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Research Article

Development and in Vitro Characterization of Nanoemulsion and Nanoemulsion Based Gel Containing Artemisia Dracunculus Ethanol Extract

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ABSTRACT:

Tarragon, or Artemisia dracunculus, is a member of the Asteraceae family that grows wild in Eastern Anatolia of Turkey. According to previously published studies, Artemisia dracunculus extracts possess antibacterial, antifungal, antioxidant and anti-inflammatory effects. Thus, these extracts can be used to heal wounds. Nanoemulsion (NE) is a suitable dosage form for the application of active substances/compounds via the skin. The aim of this study is to develop and in vitro characterize NE and NE-based gel (NEG) formulations containing Artemisia dracunculus ethanol extract.

Methods: Extract-containing (E-NE) or blank (B-NE) NE formulations were prepared using ethyl oleate, Lipoid S100, Tween 80, Pluronic F127, DMSO, and ultrapure water. NaCMC was added to NE formulations to obtain NE-based gels. The droplet size, PDI and zeta potential values of NEs were determined; pH measurement, FT-IR and rheological analyzes were also performed for NEs and NEGs.

Results: The droplet size and zeta potential values of B-NE and E-NE were found as 139.13±5.15 nm and 135.59±4.81 nm, (-)27.53±2.05 mV and (-)26.28±3.21 mV, respectively. Also, PDI values of NE formulations were <0.3, indicating monodispersity. The pH values of NEs and NEGs were found in the range of 4.26±0.10 - 6.16±0.03, using suitably for topical application. In addition, NEGs formulations showed a pseudoplastic behavior which is important for the topical application. FT-IR results showed that the extract is completely dissolved in the oil phase of formulations.

Conclusion: The NE and NEG may be useful for the topical application of Artemisia dracunculus ethanol extract.

Keywords: Artemisia dracunculus, extract, nanoemulsion, nanoemulsion-based gel, topical application.

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1. INTRODUCTION

Tarragon, or *Artemisia dracunculus*, is a member of the Asteraceae family that grows wild in Eastern Anatolia of Turkey [1]. *Artemisia dracunculus*, which has its origins in Siberia and Mongolia, can also be found growing naturally throughout Central Asia, Eastern Europe, and the Mediterranean. It has been used for its analgesic, hypnotic, antiepileptic, antipyretic, and anti-inflammatory effects in traditional Asian medicine (especially in Iran, Azerbaijan, India and Pakistan). Besides, Artemisia dracunculus is commonly used to treat skin wounds, allergic rashes, dermatitis, and irritations in Central Asia and Russia.

Some articles emphasized that, *Artemisia dracunculus* extracts can be used to heal wounds due to their antibacterial, antifungal, antioxidant, and anti-inflammatory effects [2,3].

Minda et al. [4] investigated the wound healing activities of some *Artemisia sp.* (*Artemisia annua , Artemisia dracunculus, Artemisia absinthium*). For this purpose, the authors first prepared their ethanol extracts and later showed that these extracts had high antioxidant activity comparable to ascorbic acid by DPPH test. In addition, the wound healing effects of the three ethanol extracts (at 100 µg/mL concentrations) were evaluated on human keratinocyte cells. The obtained results showed that stimulated keratinocyte proliferation and wound closure achieved. On the other hand, in ovo evaluation has shown that these extracts were well tolerated and have anti-irritation properties. The authors stated that ethanol extracts of *Artemisia sp.*, which are rich in polyphenolic compounds, can be a low-cost and safe alternative in wound treatment [4].

NEs are referred to in the literature as mini-emulsions, ultrafine emulsions, submicron emulsions. They are colloidal dispersions of two immiscible phases (water phase and oil phase, in combination with suitable surfactant/s. The droplet sizes of NEs are generally in the range of 100-600 nm, and NEs are kinetically stable systems. In addition, NEs are efficient drug delivery systems for increasing the solubilization of poorly water-soluble drugs. They can be administered via different routes (parenteral, topical, oral, etc.). For topical application, NEs are considered efficient systems that favor drug penetration into skin layers. Their small-sized droplets with high surface area enable distribution homogeneously on the skin [5- 7]. They have a high potential in the treatment of skin diseases and wound healing due to these properties [8].

The penetration of the active compound (essential oils, other lipophilic compounds, etc.) to the deep layers of the skin is significant in the emergence of the expected effect after topical application. Therefore, with NE formulations used, the effectiveness of these active compounds with wound healing properties can be increased due to their increased penetration [8-10]. However, due to its low viscosity, the poor retention on skin and spreadability issue limit the clinical use of NE formulations for topical application. Therefore, nanoemulgel, basically an oil-in-water nanoemulsion-based topical gel formulation, has been proposed as a strategy to overcome this problem [11,12].

The gelling system, which enhances the viscosity of NEs, is prepared using gel-forming agents such as Carbopol, chitosan, hydroxyl propyl methyl cellulose [4, 11-13]. The aim of this study is to develop and in vitro characterize NE and NEG formulations containing Artemisia dracunculus ethanol extract for topical application.

2. MATERIALS AND METHODS

2. 1. Materials

In this study, ethyl oleate (Merck, Germany), Lipoid S100 (Lipoid, Germany), Tween 80 (Merck, Germany), Pluronic F127 (BASF, Germany), DMSO (Lab-Scan, Ireland) were used. Also, the water was purified by Direct-Q®3 UV water purification system (Millipore, USA).

2.2. Methods

2.2.1. Ethanol Extract Preparation

10 g of the powder of dried leaves of *Artemisia dracunculus* suspended in ethanol (500 mL) was kept in horizontally shaking water bath at 50°C for 72 hours. This mixture was filtered every 24 hours, and extraction was continued by adding ethanol. The filtrates obtained were combined and the organic solvent was evaporated under reduced pressure at 50°C. The extract was stored for further studies in a refrigerator (2-8 °C) in an airtight bottle and protected from light.

2.2.2. Artemisia dracunculus Ethanol Extract-Containing Formulations Preparation

A high energy method was used for the preparation of B-NE and E-NE formulations. Briefly, oil (ethyl oleate and Lipoid S100) and water (Tween 80, Pluronic F127 and ultra-pure water) phases were prepared separately. The extract was dissolved in DMSO and then added to the oil phase. The aqueous phase was added to the oil phase under magnetic stirring to obtainthe coarse emulsion. Later, this emulsion was homogenized at 25000 rpm for 5 min using a T10 Ultraturrax (IKA, Germany), and then ultrasonicated for 15 min (40% power; Sonoplus HD 2070; Bandelin Electronics, Germany) to ensure nano-sized droplets. B-NEs were prepared according to the above procedure without the extract. NaCMC (1%) was added to NEs and stirred overnight at room temperature on a magnetic stirrer to obtain NE-based gels (NEGs).

2.2.3. Formulations Characterization

2.2.3.1. Droplet Size, Polydispersity Index (PDI), Zeta Potential and Morphological Analysis

Zetasizer Nano ZSP (Malvern Ins. Ltd, UK) was used to determine the mean droplet size, polydispersity index (PDI), and zeta potential values of the NE formulations. In addition, the E-NE was imaged using TEM (Hitachi HighTech HT7700, Japan). After dilution 100 times, the E-NE was placed on a copper grid and dried at room temperature over 24 h. Images of the grids were then obtained at 120 kV.

2.2.3.2. pH

The pH values of NEs and NEGs were determined at room temperature using a pH meter (Thermo Scientific, Orion 3 Star, USA).

