Prognosis of possible implant loss after immediate placement by the laboratorial blood analysis and evaluation of intraoperatively derived bone samples

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Abstract

Results of Cochrane systematic review has shown that even immediate or immediate-delayed implant placement could be characterized with higher risk of possible implant loss and corresponding implant-related complications compared to the delayed protocol, but in fact there is a deficiency of evidence-proved data to evaluate direct advantages and disadvantages of immediate, immediate-delayed or delayed implants placement. Objective of research was to evaluate possibility of prognosis for implant loss after immediate placement by the results of laboratorial blood analysis and intraoperatively derived bone samples. By the inclusion criteria sample of 48 patients was formed, among which 22 were males and 26 were females, who undergone procedure of immediate implant placement. Venous blood samples were collected from the patients two weeks before scheduled implantation procedure. Blood samples were analyzed by the levels of free thyroxine concentration, amount of thyrotrophic hormone, calcium level in blood plasma and activity of alkaline phosphatase. During the miniinvasive tooth extraction stage bone tissue samples were collected from the area of alveolar socket. After homogenization procedure, bone biopsy samples were studied on the amount of Gla-proteins and fibronectin. Among the group of patients with dental implants loss higher levels of free thyroxine and thyrotrophic hormone were registered, which confirms the involvement of the thyroid gland in the processes of osseointegration. In the group of patients with loss of dental implants also higher levels of free ionized calcium were determined, while there was no statistical difference among levels of total calcium and inorganic phosphate levels ($P > 0.05$). Findings suggest that patients with dental implant loss demonstrate lower levels of fibronectin, Gla-protein and acidic phosphatase activity compare to the patients with successful immediate implant placement results during 12 months monitoring. The multivariate correlation analysis showed that the number of rejected dental implants demonstrate a positive linear statistically significant association with values of acid phosphatase activity ($P < 0.05$). The outcome of this research shows that preoperative laboratorial blood analysis and intraoperative analyses of bone samples could help to determine possible risk associated with implant loss after immediate placement during 1st year of monitoring.

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Introduction

Immediate implant placement, which by the definition proposed by the Glossary of Implant Dentistry corresponds to the immediately implant installation into the tooth extraction socket, over the years has been a subject for discussion corresponding to the parameters of its' success, predictability and remote prognosis.[1-5] Results of Cochrane systematic review, provided by Esposito et al., has shown that even immediate or immediate-delayed implant placement could be characterized with higher risk of possible implant loss and corresponding implant-related complications compared to the delayed protocol, but in fact there is a deficiency of evidence-proved data to evaluate direct advantages and disadvantages of immediate, immediate-delayed or delayed implants placement.[6] By the results of

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Wagenberg et al. overall survival rate of 1081 implants placed right into extraction socket reached level of 95%, while most of the fixtures were monitored for the period of 2-11 years.[7] By the criteria of bone-implant contact Chang and colleagues has proved that immediate implant placement could be effective even during the installation of titanium screws into extraction sockets with previous periradicular lesions.[8] Overall patient satisfaction with immediate implants varies in the range of 90-96% by the results of visual analog scale, which helps to conclude that such procedure is applicable for the dental patients.[9]

On the other hand, numerous clinical studies have shown that waiting for full healing of the post-extraction socket for further provision of implant placement is not categorized as compulsory fundamental condition anymore.[3,6,9] The choice of immediate implantation method depends on a number of local clinical factors, that includes absence of inflammation in the soft tissues, surrounding the tooth socket, and in alveolar bone adjacent to the implant; sufficient amount of surrounding bone tissue; enough bone volume at the bottom of the alveolar socket to provide sufficient primary stabilization of the implant; absence of non-corrected inflammatory alteration of bone structure.[10]

A number of studies have shown a positive suppressive effect of immediate implantation on bone resorption after tooth extraction and on further bone atrophy. Fresh-opened alveolar socket has a number of undeniable biological advantages in relation to the processes of osteogenesis and osteointegration.[11,12] According to numerous authors, the immediate placement of the implant in the freshly opened alveolus after tooth extraction allows to use physiologically active bone healing mechanism to achieve effective osteointegration of the implant.[11-14] Also, such approach saves the time usually needed for the achievement of total ridge healing.

However, immediate implant placement analogically to delayed implant placing protocol characterized by some level of implant-associated risks that in future can provoke implant loss. In the research provided by Heitz-Mayfield L., which was dedicated to the analysis of possible peri-implantatis risk factors, author summarized that for the development of biomarker-associated peri-implantitis diagnostic approach there is a need of further prospective studies which should evaluate inter-relation between clinical symptoms of peri-implant pathology and corresponding biological markers variations.[15] Up to date there is still a small amount of evidence for possible use of biochemical diagnostic tools that could be clinically available for prediction of peri-implantitis and periodontitis progression.

