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X. Wu[1], K. Al-Abedalla[1], E. Rastikerdar[1], S. Abi Nader[1], N.G. Daniel[2], B. Nicolau[1], and F. Tamimi[1]*

[1]Faculty of Dentistry, McGill University, Montreal, Quebec, Canada; and [2]East Coast Oral Surgery, Moncton, New Brunswick, Canada; *corresponding author, faleh.tamimimarino@mcgill.ca

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Selective Serotonin Reuptake Inhibitors and the Risk of Osseointegrated Implant Failure: A Cohort Study

ABSTRACT

Selective serotonin reuptake inhibitors (SSRIs), the most widely used drugs for the treatment of depression, have been reported to reduce bone formation and increase the risk of bone fracture. Since osseointegration is influenced by bone metabolism, this study aimed to investigate the association between SSRIs and the risk of failures in osseointegrated implants. This retrospective cohort study was conducted on patients treated with dental implants from January 2007 to January 2013. A total of 916 dental implants in 490 patients (94 implants on 51 patients using SSRIs) were used to estimate the risk of failure associated with the use of SSRIs. Data analysis involved Cox proportional hazards, generalized estimating equation models, multilevel mixed effects parametric survival analysis, and Kaplan-Meier analysis. After 3 to 67 mo of follow-up, 38 dental implants failed and 784 succeeded in the nonusers group, while 10 failed and 84 succeeded in the SSRI-users group. The main limitation of this retrospective study was that drug compliance dose and treatment period could not be acquired from the files of the patients. The primary outcome was that compared with nonusers of SSRIs, SSRI usage was associated with an increased risk of dental implants failure (hazard ratio, 6.28; 95% confidence interval, 1.25-31.61; $p = .03$). The failure rates were 4.6% for SSRI nonusers and 10.6% for SSRI users. The secondary outcomes were that small implant diameters (≤4 mm; $p = .02$) and smoking habits ($p = .01$) also seemed to be associated with higher risk of implant failure. Our findings indicate that treatment with SSRIs is associated with an increased failure risk of osseointegrated implants, which might suggest a careful surgical treatment planning for SSRI users.

KEY WORDS: medical devices, risk factors, dental implants, bone remodeling, osseointergration, epidemiology.

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INTRODUCTION

Depression—a state of low mood that affects a person's thoughts, behavior, feelings, and sense of well-being—has become a threatening global disease because of its high prevalence and associative public health problems (Murray and Lopez, 1997; Krishnan and Nestler, 2008). The World Health Organization estimates that more than 350 million people worldwide suffer from depression. Serotonin (5-hydroxytryptamine [5-HT]) is a monoamine neurotransmitter in the brain that contributes to the feelings of well-being and happiness (Krishnan and Nestler, 2008). Lower levels of serotonin or obstacles for its utilization can lead to depression (Krishnan and Nestler, 2008). Selective serotonin reuptake inhibitors (SSRIs)—such as Celexa, Paxil, Lexapro, Prozac, and Zoloft—are drugs designed to inhibit the reuptake of serotonin and boost its levels to treat depression (Liu *et al.*, 1998). Because of their unique effectiveness in depression treatment, SSRIs have become the most widely used antidepressants all over the world (Tsapakis *et al.*, 2012).

Serotonin receptors can be found in not only the nervous tissue but also peripheral tissues such as the digestive tract, blood platelets, and bones; accordingly, SSRIs can affect the function of the digestive, cardiovascular, and skeletal systems (Tsapakis *et al.*, 2012). In bone metabolism, serotonin regulates bone cells by acting on 5-HT1B, 5-HT2B, 5-HT2C receptors and serotonin transporters (5-HTTs), resulting in complex signal transmissions in osteoblasts and osteoclasts (Tsapakis *et al.*, 2012). Therefore, SSRIs block 5-HTTs on bone cells, resulting in a direct negative effect in bone formation (Diem *et al.*, 2007; Yadav *et al.*, 2008) and metabolism (Tsapakis *et al.*, 2012) by increasing osteoclast differentiations (Battaglino *et al.*, 2004) and inhibiting osteoblast proliferation (Tsapakis *et al.*, 2012). As a result, SSRIs decrease bone mass and bone mineral density (Battaglino *et al.*, 2004; Diem *et al.*, 2007), at an annual reduction rate of 0.60% to 0.93% (Diem *et al.*, 2007), increasing the risk of osteoporosis (Verdel *et al.*, 2010), bone fracture (Liu *et al.*, 1998; Verdel *et al.*, 2010), and osteoporotic fracture (Verdel *et al.*, 2010).

