وزارة التعليم العالي والبحث العلمي
جامعة ميسان
كلية التربية الاساسية

Misan jas
Misan Journal of Academic Studies

مجلة ميسان للدراسات الاكاديمية

العلوم الانسانية والاجتماعية والتطبيقية

ISSN (Paper)- 1994-697X
(Online)- 2706-722X

المجلد 23 العدد 49 السنة 2024

مجلة ميسان للدراسات الاكاديمية

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كلية التربية الاساسية - جامعة ميسان - العراق

ISSN (Paper)- 1994-697X
(Online)- 2706-722X

مجلد (23) العدد (49) اذار (2024)

OJS / PKP
www.misan-jas.com

http://www.misan-jas.com/index.php/ojs

journal.m.academy@uomisan.edu.iq

رقم الايداع في دار الكتب والوثائق بغداد 1326 في 2009

ISSN (Paper) 1994-697X

ISSN (Online) 2706-722X

DOI: https://doi.org/10.54633/2333-023-049-016

The occurrence of Lactobacillus *and* Candida albicans *in patients with thyroid disorders*

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Abstract:

Background: Thyroid disease can disrupt the body's balance and affect its ability to heal tissues. Research has indicated that those with thyroid problems have an increased susceptibility to dental caries. This may be from the illness process itself, surgical intervention (thyroidectomy), or drug side effects that exacerbate dental and oral health conditions. The case-control study was conducted 87 precipitate. Precipitate was divided into three groups as the following: hyperthyroidism, hypothyroidism, and healthy control group. Each group comprised 29 subjects, all participants aged between 30 and 60. Saliva was cultured on orgasm agar for lactobacilli, sabouraud's dextrose agar for *Candida albicans*. Additionally, thyroid function test was measurement by cobas. Concerning (salivary flow rate), results show that a lower mean value was recorded in the "Hyperthyroid" patient group, whereas in the "Hypothyroid" group, patients accounted for the second-ordered mean value, and the healthy group accounted for a high-level mean value within the normal range, as significant differences at $P<0.05$ were accounted for among the studied groups. Concerning microbial types, comparing hyperthyroid and control groups, results show that substantial differences are accounted for in at least $P<0.05$ (*C. Albicans and Lactobacillus*). Also, comparing hypothyroid and control groups shows significant differences, at least at P<0.05. This study concluded that salivary flow rate (SFR) **is** too sensitive due to hyperthyroid patients, and C. *Albicanis and Lactobacillus*) have a higher count in Saliva of both hyperthyroid and hypothyroid patients compared with the control group,

Keywords*: Thyroid disease. C.albicans, Lactobacillus*. tsh.ft3

Introduction:

The thyroid gland synthesizes thyroid hormones and is the most significant organ specialized for endocrine function in the human body (Aboud, 2011). Thyroid diseases occur worldwide, but the incidence of different pathologies varies depending on factors such as iodine deficiency or replacement (Sulaiman et al, 2009). The oral microbiome has billions of microorganisms inhabiting the oral cavity (Zheng et al, 2013). Researchers and clinicians are increasingly interested in the accessibility of the microbiome in this site compared to others (Krishnan et al, 2017). The oral microbiome regulates nutrient absorption, substance metabolism, and immune responses (Gao et al , 2018).

The typical oral microbiome includes streptococcus mutans, lactobacillus, candida, Staphylococcus, and Porphyromonas gingivalis (Dzidic et al, 2018). Healthy individuals from various countries have similar oral microbiota compositions (Baker et al, 2017). Different bacterial communities may be found in saliva (Al-Saad , abd Burghal and Al-Maqtoofi 2023). Saliva contains organic and inorganic ions (Al-Mahmood et al, 2019). Saliva has essential functions in the oral cavity, including maintaining a moist oral mucosa that is less susceptible to abrasion, neutralizing acids or bases, and protecting against demineralization (Fathallh and Mahmood, 2020). Saliva contains serum-derived components; systemic inflammatory diseases may alter the levels of some salivary indicators (Nsaif and Hassan 2023).

