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# Application of Laboratory Medicine in the Field of Oral Medicine

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Various diseases of the orofacial region that are treated in the field of oral medicine not only are associated with local factors but may also be affected by systemic factors. Knowledge about laboratory medicine is needed to identify the systemic factors that can influence these diseases. Therefore, oral medicine specialists should be able to use diagnostic tests of laboratory medicine and interpret the results in diagnosing and treating diseases in the field of oral medicine. The aim of this article is to examine the diagnostic tests used in laboratory medicine that might be applied to assess the systemic aspect of diseases in the field of oral medicine and to interpret the significance of the findings.

**Keywords:** Medical laboratory science; Oral medicine

## INTRODUCTION

Laboratory medicine is defined as the study of the quantitative and qualitative evaluation of various substances that can be analyzed in specimens collected from the body for medical or research purposes [1]. A variety of diagnostic tests that measure, analyze, and read certain substances are included in laboratory medicine. The results obtained through these tests are used for differential diagnosis and the evaluation of severity, course, and prognosis of diseases. According to the type of specimen and analysis method used, laboratory medicine can be divided into the following major fields: (1) diagnostic hematology, (2) clinical chemistry, (3) diagnostic immunology, and (4) genetic diagnostics.

Oral medicine, one of the specialties of dentistry, includes the diagnosis and nonsurgical treatments of disorders (e.g., oral mucosal and salivary gland diseases, orofacial pain) affecting the orofacial region [2]. These disorders are not only associated with local lesions in the orofacial region but may also be affected by systemic medical conditions. For example, several oral mucosal alterations arise as oral symptoms of hematological disorders. It has been reported that oral candidiasis, recurrent aphthous ulcer, erythematous mucositis, and burning mouth symptoms occur frequently in anemic patients [3-6]. Complete blood cell count (CBC), one of the most commonly performed laboratory tests, can be used to identify the presence of hematological abnormalities related to the development of oral mucosal diseases. In addition, CBC can be usefully applied to monitor the serious hematological diseases that arise from the long-term administration of carbamazepine, which is used extensively to treat paroxysmal pain disorders [7,8]. Therefore, oral medicine specialists should be able to use diagnostic tests of laboratory medicine and interpret the results in diagnosing and treating diseases in the field of oral medicine.

The purpose of this review is to summarize the diagnostics tests used in laboratory medicine that can be applied to the evaluation of systemic etiologic factors or the diagnosis of disorders in the field of oral medicine and to explain the meaning of the results of these tests.

## EVALUATION OF SYSTEMIC ETIOLOGIC FACTORS BY LABORATORY MEDICINE

Various diseases that are dealt with in the field of oral medicine are influenced by both local and systemic factors. Knowledge about laboratory medicine is essential for accurate diagnosis. In this section, diagnostic tests of laboratory medicine that can be used for discrimination of the influence of systemic conditions and their interpretation will be explained.

### 1. Recurrent Aphthous Ulcer (RAU)

RAU is a mucosal disease characterized by recurring ulcers confined to the oral cavity. The etiology and pathogenesis of RAU have been extensively studied; however, they are still not entirely understood. Based on the research conducted to date, the major factors currently linked to RAU are known as genetic, immunologic, local trauma, and hematological factors [3]. A previous study found that hematinic deficiencies (i.e., iron, ferritin, folate, vitamin $B_{12}$) are more common in patients with RAU than in healthy controls, with up to 20% of patients with RAU having hematinic deficiencies [4].

Iron is an essential trace element for the production of red blood cells (RBCs). Iron ingested from food is transported throughout the body by transferrin produced in the liver. Iron is a major component of hemoglobin, and about 70% of the iron absorbed into the body is distributed in the hemoglobin in the RBCs. Most of the remaining iron is stored in the tissues in the form of ferritin [9]. Iron deficiency can result from severe bleeding, increased demand, and decreased intake. A laboratory panel to identify iron deficiency includes serum iron, total iron-binding capacity (TIBC), and ferritin. Serum iron refers to the amount of iron in the blood combined with transferrin. TIBC refers to the total amount of iron that can be transported by binding to proteins in the blood. This parameter indirectly reflects the level of transferrin. The ferritin test measures the amount of ferritin in the blood and indicates the total amount of iron stored in the body. In the early stage of iron deficiency, ferritin (stored iron) first decreases slowly. In the late stage, in which stored iron is further depleted, the serum iron level also decreases, and TIBC tends to increase.