Osseointegrated medical devices, mainly made of titanium, can create a firm and lasting connection with the recipient bone (Albrektsson *et al.*, 1981), and these have been applied as bone-anchored craniofacial prostheses, joint replacements, and dental implants (Albrektsson *et al.*, 1981; Del Valle *et al.*, 1995; Esposito *et al.*, 1998). They have become a revolutionary step in achieving soft or hard tissue replacement, and they have proven to be a routine and reliable treatment choice (Carlsson *et al.*, 1986). Failure of osseointegration between the device and the host bone can cause treatment failure and need for reintervention and in some cases (*e.g.*, hip replacement) can shorten patients' life expectancy (Schep *et al.*, 2004).

Osseointegration of implants is highly dependent on the quality of the recipient bone (Wong *et al.*, 1995), and since SSRIs seem to have a negative effect on bone formation (Battaglino *et al.*, 2004; Gustafsson *et al.*, 2006; Diem *et al.*, 2007), we hypothesize that SSRI treatment might have a negative effect on titanium implant osseointegration and survival rate. Given the large portion of the population taking SSRIs, and the increased number of surgeries using osseointegated implants, it is vital to investigate whether SSRI treatment can affect osseointegated implant survival rate. In order to test our hypothesis, a cohort study was carried out on patients treated with one type of osseointegrated medical devices, titanium dental implants, to investigate whether the use of SSRIs is associated with higher risk of titanium implant failure.

MATERIALS & METHODS

Patients and Data Sources

Approval (12-321 GEN) was obtained from the Ethical Committee for Clinical Trials of McGill University to carry out a retrospective cohort study in the dental clinic East Coast Oral Surgery (Moncton, Canada). Written informed consent was granted from all subjects. Our study is a human observational study and has conformed to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Records of patients with dental osseointegrated prosthesis for this retrospective cohort study were identified in the clinic database, and the original hard copy files were retrieved for manual examination. The overall study period was 6 yr, between January 1, 2007, and September 8, 2013. Preoperative patient information, including medication, habits, and behavioral factors, was self-reported through a standardized questionnaire that was filled prior to the surgical intervention. Patients were excluded if they had a severe systemic disease (American Society of Anaesthesiology III or IV), were pregnant, or had a medical disorder known to substantially affect bone metabolism, such as osteoporosis, osteomalacia, Paget's disease, vitamin D deficiency, hyperthyroidism, cancer (excluding nonmelanoma skin cancer), or alcoholism, as were those on corticosteroids, antiepileptic drugs, antihypertensive drugs, proton pump inhibitors, or bisphosphonates (Tamimi *et al.*, 2012). Smoking habit was considered in our analysis; subjects who smoked more than 10 cigarettes per day were defined as smokers (Tonetti *et al.*, 1995).

SSRI Medication Definition

SSRI usage was defined as filling a prescription for SSRIs at the time of implant placement (citalopram, dapoxetine, escitalopram, fluoxetine, fluvoxamine, indalpine, paroxetine, sertraline, venlafaxine, and zimelidine; Diem *et al.*, 2007).

Surgical Protocol and Postoperative Treatment

In patients with sufficient native bone, implant (Nobel Biocare) surgery was performed under local anaesthesia, with or without intravenous sedation, according to the manufacturer's recommended protocol (Finkemeier, 2002). In cases with inadequate bone volume for implant placement, bone augmentation (*i.e.*, lateral bone grafting, sinus lifting) was performed 6 mo prior to implant placement *via* a mixture of autogenous and allogenic bone substitutes (allogeneic bone, Straumann, Andover, MA, USA; Finkemeier, 2002).

