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Influence of diabetes on the character of changes of resorption and repair processes in the parodontium and mandibular tissues after tooth extraction

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Today, diabetes mellitus (DM) represents a problem on which the attention of endocrinologists, general practitioners, and dentists is focused. Early pathological changes, which manifest themselves in the oral cavity, determine the relevance and social significance of this pathology, because dentists are usually the first to diagnose disorders of carbohydrate metabolism based on the results of the analysis of specific complaints and typical clinical symptoms of damage to the mucous membrane and periodontal tissues.

The aim of the work is to find out the pathogenetic characteristics of the reparative component of the post-extraction alveolar socket depending on the time after tooth extraction in experimental diabetes.

Materials and methods. In total, 120 sexually mature (age 8–10 months) male Wistar rats, divided into 8 groups of 15 animals each, were used for research. Complex immunohistological, radiographic and biochemical studies were used for the purpose of detailed analysis of the features of the course and mechanisms of development of complications after tooth extraction against the background of DM. In order to assess the state of the innate link of local immunity, the specifics of the course of repair processes at different times of the post-extraction period, the levels of cell proliferation (by expression of Ki-67) and the concentration and content of CD68-positive macrophages in the mucous membrane were determined immunohistochemically. In order to determine the state of the bone tissue of the dental and jaw apparatus and the levels of mineralization of the hard tissues of the molars in the animals of the experimental groups, radiovisiographic images of the right half-mandible were analyzed with determination of the radiographic density.

Results. Analysis of proliferative-reparative relationships showed almost no macrophages and very low proliferative activity in the intact periodontium, on the other hand, in DM, initial significant diffuse infiltration by CD68-immunopositive cells with high levels of Ki-67 expression was found. Analysis of X-ray images of the half-mandible revealed that induced DM in rats, even without prior surgical intervention, led to the intensification of resorption processes in bone tissue, which was evidenced by a decrease in radiographic density in the root region of the 1st molar and intraalveolar bone membranes of all three lower molars.

Conclusions. In the intact periodontium, there are almost no CD68-immunopositive macrophages and very low proliferation activity in the periodontal soft tissues. In experimental diabetes, on the contrary, initial significant diffuse infiltration by CD68-immunopositive macrophages with high proliferative activity of most fibroblasts is determined. Induced diabetes in rats, even without prior surgical intervention, leads to increased resorption processes in the bone tissue of the mandible and long-term prolongation of the inflammatory process after tooth extraction.

Вплив цукрового діабету на характер змін процесів резорбції та репарації в тканинах пародонта та нижньої щелепи після видалення зуба

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Ключові слова: цукровий діабет, репарація, пародонт, нижня щелепа, видалення зуба, радіовізіографія, щільність кісткової тканини, CD68, Ki-67, щури.

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Нині цукровий діабет (ЦД) залишається складним питанням, вивченням якого займаються ендокринологи, лікарі загальної практики, а також стоматологи. Ранні патологічні зміни, що маніфестують саме в ротовій порожнині, визначають актуальність і соціальну значущість цієї патології, адже лікарі-стоматологи здебільшого першими діагностують розлади вуглеводного обміну за результатами аналізу специфічних скарг і типової клінічної симптоматики ушкодження слизової оболонки та тканин пародонта.

Мета роботи – визначити патогенетичні характеристики репаративного компонента постекстракційної альвеолярної лунки залежно від терміну після екстракції зуба при експериментальному ЦД.

Матеріали і методи. Під час досліджень використали 120 статевозрілих (вік – 8–10 місяців) щурів самців лінії Wistar, яких поділили на 8 груп по 15 тварин у кожній. Для детального аналізу особливостей перебігу та механізмів розвитку ускладнень після екстракції зуба на тлі ЦД виконали комплексні імуногістологічні, радіографічні та біохімічні дослідження. Для оцінювання стану вродженої ланки місцевого імунітету, особливостей перебігу процесів репарації в різні терміни постекстракційного періоду імуногістохімічно визначили рівні клітинної проліферації (за експресією Ki-67), концентрації та вмісту CD68-позитивних макрофагів у слизовій оболонці. Для визначення стану кісткової тканини зубощелепного апарату та рівнів мінералізації твердих тканин молярів у тварин експериментальних груп проаналізували радіовізіографічні знімки правої напівмандибули з визначенням радіологічної щільності.

