Effectiveness of implant therapy in Sweden

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To my parents and Maria, with love and gratitude.

Content

Abstract

Dental implants are commonly used in restorative therapy in patients with partial or full edentulism. Knowledge regarding the outcome of this kind of treatment has been limited to evaluations of efficacy, i.e. therapy performed under optimal conditions. The current series of studies evaluated effectiveness of dental implant therapy including patient-reported outcomes, the occurrence of implant loss as well as peri-implantitis.

Using the national data registry of the Swedish Social Insurance Agency, 4,716 patients were randomly selected. All had been provided with implant-supported restorations in 2003/2004. Patient-reported outcomes were analyzed by questionnaire 6 years after completion of therapy **(Study I)**. Patient files of 2,765 patients were collected from more than 800 clinicians. Information on patients, treatment procedures, and outcomes related to the implant-supported restorative therapy was extracted from the files. 596 of the 2,765 subjects attended a clinical examination 9 years after therapy. Early implant loss was assessed in patient files, while late implant loss was recorded at the clinical examination **(Study II)**. The prevalence of peri-implantitis was determined from clinical and radiographic data collected at the 9-year examination **(Study III)**. Radiographs obtained from the patient files were used to evaluate the onset and pattern of progression of peri-implantitis **(Study IV)**.

It was demonstrated that:

- the overall patient satisfaction was high but influenced by (i) age and gender of the patient, (ii) the extent of restorative therapy and (iii) the training of the clinician performing the treatment **(Study I)**.
- implant loss occurred in 7.6% of all patients over a follow-up of 9 years; patient and implant characteristics influenced the outcome **(Study II)**.
- 14.5% of all patients exhibited moderate/severe peri-implantitis, and several patient- and implant-related characteristics were identified as risk indicators **(Study III)**.
- progression of peri-implantitis occurred in a non-linear, accelerating pattern, and, in the majority of cases, the onset of the disease had occurred early **(Study IV)**.

Sammanfattning på svenska

Behandling med tandimplantat är en vanlig metod vid tandlöshet och Sverige tillhör de länder som har flest patienter med tandimplantat i förhållande till sin folkmängd. Klinisk forskning som utvärderat metoden har ofta varit begränsad till beskrivande observationsstudier på små, selekterade patientgrupper och där vården huvudsakligen utförts inom specialisttandvård. Få studier har analyserat förekomsten av biologiska komplikationer, s.k. peri-implantit. Peri-implantit är ett sjukdomstillstånd som kännetecknas av inflammation i implantatets angränsade vävnader och förlust av stödjevävnad.

I ett nationellt projekt har behandling med tandimplantat utvärderats med avseende på (i) patientupplevd nytta, (ii) implantatförluster och (iii) förekomst av peri-implantit. Projektet genomfördes som en populationsbaserad fältstudie och utgick från 4,716 slumpmässigt utvalda patienter från Försäkringskassans register. Behandlingen med tandimplantat utfördes under 2003/2004. I en inledande studie skickades en enkät till alla 4,716 patienter för att analysera den patientupplevda nyttan med behandlingen. Journaluppgifter och röntgenbilder från 2,765 patienter insamlades från c:a 800 tandläkare. 9 år efter behandlingen med tandimplantat undersöktes 596 av de 2,765 patienterna vid 37 olika kliniker i Sverige.

Resultaten från enkätundersökningen visade att patienterna överlag var nöjda med behandlingen och att män och äldre patienter var mer nöjda än kvinnor och yngre patienter. Vid 9-års undersökningen hade 7.6% av alla patienter förlorat minst ett implantat och 14.5% av patienterna drabbats av en allvarlig form av peri-implantit. Rökare och patienter med parodontit visade ökad risk för tidiga implantatförluster. Parodontitpatienter visade även ökad risk för svår peri-implantit. Typen av implantat inverkade på risken för att förlora implantat eller drabbas av peri-implantit. Peri-implantit förefaller debutera tidigt efter installation och utvecklas snabbt i ett accelererande mönster.

List of papers

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Derks J, Håkansson J, Wennström JL, Klinge B, Berglundh T (2015). Patient-reported outcomes of dental implant therapy in a large randomly selected sample.
Clin Oral Implants Res 26:586-591.

II. Derks J, Håkansson J, Wennström JL, Tomasi C, Larsson M, Berglundh T (2015). Effectiveness of implant therapy analyzed in a Swedish population: early and late implant loss.
J Dent Res 94 Suppl 3:44-51.

III. Derks J, Schaller D, Håkansson J, Wennström JL, Tomasi C, Berglundh T (2015). Effectiveness of implant therapy analyzed in a Swedish population: prevalence of peri-implantitis.
J Dent Res accepted for publication.

IV. Derks J, Schaller D, Håkansson J, Wennström JL, Tomasi C, Berglundh T (2015). Peri-implantitis - onset and pattern of progression.
Manuscript.

Abbreviations

BoP	Bleeding on probing
CI	Confidence interval
EWoP	European Workshop on Periodontology
OR	Odds ratio
PPD	Probing pocket depth
PROM	Patient-reported outcome measure
RCT	Randomized controlled clinical trial
SSIA	Swedish Social Insurance Agency
SUP	Suppuration
VAS	Visual analogue scale
AT	Astra Tech implants group
NB	Nobel Biocare implants group
S	Straumann implants group
R	Remaining implants group

Introduction

1 Implant-supported restorative therapy

The placement of dental implants in the rehabilitation of partially and fully edentulous patients constitutes a safe, accepted and commonly applied method (e.g. Jung et al., 2012; Pjetursson et al., 2012). In fact, it was estimated that, on an annual basis, more than 12 million implants are placed, globally (Albrektsson et al., 2014). The concept of osseointegration was first presented in the 1960s and 70s by P.I. Brånemark and his coworkers in Sweden (1969; 1977). Early research was also carried out in Switzerland and Germany by teams headed by H. Schroeder (1976) and W. Schulte (1976). On a global perspective, acceptance of the clinical application followed the Toronto conference held in 1982.

In Sweden, extensive financial support for dental care is provided and administered by the Swedish Social Insurance Agency (SSIA). Both public and private providers offer dental care, and the federal reimbursement is similar, regardless of the clinical setting. In 1986, implant-supported restorations became an officially recognized treatment and, hence, were reimbursed by the SSIA. As of July 1st in 2002, this reimbursement system was modified, and the federal subsidy for implant-supported restorative therapy for patients ≥65 years of age was increased. Thus, out-of-pocket expenditure for subjects in this age category should not exceed SEK 7,700 (+ laboratory costs), regardless of the extent of the implant-supported restoration. In contrast, patients <65 years of age had to cover as much as half of the actual costs themselves. In the period between 2002 and 2008, the majority of such restorations was placed in patients ≥65 years.

Records from the SSIA revealed that, in 2003, about 100,000 implants were placed in more than 25,000 subjects. Since then, these numbers have, in contrast to what has been observed globally, decreased. Data from the SSIA registry further revealed that the placement of slightly more than 50,000 implants in about 18,000 patients was reimbursed in 2014. Details regarding restorative therapy including implants that was reimbursed between 2012 and 2014 are shown in Table 1. Reasons for the decrease from 2003 to 2014 in numbers of implants placed are currently unknown, but may be related to differences in treatment needs and the changes in the reimbursement system introduced in 2002 and in 2008.

Table 1.Number of patients treated with dental implants and number of implants placed in Sweden (reimbursed therapy, SSIA registry)

	2012	2013	2014
Patients	13,186	15,174	17,717
Implants	45,591	47,795	53,859

The main outcome variable reported in longitudinal studies on implant therapy was the rate of implant survival, while complications other than implant loss were less frequently presented (Berglundh et al., 2002; Needleman et al., 2012). Furthermore, documentation was predominantly based on assessments made in selected patient groups (i.e. so-called convenience samples) (Tomasi and Derks, 2012), in which treatment was carried out by clinicians in specialist and/or university clinical settings. Berglundh & Giannobile (2013) questioned the external validity of this type of efficacy documentation (i.e. the probability of an intervention being beneficial to patients under optimal conditions) and suggested that future research should consider evaluations of effectiveness (i.e. the care provided to the general population under conditions found in practice).

The present series of studies describes an attempt to address potential shortcomings of the current scientific documentation regarding outcomes of implant-supported restorative therapy. These shortcomings may be highlighted by the following questions:

1. Are we considering the appropriate variables?

2. Are we analyzing data and presenting results in such a way that they may be appreciated by dental professionals and patients?