The use of antibiotics in implant dentistry is controversial, so postoperatively, patients were instructed to rinse 4 times per day for a period of 7 d with 0.2% chlorhexidine solution (Peridex, Periogard, Allentown, PA, USA) and to follow a soft diet. They also received prophylactically a prescription of antibiotics for a period of 7 d (amoxicillin, 500 mg, orally, 3 times per day [GlaxoSmithKline, Middlesex, UK], or clindamycin, 300 mg, orally, 4 times per day [Sandoz, Boucherville, Canada]). Analgesic agents were prescribed as needed (acetaminophen, 500 mg, 3 times per day [Tylenol, McNeil Consumer Healthcare, Fort Washington, PA, USA]; or ibuprofen, 400 mg, 3 times per day [Advil, Wyeth Consumer Healthcare, Madison, NJ, USA]).

Patients were seen for follow-up examinations 10 d after surgery; all sutures were removed; and hygiene instructions were reinforced. Before delivery of the final implant-supported prosthesis, osseointegration was evaluated clinically by assessing vertical, lateral, and rotational signs of mobility. Implants with at least one of the following complications were defined as failures: pain on function; mobility; radiographic bone loss equivalent to one-half of the implant length; uncontrolled exudate; or implant no longer in mouth (Misch *et al.*, 2008).

Study Outcomes and Follow-up

The primary study endpoint was a binary dental implants outcome, comprising successful implants and failed implants. For either outcome, we followed patients until they experienced dental implant failure, died, or were censored for losing the track or reaching the end of the study period, whatever came first. The following parameters were retrieved from the patients' files and standardized questionnaires: patient age, sex, implant dimensions, bone augmentation, smoking habit, physical condition, medicine undertaken, and follow-up time.

Sample Size Calculation and Statistical Analysis

This cohort study was designed to examine the association between dental implant failure and SSRI treatment along with other factors. Sample size calculation based on Cohen's F test indicated that a minimum of 645 implants was required to achieve a power of 0.8 at an effect size (f^2) of 0.25 and a probability level of 0.05 with 8 covariates (Kemp, 2003). Accordingly, differences were considered of no clinical relevance if <1.1% based on Cohen's F test with a 25% standard deviations difference between the 2 groups' means (Pjetursson *et al.*, 2012).

Comparison between SSRI users and nonusers in terms of demographic systemic conditions and other factors, as well as the healing period calculation, was done through the chi-square test. Cox proportional hazards model was performed to assess the association between potential risk factors, including SSRI usage, and dental implant failure rate, adjusting for potential confounders factors. In addition, we used generalized estimating equation (GEE) models and multilevel mixed effects parametric

