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A retrospective study on 1592 consecutively performed operations in one private referral clinic. Part II: Peri-implantitis and implant failures

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Abstract

Background: Few large-scale follow-up studies are reported on routine implant treatment.

Purpose: To report retrospective data on peri-implantitis and overall implant failures at one private referral clinic (effectiveness study).

Materials and Methods: A total of 1017 patients were consecutively provided with 3082 implants with an anodized surface during 1592 operations between 2000 and 2011. All patients with any of four events of problems were identified; "peri-implantitis," "surgery related to peri-implantitis," "overall implant failure," and "late implant failures." A logistic multivariate analysis was performed to identify possible factors with association to the four events.

Results: "Lower jaw surgery" (HR = 3.03) and "immediate gingival grafting" at implant surgery (HR = 3.34) were factors with the highest risk associated to the two peri-implantitis events, respectively. Risk of peri-implantitis increased by year of inclusion from year 2000 (HR = 1.28). "Overall implant failures" were associated to "smoking" (HR = 2.11), "surgical technique" (highest for direct placement; HR = 1.67), and "type of implant" (NobelActive CC; HR = 2.48). NobelActive CC was more used in upper jaws, using immediate or one-stage surgery with bone and mucosa grafting procedures than other implants ($P < .05$). Implants lost after first year only showed an association to "lower jaw" (HR = 2.63) and "early inflammation" (HR = 17.95).

Conclusion: Peri-implantitis seem to be associated to surgical protocols more often in the posterior lower jaw in routine practice. The problems seem to increase during the inclusion period, possibly related to increased use of direct implant placement technique and grafting protocols. Early inflammatory problems have in the previous report on the present patient group been associated to the mid-aged patient. Overall/late implant failures were shown to be associated to earlier inflammatory problems, smoking habits, surgical technique, and treatment in the posterior lower jaw.

KEYWORDS
bone loss, complication, follow-up, implant failure, peri-implantitis

1 | INTRODUCTION

It is reasonable to assume that both patient follow-up compliance as well as implant survival/success rates could be expected to be higher when reporting results from small, well controlled prospective efficacy studies, as compared to results from large, retrospective effectiveness studies, based on routine clinical performance.[1–3] Thus, data using patients and dentists that are enthusiastic pioneers when using new clinical protocols or take part in prospective studies where the follow-up examinations per se become important parts of the treatment may

result into better clinical results and higher follow-up compliance than following up patients in more routine situations.[2–5] This assumption could be supported by comparing literature reviews on for example, implant surgical loading protocols based on studies comprising only prospective randomized studies[6] with reviews based on both prospective and retrospective studies,[7] indicating better and smaller differences between results when using prospective study protocols.

Based on this assumption, comparisons between results from efficacy studies and effectiveness studies could allow for an assessment of the robustness of a clinical protocol, where a small difference could indicate a robust technique while a larger difference could indicate a more technique sensitive protocol. The different results discussed above could make a good example for this assumption, indicating a more biological and secure approach in routine treatment when using a two-stage surgical protocol as compared to an immediate placement/loading protocol.[3,7]

Implant failure is based on clinical and radiographic information which is a clear and easy endpoint to study and report. The only factor to discuss may be where the cut-off time-point should be placed after implant surgery, separating "early" from "late" implant failures, resulting into either slightly under- or over-estimation of the two different observations.[3,8,9] Irrespective of where the cut-off time-point is placed, clinical follow-up studies have shown that most dental implants are lost early after implant surgery during establishing of osseointegration and early function.[9] Thereafter, the clinical objective is to maintain established osseointegration and to try to maintain a biological healthy situation without severe mucosal inflammation, bone loss at the implant or loss of osseointegration. Long-term experience of implant treatment has been encouraging with few implant failures during periods of 10-20 years or even longer.[2,4,5,9–12] However, even though no obvious trend of increasing implant failure rates over time has been observed yet, much attention has lately been focused on mucosa health and bone loss at the implants, referred to as "peri-implantitis."[13,14]

This complication seems to be much more difficult to define and report, however.[15] Recently, a literature-review on 11 different patient groups reported a prevalence of peri-implantitis to range between 1% and 47% of the implant populations.[14] A closer evaluation of included studies indicates the challenge to define strict and comparable inclusion criteria for peri-implantitis. Thus, one of the eleven included references[14] identified first patients at a risk by a radiographic examination according to definitions, but the following clinical examination covered only 45% of these original patients.[16,17] An extrapolation of the results from these few clinically examined patients was performed, thereby resulting in a radiographic and clinical diagnosis of peri-implantitis for the entire population.[17] It must be questionable if this patient group could be used at all for prevalence of peri-implantitis. Another three of the included studies did not report any threshold of bone loss for inclusion as a peri-implantitis problem at all,[18–20] and another three studies reported a threshold for inclusion given as a bone level rather than bone loss.[21–23] For the remaining four included references in the review,[24–27] thresholds for bone loss for inclusion as peri-implantitis ranged between 0.4 and 5.0 mm, with higher prevalence of peri-implantitis (47%) for the lower thresholds (0.4 mm)[25] and lower prevalence (1%) for the higher threshold (5.0 mm).[26] Thus, it can be observed that available inclusion parameters for diagnosis of peri-implantitis show an obvious variation in the present literature,[14] and it would be of value to further analyze and report the problems with peri-implantits and implant failures in another larger patient groups in routine practice.