Результати. Аналіз проліферативно-репаративних зв'язків показав, що в інтактному пародонті майже не було макрофагів, а також дуже низьку проліферативну активність. При ЦД виявлена вихідна істотна дифузна інфільтрація CD68-імуно-

позитивними клітинами з високими рівнями експресії Ki-67. У результаті аналізу рентгенівських знімків напівмандибул виявлено, що індукований ЦД у щурів навіть без попереднього хірургічного втручання призводив до інтенсифікації процесів резорбції в кістковій тканині. Це підтверджено зниженням радіологічної щільності в кореневій ділянці першого моляра й внутрішньоальвеолярних кісткових мембран усіх трьох нижніх молярів.

Висновки. В інтактному пародонті майже не виявляли CD68-імунопозитивні макрофаги, визначена дуже низька активність проліферації у м'яких тканинах пародонта. При експериментальному цукровому діабеті виявлена вихідна значна дифузна інфільтрація CD68-імунопозитивними макрофагами з високою проліферативною активністю більшості фібробластів. Індукований цукровий діабет у щурів навіть без попереднього хірургічного втручання зумовлює посилення процесів резорбції в кістковій тканині мандибули та тривалу пролонгацію процесу запалення після екстракції зуба.

Today diabetes mellitus (DM) is a problem that attracts close attention not only of endocrinologists, but also of other specialists, including dentists. The relevance and social significance of this problem is due to the fact that early pathological changes occur precisely in the oral cavity, and dentists are the first to diagnose a violation of carbohydrate metabolism based not only on specific complaints, but also on a certain clinical picture of the mucous membrane and periodontal tissues damages [1].

In patients with diabetes mellitus, a decrease in periodontal endurance with the development of diabetic periodontopathy is noted, osteoporosis progresses, the ability to regenerate bone tissue decreases, inflammatory changes in the mucous membrane are formed [2]. A few months after the diagnosis of DM, almost all patients have signs of periodontitis [3,4]. Exactly these problems of patients with DM that become a difficult obstacle when planning dental surgical manipulations. In the works of many researchers and dentists, there is enough evidence that the removal of a tooth in a patient with diabetes mellitus can provoke an inflammatory process in the oral cavity [5].

Moreover, the procedure itself often causes decompensation of the underlying disease. The clinical aspects of this problem are caused by a significant frequency of post-extraction complications and the development of purulent-inflammatory processes [6,7,8]. The pathogenetic mechanisms leading to such a situation occur according to the type of mutual aggravation syndrome. At the same time, some kind of "vicious circle" is formed, in which metabolism and microcirculation disorders slow down the course of reparative-regenerative processes in the alveolar socket, and the developing inflammation has a negative effect on metabolic processes, increasing insulin deficiency and acidosis. Such a symbiosis of the two conditions creates a risk of development of post-extraction complications, infection of the maxillofacial area and neck with the damage to adjacent tissues [9,10].

The identifying of the mechanisms of their formation will provide an opportunity to reduce the risk of development of complications and to develop pathogenetically based methods of their treatment.

Aim

The purpose of the study was to determine the pathogenetic features of the reparative component of the post-extraction alveolar socket under conditions of experimental diabetes mellitus depending on the time after tooth extraction.

Materials and methods

Research was conducted on 120 sexually mature male Wistar rats aged 8–10 months, which were divided into eight groups of 15 animals each: Control-0 – intact rats without tooth extraction; Control-1 – animals that underwent extraction of the first lower molar under thiopental anesthesia (dose 40 mg/kg) with additional local infiltration anesthesia "Ubistesin" (3M Deutschland GmbH, Germany). The animals were removed from the experiment on the first day after tooth extraction under thiopental anesthesia (40 mg/kg body weight, intraperitoneally). In the Control-7 and Control-14 groups, a similar tooth extraction was performed, animals were removed from the experiment on the seventh and fourteenth day, respectively. Diabetes-0 group – rats in which experimental diabetes mellitus (EDM) was modelled by a single intraperitoneal injection of streptozotocin (SIGMA Chemical, USA), dose of 50 mg/kg, dissolved in 0.5 ml of 0.1 M citrate buffer (pH 4.5) ex tempore. The animals were removed from the experiment after 21 days (glucose concentration 22.65 ± 0.88 mM/l), tooth extraction was not performed. Diabetes-1, Diabetes-7 and Diabetes-14 groups are rats that, after the induction of EDM on the 21st day, the extraction of the first lower molar on the right was carried out according to the previously described method. The animals were removed from the experiment on the first, seventh and fourteenth day, respectively, after tooth extraction.