2.2.3.3. Rheology

Brookfield RV DV2T cone and plate viscometer was used to measure the viscosity of the NEs and NEGs at room temperature.

2.2.3.4. FT-IR Analysis

FT-IR analyzes (4000-400 cm-1) of the extract, NEs, and NEGs were performed using Fourier transform infrared spectroscopy (Shimadzu IRSprit-T).

2.2.3.5. Statistical analyses

Statistical analyses were performed using SPSS Statistics Version 22.0 (SPSS Inc., Chicago, USA) software. The "Independent t- test" was used to compare the differences between two independent samples. The significance of the difference between test results was determined and the difference was accepted to be significant if $p < 0.05$.

3. RESULTS & DISCUSSION

3.1. Droplet Size, PDI, Zeta Potential and Morphological Analysis

The droplet size, PDI and zeta potential values of the NE formulations are given in Table 1. Statistical comparison of droplet sizes of B-NE and E-NE showed that the droplet size did not change with the addition of the extract to the formulation ($p>0.05$). Zeta potential value, which is a significant parameter for the physical stability of colloidal dispersions, is considered sufficient for stability if it is ±20 mV and above in the presence of both electrostatic and steric barriers [14]. There was no significant difference between the zeta potential values of B-NEs and E-NEs ($p>0.05$). Furthermore, PDI values of NEs were less than 0.3, indicating monodispersity (15).

Table 1. The mean droplet size, PDI and zeta potential values of NEs.

Formulation	Droplet size (nm)	PDI	Zeta Potential (mV)
B-NE	139.13±5.15	0.214±0.023	-27.53±2.05
E-NE	135.59±4.81	0.238±0.022	-26.28±3.21

The TEM image of E-NE is shown in Figure 1. Figure 1 shows that the droplets of NE were approximately spherical.

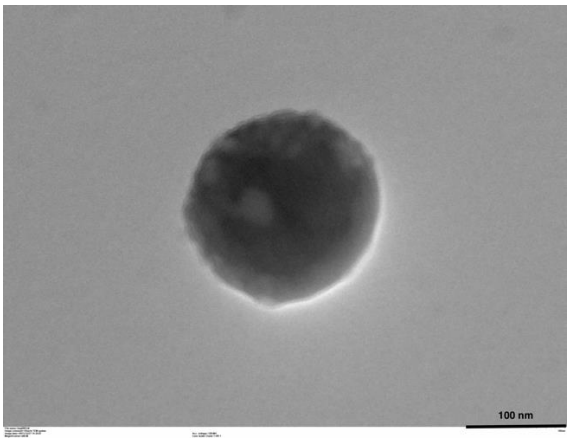

Figure 1. The TEM image of E-NE.

3.2. pH

It was determined that the mean pH values of the B-NE and E-NE formulations were 5.52±0.06 and 4.26±0.10, respectively, and the pH value of the NE formulation decreased in the presence of the extract ($p<0.05$). In addition, pH values of B-NEG and E-NEG formulations were 6.16±0.03 and 5.84±0.07, respectively, and an increase in pH

values after gelation was observed ($p<0.05$). Formulations with very high or very low pH values cause irritation when applied to the skin. Human skin pH is generally acidic, but the pH ranges widely from 4.0 to 7.0 [15, 16]. The pH values of the NE and NEG formulations prepared in our study are suitable for application to the skin without causing irritation.

3.3. Rheology

For topical formulation, another important parameter is Viscosity related to the applicability of the formulations. The viscosity values of NEs and NEGs are shown in Figure 3. Flow behaviors of NEs and NEGs were described using "power-law the flow behavior index (n) was calculated. While n is 1 for Newtonian systems, it is <1 for shear-thinning systems. In our study, the n values of the NE formulations were very close to 1 (0.9997 for B-NE and 0.9998 for E-NE), and these formulations exhibited Newtonian flow. On the other hand, the n values of the NEG formulations were less than one (0.7088 for B-NEG and 0.7099 for E-NEG), and they showed pseudoplastic flow. The shear-thinning flow is significant for NEG formulations applied to the skin because a thick product thins under shear stress and can spread smoothly over the skin [5,17].

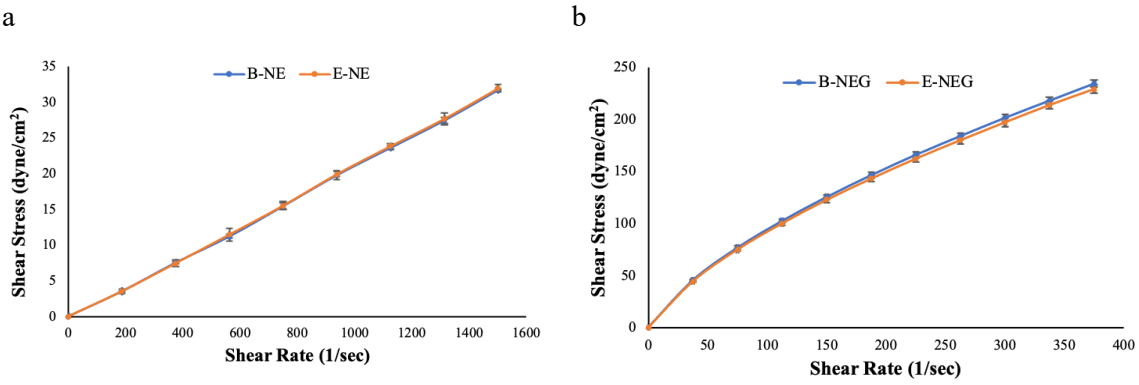

Figure 2. Flow curves of NEs (a) and NEGs (b).

3.4. FT-IR Analysis

FT-IR spectra of the extract, NE, and NEG formulations were taken to determine the structural properties of the extract and the interactions between the extract and other formulation components. The FT-IR spectra of blank formulations (B-NE or B-NEG) and extract-containing formulations (E-NE or E-NEG) were similar (Figure 3). The characteristic peaks of the extract were not observed in the FT-IR spectra of E-NE and E-NEG (Figure 3). Thus, it was confirmed that the extract is dispersed in the formulations at the molecular level [5, 18].