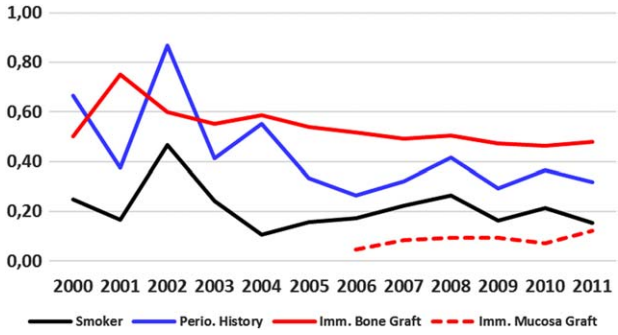

FIGURE 1 Proportions of patients per year of inclusion with reported history of periodontitis, smoking, immediate bone graft, and immediate mucosa graft at surgery (2000-2011)

The aim of the present study was to report problems with peri-implantitis and overall/late implant failures in a large private implant referral clinic where patients have been treated on a routine basis over a period of time. The aim was also to analyze the impact of different clinical and patient factors over time with regard to clinical observations related to peri-implantitis, surgery related to peri-implantitis, and overall/late implant failures.

2 | MATERIAL AND METHODS

The present study is a retrospective study covering all consecutively treated patients provided with dental implants with an anodized, moderately rough, implant surface between March 2000 and December 2011 at one private dental referral clinic. All patients were scheduled to be followed-up on annual basis at the clinic up to December 2015. The present patients have been accounted for in more detail in a previous publication,[3] and here most data on patients are reported starting from the first annual examination, 1 year after prosthesis placement.

In brief, altogether 1017 individual patients were treated at the referral clinic, mean age at implant surgery was 54.5 years (SD 13.93) and age ranged between 17 and 91 years.[3] A majority of the patients (60%) reported no general health problems at the time of implant surgery, and information on smoking habits was available for 963 patients (95%) of whom 181 patients were smokers (19%). Altogether 304 of the patients had a history of periodontitis at the time of first implant operation (30%).[3] Distribution of operations with regard to patients with history of periodontitis and smoking during inclusion are presented in Figure 1.

The patients were treated with 3082 Brånemark System implants (Nobel Biocare, Sweden), all provided with an anodized implant surface (TiUnite, Nobel Biocare).[3] The implants were placed at 1592 implant

operations performed by one surgeon (Dr H. Antoun), where a one-stage surgical protocol was performed for the majority of the operations ($n = 1086$; 68%). The remaining operations were performed by placing the implants directly into the extraction socket as a one-stage protocol or using a two-stage surgical protocol. Two-stage surgery was mostly associated with a guided bone regeneration technique (GBR) protocol (85%). Altogether 784 (49%) operations involved immediate local grafts at implant surgery, predominately using BioOss, nonautologous grafting materials (Geistlich Pharma AG, Switzerland).[3] Distribution of operations with regard to patient characteristics and type of surgery is more in detail presented in the previous publication.[3]

After surgery, the majority of the patients were restored by the referring dentists (n-184) not working at the present referral clinic (97%). Altogether 459 and 823 of the operations were followed by placing screw retained and cemented prostheses, respectively (information not available for 310 operations/prostheses). Thereafter, basic follow-up of the referred patients was performed by the referring dentists, but all patients were invited to participate in a routine follow-up program at the present clinic, including clinical examinations and intraoral radiographs just after prosthesis placement and then every year. Furthermore, information was given that the clinic should be contacted whenever a problem was observed at the implants.[3]

Annual follow-up examinations were performed in collaborations between the referring dentists and the periodontist at the present clinic. The examination comprised; palpation for any signs of inflammation, probing at the implants recording probing depths and bleeding at probing and pus and panoramic and/or intraoral apical radiographs of the implants. All patients with obvious signs of inflammation at the implants were referred to the surgeon at the referral clinic.[3] The surgeon made a careful clinical and radiological examination using periapical radiographs and recommended special treatment related to peri-implantitis problems when considered indicated. Only those patients participating in this special program are in the present study referred to as patients with "peri-implantitis problems."[3] Peri-implantitis was in the present study diagnosed first after 1 year of implant function after prosthesis placement. "Peri-implantitis" was defined as obvious bleeding at probing and/or suppuration in combination with more than one thread of bone loss (>0.6 mm) after first year in function which was considered to need special attention including reinforced oral maintenance. Extra peri-apical radiographs, outside the routine, were often taken for these patients. Final judgement to recommend the patient to special peri-implantitis treatment was performed by the surgeon.