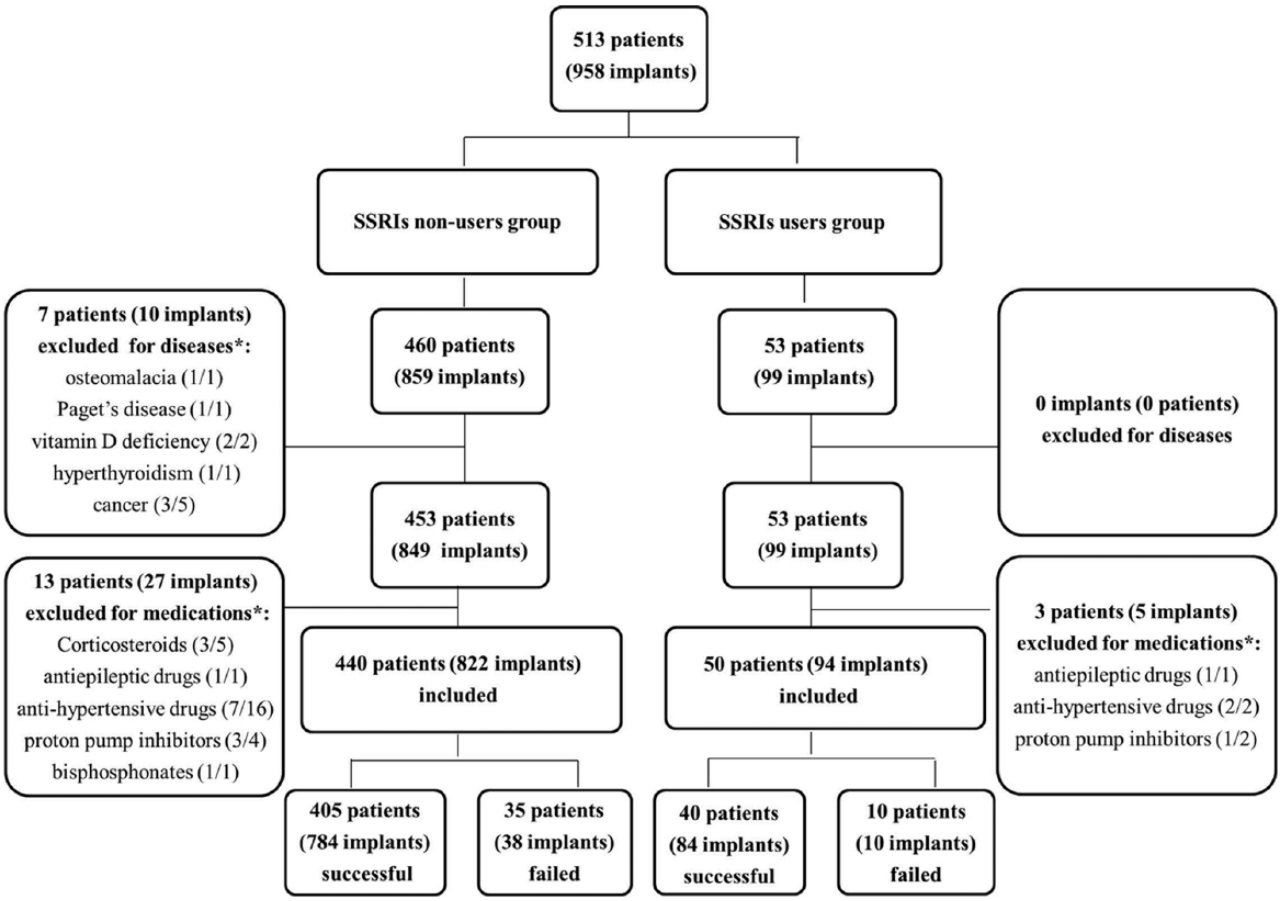

Figure 1. Flow diagram of participants.
*Patients/implants.

survival analysis (Stephenson *et al.*, 2010) to account for cluster effects of multiple implants when placed and evaluated in a single patient (repeated observations; Zeger and Liang, 1986; Stephenson *et al.*, 2010).

Analyses were adjusted to the following potential confounders: sex, age, implant diameter, implant length, bone augmentation, smoking habit. These covariates were selected because of their associations with bone status or dental implant survival rate and have been controlled for in studies of similar design (Verdel *et al.*, 2010). Statistical analysis was performed with the software SPSS 19.0 and STATA13 for Windows. The results were considered statistically significant if the corresponding p value was $< .05$. *Post hoc* power calculation was done with Cohen's F test. Kaplan-Meier survival curves were plotted for the primary outcome "dental implant failure."

RESULTS

During the study period between 2007 and 2013, 42 implants in 23 patients were excluded for bone-related diseases and medications (Fig. 1). In sum, the 490 patients who met our inclusion consisted of 292 women and 198 men, with ages spanning 17 to 93 yr, averaging 56.4 ± 13.7. A total of 916 dental implants were placed in the included patients, out of which 94 were placed in SSRI users whereas 822 were placed in SSRI nonusers. Also, 436 implants were placed in nonsmokers, whereas 54 were placed in smokers. Implants had diameters ranging from 3.0 to 5.5 mm, lengths ranging from 7.0 to 42.0 mm, and torque at insertion from 10 to 65 N·cm (Appendix Table 2). The healing period for all implants was ranging from 0 to 8 mo (5.1 ± 1.6). Other relevant information is shown in Appendix Tables 1 and 3.