Considering above-mentioned facts, the present research aims to evaluate possibility of prognosis for implant loss after immediate placement by the results of laboratorial blood analysis and intraoperatively derived bone samples

Materials and methods

Patients sample for further research was formed by selecting individuals out of number of dental patients from University Dental Clinic (Uzhhorod National University). Process of patients selection was based on principles described in research of Goncharuk-Khomyn & Keniuk[16] and Hayacibara et al[17] that were the next: 1) the necessity of tooth extraction because of prosthetic, therapeutic or surgical considerations due to the planned treatment algorithm that was previously discussed with the patient; 2) patient agreement on proposed treatment algorithm provided by the signature of Patient Informed Consent Form; 3) the absence of attendant somatopathologies or coterminous absolute or relative contraindications that would limit the possibility to provide immediate dental implantation procedure; 4) the availability of a competent bone volume parameters by the results of CBCT evaluation that allow immediate implantation procedure (absence of any bone dehiscence or bone fenestration, no facts of endodontic treatment failure in anamnesis in the area of future implant position, presence of minimum 3 mm between proposed dental implant position to adjacent tooth roots and 3 mm of bone thickness to the location of mandibular channel or maxillary sinus).[17]

By the inclusion criteria sample of 48 patients was formed, among which 22 were males and 26 were females.

Venous blood samples were collected from the patients two weeks before scheduled implantation procedure. Blood samples were analyzed by the levels of free thyroxine

concentration, amount of thyrotrophic hormone, calcium level, ionized blood calcium, inorganic phosphorus concentration and activity of alkaline phosphatase. Free thyroxine level was determined by competitive immunoassay using TOSOH (Japan) kits on the autoimmune enzyme analyzer. The reference range for the free thyroxine levels was interpreted as 13.0-18.0 pmol/l.[18] The amount of thyroid-stimulating hormone (TTG), also known as thyrotrophic hormone, was determined by the immune enzyme method (sandwich method). The reference range for thyroid stimulating hormone was interpreted as 0.4-4.0 mIU/L.[19] The total amount of calcium was determined with the use of biochemical analyzer BT 3000 (Italy) using Diasys (Germany) kits. The reference range was interpreted as 2.20-2.60 mmol/l.[19] The concentration of ionized blood calcium was investigated on the ion-selective Easy Lyte Calcium analyzer. The reference range of ionized blood calcium values was 1.15-1.34 mmol/l.[20] Determination of inorganic phosphorus concentration in blood plasma was performed on biochemical analyzer BT 3000 (Italy) using Diasys sets (Germany). The reference range of inorganic phosphorus values was 0.8-1.5 mmol/l.[20] The activity of alkaline phosphatase (AF) was determined on the automatic biochemical analyzer AU640 (Japan) using Olympus kits (Japan). Reference range of values was interpreted as 50-120 U/l.[20]

Selected dental patients were treated by algorithm of miniinvasive tooth extraction with further implant placing in the formed edentulous area.

During the mini-invasive tooth extraction stage, bone tissue samples were collected from the area of alveolar socket. After homogenization procedure, bone biopsy samples were studied on the amount of Gla-proteins and fibronectin. Bradford protein assay was used with calibration curve in the range of 1-20 mcg/ml. Determination of the amount of fibronectin (FN) was carried out by immunoassay solid phase method using the test system REF TS 12030. The concentration of fibronectin in μg/g was calculated from the calibration curve. Determination of the amount of Gla-protein was carried out by immunoassay solid phase method using the test system B1-200G2 (Biomedica). The amount of Gla-protein was calculated according to standard samples and expressed in nmol/g.

K3Pro implants with parameters of 9.0 mm by the length and 3.5 mm in diameter were used in all clinical cases. After carrying out the appropriate anesthesia, atraumatic tooth extraction procedure was provided, with further implant installation into extraction sockets. Depending on the quality of the alveolar bone, an appropriate bone preparation was performed to achieve prognostic implant position. Due to the fact that the anatomical shape of the alveolar socket never corresponds to the shape and size of the implant, especially in the marginal region, a slit-like defect occurs between the implant surface and the bone wall, which disturbs parameters of primary implant stability and creates conditions for connective and epithelial tissues invaginations. In order to increase the stability of the implant, gap closure was achieved with the use of biocomposite bone substitute material «SYNTHEKIST» (Ukraine) and collagen membrane. After surgical intervention patients were assigned with an antibiotic «Amoxiclav» for one day after the operation and rinses for seven days with «Aqua-paragel» (an antimicrobial agent with prolonged immunocorrective action), which helps to strengthen the processes of physiological self-cleaning of the oral cavity (by the conclusion of the State Sanitary and Epidemiological Expertise of the Ministry of Health of Ukraine No. 05.03.0204 / 66185 dated 25.12.2007).