Accordingly, all patients with peri-implantitis problems were first referred to the surgeon at the referral clinic to establish a good oral hygiene. Treatment focused onto establish plaque control, irrigation with Dakin solution (Cooper laboratory Ltd. Melun, France) and thereafter local antibiotics in the pockets (Minocycline/Parocline gel 2%, Sunstar Laboratory Ltd. Levallois-Perret, France), given at three occasions with an interval of 2 weeks between the occasions. The treatment was thereafter evaluated after 2 months. Patients that responded well to the hygiene treatment were followed-up without peri-implantitis surgery.

TABLE 1 Retrieved baseline parameters tested for significant prediction of risk of early inflammation and failure

1	Age at surgery (year)
2	Cardiovascular disease (yes/no)
4	Gender (male/female)
5	General health (yes/no)
6	History of periodontitis (yes/no)
7	Immediate grafting procedure (yes/no)
8	Immediate mucosal grafting procedure (yes/no)
9	Jaw (upper/lower)
10	Numbers of operations per patient (1 operation/>1 operation)
11	Number of placed implants (1-8)
12	Number of placed implants (1-3/4-8)
13	Retention of prostheses (cemented/screw retained)
14	Smokers (yes/no)
15	Surgical technique (immediate/one-stage/two stage)
16	Type of implant (as given in Table 2)
17	Type of jaw (single/partially edentulous/edentulous)
18	Year of surgery (2000-2011)

However, patients where suppuration and profound bleeding were persistent after the hygiene treatment were recommended surgery for removal of submucosal plaque and calculus, debridement of inflamed tissue, establish access for cleaning and when possible trying to do some guided bone regeneration. This was performed when infra-bony defects were detected. Bovine, nonautologous, bone grafting material (Bio-Oss; Geistlich) was used to fill the defects in addition to a resorbable bilayer collagen membrane (Bio-Gide; Geistlich).

Information on treated patients was retrospectively retrieved from all patient files regarding basic data on patients, operations, and implants at implant surgery. The same parameters as used in the previous study (Table 1) were analyzed in relation to peri-implantitis problems and overall as well as late implant failures (after first annual examination).[3]

3 | STATISTICS

Descriptive statistics are presented as numbers, frequencies, percentages, means, and standard deviations. Cumulative Survival Rates for operations without peri-implantitis or without implant failures were estimated. Statistical analyses were performed by a bio-statistician regarding four different events; "per-implantitis," "surgery related to peri-implantitis," "overall implant failure," and "late implant failure." "Late implant failure" were observed after first year in function, using a new baseline (≥1 year). Same available factors which could have an impact on the four events were used as in the previous study (Table 1).[3] Hazard Ration (HR) was calculated and presented with 95% Confidence Intervals (95% CI). For testing the association between available

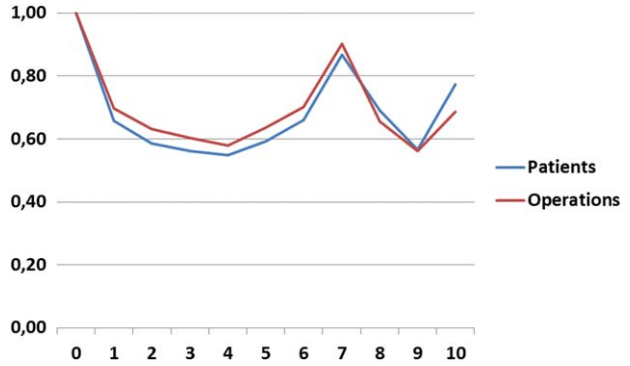

FIGURE 2 Proportion of treated patients/operations (%) followed-up during 10 years

factors and the four endpoint outcomes, an extension of Poisson regression model was used. In contrast to logistic regression, the Poisson regression model utilizes the length of each individual's/operation's follow-up period. The observation period of each patient/operation was divided into intervals of 1 month.[28] One endpoint of each kind per individual/operation was considered. Factors showing a statistical significant univariate association to the four different endpoints were thereafter tested with a multivariate model to show significant association to the endpoints ($P < .05$). The Poisson model was then also used to analyze if the significant factors have a different association to the endpoints in the early and/or later part of the follow-up period, using an interaction between time since baseline and current risk factor.

However, these analyzes fail to reveal any interactions that are nonlinear in time since baseline. Therefore, also a nonlinear model was used based on a spline Poisson regression model.[3] Data were fitted using knots after 0.5 years, 2 years, and 6 years after implant surgery to study possible nonlinear associations between different factors and time of follow-up.[3,29] The splines were second-order functions between the breakpoints and linear functions at the tails resulting in smooth curves.[3] *P*-values below 5% were considered as statistical significant.

4 | RESULTS

4.1 | Patients lost to follow-up

It was observed that the proportion of noncompliant patients with regard to follow-up increased by time from 2000 to 2011 even though all patients were invited for follow-up at the clinic after implant surgery. Mean compliance per year of follow-up is presented in Figure 2, indicating that about 60% of treated patients/operations were available for examination after 5 years at the referral clinic. Higher proportions of follow-up could be observed for those relatively few patients that were treated and followed up for 8-10 years (Figure 2).