Infectious thyroiditis is usually caused by a bacterial infection, which can be caused by either a Gram-positive or Gram-negative organism from the oropharynx. Saliva flow, composition, buffering capacity, tooth location, enamel surface features, and the colonization of cariogenic bacteria all contribute to tooth decay. It is important to note that these factors are subject to environmental changes (Belstrøm, 2020). Caries are a common lifelong oral disease with varying susceptibility (Jasem and Mahmood, 2023).

Acute infectious thyroiditis caused by mycobacteria or fungi is rare and usually affects only immunocompromised individuals (Belstrøm, 2020). Lactobacilli are rod-shaped, fermentative, Gram-positive, facultative anaerobic, or microaerophilic organography that plays varied roles in human health (Khalil, 2015). Lactobacilli are a type of lactic acid bacteria that form the central part of this group. These bacteria produce lactic acid and obtain energy through the fermentation of glucose, lactose, and other sugars, producing lactate through homofermentative metabolism. Approximately 85-90% of the sugar is converted into lactic acid (Cannon et al, 2005) (Winn et al, 2006). However, some heterofermentative lactobacilli produce alcohol in addition to lactic acid from sugars (Altermann et al , 2005). This mechanism inhibits the growth of other organisms, favoring lactobacilli in low-pH environments by producing acid (Azcarate-Peril et al, 2004) (Claesson et al,2007). Lactobacilli significantly form dental caries, adhering to the tooth and making acid from sucrose dietary (Al-Ezzi et al ,2018).

Unlike other oral bacteria native to the region, Lactobacilli are present in the mouth in limited numbers or are often undetectable. Due to their association with tooth decay, much research has been undertaken to comprehend the factors that control their presence in the mouth (Azcarate-Peril et al, 2004). Caries occur when cariogenic bacteria, such as Streptococcus and Lactobacillus, produce a weak acid due to the fermentation process of carbohydrates. This process leads to a decrease in local pH below the critical value, which in turn causes demineralization of the tooth surface (Fathallh and Mahmood, 2021). The increased incidence of caries is due to low salivary pH (reduced buffering capacity) and low salivary flow rate (Al-Anbari and AL-Ani ,2021).

Candida is a type of yeast in the human intestines and mouth. It performs an essential function by aiding digestion and nutrient absorption. However, a small amount of *candida* is the only acceptable level in the body under normal circumstances. Various strains of candida can lead to infections in the human body (Walker and White, 2017) (Molero et al, 1998), but the most common is candida albicans. Under normal conditions, this type of *candida* is an essential member of the normal gut flora. However, it can become overgrown when conditions allow, making it transition to an opportunistic pathogen. Yeast infections can occur in various parts of the body, including the gut, mouth, nasal cavity, vagina, and rectum. In rare cases, candida overgrowth may spread into the bloodstream, reaching the brain, heart, liver, spleen, bones, muscles, joints, and eyes. Candidiasis, another term for yeast overgrowth, may cause many symptoms. However, little evidence supports many of these symptoms now (Kornitzer,2019). People who have yeast overgrowth in common areas like the mouth and vagina have burning and itching in the affected areas. Often, you can also see evidence of white overgrowth (Azcarate-Peril et al, 2004). *Candida* species are typically found as part of the normal flora on the skin, in the oral cavity, in the intestinal tract, and the vagina of many individuals (Ibrahim and Dabbagh, 2005).

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C. albicans (fungus) are eukaryotic organisms that can come in the form of yeasts (round fungi), molds (filamentous fungi), or a combination of the two (dimorphic fungi). A common fungal infection that affects the mucosa of the mouth is oral candidiasis. The *C. albicans* yeast that causes these sores. *C. albicans* is a normal oral microbiota component; approximately 30% to 50% of people carry this bacterium. The rate of carriage rises with the patient's age. Candida species can be found in the oral cavity in various forms (Azcarate-Peril et al, 2004). Candida albicans is a fungus that is found all over the world. It's been found in dirt, animals, hospitals, inanimate items, and food. (Terézhalmy and Huber, 2011). Although *C. albicans* can cause mucous cutaneous candidiasis in both immunocompetent and immunodeficient individuals, which can develop invasive candidiasis, such as candidemia /systemic illness, is only found in highly immunocompromised people (Terézhalmy and Huber, 2011). *C. albicans* has a group of proteins called adhesions. Adhesions allow the fungus to stick to other fungi, surfaces, microorganisms, and host cells (Ali et al , 2015).

