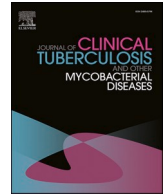




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Assessing physical and chemical properties of saliva among tuberculosis patients on anti-tuberculosis treatment - An observational study

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ABSTRACT

Background: Tuberculosis (TB) is one of the major systemic conditions which is a preventable and curable infection but remains a significant cause of death. The WHO, in its global plan to stop TB reports, that poor treatment has resulted in the evolution of *Mycobacterium tuberculosis* strains that do not respond to treatment with the standard first-line combination of anti-tuberculosis medicines, resulting in the emergence of multidrug-resistant tuberculosis in almost every country of the world.

The present study was aimed to assess the physical and chemical property of stimulated and unstimulated saliva and identify if any association exist with alterations in taste perception in patients with antituberculosis medications.

Methods: A total of 30 patients on anti-tuberculosis drugs were considered as cases and 30 healthy volunteers were considered as controls and included in the study. All study subjects were assessed for their physical property like flow rate, viscosity, pH and chemical property like sodium, potassium, calcium, phosphorous of stimulated and unstimulated saliva. All the subjects on Anti-tuberculosis drugs were assessed for change in taste perceptions using the standard questionnaire.

Results: There is a significant decrease in the flow rate (0.34 ± 0.06) and pH (5.89 ± 0.37) of unstimulated saliva of patients and the flow rate (0.38 ± 0.07) and viscosity (1.34 ± 0.28) of stimulated saliva among the case group compare to the control group. All the electrolytes' concentrations such as sodium, potassium, calcium, and phosphorous values were significantly altered in stimulated and unstimulated saliva of the case group compared to the control group in which p-value < 0.05 was considered.

Conclusion: There are significant changes in physical and chemical properties of both stimulated and unstimulated saliva which has an effect on taste perception inpatient with anti-tuberculosis medications. Hence, salivary flow rate, pH, viscosity, and salivary electrolytes of tuberculosis patients should be considered as important parameters in guiding the diet, so that there will be an improvement in their taste perception and medication protocol, thus maintaining their nutritional status which leads to improving their health.

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1. Introduction

Tuberculosis (TB) is a major global health problem as a leading cause of mortality worldwide. In 2019, an estimated 1.4 million people died as a result of tuberculosis infection and 10 million people suffer due to mycobacterium tuberculosis. The standard treatment regimen lasts a minimum of six months. Tuberculosis patient take three or four drugs, typically isoniazid, rifampicin, pyrazinamide, and ethambutol dihydrochloride, in combination for two months (intensive phase), followed by rifampicin and isoniazid for four months (continuation phase) [1].

The newer WHO has recommended new guidelines for the treatment of tuberculosis patients. First, the conditional recommendation for a one month of rifampicin (2HRZE/6HE) and isoniazid regimen and 4 months daily rifampicin (2HRZE/4HR) will reduce the number of relapses and failures. This will alleviate patient suffering resulting from a second episode of tuberculosis and conserve patient and program resources [2].

Impediments to successful treatment include the availability of these drugs and patient non-adherence to treatment regimens. Unsuccess in the treatment of tuberculosis patients due to many reasons which are the complex nature of the treatment regimen, an inability to meet the financial burden of treatment, and an inability to complete treatment due to side effects of the drugs. The main side effect of the anti-tuberculosis drug especially Rifampicin may cause gastrointestinal reactions (abdominal pain, nausea, vomiting), fever, pruritus with or without rash, loss of appetite, weight loss, metallic taste sensation, the reddish coloration of body secretions like saliva, urine, sweat [3].

Oral fluid is a mixture of saliva secreted by all salivary glands present in the oral cavity. The terms saliva and oral fluid are used interchangeably in the literature. Saliva is a unique biologic fluid produced by different salivary glands. It is composed of approximately 99% water and 1% solid i.e., protein, enzyme, and electrolytes [4]. A Salivary pH value, salivary flow rate, and other physiological properties of saliva may influence and determine by the various drugs i.e., the drug distribution and concentration of the free (unbound) or bounded drug at a certain ratio [5]. At present, there is little knowledge regarding the influence of the antituberculosis drug on oral fluid i.e., quality and quantity of saliva.

