Selective Serotonin Reuptake Inhibitors May Increase Implant Failure

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Background: Patients receiving dental implants may take selective serotonin reuptake inhibitors (SSRI). There may be an association with taking an SSRI at implant placement and implant failure.

Purpose: The study's purpose was to estimate the association between SSIR exposure and implant failure.

Study design: The study design was a retrospective cohort study. The sample was patients who received dental implants between December 1, 2007, and February 29, 2020. Patients were excluded if the follow-up was <12 months.

Predictor variable: The predictor variable was SSRI exposure at the time of implant placement coded as exposed or not exposed.

Outcome variable: The primary outcome variable was implant status at 1 year, coded as survived or failed.

Covariates: The covariates were age, sex, and implant location and per subject, and comorbidities included smoking, diabetes, osteoporosis, and frailty.

Analyses: Bivariate statistics assessed the association between SSRI exposure at the time of implant placement and failure with significance at P value < .05.

Results: The sample was composed of 1,611 subjects (mean age 57.3 ± 15.8 years, 893 (55.4%) females) with 3,184 implants placed. There were 1,514 (94%) subjects who did not take an SSRI at implant placement (mean age 57.5 ± 15.5 years, 813 (53.7%) females) and there were 97 (6%) subjects who did take an SSRI at implant placement (mean age 61.6 ± 13.1 years, 80 (82.5%) females). The failure rate was 6.7% (101 subjects) for non-SSRI exposed subjects and 18.6% (18 subjects) who took an SSRI at implant placement. SSRI exposure was associated with implant failure at 1-year relative risk = 2.8; 1.8-4.4 (relative risk, 95% confidence interval). Covariates with association with failure: smoking odds ratio (OR) = 0.98, 1.5-5.5 (OR, 95% confidence limits, P < .0001), diabetes (OR = 1.8, 95% confidence interval [CI], P = .048), alcohol (OR = 1.9, 95% CI, P = .045), osteoporosis (OR = 14.1, 95% CI, P < .0001), debilitation (OR = 20.7, 95% CI, P < .0001), and bisphosphonates (OR = 0.09, 95% CI, P = .004).

Conclusions: Patients who take SSRI at the time of implant surgery may have an increased risk for implant failure.

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There was evidence in our previous report[1] that depression was associated with implant failure. Systematic reviews indicated that there was an increased risk of dental implant failure with patients taking a selective serotonin reuptake inhibitor (SSRI) which is commonly used to treat depression. The pooled relative risk (RR) was reported to be 2.45 for patients and 2.34 for implants. They did not mention comorbidities in their reviews.[2,3]

Carr et al[4] performed a retrospective chart review for patients taking an SSRI. They reported a higher risk for failure for patients taking an SSRI with a hazard ratio of 1.6. They did not evaluate comorbidities affecting success or failure. Wu et al[5] reported a 4.6% failure rate in non-SSRI patients compared to 10.6% for patients taking an SSRI. They did find an association with smaller diameter implants and smoking as significant factors affecting failure. This was confirmed by Harutyunyan et al[6]

In the retrospective evaluation by Rodriquez et al,[7] 18.3% of the implants placed failed in patients taking SSRI compared to 4.4% implant failure in patients who did not take an SSRI. The survival rate of implants at 7.5 years was 84.3% in patients taking SSRI and 96% in patients who did not take an SSRI.

Chrcanovic et al[8] evaluated patients who only took an SSRI and had no comorbidities such as smoking or bruxism. Even though the reported failure rate was higher in patients taking an SSRI, they suggested that SSRIs alone may not cause an increased risk of implant failure. This study's purpose was to measure the association between SSRI exposure and implant failure, defined as implant removal.

The investigator's hypothesis is that there will be an increased risk for implant failure among patients taking SSRIs at the time of implant placement.

