REVIEW ARTICLE

Expression of Salivary Resistin may Indicate Progression in Oral Pre-Malignant Lesions

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ABSTRACT

Resistin is a pro-inflammatory cytokine, expressed by cells of the immune-inflammatory cells. Levels of this cytokine were significantly increased in premalignant oral lesion tissues. "The association between inflammation and tumorigenesis is well established and epithelial-to-mesenchymal transition (EMT) links these two processes. EMT is a reversible process during embryonic development and is involved in organ fibrosis, tissue regeneration, wound healing and cancer progression. EMT endows cancer cells with enhanced abilities for migration, invasion and resistance to chemotherapy". Resistin plays an important role in innate defense mechanisms. The immune-inflammatory response against microbes is caused by local tissue destruction, which is an attempt to wall off infection, and produces pro-inflammatory mediators such as Tumor Necrosis Factor (TNF) α, Prostaglandin E2 (PGE2) and Interleukin IL 1, IL 6, etc. Resistin's role was strongly suggested in inflammation by TNF-α, IL-1β, 6 and lipopolysaccharide, by increasing its expression in peripheral blood mononuclear cells. The process of inflammation may enable cancer cell to metastasize by encouraging mesenchymal properties and cancer cell stemness. The objective of this review was to assess potential early biomarkers of malignant transformation such as biomarkers that could assist in early diagnosis of individuals at high risk. The data was collected through a comprehensive search using the keywords, "Oral Pre-malignant Lesions, Resistin, Saliva, Tumorigenesis" from Medline and Google Scholar, from 2000 to 2019.

Keywords: Oral Pre-malignant Lesions; Resistin; Saliva; Tumorigenesis.

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INTRODUCTION

Cytokines are intercellular signaling proteins produced in and by peripheral nerve tissue during physiological and pathological processes. Followed by injury, Schwann cells and macrophages gather around the injured site of the nerve secrete cytokines[1]. It helps in a number of processes such as metabolism, immunity, and inflammation[2]. Various infections and certain muco-cutaneous inflammatory diseases cause inflammation in the oral cavity. These proteins, present in serum, saliva and tissues, may more accurately reflect the progression of inflammation[3] and affect cell behavior in diverse manners[4]. Cytokines play a major role in suppressing or enhancing oncogenesis and balance shifts assays can aid in the diagnosis of pre-malignancy[5]. They also provide information about presence of disease, epithelial behavior, local inflammatory response, and carcinogenesis[4].

Various underlying physiological or pathological processes in the body can be assessed by the use of such biomarkers. With the ongoing advancements in technology, early diagnosis and timely therapeutic interventions have turned out to be easily attainable. In this review, one such new biomarker that can be used to monitor the progression of inflammation in oral pre-malignant lesions will be discussed[6]. Pre-malignant lesions often progress to oral squamous cell carcinoma which, unfortunately, is usually diagnosed when in advanced stages resulting in a high mortality rate[7].

DISCUSSION

A premalignant lesion is a disease, syndrome, or finding that, if left untreated, may lead to cancer[8-10] and 30% pre-malignant lesions progress to malignancy[11].

Oral Premalignant Lesions and Resistin

In the oral mucosa, distinct visible premalignant changes occur with distinctly visible alterations in the majority of cases[12]. Common oral premalignant disorders (OPMD) such as oral sub mucous fibrosis, leukoplakia, erythroplakia[13], and erosive lichen planus show early signs of carcinogenic damage to oral mucosa, which usually appears as white patches with or without included red patches[14]. Premalignant lesions are most commonly seen in early adulthood[15].

In the oral cavity, oral leukoplakia (LP) appears as white patches whereas; reddish, oral lesions are termed as erythroplakia which may have greater malignant potential. Additionally, the thinning and loss of elasticity of the oral mucosa may cause a burning sensation and difficulty in opening the mouth due to oral sub-mucous fibrosis[12]. Oral lichen planus presents as lacy white striae or plaques with or without red patches[16].

