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British Journal of Oral and Maxillofacial Surgery xxx (2022) xxx–xxx

BRITISH Journal of Oral and Maxillofacial Surgery

www.bjoms.com

Selective serotonin reuptake inhibitors as a risk factor for dental implant failure: A retrospective clinical study

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Accepted 23 September 2022

Abstract

The trend in recent decades in Europe and the United States points to an exponential increase in the consumption of antidepressant drugs and, in particular, selective serotonin reuptake inhibitors (SSRIs). This retrospective study aimed to investigate whether there is an association between SSRI intake and dental implant (DI) failure or survival and, secondarily, to investigate the influence of other systemic and local factors. This retrospective cohort study was done in accordance with the the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for observational studies. A total of 170 patients received 573 DIs between 2014 and 2020.The reported DI failure rate was 6.11% (n = 35 DIs). Of these 18.31% failed in patients treated with SSRIs while 4.38% failed in patients who were not prescribed SSRIs ($p < 0.001$). Specifically, use of these drugs was associated with a hazard ratio rate of DI failure that was 4.53 times higher (95% CI: 1.93 to 10.61), and in the multivariate analysis, a 3.70 times higher adjusted risk was found. A lower DI survival rate at 90 months' follow up was also observed in these patients compared with those not taking them (84.30% vs 96%, respectively; $p = 0.00014$). With the limitations of the present study it can be affirmed that there is a relation between the intake of SSRIs and DI failure, as well as a lower survival rate in these patients.

Keywords: Dental implant failure; Dental implant complications; Dental implants; Selective serotonin reuptake inhibitors; SSRI; Antidepressant

Introduction

Dental implants (DIs) are the most predictable therapeutic option for the total or partial replacement of missing teeth, but certain risk factors may predispose to lower success rates.[1] Recently, a relation between the ingestion of antidepressant drugs and a higher rate of DI failure has been suggested. Antidepressants are among the most prescribed drugs in Europe, particularly selective serotonin reuptake inhibitors (SSRIs), and between 2000 and 2010 the prescription of antidepressants increased by 20% per year.[2] Data published by the Norwegian Institute of Public Health[3] (2014) indicate that between 2000 and 2012 there was a 107% increase in the consumption of these drugs in Europe. In 2018 in the United States, 7.20% of the adult population had reported a major depressive episode in the last year and 13.20% had been prescribed antidepressants in the last 30 days.[4]

Current evidence suggests lower mental health quality, elevated anxiety, depression, and post-traumatic stress disorder in individuals who have recovered from acute COVID-19. In a recent US cohort analysis, close to one in five COVID-19 survivors was found to have received a psychiatric diagnosis within three months of their COVID-19 diagnosis, including 5.80% that were new-onset conditions. Indeed, the risk of being newly diagnosed with a psychiatric disorder was more than twice that of other health events.[5]

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https://doi.org/10.1016/j.bjoms.2022.09.009

Despite this, during the first months of the pandemic, oral problems did not cease to exist, and in addition, the fear of contagion caused a significant percentage of patients (24.50%) not to visit the dentist.[6] These factors have acted to the detriment of the population's oral health. In addition, psychiatric disorders have been associated with worse oral health due to lifestyle changes, dietary habits, and dry mouth secondary to the use of antidepressant medication. In particular, the risk of caries and tooth loss is 1.21 and 1.22 times higher, respectively, in these patients.[7] For all these reasons, an increasing percentage of patients on antidepressant medication will need to have their missing teeth replaced by DIs.

The main aim of the present study was to evaluate the influence of SSRI consumption on DI failure and, secondarily, the influence of other systemic and local factors.

Material and methods

This retrospective cohort study was based on all 170 patients who received 573 DIs and were consecutively treated with implant-supported prostheses (ISP) between 1 January 2014 and 15 March 2020. The study was conducted according to the guidelines of the Declaration of Helsinki, and is in concordance with the STROBE [8] (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for observational studies. The patient sample was selected using the following inclusion and exclusion criteria.

Inclusion criteria

Included patients were both genders over 18 years of age who were fully/partially edentulous, and had had maxillary/-mandibular rehabilitation with DIs. They had had at least 12 months of follow up after ISP loading, were type I or II patients according to the American Society of Anesthesiologists (ASA) classification, and smoked <10 cigarettes/day. Patients taking SSRIs should have been on treatment for at least one year prior to the placement of the DIs.