Evaluation of implant success was provided by Implant Quality Scale proposed by ICOI[21] with additional evaluation of symptoms for sinus infection or inflammation, the presence of an adequate area of keratinized gum attachment and X-ray confirmation for perforation absence at the level of maxillary sinus. During the period of 12 months monitoring by the fact of implant survival/loss patients were divided into 2 groups (group 1 – patients with no signs of implant loss after immediate implantation, group 2 – patients with facts of at least one implant loss after immediate implantation) for further comparative analysis of laboratorial parameters.

Between-group comparison of patients with successful implant placing results and implant loss by the parameters of means was provided by non-parameteric Kruskal–Wallis H test with the use of IBM SPSS Statistics 18 (SPSS). Principles of linear and quadratic regression analyses were used to discover relationship values between a scalar dependent

variable (implant loss/implant survival) and independent variables (age, gender, implant localization parameters).[22-24] All statistical analysis was provided in Microsoft Excel software (Microsoft Office 2016, Microsoft).

Results

Among 48 patients (22 male and 26 female) requiring dental implantation procedure and agreed on provision of immediate implant placing after mini-invasive tooth extraction, 61 dental implants were installed. 23 patients received implants only in mandible region, 19 patients were treated with implants only at maxilla region, while 6 patients received implants on both jaws. The age of patients varied from 24 to 68 years and amounted to an average of 46 ± 2.16 years. During the period of 12 months monitoring 8 implants were lost accounting for 13.1% of the total immediately placed implants. By the fact of implant survival/loss patients were divided into two groups. The first group consisted of 40 patients who did not show any case of dental implants rejection, hereinafter referred to as group 1. The second group consisted of 8 patients who presented with the loss of at least one dental implant, these patients formed group 2. The age of the patients in the group 1 ranged from 22 to 67 years and amounted to an average of 45.5 ± 11.2 years. The age of patients in the group 2 fluctuated in the nearly same interval from 24 to 67 years, but because of different distribution amounted to an average of 46.5 ± 11.9 years.

No significant association (either linear or curvilinear) was found between age, gender and implant site installation parameters and a fact or period of implant loss during 12 month monitoring period ($p > 0.05$) (Table 1).

Parameters	Fact/Period of implant loss	Linear	Quadratic
Age	Implant loss during 1st week Implant loss during 1st month Implant loss during 6 months Implant loss during 7-12 months	P > 0.05	P > 0.05
Gender	Implant loss during 1st week Implant loss during 1st month Implant loss during 6 months Implant loss during 7-12 months	P > 0.05	P > 0.05
Implant position	Implant loss during 1st week Implant loss during 1st month Implant loss during 6 months Implant loss during 7-12 months	P > 0.05	P > 0.05

Table 1. Regressions Between Age, Gender and Implant Position parameters and Fact/Period of implant loss.

Comparison of the hormonal status in the preoperative period among patients of the two groups revealed certain features. The analysis of the obtained results showed that the level of free thyroxine in the blood plasma among patients with successful integration of dental implants was in the range from 9.7 to 18.4 pmol/l. In the group 2 with dental implant rejection this indicator ranged from 12.7 to 17.6 pmol/l. It should be noted that the concentration of free thyroxine was not statistically significantly higher in patients who had cases of dental implants rejection ($p > 0.05$). The levels of thyroid stimulating hormone were in the range of from 0.57 to 2.88 mIU/L among patients in group 1 and were statistically significantly lower than the levels of this hormone determined among patients in group 2 that varied from 0.99 to 4.82 mIU/L ($p < 0.05$). Thus, in the group of patients with dental implants loss higher levels of free thyroxine and thyroid hormone were registered, which confirms the involvement of the thyroid gland in the processes of osseointegration.