A large number of these oral mucosal disorders have a tendency to transform into malignancy[17]. According to Arakeri, an estimated rate of malignant transformation is between 7% to 30%[18] whereas Hosein et al. in one of his studies have reported between 3% to 19%[19]. In Pakistan, oral cancer ranks second most common with an increase in incidence of 16000 cases/year[20]. Alterations in protein expression, which can be monitored both qualitatively and quantitatively, are involved in malignant transformation[21]. Oral squamous cell carcinoma (OSCC) is usually identified when it has proceeded to a late stage resulting in poor prognosis and high mortality rate [22,23]. Worldwide, prevalence of OPMD has been reported to be as low as 0.2% and as high as 11.3% [24] out of which 30% have the ability to transform to malignancy[11]. Since 30% of OPML have the ability to transform in to carcinoma the burden of morbidity and mortality can be reduced if early pre-malignant changes can be detected[11].

The overall prevalence of tobacco use was 19.1% as shown by Global Adult Tobacco Sheet Pakistan[25]. In Asians, oral pre-malignant lesions (OPMLs) are known to be largely associated with oral carcinogen habits. More than sixty known carcinogens have been found in tobacco alone. These carcinogens irritate the oral mucosa and accelerate the inflammatory process[17]. Over a period of time they may induce histological and often produces clinically visible changes in the oral mucosa[17]. Breaching of the basement membrane with cellular invasion into the underlying stroma constitutes malignancy[24]. When oral epithelium transforms it sheds cells and molecules in to the salivary environment[26]. It would be valuable and possibly lifesaving to detect salivary proteome biomarkers for the early diagnosis of Oral Pre-Malignant Disorders before conversion[13].

Resistin (RETN) also known as a pro–inflammatory cytokine[27] belongs to a family of proteins, which accumulate at the site of inflammation[28]. It is also recognized as FIZZ3 (found in inflammatory zone-3)[29] or ADSF (adipocyte-specific secretory factor)[30]. It is expressed by cells of the immune-inflammatory system like monocytes[31], macrophages and polymorphonuclear cells (PMNs) in inflammatory conditions[6]. Levels of RETN were significantly increased in premalignant oral lesion tissues[11]."Epithelial to mesenchymal transition (EMT) is a reversible process, which links the association between inflammation and tumorigenesis. EMT is also involved in tissue regeneration, organ fibrosis, and wound healing and cancer progression. EMT endows cancer cells with enhanced abilities for migration, invasion and resistance to chemotherapy"[32].

Structure of Resistin

Resistin is a 12.5 kDa[33] cysteine-rich protein[34] consisting of 108 amino acids in humans[35] including a 17-amino acid signal peptide, a variable region of 37 amino acids, and a conserved C terminus. The human resistin gene is located on chromosome 19[2].

In macrophages and monocytes both the forms of resistin (dimeric and oligomeric forms) are able to activate interleukin-12 (IL-12) and tumor necrosis factor (TNF-α). Biologically active resistin circulates as an oligomer[2]. It has been stated that "Its protomer contains a helical 'tail' region at the N terminus linked by a disulfide-rich beta-sandwich 'head'domain at the C terminus" [2].

Sites of Resistin Production

As compared to other tissues, RETN is significantly expressed in the trophoblastic cells of primary cell leukemia (PCL), bone marrow, pancreas, placenta, circulating blood, synovial tissue and fluid[36]. Pro inflammatory cytokines IL-1[28] IL-6, IL-β and TNF-α elevate the expression of RETN in human Peripheral Blood Mononuclear cells (PBMC)[15,37], whereas TNF-α and monocyte chemo-attractant protein is a "negative regulator of expression of RETN"[37]. Resistin is mainly secreted by macrophages which suggest that "Resistin is linked to inflammation"[38]. It is primarily expressed and produced by "monocytes and macrophages" in humans. These outcomes propose "Resistin plays an important role in the pathophysiology of systemic inflammatory conditions"[31].

Resistin and Signaling Pathways

It has been demonstrated that "Resistin can activate a pro-inflammatory state" and initially Resistin was named for "resistance towards insulin" [31,39,40]. It plays an essential role in innate defense mechanisms[41]. The immune-inflammatory response against microbes is caused by local tissue destruction which is an attempt to wall off infection and produces pro-inflammatory mediators suc

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h as prostaglandin E2 (PGE2), tumor necrosis factor (TNF) α, and interleukin IL 1, IL 6, etc. In addition to local tissue destruction,[31] Resistin's role was strongly suggested in inflammation by TNF-α, IL-1β, 6 and lipopolysaccharide, by increasing its expression in peripheral blood mononuclear cells [2, 15]. As illustrated by Nagaev et al. in vitro the expression of the pro-inflammatory cytokines Interleukin 6,8 and TNF-α by white adipose tissue can be induced by RETN[2]. Results of one of the studies conducted by Wang showed that Resistin promoted EMT and stemness-like properties through activation of NF-κB and STAT3, two major factors involved in cancer progression[32].