material and methods:

2.1 patients group:

This case-control study was conducted during the period from January 2023 to May 2023 in Baghdad Teaching Hospital samples collected as saliva and serum were taken from eighty-seven patients with thyroid disorders (29 having hypothyroidism and 29 hyperthyroidism condition compared with

2.3 control group:

29 normal healthy subject as control) will be enrolled in this study. There will be special case sheet to obtain information about name, age and sex (male & female). The inclusion criteria for patients included in this study were that they had been diagnosed with thyroid dysfunction for at least six months. The exclusion criteria included any systemic diseases, medications or therapies for chronic diseases, adverse habits like tobacco use, and past periodontal treatments—additionally, pregnant women.

2.3 collection of saliva

To collect the saliva sample, the subject was asked to refrain from eating or drinking for three hours before the procedure. Saliva was organized early in the morning, between 8 and 10 am. The subjects were instructed to rinse their mouth with distilled water for one minute and then relax for five minutes before starting the collection. The subjects were asked to spit their saliva into sterilized cups with graduations, and a volume of 2-3 ml was collected. Then 0.1 ml of saliva was taken by micropipette to make serial dilution for microbial counting, and culture on Rogosa agar for lactobacilli, sabouraud's dextrose agar for *C. albicans*

The 3ml of blood, which is aseptically drawn by venipuncture, after clotting and centrifugation at 3000rpm for 10 min, the serum sample was used for the detection and quantitative determination of human T3, T4, and TSH (Roche, Germany) in serum using cobas e411 technique.

2.4 Statistical Analysis:

The study's results were analyzed using SPSS version 22.0, with various statistical data analysis approaches. Kruskal-Wallis H will compare variables among groups. Mann-Whitney U tests significant differences between groups. Spearman's rank correlation coefficient test for a relationship between variables in each group. Contingency coefficients (C.C.) measure the association between nominal variables. Chi-square test to determine the significant relationship between variables. One-Sample Kolmogorov-Smirnov: compare observed and theoretical distributions. The binomial test distributed two categories on a nominal/ordinal scale, with no restricted expected outcomes at 50%.

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Results and discussion:

Table (1) summarizes salivary flow rate(SFR) statistics by study groups, including mean values, standard deviation, standard error of mean values, 95% confidence interval, and minimum/maximum extreme values.

Table (1): Descriptive Statistics of salivary flow rate (SFR) for study groups

Marker	Group	No.	Mean	SD	SE	95% C.I. for Mean		Min.	Max.
						L.b.	U.b.		
SFR	Control	29	0.502	0.118	0.022	0.458	0.547	0.250	0.660
	Hyperthyroid	29	0.340	0.130	0.025	0.290	0.391	0.150	0.510
	Hypothyroid	29	0.463	0.121	0.023	0.417	0.509	0.300	0.660

Regarding salivary flow rate, results show a lower mean value was recorded in the "Hyperthyroid" patients' group and "Hypothyroid" patients with the second-ordered mean value. In contrast, the healthy group showed high mean values, which were within the normal range, and according to 95% confidence intervals for the population sampling estimates mean values, results showed that patient groups had disjoint intervals, which reflects the true of differentiated readings among patient's groups in light of studied marker. Based on the current findings, further testing the alternative statistical hypothesis, which suggests that at least two groups differ in their mean values, is recommended. Table (2) shows that the Least Significant Difference (LSD) test is the appropriate method for this case, assuming that the groups being studied have equal variances.

Table (2): Probable pair's comparisons for all studied groups

Group	Group	Sig.	C.S. (*)
Control	Hyperthyroid	0.000	HS
	Hypothyroid	0.224	NS
Hyperthyroid	Hypothyroid	0.000	HS

(*) HS: Highly Sig. at $P<0.01$; NS: Non Sig. at $P>0.05$; Testing based on LSD test.

Results show that significant differences at $P<0.01$ are accounted for between hyperthyroid patients and control groups concerning SFR, as well as between patient's groups, while no significant differences at $P>0.05$ are accounted for between hypothyroid patients and control groups,

Table (3) shows the Kruskal Wallis test's statistic for testing differences regarding microbial count among studied groups.