4.2 | Inflammation and diagnosis of peri-implantitis

Distribution of operations with diagnosis of inflammation (0-1 year) and peri-implantitis according to definition is presented in Table 2. Altogether, 125 operations (7.9%) presented an early or late inflammation where 92 operations were diagnosed as peri-implantitis problems (Table 1; >1 year after loading). Inflammation was reported in a total of 99 patients (66 new patients after first year), affecting 49 and 146 implants in the early and late period of follow-up, respectively.

TABLE 2 Distributions of numbers of operations with recorded early (≤1 year in function) and late inflammation (>1 year in function; peri-implantitis) at the implants in different types of treated jaws. Treated jaws were; edentulous (Edent.), partially edentulous jaws (Part), and single implant placement (Single)

	Numbers of operations						
	Early inflammation			Peri-implantitis			
Implants	Edent	Part	Single	Edent	Part	Single	Total
Upper jaw	0	7	2	6	22	7	44
Lower Jaw	3	12	9	4	40	13	81
Total	3	19	11	10	62	20	125

Final multivariate regression analysis resulted into five factors that had a significant association with overall inflammation/peri-implantitis at the implants (Table 3). The risk for peri-implantitis increased by 28% per year during inclusion (from 2000 to 2011) as exemplified in Figure 3.

The nonlinear analysis using a spline Poisson regression model showed that "history of periodontitis" (Figure 4) had a significant association to inflammation at the implants ($P < .05$) from 0.4 years (HR 3.80, 95% CI: 1.0-13.9) to 1.4 years after implant surgery (HR1.8, 95% CI; 1.0-3.2). It was also shown that the risk for inflammation increased (step wise) related to "surgical technique" from direct placement surgery to one-stage and with the highest risk for two-stage surgery (Figure 5). The increased risk for inflammation/peri-implantitis was significant between 0.8 years (HR 1.8, 95% CI; 1.0-3.3) and 2.9 years after surgery (HR 1.5, 95% CI; 1.0-2.3) with the highest risk at 1.5 years after surgery (HR 2.5, 95% CI; 1.5-4.2). Most two-stage implant operations involved immediate grafting procedures with resorbable membranes (GBR; 85%).

An analysis was also made to test difference between upper and lower jaws provided with single implants and implants in the posterior partially edentulous jaws (Kenned class 1 and 2) with regard to inflammation. It was observed that single implants had a significantly higher risk for inflammation in the lower jaw (HR 3.03; 95% CI: 1.38-6.67). Posterior partially edentulous lower jaws had also a significantly higher risk for inflammation as compared to corresponding situations in the upper jaw ((HR 4.00; 95% CI: 2.08-7.69).

4.3 | Peri-implantitis surgery

A total of 30 patients (34 operations) were treated surgically for problems with early or late (peri-implantitis) inflammation and bone loss at the implants, corresponding to 30% of all patients with a diagnosis (26% of operations).

Both the univariate and the following multivariate regression analyses revealed three significant factors associated with risk for peri-

TABLE 3 Final multivariate Poisson regression analysis on identified significant parameters related to "peri-implantitis" and "surgery related to peri-implantitis"

Factors with significant association with risk for peri-implantitis			
	HR	95% CI	Comments
Lower jaw	3.03	2.11-4.35	Higher risk in lower jaw
Partially edentulous jaws (posterior)	1.59	1.09-2.32	Higher risk in partially edent. jaws
Number of implants	1.32	1.18-1.48	Higher risk with more implants
Surgical technique (direct/1-stage/2-stage)	1.82	1.32-2.52	Highest risk for direct placement and lowest for two-stage surgery
Year of surgery	1.28	1.16-1.41	Higher risk for later inclusion
Factors with significant association to risk for "peri-implantitis surgery"			
	HR	**95% CI**	**Comments**
Gingival grafting	3.34	1.06-10.54	Higher risk with immediate gingival grafting
Lower jaw	2.56	1.18-5.56	Higher risk for lower jaws
Year of surgery	2.10	1.57-2.80	Higher risk for later year of inclusion

implantitis surgery; "Immediate gingival grafting," "Type of jaw," (Upper/lower) and "Year of surgery" (Table 3).

4.4 | Overall and late implant failures

Altogether, 28 patients were identified with late implant failures after 29 implant operations (Table 4). Seven of the patients experienced more than one event with implant failure, six of them recorded as first early failures followed by late failures. All but six of the events with implant failures were associated with an earlier diagnosis with early inflammation or peri-implantitis problems before or at time of implant removal (79.3%). Average time between diagnosis with inflammation problems and implant removal was 4.6 years (SD 1.76).

The multivariate regression analysis resulted into three factors that had a significant association with overall implant failures (Table 5); "Type of implant" (NobelActive CC), "Smoking habits," and "Surgical technique" (direct/one-stage/two-stage).