The specific aims of this study are to estimate the 1-year incidence for subjects with at least one implant failure when taking an SSRI at the time of implant treatment, and to identify risk factors associated with implant failures for patients taking SSRI medication at time of implant placement.

Methods

STUDY DESIGN/SAMPLE

The author implemented a retrospective cohort study and enrolled a sample derived from the population of patients who had implants placed by the author, at the author's private practice clinic between December 1, 2007, and February 29, 2020. To be included in the study, the patients must have had at least 1-year follow-up. Patients were excluded from the sample if they did not have at least 1-year follow-up from implant placement. There were no other exclusion criteria.

Institutional Review Board (IRB) exempt approval for this retrospective chart review was obtained (IRB# 20-756). The subjects' names and actual dates of service were removed from the spreadsheet as per IRB guidelines.

The subject's electronic medical record was evaluated, and data entered into a spreadsheet which was created to deidentify subject identifiers from the data for analysis.

VARIABLES

Predictor Variable

The predictor variable was SSRI exposure recorded as yes or no.

SSRI exposure was determined by evaluating the electronic medical record for mediations listed and by the subject's completion of a history form as well as an interview with the author, who specifically inquired about medications that they would be taking at the time of implant placement. The SSRI medications included: fluoxetine, sertraline, paroxetine, citalopram, and escitalopram. When needed a call to the subject's pharmacy confirmed the medications prescribed for the subject. The subject was asked if they take their medications as prescribed as well. If they did not take the SSRI they were included in the non-SSRI group.

Outcome Variable

The outcome variable was implant failure within 1 year of follow-up as defined as implant removal as documented in the follow-up evaluation.

Covariates

The covariates were potential risk factors for implant failure. Demographic variables (Table 1) included age in years at the time of the first implant placement and sex coded as male/female by self-report.

For this study, covariates were those that were reported in a previous publication which were identified to be associated with failure.[1] Medical comorbidities included smoking, diabetes (type 1 or 2), hypertension, peripheral vascular disease as determined by presence of vascular disease or cardiac disease, depression determined by self-report or medications, opioid ingestion as determined by self-report or medications, daily alcohol ingestion by response to direct inquiry by author, osteoporosis by self-report or bone mineral density (BMD) index, debilitation/frailty was determined by frailty evaluation including strength, tissue tone, and an interview concerning the subject's ability to walk without an aid and the need for home care, reflux by self-report and medications, and bisphosphonate ingestion by self-report and medications.

Table 1. SUMMARY OF STUDY VARIABLES GROUPED BY COVARIATES AND SSRI EXPOSURE

Covariate	Total	SSRI Exposure	No SSRI Exposure	*P* Value
Sample size	1,611 subjects	97 (6%)	1,514 (94%)	
Gender – male	718	17 (17.5%)	701 (46.3%)	<.001
Age	57.3 ± 15.8	61.6 ± 13.1	57.5 ± 15.5	.4
Implants per subject	1.98 ± 1.72	2.39 ± 1.93	1.80 ± 1.89	.003
Implant location				.8
Anterior maxilla	666 (20.9%)	43 (18.5%)	623 (21.1%)	
Posterior maxilla	1,085 (34.1%)	90 (38.8%)	995 (33.7%)	
Anterior mandible	256 (8%)	29 (12.5%)	227 (7.7%)	
Posterior mandible	1,177 (37%)	70 (30.2%)	1,107 (37.5%)	
Smoking (yes)	93 (5.8%)	8 (8.2%)	85 (5.6%)	.3
Diabetes (yes)	178 (11%)	7 (7.2%)	171 (11.3%)	.3
Hypertension – (yes)	525 (32.6%)	45 (46.4%)	480 (31.7%)	.04
Peripheral vascular disease (yes)	130 (8.7%)	14 (14.4%)	116 (7.7%)	.03
Depression (yes)	185 (11.5%)	69 (71.1%)	116 (7.7%)	.001
Opioid use (yes)	25 (1.6%)	4 (4.1%)	21 (1.4%)	.04
Alcohol use (yes)	36 (2.2%)	15 (15.5%)	21 (1.4%)	.0001
Osteoporosis (yes)	115 (7.1%)	9 (9.3%)	106 (0.7%)	.4
Frailty (yes)	4 (0.2%)	4 (4.1%)	0 (0.0%)	<.001
Bisphosphonate (yes or no)	26 (1.6%)	5 (5.2%)	21 (1.4%)	.006

