NARRATIVE REVIEW

Adipokines: Diagnostic and prognostic markers for oral diseases

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Abstract

Adipose tissue or fat tissue is a loose connective tissue that consists mainly of adipocytes. Adipocytes are classified on the basis of their secretory origin, differentiation, distribution, cell characteristics, such as amount of mitochondria, size and type of lipid droplets, and expression of uncoupled protein-1. Adipocytes secrete adipokines that are divided as white adipokines, brown adipokines and beige adipokines. Adipokines have been used as diagnostic and prognostic markers for different oral diseases. Irisin, chemerin, resistin, adiponectin, zinc alpha 2 macroglobulin, leptin, visfatin, tumour necrosis factor-alpha and interleukin-6 are some important adipokines associated with oral diseases, such as dental caries, periodontal diseases, recurrent aphthous stomatitis, oral cancers, oral premalignant lesions, Sjogren's syndrome, Kawasaki disease and Behcet's disease. The current narrative review was planned to focus on the pathophysiological role of adipokines in oral diseases and their role as biomarkers for early diagnosis and prompt treatment.

Keywords: Adipokines, Oral diseases, Oral cancers, Sjogren's syndrome, Kawasaki disease.

DOI: https://doi.org/10.47391/JPMA.4737
Submission completion date: 07-12-2021
Acceptance date: 31-08-2022

Introduction

Adipokines are proteins or cell signalling molecules secreted by adipose tissue and regulate key physiological processes. They act in paracrine, autocrine and even in endocrine fashion. Adipose tissue is classified into three types; white adipose tissue (WAT), beige adipose tissue and brown adipose tissue (BAT) on the basis of their respective secretory adipose tissues consisting of white, beige and brown adipocytes, respectively. The three types of adipocytes differ on the basis of characteristics (Table 1). Adipokines are classified depending on their respective secretory adipose tissues.[1,2] White and beige adipocytes reside within the white depots, whereas brown adipocytes resides within the brown depots. Beige adipocytes (brite adipocytes) have the potential to switch from white to brown adipocytes, and the process is known as browning or beigeing of WAT.[1]

Table-1: Characterisation of three types of adipocytes.

Characteristics	White adipocytes	Beige adipocytes	Brown adipocytes
Origin	Lateral mesoderm	Lateral mesoderm	Paraxial mesoderm
Myf5 precursor	Negative	Negative	Positive
Differentiation	Shortly after birth	After birth	Before birth
Lipid droplets	Unilocular, large	Unilocular, small	Multilocular, small
Mitochondria	Few mitochondria	Iron rich cristae Dense mitochondria	Iron rich cristae Dense mitochondria
Expression of UCP1/Thermogenin	Absent	Present	Present
Residence	White depots	White depots	Brown depots
Distribution	Adults: Subcutaneous (sWAT), Visceral (vWAT),	Inguinal WAT	Infants: intercapsular region, interscapular region, perirenal region Adults: upper trunk regions

WAT: White adipose tissue, sWAT: Subcutaneous white adipose tissue, vWAT: Visceral white adipose tissue, Myf5: Myogenic factor 5, UCP1: Uncoupled protein 1.

Pro-inflammatory and anti-inflammatory adipokines, such as leptin, apelin, adiponectin, chemerin, omentin,[3] visfatin, resistin, interleukin-6 (IL-6), IL-10, tumornecrosis factor-alpha (TNF-α) and irisin are mainly derived from WAT.[4] Fibroblast growth factor-21 (FGF-21), myostatin-E, vascular endothelial growth factor-alpha (VEGF-α), and bone morphogenic protein-8b (BMP-8b) are derived from BAT.[1] Insulin-like growth factor-1 (IGF-1), IL-6, meteorin-like (Metrnl), insulin-like growth factor binding protein-2 (IGFBP-2), neuregulin-4 (NRG-4), nerve growth factor (NGF) and Slit homologue 2-C fragment (SLIT2-C) are secreted by brown/beige adipocytes(1). More than 600 adipokines have been identified and the list is fast growing. Adipokines are present in all biological fluids, including saliva, gingival crevicular fluid (GCF), serum, plasma, cerebrospinal fluid (CSF), synovial fluid, circulation and breast milk, making its distribution noteworthy.[5] Adipokines play significant roles as biomarkers, therapeutic agents, inflammatory mediators and immune molecules in diagnosis and prognosis of oral diseases, such as dental caries, recurrent aphthous stomatitis (RAS), periodontal diseases, oral cancers, Sjogren's syndrome (SS), oral premalignant lesions, Kawasaki disease (KD) and Behcet's disease (BD) (Table 2).