Anti-tuberculosis drugs affect the taste, smell, or salivation and lead patients to change their patterns of food or fluid intake. This may lead to nutritional deficiencies, loss of appetite, and weight loss resulting in some other diseases [1,5,6]. Therefore, predictably these may cause some physical and chemical changes in the saliva of these patients.

Despite knowing, there is a lack of quantitative and qualitative data available regarding the physical and chemical properties of saliva, this represents a major problem in the knowledge base for tuberculosis treatment. These drugs have been reported to be unpalatable by patients in the literature because of their bitter taste and are often considered as a major barrier during the treatment of these patients [7].

However, despite numerous reports of the bitter taste of tuberculosis medicines being a barrier to treatment adherence and **there are no studies that quantified the physical and chemical composition of saliva**. Now we are trying to determine the physical and chemical properties of stimulated and unstimulated saliva among patients who were on anti-tuberculosis drugs.

2. Material and method

2.1. Study design

Observational study.

2.2. Data collection

The present study was conducted in the DOT centre of JSS hospital, JSS Academy of Higher Education & Research, and other DOT centres in Mysuru city. About 30 new patients with tuberculosis on the anti-

tuberculosis drug as the case group and 30 healthy individuals with age and sex matched were also included in the study as a control based on the inclusion and exclusion criteria. The participants were asked not to eat or drink anything except water, not to smoke, and not to brush their teeth until one hour before the collection of saliva samples.

2.3. Inclusion criteria

- The participant is willing to participate in the study and give informed consent for both case and control group
- Participants' age should be 18–60 years of both genders for both case and control groups.
- A patient who is having a new case of Tuberculosis disease (Pulmonary or Extrapulmonary are in an intense phase of treatment).

The daily regime for New TB cases as per the Revised National Tuberculosis Control Programme (RNTCP).

- Treatment of intensive phase (IP) consists of 8 week of INH, Rifampicin, pyrazinamide, and ethambutol daily as per four weight band categories.
- Only pyrazinamide will be stopped in the continuation phase (CP) and the other three drugs will be continuing for another 16 weeks as a daily dosage.
- The patient should be taking an anti-tuberculosis drug at least from 2 weeks in routine care.

2.4. Exclusion criteria

- Persons with any other underlying systemic (HIV) or oral diseases for both case and control group.
- Patient under medications other than antitubercular drugs for both case and control group.
- A participant should be devoid of allergy to any drugs for both case and control group.
- Patients who underwent any surgery/radiation therapy in the last 6 months for both case and control groups.
- Patient with any dental prosthesis for both case and control group.

The Institutional Scientific Ethical Board granted ethical approval for this study with number: 63/2020 with dated 7-01-2021, and all subjects gave their consent.

All the case participants who complained of altered or loss of taste sensation were interviewed by several questionnaires on general health information, oral habits, systemic health, drug intake, oral diseases, surgeries, and regarding the type of taste changes they were experiencing.

2.4.1. To identify the physical properties of saliva

The unstimulated saliva sample was collected from both case and control groups by using a standardized method. The subjects were advised to rinse their mouth 1 or 2 times with deionized (distilled) water and then relax for 5 min before the procedure. The subjects were asked to sit comfortably with their head tilted slightly forward and expectorate the saliva accumulated on the floor of the mouth into disposable plastic containers for 5 min. The salivary samples were quantified volumetrically using a graduated measuring cylinder. The saliva samples were centrifuged (centrifugal force: 1000 rpm) for the removal of bacteria and extraneous material.

Similarly, the stimulated whole saliva was collected from both case and control groups by chewing a piece of paraffin wax (1 g) at a habitual pace. After the 60 s of pre-stimulation, the secreted saliva was spit in graded disposable plastic cups for 5 min. The saliva samples were centrifuged (centrifugal force: 1000 rpm) for the removal of bacteria and extraneous material [8].

All the physical properties of stimulated and unstimulated saliva like

salivary flow rate were expressed as ml/min, salivary pH was measured by using a pH meter, and the viscosity of the saliva was measured through the Brookfield viscometer.

2.4.2. To identify the chemical properties of saliva

The sodium, potassium, calcium, and phosphorous concentrations was measured by flame photometer CL378 (Elico Ltd. India).

The obtained data of the values of electrolyte concentrations of stimulated and unstimulated saliva from the study subjects were entered in the excel sheet and the data analysis was done using SPSS software version 22.0.

