

How to Cite:

Gupta, S., Sharma, M., Kumar, M., Dabla, U., Prakash, S., & Sangra, V. (2022). Biofluids in orofacial pain: Review. *International Journal of Health Sciences*, 6(S3), 3409–3418. <https://doi.org/10.53730/ijhs.v6nS3.6475>

Biofluids in orofacial pain: Review

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Abstract---Orofacial pain is a dental specialty that focuses on diagnosing and treating long-term, complicated facial discomfort caused by oromotor disorders. This pain is similar to pain elsewhere in the body and is generally caused by tissue damages. The pathogenesis of orofacial pain might be caused by orofacial structures illness, musculoskeletal system disorders, peripheral or central nervous system disorders, systemic diseases, psychological problems, or the result of inadequate sleep. One method to diagnose is evaluating the molecular and microbial cues of biological fluids, which may indicate the occurrence or progression of the disease. This article provides an overview of these biofluids and biomarkers and their role in progression of orofacial diseases.

Keywords---biofluid, biomarkers, neural pain, serum, saliva.

Introduction

Orofacial pain is a dental specialty that focuses on diagnosing and treating long-term, complicated facial discomfort caused by oromotor disorders [1]. This dental specialty has developed through time as a result of a need for better identification of a segment of patients who were not impacted by dental ache but appeared to have no well-defined medical illness [4]. This pain is similar to pain elsewhere in the body and is generally caused by tissue damage caused by nociceptors, which convey a noxious sensation to the brain [5]. However, because of the extensive innervation of the head, face, and oral tissues, orofacial pain entities are frequently complicated and difficult to identify [4,5]. The teeth and oral structures are responsible for 90% of orofacial discomfort. After dental issues have been ruled out, the most prevalent causes of facial discomfort are musculoskeletal and neuropathic pain conditions [1].

The pathogenesis of orofacial pain might be caused by orofacial structures illness, musculoskeletal system disorders, peripheral or central nervous system disorders, systemic diseases, psychological problems, or the result of inadequate sleep [5]. OFP can occur as a primary symptom or as a result of a transmission from another source, such as the cervical or intracranial structures. [2]. Many efforts were made to develop innovative techniques for properly diagnosing chronic pain syndromes, however, the most effective approaches have yet to be discovered [4]. One method involves evaluating the molecular and microbial cues of biological fluids, which may indicate the occurrence or progression of the disease [6]. Although blood is considered the gold standard for these uses, recent evidence suggests that saliva and synovial fluid may also be used [2].

A biofluid is defined as an aqueous solution produced by the body. From digestion to lubrication of joints, these fluids may include serum, sweat, saliva, gastric acid, synovial fluid, tears, etc. [2,6]. Biomarkers supersede more difficult-to-observe clinically relevant endpoints or intermediate outcomes, ideally predictive biological observations. The use of clinical biomarkers is simpler and cheaper than directly measuring the final clinical endpoint, and biomarkers are usually measured in a shorter time [7]. They can be used for the examination, diagnosis, characterization, and monitoring of diseases. As a prognostic indicator; to develop individual therapeutic interventions. Prediction and treatment of adverse events; to identify cell types; Pharmacodynamic and dose-response studies. To understand the value of biomarkers, it is necessary to know the pathophysiological relationship of the biomarkers and their associated clinical endpoints [3]. Therefore, this article provides an overview of these biofluids and the biomarkers present in them.

Biofluids

Biofluid is a clinically informative biologic fluid that may be used for new prognosis, laboratory, or clinical diagnosis, as well as monitoring and care of

patients with oral and systemic diseases [13]. We'll go through blood serum, plasma, saliva, GCF, and synovial fluid in-depth in this article.

Biomarkers

The term "biomarker" arises from the term "biological marker." Biomarkers are described as "a feature that is objectively measured and assessed as an indication of normal biological processes, pathogenic processes, or pharmacological reactions to a therapeutic intervention" by the National Institutes of Health Biomarkers Definitions Working Group[3].

Use of biomarkers in clinical studies

- Assist in diagnosis, screening, or prognosis.
- Determine the association between exposure and illness.
- Examine the mechanisms of pain.
- Evaluate pain management effectiveness and dose-response interactions in clinical studies [7].

Blood serum

Blood serum is the light yellow substance that remains after centrifuging coagulated blood samples at high rates. The serum is free of fibrinogens and is the most frequent cause of blood-based diagnostic analyses [6]. It is not to be mistaken with blood plasma, which is the product of the forced separation of blood cells before clotting. Function- Blood serum is the main carrier of small molecules in the body [33]. This fluid plays an important role in the transport of dissolved gases, nutrients, hormones, and metabolic wastes, as well as in the restriction of loss of fluid to sites of impaired regulation of the pH and ionic components of the interstitial fluid. Defense against toxins and pathogens and stabilization of body temperature [17]. Blood essentially serves as a liquid highway for all molecules that are secreted, excreted, or discarded by different tissues in response to different physiological needs and stresses to wet every tissue and every organ in the body [2]. Of great clinical importance is the fact that tissue lesions, organ dysfunction, and pathological conditions can alter both plasma/serum chemistry and protein composition. As a result, most of today's clinical tests are based on plasma or serum analysis [6].