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Table-2: Oral diseases and their respective adipokines.

S. No.	Oral Diseases	Adipokines
1	Dental caries	Leptin
		IL-6
		TNF-α
2	Periodontal diseases	Adiponectin
		Chemerin
		Leptin
		Resistin
		Visfatin
		Vaspin
3	Recurrent aphthous stomatitis	Irisin
4	Oral cancers	Adiponectin,
		Leptin
		Visfatin
		Chemerin
		ZAG
5	Oral premalignant lesions	Chemerin
		Visfatin
		IL-6
		TNF-α
6	Kawaski disease	Resistin
7	Sjogren's Syndrome	Adiponectin
8	Behcet's Disease	Adiponectin
		Leptin
		Resistin
		Visfatin

IL-6: Interleukin-6, ZAG: Zinc-alpha macroglobulin, TNF-α: Tumour necrosis factor-alpha.

The current narrative review was planned to provide an up-to-date information on roles of different adipokines in oral diseases. For this purpose, the research papers published in the last six years (2016-2021) were accessed using Google Scholar and PubMed databases. Studies published in the English language were included, while those in any other language were excluded. Medical subject headings (MeSH) terms used for the search included adipokines, adipose tissues, Sjogren's syndrome, oral cancers, oral premalignant lesions, Kawasaki disease and recurrent aphthous stomatitis. They were used interchangeably during the search.

Role of adipokines in dental caries

Dental caries is caused by interaction of oral bacteria that results in the formation of fermentable carbohydrates and acidity, leading to tooth decay.[6] In Pakistan, the prevalence of dental caries is 60-80% and it is commonly affecting children aged 8-12 years.[7] The prevalence of dental caries reported in Karachi and Sargodha is 71.7%[8] and 45.9%[8] in children aged 6-14 years and 3-12 years, respectively. The prevalence of dental caries in Islamabad is 44.4% in children aged 5 years.[8] A study conducted in Khyber Pakhtunkhwa (KP) has shown 31.5% prevalence of dental caries in adults aged 25-45 years.[9]

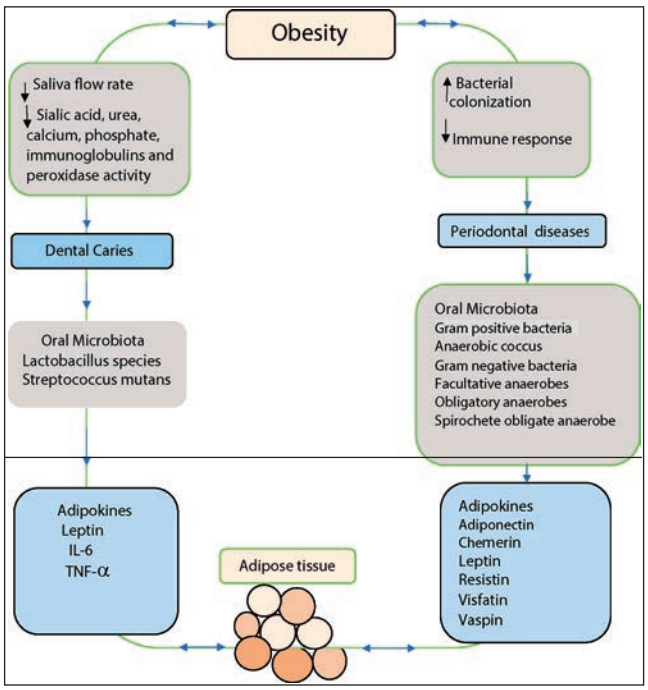

Figure: Relationship of obesity, oral microbiota and adipokines with dental caries and periodontal diseases.