3. Do we distinguish between efficacy and effectiveness?

In regard to question 1, the consensus statement from the 8th European Workshop on Periodontology (EWoP) suggested that, in order to advance the understanding in the field, future clinical research in implant dentistry should consider three outcome domains: patient-reported outcomes (PROMs), peri-implant tissue conditions and outcomes related to implant-supported reconstructions (Tonetti and Palmer, 2012).

Even though treatment outcomes are often assessed for single implants, it is the patient who is ultimately affected by potential complications. In regard to

question 2, it has therefore been suggested that the occurrence of complications is presented for the individual rather than for the implant (Tonetti and Palmer, 2012). It was argued that such data presentation makes the results more meaningful for both clinicians and patients.

Data from clinical trials and observational research should ideally be of high internal and external validity (question 3). However, these two aspects of validity are often trade-offs (Grimes and Schulz, 2002b). While internal validity refers to the level of selection and information bias as well as confounding, external validity is the ability to generalize findings from the study sample to the general population. Randomized controlled clinical trials (RCTs), for instance, commonly enroll selected participants who might differ significantly from the overall population. Participants in such trials have been shown to be healthier than background populations studied (Halbert et al., 1999; Moinpour et al., 2000). The trade-off exists in that RCTs are usually superior to observational studies in terms of internal validity, while external validity often suffers (Chalmers et al., 1983; Feinstein, 1985). As scientific reports in the field of implant dentistry are frequently based on case series originating from small populations treated at single centers, often university clinics (Tomasi and Derks, 2012), the external validity of existing evidence has been questioned (Berglundh and Giannobile, 2013). In order to evaluate effectiveness of implant therapy, it was stated, studies should consider treatment outcomes in different demographic groups of patients and evaluate the influence of training and skill level among clinicians (Berglundh and Giannobile, 2013).

2 Patient-reported outcome measures following implant-supported restorative therapy

PROMs are related to the patient as the unit of analysis rather than the restoration or the single implant. For implant dentistry, this line of research is fairly new, while other fields have considered PROMs for many years. Current systematic reviews on PROMs related to hip and knee replacements include over 70 trials dating back to the early 80s (e.g. Ethgen et al., 2004). Patient-reported assessments in the dental field are concerned with assessing the impact of oral health on patients' day-to-day life and patients' satisfaction with their oral health status (Newsome and McGrath, 2006). Several studies have demonstrated that both full and partial edentulism are associated with a reduced "quality of life" (e.g. Blomberg and Lindquist, 1983; Albrektsson et al., 1987; Locker, 1992; Gerritsen et al., 2010).

Tools to assess PROMs

PROMs following implant therapy have been assessed by one of two approaches. Subjects were either interviewed by investigators trained in psychological techniques (e.g. Johannsen et al., 2012; Hamdan et al., 2013) or asked to complete a questionnaire (e.g. Cune et al., 1994; Lam et al., 2013). In a systematic review presented at the 8th EWoP, the high degree of heterogeneity of tools in the assessment of PROMs through questionnaires was discussed (McGrath et al., 2012). It was found that, while some studies were limited to assessing patient preference, others evaluated specific aspects of satisfaction. Furthermore, different rating systems were employed including the use of visual analogue scales (VAS) and scaled questions. The systematic review noted that investigators often used "ad hoc" scales without evidence of their psychometric properties in terms of validity and reliability.

PROMs following implant-supported restorative therapy

The majority of studies assessing PROMs in the field of implant dentistry focused on edentulous patients (Emami et al., 2009).

PROMs have been primarily assessed in short-term studies, evaluating the effect of the prosthetic rehabilitation by comparing pre- and post-treatment measures (Emami et al., 2009). Thus, the positive impact of implant-retained restorations over 6 and 12 month periods has been demonstrated, in particular, when compared to traditional removable complete dentures (e.g. Awad et al., 2013; Hamdan et al., 2013). Only one study included randomly selected individuals and assessed satisfaction following treatment with implant-supported overdentures (Cune et al., 1994). The sample size, however, was small and the time period of observation did not exceed 12 months following prosthesis delivery. In the systematic review by McGrath et al. (2012), it was stated that PROMs assessed in studies with limited follow-up periods were unlikely to explain much beyond healing, recovery or perhaps an outcome tainted with the euphoric effect of treatment. The authors of the review therefore recommended studies of longer follow-up. Few studies have considered PROMs of implant therapy over extended time periods of >5 years and in patient groups provided with different types of restorations (Pjetursson et al., 2005; Simonis et al., 2010). While such studies indicated a high degree of patient satisfaction, study samples were small, not randomly selected and treated in specialist clinics. Selected studies assessing PROMs related to implant therapy and their findings are presented in Table 2.

Table 2.Studies on PROMs following implant-supported restorative therapy

First author, year	Study type	Sampling & sample size	Intervention	Function time	PROM	Findings
Albrektsson et al. (1987)	Case series Longitudinal	Convenience 152 edentulous subjects	Implant-supported dental prosthesis	3-13 years	Questionnaire 13 questions	High degree of satisfaction. Significantly improved function and esthetics as well as psychological benefit following treatment.
Awad et al. (2013)	Multi-center RCT Longitudinal	Convenience 203 edentulous subjects	104 subjects Implant-supported overdenture 99 subjects Conventional full denture	6 months	Questionnaire 20 questions 6-point scale	Implant-supported overdentures were more likely to improve quality of life than conventional dentures. Cultural differences in the impact of implant overdentures were observed.
Cune et al. (1994)	Case series Longitudinal & cross-sectional	Random selection from implant registry 65 edentulous subjects (longitudinal) & 114 edentulous subjects (cross-sectional)	Implant-supported overdenture	12 months	Questionnaire 20 statements 5-point scale	High degree of satisfaction. Greatest benefit in mandible and in terms of comfort.
Emami et al. (2015)	Case series Longitudinal	Convenience 135 edentulous subjects	Implant-supported overdenture	3-36 months	Questionnaire 20 questions 6-point scale	High degree of satisfaction. Significantly improved function and less psychological discomfort following treatment.
Hamdan et al. (2013)	RCT Longitudinal	Convenience 207 edentulous subjects	103 subjects Implant-supported overdenture 114 subjects Conventional full denture	12 months	Telephone interview Dietary recall was used to calculate dietary intake values	No evidence of nutritional advantages following treatment with implant-supported overdentures over conventional dentures.
Harrison et al. (2009)	Cross-sectional	Convenience 68 subjects	Implant-supported single, partial and overdenture restorations	0-60 months	Questionnaire 7 questions VAS and point scale	High degree of satisfaction.

First author, year	Study type	Sampling & sample size	Intervention	Function time	PROM	Findings
Johannsen et al. (2012)	Cross-sectional	Convenience 17 subjects	Implant-supported dental prosthesis including ≥3 implants	3-10 years	Semi-structured interview aiming for saturation	Negative impact of tooth loss. Implant therapy lead to improved chewing ability and esthetic appearance. Improved quality of life.
Lam et al. (2013)	Retrospective cohort study (cross-sectional data collection)	Convenience 78 subjects	39 subjects Implant-supported single crown 39 subjects 2-unit cantilevered resin bonded bridge	≥5 years	Questionnaire 49 questions 5-point scale	Similar level of satisfaction in both groups. Experience of complications decreased the degree of satisfaction, especially in patients treated with implants.
Pjetursson et al. (2005)	Cross-sectional	Convenience 104 subjects	Implant-supported single and partial restorations	5-15 years	Questionnaire 12 questions VAS and point scale	High degree of satisfaction in terms of function and esthetics.
Simonis et al. (2010)	Cross-sectional	Convenience 46 subjects	Implant-supported single and partial restorations	10-16 years	Questionnaire 12 questions Point scale	High degree of satisfaction in terms of function and esthetics.

3 Biological complications of implant-supported restorative therapy

Long-term success of dental implant therapy depends on the initial and long-term integration of the implant with hard and soft tissues. In line with this prerequisite for success, the second field of interest for implant research is the occurrence of biological complications (Tonetti and Palmer, 2012). By definition, such complications include issues related to the soft and hard tissues surrounding the implant.

Implant loss

The most dramatic complication, which occurs when both soft and hard tissue integration has failed, is the complete loss of the implant. From a research point of view, implant loss is an easy outcome to study and is rarely disputed. No specific case definition is required. In fact, loss of dental implants is the most commonly reported outcome in the literature (Needleman et al., 2012). As mentioned earlier, implant loss has usually been presented as a percentage of implants installed. This in itself is not incorrect but somewhat misleading. Thus, it was argued that, in addition to implant-related figures, the proportion of affected patients should be presented as it is the patient who is facing a complication (Berglundh et al., 2002; Berglundh and Giannobile, 2013).