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DATA COLLECTION

The data were collected and entered into a spreadsheet by recording information from the electronic medical record onto the spreadsheet. The data entered into the spreadsheet were updated as needed.

DATA ANALYSIS

For this analysis, a subject with an implant failure was the study unit. If the subject had one or more implant failures it was counted as 1 failure. Demographic factors for subjects were compared across the control group and subjects taking a SSRI, using χ^2 tests of independence for sex and analysis of variance for age. Implant location was included and evaluated using analysis of variance to determine if location of the implant was associated with failure. Anterior was defined from canine teeth to canine teeth and posterior was defined as premolar and molar teeth, in each arch.

Data was summed for each group including the SSRI failure/nonfailure groups and compared using χ^2 test for independence. The χ^2 test for independence was used to determine the RR with significance for *P* values less than .05.

Multiple logistic regressions were used to assess the association between implant failure and SSRI exposure adjusting for covariates. A backward elimination modeling procedure was used where, at each step, the model was rerun after removing the variable with the largest *P* value greater than 0.05 until all remaining variables had *P* values less than or equal to 0.05.

Results

The total number of subjects was 1,865. There were 254 (13.6%) who did not have follow-up and were excluded. After applying exclusion criteria, the sample was composed of 1,611 (86.4%) subjects with a mean age of 57.3 ± 15.8 years and 893 (55.4%) were females. There were 3,184 implants placed (1.98 ± 1.72 per subject) (Table 1).

The number of subjects who did not take an SSRI at time of implant placement was 1,514 (94%) (mean age 57.5 ± 15.5 years, 813 (53.7%) females). The number of subjects who did take an SSRI at time of implant placement was 97 (6%) (mean age 61.6 ± 13.1 years, 80 (82.5%) females). The difference in sex between the groups was significant (*P* value < .001) (Table 1).

There was no significant difference in location of implants comparing the SSRI exposure. For covariates hypertension, peripheral vascular disease, depression, opioid use, alcohol use, and bisphosphonates, the difference was significant (95% confidence interval [CI]) (Table 1).

Table 2 summarizes the survival and failure for all of the covariates for all subjects. Smoking (*P* value = .01, RR 1.15, CI 1.04-1.27), depression (*P* value = .002, RR 1.11, CI 1.04-1.19), and osteoporosis (*P* value < .001,