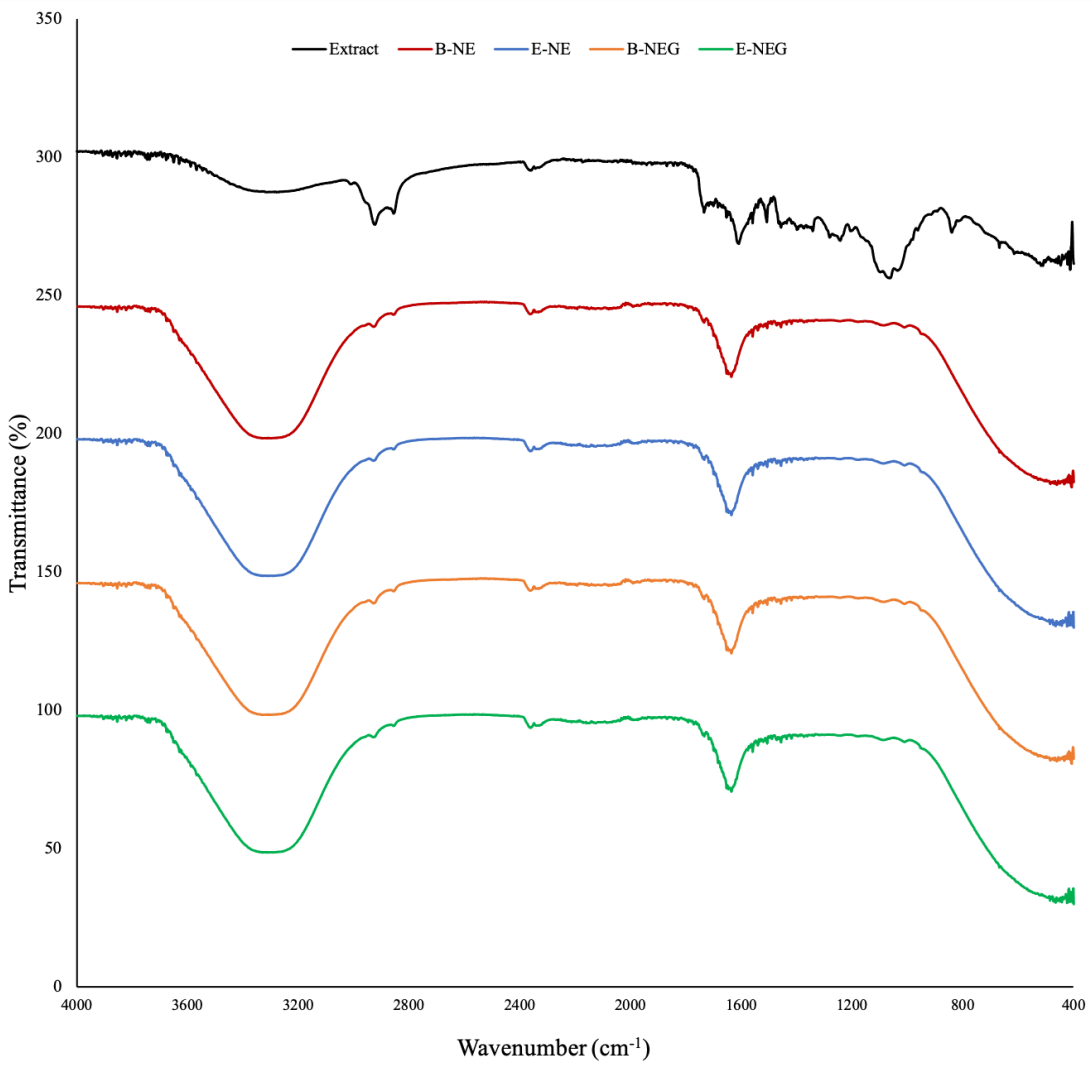

Figure 3. FT-IR spectra of the extract, NEs and NEGs.

4. CONCLUSION

In this study, NE and NEG formulations were prepared successfully and in vitro characterized. The NE and NEG may be useful for the topical application of *Artemisia dracunculus* ethanol extract.

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Conflict of Interest

Author has no personal financial or non-financial interests.

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Case Analysis

A Case Report of a Nurse Who Received the Covid-19 Vaccine

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ABSTRACT:

Tarragon, or Artemisia dracunculus, is a member of the Asteraceae family that grows wild in Eastern Anatolia of Turkey. According to previously published studies, Artemisia dracunculus extracts possess antibacterial, antifungal, antioxidant and anti-inflammatory effects. Thus, these extracts can be used to heal wounds. Nanoemulsion (NE) is a suitable dosage form for the application of active substances/compounds via the skin. The aim of this study is to develop and in vitro characterize NE and NE

Throughout history, societies have struggled with infectious diseases. It is important to prevent the spread of infectious diseases. Vaccination is the major tool of defense that prevents the rapid spread of infectious diseases in society. Therefore, the successful implementation of the vaccination program during the pandemic is very important. A variety of vaccines has been available for Covid-19, one of the biggest pandemics of the last century. This study was conducted to determine the side effects of Sinovac, one of the COVID -19 vaccines, in humans. The case presented is a 40-year-old male patient who had a blood pressure of 190/110 mmHg and a heart rate of 140 beats per minute (bpm) measured 10 minutes after vaccination on January 15, 2021. Describing dizziness, palpitations, and darkening of the eyes, the patient stated that he had never had a cardiac problem before. He applied to the emergency department of Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Education Research Hospital. Sinus tachycardia was diagnosed as a result of electrocardiography (ECG). For 20 days, blood pressure ranged between 150/90 mmHg and 140/90 mmHg while the average heart rate was generally measured to be 140 bpm. He used Metoprolol 25 mg tablet for 20 days. According to the findings of this study, Sinovac has an effect on blood pressure. However, it is recommended that larger-scale studies be conducted.

Keywords *:* Adverse effects, COVID-19, health personnel, vaccine, vaccine hesitancy.

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1. INTRODUCTION

Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus [1]. COVID-19 has caused 6,063,809 deaths as of March, 13 2022 [2]. The World Health Organization (WHO) has reported that vaccinating the global population against COVID-

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19 is the only way to control the coronavirus [3]. In their fight against COVID-19, many countries have started developing vaccines to provide immunity against the virus and stop transmission. Vaccines are biological preparations that provide active acquired immunity to a particular infectious disease. They do so by stimulating an immune response to an antigen, a molecule found on the pathogen [4]. The Turkish Medical Devices Agency granted emergency use authorization to the vaccine on January 13, 2020 [5]. In Turkey, the Sinovac CoronaVac was firstly administered to healthcare workers on January 14, 2021 [6]. The most commonly reported side effects were injection site pain, headache, fatigue as well as others including injection site swelling, itching, myalgia, nausea, diarrhea, arthralgia, cough and chills [7]. When the first dose of Coronavac vaccine was administered, tachycardia was reported within 10 minutes and one hour [8]. This study presents the case report of a nurse who experienced tachycardia after receiving the Coronavac vaccine.

2. CASE REPORT

The 40-year-old male patient with no allergic or chronic diseases is married with one child and has been working as a nurse for 14 years. He has been smoking for 20 years and smokes 15 cigarettes a day. Before vaccination, his blood pressure was generally around 120/80 mmHg. Within 10 minutes following the vaccination of the nurse on January 15, 2021, her blood pressure was 190/110 and her heart rate was 140. He reported dizziness, palpitations, and darkening of the eyes, stating that he had never had a cardiac problem before. He applied to the Emergency Service of the Hospital for Cardiovascular Surgery. Sinus tachycardia was diagnosed as a result of electrocardiography (ECG). Despite taking Metoprolol 25 mg oral tablets for 20 days after vaccination, the evaluation revealed a blood pressure of 150/90 mmHg-140/90 mmHg and an overall heart rate of 140 bpm. Within 21 days post-vaccination, the evaluation revealed a blood pressure of 90/60 mmHg and an average heart rate of 80 bpm. Following this period, he has not experienced a health problem. The patient has no history of allergic reactions to vaccines and no family history of COVID-19. He is not planning to have the second dose of the vaccine due to his health problems. Furthermore, the patient does not find the COVID-19 vaccines safe.

3. DISCUSSION

CoronaVac is a vaccine developed using the conventional method, by growing the SARS-CoV-2 virus and then inactivating it in a laboratory environment [9]. Inactivated vaccines are made from microorganisms that have been killed through physical or chemical processes, eliminating their disease-causing capacity. When they are injected into the body, they only produce antibodies against the surface antigens of the virus. One of the undesirable side effects of vaccination is that it can cause hypersensitivity [10]. Factors related to the host and the health system affect the response generated by the vaccines. Among the factors related with the vaccine are its type (live, inactivated, protein, polysaccharide, conjugate), route of administration (injection, mucosal route), dose and

adjuvant content. Factors related with the host include age, genetic factors, concomitant diseases, medications used, nutritional status and exposure to disease agent while the health system related factors are the cold chain, the vaccination scheme and the competency of the healthcare professional who prepares and administers the vaccine [11].