During the entire observation period, 868 implants survived and 48 failed. The failure rates were 4.6% for SSRI nonusers and 10.6% SSRI users. SSRI users and nonusers were comparable in terms of age, sex, bone augmentation, smoking habit, implant diameter, implant length, implant torque, and follow-up period (Table 1). Risk analysis confirmed our hypothesis by revealing that SSRI treatment ($p = .03$) was associated with an increased risk of implant failure (Table 2). Also, smoking habit ($p = .01$) and small (≤4 mm) implant diameter ($p = .02$) were associated with an increased risk of implant failure (Table 3). Multilevel survival analysis adjusted for potential confounding factors is shown in Table 1 and 2. Patient's age, sex, bone augmentation, follow-up period, implant length, and torque had no significant association with implant survival rate (Table 3). The *post hoc* power was 0.93. Kaplan-Meier survival curves for dental implant failure in terms of SSRI use, bone augmentation, smoking habit, and implant diameter are shown in Figure 2.

Table 1. Description of the Cohort by Implants (n = 916) among SSRI User and Nonusers

	SSRI Use, *n* (%)			
Variables	Yes	No	Odds Ratio (95% CI)	*p*
Age, yr				
≤60	50 (53.2)	480 (58.4)	1	
>60	40 (42.6)	315 (38.3)	1.22 (0.79-1.89)	.43
Missing	4 (4.2)	27 (3.3)	0.76 (0.26-2.23)	.62
Sex				
Male	32 (34.0)	363 (44.2)	1	
Female	62 (66.0)	459 (55.8)	0.65 (0.42-1.02)	.06
Diabetes				
Yes	5 (5.3)	43 (2.8)	1	
No	89 (94.7)	779 (97.2)	1.02 (0.39-2.64)	1.00
Smoking habits				
Yes	12 (12.8)	85 (10.3)	1	
No	82 (86.2)	737 (89.5)	1.27 (0.67-2.42)	.48
Bone regeneration				
Yes	47 (50)	339 (41.2)	1	
No	47 (50)	472 (57.4)	1.39 (0.91-2.14)	.15
Missing	0 (0)	11 (1.4)	3.22 (0.19-55.50)	.42
Implant diameter, mm				
>4	32 (34.0)	326 (39.7)	1	
≤4	61 (64.9)	445 (54.1)	0.72 (0.46-1.12)	.15
Missing	1 (1.1)	51 (6.2)	6.15 (0.84-45.04)	.07
Implant length, mm				
>10	68 (72.3)	586 (71.3)	1	
≤10	25 (26.6)	186 (22.6)	0.86 (0.53-1.41)	.61
Missing	1 (1.1)	50 (6.1)	6.02 (0.82-44.11)	.07
Implant torque, N·cm				
≥35	36 (38.3)	263 (32.0)	1	
<35	44 (46.8)	423 (51.5)	0.76 (0.48-1.21)	.28
Missing	14 (14.9)	136 (16.5)	1.13 (0.62-2.06)	.68
Implant loading time				
Immediate	3 (3.0)	34 (4.1)	1	
Delayed	91 (97.0)	736 (89.5)	0.71 (0.21-2.37)	.58
Missing	0	52 (6.4)	10.65 (0.53-212.72)	.12
Follow-up time, mo				
≥12	42 (44.7)	336 (40.4)	1	
<12	52 (55.3)	485 (59.5)	1.17 (0.76-1.79)	.51
Missing	0 (0)	1 (0.1)	0.35 (0.01-8.53)	.52
Parafunctional habits[a]				
No	91 (97.0)	801 (97.4)	1	
Yes	3 (3.0)	21 (2.6)	1.26 (0.37-4.30)	.73
Implant position				
Maxilla	65 (69.1)	571 (69.5)	1	
Mandibular	29 (30.9)	251 (30.5)	1.02 (0.64-1.61)	.52

CI, confidence interval; SSRI, selective serotonin reuptake inhibitor.
[a]Parafunctional habits include bruxism, attrition, and temporomandibular disorders.

DISCUSSION

Our hypothesis was confirmed by the present study, showing through a multivariate analysis that SSRI usage, as well as other factors, increases the risk of osseointegrated dental implant failure. Each of these factors is discussed in detail.

