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Original Article

Correlation analysis between bone metabolism factors and the stability of dental implant in the postoperative recovery of dental implanted patients

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Abstract: The aim of this research was to investigate the effect of osteoprotegerin and RANKL on the change of implant stability quotient (ISQ). Seventy-eight patients were implanted Straumann soft tissue level implants (Switzerland) through a non-submerged method. Survival rate of dental implants and postoperative complications was examined. Modified plaque index (mPLI) and modified sulcus bleeding index (mSBI) were evaluated. In the 1st, 2nd, 3rd, 4th, 6th, 8th and 12th week after operation, perio-implant crevicular fluid (PICF), gingival crevicular fluid (GCF) and ISQ were measured, respectively. Osteoprotegerin and RANKL levels in GCF and PICF samples were detected by ELISA. There was no mechanical complication. And there was no obvious marginal bone loss. Osteoprotegerin in GCF and PICF increased in the 2nd week, which was much higher than that in other time points ($P<0.05$). RANKL in GCF was the highest in the 12th week ($P<0.05$), and RANKL in PICF was the highest in the 3rd week ($P<0.05$). And there was no difference between osteoprotegerin and RANKL in GCF and PICF ($P>0.05$). Osteoprotegerin/RANKL ratio in PICF was higher than that in GCF in the 1st week ($P=0.034<0.05$). Moreover, ISQ was the lowest in the 4th week than in the 1st, 2nd, 6th, 8th and 12th week ($P<0.05$). ISQ decreased when osteoprotegerin rose, and the trends of ISQ and RANKL were similar. When osteoprotegerin/RANKL ratio increased, ISQ decreased. There were respectively opposite and same trend between ISQ and osteoprotegerin and RANKL. On the basis of the relationship between ISQ and osteoprotegerin and RANKL, there might be a method to improve the stability by regulating osteoprotegerin and RANKL in GCF and PICF.

Keywords: Implant, implant stability quotient, osteoprotegerin, gingival crevicular fluid, perio-implant crevicular fluid

Introduction

Tooth loss is a common symptom of clinical diseases, which could reflect the condition of patients' dental diseases [1, 2]. In most countries, tooth loss is often considered as an effective indication of good or bad oral health. Thus, it is necessary to constantly monitor and take care of oral health, and dental diseases need relevant lifelong treatment [3]. For patients with tooth loss, the depth and width of the tooth have an effect on the success rate of dental implant, and it is also the key factor for a successful implantation. Bad bone quality in implantation site would lead to a low success rate of dental implant [4]. The closure of bone and soft tissue, the masticatory pressure and functional recovery of dental implant are important evaluation indexes for a successful implantation. And good long-term results of these indexes are significant in improving patients' quality of life.

The stability of dental implant is an important index to evaluate the formation of implant and osseointegration. Only by being sufficiently stable, dental implant can play a role in later use. Therefore, it is crucial to evaluate the healing of bone and soft tissue and functional recovery of dental implant for patients after surgery by detecting the stability of implant. At present, resonance frequency analysis (RFA) is widely used to detect dental implant stability in early osseointegration [5, 6]. This method is simple,

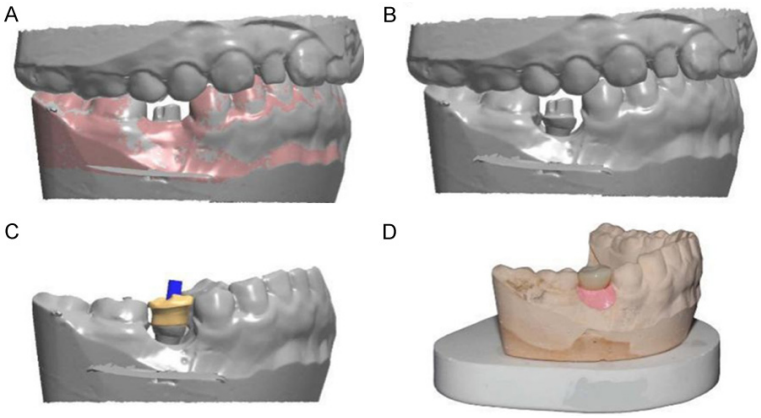

Figure 1. The model of implant-abutment.

easy and noninvasive, and it can perform a quantitative assessment on dental implant stability [7].