When considering only implant failures that were lost after the first year (baseline = 1 year; "late implant failure"), the statistical analyses reveled two significant factors related to risk for late implant failures; "Jaw (upper/lower)" with an increased HR of 2.63 for lower jaw treatment (95% CI: 1.25-5.56), and "Diagnosis of inflammation at the implant during first year" (new factor) with an increased HR of 17.95 (95% CI: 5.92-54.46).

The final nonlinear analysis using the Spline method showed that "Lower jaw" (Figure 6) had a significant association to overall implant failure ($P < .05$) from 2.9 years (HR 3.80, 95% CI: 1.0-13.9) to 5.8 years after surgery (HR1.8, 95% CI; 1.0-3.2). The nonlinear model showed

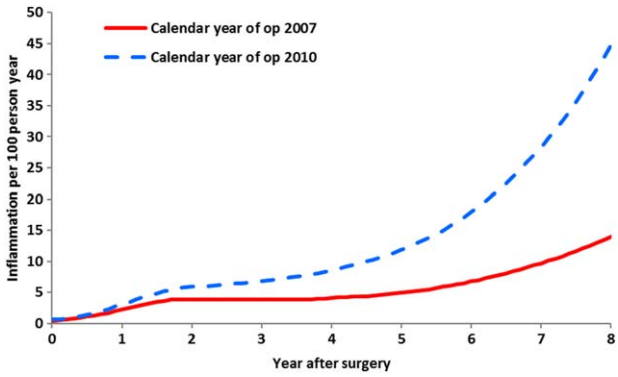

FIGURE 3 Risk of peri-implantitis per 100 person years related to year of surgery, here exemplified by years 2007 and 2010. Overall HR was calculated to 1.28 (95% CI; 1.16–1.41), indicating that the risk for peri-implantitis increased by 28% per year of later inclusion (from 2000 to 2011). HR for 2010 is placed above HR for 2007 indicating higher risk for 2010. Also, a trend of increased risk by time is indicated for both years

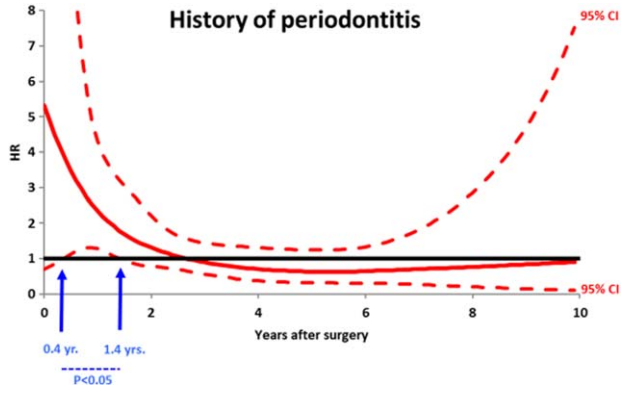

FIGURE 4 Hazard Ratio (HR) for risk for inflammation at the implants related to "history of periodontitis" during follow-up (red line). HR above HR = 1.0 (black line) indicate increased risk and below HR = 1.0 decreased risk. The risk is statistical significant related to "history of periodontitis" when both ±95% CI (dotted red lines) are above (or below) HR = 1.0 ($P < .05$). History of periodontitis increase the risk for inflammation significantly between 0.4 years (HR 3.8 (95% CI: 1.0–13.9) and 1.4 years after implant surgery (HR 1.8 (95% CI: 1.0-3.2)

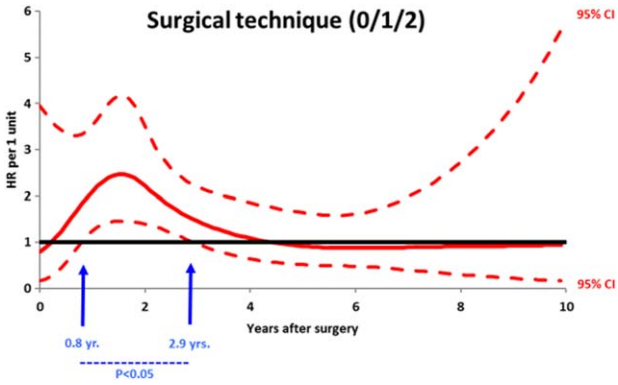

FIGURE 5 Risk for inflammation at the implants increase significantly from 0.8 years (HR 1.8 (95% CI: 1.0–3.3) to 2.9 years (HR 1.5 (95% CI: 1.0–2.3) after surgery related to surgical technique (step wise increase from direct placement to one-stage and to two-stage surgical protocol). Accordingly, two-stage surgery (85% with immediate bone grafts and membranes) presents the highest risk for inflammation during the period. Maximal HR for two-stage surgery was after 1.5 years (HR 2.5 (95% CI: 1.5–4.2). Dotted lines represent 95% CI

also that the risk for late implant failure was significantly higher for direct placement surgery as compared to one- and two-stage surgery (Figure 7) between 0.2 years (HR 2.1, 95% CI; 1.0-4.3) and 0.8 years (HR 3.0, 95% CI; 1.0-8.7).

