RELATIONSHIP BETWEEN ORAL SQUAMOUS CELL CARCINOMA AND IMPLANTS (REVIEW)

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Throughout the recent decade, dental implants have been widely used for the treatment of complete and partial edentulism. A dental implant is being placed into the oral tissues beneath the mucosa and/or periosteum and/or within, or through the bone to provide retention and support for a fixated or removable dental prosthesis. For manufacturing the dental implants, mainly the materials such as cobalt, titanium, zirconia, and others are used [1-3]. Currently, the demand for titanium dental implants has increased dramatically. Titanium is considered to be an excellent biomaterial used for the production of dental implants. This is associated with the fact that it is characterized by convenient mechanical properties such as its high strength-to-weight ratio, malleability, and low density [4]. Titanium is non-toxic and infrequently rejected by the body. Apart from this, it has favorable mechanical and osseointegration properties [5,6].

The biocompatible nature of the pure form of titanium is the main benefit of its use [7]. Markets for dental implants have been estimated at $3.4 billion in 2008, and it has been estimated that that same year, 900 000 dental implants were placed in the United States alone [8].

However, despite the fact that dental implants have seen tremendous clinical success, there are some worrying reports in the literature that describe various complications after the implantation, including the development of squamous cell carcinoma (SCC), peri-implantitis, and etc [9].

In this review, our main attention has been drawn towards the SCCs that are associated with dental implants. As it is known, dental implants made of titanium do not have known malignant potential themselves. It was suggested that one of the causes for the development of SCC can be associated with inflammatory diseases, such as peri-implantitis, maxillary sinusitis, and osteomyelitis, which may present around the implants.

Acute inflammation, the one that occurs in response to a transient infection, is not regarded as a risk factor for the development of neoplasia. However, chronic inflammation may be a causative factor in a variety of cancers. In general, the longer the inflammation persists, the higher the risk of cancer. Inflammatory mediators include metabolites of arachidonic acid, cytokines, chemokines, and free radicals. Chronic exposure to these mediators leads to increased cell proliferation, mutagenesis, oncogene activation, and angiogenesis. Thus, it can be assumed that the implants that cause chronic inflammation, can increase the risk of peri-implantitis, which in turn can be the cause of the squamous cell carcinoma formation from the tissues surrounding the implant.

Titanium implant-based factor as a possible risk for peri-implantitis

Titanium, a chemical element, is one of the most widely used materials for dental implants [10]. Physical and chemical features of implant materials influence the clinical outcome of treatment. An ideal material should have adequate strength, toughness, should be corrosion resistant and compatible biologically, mechanically, and morphologically Titanium possesses most of these favorable effects and this is why the demand for titanium dental implants has risen dramatically. Titanium has a high strength-to-weight ratio, malleability and fractures are rarely occurring [11].

Titanium is protected from corrosive breakdown via a surface oxide layer, produced by immediate oxidation when exposed to air. This layer also contributes to excellent biocompatibility [12]. It has been reported that titanium has low toxicity and allergic potential, and rarely develops rejection reactions. The risk of allergy is more prevalent in patients having sensitivity to other metals [13]. Additionally to these characteristics, titanium has an osseointegration capability [14].

These properties define the great role of titanium in the global dental implant market, which, in 2019, has been estimated at USD 4.6 billion [15].

Together with the increase of tremendous clinical success of dental implants and the use of titanium implants, concerns over its safety and efficiency are increasing as well.

There are cases where titanium causes allergic reactions and hypersensitivity. Titanium can form haptenic antigens, strong inducers of hypersensitivity which can cause degranulation of basophils and mastocytes, and also, can cause type I and IV hypersensitivity. A more common type of hypersensitivity in the oral cavity is type IV, which develops in days or years after the contact [16]. Allergic reactions to implants can be manifested as eczema, recurrent effusions, skin rash, pain, delayed healing, and in worst cases, it can even cause the loss of implant [17-19].