SSRIs and Dental Implant Failure

Our study focused on the possible association of SSRI treatment with increased dental implant failure. In Table 2, we show that SSRIs have a significant association with higher risk of dental implant failure. Despite the fact that there were no significant

Table 2. Implant-based Comparison between SSRI Group and Nonuser Group

	Implants			*p*		
SSRI	Successful	Failed	Failure Rate, %	GEE	Multilevel	HR[a] (95% CI)
No	784	38	4.6	—	—	—
Yes	84	10	10.6	.004*	0.03*	6.28 (1.25-31.61)

CI, confidence interval; GEE, generalized estimating equation; HR, hazard ratio; multilevel, multilevel mixed effects parametric survival analysis; SSRI, selective serotonin reuptake inhibitor.
[a]HRs were performed with multilevel mixed effects parametric survival analysis adjusted to the following factors: sex, age, implant diameter, implant length, bone augmentation, smoking.
*Statistically significant.

differences between the group of SSRI users and nonusers in terms of systemic and demographic conditions (Table 1), SSRI users were more susceptible (hazard ratio, 6.28; 95% confidence interval, 1.25-31.61) to implant failures than nonusers.

Osseointegrated implant failure is usually caused by failed osseointegration, peri-implantitis, mechanical overloading (Esposito *et al.*, 1998), or a combination of these factors (Tonetti and Schmid, 1994). Early failures, occurring weeks to a few months after implant placement (Tonetti and Schmid, 1994), often result from impaired healing (Esposito *et al.*, 1998), implant contamination, or lack of mechanical stability (Tonetti and Schmid, 1994). Late failures are frequently caused by peri-implantitis (plaque-induced progressive marginal bone loss) mainly occurring after two-year follow-up (Charalampakis *et al.*, 2012). The failures caused by mechanical overloading usually occur after the loading time of 4 and 6 mo (Esposito *et al.*, 1998). In our study, the stratification of the follow-up period in Kaplan-Maier curves showed that failures occurred mostly between 4 and 14 mo (8 failed cases out of 10) after implant placement. Implants placed in SSRI users had favorable primary mechanical stability (torque: 29.6 ± 8.8 N·cm), acceptable bone quality and quantity, appropriate implant dimensions, and good early healing (all implants were loaded; Table 1). Therefore, the main reason causing implant failure by SSRIs was probably associated with problems in the mechanical loading of the implants. This is in agreement with previous *in vivo* studies demonstrating that serotonin plays an important role in the anabolic response of bone to mechanical loading (Sibilia *et al.*, 2013). This study indicates that SSRIs might cause bone mass loss by inhibiting the bone-remodeling processes triggered by mechanical loading. Accordingly, SSRIs might also be impairing bone remodeling around functional implants, although this hypothesis will require further mechanistic experiments to be confirmed.

Inappropriate response to mechanical loading can be the possible cause of "the after-loading failures." Future studies are needed to confirm the hypothesis. However, the effect of SSRIs on the risk of implants failures in our study can to some extent lead to careful surgical planning in SSRI users.

Bone Augmentation and Dental Implant Failure

In our study, bone augmentation seemed to be associated with higher dental implant failure in GEE analysis, but the association was not significant on the basis of multilevel mixed effects parametric survival analysis in STATA. Bone augmentation is essential for placement of implants when bone volume is insufficient. However, previous studies (Yamazaki *et al.*, 2012) indicated that higher implant survival rate can be expected when there is no need for bone regeneration procedures. The negative impact might indicate that the quality and quantity of regenerated bone are often deficient (Yamazaki *et al.*, 2012). Moreover, bone surgeries may require more maintenance of bone integrity and more firm immobilization after surgeries (Yamazaki *et al.*, 2012).

Smoking Habit and Dental Implant Failure

In this study, we observed a significant increased risk of dental implant failure associated with smoking habits. This was in agreement with previous studies recognizing a higher rate of dental implant failure in smokers (odds ratios ranging from 3.6 to 4.6; Alsaadi *et al.*, 2008), probably because smoking impairs bone healing after dental implant surgical treatment. The adverse effect during the early stage of osseointegration may be explained by the influence of smoking on the wound-healing process (Alsaadi *et al.*, 2008) through a direct toxic effect (Krall and Dawson-Hughes, 1991) on the bone around implants. Smoking, especially nicotine, impairs new bone formation, reduces calcium absorption, and decreases bone mineral density transiently (Riebel *et al.*, 1995).

