol, 2016, 20(5):496-502.
3. 3. Agrawal AA. Gingival enlargements: Differential diagnosis and review of literature. World J Clin Cases, 2015, 3(9):779-788.
4. 4. Lafzi A, Farahani RM, Shoja MA. Amlodipine-induced gingival hyperplasia. Med Oral Patol Oral Cir Bucal, 2006, 11(6):E480-482.
5. 5. Nanda T, Singh B, Sharma P, Arora KS. Cyclosporine A and amlodipine induced gingival overgrowth in a kidney transplant recipient: case presentation with literature review. BMJ Case Rep, 2019, 12(5)
6. 6. Drozdzik A, Drozdzik M. Drug-Induced Gingival Overgrowth-Molecular Aspects of Drug Actions. Int J Mol Sci, 2023, 24(6)
7. 7. Ciavarella D, Guiglia R, Campisi G, Di Cosola M, Di Liberto C, Sabatucci A, Escudero N, Bascones A, Lo Muzio L. Update on gingival overgrowth by cyclosporine A in renal transplants. Med Oral Patol Oral Cir Bucal, 2007, 12(1):E19-25.
8. 8. Adeyemo TA, Adeyemo WL, Adediran A, Akinbami AJ, Akanmu AS. Orofacial manifestations of hematological disorders: anemia and hemostatic disorders. Indian J Dent Res, 2011, 22(3):454-461.

9. 9. Mauri-Obradors E, Estrugo-Devesa A, Jane-Salas E, Vinas M, Lopez-Lopez J. Oral manifestations of Diabetes Mellitus. A systematic review. Med Oral Patol Oral Cir Bucal, 2017, 22(5):e586-e594.
10. 10. Genco RJ, Borgnakke WS. Diabetes as a potential risk for periodontitis: association studies. Periodontol 2000, 2020, 83(1):40-45.
11. 11. Van Dis ML, Allen CM, Neville BW. Erythematous gingival enlargement in diabetic patients: a report of four cases. J Oral Maxillofac Surg, 1988, 46(9):794-798.
12. 12. Kinane DF, Marshall GJ. Periodontal manifestations of systemic disease. Aust Dent J, 2001, 46(1):2-12.
13. 13. Seymour RA, Thomason JM, Nolan A. Oral lesions in organ transplant patients. J Oral Pathol Med, 1997, 26(7):297-304.
14. 14. Hood KA. Drug-induced gingival hyperplasia in transplant recipients. Prog Transplant, 2002, 12(1):17-21; quiz 22-13.
15. 15. Chatzopoulos GS, Koidou VP, Wolff LF. Systematic review of cyclosporin A-induced gingival overgrowth and genetic predisposition. Quintessence Int, 2017, 48(9):711-724.
16. 16. Cooper CL, Loewen R, Shore T. Gingival hyperplasia complicating acute myelomonocytic leukemia. J Can Dent Assoc, 2000, 66(2):78-79.
17. 17. Pai A, Prasad S, Dyasanoor S. Acute leukemias: a dentist's perspective. Minerva Stomatol, 2012, 61(5):233-238.
18. 18. Cammarata-Scalisi F, Girardi K, Strocchio L, Merli P, Garret-Bernardin A, Galeotti A, Magliarditi F, Inserra A, Callea M. Oral Manifestations and Complications in Childhood Acute Myeloid Leukemia. Cancers (Basel), 2020, 12(6)
19. 19. Francisconi CF, Caldas RJ, Oliveira Martins LJ, Fischer Rubira CM, da Silva Santos PS. Leukemic Oral Manifestations and their Management. Asian Pac J Cancer Prev, 2016, 17(3):911-915.
20. 20. Misirlioglu M, Adisen MZ, Yilmaz S. Diagnosis of acute myeloid leukemia in a dental hospital; report of a case with severe gingival hypertrophy. Niger J Clin Pract, 2015, 18(4):573-576.
21. 21. Fernandes KS, Gallottini M, Castro T, Amato MF, Lago JS, Braz-Silva PH. Gingival leukemic infiltration as the first manifestation of acute myeloid leukemia. Spec Care Dentist, 2018, 38(3):160-162.
22. 22. Chowdhri K, Tandon S, Lamba AK, Faraz F. Leukemic gingival enlargement: A case report and review of literature. J Oral Maxillofac Pathol, 2018, 22(Suppl 1):S77-S81.
23. 23. Devine SM, Larson RA. Acute leukemia in adults: recent developments in diagnosis and treatment. CA Cancer J Clin, 1994, 44(6):326-352.
24. 24. Djuric M, Hillier-Kolarov V, Belic A, Jankovic L. Mucositis prevention by improved dental care in acute leukemia patients. Support Care Cancer, 2006, 14(2):137-146.