The condition of soft tissue surrounding the implantation site has a certain effect on a successful implantation. Gingival crevicular fluid (GCF) in periodontium and perio-implant crevicular fluid (PICF) have attracted more and more attention. GCF is the physiological solution exuding from plexus vasculosus in gingival dermis, and it can also participate in the inflammatory response as the inflammatory exudates [8]. GCF was first found in the early 19th century [9, 10]. Afterwards, Waerhaug described GCF as periodontal disease related liquid compound in his classic study [11, 12]. GCF has been found for many years, but its generation and function are still unknown to people. And the function of PICF also draws more and more attention from researchers gradually, but it is still unclear whether PICF has the same function as GCF and what is the function of PICF in the early stage of dental implant. However, some research indicated that PICF contained higher content and activity of type II collagen than GCF [13].

In addition, the process of dental implant involves bone remodeling which relates to the dynamic equilibrium of bone resorption and bone formation, and the process is closely related to the function of osteoclast and osteoblast. Both GCF and PICF contain osteoprotegerin (OPG), receptor activator of kappa B (RANK) and receptor activator of nuclear factor kappa B ligand (RANKL). These factors could induce the interaction between osteoblast and osteoclast, which plays an important role in the metabolism and growth of skeleton [14]. The latest research showed that RANKL/RANK/OPG could regulate bone metabolism and osteoclast growth during distraction osteogenesis [15]. The metabolites and factors had certain influence in distraction osteogenesis by RANKL/RANK/OPG [16, 17]. Although RANKL/RANK/OPG has an effect on bone metabolism and osteoclast growth, it still needs further research and argumentation on the effect of RANKL/RANK/OPG in implant osseointegration. In this research, we observed and analyzed the changes of detection indexes in GCF and PICF after dental implantation, and compared and analyzed the effect of OPG and RANKL on the change of implant stability quotient (ISQ).

Materials and methods

Data of patients

The data of patients in the department of stomatology of our hospital from May 2011 to December 2016 were retrospectively analyzed. Inclusion criteria: 1) patients were healthy without obviously serious illness and within 20< age <65; 2) patients suffered from tooth loss for at least three months in planning implantation region; 3) no bone grafting was needed; 4) there is no medication history of antibiotics within three months before the research; 5) for patients suffering from periodontitis, they needed basic periodontal inflammatory treatment including oral hygiene firstly; after the treatment periodontal probing depth ≤5 mm and gingival bleeding index ≤2 within the oral cavity; 6) patients were not addicted to tobacco or were non smokers; or patients were with less than 10 cigarettes per day. In addition, diabetic patients, heavy smokers, gravidas, alcoholics and drug abusers were excluded. All selected patients were given regular follow-up.

Seventy-eight patients were selected in this research: 26 males and 52 females with an average age of 41.6. This research had obtained the ethics committee approval from our hospital. All patients in this research signed informed consent forms.

Table 1. Scoring standards of mPLI

mPLI	Content
0	No dental plaque
1	Dental plaque was observed as the smooth neck of implant was slightly scratched by the top of probe
2	Macroscopic plaque
3	Mass plaque accumulation

Note: mPLI: modified plaque index.

Table 2. Scoring standards of mSBI

mSBI	Content
0	No bleeding detected along implant gingival margin by probe
1	Scattered hemorrhagic spot
2	Hemorrhagic spot inside gingival sulcus and in a linear pattern
3	Severe or spontaneous bleeding

Note: mSBI: modified sulcus bleeding index.

Dental implantation

According to the standard operating procedure, all patients were implanted (Straumann soft tissue level implants, Switzerland) by a non-submerged method. Patients rinsed their mouths with 0.1% of chlorhexidine gargle for 1 min. Perioral disinfection was performed by povidone iodine. Local infiltration anesthesia was implemented. H-shape incision was carried out in tooth loss region. Opened mucoperiosteal flaps. Fixed points by round bur, punched a hole layer by layer, and cooled the hole. The depth of the hole was measured by sounding scale. Then the implant was implanted, and abutment was placed (**Figure 1**). Mucoperiosteal flap was reposited and sutured. Before and after the end of the operation took and saved photos.

Observation indexes

Survival rate of dental implants: According to the standard issued by Buser [18], the survival rate of dental implants was examined. The specific standards were as follows: ① Clinical examination showed that the implants were stable and no mobility; ② Patients did not have any subjective feeling, such as pain or numbness; ③ There was no repeated outbreak of inflammatory response around the dental implant; ④ Imageological diagnosis results showed that there was no continuous cast shadow around the dental implant.

Postoperative complications: The main complication related to implant abutment was mechanical complication. The incidence rates of mechanical complications in implant abutment could assess the stability of the abutment, which provided a reliable evidence to implant restoration. Mechanical complications in implant abutment mainly include broken or fractured abutment, slipped thread, loosed screw, screw deformation and broken screw. In this research, we recorded the type and number of mechanical complications in implant abutment for all patients, and analyzed the total incidence of mechanical complications and the incidence of each type of complication.