Early implant loss

Traditionally adopted treatment strategies include a healing period of 3 to 6 months following implant installation (Brånemark et al., 1977). During this time, osseointegration should occur, and, thereafter, prosthetic devices replacing the missing tooth/teeth may be connected. Implant loss occurring prior to loading is considered as early implant loss (Cecchinato et al., 2004; Alsaadi et al., 2007; Bornstein et al., 2008; Esposito et al., 2010). In other words, such implants have failed to achieve osseointegration during the healing phase and need to be removed. In this context it should be realized that some authors considered implants lost during the first 6 (Vervaeke et al., 2015) or 12 months (Jemt et al., 2014; Friberg and Jemt, 2015) *of function* as early lost implants.

Evidence in regard to early implant loss originates from studies describing efficacy rather than effectiveness of treatment. In selected patient groups treated at specialist clinics, the rate of early implant loss is generally low. Figures of about 1% of implants being lost prior to prosthetic loading have been described (Bornstein et al., 2008; Roccuzzo et al., 2010; Friberg and Jemt, 2015). In contrast, findings from studies including larger patient cohorts described higher proportions (about 3%) (Cecchinato et al., 2004; Rasmusson et al., 2005; Roos-Jansåker et al., 2006a; Esposito et al., 2010). The proportion of affected patients was usually higher than the proportion of implants lost. Alsaadi et al. (2007)

reported early implant loss for 3.6% of all implants, while 8.9% of all patients were affected. Similarly, Vervaeke et al. (2015) reported on an early implant loss of 0.8% affecting 2.9% of all patients. A summary of publications presenting data on early implant loss is presented in Table 3.

The apparent variation in terms of proportion of early implant loss, ranging from 0.8% (Bornstein et al., 2008) to 3.7% (Wagenberg and Froum, 2006) on the implant level, is intriguing and may be explained by factors related to patient selection and to experience of the clinician. A systematic review on implant complications observed that the extent of the restorative therapy was of significance (Berglundh et al., 2002). While less than 1% of implants failed to integrate in situations of single-tooth replacement, the rate of early implant loss in overdenture (full jaw) cases was almost three times as high. Patient- and clinician-related factors associated with early implant loss were studied by Alsaadi et al. (2007). The authors reported that osteoporosis, Crohn's disease, smoking habits, implant length, implant diameter and implant location were all significantly associated with early implant loss. Implant installation in fresh extraction sockets (immediate installation) has also been shown to lead to an increased rate of early implant loss (Esposito et al., 2010). Analyses on the consequences of early implant loss are lacking. Ultimately, it is the consequence of a complication that is of the highest interest to the patient. Early implant loss might entail additional surgical interventions or alterations of the treatment strategy.

Late implant loss

Implant loss occurring after loading has been defined as late implant loss. Similar to what has been reported for early implant loss, the rate of late implant loss is described as low, particularly in studies originating from well-controlled clinical settings. Wagenberg & Froum (2006) reported a loss rate of 0.3% of all implants following prosthetic loading over a period of 1 to 16 years. Friberg & Jemt (2015) observed a loss of 0.7% of implants following the first year in function. Larger patient cohorts have been described to present with rates of late implant loss of around 2% or above (Roos-Jansåker et al., 2006a; Alsaadi et al., 2008; Jemt et al., 2014). Proportions of affected patients were not always reported but were higher when compared to implant-related data. Figures ranging from 2.1% (Vervaeke et al., 2015) to 16.0% (Alsaadi et al., 2008) were observed. A summary of publications presenting data on late implant loss is given in Table 3. No data on late implant loss in terms of effectiveness are available.

As late implant loss presents with different features when compared to early implant loss, associated risk indicators/factors may also differ. Few studies have evaluated risk indicators of late implant loss. History of periodontitis (Roccuzzo et al., 2010) and radiotherapy (Alsaadi et al., 2008) have been identified as

patient-related risk indicators. Implants installed in the posterior region of the mandible were also shown to be at higher risk for late loss (Alsaadi et al., 2008).

Total implant loss

Total implant loss is the sum of implants lost at an early and at a later time interval. Patients may experience one or both forms of complications. The majority of studies on implant loss reported the rate of total implant loss, not distinguishing between early and late loss. With one specific exception, studies were performed on selected patient groups and reported that between 2% and 7% of all implants were lost, while between 6% and 15% of patients lost at least one implant (for details, see Table 3). The reasons for the variation of rates of implant loss are currently not understood. Only one study included a randomly selected patient sample, in which subjects were identified in an implant registry (Antalainen et al., 2013). This study included a large cohort of individuals and reported low figures of total implant loss. In this context it must be recognized that findings were purely based on events reported to the registry by clinicians on a voluntary basis.

Table 3. Studies on the occurrence of implant loss

First author, year	Study design & function time	Sampling & sample size	Early implant loss	Late implant loss	Total implant loss	Additional findings
Alsaadi et al. (2007)	Retrospective Insertion - abutment connection	Convenience 2,004 subjects 6,946 implants	Patient level 8.9% Implant level 3.6%	-	-	Early loss was associated with systemic disease, smoking, implant diameter and implant location (posterior).
Alsaadi et al. (2008)	Retrospective Abutment connection - 2 years	Convenience 412 subjects 1,514 implants	-	Patient level 16.0% Implant level 6.7%	-	Late loss was associated with radiotherapy and implant location (posterior mandible).
Antalainen et al. (2013)	Retrospective 2-8 years	Random selection from implant registry Subjects not reported 178,146 implants	-	-	Patient level 2.3-3.1% Implant level 1.7%	More implant loss in men. Shorter implants, implants in the maxilla and implants of one implant brand showed higher loss rates.
Balshe et al. (2009)	Retrospective 2-7 years	Convenience 1,498 subjects 4,607 implants	-	-	Patient level 8.6% Implant level 4.3%	No significant differences between implants with machined and modified surfaces. Higher implant loss for modified implants in the mandible. Higher implant loss for machined implants in the posterior maxilla.
Bornstein et al. (2008)	Retrospective Insertion - abutment connection	Convenience 1,206 subjects 1,817 implants	Patient level 0.8% Implant level 0.7%	-	-	No significant influence of age, gender, smoking, indication for implant placement, jaw of treatment, implant diameter and length or type of augmentation on early implant loss.
Carlsson et al. (2000)	Prospective 15 years: mandibular implants 10.5 years: maxillary implants	Convenience 44 subjects 331 implants	Patient level Not reported Implant level 2.1%	Patient level Not reported Implant level 0.4%	Patient level Not reported Implant level 2.4%	Higher rate of implant loss in the maxilla.

First author, year	Study design & function time	Sampling & sample size	Early implant loss	Late implant loss	Total implant loss	Additional findings
Cecchinato et al. (2004)	Prospective 2 years	Convenience 84 subjects 324 implants	Patient level Not reported Implant level 2.2%	Patient level Not reported Implant level 0%	Patient level Not reported Implant level 2.3%	No differences in outcome irrespective of initial surgical protocol (submerged/non-submerged).
Esposito et al. (2010)	RCT 4 months	Convenience/ 10 private dental clinics 506 subjects 972 implants	Patient level 3.4% Implant level 2.1%	-	-	No differences in outcome irrespective of administration of prophylactic antibiotics.
Friberg & Jemt (2015)	Retrospective 5 years	Convenience 259 subjects 1,230 implants	Up to year 1 Patient level Not reported Implant level 1.4%	Patient level Not reported Implant level 0.7%	Patient level 6.6% Implant level 2.5%	More implant loss with turned surface-implants when using a non-submerged surgical protocol.
Jemt et al. (2014)	Retrospective 1-28 years	Convenience 8,528 subjects 39,077 implants	Up to year 1 Patient level 7.0% Implant level 2.0%	Patient level Not reported Implant level 2.3%	Patient level 10.1% Implant level 4.3%	More implant loss in the upper jaw. Reduction of early loss in the maxilla after introduction of moderately rough surface in 2002/2003.
Rasmusson et al. (2005)	Prospective 10 years	Convenience 36 subjects 199 implants	Patient level 13.9% Implant level 3.0%	Patient level 0% Implant level 0%	Patient level 17.9% Implant level 3.9%	-
Roccuzzo et al. (2010)	Prospective 10 years	Convenience 101 subjects 246 implants	Patient level 0% Implant level 0%	Patient level 14.9% Implant level 7.3%	Patient level 14.9% Implant level 7.3%	More implant loss in patients with a history of periodontitis and in patients not attending supportive therapy.
Roos-Jansåker et al. (2006a)	Retrospective 9-14 years	Convenience 218 subjects 1,057 implants	Patient level 6.9% Implant level 2.7%	Patient level 4.6% Implant level 1.7%	Patient level 10.1% Implant level 4.4%	More implant loss in patients with a history of periodontitis.
Vervaeke et al. (2015)	Retrospective 2-5 years	Convenience 376 subjects 1,320 implants	Up to 6 months Patient level 2.9% Implant level 0.8%	Patient level 2.1% Implant level 0.8%	Patient level 5.1% Implant level 1.6%	More implant loss in smokers.