Table 2. BIVARIATE ANALYSES OF COVARIATES VERSUS IMPLANT STATUS (SURVIVED OR FAILED) FOR ALL SUBJECTS

Covariate	Total	Survived	Failed	*P* Value	RR (CI)
Sample size	1,611 subjects	1,492	119		
Gender – male	718 (44.6%)	631 (42.3%)	48 (40.3%)	.8	
Age	57.3 ± 15.8	57.3 ± 15.9	57.2 ± 14.9	.99	
Implants per subject	1.98 ± 1.72	1.95 ± 1.5	2.2 ± 1.3	.96	
Implant location				.8	
Anterior maxilla	666 (20.9%)	587 (18.4%)	79 (28.7%)		
Posterior maxilla	1,085 (34.1%)	976 (30.7%)	109 (40%)		
Anterior mandible	256 (8%)	228 (7.2%)	28 (10.2%)		
Posterior mandible	1,177 (37%)	1,118 (35%)	59 (21.4%)		
Smoking (yes)	93 (5.8%)	75 (5%)	18 (15.1%)	.01	1.15 (1.04-1.27)
Diabetes (yes)	178 (11%)	160 (10.7%)	18 (15.1%)	.2	1.03 (0.98-1.08)
Hypertension (yes)	525 (32.6%)	482 (32.3%)	43 (36.1%)	.6	1.01 (0.98-1.04)
Peripheral vascular disease (yes)	130 (8.7%)	117 (7.8%)	12 (10.1%)	.5	1.02 (0.96-1.08)
Depression (yes)	185 (11.5%)	154 (10.3%)	31 (26.1%)	.002	1.11 (1.04–1.19)
Opioid use (yes)	25 (1.6%)	20 (1.3%)	5 (4.2%)	.1	1.16 (0.9-1.4)
Alcohol use (yes)	36 (2.2%)	32 (2.1%)	4 (3.4%)	.5	1.04 (0.93-1.17)
Osteoporosis (yes)	115 (7.1%)	77 (5.2%)	38 (31.9%)	<.001	1.38 (1.26-1.57)
Frailty (yes)	4 (0.2%)	1 (.01%)	3 (2.5%)	.1	3.7 (0.7-20.2)
Bisphosphonate (yes)	26 (1.6%)	24 (1.6%)	2 (1.7%)	.9	1.0 (0.9-1.12)

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RR 1.38, CI 1.22-1.57) were significantly different comparing implant survival and failure for all subjects.

There were 1,413 (93.3%) subjects with no SSRI exposure and no implant failure. One hundred and one (6.7%) subjects with no SSRI exposure had an implant failure. There were 79 (81.4%) subjects with SSRI exposure with no implant failure and 18 (18.6%) had an implant failure. This difference was significant (RR = 2.8, 95% CI (1.8-4.4), *P* value < .0001) (Table 3).

In the non-SSRI exposure group, 224/2,496 (9%) implants were removed. In the SSRI group, 51/232 (22%) implants were removed, with a significant difference comparing the SSRI group to the non-SSRI group (RR = 1.12, CI (1.05-1.18), *P* value < .0001).

The multiple logistic regression analysis confirmed that there were significant associations between implant failure at 1 year and the variables SSRI use, age, smoking, alcohol use, bisphosphonates use, diabetes, osteoporosis, and frailty (Table 4).

Discussion

The purpose of this study was to determine if subjects taking an SSRI had an increased incidence for implant failure and to determine if comorbidities contributed to the failure. Our previous report on implant failures confirmed that comorbidities were associated with an increased risk for implant failure.[1] These comorbidities were included in the comparison of failed to nonfailed implant subjects who took an SSRI.

The strength of this study was that the subjects who took the SSRI medication at the time of implant placement had at least 1-year follow-up to confirm implant integration. The weakness of this study was the lack

Table 3. BIVARIATE ANALYSES OF THE SSRI EXPOSURE VERSUS FAILURE

SSRI Exposure	Total Subjects	No Failure (Subjects)	Failure (Subjects)
Exposed	97 (6%)	79 (81.4%)	18 (18.6%)
No exposure[1]	1,514 (94%)	1,413 subjects (93.3%)	101 (6.7%)
Total subjects	1,611	1,492 (92.6%)	119 (7.4%)
P value			<.0001*

* Relative risk 2.8, 95% CI (1.8-4.4).

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Table 4. ODDS RATIO ESTIMATES FOR IMPLANT FAILURE FROM MULTIPLE LOGISTIC REGRESSION MODEL

Effect	Odds Ratio	95% Confidence Limits		*P* Value
SSRI	2.875	1.503	5.496	.0014
Age	0.982	0.969	0.996	.0099
Smoker	4.012	2.408	6.685	<.0001
Diabetes	1.882	1.006	3.520	.0477
Alcohol	1.891	1.015	3.522	.0446
Osteoporosis	14.079	7.341	27.001	<.0001
Debilitation	20.638	6.353	67.050	<.0001
Bisphosphonates	0.091	0.018	0.459	.0037

Note: Younger age is the reference group.