Exclusion criteria

Excluded patients were those with severe systemic disease (ASA type III or IV), patients with untreated/uncontrolled periodontal disease, pregnant women, those with medical disorders related to altered bone metabolism, and those who were not maintaining their implants; also patients undergoing current radiotherapy/chemotherapy treatment of the head and/or neck or who had undergone such treatment less than two years ago, immunosuppressed patients, and patients who smoked ≥10 cigarettes/day.[9]

Clinical protocol

Surgical phase

A preliminary study of each case was performed with radiological diagnosis and planning based on orthopantomography, and cone-beam computed tomography (CBCT). Local anaesthesia without intravenous sedation was used. DIs were inserted in patients with sufficient bone available. In the case of transverse bone deficits, horizontal guided bone regeneration was performed six months before DI placement; in cases that required a sinus lift, this was performed eight months earlier. The bone regeneration materials used were particulate bone graft of heterologous origin and resorbable collagen barrier membrane. More complex regenerative techniques were discarded from this study.[10]

Postoperative period

Patients rinsed with 0.20% chlorhexidine digluconate twice daily for 14 days. Amoxicillin 750 mg three times daily for seven days was prescribed and, in penicillin-sensitive patients, azithromycin 500 mg each day for three days. Sutures were removed at 14 days postoperatively. A clinical check up with radiographic (periapical) control was performed one and a half months postoperatively. At three months osseointegration was clinically evaluated. DIs with at least one of the following complications were considered failed: pain, mobility, radiographic bone loss equivalent to one third of the length of the DI, suppuration, exfoliation of the ID (that is, spontaneous loss of the DI),[11] or apical peri-implantitis.

Follow up

Once the ISP had been installed, patients were checked at one, three, and six months during the first year and thereafter once a year. At each annual check-up, radiological control (periapical), periodontal maintenance, and reinforcement of oral hygiene techniques were performed. Patients were followed until the first of the following occurred: DI failure, death of the patient, exclusion of the patient from the study due to treatment drop-out; or the end of the study period was reached.

Definitions

'SSRI consumption' was defined as the intake of these drugs at the time of the placement of the DIs and for at least one year before. The SSRIs included in the present study were citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline.

Statistical analyses

Statistical analysis was carried out using IBM SPSS Statistics 28 and R software (v. 4.1.2.).[12] Descriptive statistics were performed, representing the absolute and relative values of the qualitative variables, as well as measures of central tendency and variability for quantitative variables. Assumptions of normality of quantitative variables were verified through the Kolmogorov-Smirnov test, where non-parametric tests were defined. In inferential statistics, bivariate analyses were performed to correlate variables with the condition of failure or not of the DI, using the chi-squared test for ordinal variables and the Mann-Whitney test for continuous variables. DI survival was analysed by comparing the curves using the log rank test (Mantel-Cox). Taking into

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consideration the significance of the survival curves for SSRIs, diabetes, smoking, and length, univariate and multivariate analysis of these variables was performed to estimate the risk of DI failure using Cox regression. Statistical significance was determined for a p value of <0.05.

Results

Characteristics of the patients and the DIs placed

A total of 170 patients were included, in whom 573 DIs were placed. The DI failure rate was 6.11% (n = 35 DIs), with 68.57% (n = 24 DIs) being late failures and 31.43% (n = 11 DIs) early failures. The median time between symptoms and explantation of failed DIs was two weeks, and the median time to early DI failure was 13 weeks (standard deviation (SD) 12–18 weeks). The most frequent criterion for DI failure was mobility (45.71%), followed by bone loss (34.29%), suppuration (17.14%), apical peri-implantitis (8.57%), DI exfoliation (8.57%), and pain (2.86%). Characteristics of the patients and DIs placed are shown in Table 1.

Influence of systemic factors on DI failure

The influence of systemic factors on the rate of DI failure was analysed (Table 2). A statistically significant increase in DI failure was observed in patients treated with SSRIs compared with those not treated with these drugs (18.31% vs 4.38%, respectively; p < 0.001). Also, a significantly higher proportion of DI exfoliation was found in these patients (23.08% vs 0%; p = 0.044) (Table 3).