2.5. Statistical analysis

Descriptive statistics like mean and Standard deviation were calculated for the Continuous quantitative variables and percentages were calculated for discrete variables. For comparison of the mean value of the physical and chemical parameters between cases and controls *t*-test was applied and a *p*-value < 0.05 was considered as statistically significant.

3. Results

In this research study, the physical property like flow rate, viscosity, and pH of stimulated and unstimulated saliva was measured. The results showed that the flow rate and pH were significantly decreased in unstimulated saliva of patients on anti-tuberculosis drugs (0.34 ± 0.06 , 5.89 ± 0.37) compare to the control group (0.39 ± 0.03 , 6.44 ± 0.58) (Table 1). Similarly, the flow rate and viscosity showed significantly reduced in stimulated saliva of patients on anti-tuberculosis drugs (0.38 ± 0.07 , 6.87 ± 0.56) compare to the control group (1.25 ± 0.68 , 6.86 ± 0.41) (Table 2).

The chemical properties of saliva like sodium, potassium, phosphorous, calcium was estimated, and found that there were changes in the electrolyte concentration level of the saliva among patients on anti-tuberculosis drugs and the control group. Amount of sodium, potassium, and calcium in unstimulated (6.17 ± 3.14 , 10.60 ± 6.85 , 27.57 ± 1.75) and stimulated saliva (10.65 ± 6.39 , 14.16 ± 2.32 , 28.04 ± 3.99) was higher among patients on anti-tuberculosis drugs compare to the amount of sodium, potassium, and calcium in unstimulated (4.00 ± 1.50 , 2.21 ± 0.81 , 2.58 ± 0.89) and stimulated (4.37 ± 1.80 , 2.73 ± 0.94 , 2.80 ± 0.79) saliva of control group. Phosphorous level was lower in unstimulated (1.50 ± 1.57) and stimulated (1.00 ± 0.69) saliva among patients on anti-tuberculosis drugs compare to the phosphorous level in unstimulated (2.21 ± 0.81) and stimulated (2.73 ± 0.94) saliva of control group. (Tables 1 & 2) All the electrolytes concentration values were highly significant in stimulated and unstimulated saliva of patients on anti-tuberculosis drugs compare to the control group in which *p*-value < 0.05 was considered.

Similarly, we analysed the changes in the perception of the taste with age, height, weight, BMI, Oral habits (Tobacco chewing/tobacco smoking/alcohol intake), other systemic diseases, oral disease, any surgery/drugs, Dryness of mouth, Burning sensation and Bitter taste

Table 1

Comparison of physical and chemical property of unstimulated saliva in case and control groups.

	Case Mean with SD	Control Mean with SD	p-value	Significance
Flow rate	0.34 ± 0.06	0.39 ± 0.03	0.000	Highly significant
pH	5.89 ± 0.37	6.44 ± 0.58	0.000	Highly significant
Viscosity	1.22 ± 0.22	1.32 ± 0.26	0.118	Not significant
Sodium	6.17 ± 3.14	4.00 ± 1.50	0.001	Highly significant
Potassium	10.60 ± 6.85	2.21 ± 0.81	0.000	Highly significant
Phosphorous	1.50 ± 1.57	4.42 ± 2.74	0.000	Highly significant
Calcium	27.57 ± 1.75	2.58 ± 0.89	0.000	Highly significant

Table 2

Comparison of physical and chemical property of stimulated saliva in case and control groups.

	Case Mean with SD	Control Mean with SD	p-value	Significance
Flow rate	0.38 ± 0.07	1.25 ± 0.68	0.000	Highly significant
pH	6.87 ± 0.56	6.86 ± 0.41	0.941	Not significant
Viscosity	1.34 ± 0.28	1.53 ± 0.28	0.001	Highly significant
Sodium	10.65 ± 6.39	4.37 ± 1.80	0.000	Highly significant
Potassium	14.16 ± 2.32	2.73 ± 0.94	0.000	Highly significant
Phosphorous	1.00 ± 0.69	3.89 ± 2.76	0.000	Highly significant
Calcium	28.04 ± 3.99	2.80 ± 0.79	0.000	Highly significant

sensation. The results support that taste alteration was altered among alcohol consumers (*p* value-0.045) and bitter taste sensation (*p* value-0.045) was highly evident among patients who are consuming anti-tuberculosis drugs. (Tables 3 & 4).