Leptin is expressed in serum, saliva, GCF and gingival tissue of humans, and in healthy and inflamed pulp cells of both humans and rats.[10] Leptin increases the expression of chemokine cc motif ligand 20 (CCL20) which is enhanced by invasion of caries-related bacteria, such as streptococcus mutans, into dentinal tubules. Dentin pulp complex increases the production of macrophages in response to caries and leptin regulates monocyte function through protein kinase C (PKC)-dependent pathways[10]. Moreover, leptin increases proinflammatory cytokines, such as IL-6 and TNF-α, as an immune reaction to caries.[7,11] It is suggested that leptin as well as IL-6 and TNF-α can be used as biomarkers for dental caries.[10]

Obesity is a chronic multifactorial condition that can be classified into childhood obesity and adolescent obesity.[12] A decrease in salivary flow has been reported in childhood obesity. Saliva of obese child has decreased concentration of sialic acid, phosphate, urea, calcium, proteins, peroxidase activity and immunoglobulins compared to normal-weight child.[13] Saliva in less quantity and quality provokes *streptococcus (S.)*mutans and *lactobacillus (L.)* species to promote caries in obese humans(13)(Figure).

Role of adipokines in periodontal diseases

Gingivitis is a non-destructive gum disease that is characterised by inflammation of gingiva due to build-up of plaque-containing bacteria on the teeth and surrounding tissues. If gingivitis is left untreated, it leads to periodontitis. The prevalence of periodontitis is 20-50%

around the world with the highest prevalence in the elderly population (82%), followed by adults (73%) and adolescents (59%).[14] The prevalence of periodontitis is high among population of 18-30 years of age in Pakistan.[15] The local prevalence data of mild gingivitis and mild periodontitis is 46.6% and 11% respectively, and that of severe gingivitis and severe periodontitis is 4% and 6.7% respectively.[16]

Adipokines identified for periodontal diseases includes visfatin, chemerin, adiponectin, resistin and leptin.[17] Adipokines present in saliva or GCF of periodontitis patients may or may not be associated with systemic diseases, such as obesity, diabetes, cardiovascular diseases and immune diseases. Visfatin in periodontitis causes inflammation and destruction by slightly increasing the levels of TNF-α.[18]

Chemerin, an adipokine identified in GCF of patients with chronic periodontitis, plays the role of chemoattractant protein. It attracts all the inflammatory cells to the site of inflammation. Chemerin is released in an inactive form and undergoes degradation of its C terminal, resulting in active form. It has three receptors, G protein coupled receptor 1 (GPR1), chemokine receptor-like 1 (CMKLR1, also known as ChemR23), and C-C chemokine receptor-like 2 (CCRL2). CCRL2 interacts and binds chemerin with ChemR23.[19] Adiponectin has also three receptors; adiponectin receptor 1 (adipoR1), adiponectin receptor 2 (adipoR2) and T cadherin receptor.[20] Adiponectin plays anti-inflammatory role in chronic periodontitis by suppressing inflammation and promoting periodontal healing and osteogenesis. Resistin is a cysteine-rich protein and a pro-inflammatory adipokine that plays a role in inflammation through nuclear factor kappa light chain enhancer of activated B cells (NF-κB) pathway.[21]

Obesity can also accelerate periodontal disease. One of its type is known as chronic periodontitis (CP), which is a chronic inflammatory destructive disease of periodontium that occurs due to subgingival plaque accumulation and results in clinical attachment loss, tooth mobility and even tooth-loss. Obesity causes an increase in the production of adipokines from adipose tissues, and subsequently obese individuals have increased levels of leptin and decreased levels of adiponectin. Vaspin is used as a novel biomarker for obese CP individuals.[22] The microbial concentration of certain periodontal pathogens, such as aggregatibacter actinomycetemcomitans, fusobacterium nucleatum ss vincentii, prevotella melaninogenica, treponema socranskii, parvimonas micra, prevotella intermedia, eubacterium nodatum and tannerella forthytia, is higher in obese individuals compared to non-obese individuals.[13]