Tachycardia is defined as an atrial and/or ventricular rate of >100 bpm. It may be of importance as it can cause myocardial ischemia, hypotension, low cardiac output, peripheral hypoperfusion, severe symptoms (chest pain, weakness, syncope, lightheadedness), cardiomyopathy, cardiac arrest and even death [12]. In sinus tachycardia, the heart rate is usually between 100 and 150 beats/minute [13]. Symptoms such as palpitations, dyspnea, chest discomfort, and lightheadedness may be observed [14]. In hypertension, the diastolic blood pressure is measured as ≥90 mm Hg while the systolic blood pressure is ≥140 mm Hg [15].

Tachycardia is a predictor of both hypertension and cardiovascular risk [16]. According to numerous studies, future hypertension has been observed in individuals with tachycardia [16,17]. Beta blockers are used to treat tachycardia as they reduce heart rate, heart contractility, atrioventricular conduction, and ectopic activity [18].

In Hong Kong, a 61-year-old man has been hospitalized 11 days following the administration of the Sinovac Covid-19 vaccine due to chest pain and left shoulder pain. The patient was transferred to the intensive care unit and suffered from tachycardia and cardiac arrest during treatment. He died 12 days after vaccination. The man was said to be a chronic smoker [19].

In Turkey, An 85-year-old female patient with obesity and coronary artery disease was admitted to the emergency department with dyspnea 11 days after the second dose of CoronaVac® administration. Despite the oxygen therapy, the patient continued suffering from tachycardia and tachypnea leading to intubation in the intensive care unit. It was reported that the patient died on the 11th day of her follow-up [20].

Tachycardia was observed in two female patients out of 3354 healthcare workers who were vaccinated with the first dose. The first patient was 28 years old and had chronic urticaria. She was under regular antihistamine treatment at the time of vaccination. Within 1 hour following the administration, the patient reported itchy hives over her chest area and tachycardia which did not require any intervention and resolved in a short time The patient did not prefer to have the second dose of the vaccine. The second patient, who was 29 years old, had a history of allergy to several muscle relaxants. She reported urticaria and tachycardia ten minutes following the administration. The patient was admitted to the level 1 intensive care unit, where she received 45.5 mg of intravenous diphenhydramine and 80 mg of methylprednisolone. She recovered in 3 hours. The second dose of the vaccine was administered in graded doses under observation and no symptoms were observed [8].

Increased blood pressure has been continuously reported as one of the most important adverse reactions to all vaccine platforms. Thus, monitoring blood pressure has become a crucial point to be taken into consideration regarding the COVID-19 vaccination program. [21]. Since the resting heart rate is a prognostic factor regarding cardiovascular morbidity or fatal events in many conditions including hypertension, it is important to perform routine measurements together with blood pressure measurements [16,22].

More than 10.9 billion people in 184 countries have been vaccinated so far [23]. The safety regulations of the vaccine is crucial as people are hesitant to get the vaccine [24]. Vaccination is very important for public health as it reduces mortality and morbidity from infection [25]. Health professionals are influential in terms of creating behavioral changes in society [26]. Awareness campaigns should be launched to fight misinformation regarding vaccines and build trust in public so that they would demand vaccination for their own health. This will not only ensure the safety and efficacy of the vaccine but also provide transparency regarding the vaccine production process [27].

4. CONCLUSION

Although vaccines are very important in the prevention of communicable diseases, they can lead to hesitancy and anti-vaccination attitudes. The reasons why vaccines may not be accepted or rejected are based on vaccine safety and side effects. Scientifically unproven sources of information may result in the development of false beliefs in society. Targeted campaigns to provide the public with evidence-based information on vaccine side effects and safety may prevent vaccine opposition. Designing education plans and strategies to determine the reasons for vaccine refusal is of utmost importance for public health.

The incidence of tachycardia after Sinovac CoronaVac vaccination remains unclear; however, it indicates the need for caution regarding adverse cardiovascular effects. Nevertheless, it is a rare side effect. Since the COVID-19 vaccine is important for the immunity of the community, patients with heart diseases should not be prevented from vaccination. Reporting the vaccine-related side effects is important for public health. The purpose of this case report is to raise awareness among healthcare professionals regarding a potential rare side effect that may be associated with the COVID-19 vaccine.

Conflict of Interest

Author has no personal financial or non-financial interests.

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Review

Similarity in Immune Response Between Sars-Cov-2 Infection and Autoimmune Diseases

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ABSTRACT:

Autoimmune diseases are characterized by persistent inflammatory reactions that lead to organ damage and dysfunction in various organs due to the presence of autoantibodies and a deregulated immune system. Disorders of the immune system are also present in COVID-19. Autoantibody production is an important feature of autoimmune diseases. However, the underlying mechanisms are complex and still not fully understood. Infectious pathogens are believed to mimic the molecular mechanisms that trigger autoimmune diseases. The viral infection can impair immunological tolerance by exposure of antigen epitopes that elicit cross-reactive antibodies. There are numerous studies showing antigenic mimicry between viral and human proteins. Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human immunodeficiency virus (HIV) are viruses that inhibit these autoimmune abilities. Similarly, there are numerous studies showing the possibility that patients with SARS-CoV-2, COVID-19 will develop multiple types of autoantibodies and autoimmune diseases. Patients have a tendency to develop more than 15 different types of autoantibodies and more than 10 different autoimmune diseases. COVID-19 has been described along with other autoimmune conditions such as the synthesis of various autoantibodies, Kawasaki disease, anti-phospholipid syndrome, and Guillain-Barre syndrome. Since loss of smell has been described and linked to many autoimmune conditions, it is possible that hyposmia/anosmia in COVID-19 patients is at least partially induced by autoimmune mechanisms. The main mechanisms that may contribute to the development of autoimmunity in the disease are mechanisms: SARS-CoV-2's ability to overstimulate the immune system, induce neutrophil-related cytokine responses and excessive neutrophil extracellular trap formation, and molecular similarity between the host's own components and the virus. In addition, there are potential risks of COVID-19 on new-onset autoimmune diseases such as antiphospholipid syndrome, Guillain-Barré syndrome, Kawasaki disease and others. Recognizing these autoimmune manifestations of COVID-19 is essential in order to properly deal with the ongoing pandemic and its long-term post-pandemic consequences.

Keywords : Autoimmunity, COVID-19, COVID-19 structure, Post COVID, SARS-CoV-2

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1. INTRODUCTION

In December 2019, a new infection called coronavirus disease 2019 (COVID-19) emerged in Wuhan, China, and was officially declared a pandemic by WHO on March 11, 2020 [1]. The disease is caused by the newly defined severe acute respiratory syndrome (SARS)-related coronavirus strain, named SARS-CoV-2 after SARS-CoV that caused the SARS epidemic in 2002 [2]. SARS-CoV-2 belongs to the coronavirus family, which consists of enveloped viruses with a spherical morphology and a single-stranded RNA (ssRNA) genome [3]. Spike glycoproteins (S protein) cross the peplo of the virus and form a crown-like surface [4]. Via the Receptor Binding Domain (RBD) located in the S1 subunit of the S protein, the virus can bind to the host cell receptor Angiotensin Converting Enzyme 2 (ACE2) and invade the cell [5-7]. In most cases, hosts infected with SARS-CoV-2 show flu-like symptoms such as fever, fatigue, and dry cough. Headache, myalgia, sore throat, nausea and diarrhea may also be seen in patients with COVID-19 [8,9]. In severe cases, shortness of breath and hypoxemia occur. In critical cases, the disease progresses rapidly and patients may develop septic shock and multi-organ dysfunction [10]. Therefore, COVID-19 can affect multiple organ systems, including the skin, kidneys, respiratory system, cardiovascular system, digestive system, nervous system, and hematological system [11]. The dysregulated immune response and increased proinflammatory cytokines induced by SARS-CoV-2 contribute to disease pathogenesis and organ damage, which draws attention to immunomodulatory therapy in the treatment of COVID-19 [12]. Drugs used to treat autoimmune diseases are widely used in critical cases of COVID-19 [13]. In addition, some autoantibodies can be detected in patients with COVID-19 [14]. These observations suggest that examining the pathways known to contribute to the pathogenesis of autoimmunity may provide clues to better understand and treat COVID-19.