First author, year	Study design & function time	Sampling & sample size	Early implant loss	Late implant loss	Total implant loss	Additional findings
Wagenberg & Froum (2006)	Retrospective 1-16 years	Convenience 891 subjects 1,925 implants	Patient level Not reported Implant level 3.7%	Patient level Not reported Implant level 0.3%	Patient level 7.6% Implant level 4.0%	More implant loss in men, following tooth extraction due to periodontitis, with turned surface-implants and in patients unable to take post-surgical penicillin.

Peri-implant diseases

"Peri-implant diseases" is a collective term that covers two different disease entities. Peri-implant mucositis is defined as the presence of an inflammatory soft tissue infiltrate without concurrent loss of peri-implant bone tissue, while peri-implantitis denotes soft tissue inflammation in combination with crestal bone loss (Lindhe and Meyle, 2008; Sanz et al., 2011). The definitions of peri-implant diseases correspond to definitions of periodontal diseases. Thus, mucositis is the equivalent of gingivitis, while peri-implantitis is the counterpart to periodontitis.

The inflammatory response in the peri-implant mucosa to plaque has been studied in experimental and clinical studies. Inflammatory cells accumulate in the connective tissue lateral to the barrier epithelium (Abrahamsson et al., 1998; Zitzmann et al., 2001). Clinically, bleeding on probing and increased probing pocket depth are noted (e.g. Pontoriero et al., 1994; Salvi et al., 2012). The development of peri-implant mucositis upon a bacterial challenge corresponds well to early experiments on the development of gingivitis (Löe et al., 1965).

While clinical characteristics of peri-implantitis and periodontitis have many features in common, the two lesions display critical histopathological differences (Berglundh et al., 2011; Carcuac and Berglundh, 2014). Thus, in human biopsies, the inflammatory lesions associated with peri-implantitis were found to be considerably larger than in periodontitis. In addition, the proportion of e.g. neutrophils, macrophages and plasma cells were found to be higher in peri-implantitis (Carcuac and Berglundh, 2014).

Prevalence of peri-implantitis

In a systematic review, Derks & Tomasi (2015) assessed the epidemiology of peri-implant diseases. The identified studies reported a prevalence of peri-implantitis ranging from 1% to 47%, with an estimated weighted mean prevalence of 22% (95% CI: 14–30%). Findings from individual publications presenting data on the prevalence of peri-implantitis are summarized in Table 4. The systematic review identified a number of shortcomings in the available literature. All studies that fulfilled inclusion criteria and were used in the meta-analysis were based on convenience samples. The patient groups described were usually of limited size (the largest study included 239 subjects (Aguirre-Zorzano et al., 2014)), while epidemiological studies in the field of periodontal diseases included >3,000 subjects (e.g. Eke et al., 2012; 2015). A further issue that was highlighted by Derks & Tomasi (2015) was the variation in time of function of the implants. While Roos-Jansåker et al. (2006b) and Daubert et al. (2015) included patients with 9 to 14 years and 9 to 15 years of follow-up, respectively, others chose windows ranging from 1 to 16 years (Koldsland et al., 2010), and 6 months to 5 years (Ferreira et al., 2006). Since bone loss around implants is considered a time-dependent event (Fransson et al., 2010), the inclusion of subjects who have only

recently received implant-supported restorations in the assessment of the prevalence of peri-implantitis may lead to underestimation (Derks and Tomasi, 2015). Finally, the justification to compare results between the different existing reports was hampered by the use of different case definitions of peri-implantitis. While bleeding on probing was consistently used to distinguish between peri-implant health and disease, a wide range of thresholds for assessments of radiographic crestal bone loss were used. In fact, in an earlier systematic review (Tomasi and Derks, 2012) at least seven different such thresholds for crestal bone loss were identified, starting at the 0.4 mm level of loss and ranging up to 5.0 mm. The systematic review by Derks & Tomasi (2015) described (i) an inverse relationship between the chosen threshold of bone loss and the prevalence of disease and (ii) a positive relationship between the length of follow-up and the prevalence of disease. It was also noted, that not all publications evaluated actual bone loss, as, in the absence of baseline radiographic documentation, only assessments of a final bone level could be performed.

Similar to what has been described for the occurrence of implant loss, rates of peri-implantitis were higher if expressed on the patient rather than the implant level. For instance, Daubert et al. (2015) identified peri-implantitis at 16% of all implant sites but in 26% of all patients. Similarly, Dvorak et al. (2011) found 13% of all implant sites to present with peri-implantitis, while 24% of patients were affected.

While prevalence is the most frequently used variable to describe the occurrence of peri-implant diseases, additional parameters should not be disregarded, e.g. extent and severity. The proportion of implants with peri-implantitis within the same subject diagnosed with the disease is described by the term “extent”. Two publications found that around 40% of implants within peri-implantitis patients were diagnosed accordingly (Fransson et al., 2009; Mir-Mari et al., 2012). The term “severity” describes the level of disease at diseased sites or in diseased subjects. This is common practice when classifying periodontitis. While almost 50% of the adult population suffer from periodontal disease, the advanced form was found in a subgroup of <10% (e.g. Eke et al., 2012). For studies on peri-implantitis different cut-off points for bone loss were chosen to describe severity. For instance, Koldsland et al. (2010) identified peri-implantitis in 47% of all individuals, using a case definition of bleeding on probing and bone loss of >0.4 mm. The proportion of subjects presenting with peri-implantitis at ≥1 implants with inflammation and bone loss of >2 mm and of >3 mm was 20% and 12%, respectively. Similar findings were reported by Roos-Jansåker et al. (2006b) and Fransson et al. (2010). Koldsland et al. (2010) defined peri-implantitis at the level of bone loss of >2 mm as “overt peri-implantitis”.

Onset and progression of peri-implantitis

The majority of data on peri-implant diseases originate from cross-sectional studies. Thus, the understanding in regard to the onset of peri-implantitis is poor. Data on the pattern of progression is also limited. It has been shown, however, that, if crestal bone loss at implants occurs, it may progress and even accelerate over time (Fransson et al., 2010).

Risk factors and indicators of peri-implantitis

For the identification of risk factors of disease, prospective interventional studies are required (Hill, 1965). Observational cross-sectional and case-control studies can only identify risk indicators of disease.

Among systemic risk indicators of peri-implantitis, a history of periodontitis, gender and smoking have been identified (Hardt et al., 2002; Roos-Jansåker et al., 2006c). Roccuzzo et al. (2012) reported, in one of the few longitudinal studies, that significantly more peri-implantitis-related interventions were required in individuals that were periodontally compromised when compared to periodontally healthy individuals.

Potential risk indicators of peri-implantitis on the implant level include the jaw of treatment (Koldsland et al., 2011) and implant design. While no data have been reported on the effect of implant geometry on peri-implant diseases, results from pre-clinical research indicated that implant surface characteristics influenced the progression of peri-implantitis (Albouy et al., 2012; Carcuac et al., 2013). Furthermore, Mir-Mari et al. (2012), in a cross-sectional study, found that implants with one specific surface modification exhibited more peri-implantitis than two other geometrically similar implant devices.

At the 8th EWoP it was stated that research on risk factors of peri-implantitis was still in its infancy (Sanz and Chapple, 2012). Future studies were encouraged and it was recommended that patient-, clinician- and therapy-related factors should be considered. The importance of external validity of results was addressed, suggesting the use of national registries for the identification of representative patient cohorts.