Results after testing the difference between NobelActive CC and "other implants" used in the clinic is presented in Table 6. Compared to "other implants," NobelActive CC implants have been used in higher proportions when using grafting procedures, direct placement, and one-stage surgical procedures. Furthermore, it can be noticed that NobelActive CC has been used in fewer patients with history of periodontitis and/or in the lower jaw (Table 6).

A comparison was also made testing difference between upper and lower jaws provided with single implants and implants in the posterior partially edentulous jaws (Kenned class 1 and 2) with regard to implant failures. It was observed that posterior partially edentulous lower jaws (Kennedy class 1 and 2) had a significantly higher risk for late implant failures as compared to corresponding situations in the upper jaw (HR 5.88; 95% CI: 1.30-26.64).

TABLE 4 Distributions of numbers of operations with recorded early (≤1 year in function) and late implant failures (>1 year in function) in different types of treated jaws[a]

	Numbers of operations						
	Early failures			Late failures			
Implants	Edent	Part	Single	Edent	Part	Single	Total
Upper jaw	2	14	13	3	4	3	39
Lower Jaw	3	4	5	0	10	9	31
Total	5	18	18	3	14	12	70

[a]Treated jaws were; edentulous (Edent.), partially edentulous jaws (Part), and jaws provided with single implants (Single).

TABLE 5 Final multivariate logistic regression analysis on identified significant parameters related to late implant failures

Factors with significant association with risk for "implant failure"			
	HR	95% CI	Comment
Smoking habits	2.11	1.26-3.55	Higher risk for smoking
Surgical technique (direct/one-stage/ two-stage)	1.67	1.11-2.59	Highest risk for two-stage surgery and lowest for direct placement
Type of implant; Nobel Active	2.48	1.05-5.85	Nobel Active associated with higher risk

5 | DISCUSSION

There has been a discussion for many years that randomized controlled trials (RCT/efficacy studies) may sometimes lack external validity (generalisability) which makes clinicians to hesitate to introduce new clinical research into routine clinical practice.[1] Thus, many general practitioners have the perception that results from RCT studies are not or poorly covering the daily routine procedure.[1] This concern has been addressed by Cochrane already during the 1970s; "Between measurements based on RCTs and benefit . . . in the community there is a gulf which has been much under-estimated."[1,30] This and similar comments have opened up for discussions on clinical validity of alternative research protocols as using retrospective studies based on routine patient treatment (effectiveness study) instead of the more reliable and scientific more correct RCT study design. Rothwell[1] commented in an overview on external validity of RCT studies that ". . . systematic evidence we now have confirms that RCTs do often lack external validity, this issue is neglected by current researchers, medical journals, funding agencies, ethics committees, the pharmaceutical industry, and governmental regulators alike." Accordingly, limitations of retrospective effectiveness studies are well recognized, but also prospective efficacy

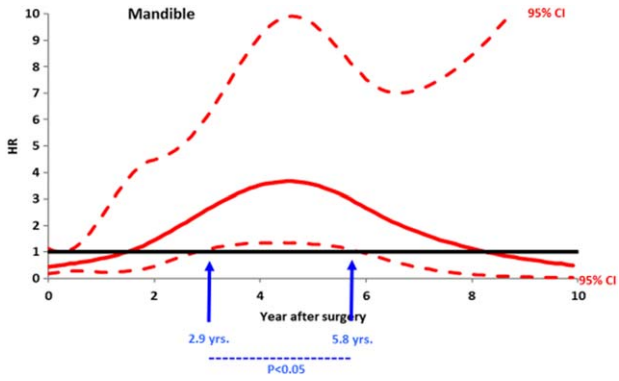

FIGURE 6 Risk for implant failures in the lower jaw as compared to the upper jaw is significantly increased between 2.9 years (HR 2.48 [95% CI: 1.05-5.85]) and 5.8 years after implant surgery (HR 2.89 [95% CI: 1.05-7.95])

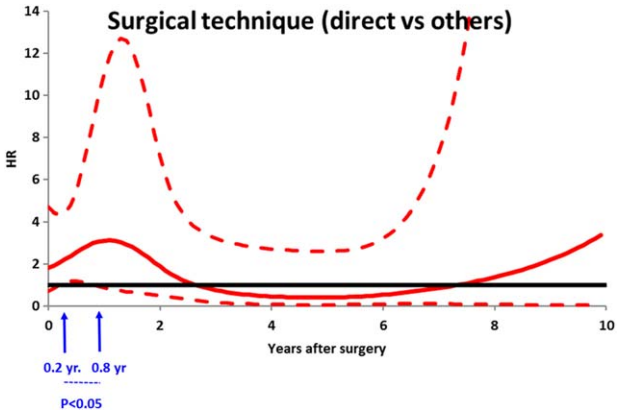

FIGURE 7 Risk for implant failures after direct implant placement protocol is significantly increased between 0.2 year (HR 2.1 [95% CI: 1.0-4.3]) and 0.8 years (HR 3.0 [95% CI: 1.0-8.7]) after implant surgery as compared to one- and two-stage surgery. This pattern is followed by a nonsignificant trend of an opposite pattern with the highest risk for two-stage surgery during later years of follow-up

studies could have its limitations as well, which should be considered when evaluating final clinical results.[1]