Resistin's Role in Inflammation

Primary targets of Resistin are PBMC (peripheral blood mononuclear cells), macrophages and vascular cells as human RETN plays a major role in the inflammatory process[38]. The process of inflammation may enable cancer cell to metastasize by encouraging properties of mesenchyme and cancer cell stemness[32]. It has been reported that in general population, circulating levels of RETN are associated with fibrinolytic and inflammatory markers such as TNF-α, C-reactive protein (CRP), Interleukin -6 and in patients suffering from Type II Diabetes Mellitus, chronic kidney disease, coronary atherosclerosis, rheumatoid arthritis, and/or sepsis. In patients with severe sepsis and acute pancreatitis, plasma RETN levels indicates disease severity and predicts the worst outcomes in non-septic but critically ill patients[38]. Additionally, it has been shown in studies that human RETN alone can promote inflammation, while other studies have also proven that human RETN may exert anti-inflammatory response to a fatal endotoxin challenge[42]. Lipopolysaccharide of Porphyromonas gingivalis was reported to induce the expression of inflammation-related molecules in epithelial cells, neutrophils, osteoblasts, osteoclasts, macrophages/-monocytes and lymphocytes in periodontal tissues, periodontal ligament (PDL) and gingival fibroblasts, proinflammatory cytokines and chemokines, and to upsurge the release of calprotectin, an inflammation- related protein, from neutrophils and the expression of calprotectin in monocytes[37].

Correlation of Resistin with Systemic Disease

Raised serum levels of RETN are equally critical for tumorigenesis and angiogenesis, and have been interrelated with gastric, lung, esophageal, and colon cancers and are linked to primary tumor progression and higher TNM stage of gastric and esophageal cancers[13, 41].

Results of a study show that freshly isolated human primary inflammatory cells co-express RETN[43]. It has been suggested that by "the increase of altered sensitivity and nociceptive signaling of opioid analgesics, RETN contributes to the exacerbation of postoperative pain intensity". At the surgical site, severity of inflammation leads to Postoperative pain intensity, which reflects nociceptive signaling. RETN can directly and indirectly induce the secretion of interleukin-1β,tumor necrosis factor (TNF-α) and interleukin-6 by local macrophages[44]. RETN may play a role in the sub-clinical inflammation associated with chronic kidney disease[45]. Human studies show that adiponectin plays an important role in insulin sensitivity, inflammation, atherogenesis,[46] inflammatory bowel disease, rheumatoid arthritis,[47] and lipid metabolism, and thus influences hyperlipidemia and coronary artery disease (CAD)[46].

Elevated levels of RETN are identified in the synovial fluid of patients with rheumatoid arthritis which is an inflammatory condition[46]. Human RETN is a highly expressed cytokine in sepsis where it is hypothesized to exacerbate inflammation[48]. In one of the study Mahmoud et al. observed that circulating Resistin levels were significantly increased in bladder cancer patients as compared to controls[49]. These particulars further support a potential role of RETN as a pro-inflammatory factor, at least in humans[46]. Endothelial cells release vasoactive and trophic substances, which are essential for controlling vasomotor reactivity, vascular growth, coagulation, inflammatory, immunologic responses and platelet function. It has been reported that resistin influences the function of endothelium by significantly elevating cellular permeability of endothelium[50] which is due to generation of high concentration of RETN from EAT (epicardial adipose tissue) in patients with acute coronary syndrome[33]. According to findings suggested by Jamaluddin et al.," Resistin secreted by epicardial adipose tissue is a major cause of damage to endothelium by the induction of hyper-permeability in HUVECs (human umbilical vein endothelial cells)"[33]. It has been stated that RETN can contribute to malignant cell transformation in the path of an inflammatory process[16]. Cancer detection is dependent on histological analysis, which does not provide a clear indication of precursor status or precancerous conditions[22].