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of a time based follow-up on a significant sample of subjects to determine failure over time. There was minimal information on whether they stopped the SSRI, or changed it, or added it after the implants were in function. This was a weakness in this retrospective study.

The stimulation to write this article resulted from a patient who was treated by the author for full arch rehabilitation of the mandible. She had multiple year history of SSRI ingestion. She lost 4 of 5 implants within 3 weeks of placement with significant osteolysis. She had no other obvious reasons for the observed severe bone loss. The available database in the author's clinic was available and queried to determine if there were other patients who had taken an SSRI and had an implant failure at a greater rate compared to those who did not have a failure.

There was a significant difference in the sex of subjects comparing subjects without SSRI exposure and those with SSRI exposure. A greater percentage of females took an SSRI than males (Table 1).

When comparing the implant survival to failure in the entire database, there were significant failures with smoking, osteoporosis, and depression (Table 2). Comorbidities increased the failure rate in those subjects who were exposed to an SSRI at the time of implant placement (Table 4).

The use of SSRI medication at the time of implant treatment did have an increased risk for failure. In this cohort, 18.6% of subjects taking an SSRI had an implant failure. Twenty-two percent of the implants in subjects taking an SSRI had a failure necessitating implant removal. Variables associated with an increased risk of failure included: smoking, the use of opioids, osteoporosis, and in the regression analysis the use of bisphosphonates. The investigators hypothesized that there will be an association with SSRI and comorbidities with implant failure. These hypotheses were confirmed to be true.

Subjects who are depressed are often prescribed an SSRI. The depressed patient often has decreased nutritional status, a lower BMD, and an increase in the covariates evaluated in this study. The SSRI usage may have an effect on implant survival alone, but when comorbidities are added by the patient, there may be an increase in adverse implant integration.

There is an adverse effect on bone metabolism with increasing serotonin levels, but patients decide that the treatment effect of taking an SSRI on their mental or other disease offsets the bone metabolism issue. There is evidence in the literature that SSRI and depression are factors associated with osteoporosis and decreased bone formation. The specific SSRI prescribed for the subject depends on their response to medication and the severity of their disease. In this database, because the sample size was too small to determine if 1 SSRI medication had a better or worse success rate for their implants, all subjects who took SSRI medications were combined rather than evaluate 1 specific medication.

In our database, depression was one of the comorbidities found associated with implant failure.[1] The mechanism for this finding may be linked to decreased BMD because of decreased bone formation. It may be difficult to predict which patient will have an implant failure solely based on being depressed and taking an SSRI.

In animal studies, a slower rate of bone formation occurred in sertraline-treated rats. The percentage of bone to implant contact was found to be lower in the sertraline-treated animals.[9] In a calvarial defect model, the sertraline-treated group had decreased bone healing with osteoclast dysfunction with increasing mature collagen fiber formation.[10]

Kindilien et al[11] used a National Health and Nutrition Examination Survey to determine that SSRI patients did had a lower BMD t-score. They suggested that nutrition may also play a role in these patients, resulting in bone density changes. In patients who have diagnosed depression and take an SSRI, a decrease in BMD was greater compared to depressed patients who did not take an SSRI.[12-14] Comorbidities such as smoking, alcohol consumption, age, and low body mass index were associated with increasing bone loss in patients who were depressed and taking SSRIs.[13,15,16] The effect of exposure to a bisphosphonate and an SSRI needs more clinical research.