Serum levels of vitamin $B_{12}$ and folate that are below the normal range indicate a vitamin $B_{12}$ complex deficiency. However, serum levels of vitamin $B_{12}$ and folate reflect only recent nutritional intake, and a deficiency in vitamin $B_{12}$ complex may still exist, even if the test results are within the normal range. If a deficiency is suspected, the administration of vitamins for therapeutic purpose could be used as a diagnostic strategy.

### 2. Oral Candidiasis

Oral candidiasis is the most prevalent opportunistic infection caused by *Candida albicans*. *C. albicans* is a normal oral microflora component and carried by more than 60% of the general population. As mentioned earlier, oral candidiasis is an opportunistic infection initiated by local and systemic factors that allow the immune system of the oral cavity to be disrupted (Table 1) [2].

Oral candidiasis is associated with immunosuppressive diseases, most notably HIV infection, and affects almost all (>90%) patients with AIDS during the progression of their HIV infection [10]. Among the subtypes of oral candidiasis, chronic pseudomembranous type, erythematosus type of the tongue and palate, and angular cheilitis are commonly observed in patients with AIDS. The laboratory tests used to evaluate HIV infection are HIV antibody, p24 protein, level of HIV virus, and CD4 counts. Among these, CD4 count shows the state of HIV infection progression and the status of the immune system and could help to determine the timing of treatments and confirm the treatment outcome. In general, it is recommended to start treatment when the CD4 count is $<200/mm^3$.

Patients with diabetes have a weakened immune system, making them more susceptible to infection. In addition, patient with diabetes have been shown to have a higher incidence of oral fungal infection, particularly caused by an opportunistic infection of *C. albicans* [11]. Diabetes can

**Table 1.** Predisposing factors for oral candidiasis

| Local factors | Systemic factors |
|---|---|
| Ill-fitting denture | Immunosuppresive diseases & drugs |
| Topical steroid | Diabetes |
| Xerostomia | Hematinic deficiency |
| Smoking | Systemic antibiotics |

be diagnosed by laboratory tests (i.e., blood glucose and HbA1c). Blood glucose is evaluated by two diagnostic tests: fasting blood glucose (FBG) and oral glucose tolerance test (OGTT). FBG measures the level of glucose in the blood after 8 hours of fasting (diabetes is indicated if the FBG is >126 mg/dL) and is used for regular checkups and as a screening test for diabetes. OGTT measures the blood glucose level 2 hours after ingesting glucose (diabetes is indicated with a glucose level of >200 mg/dL) after FBG is established. Hb1Ac is a form of glucose bound to hemoglobin A. Some of the glucose circulating in the blood naturally binds to hemoglobin A, and this binding state is maintained throughout the life of the RBC (120 days). Because of these properties, HbA1c can assess the mean level of blood glucose over 2 to 3 months (diabetes is indicated if the HbA1c level is >6.5%).

Because iron is necessary to maintain the normal function of immune cells, iron deficiency leads to a deterioration in the immune system against infection [12]. In addition, iron deficiency is the most common cause of anemia, which can affect candidiasis, as previously described. A prior study reported that 85% of patients with iron deficiency showed symptoms of oral candidiasis [5]. Even though 28 patients had severe to life-threatening anemia, they reported no anemia-related symptoms other than fatigue and oral symptoms. Vitamin B complex deficiency is also known to be associated with oral candidiasis and should be considered in the diagnostic process.