Thus, it is important to recognize the difference in how patients are included into a study when using a prospective randomized efficacy study design (RCT) as compared to the present retrospective effectiveness study. Selected research parameters should in a RCT study be carefully randomized among the patients with regard to other important factors that are considered to have an impact on the outcome. This allows for a more direct association to differences between the research groups when significant differences are revealed. In an effectiveness study, however, selected parameters as well as other factors are not evenly randomized between the patients, and reported significant differences may also be more easily associated to other underlying factors, not completely under control. This can be exemplified in a recent effectiveness study, where it was reported that one implant system presented significantly lower early implant failure rates as compared to other implant systems.[31] The readers may have been left with the perception that the system with the lowest early failure rate would be "better" than the other systems since no further comments were made on for example, differences among the groups regarding mucosa level/bone level implants, surgical loading protocols, time of risk for an early failure, grafting procedures, type of treated jaws, numbers of installed implants, and so on. Thus, the statistical tests used in many effectiveness studies may reveal statistical differences between groups with different factors, but are not necessarily able to determine causality. This problem can here be exemplified with the observation that NobelActive CC implants showed a significantly higher late implant failure rate than other types of implants used in the present clinic (Table 5). However, a further detailed comparison between the different implants revealed significant differences in clinical use of NobelActive CC implants as compared to others (Table 6). Thus, even though the use of a specific type of implant may have a real significant impact on risk for later implant failures, results from effectiveness studies are recommended to always be evaluated from a broader base, preferably combined with clinical judgements and experience. This is specifically at hand when using different ratios of risk between the parameters in the calculations (OR, HR) since these ratios basically report relative risk between parameters and not the actual levels of clinical risk for the two tested parameters.

TABLE 6 Comparisons between NobelActive CC implants (NAc.) and "other implants" used at the clinic

Factor	*P*-value (two-sided)	Comment
Males or females	.011	Males more often treated
History of periodontitis	.043	Fewer with history of periodontitis
Year at surgery	<.001	Later inclusion—more NAc.
Number of implants	.0026	Fewer implants per operation
Upper or lower jaw	<.001	More NAc. in upper jaws
Immediate grafting	<.001	More NAc. with graft
Immediat gingival graft	<.001	More NAc. with graft
Surgical technique	<.001	More NAc. immediate placement
Surgical technique	<.001	More NAc. one-stage

Brånemark used in the early period of osseointegration, a clinical protocol which was judged to provide the safest biological situation for implants to integrate into the jaw bone.[32,33] Thus, bone had to heal before implant placement, and a two-stage protocol was recommended for all patients.[32,33] Furthermore, if grafting was considered, autologous bone grafts were used.[34] By time, the protocol changed gradually into one-stage and direct placement surgery, alternative grafting techniques, and nonautologous grafting materials with membranes placed at implant surgery.[6,7,35] Part of this change can be observed in the present study over the years with an increased use of direct placement and one-stage surgical technique, both in combination with immediate nonautologous grafting technique. The most elaborate grafting approach in the present clinic was the two-stage procedure with nonautologous grafts in combination with resorbable membranes (85% using GBR technique). This latter two-stage approach is in the present study associated with lower early implant failure rate[3] but with an increased risk for peri-implantitis (late inflammation), especially when performed in the posterior lower jaw (Tables 3 and 5). A similar increased risk for peri-implantitis in association with augmented bone has been reported by others, even though not reaching statistical significant levels.[36] Based on the current observations, it could be assumed that the use of immediate nonautologous grafting materials may increase the risk for early inflammation, peri-implantitis problems, and possibly more late implant failures, especially when performed in the posterior lower jaw (Tables 3 and 5).[3]

"History of periodontitis" has in the previous study been shown to increase the risk for early inflammation at the implants in the present study group, especially related to the mid-aged patients.[3] This observation is in agreement with other studies.[37,38] "History of periodontitis"

was here shown to be a risk factor for the first 2.5 years after implant surgery, with a significant association to risk for inflammation between 0.4 and 1.4 years after surgery ((Figure 4), but not associated to implant failures. The factor related to "smoking" show a similar difference between risk for inflammation and implant failure, but here with no association to risk for inflammation or peri-implantitis in accordance with others.[36,39–41] However, smoking was a consistent risk factor in the present patient group, both for early as well as overall implant failures (Table 5), also in accordance with others.[3,42–44]

It has earlier been noticed that the risk for early implant failures decreases during the inclusion period, indicating an increased surgical experience.[3] However, it can be observed a significantly increasing problem with peri-implantitis and surgery related to peri-implantitis the later the patient is treated during inclusion (Table 3, Figure 3). This observation indicates that in one or another way there is a consistent change in the present patient group over time, treated by the same surgeon with increasing experience. In a recent study, it was shown that younger edentulous implant patients showed a higher patient mortality when treated late as compared to early during inclusion, indicating more compromised health for later treated implant patients.[45] Besides possible change of compromised general health during inclusion in the present patients, it can also be observed that an increasing number of implant operations with direct placement surgery and immediate grafting procedures has been performed, procedures which here are associated with increased risk for early inflammation/failures as well as peri-implantitis and surgery related to peri-implantitis (Tables 3 and 5).[3]