Role of adipokines in recurrent aphthous stomatitis

Recurrent aphthous stomatitis (RAS) is an inflammatory condition characterised by recurrent painful round or oval ulcers with yellow centres and erythematous margins on the non-keratinised oral mucosa. The prevalence of RAS is 1.2% in Pakistan. Females are most commonly affected and mean age for RAS is 31-40 years.[23] Irisin, a recently identified myokine, also acts as an adipokine in saliva of patients with RAS. Levels of irisin accompanied by interferon-gamma (IFN-γ) and IL-2 are found to be raised in patients with RAS. The role of irisin in RAS is such that it converts the adipose tissue macrophages from pro-inflammatory state (M1) into anti-inflammatory state (M2) with increased production of pro-inflammatory cytokines, such as IL-2, IL-5, IL-6, IL-8 and TNF-α, and decreased production of anti-inflammatory cytokines IL-10 and transforming growth factor-beta (TGF-β) in peripheral blood of RAS patients compared to healthy individuals.[24]

Role of adipokines in oral cancers

Oral cancers are sixth most common malignancies worldwide. The prevalence of oral cancer in Pakistan is 75% and it is higher in males compared to females.[25] The prevalence of oral squamous cell carcinoma (OSCC) in Pakistan is 95% with males of 4th-5th decade being affected more than the females.[26] The intracellular effects of adipokines are mediated by receptors that activate different signalling pathways, including peroxisome proliferator activated receptor (PPAR) pathway, Janus kinase (JAK) signal transducer and activator of transcription (STAT) pathway and phospatidylinositol kinase (PI3).[27] Chemerin, leptin, visfatin and ZAG are adipokines that are used as biomarkers for diagnosis of OSCC. Chemerin is an adipokine involved in tumorigenesis by cell differentiation, proliferation, invasion, progression and angiogenesis. Serum and salivary chemerin levels are elevated along with matrix metalloproteinase-9 (MMP-9) in patients of OSCC.[28] Salivary visfatin levels are higher in patients with OSCC.[29] Leptin is associated with staging of OSCC, and its serum levels are elevated in initial stages of OSCC. Leptin is not involved in cell invasion, but only in cell migration and proliferation of cell lines in OSCC.[30] ZAG belongs to macroglobulin family, and its levels in saliva of OSCC patients are found to increased.[31]

A study has reported that serum adiponectin, leptin, visfatin and IL-6 concentrations vary in both benign tumors, such as pleomorphic adenoma (PA) and Warthin's tumour (WT), and malignant tumours such as acinic cell carcinoma (ACC). Serum adiponectin and serum leptin levels have been found to be higher in PA and WT compared to ACC. Serum visfatin levels have been found to be equal in both benign tumours and malignant tumours, whereas serum

IL-6 levels are found to be the same in both PA and WT, but significantly low in ACC.[32]

Role of adipokines in oral premalignant lesions

Oral premalignant lesions include leukoplakia, erythroplakia, oral submucous fibrosis (OSMF) and oral lichen planus (OLP). OSMF is a premalignant lesion that is characterised by vertical bands on the buccal mucosa due to abnormal collagen deposition. OLP is a chronic inflammatory premalignant disease that affects the oral cavity and varies from whitish or reddish bilateral bands or patches to painful burning sores. Its different types include ulcerative, atrophic, papular, plaque, bullous and reticular.[26] The prevalence of oral premalignant lesions in Pakistan is 0-50% with OSMF being the most common, followed by OLP and leukoplakia. OSMF commonly affects males of third and fourth decade, whereas OLP affects middle-aged females more than males.[26] In patients with atrophic OLP and speckled leukoplakia, serum and salivary levels of chemerin are elevated along with matrix metalloproteinase-9 (MMP-9).[28] Patients with bullous erosive lichen planus have high levels of salivary visfatin than controls.[29] Adipocytokines IL-6 and TNF-α act as inflammatory and angiogenic mediators for tumour growth and progression. Serum and salivary levels of IL-6 and TNF-α are upregulated in oral precancerous lesions, such as leukoplakia, erythroplakia, OSMF and OLP.[33]