Titanium is well known as one of the most corrosion-resistant metals. However, it has been reported that titanium can undergo corrosion in some specific conditions to which it might be exposed in the oral environment. The factors that determine corrosion are saliva composition, dietary factors, contact with different organic compounds, pH change in the buccal region, and biofilm production [20]. The acidic environment created by the bacteria, which releases lactic acid or inflammation that causes local acidification are important contributors to corrosion [21].

Particles released during corrosion cause local changes and also affect more distant organs. It has been shown, that nanoparticles have passed through the blood-brain barrier and have been located in the central nervous system [22]. It has been reported that, in the animal and cultured cell experiments, titanium can accumulate in different organs in the body [23]. The dissemination of titanium alloy particles from a hip prosthesis has also been observed. Particles cause visceral granulomatous reaction and hepatosplenomegaly. Metallic wear particles in the patients who have had hip or knee replacement have been disseminated to the para-aortic lymph nodes, to the liver and spleen. The release of titanium particles in surrounding tissues damages oral epithelial barrier and causes inflammation, bacterial colonization and microbiofilm formation [24].

Corrosion of titanium dental implants is considered one of the triggering factors for peri-implantitis. Titanium can alleviate inflammation especially in combination with bacteria and lead to peri-implantitis and consequently implant failure. It has been reported that in peri-implantitis tissue, high titanium levels are observed [25, 26]. Two interesting cases demonstrate pyogenic granuloma and peripheral giant cell granuloma associated with titanium dental implants. The presence of metal-like particles was confirmed by histological observation. Other studies also demonstrate the presence of titanium particles in peri-implantitis tissue. They have used laser ablation inductively coupled plasma

mass spectrometry and high-resolution optical darkfield microscope to identify these particles and confirm their presence [27].

Titanium can cause chronic inflammation. The inflammatory infiltrates in the case of peri-implantitis are primarily chronic [28]. The study has shown that the mean number of chronic inflammatory cells in the area with titanium was significantly greater than in areas without titanium. Also, overexpression of cytokines, RANKL, IL-33 and TGF-B1 in areas with titanium was reported [29]. Titanium particles also increase levels of inflammatory cytokines, such as IL1β, IL-6 and TNFα [30]. It was reported that chronic stimulation by titanium particles can lead to oxidative stress and persistent inflammation [31].

Oral squamous cell carcinoma and peri-implantitis

Nowadays, it is accepted that chronic inflammation is associated with increased conversion of normal cells to preneoplastic foci and promote tumor development. Inflammation in the oral cavity plays a role in the initiation and the progression of the neoplastic process. Important components of these underlying processes are cytokines. The relationship between carcinogenesis and inflammation occurs in two ways: an extrinsic pathway driven by inflammation, and an intrinsic pathway driven by genetic alterations [32]. Also, oral squamous cell carcinoma (OSCC) is a relatively rare complication of peri-implantitis, it is something very important to take into consideration.

We have conducted a systematic search from 1996 through 2020 years using Medline (PubMed), Cochrane Database, and Google Scholar with the search terms “cancer”, “squamous cell carcinoma”, “dental implant”, “peri-implantitis”, “oral cancer”, and “implantology”.

Analysis of literature has shown that the number of reported cases that demonstrate SCC development in association with dental implants was increased through the years. For example, in 1996 article, it was reported that several cases of SCC arose around an osseointegrated dental implant [33].