### 3. Oral Lichen Planus (OLP)

OLP is a chronic inflammatory oral mucosal disease. Although the pathophysiology of OLP remains unknown, OLP is considered to be a cell-mediated immune disease that primarily targets epithelial cells in the basal layer [13]. Histological findings, including apoptosis of basal cells and infiltration of T lymphocytes and macrophages into the subepithelial area, support this. The exact etiologic factors triggering the development of OLP are also still unknown. The possibility of an association between hepatitis C virus (HCV) and thyroid diseases has been suggested; however, this is still under debate.

Numerous previous studies have suggested a link between OLP and HCV. In a systematic review study, the authors proposed that the proportion of HCV-positive subjects is 4.8 times higher in patients with OLP than in controls [14]. Notwithstanding, the pathogenetic link between OLP and HCV has not been clearly elucidated, and HCV-specific T cells are speculated to play an important role in this connection. Interestingly, the prevalence of chronic HCV in patients with OLP varies by geographic area, possibly suggesting a link to genetic factors. In the diagnosis of hepatitis, liver function tests, especially related to liver damage (aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transferase, alkaline phosphatase, and lactate dehydrogenase), are performed. These panels measure the level of enzyme present in liver cells. If hepatocytes are damaged by a virus, the enzymes enter the blood, and levels of these rise. For example, the serum level of both aminotransferases elevates to 8-50 and 2-5 times the upper reference limit in acute and chronic hepatitis, respectively.

The association between OLP and thyroid diseases, particularly with hypothyroidism, has also been suggested in a previous study [15]. A recent meta-analysis study indicated a significantly high prevalence of thyroid disease among the patients with OLP compared with controls [16]. The association between OLP and thyroid diseases appears to be due to their pathophysiological similarities, as both diseases are caused by an autoimmune mechanism involving cytotoxic T cells and are more prevalent in women. The thyroid function test consists of three panels as follows: thyroid stimulating hormone (TSH), T3, and T4. TSH is secreted by the anterior pituitary and activates the thyroid gland to produce T3 and T4. Secreted T3 and T4 inhibit the production of TSH by acting on the anterior pituitary (negative feedback). In hyperthyroidism, the TSH level is decreased; however, T3 and T4 levels are elevated or within the normal range. Conversely, in hypothyroidism, the TSH level is elevated and T3 and T4 levels are lowered.

### 4. Burning Mouth Syndrome (BMS)

BMS is a chronic orofacial pain disorder characterized by persistent oral burning symptoms in oral mucosa with a normal appearance. Oral burning symptoms may result from various local (oral soft-tissue lesions as mentioned above) and systemic (hormonal changes, systemic diseases, medications, and nutritional deficiencies) factors

[17]. Accordingly, to achieve a proper diagnosis of BMS, it is essential to identify these local and systemic factors. Diagnostic tests in laboratory medicine can be used to confirm these factors. The recommended laboratory tests are as follows: complete blood count with leukocyte differential count; erythrocyte sedimentation rate; calcium, phosphorus, blood glucose, ferritin, vitamin $B_{12}$, folate, zinc, and magnesium levels; liver function tests; thyroid function tests; and kidney function tests [18].

The laboratory panels related to kidney function are creatinine, blood urea nitrogen, and uric acid. Creatinine is produced from creatine, which is mainly present in muscles. Every day, about 1%-2% of creatine is converted to creatinine through a spontaneous and irreversible nonenzymatic dehydration process, so that a certain amount of creatinine is distributed in the blood. Urea is a major product of protein metabolism in the body. It is called "blood urea nitrogen" because the urea concentration is conventionally expressed by the amount of nitrogen contained in urea. Uric acid is the final metabolite of purine nucleic acids. These substances (creatinine, urea, and uric acid) are secreted through the kidney, and the levels of these substances may be elevated due to kidney dysfunction. Each of these panels has drawbacks in the evaluation of renal function. Therefore, renal function is confirmed by comprehensively evaluating the results of the three panels.

### 5. Sialorrhea

Sialorrhea refers to a condition with excessive salivation. It may be associated with ill-fitting dentures. Sialorrhea can also occur due to medication, neurologic diseases, hyperhydration, and heavy metal poisoning [19]. Among these, heavy metal poisoning can be evaluated by diagnostic tests in laboratory medicine.