Role of adipokines in Sjogren's syndrome

Sjogren's syndrome (SS) is an autoimmune disorder which, affects the exocrine glands of the body, mainly the salivary glands and lacrimal glands, causing dysfunctional changes and resulting in dry eyes and dry mouth. SS is of two types; primary SS and secondary SS. The local prevalence rate of primary SS and secondary SS is 0.3-0.4% respectively, predominantly affecting females aged 40-50 years.[34] Salivary adiponectin levels in SS are higher than the controls. Therefore, salivary adiponectin can be used as a biomarker for diagnosis of SS.[35]

Role of adipokines in Kawasaki disease

Kawasaki disease (KD) is a chronic inflammatory mucocutaneous disease characterised by inflammation of blood vessels throughout the body. It mainly affects lymph nodes (LNs), causing symptoms in oral cavity, nose and throat. The local prevalence of KD is 70 per 100,000 children, mainly of 1-5 years of age.[36] Resistin binds to toll-like receptor-4 (TLR-4) and regulates the secretion of inflammatory cytokines, such as IL-1β, IL-2, IL-6, which in turn increases the expression of resistin. Serum resistin levels are found to be elevated in KD compared to controls.[37]

Role of adipokines in Behcet's disease

Behcet's disease (BD) is a rare chronic inflammatory disease characterised by oral and genital ulcers, uveitis, skin lesions, joint pain, gastrointestinal and neurological involvement. This disease in Pakistan presents most commonly with oral ulcers.[38] It is predominant in young to middle aged men and women. Serum adiponectin, leptin and resistin levels are found to be upregulated, whereas serum visfatin levels are down-regulated in patients of BD.[39]

Conclusion

Altered adipokines levels are associated with oral diseases, such as dental caries, periodontal diseases, oral cancers, oral premalignant lesions, RAS, SS, KD and BD. Adipokines as biomarkers are key regulators and indicators for predicting, diagnosing and measuring the progress of oral diseases. Oral diseases need to be detected in earlier stages for better understanding of pathophysiological role of adipokines, better prognosis and treatment opportunities.

Acknowledgement: We are grateful to the Higher Education Commission (HEC) of Pakistan for providing e-library access to the University of Health Sciences, Lahore.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: M. Phil studies of one of the authors have been completely funded by The University of Health Sciences, Lahore.

References

1. Villarroya F, Gavaldà-Navarro A, Peyrou M, Villarroya J, Giralt M. The lives and times of brown adipokines. Trends Endocrinol Meta 2017; 28: 855-67.
2. Villarroya J, Cereijo R, Giralt M, Villarroya F. Secretory proteome of brown adipocytes in response to cAMP-mediated thermogenic activation. Front Physiol 2019; 10: 67.
3. Alshaikh EM, Omar UM, Alsufiani HM, Mansouri RA, Tarbiah NI, Alshaikh AA, et al. The Potential Influence of Hyperthyroidism on Circulating Adipokines Chemerin, Visfatin, and Omentin. Int J Health Sci 2019; 13: 44-7.
4. Rodríguez A, Becerril S, Hernández-Pardos AW, Frühbeck G. Adipose tissue depot differences in adipokines and effects on skeletal and cardiac muscle. Curr Opin Pharmacol 2020; 52: 1-8.
5. De Farias Lelis D, De Freitas DF, Machado AS, Crespo TS, Santos SHS. Angiotensin-(1-7), adipokines and inflammation. J.Metabol 2019; 95: 36-45.
6. Laputková G, Schwartzová V, Bánovčin J, Alexovič M, Sabo J. Salivary protein roles in oral health and as predictors of caries risk. Open Life Sciences 2018; 13: 174-200.
7. Zafar R, Urooj A, Masood S. Dental caries in relation to sugar consumption among children-a study from Southern Punjab, Pakistan. Biomedica 2021; 37: 110.
8. Kamran R, Farooq W, Faisal MR, Jahangir F. Clinical consequences of untreated dental caries assessed using PUFA index and its covariates in children residing in orphanages of Pakistan. BMC Oral Health 2017;