There were similar findings reported in other articles as well. It is mentioned that one patient had an important risk factor – was a heavy smoker with oral lichen planus, a chronic inflammatory disease with possible premalignant character. The role of evaluation of existing risk factors and the possibility of malignancy being masked as peri-implantitis is also being emphasized [34]. In 2008, a report has been made about 3 cases of patients with risk factors, in whom the development of SCC might have been associated with implants. In all cases, the patients have had a history of cigarette smoking, and in 2 cases - the history of alcohol consumption. Authors suggested that OSCC might develop in peri-implant tissues and mimic peri-implantitis [35]. There are 2 clinical cases about the development of OSCC after the implantation. In the first case, a non-painful, non-bleeding lesion on the right outer edge of the tongue has been developed after 1 year following the implantation. Since the patient considered it as the result of self-traumatism, the patient refused to take biopsy, and there were issues with follow-up appointments. Consequently, based on the biopsy results, OSCC was diagnosed and surgically treated. No recurrence has been observed. In the second case, the patient had a history of using full oral implant-supported denture for nine years. The patient had developed an ulcerated lesion in the middle third portion of the left lateral edge of the tongue. Afterwards, biopsy confirmed OSCC was successfully resected [36]. However, in 2012, the case of OSCC in patients who had no specific predisposing etiopathological risk factors was reported. There was no history of smoking, alcohol consumption, or cancer. The mucosa around the dental implant was ulcerative and had irregular margins. The bone loss surrounding the implant was shown radiographically [37]. Chronic peri-implantitis which contributed to the development of SCC has also been observed. In the patient, no major risk factors for oral carcinoma were reported. Seven years after implantation, the patient noticed swelling of the gingiva near the dental implant. A panoramic radiograph revealed bone resorption. As it is known, the prolonged inflammation may have been a major risk for OSCC development [38]. The other data suggested that implant treatment and inflammatory co-factors were important contributors to malignant transformation in two patients with neoplasm around an implant. The attention was drawn to the population with a low risk of OSCC development. They have concluded that, in non-smokers and non-drinkers, an important factor predisposing to the cancer is a previous exposure to the metal dental hardware. Also, a case was reported where OSCC was diagnosed following the failure to treat peri-implantitis [39-42].

All of the above-mentioned cases demonstrate that neoplasia must be considered in the evaluation of peri-implant pathology, and also, importance of periodic oral and radiographic examination after implantation should be underlined.

Conclusion. The purpose of this report was to raise awareness of the fact that the most frequent carcinomas associated with dental implants occur in the form of peri-implantitis. This is linked to the presence of chronic inflammation developing around an implant, which is commonly found condition that can lead to the development of OSCC. Particular attention should be drawn to the patients with peri-implantitis with risk factors such as smoking, excessive alcohol consumption, previous history of OSCC, leukoplakia or lichen planus. The possibility of SCC development must be considered in the evaluation of peri-implant pathology. We highly recommend periodic oral and radiographic examination after implant placement. In the patients that do not respond to conventional treatment methods of peri-implantitis and patients with a severe or progressive form of peri-implantitis, the biopsy should be necessary. The histopathological examination will aid with the differential diagnosis between peri-implantitis and OSCC, and hence, provide the correct diagnosis. We also suggest screening all patients even if the risk factors are absent because recently, there has been an increase of reported cases of OSCC in patients with no risk factors.

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SUMMARY

RELATIONSHIP BETWEEN ORAL SQUAMOUS CELL CARCINOMA AND IMPLANTS (REVIEW)

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In this review, we have discussed the relationships between oral squamous cell carcinoma (OSCC) and dental implants. In the last decade, dental implants have been widely used for the treatment of complete or partial edentulism. Despite the fact that they have seen incredible success and the use of dental implants increases, concerns over safety and efficiency is rising as well. The literature analysis has shown that the number of reported cases when the OSCC development is associated with peri implantitis is gradually increasing. The possibility of squamous cell carcinoma development must be considered when evaluating the peri-implantitis. We highly recommend periodic oral and radiographic examination after the implant placement. The patients with peri-implantitis that do not respond to conventional treatment methods, and the patients who have a severe or rapid progression of peri-implantitis require biopsy. The histopathological examination will aid with the differential diagnosis between peri-implantitis and OSCC, and hence, provide the correct diagnosis.

Keywords: oral squamous cell carcinoma, dental implants, peri-implantitis.