During the study of the phosphorus-calcium metabolism in venous blood specimens 2 weeks prior to surgical intervention, the levels of total and ionized calcium, inorganic phosphate content and alkaline phosphatase activity were investigated. Analysis of phosphoric-calcium metabolism indices in different groups demonstrated that total calcium levels were comparable in both groups regardless the fact of implants survival or loss. Total calcium levels ranged from 2.17 to 2.54 mmol/l among patients from group 1 and from 2.08 to 2.54 mmol/l among patients within group 2. The levels of ionized calcium were in the range from 1.18 to 1.33 mmol/l among patients without any implants loss, and such parameters were statistically significantly lower ($p < 0.05$) than those obtained from the patients with at least one implant loss, where Ca^{2+} levels ranged from 1.19 to 1.43 mmol/l. There was no statistically significant difference between groups by the level of inorganic phosphates ($p > 0.05$). The determination of activity of alkaline phosphatase among the subjects from the group 1 found that this parameter was in the range from 121 to 247 U/l, while in group 2 the activity of the enzyme was higher and ranged from 140 to 354 U/l. Thus, in the group of patients with loss of dental implants, higher levels of free ionized calcium were determined, while there was no statistical

difference among levels of total calcium and inorganic phosphate levels ($p > 0.05$). It should be noted that the activity of alkaline phosphatase in the group of patients with an adverse effect of dental implantation was higher than among patients without rejection of dental implants, even though this difference was not statistically approved ($p > 0.05$).

The obtained data showed that the concentration of fibronectin in bone samples gathered from the patients who had no rejection of dental implants ranged from 0.4 to 6.0 μg/g averaging to 2.22 μg/g and was statistically significantly higher ($p < 0.05$) compared with values obtained in the group 2 of patients with facts of implants loss, where the levels of fibronectin fluctuated within narrower limits from 0.6 to 3.2 μg /g and averaging to 1.04 μg/g. The level of Gla-protein in the bone tissue, determined in patients without implant loss ranged from 4.0 to 9.3 nmol/g averaging to 7.4 nmol/g. This indicator in group 2 of patients with dental implant rejection was in the range from 1.3 to 12.1 nmol/g and amounted to an average value of 5.9 nmol/g. The activity of acid phosphatase in samples of bone tissue varied from 0.004 to 0.182 U/g among patients in group 1 and from 0.005 to 0.068 U/g in patients in group 2. The average activity of acidic phosphatase was 0,03 U/g among patients without implant loss during monitoring period and was statistically significantly higher ($p < 0.05$) compare to the values obtained in the group of patients with loss of dental implants – 0.01 U/g.
Thus, the findings suggest that patients with dental implant loss demonstrate lower levels of fibronectin, Gla-protein, and acidic phosphatase activity compare to the patients with successful implants placing results during 12 months monitoring.

The multivariate correlation analysis showed that the number of rejected dental implants demonstrate a positive linear statistically significant association with values of acid phosphatase activity ($p < 0.05$). Also, in the group 2 statistically significant linear relationship was found between the levels of fibronectin and Gla-protein ($p < 0.05$), and a negative linear statistically significant association was discovered between the content of Gla-protein in the bone and the phosphatase activity ($p < 0.05$). In the group of patients with successful implant installation results, statistically significant positive linear correlation between acid phosphatase activity and bone fibronectin levels was found ($p < 0.05$).

Discussion

Previously provided analysis by Chen et al. has shown that both immediate and delayed implant placement are characterized by predictable level of success and survival, even though there are only few studies that demonstrate long-term results of immediately placed implants monitoring.[25] Thus, short time survival data of immediately placed implants are comparable to those that were installed not into extraction socket, but into healed residual ridge. On the other hand, Schropp & Isidor advise to allow immediate implant placement only for skilled and well-trained treatment teams of professionals.[26] Koh et al. pointed on the role of proper case selection for immediate implant realization procedure with the purpose to achieve high implant success and survival parameters.[3] With regard to the limited data author also stated, that success of immediate implant placement is not related to the localization of implant site, but area of molars is more challenging that the others. Good prognosis of immediately placed implant can be reached after immediate function and non-functional loading, but such conclusion also should be argumented by the results of further randomized controlled clinical studies.[26]

Previously provided analysis of literature data helped to systematize that potential risk of peri-implant pathology development with possible further implant disintegration associated with low level of oral hygiene, smoking habit, presence of periodontitis pathology and diabetes mellitus in the anamnesis, influence of genetic factors and characteristics of implant surface. From all the mentioned above strong correlation for peri-implantisis was established from evidence of non-adequate oral hygiene, previous or present periodontitis pathology influence and smoking.[15] In previous study of Paquette et al., it was noted that implant failures occur at relatively low rate, but they show tendency to summarize in cluster pattern among patients with common risk factors.[27] Such rick factors were categorized by author as associated directly with implant construction, procedure realization aspects, anatomical features, general health condition, occlusion parameters, microbial biofilm, specific

of host immune and inflammatory responses and genetics.