The aim for treatment of implant patients is to keep the patients free from severe inflammation, continuous bone loss and ultimate failure of implants, and implant-supported prostheses during follow-up. Clinical signs of mucositis and history of bone loss have for many years been used to try to identify risk patients for future severe problems.[14] However, by experience many more patients show signs of mucosal inflammation and signs of peri-implant bone loss during follow-up than eventually show-up with implant failures and complete failure of the entire prostheses. Thus, thresholds for degree of clinical inflammation and historic radiographic bone loss become critical, leading to a variation of inclusion criteria and following variation in prevalence of peri-implantitis in different studies, as discussed above.[14,16–27] This problem of defining peri-implantitis should also be considered in the present study, even though only patients treated for problems with peri-implantitis have been included. However, the present results with significant, and reasonably explainable, results indicate that the present definition/inclusion is not completely formulated ad hoc, and it may have some justification. Still, it can be argued whether observations of inflammation and history of bone loss parameters are precise enough to predictably identify those patients that are at a higher risk for future severe problems, and the risk for under- or over-estimation of numbers of risk patients are obvious.[46]

Accordingly, a deeper and more profound knowledge on the mechanism and factors related to later implant complications is needed which is one of the aim for this study. Results from the present patient group reveal several factors that may be of importance in the process of early osseointegration, inflammation, and later loss of integrated implants (Tables 3 and 5).[3] Present data indicate that the risk for peri-implantitis and late implant failures may be associated to surgical area (Tables 4 and 6; posterior mandible) and surgical technique (Tables 3 and 5; grafting procedures), where the risk for peri-implantitis/peri-implantitis surgery increases with later years of treatment (Table 3). Late implant failures are also associated with increased risk when smoking. The strong increased risk for late implant failures related to "earlier diagnosis of early inflammation" (HR = 17.95), when using baseline at first year of follow-up, should be judged in relation to the factors related to higher risk for early inflammation, as presented in the previous study.[3] It can be noticed that risk associated to "history of periodontitis" disappear early after the first year (Figure 4) while the remaining three factors remain as risk factors for longer periods of follow-up (Figures 5 and 6). Earlier, it has been shown that autologous bone grafts may resorb during follow-up,[47] while nonautologous grafting particles seems to remain in the bone tissue and thereby maintain long-term stability of the restored contour of the crest.[48] Histological long-term data indicate that these nonautologous particles may often be well osseointegrated but that they sometimes may be surrounded by multinucleated giant cells,[48] indicating a foreign body response in the tissue. Furthermore, long-term follow-up data in a recent study on implants placed in grafted sites indicated that even though a high survival rate was observed early after implant surgery, an increasing failure rates was observed in certain situations.[49] Implant failure rates reaching 14-35% after 5 years were reported in posterior jaws,[49] indicating an ongoing inflammatory process at these grafted sites. Present data indicate an association between grafting procedures using nonautologous material and peri-implantitis and surgery related to peri-implantitis in line with these observations (Table 3). A trend of increased failure rate for implants after two-stage GBR surgery during later periods of follow-up could also be observed (Figure 7). In the light of the present observations of a possible increased risk for peri-implantitis and late implant failures when using nonautolougus bone grafts during placement of foreign body implants,[15,50] it could be discussed if these graft materials further increase the foreign body "load" at the implant sites. It can also be discussed if these nonautologous materials should be used to restore bone defects during peri-implantitis surgery in patients that could be those that may respond with more inflammation toward foreign body materials than others.

6 | CONCLUSIONS

Within the limitations of this large retrospective effectiveness study based on 1017 consecutively treated patients provided with 3082 implants with an anodized surface at 1592 implant operations, the following conclusions could be made for routine clinical treatment after the first year of clinical function:

Factors related to "smoking habits," "surgical technique," and "type of implant" have a significant association to increased risk for overall implant failures in routine practice ($P < .05$).

Factors related to "numbers of implants," "treatment in partially (posterior) lower jaws," "surgical technique," and "year at surgery" have a significant association to the risk for peri-implantitis ($P < .05$). A majority of two-stage surgical loading protocols with highest risk for peri-implantitis problems were used in combination with GBR grafting techniques (85%).

The risk for peri-implantitis increased with 28% per year from implant surgery performed year 2000 to 2011.

Factors related to "lower jaw," "immediate gingival grafting," and "year at surgery" have a significant association to the risk for "surgery related to peri-implantitis" ($P < .05$). A majority of two-stage surgical loading protocols were used in combination with GBR grafting techniques (85%).

When using a baseline at the first year of follow-up, it was shown that factors related "early inflammation at the implant" and "lower jaw" have a significant association to the risk for late implant failures ($P < .05$).

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