Table 4.Studies on the occurrence of peri-implant diseases

First author, year	Study design & function time	Sampling & sample size	Case definition	Prevalence of mucositis	Prevalence of peri-implantitis	Extent and severity of peri-implant diseases
Aguirre-Zorzano et al. (2014)	Cross-sectional 0.5-18 years mean: 5.3 years	Convenience 239 subjects 786 implants	Mucositis BoP/SUP but no bone loss ≥1.5 mm from 6 months after loading Peri-implantitis BoP/SUP & bone loss ≥1.5 mm from 6 months after loading	Patient level 24.7% Implant level 12.8%	Patient level 15.1% Implant level 9.8%	Mucositis Estimated extent: 52% Severity: not reported Peri-implantitis Estimated extent: 30% Severity: not reported
Casado et al. (2013)	Cross-sectional 1-5 years mean: not reported	Convenience 103 subjects 392 implants	Mucositis BoP but no bone loss Peri-implantitis BoP & bone loss from implant surgery, no threshold	Patient level 19.4%	Patient level 30.1%	Mucositis Not reported Peri-implantitis Not reported
Cecchinato et al. (2013; 2014)	Cross-sectional ≥8 years mean: ≥10.7 years	Convenience 100 subjects 291 implants	Mucositis BoP but no bone loss >0.5 mm Peri-implantitis PPD ≥4 mm, BoP & bone loss >0.5 mm from ≥1 years after loading	Patient level 65% Implant level 69.8%	Patient level 23% Implant level 11.3%	Mucositis Estimated extent: 100% Severity: not reported Peri-implantitis Estimated extent: 46.3% Severity (different case definitions): • PPD ≥4 mm, BoP & bone loss >1.0 mm: 16% • PPD ≥4 mm, BoP & bone loss >2 mm: 7%
Daubert et al. (2015)	Cross-sectional 9-15 years mean: 10.9 years	Convenience 92 subjects 207 implants	Mucositis BoP/SUP but no bone loss ≥2 mm from loading Peri-implantitis PPD ≥4 mm, BoP/SUP & bone loss ≥2 mm from loading	Patient level 48% Implant level 33%	Patient level 26% Implant level 16%	Mucositis Estimated extent: 70% Severity: not reported Peri-implantitis Estimated extent: 70% Severity: not reported

First author, year	Study design & function time	Sampling & sample size	Case definition	Prevalence of mucositis	Prevalence of peri-implantitis	Extent and severity of peri-implant diseases
Dvorak et al. (2011)	Cross-sectional 1-24 years mean: 6.0 years	Convenience (post-menopausal women) 177 subjects 828 implants	Mucositis Not defined Peri-implantitis PPD >5 mm, BoP/SUP & bone loss/level, no threshold	Not reported	Patient level 23.7% Implant level 13.3%	Mucositis Estimated extent: 97% Severity: not reported Peri-implantitis Estimated extent: 56% Severity: not reported
Ferreira et al. (2006)	Cross-sectional 0.5-5 years mean: 3.5 years	Convenience 212 subjects 578 implants	Mucositis BoP but no bone loss Peri-implantitis PPD ≥5 mm, BoP/SUP, & bone level, no threshold	Patient level 64.6% Implant level 62.6%	Patient level 8.9% Implant level 7.4%	Mucositis Estimated extent: 97% Severity: not reported Peri-implantitis Estimated extent: 83% Severity: not reported
Fransson et al. (2005; 2008; 2009; 2010)	Cross-sectional 5-20 years mean: 8.6 years	Convenience Radiological 662 subjects 3,413 implants Clinical 82 subjects 482 implants	Mucositis BoP but no bone loss >0.6 mm from year 1 Peri-implantitis BoP & bone level ≥3 threads & bone loss >0.6 mm from year 1 after loading	Implant level >90%	Patient level 27.8% Implant level 12.4%	Mucositis Not reported Peri-implantitis Extent: 41.8% Severity: 32% of implants with bone loss ≥2 mm
Koldsland et al. (2010)	Cross-sectional 1-16 years mean: 8.4 years	Convenience 104 subjects 295 implants	Mucositis BoP/SUP but no bone loss >0.4 mm Peri-implantitis BoP/SUP & bone loss >0.4 mm from loading	Patient level 39.4% Implant level 27.3%	Patient level 47.1% Implant level 36.6%	Mucositis Estimated extent: 70% Severity: not reported Peri-implantitis Estimated extent: 78% Severity (different case definitions): PPD ≥4 mm, BoP/SUP & bone loss ≥2 mm: 20.4% PPD ≥4 mm, BoP/SUP & bone loss ≥3 mm: 11.7%

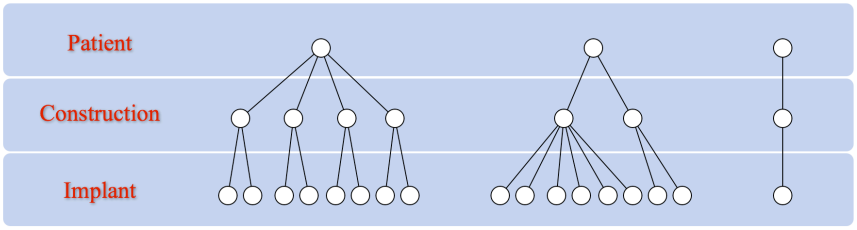
First author, year	Study design & function time	Sampling & sample size	Case definition	Prevalence of mucositis	Prevalence of peri-implantitis	Extent and severity of peri-implant diseases
Marrone et al. (2013)	Cross-sectional 5-18 years mean: 8.5 years	Convenience 103 subjects 266 implants	Mucositis PPD ≤5 mm, BoP but no bone level >2 mm Peri-implantitis PPD >5 mm, BoP & bone level >2 mm	Patient level 31% Implant level 38%	Patient level 37% Implant level 23%	Mucositis Estimated extent: 100% Severity: not reported Peri-implantitis Estimated extent: 63% Severity: not reported
Máximo et al. (2008)	Cross-sectional ≥1 year mean: 3.4 years	Convenience 113 subjects 347 implants	Mucositis BoP but no bone level ≥3 threads Peri-implantitis PPD ≥5 mm, BoP/SUP & bone level ≥3 threads	Patient level 36.3% Implant level 32.0%	Patient level 12.4% Implant level 7.5%	Mucositis Estimated extent: 88% Severity: not reported Peri-implantitis Estimated extent: 61% Severity: not reported
Mir-Mari et al. (2012)	Cross-sectional 1-18 years mean: 6.3 years	Convenience 245 subjects 964 implants	Mucositis BoP but no bone level ≥2 threads Peri-implantitis BoP/SUP & bone level ≥2 threads	Patient level 38.8% Implant level 21.6%	Patient level 16.3% Implant level 9.1%	Mucositis Estimated extent: 55% Severity: not reported Peri-implantitis Extent in patients with ≥4 implants: 37% Severity: not reported
Roos-Jansåker et al. (2006b)	Cross-sectional 9-14 years mean: 11.0 years	Convenience 216 subjects 987 implants	Mucositis PPD ≥4 mm, BoP but no bone level ≥1 thread Peri-implantitis BoP/SUP & bone loss ≥1.8 mm from year 1 after loading	Patient level 48% Implant level 16%	Patient level 16% Implant level 6.6%	Mucositis Estimated extent: 33% Severity (different case definitions): PPD ≥5 mm, BoP but no bone level ≥1 thread: 16% PPD ≥6 mm, BoP but no bone level ≥1 thread: 4% Peri-implantitis Estimated extent: 41% Severity (different case definitions): BoP/SUP & bone loss >3 mm: 7.4%

First author, year	Study design & function time	Sampling & sample size	Case definition	Prevalence of mucositis	Prevalence of peri-implantitis	Extent and severity of peri-implant diseases
van Velzen et al. (2014)	Cross-sectional 10 years	Convenience 169 subjects 374 implants	Mucositis BoP but no bone loss ≥1.5 mm after loading Peri-implantitis BoP & bone loss ≥1.5 mm after loading	Patient level 59.8% Implant level 45.5%	Patient level 14.8% Implant level 9.8%	Mucositis Estimated extent: 76% Severity: not reported Peri-implantitis Estimated extent: 67% Severity (different case definitions): BoP & bone loss ≥2 mm: 4.2% (implant level)
Zetterqvist et al. (2010)	RCT 5 years	Convenience 96 subjects 270 implants	Mucositis Not defined Peri-implantitis PPD >5 mm, BoP/SUP & bone loss >5 mm from loading	Not reported	Patient level 1% Implant level 0.4%	Mucositis Not reported Peri-implantitis Extent: 50% Severity: not reported

4 Data analysis in studies on implant-supported restorative therapy

Studies on dental implants usually result in data sets characterized by a hierarchical structure. It is common for a single patient to be provided with multiple implants, that may be included in different restorations. Thus, the hierarchical structure includes the patient at the highest and the implant at the lowest level (Figure 1). Treatment outcomes (e.g. peri-implantitis) are commonly assessed at the lowest level, i.e. the implant. However, systemic factors, e.g. smoking, potentially affect all implants within the same subject, resulting in non-independence of implants within the same individual. Traditionally, studies have not considered the issue of non-independence and used either the implant or the subject as their computational unit in so-called unilevel calculations, that assume independence. Applying such unilevel techniques on hierarchical data structures was shown to be inappropriate, as significance tests were artificially inflated and confidence intervals were too small (Imrey, 1986; Emrich, 1990).