Systematic reviews concluded that the use of an SSRI did result in lower BMD scores, especially in older individuals.[17-23] In orthopedics, SSRI ingestion increased the risk of hip and other orthopedic fractures because the patients who took an SSRI had

a decrease in their BMD compared to patients who did not take an SSRI.[24,25] A case-controlled study compared 124,655 cases with fracture to 373,962 controls. They determined that there was an increased risk of hip and vertebral fractures comparing patients taking SSRIs to non-SSRI patients.[24,25]

SSRIs increase extracellular serotonin levels and as such increases bonding of 5-hydroxytryptamine (5-HT) to osteoblasts. This inhibits the phosphorylation of cAMP resulting in the reduced expression of cyclin genes. This decreases osteoblast activity with decreased bone formation. The reason to use these drugs is that the beneficial use of SSRIs to treat depression outweighs the effects of detrimental BMD changes.[26-28] The Wnt β-catenin pathway has a role controlling osteoblast proliferation and bone formation. Serotonin influences the Wnt signaling by adversely affect osteoblast proliferation.[29-31]

The pathways for decreased bone formation with SSRI ingestion are still not completely clear. The binding of serotonin to the surface receptors on the osteoblast results in decreased osteoblast proliferation and function. In many patients, implants have integrated and have done well; however, there is an increased risk for implant failure, confirmed in multiple studies, for the patient taking an SSRI. Our database was not large enough to sort out if 1 SSRI was worse than another. The presence of comorbidities did increase the risk for failure. Based on this assessment, recommendations can be made to clinicians for risk assessment for patients treatment planned to receive a dental implant.

Patients can stop the use of the SSRI prior to implant placement. This must be carefully handled by their psychiatrist who will be responsible for adverse sequela if the SSRI is discontinued. Elimination of the SSRI medication is relatively short but most clinicians like to wean the patient off these medications with close observation.[32]

Patients who take an SSRI for multiple years can develop decreased bone density suggestive of osteoporosis.[33] Systematic reviews definitely showed the relationship of SSRI ingestion and an increased fracture rate of all types, compared to non-SSRI medications.[34] Bruyere et al[35] stated that the risk of orthopedic fracture due the secondary development of osteoporosis from SSRI decreased after discontinuation of the SSRI. Reversal of secondary osteoporosis can occur as the etiology of the secondary osteoporosis is corrected.[36-38] The time for bone replacement is not well established. The question to be answered is are there lasting effects on osteoblasts after cessation of ingestion of an SSRI? The answer to this question is not known to this author.

What happens to the 5-HT effects when the SSRI is discontinued? In rats, discontinuing the SSRI resulted in a period of deficiency of animal produced 5-HT, which supports the gradual weaning process to discontinue treatment. After a period of time the 5-HT levels were normal.[39] When discontinued, there was a rebound activation of 5-HT neurons. This was consistent with the patient developing a withdrawal state.[40]

There was a lack of clinical information on the function and proliferation of osteoblasts after discontinuing an SSRI, with proper weaning. Are the effects reversed to allow the osteoblast to regain normal function? If so this can perhaps influence the success rate of a dental implant. Unfortunately, we do not have sufficient information to answer this question.

Most studies measuring the incidence of implant failure use survival analyses, a statistical method to adjust for varying durations of follow-up. In survival analyses, an implant that survives at 1 year is weighted less than an implant that survives 5 years. This study compared frequencies of implant failure between subjects exposed to SSRIs. Comparing frequencies can be done if the follow-up is the same for all subjects allowing an estimate of the incidence, ie, percent failure per 1 year. In this case, all subjects had at least 1 year of follow-up. In addition, the duration of follow-up, 1 year, was so short that it was not clinically relevant to discriminate between an implant that failed at 3 months and 9 months, as these would be considered early failures. The estimated incidence of failure using proportions, however, would most likely underestimate the true incidence of failure at 1 year.

The recommendations for clinicians' treatment planning dental implants in patients taking SSRI medication are:

1. The clinician should assess the presence and severity of comorbidities exactly the same as for other implant patients.
2. The clinician should assess the nutritional status of the patient.
3. The clinician should advise the patient that there may be an increased risk for implant failure because of the SSRI medication, which is treating their depression, especially if they have comorbidities as listed above.

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