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Full Length Research Paper

The impact of diabetes on the success of dental implants and periodontal healing

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Dental implant is one of the restorative methods to replace missing teeth. As implants are directly anchored into bones, they provide stability, a more natural appearance, and minimize the risk of bone resorption and atrophy. However, studies found that diabetes mellitus patients had a slower healing process after surgery because of the reduction of vascular supply due to microangiopathies, decreased host defense, formation of advanced glycation end-products (AGEs), reduction of collagen production and increased collagenase activity. Diabetes mellitus patients may pose contraindications to dental implants. As a result of that, dental implantation failure rate in diabetic patients is much higher than that in non-diabetic patients. In this clinical experiment, we compared the amount of blood cells, and cytokines production 24 h post implantations, and the implant mobility 90 days post-surgery between controlled type 2 diabetic patients and the non-diabetic patients. It was aimed to investigate the suitability of diabetic patients to have dental implants and the efficacy of the amount of dental implants related to the success rates. 138 patients with type 2 diabetics and 140 healthy subjects, who had one to three adjacent edentulous spaces, were selected. Dental implantation surgeries were performed under local anesthesia. Wounds were sutured and all subjects were given 0.2% chlorohexidine mouthwash for 14 days. Complete blood picture and cytokines production were assayed before operation, as well as on days 1, 2, and 5 after implantation. Implant mobility and periodontal wound healing were monitored once in a fortnight up to 90 days. There were no statistically significant differences in the production of cytokines. In 138 diabetic patients, 255 implants were presented with second degree mobility 90 days after surgery while the same was demonstrated in 48 out of 346 implants from the healthy subjects. These implants were considered failures and were extracted. Implant failure in diabetics was significantly greater than that in non-diabetics when multiple adjoining implants were placed.

Key words: Dental implant, diabetes mellitus, bone resorption, periodontal healing, chlorohexidine mouthwash, tooth mobility.

INTRODUCTION

According to the World Health Organization, more than 180 million people worldwide are suffering from diabetes mellitus, one of the most common health problems in the world, while the number of diabetes sufferers is mounting to a double by 2030 (Chalmers et al., 2008). Diabetes mellitus is a chronic disease, which occurs when blood glucose concentration in body is in excess (Bianchi et al., 2008). This happens usually when the production of insulin, a hormone essential to regulate blood glucose level, from pancreas is inadequate, or when the body cannot effectively use the insulin it produces. Diabetes mellitus is characterized by hyperglycemia and glucose intolerance (Fonseca, 2007). The disorder, hyperglycemia, is used to describe the increased concentration of glucose in the blood while glucose intolerance is associated with insulin

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Table 1. Characteristics of the diabetic patients.

Parameters	Patients number and references values (n=138)
Mean age	45.5 years (range: 38-50 years)
<40 years	67
>40 years	71
Female	47
Male	91
Type of diabetes	II
Hypertension (mmHg)	Mean: 152/95 (+/-: 6/2.5)
Body weight (kg)	Mean:82.5(+/-:10.5)
Body height(m)	1.57(+/-:1.2)
Body mass index (kg/m^2)	(29+/-:4.46)

resistance. Among diabetes, there are mainly two types of idiopathic diabetes, type 1 and type 2 diabetes. Type 1 diabetes, previously known as insulin-dependent or childhood-onset diabetes, is characterized by a lack of insulin production. Type 2 diabetes, formerly called non-insulin-dependent or adult-onset diabetes, is caused by the body's ineffective use of insulin. It often results from excess body weight and physical inactivity. As a result of diabetes mellitus, it affects the blood circulations and is associated with many complications such as cardio-vascular diseases, particularly heart attack and stroke (Aronson, 2008; Bianchi et al., 2008). Furthermore, it is found that diabetes also reduces healing of wounds (Chaudhary et al., 2008), bones (Kotsovilis et al., 2006) and has been considered to contribute to failure in one of the dental restoration method-dental implant (Kotsovilis et al., 2006).