No significantly higher failure rates were reported in patients with hyperlipidaemia compared with patients with adequate lipid values (5.45% vs 6.26%, respectively; p = 0.750), or with arterial hypertension (AH) (AH = 7%; no AH = 5.92%; p = 0.682). In smokers, higher failure rates were obtained when compared with non-smokers (8.70% vs. 4.88%, respectively; p = 0.075). The proportion of DI failures between diabetic and non-diabetic patients showed significant differences (diabetic = 16.67%, non-diabetic = 5.52%; p = 0.003).

Survival of DIs

Survival analysis was performed for DIs that failed in the late stage in patients taking SSRIs (90 months' follow up). Specifically, a DI survival rate of 84.30% was observed compared with one of 96% in patients not consuming SSRIs (p < 0.001) (Fig. 1).

A multivariate analysis of SSRIs, smoking habit, length of DI, and diabetes was performed using Cox regression to estimate the risk of DI failure. Univariate analysis showed that SSRI intake was a risk factor for DI failure, with a 4.53-fold hazard ratio (HR) increased risk (p < 0.001; 95% CI = 1.93 to 10.61); being a smoker had a 2.44 times higher HR risk of DI failure (p = 0.029; 95%CI = 1.10 to 5.44); a DI length of ≤10 mm had a 2.55 times higher HR risk compared with DIs of >10 mm (p = 0.037; 95% CI = 1.06 to 6.16), and being diabetic had a 4.53 times higher HR risk (p = 0.002; 95% CI = 1.70 to 12.02). In the multivariate analysis it was observed that the consumption of SSRIs with a p value of 0.021 presented an adjusted risk 3.04 times the probability

Table 1
Characteristics of patients and dental implants (DI) placed due to failure or not of the DI. Data are number (%) unless otherwise stated.

Variable	Total	DI failure		CI median difference	p value
		Yes	No		
Median (IR) age (years)	61 (53–68)	64 (51–70)	61 (53–68)	(−3 to 5)	0.500
Gender:					
Female	92 (54.12)	11 (11.96)	81 (88.04)		1.000
Male	78 (45.88)	10 (12.82)	68 (87.18)		
Median (IR) No. of DIs	5 (3–8)	6 (3–8)	5 (3–8)		0.199
Location of DIs:					
Anterior maxilla	80 (13.96)	6 (17.14)	74 (13.75)		0.876
Posterior maxilla	224 (39.09)	12 (34.29)	212 (39.41)		
Anterior mandible	41 (7.16)	2 (5.71)	39 (7.25)		
Posterior mandible	228 (39.79)	15 (42.86)	213 (39.59)		
Type of failure:					
Early		11 (31.43)			
Late		24 (68.57)			
Median (IR) time (weeks) between symptoms and explantation of DI:		2 (0–5)			
Median time (weeks) of early DI failure		13 (12–18)			
DI replacement		21 (87.50)			
Median prosthetic loading moment (months)	5 (4–6)	5 (4–5)	5 (4–6)	(−0,87 to 0.27)	0.410
Median diameter (mm)	4 (3.75–4)	4 (3.50–4)	4 (3.75–4)	(0 to 0)	0.212
Median length (mm)	11 (10–12)	10 (8–12)	12 (10–12)	(−2 to 0)	0.001

CI: Confidence interval; IR: interquartile range; mm: millimetres.

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Table 2
Relation between patient systemic factors and dental implant (DI) failure. Data are number (%).

Systemic factors	DI failure		CI difference in proportions	p value
	Yes	No		
Diabetes mellitus:				
Yes	5 (16.67)	25 (83.33)	(−24.6 to 2.3)	0.030
No	30 (5.52)	513 (94.48)		
Hyperlipidaemia:				
Yes	6 (5.45)	104 (94.55)	(−4.0 to 5.6)	0.750
No	29 (6.26)	434 (93.74)		
SSRIs:				
Yes	13 (18.31)	58 (81.69)	(−23.10 to −4.80)	<0.001
No	22 (4.38)	480 (95.62)		
Smoking habit:				
Yes	16 (8.70)	168 (91.30)	(−8.4 to 1.0)	0.075
No	19 (4.88)	370 (95.12)		
Hypertension:				
Yes	7 (7.00)	93 (93.00)	(−6.5 to 4.4)	0.682
No	28 (5.92)	445 (94.08)		

CI: confidence interval.