Implant Dimensions and Dental Implant Failure

We demonstrated that smaller implant diameters were associated with higher risk of implant failure, which was confirmed by other studies (Davarpanah *et al.*, 2000). The use of narrow-diameter implants has been proposed to avoid bone augmentation procedures and reduce surgical complexity (Davarpanah *et al.*, 2000). However, they have less surface area for interaction and anchorage, which may lead to insufficient bone integration, as well as unfavorable distribution of biomechanical forces, causing reduced resistance to fracture (Davarpanah *et al.*, 2000). In our study, we did not observe a significant association between short implant length and increased failure. The implant length may be a factor in survival (Porter and von Fraunhofer, 2004), but in our study, it does not appear to be as critical as SSRI treatment, bone quality, smoking habits, and implant diameters.

Table 3. Risk Analysis for Dental Implant Failure in Terms of Different Factors

	Implants, *n* (%)			*p*		
Factor	Successful	Failed	Failure Rate, %	GEE	Multilevel	HR[a] (95% CI)
Sex						
Male	375 (43.1)	20 (42.9)	5.1			
Female	493 (56.9)	28 (57.1)	5.4	.98	.42	1.62 (0.50-5.28)
Age, yr						
>60	338 (40.0)	17 (34.7)	4.8			
≤60	500 (57.6)	30 (63.3)	5.7	.57	.88	0.91 (0.27-3.12)
Missing	30 (2.4)	1 (2.0)	3.2			
Implant diameter, mm						
≤4	472 (54.4)	34 (69.4)	6.7			
>4	345 (39.7)	13 (28.6)	3.6	.01*	.02*	0.24 (0.07-0.78)
Missing	51 (5.9)	1 (2.0)	1.9			
Implant length, mm						
≤10	201 (23.2)	10 (20.4)	4.7			
>10	617 (71.0)	37 (77.6)	5.7	.58	.97	0.98 (0.34-2.80)
Missing	50 (5.8)	1 (2.0)	2.0			
Implant torque, N·cm						
<35	283 (32.2)	16 (32.7)	5.4			
≥35	442 (51.3)	25 (53.1)	5.4	.81	NA	NA
Missing	143 (16.5)	7 (14.2)	4.7			
Implant loading						
Immediate	33 (3.8)	4 (8.2)	10.8			
Delayed	783 (90.2)	44 (91.8)	5.3	.74	NA	NA
Missing	52 (6.0)	0 (0)	0			
Bone augmentation						
No	498 (57.4)	21 (42.9)	4.0			
Yes	359 (41.3)	27 (57.1)	7.0	.04*	.05	2.73 (0.99-7.51)
Missing	11 (1.3)	0 (0)	0			
Smoking habits						
No	782 (90.1)	37 (77.1)	4.3			
Yes	86 (9.9)	11 (22.9)	11.3	.004*	.01*	7.66 (1.67-35.09)
Follow-up time, mo						
<12	508 (58.5)	29 (60.4)	5.4			
≥12	359 (41.4)	19 (39.6)	5.0	.71	NA	NA
Missing	1 (0.1)	0 (0)	0			

CI, confidence interval; GEE, generalized estimating equation; HR, hazard ratio; multilevel: multilevel mixed effects parametric survival analysis; NA, not applicable.

[a]HRs were performed with multilevel mixed effects parametric survival analysis adjusted to the following factors: sex, age, implant diameter, implant length, bone augmentation, smoking.

*Statistically significant.

Superiority and Limitations

To avoid bias, we had comparable control and experimental groups (Table 1) with sufficient sample size. We performed a comprehensive statistical analysis adjusted to multiple confounders with sufficient power and used GEE models and multilevel mixed effects parametric survival analysis to solve data cluster. Furthermore, the surgeries for all included patients were carried out by a single surgeon, avoiding most of the personal bias and operation variances.

However, there were still several factors that could not be assessed in the study. Because of the lack of detailed information, we were not able to adjust to the degree of depression (Verdel *et al.*, 2010), which might be a predictor for implant success rate. Within the limit of our knowledge, there is no evidence in the literature on whether depression is a risk factor for implant failure or oral complications. Lack of information about oral hygiene as dental implant maintenance was one of our limitations (Porter and von Fraunhofer, 2004). Moreover, drug compliance dose and treatment period could not be acquired from the files of the patients. Further studies investigating the dose-effect relationship and the influence of the treatment duration should be carried out to analyze this phenomenon in more depth. Moreover, the aspect of dose-relevant effects on bone metabolism could be of interest for prospective investigations. Randomized clinical trials should also be carried out in the future to confirm our results, since there is selection bias, such as confounding by indication, missing clinical data, and the risk of underreporting data in cohort studies.

