INDICATORS OF THE CYTOKINE SYSTEM AS MARKERS FOR THE COMPLICATIONS DEVELOPMENT IN PATIENTS WHO WENT THROUGH DENTAL IMPLANTATION

Ulyana Matolych
PhD, Associate Professor
Department of Surgical Dentistry and Maxillofacial Surgery
Danylo Halytsky Lviv National Medical University
69 Pekarska str., Lviv, Ukraine, 79010
ulyanam23@gmail.com

Abstract: According to clinical surveys, peri-implantitis develops in 12–43 % of cases, mucositis – in 60–80 % of patients with dental implants. The universal regulatory function is performed by immune system mediators – cytokines (interleukins – IL). The purpose of this research is to determine the functional condition of the cytokine system in blood serum at dental implantation in order to improve the early diagnosis of inflammatory complications. The research aim: to find out the features of immunological parameters changes in peripheral blood at mucositis, peri-implantitis in dynamics. Depending on the nosological nature of the inflammatory complications that arose in the peri-implant zone at the initial stage, the patients were divided into two groups: 1st – 14 patients with dental mucositis, 2nd – 12 patients with dental peri-implantitis of the I–II degree. The control group consisted of 15 patients who had no inflammatory complications.The level of IL-6, IL-8 and IL-17 in blood serum was defined by applying enzyme multiplied immunoassay using the set of chemical agents "Diaclone". There were no probable changes in the cytokines system with mucositis. The obtained results of laboratory and clinical studies indicate that dental peri-implantitis features with decrease in IL-6, increase in IL-8, IL-17 levels. That is why implantation requires thorough preliminary diagnostics, namely determination of patients' cytokine status. Assessment of the functional condition of the body cytokines system may be important for determining the strategy of dental implantation and prevention of early postoperative complications.

Keywords: maxillofacial area, interleukin-6, interleukin-8, interleukin-17, diagnosis, inflammation, peri-implantitis, mucositis.

1. Introduction

Dental implantation currently occupies one of the main places in the treatment of dental patients with various types of defects in dentures. Annually approximately 6 million implants are installed around the world [1, 2]. In this regard, the issue of improving the quality of dental implantation and prevention of complications acquire special significance. It is known that the successful implant integration is affected by the surgery technique, the condition of bone tissue, neurohormonal and immune homeostasis, the plaque microflora pathogenicity, the general reaction of the organism [3, 4].

Peri-implant mucositis is defined as mucosa inflammation around the dental implant cervix. Peri-implantitis is bone inflammation around the osteointegrated implant, which can lead to implant rejection and subsequent long and expensive restorative treatment [5]. According to clinical surveys, peri-implantitis develops in 12–43 % of cases, mucositis – in 60–80 % of patients with dental implants. Symptoms of inflammation can occur both immediately after the implantation, and in the long run (in many months or even years) [6]. There is no reliable data indicating which treatment (therapeutic, surgical) may be most effective in these diseases. Peri-implantitis is a complex disease that is difficult to treat and is constantly returning to the stage of recurrence. At treatment more than one year it is possible to speak about the chronic disease [7]. For a successful long-term treatment of mucositis and peri-implantitis, an integrated approach is required where an important place is given to the control of dental plaques and oral hygiene, both periodontal and dental implantation [8].

The universal regulatory function is performed by immune system mediators – cytokines (interleukins – IL). IL-17 is classified as inflammatory cytokine due to its ability to induce the expression of many inflammatory mediators, especially those involved in proliferation, ripening, and chemotaxis of neutrophils. Its main function is the induction of IL-6, IL-8 synthesis and, with this, involvement of other cells into the inflammation focus. The biological role of IL-6 is to induce inflammatory mechanisms and activate immune protection (activation and differentiation of T cells, ripening of B cells, increased hemopoiesis). IL-6 is the main inductor of the final stage of the immune response. IL-8 is one of the most important chemokines involved in the regulation of the early inflammatory response (the neutrophils' function) and helps to determine the type of further immune response. It is synthesized mainly by monocytes/macrophages, lymphocytes, fibroblasts, epithelial and endothelial cells [9, 10].

It is quite difficult to recognize the complications development at the early stages of the disease [11]. The pain and swelling of the soft tissues after implantation are always present, as the tissue injured in the course of surgical intervention doesn't heal instantly. The healing process lasts no more than a week in the absence of any complications. A meaningful answer to the question of adequate algorithm for assessing the condition of the cytokine system in blood serum in dynamics at dental implantation was not found in the available literature.

The purpose of this research is to determine the functional condition of the cytokine system in blood serum at dental implantation in order to improve the early diagnosis of inflammatory complications.

The research aim: to find out the features of immunological parameters changes in peripheral blood at mucositis, peri-implantitis in dynamics.

2. Material and Methods

The patients were on treatment in the department of maxillofacial surgery of Lviv Emergency Hospital and the Dental Medical Center Danylo Halytsky Lviv National Medical University for the period of 2014–2016.