1.1 Relationship Of Autoimmune Diseases And Covid-19

Autoimmune diseases are characterized by persistent inflammatory reactions that lead to target organ damage and dysfunction due to the presence of autoantibodies and loss of immune tolerance and dysregulated immune system [15]. Infection with SARS-CoV-2 induces immune reactions that may have important implications for the development of vaccine strategies against this virus [16]. T-cell immunity plays a central role in controlling SARS-CoV-2 infection. Antigen-specific CD4 + and CD8 + T cells and neutralizing antibody responses play protective roles against SARS-CoV-2, while impaired adaptive immune responses such as scarcity of naive T cells can lead to poor disease outcomes [17]. In clinical laboratory tests, lymphopenia (lymphocyte count ≤1000) is associated with severe disease in COVID-19 patients and may be a prognostic factor for disease severity and mortality [18-21]. Another notable haemocytological change is neutrophilia and associated excess neutrophil extracellular entrapments parallel to lung injury in severe COVID-19 patients [12]. Therefore, the immune response is a double-edged sword in COVID-19, the consequences of which are affected by the degree of cytokine imbalance and activation of immune cells.

Overproduction and release of proinflammatory cytokines and chemokines can cause severe organ damage, which is also seen in autoimmune diseases in critical situations. Proinflammatory cytokines and chemokines, including interleukin (IL)-1, IL-2, IL-6, IL-8, IL-10, IL-17, IL-18, CXCL10, and CCL2, and chemokines are increased in COVID-19 patients. Expression levels of some of these cytokines, such as IL-10 and IL-18, have been shown to be associated with disease severity [22-25]. Similar to autoimmune diseases, Damage-Associated Molecular Patterns (DAMPs) are also involved in the pathogenesis of COVID-19 and are associated with the disease. Chen et al. [26] revealed that serum S100A8/A9 and HMGB1 levels were significantly increased in patients with severe COVID-19, and a significant increase in two DAMPs was associated with higher mortality.

Activation and infiltration of immune cells are involved in the pathogenesis of organ damage in patients with COVID-19. Macrophage Activation Syndrome (MAS) may be a continuation of the cytokine storm syndrome, which leads to life-threatening complications in COVID-19 [27]. In this case, activated macrophages will produce excessive proinflammatory cytokines, polarize to the inflammatory M1 phenotype, and exhibit cytotoxic dysfunction [28]. Recently, Conti et al. [29] suggested that mast cells activated by SARS-CoV-2 may release histamine to increase IL-1 levels to initiate cytokine storm and exacerbate lung injury. Woodruff et al. [30] found extrafollicular B-cell activation in critically ill patients with COVID-19, similar to that observed in autoimmunity. Moreover, extrafollicular B-cell activation was strongly associated with the production of high concentrations of SARS-CoV-2-specific neutralizing antibodies and poor disease outcome [30]. Peripheral blood B cell subpopulations change during COVID-19. In COVID-19 patients, atypical memory B cells (CD21 lo /CD27 - /CD10 -) were significantly enlarged, while classical memory B cells (CD21 + /CD27 + /CD10 -) were significantly reduced [31]. Analysis of the immune profiles of severe COVID-19 patients revealed that the proportion of mature natural killer (NK) cells increased and the proportion of T-cell numbers decreased [32]. Neutrophil activation and Neutrophil Extracellular Trap production (NETosis) appear to have a pathogenic role in COVID-19, similar to some autoimmune and immune-mediated thromboinflammatory diseases, including lupus, antiphospholipid syndrome, and ANCA-associated vasculitis. Zuo et al. [33] reported that Neutrophil Extracellular Trap (NET) markers were increased in the serum of patients with COVID-19 and were significantly higher in patients requiring mechanical ventilation. In vitro experiments have shown that sera from patients with COVID-19 induce NETosis in normal neutrophils, similar to sera from patients with antiphospholipid syndrome [33, 34]. In severe and critical cases, immunomodulatory drugs and biologic agents targeting proinflammatory cytokines have been administered to contain the robust immune response in COVID-19. Corticosteroids, JAK inhibitors, IL-1 blockade and IL-6 receptor antagonists familiar to rheumatologists have been used to treat patients with COVID-19 [35–38]. The similarities in the immunopathogenesis of COVID-19 and autoimmune diseases are summarized in Table 1.

Table 1. Similarities in the immunopathogenesis of COVID-19 and autoimmune diseases

	COVID-19 immunological features similar to autoimmune diseases	**References**
COVID-19 immunological features similar to autoimmune diseases	Excessive activation of monocytes, macrophages, mast cells and neutrophils. Increasing proportion of mature natural killer (NK) cells.	[12, 27, 29, 32, 33]
Adaptive immune cells	Decreased T-cell numbers, altered B-cell subsets, dysregulation of T cells and B cells.	[17, 30, 31]
Cytokines and chemokines	Increased levels of IL-1, IL-2, IL-6, IL-8, IL-10, IL-17, IL-18, CXCL10, CCL2.	[22-24]
Autoantibodies	ANA, APL, lupus anticoagulant, cold agglutinins, anti-Ro/SSA antibodies, anti-Caspr2 antibody, anti GD1b antibody, anti-MOG antibody	[14, 51-58]
Clinical conditions	Immune-mediated hemolysis, decreased white blood cell count, cytokine storm syndrome, macrophage activation syndrome, a procoagulant state	[25, 28, 57]
Other immunopathogenesis	Increased DAMP levels, molecular mimicry	[26, 46]

1.2. Molecular Mimicry and SARS-CoV-2

Autoantibody production is an important feature of autoimmune diseases. However, the underlying mechanisms are complex and still not fully understood. Molecular mimicry of infectious pathogens is believed to be one of the mechanisms [39]. The viral infection can impair immunological tolerance by exposure of antigen epitopes that elicit cross-reactive antibodies. There are numerous reports of antigenic mimicry between viral and human proteins. Perhaps one of the most established examples of molecular mimicry in autoimmunity is the immune response to Epstein-Barr virus (EBV) in lupus patients [40]. An abnormal immune response to Epstein-Barr virus Nuclear Antigen-1 (EBNA-1) can induce an autoimmune response targeting the Sm and Ro autoantigen systems [41]. Cross-reactivity has also been shown between anti-EBNA-1 antibodies and myelin basic protein in patients with multiple sclerosis [42]. In addition, EBNA-1 shows structural similarity to β synuclein, a brain protein involved in multiple sclerosis, and is predicted to bind HLA class II DR2b (HLA-DRB1∗15:01) [43]. In-silicon analysis revealed that an envelope protein of human endogenous retroviruses (HERV) shares a similar sequence with three myelin proteins that induce an autoimmune response in multiple sclerosis and are predicted to bind to HLA-DRB1~15:01. Basavalingappa et al. [44] showed that Coxsackievirus B3 (CVB3) infection can induce the generation of autoreactive T cells for multiple antigens.