Levels of Resistin in Different Inflammatory Diseases

In gingival crevicular fluid (GCF) levels of RETN in a healthy Indian population were determined by Gokhale and found to be 13.32 ng/ml whereas these levels were raised to 24.55 – 37.02ng/ml in inflammatory conditions[30,37]. In a Japanese population the GCF Resistin concentration was 4.75ng/ml in healthy conditions and rose to 10.75ng/ml in cases with chronic periodontitis and uncontrolled type 2 diabetes[34]. Similarly, in one of the studies conducted in Mexico stated that hyperresistinemia, which may contribute to tumor growth and breast cancer survival, has been observed in breast cancer patients[51].

CONCLUSION

Resistin appears to show an association between inflammation and tumorigenesis. From a clinical standpoint, it may be of significant benefit to assess potential early biomarkers of malignant transformation such as biomarkers that could assist in early diagnosis of individuals at high risk. This may possibly also decrease the risk, or progression, of various inflammatory diseases when used as a therapeutic intervention.

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CONFLICT OF INTEREST

There was no conflict of interest among the authors

AUTHORS' CONTRIBUTION

SSR did the conceptualization of study, literature search and prepared the write up. AR had done the proof reading. MH did the overall evaluation of the study. SB performed the literature search and proof reading while HB also assisted in the literature search.

REFERENCES

1. Jun-Ming Zhang JA. Cytokines, inflammation and pain. Int Anesthesiol Clin. 2007.
2. Filkova M, Haluzik M, Gay S, Senolt L. The role of resistin as a regulator of inflammation: Implications for various human pathologies. Clin Immunol (Orlando, Fla). 2009;133(2):157-70.
3. Kamal Uddin Zaidi FNK, Gayatyri Yadav, Vijay Thawani and Richa Parmar. Protein Expression Profile of Oral Premalignant Lesions (OPLs). Int J cell Sci Mol Biol. 2018;5(1).
4. Prasad G, McCullough M. Chemokines and cytokines as salivary biomarkers for the early diagnosis of oral cancer. Int J Dent. 2013;813756.
5. Hsu HJ, Yang YH, Shieh TY, Chen CH, Kao YH, Yang CF, et al. Role of cytokine gene (interferon-gamma, transforming growth factor-beta1, tumor necrosis factor-alpha, interleukin-6, and interleukin-10) polymorphisms in the risk of oral precancerous lesions in Taiwanese. Kaohsiung J Med Sci. 2014;30(11):551-8.
6. Mittal M, Hassan B, Desai K, Duseja S, Kumar S, Reddy SG. GCF resistin as a novel marker in patients with chronic periodontitis and rheumatoid arthritis. JCDR. 2015;9(4):Zc62-4.
7. Peacock ZS, Pogrel MA, Schmidt BL. Exploring the reasons for delay in treatment of oral cancer. J Am Dent Assoc. 2008;139(10):1346-52.
8. Carnelio S, Rodrigues GS, Shenoy R, Fernandes D. A brief review of common oral premalignant lesions with emphasis on their management and cancer prevention. Indian J Surg. 2011;73(4):256-61.
9. Ghapanchi J, Rezaie M, Derafshi R. A mini review of histological and genetic oral lesions in adult and elderly patients referred to Shiraz Dentistry School. Comp Clin Pathol. 2017;26(2):287-90.
10. Syed SH, Ambreen SN, Rashinkar SM, Watve MV. The clinical and morphological study of 75 cases of oral premalignant lesions. J Evol Med Dent Sci. 2015;4(14):2255-63.
11. Woodford D, Johnson SD, De Costa AM, Young MR. An inflammatory cytokine milieu is prominent in premalignant oral lesions, but subsides when lesions progress to squamous cell carcinoma. J Clin Cell Immunol. 2014;5(3).
12. Mishra R. Biomarkers of oral premalignant epithelial lesions for clinical application. Oral Oncol. 2012;48(7):578-84.
13. Wu CC, Chu HW, Hsu CW, Chang KP, Liu HP. Saliva proteome profiling reveals potential salivary biomarkers for detection of oral cavity squamous cell carcinoma. Proteomics. 2015;15(19):3394-404.
14. Rao AK, Parameswar P, Majumdar S, Uppala D, Kotina S, Vennamaneni NH. Evaluation of genetic polymorphisms in glutathione S-transferase Theta1, glutathione S-transferase Mu1, and glutathione S-transferase Mu3 in oral leukoplakia and oral squamous cell carcinoma with deleterious habits using polymerase chain reaction. Int J Appl Basic Med Res. 2017;7(3):181-5.
15. Elshishtawy H, Ibrahim SE, Helmi A, Farouk N, Elshinnawy MA. Resistin in systemic lupus erythematosus: Relation to lupus nephritis and premature atherosclerosis. Egyptian Rheumatologist. 2012;34 (4):137-46.
16. Tampa M, Caruntu C, Mitran M, Mitran C, Sarbu I, Rusu LC, et al. Markers of oral lichen planus malignant transformation. Disease Markers. 2018;2018: 1959506.
17. Kumar S, Debnath N, Ismail MB, Kumar A, Kumar A, Badiyani BK, et al. Prevalence and risk factors for oral potentially malignant disorders in indian population. Adv Prev Med. 2015;2015:208519.
18. Arakeri G, Patil SG, Aljabab AS, Lin KC, Merkx MAW, Gao S, et al. Oral submucous fibrosis: An update on pathophysiology of malignant transformation. J Oral Pathol Med. 2017;46(6):413-7.
19. Hosein M, Mohiuddin S, Fatima N. Association between grading of oral submucous fibrosis with frequency and consumption of areca nut and its derivatives in a wide age group: a multi-centric cross sectional study from karachi, pakistan. J Cancer Prev. 2015;20(3):216-22.
20. Khan Z, Suliankatchi RA, Heise TL, Dreger S. Naswar (Smokeless Tobacco) use and the risk of oral cancer in pakistan: a systematic review with meta-analysis. Nicotine Tobacco Res. 2017.
21. Karley D, Gupta D, Tiwari A. Biomarker for cancer: a great promise for future. World J Clin Oncol. 2011;2(4):151-7.
22. Holmstrup P, Vedtofte P, Reibel J, Stoltze K. Long-term treatment outcome of oral premalignant