Dental implant is one of the dental restorative methods to replace missing teeth. As implants are directly anchored into bones, they provide stability to the new teeth, a more natural appearance, and minimizes the risk of bone resportion and atrophy, in contrast to other traditional restoration methods (Balshi and Wolfinger, 1999). Dental implant is therefore becoming more popular these days. It involves osseointegration as well as periodontal wound healing. Studies found that diabetes mellitus patients had a slower healing process after surgery, and therefore would expose the tissues to complications such as tissue necrosis (Rothwell and Richard, 1984; Balshi and Wolfinger, 1999). Moreover, animal studies indicated that streptozotocin-induced diabetes interfered with the process of osseointegration (Shernoff et al., 1994; Balshi and Wolfinger, 1997; Balshi and Wolfinger, 1999). Wound healing involves migration, adhesion, proliferation, and differentiation of several cell types (Grzesik et al., 2002). Diabetes mellitus will therefore cause a slower healing process because of the reduction of vascular supply due to microangiopathies, decreasing of host defense, formation of advanced glycation end-products (AGEs), reduction of collagen production and increased collagenase activity (Fiorellini and Nevins, 2000; Kotsovilis et al., 2006). Because of these unwanted effects, diabetes mellitus patients have possible contraindications to dental implants (Park, 2007). Dental implantation failure rate in diabetic patients is much higher than that in non-diabetic patients. In this experiment, we compared the amount of blood cells, and cytokines production 24 h post implantations, and the implant mobility 12 weeks post-surgery between type 2 diabetic patients and the non-diabetic patients. It was aimed to investigate the suitability of diabetic patients to have dental implants and the number of dental implants related to the success rates.

MATERIALS AND METHODS

Subject selections

From 2005 to 2007, two-hundred-and-eight patients who had dental implants were selected. The ethics committees at Sichuan University and Hospital of Stomatology approved the research protocols (reference number: 05JY029-023-3), with informed consent being obtained from these patients before joining the study. The selection criterion of patients was to have one to three adjacent edentulous spaces which presented at least one year before the study. A total of 278 subjects was divided into two groups, the diabetes group and the control group. The diabetes group consisted of 138 diabetic patients, 95 females and 43 males with an average age of 45.5, ranging from 38 to 50 (Table 1). The control group consisted of 140 patients, 64 females and 76 males, of which they were non-diabetic patients. Patients in the diabetic group were all diagnosed with type 2 diabetes and had been taking metformin 1000 mg BID monotherapy for at least one year, with a mean fasting serum glucose of 7.6 mmol/l (Table 2) and BMI of 29 kg/m^2 (Table 1). All subjects were observed over a period of 90 days.

Pre-operative preparations

Before dental implantations, pre-operative preparations were done. Conventional X-Ray and panoramic autograph were employed to check for the height of the alveolar bone and the bone density of patients. Patients consumed preventive oral antibiotic one day before the surgery to prevent inflammations caused by pathogenic bacteria. Right before the surgery, patients had mouthwash with 0.12% chlorine for three times. Blood samples were drawn from all

Table 2. Cytokines expression in two groups of dental implant patients.

Cytokines / Time points		Control group	Diabetes group	Std. deviation	*P* -value
IL2	**Before OT	27.1818	37.5843	11.48430	0.840
	Day 1	24.7273	31.7994	10.52702	0.808
	Day 2	26.0000	34.8107	11.11488	0.890
	Day 5	24.0000	29.7947	8.62554	0.812
IL6	Before OT	41.0191	48.1771	10.65488	0.545
	Day 1	45.4623	53.0605	11.31005	0.703
	Day 2	47.3927	61.6499	11.22212	0.723
	Day 5	43.7473	51.2029	11.09782	0.684
TNF	Before OT	60.5964	65.9515	7.97112	0.305
	Day 1	65.3677	80.2124	12.09657	0.58
	Day 2	65.7449	81.9706	14.15232	0.505
	Day 5	67.2144	83.4935	14.23184	0.553
*C-Reactive protein (mg/l)	Day 1	0.8 (+/- 0.23)	4.5 (+/- 1.45)	6.459	0.012

*C-Reactive Protein(High Sensitivity: normally <3 mg/l).
**Before OT (one day prior to operation).

subjects to have the biochemical tests run by COBAS, INTEGRA 400 (Roche, Germany) (Table 2).

Dental implantations

Dental implantation surgeries were performed under local anesthesia (2% xylestesin-A) using ITI implant system (Straumann Company, Switzerland). All implants had ITI neck plus implants, the diameter of implant body was 3.3 mm, and the diameter of implant neck was 3.5 mm. The incision was made on the alveolar crest and relieve incision was made on the mesio-distal side to expose the bone over the site of the implant. A full thickness flap was elevated. The area of incision was 2-3 mm larger than the titanium membrane. Then a special drill, with water passing through its center, was used to prepare the bone site. The implant was screwed and twisted into place. Soft tissue wounds were sutured and all patients were given prophylactic amoxicillin 1 g QD and acetaminophen 500 mg BID, which have been shown to prevent bacterial infections (Ottaviani et al., 1989) and relieve inflammation and pain (Guindon et al., 2007), for one week after surgery. Besides, patients were given 0.2% chlorohexidine mouthwash for 14 days after surgery to prevent bacterial growth. Diabetic patients continued anti-glycemic medication throughout the study.