25. 25. Quispe RA, Aguiar EM, de Oliveira CT, Neves ACX, Santos P. Oral manifestations of leukemia as part of early diagnosis. Hematol Transfus Cell Ther, 2022, 44(3):392-401.
26. 26. Aristizabal JA, Chandia M, Del Canizo MC, Sanchez-Guijo F. [Bone marrow microenvironment in chronic myeloid leukemia: implications for disease physiopathology and response to treatment]. Rev Med Chil, 2014, 142(5):599-605.
27. 27. Shankarapillai R, Nair MA, George R, Walsh LJ. Periodontal and gingival parameters in young adults with acute myeloid leukaemia in Kerala, South India. Oral Health Prev Dent, 2010, 8(4):395-400.
28. 28. Rohani B. Oral manifestations in patients with diabetes mellitus. World J Diabetes, 2019, 10(9):485-489.
29. 29. Stephens MB, Wiedemer JP, Kushner GM. Dental Problems in Primary Care. Am Fam Physician, 2018, 98(11):654-660.
30. 30. Sharma N, Bhatia S, Sodhi AS, Batra N. Oral microbiome and health. AIMS Microbiol, 2018, 4(1):42-66.
31. 31. Liccardo D, Cannavo A, Spagnuolo G, Ferrara N, Cittadini A, Rengo C, Rengo G. Periodontal Disease: A Risk Factor for Diabetes and Cardiovascular Disease. Int J Mol Sci, 2019, 20(6)

32. 32. Simpson TC, Weldon JC, Worthington HV, Needleman I, Wild SH, Moles DR, Stevenson B, Furness S, Iheozor-Ejiofor Z. Treatment of periodontal disease for glycaemic control in people with diabetes mellitus. Cochrane Database Syst Rev, 2015, 2015(11):CD004714.
33. 33. Loe H. Periodontal disease. The sixth complication of diabetes mellitus. Diabetes Care, 1993, 16(1):329-334.
34. 34. Bimstein E, Zangen D, Abedrahim W, Katz J. Type 1 Diabetes Mellitus (Juvenile Diabetes) - A Review for the Pediatric Oral Health Provider. J Clin Pediatr Dent, 2019, 43(6):417-423.
35. 35. Costa R, Rios-Carrasco B, Monteiro L, Lopez-Jarana P, Carneiro F, Relvas M. Association between Type 1 Diabetes Mellitus and Periodontal Diseases. J Clin Med, 2023, 12(3)
36. 36. Novotna M, Podzimek S, Broukal Z, Lencova E, Duskova J. Periodontal Diseases and Dental Caries in Children with Type 1 Diabetes Mellitus. Mediators Inflamm, 2015, 2015:379626.
37. 37. Mandura RA, Meligy OAE, Attar MH, Alamoudi RA. Diabetes Mellitus and Dental Health in Children: A Review of Literature. Int J Clin Pediatr Dent, 2021, 14(5):719-725.
38. 38. Leite RS, Marlow NM, Fernandes JK, Hermayer K. Oral health and type 2 diabetes. Am J Med Sci, 2013, 345(4):271-273.
39. 39. Penmetsa GS, Baddam S, Manyam R, Dwarakanath CD. Comparison of the number of gingival blood vessels between type 2 diabetes mellitus and chronic periodontitis patients: An immunohistological study. J Indian Soc Periodontol, 2015, 19(2):164-168.
40. 40. Zhang Z, Liu D, Liu S, Zhang S, Pan Y. The Role of Porphyromonas gingivalis Outer Membrane Vesicles in Periodontal Disease and Related Systemic Diseases. Front Cell Infect Microbiol, 2020, 10:585917.
41. 41. Pankhurst CL. Candidiasis (oropharyngeal). BMJ Clin Evid, 2012, 2012
42. 42. Lopez-Pintor RM, Casanas E, Gonzalez-Serrano J, Serrano J, Ramirez L, de Arriba L, Hernandez G. Xerostomia, Hyposalivation, and Salivary Flow in Diabetes Patients. J Diabetes Res, 2016, 2016:4372852.
43. 43. Sabharwal A, Stellrecht E, Scannapieco FA. Associations between dental caries and systemic diseases: a scoping review. BMC Oral Health, 2021, 21(1):472.
44. 44. Ramalho VL, Ramalho HJ, Cipullo JP, Burdmann EA. [Ciclosporine A-induced gingival hyperplasia]. Rev Assoc Med Bras (1992), 2003, 49(2):210-213.
45. 45. Damdoum M, Varma SR, Nambiar M, Venugopal A. Calcium Channel Blockers Induced Gingival Overgrowth: A Comprehensive Review from a Dental Perspective. J Int Soc Prev Community Dent, 2022, 12(3):309-322.
46. 46. Candotto V, Pezzetti F, Baj A, Beltramini G, Lauritano D, Di Girolamo M, Cura F. Phenytoin and gingival mucosa: A molecular investigation. Int J Immunopathol Pharmacol, 2019, 33:2058738419828259.