Figure 1.Hierarchical data structure



Recognizing the issue of non-independence, Herrmann et al. (1999) suggested the random selection of a single implant per subject that should represent the individual in the statistical analysis. The obvious disadvantage of such selection strategies is the elimination of considerable amounts of valuable data. Facing similar problems, researchers in the educational and social sciences have applied multilevel statistical techniques specifically designed for hierarchical data (Goldstein, 1987). Here, all data were included while clustering and dependence of several units within a higher ranked unit were considered. Albandar & Goldstein (1992) were among the first to discuss the use of such techniques for dental research and they have since been used in studies in dental (e.g. D'Aiuto et al., 2005; Tomasi et al., 2007; Cairo et al., 2015) and implant research (e.g. Fransson et al., 2010; Tomasi et al., 2010; Marrone et al., 2013; Aguirre-Zorzano et al., 2014). The use of multilevel analyses was recommended for future research on implants at the 8th EWoP (Tonetti and Palmer, 2012).

Aim

The present project aimed at evaluating the effectiveness of implant-supported restorative therapy in a large and randomly selected patient sample.

The different studies addressed specific research questions:

1. Are subjects provided with implant-supported restorations satisfied in the long-term?

2. How common is implant loss and which are the risk indicators?

3. How common is peri-implantitis and which are the risk indicators?

4. When does peri-implantitis commence and what is the pattern of progression?

Study sample and Methods

The present series of studies included a variety of methods and outcome measures. In **Study I**, questionnaire data were analyzed. **Studies II-IV** were, in part, based on data collected from patient records covering a time period of up to 9 years following therapy. In addition, clinical and radiographic parameters were collected at a 9-year examination for **Studies II-IV**.

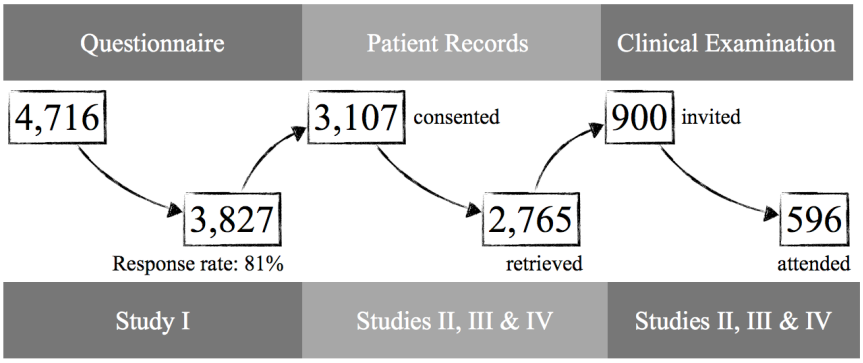
The four studies represented different approaches to observational research and were, in principal, of cross-sectional design (Grimes and Schulz, 2002a). In **Studies III & IV**, baseline documentation was considered in order to detect changes of marginal bone levels over time. Hence, these studies also included data of retrospective, longitudinal character.

The research protocol for the present series of studies was approved by the regional Ethical Committee, Gothenburg, Sweden (Dnr 290-10). **Studies II & III** were registered at ClinicalTrials.gov (NCT01825772).

1 Study sample

The target population of the present research consisted of all subjects in two specific age categories (45-54 and 65-74 years) who had, in 2003, applied for and, in 2003/2004, received reimbursement for implant-supported restorative therapy by the SSIA. These two age groups together consisted of approximately 25,000 individuals and were identified in the SSIA registry kept in Stockholm, Sweden. The registry included the submitted and approved applications for reimbursement as well as a final summary of performed treatment with basic information regarding reimbursed therapy (e.g. number and location of implants and clinicians involved). Applications for subjects between 65 and 74 years of age in 2003 were, at the time, handled in one SSIA centre located in Lund, Sweden and later stored in the SSIA headquarters in Stockholm. From this pool of about 23,000 individuals, 3,000 were selected following a simple random sampling procedure. A second sample comprised all subjects in the age of 45–54 years (n = 1,716). The treatment applications of this younger group were all submitted to and later stored at the SSIA offices in Stockholm. The total study sample included 4,716 patients in two age groups.

Figure 2.Patient samples included in the different studies



A questionnaire was mailed to all 4,716 patients about 6 years following the completion of the implant-supported restorative therapy **(Study I)**. A total of 3,827 patients responded. Of these, 3,107 subjects gave their consent for access to patient records, of which the records of 2,765 patients **(Study II)** were retrieved. From the 2,765 patients representing the patient file database, 900 subjects, stratified for age, were randomly selected and subsequently invited to a clinical and radiographic examination at a conveniently located dental clinic in Sweden about 9 years after therapy. 596 patients attended the clinical examination **(Studies II & III)**. A total of 62 patients were diagnosed with moderate/severe peri-implantitis (see case definitions, Table 8) at the 9-year examination and for 53 of these ≥3 radiographic measurements were available from the 9 years of follow-up. Onset and pattern of progression of peri-implantitis were studied in this group **(Study IV)**. The outline of patient samples included in the different studies is illustrated in Figure 2. Table 5 describes responders/non-responders together with attending and non-attending subjects.

Table 5.Responders/attendees compared with non-responders and non-attending subjects

	Initial study sample	Study I		Study II			Studies II/III		
		Res-ponders	Non-res-ponders	Consent	Patient records retrieved	Patient records not retrieved	Random selection (stratified for age)	Attendees	Non-attenders
Subjects (n)	4,716	3,827	889	3,107	2,765	342	900	596	304
Female (%)	54.2%	54.6%	52.4%	53.1%	53.9%	47.1%	54.8%	55.0%	54.3%
Age (mean, 2003)	62.1	62.4	60.8	63.0	62.8	64.1	62.9	62.3	64.2
Implants (mean)	4.2	4.1	4.4	4.2	4.1	4.6	4.1	4.0	4.4
Surgical therapy (% Spec)	73.1%	74.0%	68.9%	75.0%	78.1%	47.3%	78.4%	79.2%	76.7%
Prosthetic therapy (% Spec)	23.6%	23.1%	25.6%	22.9%	23.8%	14.5%	21.7%	26.6%	22.0%
Clinical setting (% Private)	62.8%	63.9%	57.9%	64.6%	62.2%	84.6%	63.8%	62.4%	66.4%

Spec = Specialist

2 Methods

Background information from the SSIA registry

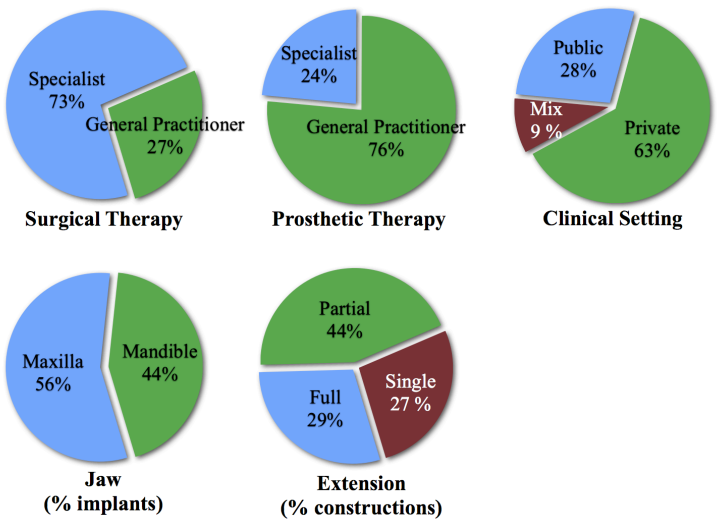
Information about gender, type of implant-supported therapy, including number and position of implants, and clinicians involved in the treatment was extracted from the treatment applications approved (2003) and reimbursed (2003/2004) by the SSIA. Patients were categorized according to the type of implant-supported restorative therapy, i.e. (i) single-crown, (ii) partial-jaw restoration or (iii) full-jaw restoration. In case of multiple reconstructions, the patient was classified according to the most extensive restoration. Further categorization included anterior/posterior and maxillary/mandibular location of the restoration. Restorative therapy involving the region 13–23 or 33–43 was considered as anterior.