РЕЗЮМЕ

ВЗАИМОСВЯЗЬ МЕЖДУ РАЗВИТИЕМ ПЛОСКОКЛЕТОЧНОЙ ОПУХОЛИ ПОЛОСТИ РТА И ЗУБНЫМИ ИМПЛАНТАМИ (ОБЗОР)

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В обзоре анализируется текущая и ретроспективная научная литература об имплантах, как риск-факторах развития плоскоклеточной опухоли полости рта. В течение многих десятилетий зубные импланты широко используются для лечения полного или частичного эдентулизма. В последние годы, вместе с ростом числа имплантаций, все чаще публикуются сведения о различных осложнениях, связанных с имплантами, вплоть до развития плоскоклеточной опухоли полости рта вокруг импланта. Отмечается, что периимплантит, как одно из осложнений импланта, играет значимую роль в инициации и прогрессировании опухолевого процесса. Исходя из вышеизложенного, при оценке периимплантита следует учитывать возможность развития плоскоклеточной опухоли полости рта. Авторы настоятельно рекомендуют проводить периодический осмотр полости рта после установки импланта с использованием как визуального, так и радиологического методов исследования. У пациентов, которые не поддаются стандартным методам лечения периимплантита, а также с вялой или быстро прогрессирующей его формой, необходимо проведение биопсии. Гистопатологические методы исследования позволяют провести дифференциальный диагноз и на ранних стадиях выявить ту или иную патологию, развившуюся в зоне зубного импланта.

რეზიუმე

პირის ღრუს ბრტყელუჯრედოვან კარცინომის განვითარებასა და კბილის იმპლანტებს შორის ურთიერთკავშირი (მიმოხილვა)

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[1]თბილისის ი. ჯავახიშვილის სახ. სახელმწიფო უნივერსიტეტი; [2]თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, საქართველო

მიმოხილვაში განხილულია პირის ღრუს ბრტყელ-უჯრედოვან კარცინომასა და იმპლანტებს შორის ურთიერთკავშირის საკითხებისადმი მიძღვნილი თანამედროვე და რეტროსპექტული ლიტერატურა. მრავალი ათწლეულის განმავლობაში კბილის იმპლანტები ფართოდ გამოიყენება ნაწილობრივი და სრული ედენტულიზმის სამკურნალოდ. ბოლო წლებში იმპლანტაციის რაოდენობის ზრდასთან ერთად ლიტერატურაში უფრო ხშირად გვხვდება იმპლანტებთან დაკავშირებული სხვადასხვა გართულება,

პირის ღრუს ბრტყელუჯრედოვანი კარცინომის განვითარების ჩათვლით. სამედიცინო ლიტერატურის ანალიზმა გვიჩვენა, რომ პერიიმპლანტიტი მნიშვნელოვან გავლენას ახდენს ნეოპლაზიური პროცესის ინიციაციასა და პროგრესიაზე. სწორედ ამიტომ ბრტყელუჯრედოვანი კარცინომის განვითარების შესაძლებლობა აუცილებლად უნდა იყოს მიღებული მხედველობაში პერიიმპლანტიტის შეფასების დროს. ავტორებს მიზანშეწონილად მიაჩნიათ იმპლანტის დაყენების შემდგომ პერიოდულად პირის ღრუს დათვალიერება და იმპლანტის შეფასება როგორც ვიზუალურად, ასევე რადიოლოგიური მეთოდის გამოყენებით. იმ შემთხვევებში,როდესაც პირის ღრუში მიმდინარეობს პერიიმპლანტიტი ნელი ან სწრაფი პროგრესიული ფორმით ან პერიიმპლანტიტის მკურნალობა სტანდარტული მეთოდით უშედეგო აღმოჩნდა,აუცილებელია ბიოფსიის ჩატარება. ჰისტოპათოლოგიური კვლევა საშუალებას იძლევა ჩატარდეს დიფერენციული დიაგნოზი და ადრეულ სტადიაზევე გამოვლინდეს იმპლანტის გარშემო განვითარებული პათოლოგია.