Studies have revealed that some epitopes from SARS-CoV-2 exhibit cross-reactivity with autoantigens. Anand et al. [45] reported that a unique S1/S2 cleavage site in SARS-CoV-2 similarly mimics a FURIN-cleavable peptide on the human epithelial sodium channel α-subunit (ENaC-α) that plays a critical role in airway homeostasis. .

Mimicry between SARS-CoV-2 and three proteins found in the human brainstem pre-Bötzinger Complex (preBötC), DAB1, AIFM, and SURF1, may contribute to respiratory failure in COVID-19 [46]. In addition, SARS-CoV-2 infection can elicit autoimmune responses through molecular mimicry. Marino Gammazza et al. [47] compared viral proteins with human molecular chaperones and suggested that chaperones, most of which are heat shock proteins, may participate in the molecular mimicry phenomenon after SARS-CoV-2 infection. In addition, Lucchese and Flöel [48] compared the viral amino acid sequence to human autoantigens associated with immune-mediated Guillain-Barré syndrome and other autoimmune disease-associated polyneuropathies, and found that peptides embedded in the immunoreactive epitopes of SARS-CoV-2, human heat shock proteins 90 and 60 They showed that they share the same series with. Venkatakrishnan et al. [49] reported 33 different 8-mer/ 9-mer peptides with potential cross-reactivity between SARS-CoV-2 and the human reference proteome; among them, 20 human peptides have not been observed in any previous strain of coronavirus. In addition, four of these human 8-mer/9-mer peptides mimicked by SARS-CoV-2 showed similarity to host pulmonary artery peptides and HLA-B∗40:01, HLA-B∗40:02 and HLA-B∗ It was predicted to connect with 35 : 01 [49]. A recent study analyzed the sharing between hexapeptides that define minimal epitopic sequences of the virus and the human proteome and documented numerous immunoreactive epitopes shared with human proteins [50]. The results of this study imply the possibility of SARS-CoV-2 causing cross-reactivity with host autoantigens and provide clues to possibly explain various clinical manifestations and pathologies involving different organs and systems after SARS-CoV-2 infection.

Autoantibodies known to occur in a number of autoimmune diseases have been identified in patients with COVID-19 (Table 2). Pascolini et al. [14] determined the presence of antinuclear antibodies (ANA), anticytoplasmic neutrophil antibodies (ANCA), and antiantiphospholipid (APL) antibodies in 33 consecutive COVID-19 patients. Results showed that 45% of patients were positive for at least one autoantibody, and patients with positive autoantibodies tended to have a worse prognosis and the significantly higher respiratory rate at presentation. The ANA positive rate was 33%, the positive rate for anticardiolipin antibodies (IgG and/or IgM) was 24%, and the three patients were positive for antiβ2-glycoprotein-I antibodies (IgG and/or IgM) 9%. However, ANCA was negative in all patients [14]. Coagulopathy is a threatening complication of SARS-CoV-2 infection. Recently, a cohort study was conducted at Montefiore Medical Center to evaluate lupus anticoagulant positivity in COVID-19 patients. The researchers found an increased incidence of lupus anticoagulant positivity in COVID-19 patients compared with controls that tested negative by COVID-19 reverse transcriptase-PCR. In addition, there was an increased rate of thrombosis in COVID-19 patients with positive lupus anticoagulant [51]. Amezcua-Guerra et al. [52] also showed a higher frequency of APL antibodies in severe and critical COVID-19 patients, and the presence of APL antibodies was associated with a hyperinflammatory state with pulmonary thromboembolism with

extremely high levels of ferritin, C-reactive protein and IL-6. The data discussed above provide a possible explanation for the hypercoagulable state in severe and critical COVID-19 cases and demonstrate that SARS-CoV-2 can induce autoimmune responses.

Table 2. Autoantibodies detected in COVID-19 patients

Autoantibodies	**Clinical Significance**	**References**
ANA	Poor prognosis and significantly higher respiratory rate	[14]
APL	Poor prognosis and markedly elevated respiratory rate Hyperinflammatory state and possible association with thrombosis and thromboembolism	[14, 52]
Lupus anticoagulant	Higher thrombosis rate	[51]
Cold Agglutinins	Hemolytic anemia. Complex laboratory evaluation and renal replacement therapy	[55, 58]
Anti-Ro/SSA antibodies	Possible association with severe pneumonia	[56]
Anti-CASPR2 antibodies	Uncertain	[54]
Anti-GD1b antibodies	Uncertain	[54]
Anti-MOG antibodies	Uncertain	[53]
Erythrocyte bound antibody	Associated with severity of anemia	[57]

The presence of autoantibodies against contactin-associated protein 2 (anti-Caspr2), ganglioside GD1b (anti-GD1b), and myelin oligodendrocyte glycoprotein (anti-MOG) in COVID-19 patients presenting with neurological symptoms has been shown in case reports or retrospectively [53, 54]. However, the clinical significance of these antibodies remains unclear. In addition, case reports showing the presence of cold agglutinins and autoantibodies against RBC antigens in critically ill patients with COVID-19 [55] and the presence of anti-Ro/SSA antibodies in patients with severe COVID-19 pneumonia have been demonstrated [56]. A study involving 113 samples examined red cell antibodies by direct and indirect antiglobulin testing (DAT or IAT). Positive DAT was found in 46% of COVID-19 patients, which was significantly higher than in non-COVID-19 controls. The presence of red cell membrane-bound immunoglobulins contributes to hemolytic anemia and correlates with the severity of anemia in COVID-19.

1.3. Development Of Autoimmune Diseases After Sars-Cov-2 Infection

Since the SARS-CoV-2 infection can impair immune tolerance and trigger autoimmune responses, it is likely to trigger clinical autoimmunity as well. Indeed, many reports have confirmed the development of autoimmune diseases after SARS-CoV-2 infection.

Cold agglutinin syndrome (CAS) and autoimmune hemolytic anemia have been reported as a complication of COVID-19 [55, 58, 59]. Meanwhile, Guillain--Barré syndrome (GBS) is also emerging as an autoimmune disease that can occur in patients with COVID-19. In most cases of COVID-19, GBS SARS-CoV-2 antibodies are undetectable in the cerebrospinal fluid (CSF). Besides that, Gigli et al. [60] recently reported a case of GBS with a positive test for SARS-CoV-2 antibodies in the CSF [61, 6]. The mechanisms of how SARS-CoV-2 triggers GBS are discussed. However, immune cross-reactivity between epitopes and host antigens may be a possible explanation [62]. Recently, a case of systemic lupus erythematosus has also been reported to be triggered by SARS-CoV-2 [63]. Additional autoimmune diseases caused by SARS-CoV-2 are likely to be reported in the future.

2. CONCLUSION

COVID-19 is a new pandemic with significant global health consequences. Similar to systemic autoimmune diseases, COVID-19 may present with heterogeneous and systemic clinical manifestations. There are similarities in immune response in both disease states, and organ damage in COVID-19 appears to be largely immune-mediated, similar to autoimmune diseases. The SARS-CoV-2 virus can, at least in part, impair the self-tolerance of host antigens through molecular mimicry. The development of autoantibodies and sometimes organ-specific (eg GBS) or systemic (eg SLE-like disease) autoimmunity has been observed in COVID-19. Further research will shed light on this issue.

Conflict of Interest

Author has no personal financial or non-financial interests.

