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Clinical Paper
Dental Implants

Is the intake of selective serotonin reuptake inhibitors associated with an increased risk of dental implant failure?

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B.R. Chrcanovic, J. Kisch, T. Albrektsson, A. Wennerberg: Is the intake of selective serotonin reuptake inhibitors associated with an increased risk of dental implant failure?. Int. J. Oral Maxillofac. Surg. 2017; 46: 782–788.

Abstract. The aim of this retrospective study was to investigate the association between the intake of selective serotonin reuptake inhibitors (SSRIs) and the risk of dental implant failure. Patients were included if they were taking SSRIs only and no other medication, did not present any other systemic condition or compromising habits (bruxism, smoking, snuff), and complied with the use of prophylactic antibiotics for implant surgery. The multivariate generalized estimating equation (GEE) method and multilevel mixed-effects parametric survival analysis were used to test the association between SSRI exposure (predictor variable) and the risk of implant failure (outcome variable), adjusting for several potential confounders (other variables). The total number of implants with information available and meeting the necessary eligibility criteria was 931 (35 failures). These were placed in 300 patients. The implant failure rate was 12.5% for SSRI users and 3.3% for non-users ($P = 0.007$). Kaplan–Meier analysis showed a statistically significant difference in the cumulative survival rate ($P < 0.001$). The multivariate GEE model did not show a statistically significant association between SSRI intake and implant failure ($P = 0.530$), nor did the multilevel model ($P = 0.125$). It is suggested that the intake of SSRIs may not be associated with an increased risk of dental implant failure.

Key words: dental implant; implant failure; selective serotonin reuptake inhibitors; multivariate generalized estimating equation analysis; multilevel mixed-effects parametric survival analysis.

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Nowadays dental implant placement is an effective and predictable treatment modality for replacing missing teeth in both fully and partially edentulous patients. Nevertheless, failures still happen despite high implant survival and success rates.[1] Several risk factors have been suggested to influence the failure of implants. Surgical conditions, radiotherapy, the oral microbial environment, parafunctional habits, and prosthetic variables are some of these factors. Systemic diseases and compromising risky habits may affect the oral tissues by increasing their susceptibility to other diseases or by interfering

with wound healing. The patient's intake of medications that directly or indirectly affect bone metabolism may also play a role in the outcome of implants.[2]

Among the drugs commonly prescribed today are the selective serotonin reuptake inhibitors (SSRIs). SSRIs are a class of drugs typically used as antidepressants in the treatment of major depressive and anxiety disorders. Studies have shown that the use of antidepressants predicts decreased bone mineral density in women,[3] and both depression and the use of antidepressants are suggested to be possible risk factors for osteoporosis in men.[4] It is possible that neuroendocrine mechanisms related to the serotonin system could regulate osteoclast differentiation/activation, because osteoclasts derive from haematopoietic cell precursors and a relationship between bone and the immune system has been established.[5–7] Studies have identified a functional serotonin system in osteoblasts and osteoclasts,[8–10] in which the serotonin transporter and several receptors are expressed in osteoblasts as well as in osteoclasts.[9,10] The presence of serotonin receptors and the serotonin transporter in bone raises the question whether medications that antagonize serotonin reuptake could influence bone metabolism.

It has been shown in in vitro studies that activity of the serotonin transporter is required for osteoclast differentiation. While blockage of the serotonin transporter was found to reduce osteoclast differentiation when fluoxetine, an antidepressant, was administered to produce micromolar concentrations,[8,11] there was an increase in osteoclast differentiation for the same medication in the nanomolar concentrations.[11] In vivo studies have demonstrated detrimental effects of fluoxetine on the trabecular architecture[12] and on bone mineral density[12,13] in mice. Another in vivo study showed that serotonin acts on osteoblasts, inhibiting their proliferation.[14] These animal studies indicate a negative effect of SSRIs on bone mass and suggest that these antidepressants may possess direct anti-anabolic skeletal effects through the pharmacological inhibition of the serotonin transporter.