4. Discussion

One of the greatest dilemmas and challenges facing most Tuberculosis (TB)-programs is a patient do not complete tuberculosis treatment for one reason or another [9]. Therefore, a trend is seen towards integrating medical and odontological knowledge through novel therapeutic techniques and drug usage for the elimination of the disease for the better health care of tuberculosis patients.

The saliva circulating in the mouth is called the whole saliva which comprises a mixture of secretions from the major, minor salivary glands and traces from the gingival crevicular fluid [10]. Saliva is considered as a "body mirror" that can reflect the physiological and pathological state of the body. Saliva is gaining popularity as well as the attention of many researchers were attracted towards saliva as a diagnostic and monitoring tool due to simple to collect, low cost, and non-invasive method [11,12]. Therefore, we conducted the study on physical and chemical properties of saliva among patients on antituberculosis drugs.

The present study consists of two groups as described in the methodology. Stimulated and unstimulated saliva was collected to measure the flow rate, pH, and viscosity of patients on anti-tuberculosis drugs as case and healthy volunteers as control groups. Unstimulated whole saliva plays a key role in protecting the oral tissues representing the salivary gland status and is considered to be present for about 14 h a day whereas, stimulated saliva which is present in the oral cavity for about 2 h a day represents the secretion during food intake (physiologic stimulation) [12]. In our study, we had chosen to measure both stimulated and unstimulated saliva to evaluate the physical and chemical

Table 3

Comparison of taste alteration with age, height, weight, BMI among tuberculosis patients' group.

	Altered taste sensation	Number	Mean with SD	p-value	Significance
Age	Yes	20	48.90 ± 9.324	0.192	Non-significant
	No	10	43.20 ± 13.935	0.263	Non-significant
Height	Yes	20	5.46 ± 0.289	0.973	Non-significant
	No	10	5.46 ± 0.430	0.977	Non-significant
Weight	Yes	20	42.65 ± 9.631	0.434	Non-significant
	No	10	39.70 ± 9.487	0.435	Non-significant
BMI	Yes	20	15.043 ± 3.6698	0.793	Non-significant
	No	10	14.650 ± 4.1118	0.802	Non-significant

Table 4

Comparison of taste alteration with age, height, weight, BMI among tuberculosis patients' group.

		Altered taste sensation		p-value	Significance
		Yes	No		
Tobacco chewing	Yes	3	3	0.306	Non-significant
	No	17	7		
Tobacco smoking	Yes	15	10	0.109	Non-significant
	No	5	0		
Alcohol intake	Yes	14	3	0.045	Significant
	No	6	7		
Other disease	Yes	6	0	0.074	Non-significant
	No	14	10		
Oral disease	Yes	3	3	0.372	Non-significant
	No	17	7		
Any surgery	Yes	3	5	0.078	Non-significant
	No	17	5		
Any drugs	Yes	3	0	0.532	Non-significant
	No	17	10		
Dryness	Yes	8	1	0.204	Non-significant
	No	12	9		
Burning sensation	Yes	3	3	0.372	Non-significant
	No	17	7		
Bitterness	Yes	16	4	0.045	Significant
	No	4	6		

properties of saliva among the case and control groups.

The present study showed that anti-tuberculosis medication had an effect on salivary flow rate, pH, and viscosity of unstimulated and stimulated saliva. This indicates that there is a significant decrease in stimulated salivary flow and viscosity as well as in unstimulated salivary flow and pH which may cause xerostomia resulting in dehydration, burning sensation, and other oral diseases like dental caries, periodontal diseases, etc.

The present study also showed there is an alteration in the chemical composition such as sodium, potassium, phosphorous, calcium of stimulated and unstimulated saliva among case and control groups. The electrolyte alteration of saliva may result in alteration of taste sensation, so that intake of food may be reduced, resulting in malnutrition which may affect the immune system. This indicates that anti-tuberculosis drugs affect the saliva of the patient who is having antituberculosis drugs.