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Review

Diagnostic Efficiency and Usage of Cbct in Pediatric Dentistry

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ABSTRACT:

X-ray images are mostly needed in order to diagnose the problems of our patients who apply to dentistry clinics with many complaints. In cases where the diagnosis cannot be made with conventional x-ray techniques, it may be necessary to resort to advanced imaging techniques such as cone beam computed tomography (CBCT). Although CBCT applications provide a lower x-ray spread compared to imaging methods with computed tomography, when pediatric dentistry applications are considered, the high x-ray spread compared to conventional x-rays requires careful selection of areas of use in children. Since children are highly sensitive to ionizing radiation, exposure should be kept reasonably low. There are a significant number of published guidelines on the clinical use of CBCT in the literature. However, there is limited literature information on when and how often CBCT is indicated in pediatric dentistry. The purpose of this article is to evaluate the diagnostic efficacy and usage areas of CBCT in pediatric dentistry.

Keywords : Cone beam computered tomography, dental imaging, pediatric dentistry.

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1. INTRODUCTION

Dental imaging is a method used in the diagnostic evaluation of oral pathologies. Cephalometric radiography was discovered in 1895, right after the great progress that started with the discovery of X-rays by Röntgen [1]. With the introduction of orthopantomography in dental radiology in the 1960s, it was possible to visualize maxillofacial structures with only one radiography. However, 3D imaging techniques were needed because two-dimensional (2D) radiographic images of the three-dimensional (3D) anatomical structure of the maxillofacial region, created by extraoral and intraoral methods, have disadvantages such as superposition and magnification. With the developing technology, digital imaging, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and cone-beam computed tomography (CBCT) were discovered, thus making it possible to visualize the maxillofacial region in 3D [2]. CBCT was first produced for angiography in 1982. The first CBCT device produced for dentistry was put into the service of medicine in 1987, and the development of this device continues today [3].

CBCT produces 3D digital imaging with less cost and less radiation to the patient than traditional CT scans, and also provides faster and easier image acquisition [4]. Due to

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these advantages, it is an alternative three-dimensional imaging technology used in dentistry fields such as periodontology, implantology, endodontics, orthodontics, and oral surgery [5]. Considering the pediatric dentistry applications of CBCT, it causes a very high x-ray spread compared to traditional imaging methods, which requires careful selection of application areas in children. Since children are highly sensitive to ionizing radiation, exposure should be kept reasonably low [6]. There are a significant number of published guidelines on the clinical use of CBCT in the literature. However, literature information on when and how often to apply CBCT imaging in pediatric dentistry is limited. Our purpose of this review is to reveal the diagnostic effectiveness and usage areas of CBCT in pediatric dentistry by examining the studies published so far.

Dental Trauma

Dental trauma is a common condition in children and adolescents, and accurate diagnosis and treatment are essential for a good prognosis. Traumatized teeth pose a clinical challenge in terms of diagnosis, treatment plan and prognosis. Unfortunately, the sensitivity of two-dimensional radiographs for the detection of minimal tooth displacements, root and alveolar fractures remain poor [14]. This is due to projection geometry, overlapping of anatomical structures, and processing errors. The use of CBCT in dental traumatology was first described in 2007 [15], [16]. Cases that may appear simple on periapical radiographs may present a different and more complex situation when evaluated in three dimensions. CBCT will contribute to more accurate diagnosis and treatment planning in traumatic dental injuries.

Crown Root Fractures

Crown root fractures are injuries that affect enamel, dentin, and cementum. The pulp may or may not be exposed as a result of injury. In order to accurately detect the crown-root fracture, the periodontium and the tooth should be examined in detail. If the contact of the broken pieces with the periodontal continues, it may be mobile. Accurate determination of the apical extent of the fracture is not always possible when using two-dimensional periapical radiographs, and it is therefore recommended to use CBCT to assess the location and extent of the fracture [16].

Root Fractures

Root fractures are observed in the root part of the tooth affecting the cementum, dentin and pulp by the collateral effects in the periodontium. Root fractures pose a diagnostic challenge due to limitations of two-dimensional images such as projection geometry, overlapping of anatomical structures, and processing errors [15, 17-19]. For this reason, it has been suggested to use the periapical imaging technique with different angles such as 45°, 90°, and 110° [26]. In a retrospective clinical study, it was reported that while 30_40% of root fractures were detected with periapical imaging, this rate increased to 90% with CBCT [21]. Results from systematic reviews of predominantly ex vivo studies have shown that CBCT for root fractures has very high diagnostic accuracy. In addition, these accuracy levels were found to be higher than using periapical radiographs [22–26]. The 47 studies included in the systematic review of the

radiographic diagnosis of root fractures analyzed CBCT images and other image types. Only one study did not achieve better results using CBCT. In this study, the authors concluded that Periapical radiography showed fewer false positive cases (high specificity) [26]. It has been stated that cervical fracture detection is more common, especially in CBCT, which affects the treatment management [27]. Since fractures in the cervical region are considered to have the worst prognosis, failure to identify the cervical fracture line may lead to incorrect treatment and adverse outcomes.

CBCT should be strongly considered when conventional radiography gives poor results or shows a fracture of the middle third of the root. CBCT can more precisely confirm or rule out a root fracture that cannot be visualized by conventional radiography. Accurate diagnosis will provide critical information needed to develop a comprehensive and an appropriate treatment plan [27].

Luxation Injuries

Luxation is defined as injury to periodontal tissues due to damage and clinical and/or radiographic displacement. The luxation can be intrusive, lateral, extrusive, or a combination of these. The amount of luxation can range from mild to severe, depending on the magnitude and angle of the forces absorbed by the dental and surrounding anatomical structures. Luxation injuries cause damage to the periodontium and often occurs in combination with alveolar fractures. This is particularly the case in luxation injuries in which the crown is displaced lingual/palatal and the apical third is buccally displaced. An accurate diagnosis is essential to properly manage these injuries. Because movements and subsequent displacements are mostly in the sagittal plane, intraoral two-dimensional radiographs will not always reveal the severity of the injury. Failure to diagnose alveolar fractures can lead to incorrect treatment planning and further complications, particularly pulp necrosis and infection. Furthermore, improper tooth repositioning can result in poor alveolar healing and chronic pain due to apical fenestration [28].

Intrusion and avulsion of primary teeth are considered serious dental injuries due to most of the developmental disorders seen in permanent teeth as sequelae of trauma [29, 30]. Among developmental disorders, dental morphology and eruption disorder poses a clinical challenge in terms of diagnosis, treatment plan and prognosis. These situations indicate the need for advanced imaging techniques rather than conventional radiographs, and CBCT may be useful. It shows sections at various depths of the region of interest and allows clinicians to accurately assess the exact position of the crown, apex, and the degree of dilaceration [31]. By showing cross-sections at various depths of the region of interest, CBCT allows clinicians to accurately assess the exact position of the crown, the apex and the degree of dilation, and to plan the correct treatment [31].

The International Union of Dental Traumatology (IADT) published a report in 2020, and it was stated that the image quality of CBCT improves in dental traumatic injuries such as root fractures, crown-root fractures and lateral luxations [38]. However, before

using CBCT in such specific injuries, the radiation dose to which the patient will be exposed should be considered [33].