Heavy metal poisoning arises in industrial facilities where heavy metals are used. Arsenic, lead, mercury, and thallium are the representative heavy metals related to excessive salivation [20]. Heavy metal tests are usually performed using blood or urine collected over 24 hours, through which information on heavy metal exposure can be obtained. Although hair and nail samples are also used for heavy metal testing, there is a disadvantage in that recent exposures cannot be determined through these samples.

## DIAGNOSIS USING LABORATORY MEDICINE

### 1. Sjögren Syndrome (SS)

SS is a chronic autoimmune disease characterized by oral and ocular dryness, lymphocytic infiltration, and destruction of the exocrine glands. Several classification criteria have been proposed to standardize the diagnosis of SS. Recently, the 2016 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria were published [21]. According to these criteria, scores are given for each of the five items (minor salivary gland biopsy, anti-SSA/Ro, ocular staining score, Schirmer's test, and flow rate of unstimulated whole saliva), and SS can be considered when the total score is 4 or greater (Table 2).

Diagnostic immunological tests may be performed to identify SS-related autoantibodies. Representative autoantibodies of SS include anti-SSA/Ro antibody and anti-SSB/La antibody, which are present in 60%-75% and 25%-50% of patients with SS, respectively. These two autoantibodies newly appear in the 2012 ACR criteria. However, the presence of anti-SSB alone is rare and has no significant association with SS phenotypic features [22]. Therefore, only anti-SSA/Ro antibody was recognized in the 2016 ACR/EULAR criteria.

Nevertheless, the presence of anti-SSA/Ro is not confirmed in all SS patients. Even if the 2016 ACR/EULAR criteria are followed, it is possible to diagnose SS even in the absence of anti-SSA/Ro. However, it has been reported that patients with anti-SSA/Ro antibodies show more aggressive clinical symptoms than do patients without anti-SSA/Ro antibodies. Conversely, the presence of anti-SSA/Ro can

**Table 2.** American College of Rheumatology/European League Against Rheumatism Sjögren syndrome 2016 classification criteria

| Criterion | Weight/Score |
|---|---|
| Labial salivary gland with focal lymphocytic sialadenitis and focus score ≥1 | 3 |
| Anti-SSA-positive | 3 |
| Ocular staining score ≥5 (or van Bijsterveld score ≥4) in at least one eye | 1 |
| Schirmer ≤5 mm/5 min in at least one eye | 1 |
| Unstimulated whole saliva flow rate ≤0.1 mL/min | 1 |

Anti-SSA, anti-Sjögren's syndrome-related antigen A.
Table were obtained from Shiboski et al. (Ann Rheum Dis 2017;76:9-16) [21].

be identified among the normal population at a rate of 1.7% to 17.5% and can also be detected in patients with autoimmune diseases other than SS [23]. Therefore, the diagnosis of SS should be determined by comprehensively evaluating the presence of autoantibody and other diagnostic criteria.

### 2. Rheumatoid Arthritis (RA)

RA is a chronic inflammatory disorder that arises from an autoimmune reaction. It primarily affects the periarticular tissue and bone. Previous studies reported a prevalence of involvement of the temporomandibular joints in 40%-80% of patients with RA [24,25]. However, signs of osteoarthritis were observed in half of the normal control group using the same imaging test [25]. Taking this into consideration, a conclusion cannot be made that a high proportion of patients with RA has temporomandibular disorders that require treatment.

The ACR/EULAR classification criteria for RA established in 2010 is usually applied for diagnosing RA (Table 3) [26]. According to this classification, scores are given on four criteria, and a definite diagnosis of RA can be made if the total score is 6 points or greater. Among the four criteria, serology and acute phase reactants are related to laboratory medicine.