Study also has shown that the anti-tuberculosis drugs resulted in altering the taste perception in patients to a different extent. Additionally, we observe that taste alteration was associated with alcohol intake among these patients who are consuming anti-tuberculosis drugs. According to Neto et al. drinking alcohol in high amounts can compromise the functions of taste, by changing the sensitivity of taste receptors [13]. Alcohol interferes with the absorption of nutrients (such as vitamin B complex, vitamin A and zinc), which generates functional and morphological changes in the saliva and taste buds of excessive drinkers [14]. In addition, it has been proposed that Zn present in the sensory receptors and certain brain regions mediates perception and interpretation of sensations produced by the sensory organs and is also necessary for the functioning of the taste buds [15]. Thus, deficiencies of Zn caused by alcohol consumption can be a factor in reducing taste sensitivity. The sensory qualities like a deficiency in the perception of taste can disturb food intake, leading to nutritional and even immune deficiencies [13,16].

On furthermore, the present study also observes about bitter taste sensation in patients who are consuming anti-tuberculosis drugs. There is very little information known in the literature concerning the influence of anti-tuberculosis drugs on oral health and their function. There are few studies reported about the use of antituberculosis medications, which suggested that drugs that could induce a possible change in the saliva and taste perception, resulting in the improper intake of diet. Unbalanced nutrition contributes to decreasing the effectiveness of treatment and resulting in the development of other diseases, such as

caries, periodontal diseases, oral infection, dysphagia, etc. [17,18]. The dose of medication was not considered in this study, since it is known that a combination of the number of anti-tuberculosis medications is associated with an overall effect on the saliva and taste sensation. The side effects of the anti-tuberculosis medication may be related to a reduction in the stimulus of the cholinergic and parasympathetic innervation of the salivary gland, which results in hyposalivation.

Changes in taste perception are a common reason for discontinuing the drug therapy by patients suffering from tuberculosis, which poses a serious threat to their lives [19]. Henkin noted that the therapy of taste perception disorders related to used drugs should include the functioning of the receptors of senses and physiological factors affecting the correct functioning of the sense of taste [20]. Therefore, there is little information regarding anti-tuberculosis drugs' effect on saliva and taste. Based on our study result, the efforts to improve our understanding of the physical and chemical property of the saliva and alteration of taste sensation among patients with anti-tuberculosis drugs. It needs to introduce measures to improve compliance with treatment and to promote positive behavior changes in their lifestyle and improve their nutritional status. Hence knowledge of effect of anti-tuberculosis drug on salivary physical and chemical properties is very important.

Based on the obtained results it can be concluded that it is necessary to continue the research on the way different strategies of drugs and combined therapies affect the taste sensitivity in patients and design the methods of preventing or decreasing the adverse effects of these drugs as well as the adherence of anti-tuberculosis drugs regimen. These newly emerging and fast-growing technologies have broadly widened the possibilities of saliva testing in the oral cavity, making the clinical salivary diagnosis a reality that can be very precise and useful in the assessment of the health of an individual.

5. Limitation and future prospective of the study

It is required to conduct in larger sample size for a longer duration to compare with salivary parameters among these patients and also necessary to better understand the magnitude of the problem including the complicated cascades and cellular events at the molecular level that produce an alteration of taste from these medications. We need more clinical and laboratory studies are needed to determine the exact relationship between these physicochemical properties of saliva and bitter taste sensation among these patients.

6. Conclusion

The conclusion was drawn from the present study, there is a significant decrease in the flow rate and pH of unstimulated saliva and the flow rate and viscosity of stimulated saliva among the patients on anti-tuberculosis medication as compared to healthy individuals. The amount of sodium, potassium, and calcium in unstimulated and stimulated saliva was higher among patients on anti-tuberculosis drugs compare to the control group, but the phosphorous level was lower among patients on anti-tuberculosis drugs compare to the control group. Also, there was evident in bitter taste perception was very high among patients on anti-tuberculosis as compared to healthy individuals. Hence, physical and chemical parameters of saliva among tuberculosis patients on anti-tuberculosis drugs should be considered as important parameters in guiding the diet and medication protocol for tuberculosis patients, thus maintaining their oral and overall health.

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Author contributions

VGD & MB contributed to study design, study implementation, analysis, and interpretation of data. BMG & SS contributed to study implementation with major contributions in fieldwork, analysis, and interpretation of data. JBS contributed inputs for the improvement of the protocol and implementation of the study. VCS involved in the conception of the research idea. All authors had contributions to writing up the manuscript and read, approved the final version. The diagnostic use of saliva has attracted the attention of many researchers due to its non-invasive nature and relative simplicity of collection. In addition, it should be noted that the determination of chemical and physical saliva parameters can be effectively performed.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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