Biological complications: Biological complications were evaluated by the health status of peri-implant soft tissue. We recorded the condition of peri-implant soft tissue of patients during the follow-up. The main evaluation indexes were modified plaque index (mPLI) and modified sulcus bleeding index (mSBI) [19]. MPLI could implement an objective and effective assessment on peri-implant plaque. The higher the mPLI value was, the worse the oral hygiene became. No dental plaque was a score of 0. As the smooth neck of implant was slightly scratched by the top of the probe, observed dental plaque was a score of 1. A macroscopic plaque was a score of 2. Mass plaque accumulation was a score of 3. mSBI could effectively reflect the health status, mainly the bleeding condition, of peri-implant mucosa. No bleeding detected along implant gingival margin by the probe was a score of 0. Scattered hemorrhagic spot was a score of 1. Hemorrhagic spot inside gingival sulcus in a linear pattern was a score of 2. Severe or spontaneous bleeding was a score of 3. Specific scoring standards of mPLI and mSBI were shown in **Tables 1** and **2**.

Detection indexes

Before operation, GCF was absorbed by absorbent paper from the loci locating in the medial and distal surface of implant and its two adjacent natural teeth. The weight of absorbent paper before and after the absorption of GCF was measured by AE240 electronic balance (METTLER, Sweden), then the weight of GCF

Table 3. Basic information of patients

Terms		Maxillary posterior teeth	Mandibular teeth	Number
Gender	Male	18	17	35
	Female	18	25	43
Age (years, mean)		41.6±14.2		

Table 4. The results of soft tissue examination

Parameters	Min	Max	Mean	Std
mPLI	0	3	0.75	0.51
mSBI	0	3	0.45	0.62

Note: mPLI: modified plaque index; mSBI: modified sulcus bleeding index.

was calculated. GCF was cryopreserved at -70°C. The same method was used to measure the weight of PICF. On further consultation in the 1st, 2nd, 3rd, 4th, 6th, 8th and 12th week after operation, patients were measured PICF and GCF, respectively. Osstell Mentor RFA (Integration Diagnostics, Savedalen, Sweden) was used to detect implant stability quotient (ISQ) on each further consultation because ISQ is very important to evaluate the integration of implant and bone. The detection was taken once by the probe on the medial surface of implant, buccal side and the lingual side, respectively. The mean value of ISQ in the three sites was ISQ value of implant. Data obtained were entered in a database. Then using ISQ-related monitoring data, each implant was completed by inserting a final crowns.

Implant periapical film was taken immediately after the operation and on further consultation, and the shadow and bone resorption around the implant were detected. The levels of OPG and RANKL in GCF and PICF samples were detected by ELISA, and the changes of OPG and RANKL in the early period of postoperation were observed.

Statistical analysis

SPSS21.0 statistical software was used to analyze the levels of OPG and RANKL in GCF and PICF at different points in time. The levels were shown as mean ± standard deviation. The changes of ISQ, OPG and RANKL in GCF and PICF were analyzed by ANOVA for repeated measurement. The differences between OPG and RANKL in GCF and PICF at same points in time were detected by t test. Relations of ISQ to OPG and RANKL at different points in time were analyzed by logistic regression, excluding the effect of age and gender. When *p* value was less than 0.05, the differences were significant.

Results

Basic information

There were 78 patients participated in this research, in which there were 43 females and 35 males (**Table 3**) with an average age of 41.2±12.9. There were 36 patients with maxillary posterior teeth missing (18 males and 18 females) and 43 patients with mandibular teeth missing (17 males and 25 females). And 78 implants (Straumann, Wandenburg, Switzerland) were inserted. All patients accepted further consultation after the 1st, 2nd, 3rd, 4th, 6th, 8th and 12th week. The retention rate, ISQ, OPG and RANKL in GCF and PICF were detected.

Retention rate of implants and postoperative complications

Mechanical complications and biological complications for all patients post operation were observed. There were no broken, loose, fall and obvious periodontal inflammations characterized by gum red and swell. Postoperative mPLI and mSBI were 0.75±0.51 (0-3) and 0.45±0.62 (0-3), respectively. The imaging examination results showed that there was no obvious marginal bone loss. Details about soft tissue condition were shown in **Table 4**.

On the basis of Buser's standard of implant retention rate, the implants of all patients were stable. And there was no recurrent inflammation around the implants. The results of imageological examination demonstrated that there was no continuous cast shadow surrounding dental implants. As a conclusion, the implant retention rate of our patients was 100%.