lesions. Oral Oncol. 2006;42(5):461-74.
23. Tsiknakis M, Grangeat P, Binz PA, Potamias G, Lisacek F, Gerfault L, et al. Functional specifications of an integrated proteomics information management and analysis platform. Conf Proc IEEE Eng Med Biol Soc. 2007;6065-9.
24. Dionne KR, Warnakulasuriya S, Zain RB, Cheong SC. Potentially malignant disorders of the oral cavity: current practice and future directions in the clinic and laboratory. Int J Cancer. 2015;136 (3):503-15.
25. Saqib MAN, Rafique I, Qureshi H, Munir MA, Bashir R, Arif BW, et al. Burden of tobacco in pakistan - findings from global adult tobacco survey 2014. Nicotine Tob Res. 2017.
26. Ni YH, Ding L, Hu QG, Hua ZC. Potential biomarkers for oral squamous cell carcinoma: proteomics discovery and clinical validation. Proteomics Clin Appl. 2015;9(1-2):86-97.
27. Suragani M, Aadinarayana VD, Pinjari AB, Tanneeru K, Guruprasad L, Banerjee S, et al. Human resistin, a proinflammatory cytokine, shows chaperone-like activity. Proc Natl Acad Sci USA. 2013; 110(51):20467-72.
28. Bokarewa M, Nagaev I, Dahlberg L, Smith U, Tarkowski A. Resistin, an adipokine with potent proinflammatory properties. J Immunol. 2005;174(9): 5789-95.
29. Mojiminiyi OA, Abdella NA. Associations of resistin with inflammation and insulin resistance in patients with type 2 diabetes mellitus. Scand J Clin Lab Invest. 2007;67(2):215-25.
30. Gokhale NH, Acharya AB, Patil VS, Trivedi DJ, Setty S, Thakur SL. Resistin levels in gingival crevicular fluid of patients with chronic periodontitis and type 2 diabetes mellitus. J Periodontol. 2014;85(4):610-7.
31. Devanoorkar A, Kathariya R, Guttiganur N, Gopalakrishnan D, Bagchi P. Resistin: a potential biomarker for periodontitis influenced diabetes mellitus and diabetes induced periodontitis. Disease Markers. 2014;2014:930206.
32. Wang CH, Wang PJ, Hsieh YC, Lo S, Lee YC, Chen YC, et al. Resistin facilitates breast cancer progression via TLR4-mediated induction of mesenchymal phenotypes and stemness properties. Oncogene. 2017;37:589.
33. Jamaluddin MS, Weakley SM, Yao Q, Chen C. Resistin: functional roles and therapeutic considerations for cardiovascular disease. Br J Pharmacol. 2012;165(3):622-32.
34. Patel SP, Raju PA. Resistin in serum and gingival crevicular fluid as a marker of periodontal inflammation and its correlation with single-nucleotide polymorphism in human resistin gene at -420. Contemp Clin Dent. 2013;4(2):192-7.
35. Adeghate E. An update on the biology and physiology of resistin. CMLS. 2004;61(19-20):2485-96.
36. Kisacik B, Erol MF, Yilmaz G, Yilmaz FM, Maras Y, Kalyoncu U, Karadag O, Kiraz S, Ertenli I, Calguneri M. Resistin and visfatin: are they valuable enough to be the differential diagnosis in familial Mediterranean fever with acute appendicitis?. Clin Rheumatol. 2012;31(2):225-9.