17: 108.
9. Naeem M, Ishtiaq M, Hussain A, Ijaz B, Iftikhar B, Marwat I. Frequency and determinants of dental caries in local inhabitants of a rural district of khyber pakhtunkhwa Pakistan. J Med Sci (Peshawar) 2021; 29: 30-3.
10. Pérez-Pérez A, Vilariño-García T, Fernández-Riejos P, Martín-González J, Segura- Egea JJ, Sánchez-Margalet V. Role of leptin as a link between metabolism and the immune system. Cytokine Growth Factor Rev 2017; 35: 71-84.
11. Sharma V, Gupta N, Srivastava N, Rana V, Chandna P, Yadav S, et al. Diagnostic potential of inflammatory biomarkers in early childhood caries-A case control study. Clin Chim Acta 2017; 471: 158-63.
12. Sommer A, Twig G. The impact of childhood and adolescent obesity on cardiovascular risk in adulthood: a systematic review. Curr Diab Rep 2018; 18: 91.
13. Roa I, Del Sol M. Obesity, salivary glands and oral pathology. Colomb Med (Cali) 2018; 49: 280-7.
14. Nazir M, Al-Ansari A, Al-Khalifa K, Alhareky M, Gaffar B, Almas K. Global prevalence of periodontal disease and lack of its surveillance. Sci. World J. 2020; 2020: 2146160.
15. Asad M, Mirza AJ, Siddiqui MA. Periodontal Status of the Residents of a Rural Community in Gadap Town, Karachi, Pakistan. JPDA 2016; 25: 94.
16. Shehzad S, Waheed Z, Khan K, Shah M, Durrani SH, Farooq A. Comparison of Periodontal Diseases among Genders in Khyber Pakhtunkhwa, Pak. Int. J. Sci. Innov. Res. 2021; 02: 12-8.
17. Ghallab NA. Diagnostic potential and future directions of biomarkers in gingival crevicular fluid and saliva of periodontal diseases: Review of the current evidence. Arch Oral Biol 2018; 87: 115-24.
18. Rezaei M, Bayani M, Tasorian B, Mahdian S. The comparison of visfatin levels of gingival crevicular fluid in systemic lupus erythematosus and chronic periodontitis patients with healthy subjects. Clin Rheumatol 2019; 38: 3139-43.
19. Ozcan E, Saygun NI, Ilıkçı R, Karslıoğlu Y, Muşabak U, Yeşillik S. Evaluation of chemerin and its receptors, ChemR23 and CCRL2, in gingival tissues with healthy and periodontitis. Odontolog 2018; 106: 29-36.
20. Wang Z, Chen Z, Fang F, Qiu W. The role of adiponectin in periodontitis: Current state and future prospects. Biomed Pharmacother 2021; 137: 111358.
21. Akram Z, Rahim ZHA, Taiyeb-Ali TB, Shahdan MSA, Baharuddin NA, Vaithilingam RD, et al. Resistin as potential biomarker for chronic periodontitis: A systematic review and meta-analysis. Arch Oral Biol 2017; 73: 311-20.
22. Pradeep AR, Karvekar S, Nagpal K, Patnaik K. Vaspin: a new adipokine correlating the levels of crevicular fluid and tear fluid in periodontitis and obesity. J Investig Clin Dent 2016; 7: 232-8.
23. Maqbool S, Fatima N, Siddiqi KM, Jamal M, Baig MZ, Noor S, et al. Frequency and pattern of recurrent apthous ulcers in patients reporting to oral medicine and diagnosis department of islamabad dental hospital. Pak Oral Dent J 2019; 39: 30-3.