Therefore, the intake of SSRIs could in theory interfere with the osseointegration process. In the case of dental implants in particular, the findings of recent studies suggest that treatment with antidepressants is associated with an increased risk of failure of osseointegrated implants,[2,15] while others have not found a relationship between these two factors.[16–18] Thus, there is still no clear consensus on the influence of antidepressants on the risk of dental implant failure.

As the recognition of conditions that place the patient at a higher risk of failure will allow the surgeon to make informed decisions and refine the treatment plan to optimize the clinical outcome, the purpose of this study was to investigate the association between the intake of SSRIs and the risk of dental implant failure. It was hypothesized that patients taking SSRIs would have a higher implant failure rate than patients not taking this class of drugs. The specific aims of the study were to compare the implant failure rates between users and non-users of SSRIs, and to estimate the influence of several variables on the prevalence of implant failure in regression models, with the intake of these medications as the predictor variable.

Materials and methods

Study design/sample

A retrospective cohort study was designed and implemented to address the research purposes. The study population comprised all patients treated consecutively with implant-supported prostheses between 1980 and 2014 at one specialist clinic (Clinic for Prosthodontics, Centre of Dental Specialist Care, Malmö, Sweden).

To be included in the study sample, the patient had to be taking only SSRIs and no other medication and not present any other systemic condition. The analysis was based on complete cases only; i.e. only those implants with information available for all variables investigated here (see section on Data collection below) were included in the analysis. As it has been suggested that the use of antibiotics in healthy patients significantly decreases early implant failure,[19] all patients had to have taken prophylactic antibiotics for implant surgery in order to be included. All modern endosseous dental implants with a cylindrical or conical design were included.

Patients were excluded as study subjects if they presented a severe systemic disease (American Society of Anesthesiologists physical status III or IV) or had been subjected to irradiation of the head and neck region, were pregnant, alcoholic, bruxers, or smokers, presented a medical disorder known to substantially affect bone metabolism (such as hyperthyroidism, hypothyroidism, vitamin D deficiency, osteomalacia, osteoporosis, Paget's disease, cancer (excluding non-melanoma skin cancer), diabetes), or were taking corticosteroids, antihypertensive drugs, immunosuppressive drugs, antithrombotic agents (antiplatelet, anticoagulant, thrombolytic drugs), antiepileptic drugs, proton pump inhibitors, bisphosphonates, medications for asthma, or medications to decrease high levels of cholesterol. Thus, the status 'taking SSRIs' was isolated as much as possible from the influence of other systemic conditions or medications. Zygomatic implants were not included in the study, nor were implants detected in radiographs but without basic information about them in the patient's files.

In accordance with the standard protocol at the study clinic, the patients' dental hygiene was followed up by a dental hygienist within 6 months after the final implant-supported/retained restoration. Each patient then attended a dental hygiene recall programme based on individual needs.

The trial from which data in this study were derived is registered with the US National Institutes of Health (clinicaltrials.gov, NCT02369562).

Variables

In this study, the patient's SSRI status was the predictor variable. SSRI users were defined as patients who reported taking this type of medication during the presurgery appointment that was scheduled 1 to 2 weeks prior to implant placement. The SSRIs verified included citalopram, dapoxetine, escitalopram, fluoxetine, fluvoxamine, indalpine, paroxetine, sertraline, venlafaxine, and zimelidine.

The outcome variable was implant failure. An implant was considered a failure in the presence of signs and symptoms that led to implant removal, including lack or loss of osseointegration, implant mobility, continuous pain, advanced marginal bone loss, and refractory infection.

The following factors were the other variables investigated: implant surface (turned/machined or enlarged surfaces, the latter including sandblasted, acid-etched, sandblasted + acid-etched, anodized), implant length (three categories: 6.0–10.0, 10.5–14.0, 15.0–20.0 mm), implant diameter (three categories: 3.00–3.50, 3.70–4.10, 4.20–5.00 mm), prescription of antibiotics (the prophylactic antibiotic regimen was usually started 1–2 h before surgery and continued for 5–7 days postoperatively), bone graft procedures, implant jaw location (maxilla/mandible), anterior or posterior location of the implant (locations 13–23 and 33–43 were considered anterior), patient sex, patient age at implant insertion surgery (three categories: $\leq$30, >30 to $\leq$60, >60 years),