37. Hiroshima Y, Bando M, Inagaki Y, Mihara C, Kataoka M, Murata H, et al. Resistin in gingival crevicular fluid and induction of resistin release by Porphyromonas gingivalis lipopolysaccharide in human neutrophils. J Periodontal Res. 2012;47(5):554-62.
38. Park HK, Kwak MK, Kim HJ, Ahima RS. Linking resistin, inflammation, and cardiometabolic diseases. Korean J Intern Med. 2017;32(2):239.
39. Assiri AM, Kamel HF. Evaluation of diagnostic and predictive value of serum adipokines: Leptin, resistin and visfatin in postmenopausal breast cancer. Obes Res Clin Pract. 2016;10(4):442-53.
40. Lee YC, Chen YJ, Wu CC, Lo S, Hou MF, Yuan SS. Resistin expression in breast cancer tissue as a marker of prognosis and hormone therapy stratification. Gynecol Oncol. 2012;125(3):742-50.
41. Bostrom EA, Tarkowski A, Bokarewa M. Resistin is stored in neutrophil granules being released upon challenge with inflammatory stimuli. Biochim Biophys Acta. 2009;1793(12):1894-900.
42. Zhao C-W, Gao Y-H, Song W-X, Liu B, Ding L, Dong N, et al. An update on the emerging role of resistin on the pathogenesis of osteoarthritis. Mediators Inflamm. 2019;8.
43. Nagaev I, Bokarewa M, Tarkowski A, Smith U. Human resistin is a systemic immune-derived proinflammatory cytokine targeting both leukocytes and adipocytes. PloS one. 2006;1:e31.
44. Hozumi J, Sumitani M, Nagashima M, Kato R, Yamada Y. Resistin Is a Novel Marker for Postoperative Pain Intensity. 2019.
45. Yaturu S, Reddy RD, Rains J, Jain SK. Plasma and urine levels of resistin and adiponectin in chronic kidney disease. Cytokine. 2007;37(1):1-5.
46. Gomez-Ambrosi J, Fruhbeck G. Evidence for the involvement of resistin in inflammation and cardiovascular disease. Curr Diabetes Rev. 2005;1(3): 227-34.
47. Park HK, Ahima RS. Resistin in rodents and humans. Diabetes Metab J. 2013;37(6):404-14.
48. Jang JC, Li J, Gambini L, Batugedara HM, Sati S, Lazar MA, et al. Human resistin protects against endotoxic shock by blocking LPS-TLR4 interaction. Proc Natl Acad Sci USA. 2017;114(48):E10399-e408.
49. Mahmoud Mohammadi JH, Morteza Fallah Karkan, Mehdi Hedayat. Serum Resistin Levels in Bladder Cancer. Mens Health J. 2018; 2(1).
50. Langheim S, Dreas L, Veschini L, Maisano F, Foglieni C, Ferrarello S, et al. Increased expression and secretion of resistin in epicardial adipose tissue of patients with acute coronary syndrome. Am J Physiol Heart Circ Physiol. 2010;298(3):H746-53.
51. Munoz-Palomeque A, Guerrero-Ramirez MA, Rubio-Chavez LA, Rosales-Gomez RC, Lopez-Cardona MG, Barajas-Avila VH, et al. Association of RETN and CAP1 SNPs, expression and serum resistin levels with breast cancer in mexican women. Genet Test Mol Biomarkers. 2018;22(4):209-17.