**Table 3.** American College of Rheumatology/European League Against Rheumatism 2010 classification criteria for rheumatoid arthritis

| Criterion | Score |
|---|---|
| Joint involvement | |
| 1 large joint | 0 |
| 2-10 large joints | 1 |
| 1-3 small joints (with or without large joint) | 2 |
| 4-10 small joints (with or without large joint) | 3 |
| >10 joints (at least one small joint) | 5 |
| Serology (at least one test result is needed) | |
| Negative RF and negative ACPA | 0 |
| Low positive RF or low positive ACPA | 2 |
| High positive RF or high positive ACPA | 3 |
| Acute phase reactants (at least one test result is needed) | |
| Normal CRP and normal ESR | 0 |
| Abnormal CRP or abnormal ESR | 1 |
| Duration of symptoms | |
| <6 wk | 0 |
| ≥6 wk | 1 |

RF, rheumatoid factor; ACPA, anti-citrullinated protein antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.
Table were obtained from Aletaha et al. (Arthritis Rheum 2010;62:2569-2581) [26].

There are two known types of autoimmune antibodies to RA. Rheumatoid factor (RF) was the first discovered autoantibody in patients with RA and was also used in the ACR classification criteria for RA published in 1987 [27]. About 70% of patients with RA are positive for RF. However, contrary to its name, RF is found not only in RA patients but also in about 60%-70% of patients with SS [28]. In addition, RF is detected in patients with persistent infections; tumors; pulmonary, liver, and renal diseases; and even in healthy people. Because of this, the sensitivity and specificity of RF for the diagnosis of RA are not excellent. Anti-citrullinated protein antibody (ACPA), also referred to as an anti-cyclic citrullinated peptide, is a more recently discovered autoantibody of RA. It is detected in 50%-60% of patients with RA in the early stage (within 3-6 months after the onset of symptoms) [29]. ACPA is known to have superior sensitivity and specificity and shows a positive sign earlier than RF does. If RF is negative but ACPA is positive and RA symptoms are present, early stage RA can be determined. If ACPA is negative but RF is positive, it is necessary to differentiate other inflammatory diseases based on clinical signs and symptoms. If both ACPA and RF are negative, the likelihood of RA is low. However, RA is basically diagnosed clinically by signs and symptoms, and its diagnosis does not necessarily require a positive autoantibody test result.

Acute phase reactants are substances whose concentrations increase or decrease in response to acute tissue inflammation or trauma [30]. Representative items related to these are erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and the levels of both increase in response to inflammation. However, ESR and CRP do not indicate the location of the inflammation and are also affected by conditions other than inflammation. Nonetheless, these tests are widely used as screening and monitoring tools because they serve as general indicators for infection and inflammation.

ESR, a diagnostic test that has been used for a long time, is measured by the distance at which erythrocytes are separated from plasma and sink in a pipette for 1 hour. An elevated ESR is associated with elevated levels of fibrinogen and globulin in the blood, indicating the presence of

inflammation or infection. In patients with RA, ESR is used to identify active RA and for the differential diagnosis of osteoarthritis [31].

CRP is an acute phase reactant produced by the liver and secreted into the bloodstream within a few hours after the onset of infection or inflammation. It is involved in activating the complement system. Compared with ESR, CRP is less affected by other factors and responds rapidly to inflammation [31]. It begins to increase 6-12 hours after the onset of inflammation and reaches its highest level after 48 hours; it may also rise before pain or fever. CRP has also shown a good correlation with RA activity and is used as an index to confirm RA remission [32]. In addition, CRP does not elevate lupus, so it can be used for differential diagnosis.

## CONCLUSION

The oral cavity is a part of the body, and it has long been known that oral health is strongly linked to the health of the whole body. Therefore, to accurately diagnose and treat diseases that appear in the orofacial region, it is essential to evaluate the patient's systemic condition. Moreover, several diseases require collaboration with medical doctors, and knowledge of laboratory medicine is required for communication about the patient's condition. Thus, it is necessary for oral medicine specialists to have an interest and deep understanding of laboratory medicine. Furthermore, the development of a novel diagnostic tests panel that can evaluate diseases of the orofacial region will help improve both diagnosis and treatment.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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