Composition- Blood is composed of red blood cells, white blood cells, and platelets, and is composed of two parts, a cellular component and a liquid carrier called plasma. Plasma is a straw-colored liquid in which blood cells float, occupying about 50-55% of the blood volume, and the rest are blood cells (red blood cells, white blood cells, and platelets) [6]. If an anticoagulant is introduced, simply centrifuge the sample to remove the most buoyant (non-cellular) part or tilt it to obtain plasma from the blood sample. If the blood coagulates without the addition of anticoagulants, the supernatant is called serum, which is less viscous than the plasma and is deficient in fibrinogen, prothrombin, and other coagulation proteins [12]. Both plasma and serum proteins and peptides (egg albumin, globulin, lipoproteins, enzymes, and hormones), nutrients (eg

carbohydrates, lipids, and amino acids), electrolytes, organic waste, and abundant or dissolved therein various other small organic molecules [8].

Biomarker present in serum to detect orofacial pain

- Interleukins[31]- IL-1, IL-2, IL-6, IL-8
- 15 HETE[2]
- Neurokinin A[32]
- Serotonin [2]
- 8-OHdG[33]
- Malondialdehyde[33]
- C-reactive protein[32]

Blood plasma

Blood plasma is a yellowish fluid component of the blood that binds whole blood's blood cells together. When red blood cells (erythrocytes), white blood cells (leukocytes), and platelets (thrombocytes) are isolated from whole blood, plasma is formed [8]. Function- Plasma acts as a transport channel for nutrients to reach the cells of the body's numerous organs, as well as waste products generated from cellular metabolism to the kidneys, liver, and lungs for elimination [12]. It also serves as a transport mechanism for blood cells and aids in the maintenance of appropriate blood pressure. Plasma aids in the distribution of heat throughout the body as well as the maintenance of homeostasis, or biological stability, which includes maintaining acid-base balance in the blood and body [6]. Composition: 90%–92% water, however, it also includes essential solutes for maintaining health and life. Electrolytes such as sodium, potassium, chloride, bicarbonate, magnesium, and calcium are important components. Other compounds, including amino acids, vitamins, organic acids, pigments, and enzymes, are also present in trace levels. [2]

Biomarker present in plasma to detect orofacial pain

- Dopamine[24]
- Serotonin[3]

Synovial fluid

Synovial fluid, a protective lubricant found in and around complex joints, might be a useful source of biochemical data. The information gleaned from analyzing synovial fluid might be utilized to pinpoint localized physiological changes such as TMDs [19]. Function- While synovial fluid has several functions, its principal role is to lubricate cartilaginous tissues in areas where proximal bone structures are present [21]. It helps coordinate physical activities by maintaining and protecting neighboring bone tissues, which protects joints from frictional wear and extends their life. Synovial fluids are therefore required for the long-term use of complex skeletal structures [20].

Composition- Synovial fluid's molecular composition is obtained from blood plasma, chondrocytes, and other cell types that line the synovial cavity [8]. The synovium, a semipermeable membrane that surrounds the non-cartilaginous surfaces of synovial joints, may alter its biological makeup [19]. Synovial fluid, as a result, is mostly a dialysate of blood plasma augmented with locally generated components such as hyaluronic acid, lubricin, and other joint-lubricating macromolecules [2]. The varied nature of synovial-based chemicals, along with the synovial space's close anatomical context, implies that fluids drained from this region may include a unique collection of biomarkers that might provide important information about joint health. Examining the molecular makeup of synovial fluids may lead to the discovery of disease pathogenesis-related variables that might help prevent chronic pain [21].

Biomarker present in synovial fluid to detect orofacial pain

- Interleukins[31]: IL-1 β , IL-6, IL-7, IL-8, IL-13, and MCP-1
- Proteinases[34]: MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP
- TNF [19]
- Neuropeptides Substance P and CGRP[32]
- Glutamate[24]
- Dopamine[24]
- Chondroitin-4, Chondroitin-6[39]
- Aggrecanase[34]
- Lubricin[24]
- Hyaluronic acid[24]
- Nitric oxide[2]

Saliva

Saliva is a constantly produced, slightly acidic, transparent, hypotonic fluid that is mostly made up of water and inorganic ions [4]. The parotid, submandibular, sublingual, and minor salivary glands, as well as the posterior deep lingual glands (von Ebner's glands), are salivary glands found within and surrounding the mouth cavity [6]. Each gland is made up of acini, which are clustered acinar cells that generate 500–1500 mL each day [16]. Function-Saliva is easy to collect and store, and it includes unique soluble biologic markers, making it suitable for early illness detection [13]. Saliva includes a variety of indicators, making it ideal for multiplexed assays being developed as point-of-care (POC) devices, fast tests, or more standardized formats for centralized clinical laboratory operations [15]. Salivary diagnostics is a rapidly evolving area that is increasingly being used in illness diagnosis, clinical monitoring, and crucial clinical choices for patient care [14]. Furthermore, recent research has revealed that saliva includes a range of genomic, transcriptomic, proteomic, microbiologic, and immunologic analytes [17] that might be used to diagnose both local and systemic diseases in patients. As a result, saliva is currently the focus of several studies targeted at making oral fluids the preferred diagnostic medium. [18]. Composition-Saliva is 99.5 percent water, with the remaining 0.5 percent made up of inorganic ions like sodium, chloride, potassium, and calcium, as well as organic components including amino

acids, proteins, antibodies, hormones, enzymes, lipids, and cytokines, to name a few. [13].