Due to the need of implant loss prognosis, previous researches also were dedicated to the possible identification of biomarkers in the peri-implant crevicular fluid that can be used for the prognosis of possible peri-implantitis development. Protease, interleukin-1beta, neutrophil elastase, myeloperoxidase, glucuronidase, neutral proteolytic enzyme, collagenase-2, prostaglandin E2, aspartate aminotransferase, tumour necrosis factor-alpha, osteocalcin deoxypyridinoline, matrilysin-1, pro-inflammatory cytokine IL-6, anti-inflammatory cytokine IL10 and cathepsin K were tested as possible peri-implantitis prognostic markers with different predictive values and different sensitivity and specificity parameters.[28-30] Approbation of osteocalcin, urinary pyridinoline and deoxypyridinoline as possible markers of implant failure prediction has shown no statistical evidence.[31]

Results of provided study on the content of fibronectin, Gla-protein, and acid phosphatase in bone tissue samples among patients undergoing procedure of immediate dental implantation allowed to reveal certain patterns. Obtained data suggest that patients who undergone procedure of immediate dental implantation and further implant loss within 12 month monitoring period demonstrate lower levels of fibronectin, Gla-protein, and acid phosphatase activity compare to the patients with successful implantation results during the same remote period. At the same time, it should be noted that in more than 30% of the surveyed, the activity of acid phosphatase was so low that it was outside the sensitivity of the method. In addition, patients with dental implants loss demonstrated higher levels of free thyroxine and thyroid hormones and statistically higher levels of Ca^{2+} compare to the group of patients without any dental implant loss. In the research of Du and colleagues, authors has shown that serum level of bone formation markers such as bone-specific alkaline phosphatase and bone Gla-protein could be used for the evaluation of osseointegration degree of titanium implants.[32] Even though this research was provided on the osteoporotic rats treated with simvastatin, obtained results shows that the raise of bone Gla-protein produced by mature osteoblasts positively correlates with osseointegration progressing at the later stages of monitoring.

Previous research of Paknejad et al. has found that raise of aminotransferase activity levels in peri-implant crevicular fluid was strongly associated with amount of bleeding on probing around implant fixture, while activity levels of alkaline phosphatase demonstrated no statistical correlation with increased amount of bleeding on probing (p = 0.05).[33] In our research, we have found that activity levels of alkaline phosphatase greater than 185 U/l with the increase of ionized calcium level and tyreotropic hormone level could be interpreted as biomarkers of possible risk of implant desintegration. However, it should be noted that even the activity of alkaline phosphatase in the group of patients with an adverse effect of dental implantation was higher than among patients without rejection of dental implants, obtained data difference was not statistically approved. Even though expression of alkaline phosphatase during the early period after implant installation interpreted as normal reaction to the procedure, further evaluation of its level changes could be used as a predictive test during monitoring of remote implant condition. Number of other researches has proved association between raise of alkaline phosphatase level and prognostic risk of dental implant disintegration.[34-36]

In the research of Tirachaimongkol and collegues, author has found correlation between alkaline phosphatase marker and values of implant stability quotient at all measurements made from 1 week after implantation to the 12th week after implantation.[37] Weak level of correlation could be interpreted in the way, that greater raise of alkaline phosphatase could be noted only during peri-implant pathology development, while in Tirachaimongkol's study no implant loss was registered during monitoring period.

The outcome of this research shows that preoperative laboratorial blood analysis and intraoperative analyses of bone samples could help to determine possible risk associated with implant loss after immediate placement during 1st year of monitoring. Further perspective of the research will be aimed at evaluation of interaction between fibronectin, Gla-protein, acid phosphatase activity, Ca^{2+} levels and free thyroxine and thyroid hormones changes with corresponding clinical signs of implant failure.

Conclusions

It has been shown that early disintegration of immediately placed dental implants could be associated with lower level of acid phosphatase activity, fibronectin and matrix Gla-protein content in bone biopsy samples, because of these markers involvement in osteointegration process. Also, it has been established that the level of ionized calcium above 1.20 mmol/l and the activity of alkaline phosphatase more than 185 U/l with increased level of TSH in the blood to the indicators of the upper limit of norm or higher, could serve as risk markers for possible prognosis of dental implants disintegration after immediate placement.

Declaration of Interest

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