Table (3): Kruskal Wallis test for testing difference's in microbial cell counting among study groups.

Test Statistic	Microbial Types	*C. albicanis*	*Lactobacillus*
	Statistics		
Kruskal Wallis	Chi-Square	39.306	8.356
	d.f.	2	2
	Asymp. Sig.	0.000	0.015
C.S. (*)		HS	S

(*) HS: Highly Sig. at $P<0.01$; S: Sig. at $P<0.05$; NS: Non Sig. at $P>0.05$.

Results indicating that significant differences in at least at $P<0.05$ were accounted for among studied groups concerning microbial types, as illustrated in table (4) by applying (The Mann-Whitney-U) test, taking into consideration the correction of the significant levels.

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Table (4): Mann-Whitney-U test for comparing all probable combinations of studied groups concerning Microbial types

Combination (*)	Groups Mann-Whitney U test	C. albicanis	Lactobacillus
I X II	Z-value	-5.719	-2.458
	Asymp. Sig. (2-tailed)	0.000	0.014
	C.S. (**)	HS	S
I X III	Z-value	-5.003	-2.711
	Asymp. Sig. (2-tailed)	0.000	0.007
	C.S. (**)	HS	S
II XIII	Z-value	-0.980	-0.444
	Asymp. Sig. (2-tailed)	0.327	0.657
	C.S. (**)	NS	NS

(*) I: Control (Healthy Group); II: Hyperthyroid (Disease Group); III: Hypothyroid (Disease Group).

Significant at level of 0.05 is [(0.05/3)=0.0167], and highly significant at P<0.01 is [(0.01/3)=0.003], since 3 combinations are accounted independently.

For comparing between hyperthyroid and control groups, results show that significant differences are accounted in at least at P<0.05 concerning C. albicans and Lactobacillus colony count; for comparing between hypothyroid and control groups, results show that significant differences are accounted in at least at P<0.05 concerning colony count of both *C. albicanis*, *Lactobacillus* of microbial types.

Various research studies have stated the association of salivary function with numerous systemic illnesses. There is a strong relationship between salivary function and joint diseases like thyroid dysfunction, which is one of the most common endocrine disorders worldwide; results show that significant differences at P<0.01 are accounted for between hyperthyroid patients and control groups concerning SFR, as well as between patient's groups, while no significant different at P>0.05 are accounted between hypothyroid patients and controlled groups, that SFR marker is too sensitive due to hyperthyroid patients, the present results agree with previous research. The study found a decrease in SFR in the study group compared to the control group. A different research (Al-Rubbaey. 2010). Found that people with thyroid dysfunction have less saliva flow than healthy individuals. The statistical analysis determined that these differences were highly significant (Azcarate-Peril et al, 2004). This conflicts with a study conducted by (Al-Naif and Al-Aswad 2013), which found a decrease in SFR among patients with hyperthyroidism (Al-Naif and Al-Aswad 2013). Reduced salivary flow correlates with a decreased buffering capacity and impairs oral sugar clearance, increasing the risk of severe dental caries in individuals with thyroid dysfunction (Turner and Ship, 2007). Research studies show that dry mouth can occur with various thyroid conditions, although it is most often associated with hypothyroidism, which disagrees with the previous research (Agha-Hosseini et al, 2016). Current results also show that significant differences are accounted in at least at P<0.05 concerning colony count of C. Albicans and Lactobacillus in saliva; for comparing between hypothyroid and control groups, results show that significant differences are accounted in at least at P<0.05 concerning count of both *C. Albicans*, *Lactobacillus*. These results agree with previous research that showed thyroid dysfunction increases the species variety and the quantitative counts of oral microbial flora (Shcherba et al ,2020). According to previous research, *Lactobacillaceae* frequently decreases in hypothyroid and hyperthyroid cases. On the other hand, recent research shows that *Lactobacillus* supplements improve thyroid function. Increased thyroid mass, free T4, and physical indicators like more energetic behavior. This effect is thought to be triggered by interleukin-10, which enhances T-regulatory cells (Virili et al, 2018). Relatively sparse research has been conducted on the correlation between thyroid disease and microbiota (Lerner et al , 2017). One possible reason for the lack of studies investigating the thyroid-gut axis in the last decade is the distant location of