47. 47. Ramirez-Ramiz A, Brunet LL, Lahor-Soler E, Miranda-Rius J. On the Cellular and Molecular Mechanisms of Drug-Induced Gingival Overgrowth. Open Dent J, 2017, 11:420-435.
48. 48. Bajkovec L, Mrzljak A, Likic R, Alajbeg I. Drug-induced gingival overgrowth in cardiovascular patients. World J Cardiol, 2021, 13(4):68-75.
49. 49. Penarrocha-Diago M, Bagan-Sebastian JV, Vera-Sempere F. Diphenylhydantoin-induced gingival overgrowth in man: a clinico-pathological study. J Periodontol, 1990, 61(9):571-574.
50. 50. Kato T, Okahashi N, Kawai S, Kato T, Inaba H, Morisaki I, Amano A. Impaired degradation of matrix collagen in human gingival fibroblasts by the antiepileptic drug phenytoin. J Periodontol, 2005, 76(6):941-950.
51. 51. Ponnaiyan D, Jegadeesan V. Cyclosporine A: Novel concepts in its role in drug-induced gingival overgrowth. Dent Res J (Isfahan), 2015, 12(6):499-506.
52. 52. Miller CS, Damm DD. Incidence of verapamil-induced gingival hyperplasia in a dental population. J Periodontol, 1992, 63(5):453-456.
53. 53. Sabarudin MA, Taib H, Wan Mohamad WM. Refining the Mechanism of Drug-Influenced Gingival Enlargement and Its Management. Cureus, 2022, 14(5):e25009.

54. 54. John K, Mishra AK, Gunasekaran K, Iyyadurai R. Amlodipine-Induced Gingival Hyperplasia in a Young Male with Stage 5 Chronic Kidney Disease. Case Rep Nephrol, 2020, 2020:7801546.
55. 55. Steele RM, Schuna AA, Schreiber RT. Calcium antagonist-induced gingival hyperplasia. Ann Intern Med, 1994, 120(8):663-664.
56. 56. Fattore L, Stablein M, Bredfeldt G, Semla T, Moran M, Doherty-Greenberg JM. Gingival hyperplasia: a side effect of nifedipine and diltiazem. Spec Care Dentist, 1991, 11(3):107-109.
57. 57. Lauritano D, Palmieri A, Lucchese A, Di Stasio D, Moreo G, Carinci F. Role of Cyclosporine in Gingival Hyperplasia: An In Vitro Study on Gingival Fibroblasts. Int J Mol Sci, 2020, 21(2)
58. 58. Imshenetskii AA, Kozlova V. [Cholesterol-degrading capacity of several strains of Actinomyces lavendulae]. Mikrobiologiia, 1977, 46(1):104-108.
59. 59. Seymour RA, Jacobs DJ. Cyclosporin and the gingival tissues. J Clin Periodontol, 1992, 19(1):1-11.
60. 60. Kataoka M, Kido J, Shinohara Y, Nagata T. Drug-induced gingival overgrowth--a review. Biol Pharm Bull, 2005, 28(10):1817-1821.
61. 61. Ali I, Patthi B, Singla A, Gupta R, Dhama K, Niraj LK, Kumar JK, Prasad M. Oral Health and Oral Contraceptive - Is it a Shadow behind Broad Day Light? A Systematic Review. J Clin Diagn Res, 2016, 10(11):ZE01-ZE06.
62. 62. Dongari A, McDonnell HT, Langlais RP. Drug-induced gingival overgrowth. Oral Surg Oral Med Oral Pathol, 1993, 76(4):543-548.
63. 63. Guncu GN, Tozum TF, Caglayan F. Effects of endogenous sex hormones on the periodontium--review of literature. Aust Dent J, 2005, 50(3):138-145.
64. 64. Castro MML, Ferreira MKM, Prazeres IEE, de Oliveira Nunes PB, Magno MB, Rosing CK, Maia LC, Lima RR. Is the use of contraceptives associated with periodontal diseases? A systematic review and meta-analyses. BMC Womens Health, 2021, 21(1):48.
65. 65. Mascarenhas P, Gapski R, Al-Shammari K, Wang HL. Influence of sex hormones on the periodontium. J Clin Periodontol, 2003, 30(8):671-681.
66. 66. Gawron K, Lazarz-Bartyzel K, Potempa J, Chomyszyn-Gajewska M. Gingival fibromatosis: clinical, molecular and therapeutic issues. Orphanet J Rare Dis, 2016, 11:9.
67. 67. Decani S, Lodi G, Sardella A, Varoni EM. Localised juvenile spongiotic gingival hyperplasia: A case of spontaneous resolution and a literature review. Eur J Paediatr Dent, 2021, 22(2):159-162.