Table 3
Criteria for failure of dental implants (DI) by intake or non-intake of selective serotonin reuptake inhibitors (SSRIs). Data are number (%).

Failure criteria	Total	SSRI intake		CI difference in proportions	p value
		Yes	No		
Pain	1 (2.86)	1 (4.55)	0	–	1.000
Mobility	16 (45.71)	4 (30.77)	12 (54.55)	(−8.8 to 56.4)	0.172
Bone loss ≥1/3	12 (34.29)	4 (30.77)	8 (36.36)	(−26.6 to 37.7)	1.000
Apical peri-implantitis	3 (8.57)	0	3 (13.64)	–	0.279
Exudate	6 (17.14)	3 (23.08)	3 (13.64)	(−36.5 to 17.6)	0.648
Exfoliation of DI	3 (8.57)	3 (23.08)	0	–	0.044

CI: confidence interval

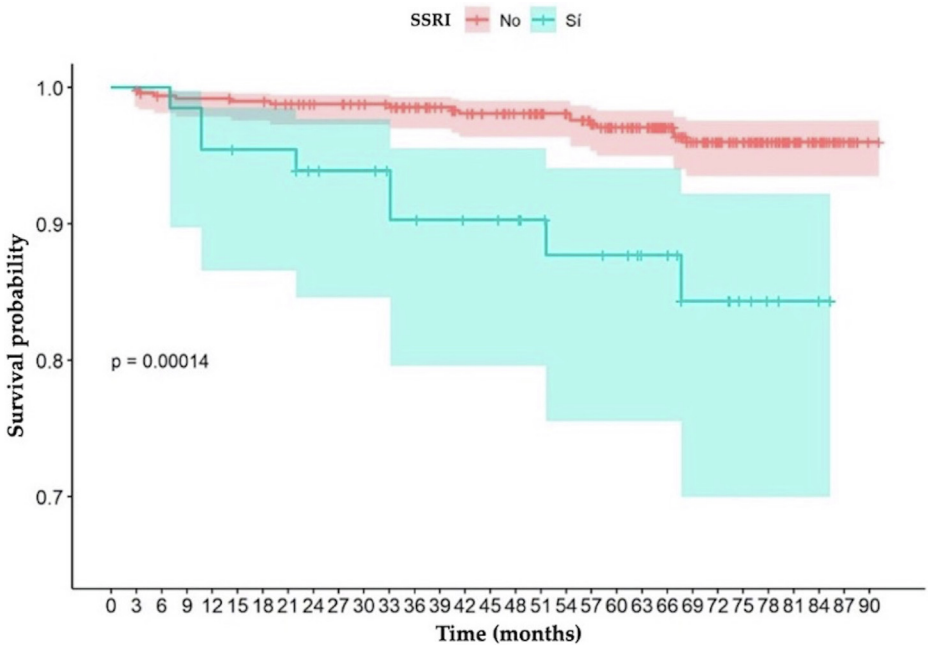

Fig. 1. Implant survival curves according to the intake or non-intake of selective serotonin reuptake inhibitors (SSRIs).

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of DI failure in relation to patients who did not consume these drugs (Table 4).

Discussion

The World Health Organization (WHO) has estimated that more than 350 million people worldwide suffer from depression. Serotonin, or 5-hydroxytryptamine (5-HT), is a monoamine that acts to contribute to feelings of well-being and happiness. Low levels or difficulties in the use of this neurotransmitter can lead to depression.[13] Due to their success in treating depression, SSRIs have become the most widely prescribed antidepressant drug in the world. Serotonin receptors can be found not only in nervous tissue, but also in peripheral tissues, such as the digestive tract, platelets, and bones, so SSRIs may affect the function of the digestive, cardiovascular, and skeletal systems.[14] In addition, these drugs have been found to concentrate to a greater extent in the bone marrow than in the brain or blood. Specifically, serotonin acts on receptors (5-HT1B, 5-HT2B, and 5-HT2C) and serotonin transporters (5-HTTs) that are present in bone cells, resulting in a complex cascade of signals to osteoblasts and osteoclasts. In this regard, SSRIs block 5-HTTs in bone cells, causing negative effects on bone formation and metabolism, increasing osteoclast differentiation, and inhibiting osteoblast proliferation. As a result, SSRIs decrease bone mass and bone mineral density (BMD).[14]