A complex of immunohistological, radiographic and biochemical studies was carried out in order to study in detail the features of the course and the mechanisms of the formation of complications after tooth extraction amid DM, which provided an opportunity to analyze in detail the state of the innate local immunity link, the nature of the course of reparative processes in the periodontal tissues, to evaluate the state of the bone tissue of the dental and jaw apparatus and mineralization of the hard tissues of the molars.

To study the state of the innate local immunity link, the peculiarities of the course of reparative processes within different time periods of the post-extraction period, immunohistochemical determination of the level of cell proliferation (by Ki-67 expression) and the concentration and content of CD68-positive macrophages in the mucous membrane in the area of the first molar of the mandible in rats (CD68 expression was studied by immunohistochemical staining with primary rabbit IgG to CD68 (Santa Cruz Biotechnology, USA), dilution 1:200 and secondary mouse IgG to the complete molecule of rabbit IgG conjugated with FITC (Santa Cruz Biotechnology, USA), dilution 1:64; the evaluation of the proliferative activity of periodontal tissues

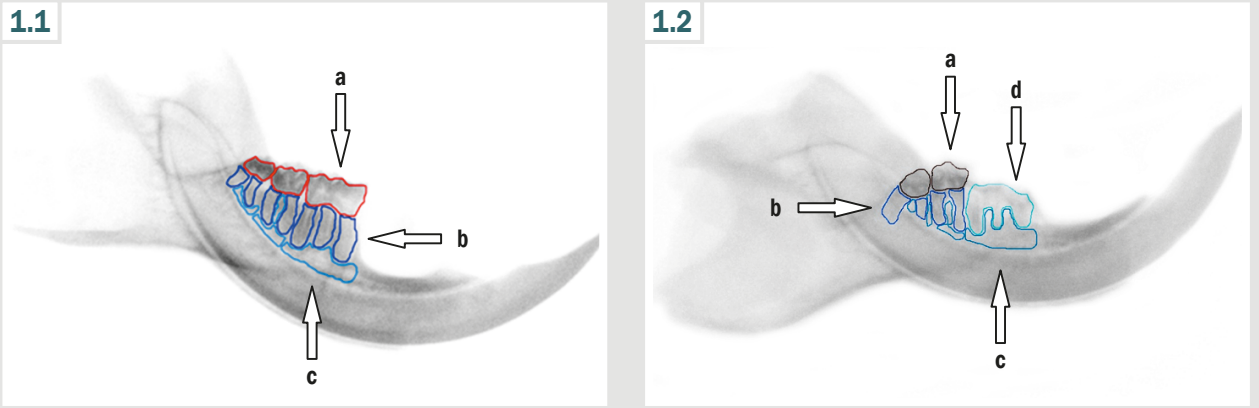

Fig. 1. Radiographic photograph of the right half-mandible of rats before (**1**) and after tooth extraction (**2**). Designation of "zones of interest" for digital analysis of the radiographic density of the studied parameters: crown of the tooth – **a**, root of the tooth – **b**, interalveolar and interradicular spaces – **c**, zone of the alveolar socket – **d**.

was determined after incubation with specific primary antibodies to Ki-67 (Santa Cruz Biotechnology, USA), dilution 1:200 and subsequent exposure in a thermostat with secondary antibodies conjugated with FITC (Santa Cruz Biotechnology, USA), dilution of 1:64).

In order to evaluate the state of the bone tissue of the dentoalveolar apparatus and the mineralization of the hard tissues of the molars in the rats of the experimental groups, radiovisiographic images of the right half-mandible were analyzed and the radiographic density of the alveolar socket of the removed 1st molar, the crowns of the molars and their roots, the interalveolar and interradicular bone membranes of the alveolar part were determined as per the 1st, 7th and 14th day after tooth extraction. The radiographic images of the half-mandible of rats were taken after the animals were removed from the experiment in the corresponding periods by one-stage decapitation under thiopental anesthesia (40 mg/kg body weight). The jaw bones were immediately separated from the animal's head, the soft tissues were removed and placed in a cold 0.9 % NaCl solution.