Dental Anomalies

CBCT is used to locate the anomalies observed in the oral region. Some centers have reported an increased incidence of oral anomalies (oral cysts, ectopic/impacted teeth, and supernumerary teeth) with the use of CBCT in their routine dental examinations [5]. In a clinical study to determine the positions of impacted and supernumerary teeth, CBCT was found to be successful with a high rate of 96.7% in determining the correct preoperative localization of the bucco-palatal position of the teeth using CBCT and conventional radiographs [34]. In the diagnosis and treatment management of impacted and supernumerary teeth, 3D imaging can significantly affect the treatment approach, increase confidence and predictability, and reduce invasiveness [35]. Dens invaginatus (DI) is a developmental dental anomaly with complex anatomical features and a wide range of morphological variations that creates diagnostic and therapeutic challenges for dentists. CBCT can provide a more detailed 3D view of complex anatomical variations in DI and help dentists validate DI classification and improve diagnostic accuracy [36]. Studies of the diagnostic value of CBCT have focused on tooth resorption and mostly on the resorption of the unerupted maxillary canine and incisor. In this context, it is seen that the most common pediatric use of CBCT is on this subject.

Developmental Anomalies

When the publications on developmental disorders are examined, it has been seen that CBCT should be used as an alternative to CT in patients with cleft lip and palate and that volumetric data should be obtained before bone grafting [37]. Pediatric dentists have a role as a part of the multidisciplinary approach in the treatment of cleft lip and palate. They can get it. Apart from case studies, there is little evidence of the value of CBCT in certain craniofacial syndromes.

Pathological Conditions

Conventional radiographs show bone pathologies in 2D only. However, 3D imaging is absolutely needed to evaluate the expansion of these pathologies in the antero-posterior direction. CBRT; It allows the evaluation of cortical expansion, bone resorption, adjacent bone sclerosis, internal and external calcifications, and adjacent anatomical structures [38]. CBCT may be needed in the evaluation of the relationship of pathological lesions encountered in the mixed dentition with neighboring teeth and tissues and permanent tooth germs. CBCT provides useful and precise results in distinguishing pathologies with adjacent teeth and tissues, thus facilitating treatment planning and reducing treatment time [39].

2. CONCLUSION AND RECOMMENDATIONS

As pediatric patients are more vulnerable to radiation dose, CBCT should be justified and exposure should be kept reasonably low. The application of CBCT in pediatric patients should only be considered when conventional radiography cannot provide relevant information. In addition, the cooperation of the child patient and the

movement during the long procedure are other issues that should be taken into account, as well as the resulting decrease in image quality. However, we recommend developing guidelines for the use of CBCT in pediatric patients and that more research is needed.

Conflict of Interest

Author has no personal financial or non-financial interests.

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Review

The Role of Gut Microbiota on Appetite Hormones

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ABSTRACT:

The fact that obesity has reached alarm level worldwide shows that this problem has practical and manageable limitations, both prevention and treatment options. It is known that obesity is effective in the emergence of many diseases such as asthma, depression and cancer, especially cardiometabolic diseases. Obesity, which shows a complex development, is mainly due to the chronically positive energy homeostasis. Intestinal microbiota plays a key role in maintaining this homeostasis. Microbiota is called all the microorganisms in the human body, and it acts as an organ by contributing directly or indirectly to many metabolic, structural and protective physiological functions of the host. Many of these functions are mediated by short-chain fatty acids (SCFA) produced from carbohydrates that are resistant to digestion by the microbiota. SCFA (butyrate, propionate, acetate) activate some hormone and signaling pathways and have a significant effect on appetite and body weight regulation. In this review, the effects of SCFAs on some gastrointestinal appetite hormones will be explained and predictions will be shared about their role in metabolism and their potential to be used as new molecular targets.

Obesity is one of the serious public health problems due to its increasing prevalence globally and its contribution to common metabolic disorders. The main goal of the methods used in the treatment of obesity is to reduce food intake by providing appetite regulation. SCFAs produced by the microbiota regulate appetite by decreasing food intake and increasing energy expenditure, anorexigenic hormones PYY and GLP-1.

Keywords *:* Appetite hormones, gut microbiota, short-chain fatty acids.

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1. INTRODUCTION

Obesity is defined as the excessive accumulation of fat in the body as a result of the deterioration of the energy balance [1]. Recently, the role of gut microbiota has come to the fore in the pathogenesis of obesity, which shows a complex development multifactorially. Microbiota is called all the microorganisms in the human body, and it acts as an organ by contributing directly or indirectly to many metabolic, structural and protective physiological functions of the host [2]. Many of these functions are mediated by short-chain fatty acids (SCFA) produced from carbohydrates that are resistant to digestion by the microbiota. SCFAs (butyrate, propionate, acetate) have a significant effect on maintaining appetite and body weight regulation by activating some hormone and signaling pathways [3]. SCFAs are generally produced by digestion-resistant carbohydrates and serve as an important substrate for gluconeogenesis. Acetate, propionate and butyrate from SCFAs produced in different amounts are important in

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ensuring energy regulation by acting on a number of hormones [4]. Acetate is transported to the liver via the portal vein after intestinal absorption and distributed throughout the body, where it serves as a substrate for cholesterol synthesis. Propionate, on the other hand, is used as the primary substrate in gluconeogenesis by reaching the liver through the portal circulation after intestinal absorption [3,5]. The physiological effects of other SCFA butyrate are quite remarkable. As a result of in vitro studies, it has been determined that 70% of the energy needs of intestinal epithelial cells and colonocytes are met by butyrate [6]. In addition, butyrate plays a role as a regulator in epithelial cell growth and differentiation. At the same time, ~10% of the host's daily energy requirement is provided by butyrate [7]. In particular, butyrate has positive effects such as the differentiation of beta cells, proliferation and prevention of beta cell apoptosis, similar to histone deacetylase inhibitör [8]. In addition to all these, butyrate glycemic control; It increases insulin transcription and translation as a result of induction of signaling pathways directly or indirectly, and has a positive effect by inhibiting gluconeogenesis and glycogenolysis in the liver (via indirect glucose production) [9].

2. DISCUSSION

Microbiota is called all the microorganisms in the human body, and it acts as an organ by contributing directly or indirectly to many metabolic, structural and protective physiological functions of the host [10]. Many of these functions are mediated by short-chain fatty acids (SCFA) produced from carbohydrates that are resistant to digestion by the microbiota [11]. The fact that the total amount of SCFA (butyrate, propionate, acetate) is higher in obese people than in lean individuals and the decrease in fecal SCFAs in treated obese individuals indicates that SCFAs may contribute to obesity [12]. To determine the effects of SCFAs on appetite hormones, we focused on the expression and function of the receptors of GPR41 and GPR43 in subtypes of enteroendocrine cells such as L and K cells [13]. The anorexigenic hormones PYY and GLP-1 activated through GPR41 and GPR43 reduce food intake and increase energy expenditure and provide appetite regulation.In addition, hormones increase satiety by delaying gastric emptying [12]. In vitro and in vivo studies have shown that SCFAs activate gastrointestinal satiety hormones PYY and GLP-1 [7,8,9,10,11]. Indigestible carbohydrates found in dietary fibers promoted the growth of SCFA-producing strains, resulting in metabolic improvement in individuals with obesity [14]. However, the amount of SCFA increased with the change in the microbial composition of the mice administered probiotics. This increase induces the release of the GLP-1 hormone, resulting in a decrease in food intake and an increase in glucose tolerance [15]. In the studies, intestinal microbial dysbiosis and the development of diet-related obesity were prevented by the supplementation of SCFA [6, 13]. In addition, free SCFAs cross the blood-brain barrier as monocarboxylate transporters, allowing the gut to act as signaling molecules to transmit the state to the brain [4].

Conflict of Interest

Author has no personal financial or non-financial interests.

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