Post-operative measurements

After dental implants were placed, blood was drawn from all patients 24 h after the surgery for the assay on complete blood picture using KX-21N (SYSMEX, Japan). The serum level of cytokines of IL2, IL6, and IFN α were measured by R & D ELISA kit (R & D Systems, Minneapolis, USA) before operation, as well as on days 1, 2, and 5. For the serum extracted from patients' blood, 100 µl of the serum was pipetted into a 96 wells plate to be incubated for 75 min at 350 rpm and washed with washing buffer for three times. The wells were dried and read at 450 nm wavelength using Universal Microplate Reader (Sunrise, Tecan Co., Grödingen, Austria). The levels of cytokines in the samples were obtained by comparison with the standard curve generated from standards supplied by the manufacture. Each sample was analysed in triplicates. The production levels of cytokines before and after the dental implants were compared.

Implants mobility

Follow up measurements included investigation on implant mobility and periodontal wound healing were performed every 14 days after surgery for 90 days. Implant mobility was expressed as I^o or II^o. The number of teeth integrated into bone was recorded for each subject. A maximum of three implants were allowed in an adjacent edentulous space while multiple implantations could be integrated in different dental sites for each subject.

Statistical analysis

The cytokine expression, biochemical parameters and complete blood counts were analysed by student t-test in SPSS 15.0 (SPSS Inc., USA).

RESULTS

Biochemical parameters in blood before dental implants

Among all biochemical parameters in serum tested, most of the average parameter levels had shown no significant differences between the control and diabetes group except for glucose during fasting (Table 2). For diabetes group, the average glucose level during fasting was significantly higher ($p<0.05$) than the levels of the control group (Table 2).

Cytokine production and complete blood picture 24 h after surgery

For the control group, the average production of IL-2 was

Table 3. The biochemical parameters in serum of two groups of subjects.

Parameters	Control group (n=70)	Diabetes group (n=138)	Unit	Normal Range
Urea	7.2.0(+/- 2.1)	8.0(+/- 1.67)	mmol/L	<11.9
Creatine	63.2(+/- 11.2)	78.6(+/- 9.78)	umol/L	44-106
Chloride	102(+/- 3.2)	104(+/- 4.5)	mmol/L	100-117
Postassium	3.52(+/- 1.03)	3.98(+/- 0.6)	mmol/L	3.6-5.0
Sodium	138.65(+/- 3.4)	142(+/- 4.35)	mmol/L	134-148
*Glucose (Fasting)	5.01(+/- 0.35)	7.2(+/- 2.4)	mmol/L	<6
Hemoglobin A1c	4.5(+/- 0.5)	8.5(+/- 1.25)	%	<5.9% (NGSP)
High density lipoproteins	2.0(+/- 0.25)	1.36(+/- 0.16)	mmol/L	Females>1.68; Males>1.45
*Low density lipoproteins	2.89(+/- 0.86)	4.31(+/- 0.45)	mmol/L	<2.59
Triglycerides	0.85(+/- 0.15)	1.96(+/- 0.56)	mmol/L	<2.3

*Indicated statistical significance between control and diabetes groups p<0.05.
Data were presented as mean±95% confidence interval (95% CI).

Table 4. Complete blood picture on two groups of subject 24 hours after implantation on

Parameters	Control group (n=70)	Diabetes group (n=138)	Unit	Normal range
White blood cell	6.0(+/- 2.5)	*10.3(+/- 2.35)	$x10^9$/L	4.00-11.00
Lymphocytes	1.8(+/- 0.57)	*3.0(+/- 0.5)	$x10^9$/L	1.50-4.00
Middle cells: (eosinophils, basophils, monocytes)	0.2(+/- 0.05)	0.8(+/- 0.2)	$x10^9$/L	0.2-1.30
Neutrophils	3.0(+/- 0.25)	*5.8(+/- 0.96)	$x10^9$/L	2.0-7.5
Red blood cell	4.0(+/- 1.5)	3.84(+/- 0.8)	$x10^{12}$/L	3.8-5.80
Hemoglobin	12.5(+/- 1.5)	13.6(+/- 0.95)	g/dL	11.5-16.5
Platelet	188(+/- 35)	235(+/- 17)	$x10^9$/L	150-400

*Compared control and diabetes group (p<0.05) showed statistical significant.
Data were presented as mean±95% confidence interval (95% CI).

decreased while the production of IL-6 and TNF-α were increased 24 h after implants (Table 3). For test group, patients with diabetes mellitus, increased production of IL-2, IL-6 and TNF-α were measured 24 h the implants (Table 3). There was no statistical significance among those cytokines between the groups. White blood cells (WBC), lymphocytes and neutrophils levels were significantly higher (p<0.05) in diabetes group than that measured in the control group 24 h post-implantations (Table 4).