Interestingly, SSRI medication significantly reduces osteogenic differentiation and mineralisation with a concomitant reduction of osteoblast marker genes including alkaline phosphatase, osterix, and osteocalcin, indicating its putative impact on the regulation of bone metabolism.[15] Hence, such cellular findings would be in concordance with the results obtained by Wu et al[13] who demonstrated that patients who took SSRIs experienced an increased risk of DI failure (HR = 6.28; p = 0.03). In addition, it should also be considered that the higher risk of DI failure may be influenced by the psychological condition of the patient rather than by the intake of SSRIs. In this sense, depression per se has a negative influence on oral health, leading to a lack of hygiene and oral health care, and reduced cooperation regarding dental treatments, as a consequence of epigenetic modifications.[16] These factors increase the risk of periodontal disease and therefore of peri-implant diseases.[17,18] Furthermore, depression, through the pathological activation of various molecules of the adrenergic signalling axis (norepinephrine, adenosine triphosphate, and neuropeptide Y, and the hypothalamic-pituitary-adrenal axis, mainly through cortisol) affects the physiological homeostasis of the organism. This generates a cascade of hormonal, biologically active peptides and cytokines that are neurobiologically associated with depression, and possibly even periodontitis and peri-implantitis.[16] On the other hand, SSRIs influence the onset and increased severity of sleep bruxism,[19] acting as a factor of functional overload of the DI system, and causing mechanical complications that may lead to DI failure.[20]

Focusing on the available systematic reviews and meta-analyses, Silva et al[21] analysed a sample of 2056 patients with 5302 DIs and found a risk ratio (RR) for DI failure associated with the consumption of these drugs of 3.73 (p = 0.0002). In another study, the fixed effects model estimated an odds ratio (OR) for DI failure in the experimental group against failure in the control group of 2.92. The random-effects model resulted in 3.00. Thus, a significant effect of SSRIs was found (p < 0.05).[22] On the other hand, Cheng et al[23] found that the fixed-effects and the random-effects models estimated a difference in DI failure of 7.48% (p < 0.01) and 7.50% (p < 0.01), respectively, with higher DI failure rates in the experimental group (SSRIs) than in the control group, and an OR of DI failure of 3.00 (p = 0.36) in the SSRI group. These results agree with those obtained in the present study, in which HRs of 4.53 (p < 0001) and 3.04 (p = 0.021), respectively, were obtained in the univariate and multivariate analyses. Likewise, a survival rate associated with SSRI use of 84.30% vs 96% was obtained in patients not taking these drugs (p = 0.00014), which is lower than that described by other studies (89.4% – 94.49% vs 95.40% – 98.15%, respectively).[24]

Limitations

The main limitation in the present study, as well as in previous research in the literature, is that the doses and patterns, and the time of intake before and after placement of the DI are not recorded in patients treated with SSRIs.

Future lines of research

Future lines of research should aim to study the relation with new antidepressant drugs with multimodal action and the

Table 4
Univariate and multivariate analysis for dental implant (DI) failure.

Variable	Univariate		Multivariate	
	HR (95% CI)	p value	HR (95% CI)	p value
SSRIs	4.53 (1.93 to 10.61)	<0.001	3.04 (1.18 to 7.85)	0.021
Smoking habit	2.44 (1.10 to 5.44)	0.029	2.06 (0.93 to 4.57)	0.075
DI length ≤10 mm	2.55 (1.06 to 6.16)	0.037	2.25 (0.98 to 5.17)	0.057
Diabetes mellitus	4.53 (1.70 to 12.02)	0.002	2.40 (0.79 to 7.32)	0.123

SSRI: selective serotonin reuptake inhibitors; HR: hazard ratio; CI: confidence interval.

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ability to modulate several neurotransmitters, as well as to study the influence of depression, without the influence of SSRIs, on the survival of DIs. To generate guidelines for action in these patients according to the active ingredient, dosage, and treatment times, it would be advisable to carry out studies with larger samples and methodological rigour.

Conclusions

With the limitations of the present study, it can be confirmed that there is a relation between the intake of SSRIs and depression, and an increased risk of DI failure. The consumption of these drugs has been associated with a 4.53 times higher rate of DI failure. In addition, a lower survival rate at 90 months' follow up was observed in these patients compared with those not taking these drugs.

Conflict of interest

None.

Ethics statement/confirmation of patients permission

Not applicable.

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