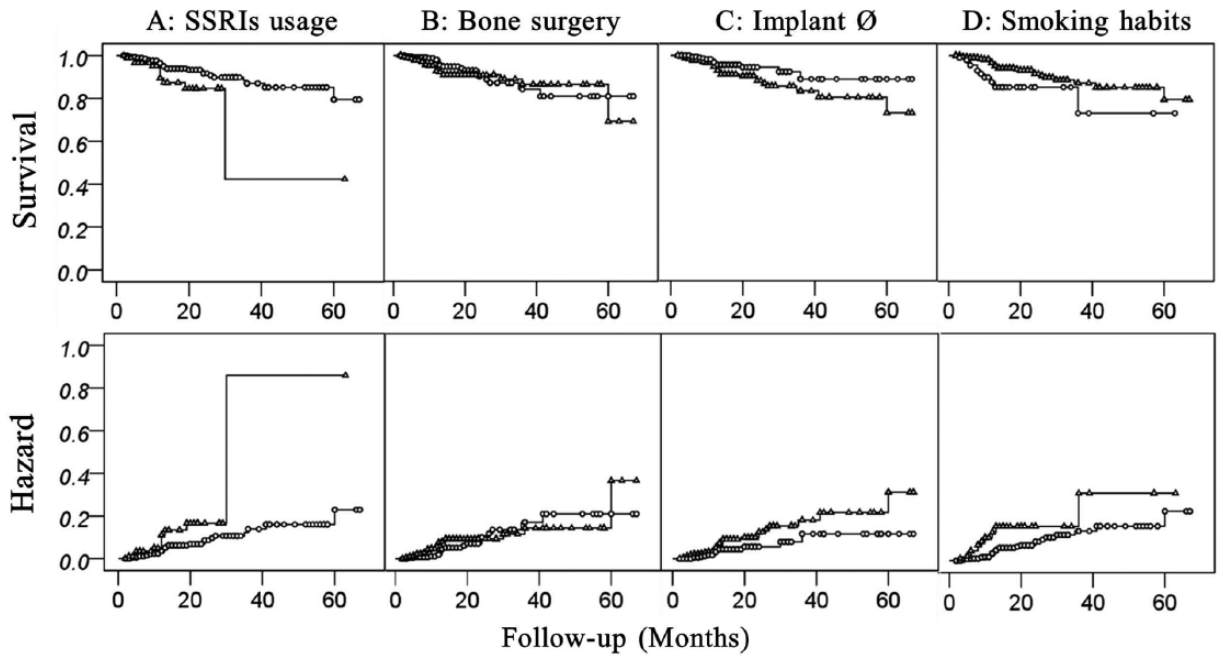

Figure 2. Kaplan-Meier hazard curves and survival curves for dental implant failure in terms of (**A**) SSRI (selective serotonin reuptake inhibitor) usage (Δ: usage, o: nonusage), (**B**) bone surgery (Δ: yes, o: no), (**C**) implant ∅ (Δ: <4 mm, o: ≥4 mm), and (**D**) smoking habits (Δ: smoker, o: nonsmoker).

Nevertheless, our study indeed, for the first time, indicated an association between SSRI treatment and higher risk of dental implant failure. Thus, this study might suggest careful surgical treatment planning for SSRI users.

CONCLUSION

Within the limits of our study, we can conclude that SSRI treatment is associated with higher risk of osseointegrated implant failure. Implant survival rate could also be significantly influenced by other factors, such as implant diameter, bone augmentation, and smoking habits.

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DETAILS OF CONTRIBUTORS

All authors substantially contributed to: study design (FT, XW), data collection (SAN, NGD, XW, KA, ER), data analysis and interpretation (XW, FT, BN, KA), manuscript writing (XW, FT, BN), and approval of the final version of the manuscript (XW, FT, BN, SAN, NGD, KA, ER). The authors take responsibility for the integrity of the data analysis.

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