Mobility of dental implants

There were 255 dental implants placed in 138 patients with type II diabetes. 174 implants (68%) presented with second degree mobility at 90 days after surgery, at which point, these implants were considered failures and were extracted (Table 5). Eighty-one implants (32%) were integrated into bone with first degree mobility, at which point, these implants were considered as successful. In control group, 48 implants out of the 346 (14%) have failed and 298 implants were successfully retained into bone with periodontal healing. There was statistical significance between the two groups on both success and failure rate (X^2: 89.638, $p < 0.05$). Within the diabetic patients group, all patients with three adjacent implants failed. 31 out of 72 cases with two implants failed where as only 25% cases with one implant failed.

DISCUSSION

Despite the well controlled serum glucose levels on diabetic patients, no significant enhancement was shown in the successful rates of dental implants. As indicated from the experiment, type 2 diabetic patients had a significantly less successful rate of dental implants than that of non-diabetic patients. It was consistent with similar research results that diabetes mellitus patients had a higher risk of dental implant failure (Mellado-Valero et al., 2007; Scully et al., 2007; Klokkevold and Han, 2008). Type 2 diabetic patients demonstrated a higher mean level of WBC, lymphocyte, and neutrophil counts than those of the non-diabetic patients 24 h after implant placement. It was revealed that diabetes mellitus induced acute inflammation after dental implants and contributed instability to teeth replacement. For cytokine production

Table 5. Implant mobility of two groups 90 days after dental implants.

Degree of mobility	Control Group (n= 346)		Diabetes Group (n= 255)	
	Number of mobile implants	Percentage	Number of mobile implants	Percentage
0-I° Mobility	298/346	86%	*81/255	32%
II° Mobility	48/346	14%	*174/255	68%

*Compared control and diabetes group ($p<0.05$) showed statistical significant.

24 h after surgery, IL-2 level was decreased in the diabetes group while IL-2 was increased in the control group. However, there were no significant differences between the two groups. IL-2 is a pro-inflammatory cytokine which will enhance the inflammatory response. Having decreased level of IL-2 could be explained by the poor microcirculation of blood.

Traumatic tooth loss always causes problems and is inconvenient and frustrating to patients. For example, it directly affects chewing, cutting of food, and pronunciations. Besides, it also affects one's physical appearance. The current methods to restore missing teeth include removable dentures, tooth-supported, and implant-retained provisional restorations (Shernoff et al., 1994; Cho et al., 2007). Each method has its own pros and cons. Placing dental implants, compared to other teeth restorative methods, will eliminate the discomfort of removable dentures and will make chewing easier than dentures, as sliding of dentures make chewing difficult (Wolfinger and Balshi, 2002). Furthermore, because adjacent natural teeth are not altered to support the implant, more teeth will remain intact. In contrast, as dental implant involves osseointegration, it may cause rejection, inflammation and allergic response to metal-sensitive patients (Stejskal et al., 2006). As indicated by other studies, patients with uncontrolled chronic disease, such as diabetes and heart disease, are contraindicated to dental implants (Fonseca, 2007; Bianchi et al., 2008).

The reduced success rate of multiple implants in adjacent edentulous space in diabetic patients was mainly due to the large masticatory force. Normally, when one implant is integrated into bone, the force during mastication is dispersed to the surrounding healthy teeth. However, if multiple implants are integrated into the same edentulous space, little force during mastication is dispersed to the healthy teeth. Instead, this force acts on implants because of the edentulous space. It increases the mobility of implants, loosens the implants and eventually they fail to anchor to bone. Besides the force that acts on the implants, the process of healing also leads to a lower success rate in multiple implants in an edentulous space. In addition to the slow healing process of diabetic patients, multiple implants in an edentulous space creates a larger wound, which will further lengthen the time for healing and increase the risk of infection due to pathogenic bacteria surrounding the incision.

In conclusion, diabetes mellitus had a less success rate on dental implants and this method of restoration slightly triggered inflammation to diabetes mellitus patients. Therefore, the larger the number of implants placed adjacent to each other in an edentulous space in these patients, the more likely they will fail because the wound is much larger. Further investigation should be done on the control of blood glucose level to improve success rate of dental implants on diabetes mellitus patients.

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