The change of OPG and RANKL in GCF and PICF

During the 12-week follow-up visit, all patients were reexamined OPG and RANKL in GCF and PICF in the 1st, 2nd, 3rd, 4th, 6th, 8th and 12th week

Table 5. OPG in GCF and PICF

Time/week	OPG		t	*P*
	GCF	PICF		
1st	418.7±18.7[a]	431.2±19.6[a]	-1.012	0.295
2nd	434.4±20.8	486.4±28.8	-0.839	0.414
3rd	415.2±17.1[a]	443.5±32.6[a]	-0.679	0.500
4th	391.4±16.8[a]	419.6±26.3[a]	-1.121	0.305
6th	390.5±17.9[a]	411.2±24.3[a]	-0.434	0.657
8th	384.1±21.2[a]	402.7±22.9[a]	-0.613	0.590
12th	381.1±18.9[a]	397.6±23.6[a]	-0.815	0.375

Note: Repeated measures analysis of variance, $P<0.05$. a: means there is a significant difference when compared with the OPG of 2nd week, $P<0.05$. OPG: osteoprotegerin; GCF: gingival crevicular fluid; PICF: perio-implant crevicular fluid.

Table 6. RANKL in GCF and PICF

Time/week	RANKL		t	*P*
	GCF	PICF		
1st	251.4±12.7	232.1±20.6[c]	0.791	0.471
2nd	241.3±16.8	256.3±26.7	0.314	0.817
3rd	237.7±18.3[b]	267.2±29.7	-0.579	0.691
4th	238.5±20.6[b]	251.8±26.1[c]	0.509	0.613
6th	241.2±19.6[b]	243.6±20.1[c]	0.497	0.561
8th	247.6±18.4	238.7±19.6[c]	0.348	0.590
12th	256.8±19.7	237.8±20.1[c]	0.051	0.914

Note: Repeated measures analysis of variance, $P<0.05$. b: means there is a significant difference when compared with the RANKL of 12th week, $P<0.05$. c: means there is a significant difference when compared with the RANKL of 3rd week, $P<0.05$. RANKL: receptor activator of nuclear factor kappa B ligand; GCF: gingival crevicular fluid; PICF: perio-implant crevicular fluid.

Table 7. OPG/RANKL Ratio

Time/week	OPG/RANKL		t	*P*
	GCF	PICF		
1st	1.66±0.12	1.89±0.65	-1.706	0.034
2nd	1.80±0.34	1.92±0.56	-0.811	0.423
3rd	1.75±0.14	1.65±0.35	0.233	0.825
4th	1.64±0.17	1.67±0.36	-0.509	0.633
6th	1.63±0.21	1.69±0.54	-0.497	0.743
8th	1.55±0.20	1.68±0.73	-0.348	0.792
12th	1.48±0.13	1.67±0.84	-0.530	0.614

Note: ANOVA, $P<0.05$. The ratio OPG/RANKL of PICF was remarkably higher than GCF at 1st week. There was no difference at other time. OPG: osteoprotegerin; RANKL: receptor activator of nuclear factor kappa B ligand; GCF: gingival crevicular fluid; PICF: perio-implant crevicular fluid.

after operation. The result showed OPG in GCF and PICF increased in the 2nd week which was much higher than those at other time ($P<0.05$). However, there was no difference between OPG in PICF and GCF ($P>0.05$) (**Table 5**). This demonstrated that 1-2 weeks after operation the proliferation and differentiation of osteoblast have been initiated. And in the 2nd week, the level of OPG in GCF also increased which indicated there were plenty of active osteoblasts and the periodontium of adjacent teeth may also participate in the bone remodeling.

Moreover, analysis on RANKL in GCF and RANKL showed that RANKL in GCF was the highest in the 12th week ($P<0.05$), and RANKL in PICF was the highest in the 3rd week ($P<0.05$). And there was no difference between RANKL in GCF and PICF ($P>0.05$) (**Table 6**). This might be due to OPG high affinity combined with RANKL and reduced the differentiation of osteoclast by inhibiting function of RANKL.

On the basis of OPG and RANKL, we calculated OPG/RANKL in GCF and PICF at each time point. In the 1st week, OPG/RANKL in PICF was much higher than that in GCF ($P=0.034<0.05$). This also demonstrated the initiation of proliferation and differentiation of osteoblast. There was no difference at other time points (**Table 7**).