Table 6.Characteristics of the initial study sample (n=4,716)

Female	54.2%
Number of reconstructions	6,653
Number of implants	19,350
Mean number of implants per patient	4.2

Clinicians involved in the treatment were categorized with regard to (i) private or public dental clinical setting and (ii) general practitioner or registered specialist by the Swedish National Board of Health and Welfare at the time of treatment. For surgical treatment, specialists in oral/maxillofacial surgery and periodontics were considered, while prosthetic treatment involved specialists in prosthodontics, stomatognathic physiology and periodontics. Characteristics of the initial study sample are illustrated in Table 6 and Figure 3.

Figure 3.Characteristics of the initial study sample (n=4,716 subjects)



PROMs following implant-supported restorative therapy

A questionnaire (Figure 4) was developed and mailed to 4,716 patients about 6 years following the completion of the implant-supported restorative therapy **(Study I)**. The questionnaire was distributed through the official mail service of the SSIA in Stockholm, and a letter of information for study participants was included. A reminder was sent 4 weeks later. The questionnaire consisted of ten questions of multiple-choice character. The initial seven questions related to the

degree of satisfaction, while the remaining three questions were aiming at background information.

Figure 4.Questionnaire mailed to 4,716 subjects

Questionnaire

Question 1. Are you satisfied with the overall result?

- ☐ Fully satisfied
- ☐ Rather satisfied
- ☐ Not satisfied

Question 2. Are you satisfied with the esthetic result?

- ☐ Fully satisfied
- ☐ Rather satisfied
- ☐ Not satisfied

Question 3. Has the implant therapy improved your chewing ability?

- ☐ Greatly improved
- ☐ Somewhat improved
- ☐ No improvement

Question 4. Has the implant therapy improved your self-confidence?

- ☐ Much more secure
- ☐ Somewhat more secure
- ☐ No improvement

Question 5. Have you experienced any complications?

- ☐ Never
- ☐ Yes, but rarely
- ☐ Yes, frequently

Question 6. Was the implant therapy worth the cost?

- ☐ Yes
- ☐ Doubtful
- ☐ No

Question 7. Would you consider implant therapy again?

- ☐ Yes
- ☐ Doubtful
- ☐ No

Question 8. Who suggested the implant therapy?

- ☐ Myself
- ☐ Dental professional

Question 9. How long before implant therapy was the tooth extraction performed?

- ☐ <6 months
- ☐ 6 months - 2 years
- ☐ >2 years

Question 10. Have you attended regular follow-up visits?

- ☐ Yearly
- ☐ Every second year
- ☐ No

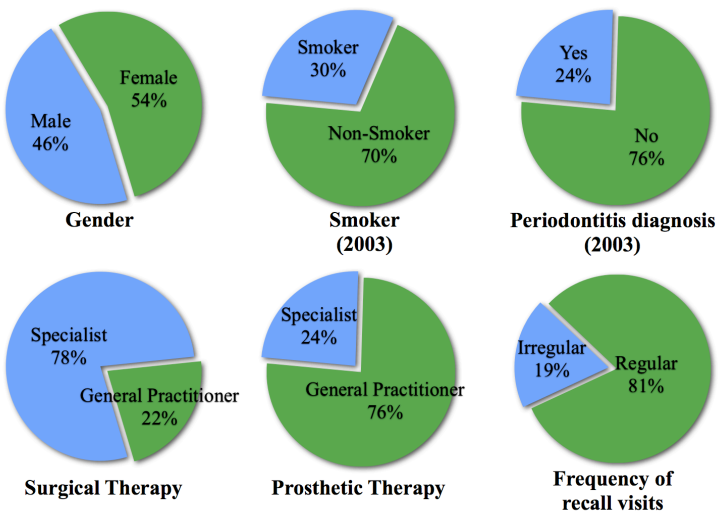
Participants were invited to give written comments related to the implant therapy and asked for consent to access their patient records. A return envelope was included and collected at the SSIA main office. Completed questionnaires were scanned and responses were stored digitally, together with a code number (see *Data collection and analysis*).

Collection of patient records

More than 800 dental clinicians were contacted by letter, and documentation related to the implant-supported restorative therapy of all consenting patients (from **Study I**) was requested. Clinicians were asked to provide available

documentation regarding (i) treatment planning, (ii) surgical and prosthetic therapy (in 2003/2004) and (iii) follow-up (from 2003/2004 to latest). Patient records were collected at the Department of Periodontology, Institute of Odontology, Sahlgrenska Academy, University of Gothenburg, copied and returned. Reported information regarding patients, treatment procedures, and treatment outcomes was extracted from the patient records and entered into a database. Patient data included medical information, e.g. history of diabetes, cardiovascular diseases, and associated medication. Patients were categorized as smokers if reported to be smoking at the time of implant therapy. All other patients, including former smokers, were categorized as non-smokers. The reason for tooth extraction(s)/implant therapy was also documented and, if recorded, history of periodontitis at the time of implant therapy was noted. In addition, the frequency of recall visits following the completion of implant-supported restorative therapy was assessed and categorized as "regular" if the patient had attended on an annual basis. Selected patient-related information retrieved from the patient records is presented in Figure 5.

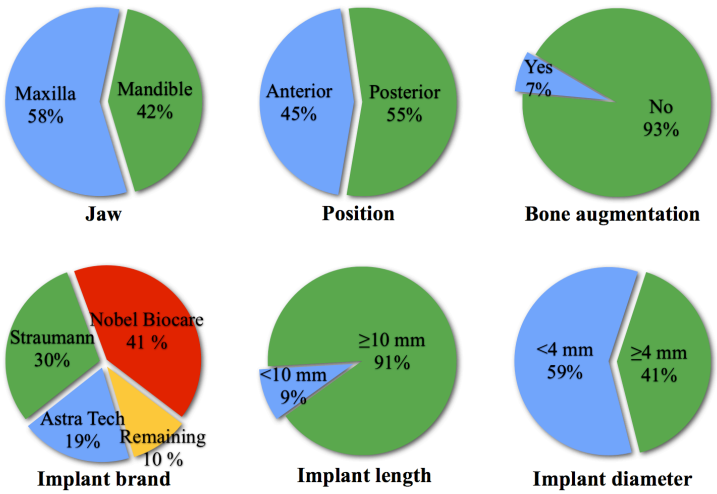
Figure 5.Patient-related information retrieved from patient records (n=2,765 subjects)



Based on patient records, implants were categorized according to brand, as defined by implant system and provider. Three brands (termed Astra Tech (AT), Nobel Biocare (NB), and Straumann group (S) of implants) represented 90% of all implants. Among AT implants, 99.2% had a TiOblast surface; 98.7% of all NB implants had a TiUnite surface; and 99.9% of all S implants had an SLA surface. Among the 10% of remaining implants (R), the predominant brands were Biomet 3i (3.3% of all implants; Palm Beach Gardens, FL, USA), CrescoTi (1.7%;

Kristianstad, Sweden), XiVE (1.3%; Mannheim, Germany), Frialit (1.3%; Mannheim, Germany), and Lifecore (1.2%; Burlington, MA, USA). Implants were also grouped regarding length (<10 mm and ≥10 mm), diameter (<4 mm and ≥4 mm), and installation protocols (1-stage and 2-stage). Bone augmentation procedures, including ridge and sinus augmentation, and the use of prophylactic antibiotics were recorded. Implants were categorized according to jaw and anterior/posterior position. Anterior was defined as the region corresponding to tooth position canine to canine. Further categorization included type of prosthetic retention, design of suprastructure, type of connection, and prosthetic loading protocols. Loading was categorized as "early" if the supraconstruction was connected <4 weeks after implant placement. Selected implant-related information retrieved from the patient records is presented in Figure 6.

Figure 6.Implant-related information retrieved from patient records (n=11,311 implants)



Radiographs from the time period of treatment planning, the active treatment and throughout follow-up that were stored in the patient records were also copied. Analogue images were digitized using a digital camera (Nikon Coolpix 5700, Chiyoda, Japan).

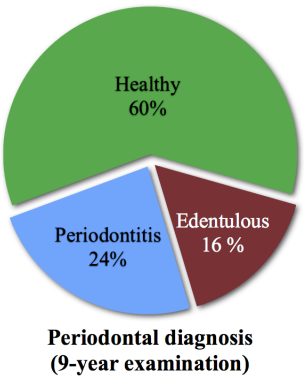
If implant loss occurred prior to connection of the supraconstruction, it was considered an early implant loss. Early implant loss was assessed in the records of 2,765 patients **(Study II)**. In addition, consequences of early implant loss were noted. Changes in treatment planning, placement of new implants, and non-continuation of treatment were recorded as reported in patient records.