Biomarker present in saliva to detect orofacial pain

- Interleukins[31]: IL-1 β , IL-2, IL-6
- CGRP[32]
- Chondroitin sulfate[2]
- Kallikrein[13]
- CD14[24]
- TLR-2[13]
- Magnesium[35]
- Albumin[35]
- Alkaline phosphatase[13]
- Aspartate aminotransferase[35]
- Calprotectin[35]
- Cystatins[33]
- Defensins[35]
- 8-OHdG[33]
- Malondialdehyde[33]

Gingival crevicular fluid (GCF)

The GCF, which is an interstitial biofluid or inflammatory transudate that flows out via the gingival crevice, is another oral fluid of interest for clinical diagnosis [26]. Function- the GCF protects the oral cavity by eliminating potentially dangerous cells, chemicals, and pathogens, as well as acting as an antibacterial agent thanks to its pathogen-neutralizing antibodies [2]. Many salivary or GCF-derived molecules are employed as diagnostic biomarkers for oral illnesses caused by a fungus (*Candida* species), viruses (HPV, Epstein-Barr virus [EBV], cytomegalovirus [CMV]), and bacteria, including oral cancer (multiple species involved in periodontal diseases and caries)[15]. Composition- It is composed of cells (desquamated epithelial cells, neutrophils, lymphocytes, and monocytes, as well as pathogens such as bacteria), electrolytes (potassium and calcium), and organic components that are comparable to plasma (eg, albumin, globulins, complement s, protease inhibitors, lactate, urea, and multiple enzymes) [8].

Biomarker present in gcf to detect orofacial pain

- Interleukins[31](IL-1 β , IL-6)
- TNF- α [19]
- interferon-gamma[34] [IFN- γ]
- matrix metalloproteinase [34][MMP]-8

Future aspects

In the early phases of biomarker research, obstacles included an incomplete, changing understanding of the causes of chronic facial pain and inaccurate measuring methodologies [24]. The area of pain biomarker research will continue

to develop as the demand for precision medicine approaches and individualized pain management grows [15]. Biofluids and associated biomarkers have the potential to alleviate a significant deal of patient suffering while also assisting in the development of innovative preventative care, treatment strategy planning, and improving our understanding of disease processes [2].

Biomarker identification is a critical aim in pain research, and the findings will change how we think about pain and how we manage it in the future [25]. One of the most difficult tasks for a clinical laboratory is to decrease the number of factors that affect the outcome. The clinical analysis process has grown highly complicated, necessitating its separation into three separate phases: pre-analytical, analytical, and post-analytical [29]. The pre-analytical step is the most important since it allows the effect of the analytical factors to be reduced by getting a high-quality biological sample [26]. This necessitates proper patient orientation, such as particular fasting periods, as well as active engagement of specialist health providers who are familiar with the clinical analyses to be done [27].

Because biofluids come into close touch with the human body's organs, they include numerous chemicals that can be utilized as handy biomarkers for the diagnosis of a variety of illnesses [28]. Another benefit is the simplicity with which blood can be collected, as well as the convenience with which urine may be collected for repeat testing. Biofluids' advantages may allow them to be used to track illness development or therapy success [30]. Biofluids can give a significant quantity of information about each patient, allowing for better clinical analysis.

Conclusion

Orofacial pain is one of the most common causes of chronic pain after back, neck, and knee pain. Acute orofacial pain is frequently caused by teeth, but chronic orofacial pain is caused by musculoskeletal diseases, temporomandibular disorders, and other factors (TMDs). Orofacial pain is a common medical complication with a variety of causes. Left misdiagnosed and without treatment, suffering individuals might be susceptible to chronic discomfort, loss of appetite, and lack of sleep. Unfortunately, most diseases presenting with chronic orofacial pain are difficult to distinguish, and creating quick and reliable patient evaluation procedures might alleviate a significant lot of suffering by identifying afflicted individuals early in the pathogenesis process. Blood serum has traditionally been the most widely used biofluid for the molecular diagnosis of systemic illness and some orofacial disorders. However, new research has found that saliva might replace blood in this capacity, allowing clinicians to better detect the beginning of the disease and track therapy success. Oral fluids are used in this context to not only use a novel patient evaluation approach, but also to present the potential of pain-free treatment, which has long been a dream of scientists, doctors, and patients alike. Synovial fluid, a protective lubricant found in and around complex joints, might prove to be a useful source of biochemical information, in addition to saliva, serum, and plasma. Biofluids include biomarkers that are suggestive of certain illness states, both local and systemic; however, none of these indicators are considered complete, necessitating continuous study for customized diagnoses and treatments.

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