Visiography of the half-mandible was performed not later than 2–3 hours after the macropreparation was released. Images of the half-mandibles were obtained using a Panoura 18S Panoramic 3D (Japan) cone-beam computed tomography scanner. For digital image analysis and determination of radiographic density (RD) of the tissues of the half-mandible and hard tissues of the molars on the received images in interactive regime the "areas of interest" were distinguished corresponding to the alveolar socket of the removed 1st molar, crowns of the 1st, 2nd and 3rd molars, their roots and bone membranes of the alveolar part (interalveolar and interradicular membranes, IRB). The prepared images were calculated using the software AxioVision 4.8.2 (Carl Zeiss, Germany) and Excel 7.0. 15 images of the right half-mandible from each experimental group were studied *(Fig. 1)*.

The statistical processing of the obtained results was carried out on a personal computer using the program Statistica for Windows 13 (StatSoft Inc., No. JPZ804I382130ARCN10-J). The hypothesis about the normality of the distribution of the studied indicators was tested using the Shapiro–Wilk test. For all indicators, the value of the arithmetic mean of the sample (M), its mean-square deviation and the error of the mean (m) were calculated. To identify the significance of differences in research results in experimental and control groups of rats, Student's coefficient (t) was calculated, after that the probability of sample difference (p) and the confidence interval of the mean were determined according to Student's distribution tables. Values for which $p_{St} < 0.05$ were considered significant.

Results

The analysis of proliferative and reparative relations showed that in the intact parodontium there are practically no macrophages and proliferative activity is very low, in case of diabetes mellitus, on the contrary, initial significant diffuse infiltration by CD68-immunopositive cells and high expression of Ki-67 were observed.

One day after tooth extraction in control rats and animals with DM, the content of CD68 did not change reliably, while the expression of Ki-67 increased significantly. The 7th day showed an increase in expression parameters to CD68 and Ki-67 in control by more than a third, but insignificantly in case of diabetes. The 14th day in control showed a decrease of CD68 and Ki-67, while in case of DM the area of immunoreactive material to CD68 became slightly larger, which can be considered as an important indicator of the prolongation of the inflammatory process with the spread of infiltration of parodontium tissues by activated macrophages. In the same period, on the 14th day, Ki-67 expression indicators in animals with DM did not decrease, as in animals of the control group, but, on the contrary, increased. Thus, when compared with the corresponding control (14th day), the Ki-67 content was 2.26 times higher and the concentration was 2.4 times higher. Comparing the indicators of Ki-67 expression with the values of animals with EDM of the previous term (7th day), their predominance by almost a third was established.

The result of the conducted study showed that in diabetes mellitus after tooth extraction, the high initial

Table 1. Mandible tissues radiographic density after tooth extraction in rats of experimental groups, M ± m

Control groups		Radiographic density, conventional unit			
Rats with DM		Without extraction, n = 15	1st day after extraction, n = 15	7th day after extraction, n = 15	14th day after extraction, n = 15
1st molar	tooth crown	0.518 ± 0.011	alveolar socket of the 1st molar		
		0.509 ± 0.008			
	tooth root	0.469 ± 0.014	0.172 ± 0.006[1]	0.182 ± 0.006[1]	0.280 ± 0.006[1,2]
		0.425 ± 0.009	0.187 ± 0.005[1]	0.198 ± 0.007[1]	0.154 ± 0.008[1,2]
	IRB	0.408 ± 0.012	0.247 ± 0.008[1]	0.356 ± 0.012[1,2]	0.367 ± 0.015[1]
		0.320 ± 0.006	0.391 ± 0.016	0.387 ± 0.009[1,2]	0.291 ± 0.009[1,2]
2nd molar	tooth crown	0.527 ± 0.018	0.432 ± 0.011[1]	0.508 ± 0.012[2]	0.522 ± 0.011
		0.515 ± 0.009	0.521 ± 0.008	0.496 ± 0.011[1,2]	0.458 ± 0.008[2]
	tooth root	0.481 ± 0.017	0.450 ± 0.012	0.463 ± 0.009	0.471 ± 0.013
		0.476 ± 0.015	0.485 ± 0.013	0.427 ± 0.012[1,2]	0.356 ± 0.009[1,2]
	IRB	0.392 ± 0.016	0.315 ± 0.007[1]	0.368 ± 0.009[2]	0.370 ± 0.012
		0.325 ± 0.006	0.396 ± 0.007[1]	0.318 ± 0.019	0.269 ± 0.007[1,2]
3rd molar	tooth crown	0.511 ± 0.016	0.484 ± 0.012	0.499 ± 0.014	0.492 ± 0.014
		0.491 ± 0.009	0.472 ± 0.017	0.469 ± 0.013	0.481 ± 0.008
	tooth root	0.474 ± 0.014	0.435 ± 0.015	0.455 ± 0.016	0.467 ± 0.009
		0.478 ± 0.013	0.453 ± 0.013	0.476 ± 0.011	0.411 ± 0.013[1,2]
	IRB	0.384 ± 0.014	0.341 ± 0.012[1]	0.369 ± 0.014	0.397 ± 0.015
		0.316 ± 0.014	0.374 ± 0.015[1]	0.275 ± 0.011[1,2]	0.269 ± 0.011[1]