41 patients before dental implantation and on the 5^{th}, 9^{th} day after surgical intervention have been examined. All patients were practically healthy. Among them – 23 men and 18 women aged 29 to 56 years. Depending on the nosological nature of the inflammatory complications that arose in the peri-implant zone at the initial stage, the patients were divided into two groups: 1^{st} – 14 patients with dental mucositis, 2^{nd} – 12 patients with dental peri-implantitis of the I-II degree. The control group consisted of 15 patients who had no inflammatory complications. Clinical-radiological, laboratory examination has been made to all patients.

The level of IL-6, IL-8 and IL-17 in blood serum was defined by applying enzyme multiplied immunoassay using the set of chemical agents and following the instructions set by the "Diaclone" producer (France).

The research results are shown as arithmetic average values and standard deviations (M±m). t Student criteria were applied for estimating possible differences between the two groups. Main calculations were made in Excel 2013.

3. Results

After the dental implantation surgical phase patients showed various relevant local reactions to surgical trauma. Clinical signs of the local reaction: pain, mucosa swelling and hyperemia, fibrinous pellicle on the suture line – found in patients of all groups. Local inflammation symptoms disappeared in the majority of control patients on the 5.6±0.6 day after the implantation. In this period, the mucosa became pale pink in color, the wound edges were adjacent to each other, their contours were even and clean, there was no pain and bleeding when palpation of the surgical area. Peri-implantitis is hard to differentiate from mucositis at the early stages after the implantation in case of appearance of the oral cavity acute inflammation signs. In patients of the 1st and 2nd comparison group unequal severity of edema, hyperemia, pain in the operation sites have been noted on the 5th day after the implantation. Thus, half of the patients demonstrated the maximum intensity of these signs manifestation; while the rest showed only their slight decrease. Regression of inflammatory phenomena in patients of the 1st group took place on the 9th day. Patients of the 2nd group demonstrated significant swelling and rubor of the soft tissues surrounding the implant, severe pain in the area of artificial root implantation, gums bleeding, the appearance of pockets in the gums tissues, formation of fistulas in the area adjacent to the implant with exudates and pyorrhea, fever.

Indicators of levels of IL-6, IL-8, IL-17 of the patients in the control group are presented in **Table 1–3**.

Table 1

The level of IL-6 in blood serum of patients with dental mucositis and dental peri-implantitis (ng/l)

Research groups	Research terms		
	the 1st day	the 5th day	the 9th day
Control rate	5.8±0.4	5.8±0.4	5.8±0.4
The 1st group	6.2±0.3	6.6±0.2*	6.3±0.3
The 2nd group	13.6±0.2*,**	22.4±0.2*,**	26.4±0.3*,**

Note: ** – P<0.05 as compared to the control rate; ** – P<0.05 as compared to the 1st group*

In the 1st group there was no significant change in the level of IL-6 in comparison with the control group. On the 1st day in the 2nd group the level of IL-6 was by 2.3 times higher than in the control group and twice as much as in the 1st group. Increase in the level of IL-6 was until the 9th day.

Table 2

The level of IL-8 in blood serum of patients with dental mucositis and dental peri-implantitis (ng/l)

Research groups	Research terms		
	the 1st day	the 5th day	the 9th day
Control rate	2.0±0.2	2.0±0.2	2.0±0.2
The 1st group	5.3±0.2*	3.2±0.6	2.8±0.4
The 2nd group	19.6±0.2*,**	16.4±0.4*,**	13.2±0.3*,**

Note: ** – P<0.05 as compared to the control rate; ** – P<0.05 as compared to the 1st group*

The highest level of IL-8 (by 9.8 times as compared to the control group) on the 1st day was recorded in the 2nd group, which corresponded to the maximum activation of the immune cells in the inflammatory focus and allows predicting the development of the peri-implantitis. During the 9-days period there was a tendency to decrease of IL-8 content but in the 2nd group the level remained significantly higher by 6.6 times as to the control group and by 4.7 times than in the 1st group.

Table 3

The level of IL-17 in blood serum of patients with dental mucositis and dental peri-implantitis (ng/l)

Research groups	Research terms		
	the 1st day	the 5th day	the 9th day
Control rate	2.2±0.8	2.2±0.8	2.2±0.8
The 1st group	5.6±0.2*	4.6±0.2*	3.1±0.2
The 2nd group	14.5±0.4*,**	10.2±0.3*,**	8.3±0.2*,**

Note: ** – P<0.05 as compared to the control rate; ** – P<0.05 as compared to the 1st group*

The patients demonstrated the increase in IL-17 concentration before the surgical intervention, which indicated pronounced inflammatory process. The 1st group patients manifested decrease in the pain intensity, improvement of the general-somatic condition on the 9th day. The content of IL-17 decreased by 1.8 times when compared with its level on the first day but remained above the control group by 4 times. High level of IL-17 further preserved on the 9th day in the 2nd group indicating pronounced inflammatory process.

4. Discussion

It has been shown that when IL-17 level decreases, IL-8 production decreases and IL-6 production increases, indicating cytokine disregulation and determines the complicated clinical course. The obtained data confirm high sensitivity of interleukins as inflammation markers.