ISQ detection

After the implanting operation, ISQ was tested. ISQ at different time was compared by repeated measures analysis of variance. In the 1st week, there was a slight rise of ISQ and then decreased. The lowest ISQ was appeared in the 4th week, and then an increase followed. Statistical analysis showed that ISQ in the 1st, 2nd, 6th, 8th and 12th week were significantly higher than that in the 4th week ($P<0.05$) (**Table 8**). This related to the resorption- immersion remodeling process which occurred in the 2-4 weeks after operation.

Relationships between ISQ and OPG/RANKL

Compared with the trend of ISQ, OPG and RANKL, OPG and RANKL in GCF were more closely related to ISQ. ISQ decreased when OPG rose, and the trends of ISQ and RANKL were similar. And OPG/RANKL ratio in GCF and PICF also had a relationship with the change of ISQ. When the ratio increased, ISQ decreased.

Table 8. ISQ of different time

Time/week	1st	2nd	3rd	4th	6th	8th	12th
ISQ	66.5±1.1[a]	64.8±1.2[a]	62.9±0.8	62.2±0.9	69.8±1.0[a]	72.6±1.1[a]	74.9±1.0[a]

Note: Repeated measures analysis of variance, $P<0.05$. a: means there is a significant difference when compared with the ISQ of 4th week, $P<0.05$. ISQ: implant stability quotient.

The changes of OPG, RANKL and OPG/RANKL appeared before the change of ISQ.

Discussion

Damage and missing of implants could have a great influence on life quality. Recently, with the development of science and technology, dental implants which have accepted a well effect in the reconstruction of teeth, were more and more widely used and gradually become the common treatment method of dental missing [20, 21]. And it is also one of the most successful recovery techniques in clinical treatment [22]. There will be variable problems during the operation and postoperation, which have a great effect on the success of implantation. Implant stability index could effectively evaluate the implant stability, which has a remarkable clinical value in estimating the recovery of implants and could decide whether it could load immediately or not [23]. Moreover, doctors could estimate the implant osseointegration and mechanical characteristics through continuous monitoring of implant stability in order to play guidance in future treatment.

However, the sclerotin around the implants, adjacent teeth, inserting ways, material of implants and the recovery condition post operation could affect the stability of implant-abutment [24]. Otherwise, smoking, diseases such as diabetes also have an impact on it [24]. RANKL/RANK/OPG system could influence tooth resorption by the regulation of differentiation and activation of osteoclast. And it also involves in the reconstruction of periodontal tissue and the regulation of tooth eruption, tooth germ formation and tooth absorption [25-27]. All of these were reflected in our research.

Otherwise, the balance between bone resorption and formation is essential for the reconstruction of bone, in which osteoclast and osteoblast participated. RANK expresses in the surface of osteoclast precursors, and RANKL expresses in the surface of osteoblasts/matrix cells. The combination of RANK and RANKL could activate osteoclasts, which is dose-dependent to extend the survival time of osteoclasts, and to improve the ability of osteoclast movement and the formation of bone resorption pits [28, 29]. And some research shows that RANKL not only regulates the activation of osteoclast, also plays an effect on the absorption function of osteoclast [30]. For the function of RANKL/RANK/OPG system in the regulation of differentiation and activation of osteoclast, the expression of OPG and RANKL could influence the formation and reconstruction of new bone [31]. RANKL could promote the differentiation and maturation of osteoclasts, inducing bone resorption. However, OPG belongs to tumor necrosis factor superfamily and is a natural inhibitor of RANKL. It could competitively inhibit the combination of RANKL and RANK and to inhibit bone resorption [32]. So the changes of OPG and RANKL are different which is demonstrated by this research.

In this research, OPG in GCF and PICF increased in the second week post operation, which was higher than the other time, especially OPG in PICF ($P<0.05$). There was no difference between OPG in GCF and PICF. However, there was different variation trend of RANKL in GCF and PICF post operation. The trend of RANKL in GCF was decreased first and then rose. The level of RANKL in GCF in the third, fourth and fifth week after operation was remarkably lower than that in the 12th week. However, the level of RANKL in PICF in the 3rd week was higher than those in the 1st, 4th, 6th, 8th and 12th week ($P<0.05$). There was no difference between RANKL in GCF and in PICF. The different trends of OPG and RANKL were mainly caused by the competitive inhibition between OPG and RANKL.

In this research, there were relationships between ISQ and OPG or RANKL. The higher the OPG was, the lower of ISQ would be. However, trends of RANKL and ISQ were same. This was related to the competitive inhibition between OPG and RANKL, which both could combine with RANK to regulate osteoclast. So

in future treatment, we could improve the implant osseointegration and primary stability by regulating the level of OPG and RANKL.

Disclosure of conflict of interest

None.

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