24. Altay D, Kormaz M, Ergun S, Kormaz H, Noyan T. Salivary irisin: potential inflammatory biomarker in recurrent apthous stomatitis patients. Eur Rev Med Pharmacol Sci 2021; 25: 2252-9.
25. Javed A, Zahra G, Qureshi AM. Epidemiology of oral cancer in Pakistan. American Academic Scientific Research Journal for Engineering, Technology, and Sciences 2020; 72: 118-27.
26. Iqbal HA, Umer N, Malik AW, Ghafoor S. Ten-year presentation pattern of oral premalignant & malignant lesions at a tertiary care hospital of Lahore Pakistan. J Khyber Coll Dentistry 2020; 10: 98-101.
27. Tzanavari T, Tasoulas J, Vakaki C, Mihailidou C, Tsourouflis G, Theocharis S. The Role of Adipokines in the Establishment and Progression of Head and Neck Neoplasms. Curr Med Chem 2019; 26: 4726-48.
28. Ghallab NA, Shaker OG. Serum and salivary levels of chemerin and MMP-9 in oral squamous cell carcinoma and oral premalignant lesions. Clin Oral Investig 2017; 21: 937-47.
29. Abdel Moneim W, Maged A, Shaker O. Evaluation of salivary and serum visfatin in oral bullous erosive lichen planus and oral squamous cell carcinoma. Egypt Dent J 2017; 63: 1541-9.
30. Sobrinho Santos EM, Guimarães TA, Santos HO, Cangussu LMB, de Jesus SF, Fraga CAC, et al. Leptin acts on neoplastic behavior and expression levels of genes related to hypoxia, angiogenesis, and invasiveness in oral squamous cell carcinoma. Tumour Biol 2017; 39: 1010428317699130.
31. Heawchaiyaphum C, Pientong C, Phusingha P, Vatanasapt P, Promthet S, Daduang J, et al. Peroxiredoxin-2 and zinc-alpha-2-glycoprotein as potentially combined novel salivary biomarkers for early detection of oral squamous cell carcinoma using proteomic approaches. J. Proteomics 2018; 173: 52-61.
32. Sowa P, Misiolek M, Orecka B, Czecior E, Adamczyk-Sowa M. Serum levels of selected adipocytokines in benign and malignant parotid gland tumor patients. Cytokine 2018; 106: 40-4.
33. Kaur J. Salivary markers for detection of oral (pre) cancerous lesions. 2018. Doctoral dissertation, KU Leuven available at https\omfsimpath.be\oncutbmedia\thesis%20jasdeep.pdf.
34. Ahsan T, Khowaja D, Jabeen R, Erum U, Ali H, Farooq MU, et al. Burden of rheumatological disorders in a tertiary care hospital. J Pak Med Assoc 2016; 66: 563-7.
35. Padern G, Duflos C, Ferreira R, Assou S, Guilpain P, Maria ATJ, et al. Identification of a novel Serum Proteomic Signature for Primary Sjögren's Syndrome. Front Immunol. 2021;12: 631539.
36. Mahmud S, Shah SAH, Shahneela. Kawasaki disease experience at tertiary care hospital Rawalpindi, Pakistan. Pak Armed Forces Med J 2018; 68: 1143-8.
37. Cai X, Zhu Q, Wu T, Zhu B, Liu S, Liu S, et al. Association of circulating resistin and adiponectin levels with Kawasaki disease: A meta-analysis. Exp Ther Med 2020; 19: 1033-41.
38. Khan A, Haroon M, Bashir F, Din Z. Behcet's Disease: Pakistani Experience. Pak J Med Sci 2020; 36: 1005-10.
39. Lee YH, Song GG. Association of circulating resistin, leptin, adiponectin and visfatin levels with Behçet disease: a meta-analysis. Clin Exp Dermatol 2018; 43: 536-45.