ISSN (Paper)-1994-697X (Online)-2706-722X

the thyroid gland. However, recent advancements in microbial research and microbiome assays have made such studies possible. Recent studies have shown that microbiota, which refers to microorganisms living inside our bodies, plays a crucial role in developing and progressing thyroid diseases. This can happen in several ways. For example, the microbiota can affect thyroid function by absorbing essential micronutrients for thyroid health (Knezevic et al, 2020). Additionally, the metabolic enzymes produced by the microbiota can regulate iodothyronine or metabolism, which can impact thyroid hormone balance (Virili and Centanni, 2017). Lastly, the microbiota can interact with the immune cells and cytokines in the body to regulate thyroid immunity (Kohling et al, 2017). The thyroid gland needs iodine as a micronutrient to produce thyroid hormones. Iodine is absorbed through the gastrointestinal tract and transferred to the thyroid gland, with trillions of microorganisms playing a critical role in regulating iodine metabolism. Recent research shows that LPS can cause dysregulation of thyroid homeostasis through essential mechanisms. Firstly, LPS directly affects thyroid cells by increasing the expression of thyroid-stimulating hormone (TSH) and stimulated thyroglobulin (Tg) (Nicola et al ,2010) (Velez et al , 2006).

Activation of nuclear factor kappa-B (NF-κB) is regulated by LPS through toll-like receptor 4 (TLR-4) on thyroid cells, which affects thyroid cell function (Nicola et al , 2008). In the human body, the thyroid gland contains higher concentrations of selenium than any other tissue. This mineral and iodine can negatively impact thyroid homeostasis (Duntas,2015). Selenium exerts its biological function through selenoproteins like glutathione peroxidase and deiodinase, primarily in thyroid hormone metabolism (Zimmermann and Kohrle, 2002). Interestingly, the microbiota can successfully lower the requirement for levothyroxine (L-T4) and positively impact thyroid hormone homeostasis. The effect of a probiotic mixture combining *Lactobacillus* and Bifidobacterium on L-T4 in patients with hypothyroidism was assessed in a study by Spaggiari et al. By drastically lowering the need for L-T4, the probiotic cocktail helped to prevent variations in serum thyroid hormone levels (Spaggiari et al, 2017). Yao et al. reported similar results, showing a correlation between L-T4 dose and microbiota for stable TSH levels (Yao et al, 2020). This conflicts with prior studies showing decreased Lactobacillus in hyperthyroid patients (Zhou et al, 2014).

The most prevalent place to find candidiasis, a fungal infection from Candida species, is in the oral cavity. In the past, 35–80% of people were considered oral Candida carriers. On the other hand, a new study using molecular identification techniques indicates that Candida spp. Constitute a standard component of the oral flora in all humans (Peters et al ,2017). The most prevalent species in both healthy and diseased lips is Candida albicans. It is thought to be found in more than 80% of fungal isolates from the mouth. Other Candida species types, known as non-albicans Candida species, can also be found in the mouth. These include *C. dubliniensis, C. glabrata, C. kruse, C. parapsilosis, and C. tropicalis* (46, 48, 49, 50). Various factors, such as systemic, hereditary, local and environmental, can lead to disturbances in the balance of the mouth. This can result in the normal bacteria being replaced by harmful pathogens and opportunistic infections. These changes can cause an overgrowth of Candida or alter how its virulence factors are expressed (Lewis and Williams, 2017) (Arya, Rafiq ,(2023). The most frequent local factors that can lead to candidiasis aremobile prosthetic replacements, poor oral hygiene, orthodontic appliance obturators, smoking, dry mouth (xerostomia), and steroid inhalers. A diet that is high in carbohydrates and endocrinopathies such as diabetes, hypothyroidism, autoimmune diseases, HIV, and primary immunodeficiency can also increase the risk of developing candidiasis (Zdanavičienė et al,2017) (Serrano et al, 2020)

4-conclusion :This study concluded that salivary flow rate (SFR) is too sensitive due to hyperthyroid patients, and *C. Albicanis* and *Lactobacillus* have a higher count in the saliva of both hyperthyroid and hypothyroid patients than the control group.

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