[1]: significant differences in group indicators after tooth extraction ($p_{st} < 0.05$) relative to the corresponding Control-0 and Diabetes-0; [2]: significant differences in indicators of groups after tooth extraction ($p_{st} < 0.05$) relative to the corresponding group of the previous term.

proliferative activity of parodontium cells is preserved and even becomes greater for a long time. However, the efficiency of such proliferation is low, the remodeling of the alveolar socket doesn't finish due to the constant maintenance of the inflammatory process, which was evidenced by the high content of iNOS and the increased number of CD68-immunopositive cells.

The analysis of X-ray images of the half-mandibles showed that diabetes mellitus formed in rats, even without surgical interventions, leads to increased resorptive processes in bone tissue, which was manifested by a decrease in RD in the root area of the 1st molar and IRB of all three lower molars *(Table 1)*.

Discussion

The established fact of previously formed osteopenia in case of DM is considered by many researchers as one of the main unfavourable factors affecting the course of the postoperative period in patients. Thus, according to the results of numerous clinical observations and experimental studies, pathological changes in bone tissue, significant microcirculatory disorders, and neurotrophic disorders were revealed in patients with DM [11,12]. At the same time, it is believed that osteopenia and osteoporosis, as the most common pathological changes in bone tissue, are of diffuse nature, since both cancellous and tubular bones "suffer" [13,14,15].

Tooth extraction in control rats was accompanied by dynamic changes in RD not only in the area of extraction, but the inflammatory process also affected the surrounding 2nd and 3rd molars, leading to a decrease in radiographic density in the areas of IRB. In rats with DM, on the contrary, there was an increase in RD in the IRB zone of the 1st, 2nd, and 3rd molars, which was probably associated with severe edema. On the 7th day, in control rats, the early resorptive phase of the local inflammatory reaction ended, while in animals with diabetes, it continued and was characterized by a decrease in radiographic density in the area of the IRB of the 2nd and 3rd molars and in the root area of the 2nd molar by 13.5 %. The 14th day of observation showed the end in the control, and in case of diabetes the prolongation of the inflammatory process because there was a decrease in the RD index in the area of the alveolar socket and IRB of the 1st molar, the crown and root of the 2nd molar and the root of the 3rd molar *(Table 1)*.

Based on the literature data and conducted researches, it can be stated that in the pathogenesis of the formation of complications in case of DM after surgical interventions, a key role is played not only by established by us earlier the violation of the state of the local nitric oxide system of the mucous membrane with the excessive formation of iNOS, but also by the combination of these changes with macrophage infiltration by CD68-immunopositive cells. Complex changes prolong secondary alteration, disrupt vascularization and innervation of tissues. The result of it is chronic inflammatory process, ineffective proliferation with violation of resorption and reparative relations and bone mineralization [16].

Conclusions

1. There are practically no CD68-immunopositive macrophages in the intact parodontium, the proliferative activity in the soft parodontium tissues is very low, there are no significant differences in the radiographic density of the tissues of the interalveolar and interradicular bone membranes, crowns and roots of the first, second and third molars.

2. In case of experimental diabetes mellitus, on the contrary, there is an initial significant diffuse infiltration by CD68-immunopositive macrophages with high proliferative activity, mainly fibroblasts.

3. Induced diabetes mellitus in rats, even without surgical interventions, leads to increased resorptive

processes in the bone tissue of the mandible and long-term prolongation of the inflammatory process after tooth extraction.

Prospects of further research. To confirm these conclusions, we plan to investigate the features of local and systemic complications after tooth extraction, including considering systemic diseases.

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