КРАНИОМЕТРИЧЕСКИЕ ПАРАМЕТРЫ И МОРФОЛОГИЧЕСКИЕ ОСОБЕННОСТИ ВЕРХНЕЙ ЧЕЛЮСТИ ЧЕЛОВЕКА

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В современной челюстно-лицевой хирургии для повышения эффективности оперативных вмешательств, особенно в условиях обеспечения минимально инвазивных операций, необходимы точные знания краниотопографии костных структур лицевого отдела головы и их взаимоотношений с значимыми сосудисто-нервными образованиями. На основе этих знаний возможно правильное и безопасное выполнение оперативных вмешательств, понимание механизмов развития патологических процессов, осуществление топической диагностики [11].

Антропологические закономерности определяют стандартные подходы к оперативному лечению заболеваний органов и тканей челюстно-лицевой области, однако индивидуальная вариабельность тех или иных признаков весьма значительна и зависит от целого ряда факторов, в том числе возрастных, гендерных и других [3]. В связи с этим, важно представлять границы изменчивости, учитывать их в ходе оперативных мероприятий и прогнозировать возможные результаты вмешательств и исходы заболеваний. Предиктивные аспекты особую роль играют в пластической и реконструктивной челюстно-лицевой хирургии, которая в последние десятилетия максимально востребована [9].

Лицевой отдел черепа образует передний отдел головы. Форма и параметры лица определяются известными антропологическими признаками и, как правило, зависят от телосложения и роста человека [4]. Для описания формы лица достаточно часто используют различные геометрические фигуры [1].

Верхняя челюсть занимает передне-верхний отдел лица и является парной костью, которая участвует в формировании полостей для органов глазницы, носа и рта. Она состоит из тела и четырех отростков: лобного, альвеолярного, небного, скулового, а также имеет воздухоносную гайморову пазуху [2]. Для определения степени вариабельности формы, параметров и положения верхней челюсти необходимо учитывать их зависимость от возраста, пола, конституциональных и индивидуальных особенностей человека.

В области верхней челюсти проводят многочисленные и разнообразные оперативные вмешательства, необходимые в комплексном лечении при устранении деформаций и врожденных пороков развития верхней челюсти у детей, причем в сложных клинических ситуациях, связанных с минимальной площадью операционного поля, успех определяют точные и выверенные действия, зависящие, в основном, от топографически обоснованных расчетов [14]. Нередко вынужденно прибегают к оперативному лечению переломов верхней челюсти, скуловых костей, а также исправлению хирургическим путем патологического прикуса [8]. Хирургические вмешательства показаны в ходе лечения некоторых хронических воспалительных заболеваний с локализацией в области верхней челюсти, в частности одонтогенного гайморита, остеомиелита, а в случае верифицированной диагностики доброкачественных или злокачественных новообразований проводят резекцию верхней челюсти с последующим, при наличии соответствующих условий и показаний, пластическим возмещением эстетического дефекта, что влияет на качество жизни пациентов и обеспечивает им определенную социализацию и психологический комфорт [7].

Целью исследования явилось изучение морфологических особенностей верхней челюсти у лиц различного возраста по результатам краниометрического исследования.

Материал и методы. Материалом для исследования служили 50 костных препаратов черепов человека различного пола в возрасте от 22 до 63 лет из коллекции кафедры топографической анатомии и оперативной хирургии Луганского государственного медицинского университета Министерства здравоохранения Украины, в частности 36 (72%) черепов мужчин и 14 (28%) черепов женщин. Исследование, выполненное в 2012-2013 гг., проведено в полном соответствии с требованиями биоэтической экспертизы, принципами Хельсинкской декларации, принятой Генеральной ассамблеей Всемирной медицинской ассоциации (1997-2000 гг.), и Конвенции Совета Европы о правах человека и биомедицине (1997 г.).

Краниометрические исследования включали изучение формы черепа и его размеров, параметров лицевого отдела и верхней челюсти. Для проведения измерений череп раз-