The inflammatory process of the patients with mucositis was accompanied by catarrhal phenomena on the 9th day. Chronic inflammation of the peri-implant cuff mucosa, congestive hyperemia and edema have been noted. There was no pain. Hypertrophic phenomena prevailed in the clinical aspect of another part of the patients. Patients complained of unusual appearance of gum, their growth, bleeding, pain when eating solid food. There was the increase in the gingival papilla at the teeth adjacent to the implant and the gingival margin of the peri-implant cuff, the mucosa of which sometimes expanded to such an extent that it partially closed the implants crowns, forming cavities containing food residues, dental plaque. No pathological changes were detected on radiograph. There were no probable changes in the cytokines system with mucositis. In the absence of timely and adequate treatment, the spread of inflammation from the tissue cuff to the bone tissue surrounding the implant and the development of the peri-implantitis is possible. Patients with peri-implantitis complained of pain in the implant area. At objective examination: presence of edema and hyperemia of the peri-implant gum, serous and purulent discharge, the presence of granulations and peri-implant pocket, mobility of the implant of varying degrees. The radiograph demonstrated destruction of bone tissue.

It has been revealed that one of the main factors of the increased risk of dental peri-implantitis is cytokine system imbalance.

The obtained results of laboratory and clinical studies indicate that dental peri-implantitis features with decrease in IL-6,

increase in IL-8, IL-17 levels. That is why implantation requires thorough preliminary diagnostics, namely determination of patients' cytokine status.

Thus, the results of the research carried out substantially complement the idea of the etiology of dental mucositis and dental peri-implantitis.

Assessment of the functional condition of the body cytokines system may be important for determining the strategy of dental implantation and prevention of early postoperative complications. Further researches will determine the scheme of complex therapy of peri-implant tissues diseases, which includes monitoring the immunological condition of patients.

References

1. Mesmer, C., Forster, A., Antal, M., Nagy, K. (2012). Clinical, microbiological and immunological findings in peri-implantitis patients with bar-retained lower removable partial dentures, compared to a healthy control group (12-month-follow-up). Fogorvosi Szemle, 105 (2), 59–64.
2. Schar, D., Ramseier, C. A., Eick, S., Arweiler, N. B., Sculean, A., Salvi, G. E. (2012). Anti-infective therapy of peri-implantitis with adjunctive local drug delivery or photodynamic therapy: six-month outcomes of a prospective randomized clinical trial. Clinical Oral Implants Research, 24 (1), 104–110. doi: 10.1111/j.1600-0501.2012.02494.x
3. Bykova, N. I., Budzinskiy, N. E., Maksimova, Ye. M. (2017). Rol mikrobnoy flory v patogyenyezye pyeriimplantita i vospalityelnykh zabolyevaniy tkanyey parodonta [The role of microbial flora in the pathogenesis of perimplantite and inflammatory diseases of parodonta tissues]. Scientific Almanac, 2-3 (28), 319–325.
4. Suarez-Lopez del Amo, F., Yu, S.-H., Wang, H.-L. (2016). Non-Surgical Therapy for Peri-Implant Diseases: a Systematic Review. Journal of Oral and Maxillofacial Research, 7 (3), e13. doi: 10.5037/jomr.2016.7313
5. Serino, G., Turri, A. (2011). Outcome of surgical treatment of peri-implantitis: results from a 2-year prospective clinical study in humans. Clinical Oral Implants Research, 22 (11), 1214–1220. doi: 10.1111/j.1600-0501.2010.02098.x
6. Candel-Marti, M., Flichy-Fernandez, A., Alegre-Domingo, T., Ata-Ali, J., Penarrocha-Diago, M. (2011). Interleukins IL-6, IL-8, IL-10, IL-12 and periimplant disease. An update. Medicina Oral Patologia Oral y Cirugia Bucal, 16 (4), e518–e521. doi: 10.4317/medoral.16.e518
7. Esposito, M., Grusovin, M. G., Worthington, H. V. (2012). Treatment of peri-implantitis: what interventions are effective? A Cochrane systematic review. European Journal of Oral Implantology, 5, 21–41.
8. Vered, Y., Zini, A., Mann, J. (2011). Teeth and implant surroundings: Clinical health indices and microbiologic parameters. Quintessence International, 42, 339–344.
9. Matolych, U. D., Masna-Chala, O. Z., Lapovets, L. Y. et. al. (2017). Dynamics of proinflammatory cytokines at phlegmons of the maxillofacial area. Fiziolohichnyi Zhurnal, 63 (2), 40–45. doi: 10.15407/fz63.02.040
10. Li, J. Y., Wang, H. L. (2014). Biomarkers associated with periimplant diseases. Implant Dentistry, 23 (5), 607–611. doi: 10.1097/id.0000000000000129
11. Faot, F., Nascimento, G. G., Bielemann, A. M., Campao, T. D., Leite, F. R. M., Quirynen, M. (2015). Can Peri-Implant Crevicular Fluid Assist in the Diagnosis of Peri-Implantitis? A Systematic Review and Meta-Analysis. Journal of Periodontology, 86 (5), 631–645. doi: 10.1902/jop.2015.140603