Examination at 9 years

The clinical examinations took place at conveniently located dental clinics. In total, 37 centers were established, distributed over all parts of Sweden. The examinations were carried out by specialists in periodontics, predominantly by two calibrated investigators and were free-of-charge. Patients were reimbursed for travel expenses.

Upon meeting the patients, a specifically designed scoresheet was completed, designating the implants and supraconstructions of interest. Thus, the examiner was aware of the number and location of implants placed in 2003/2004 prior to the examination. Background information, including smoking habits and systemic health conditions, was reviewed. Following a periodontal examination of the remaining natural dentition, all subjects were categorized as (i) periodontally healthy, as (ii) periodontitis patients or as (iii) edentulous. Periodontitis assessments were based on the presence of ≥2 teeth exhibiting bleeding on probing and/or suppuration on probing (BoP/SUP) and attachment loss ≥2 mm as well as probing pocket depth (PPD) ≥6 mm (Figure 7).

Figure 7.Periodontal status at the 9-year examination (n=596 patients)

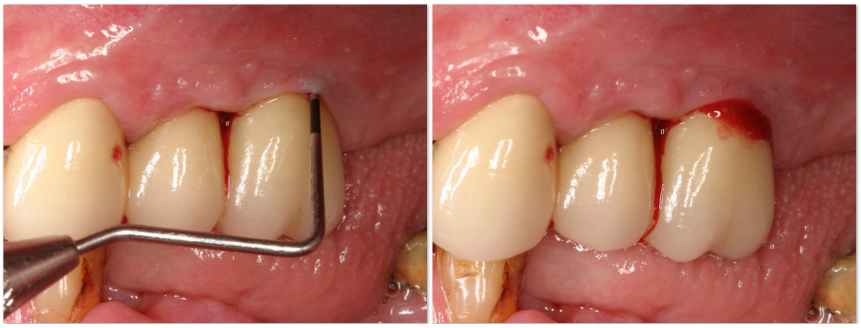


Implant loss was noted and categorized. Any implant loss occurring after the connection of the supraconstruction was considered a late implant loss and was determined in 596 individuals attending the 9-year examination **(Study II)**. Consequences of late implant loss were recorded as reported in patient records; placement of new implants, renewed prosthodontic therapy, and partial or total loss of reconstructions were scored.

The clinical examination of the implants in-situ included assessments at mesial, buccal, distal and lingual aspects **(Study III)**. PPD (mm): measured with a manual periodontal probe (PCP15, Hu-Friedy, Chicago, IL, USA). BoP: within 15 seconds following pocket probing. SUP: within 15 seconds following pocket

probing (Figure 8). Accessibility for self-performed oral hygiene measures: assessed for every implant as yes/no.

Figure 8.Peri-implant probing at the 9-year examination



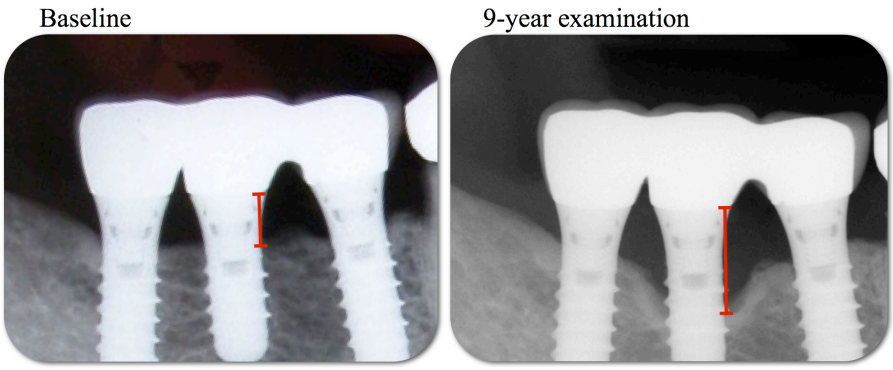
Assessments of marginal bone loss

In addition to the clinical recordings, radiographs of implants were obtained at the 9-year examination. 78% of the implants were examined by intra-oral and 22% by panoramic radiographs.

Radiographs retrieved from patient records were analyzed together with the radiographs sampled at the 9-year examination **(Studies III & IV)**. First, the time point of the radiographic examination was recorded in months from prosthetic loading. Secondly, a quality assessment of all radiographs following prosthesis connection was performed. Radiographs were categorized as (i) fully readable, (ii) readable or (iii) not readable with regard to peri-implant marginal bone level assessment. Unreadable radiographs were excluded from further analysis.

In all readable radiographs, the position of the marginal bone was assessed by the use of a software program (ImageJ 1.48a, Wayne Rasband, U.S. National Institutes of Health). The inter-thread pitch distance reported by the manufacturer or the length of the implant was used for the calibration of the "apical-coronal" measurements in each radiograph. Landmarks were chosen for the different implant systems and the distance to the crestal bone was measured at the mesial and the distal aspects of the implant. The largest value was recorded. Bone loss was calculated by comparing the different measurements to the baseline measurement. Radiographs obtained up to 12 months after prosthesis connection were used as baseline. In the absence of 12-month radiographs, documentation up to 24 months after prosthesis connection was used (Figure 9).

Figure 9.Assessment of bone loss



In addition, the distance from the prosthetic margin to the crestal bone was measured in baseline radiographs (Figure 10, Table 7).

Figure 10.Assessment of distance from the prosthetic margin to the crestal bone at baseline

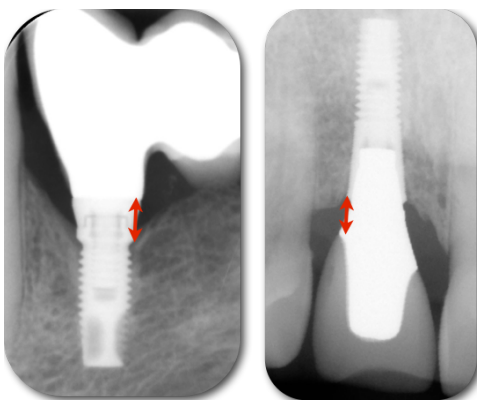


Table 7.Distance from the prosthetic margin to the crestal bone at baseline (n=1,578 implants)

Mean (mm)	2.56 ±1.14
≤1.5 mm	16.2%
>1.5 mm	83.8%

Prevalence of peri-implant health and diseases

Following the collection of clinical and radiographic data at the 9-year examination, the prevalence of peri-implant health and diseases was determined in 588 patients and 2,277 implants **(Study III)**. For 427 patients and 1,578 implants, baseline radiographs were available. Case definitions applied are outlined in Table 8.

Table 8.Case definitions for peri-implant health and diseases used in Study III

Peri-implant health	Absence of BoP/SUP
Peri-implant mucositis	BoP/SUP but no detectable bone loss
Peri-implantitis	BoP/SUP and detectable bone loss (>0.5 mm; exceeding the measurement error)
Moderate/severe peri-implantitis	BoP/SUP and bone loss >2.0 mm

Radiographic assessments of bone loss were based on comparisons from baseline radiographs and radiographs obtained at the 9-year examination. Severity was expressed as the proportion of implants presenting with varying degrees of bone loss together with BoP/SUP. Implant sites presenting with BoP/SUP and bone loss of >2 mm were considered as moderate/severe peri-implantitis. Extent of peri-implantitis was assessed in subjects with >1 implants (n=329 subjects). The mean number as well as the percentage of implants with moderate/severe peri-implantitis for each individual was calculated.

In cases with no available baseline radiographs (n=699 implants), marginal bone levels located >2 mm apical of a reference landmark were registered at the 9-year examination. The reference landmarks were the following. Brånemark System: first thread (Åstrand et al., 2004a; 2004b), Straumann Dental Implant System: 2.8 (Standard) or 1.8 mm (Standard Plus) apical of implant shoulder (Åstrand et al., 2004a; Buser et al., 2012; Thoma et al., 2014) and Astra Tech Implant System: 1.5 mm apical of implant shoulder (Åstrand et al., 2004b; Cecchinato et al., 2004).

Onset and pattern of progression of peri-implantitis

Radiographs from all subjects diagnosed with moderate/severe peri-implantitis at ≥1 implants in Study III were further analyzed. Only implants diagnosed with moderate/severe peri-implantitis and with ≥1 additional radiographic measurements beyond the baseline and the 9-year assessment were considered. A sample of 53 patients with 105 affected implants was included (**Study IV**). Radiographic measurements were now expressed as years from prosthetic loading. If two or more radiographs were available for one time point, the one with the highest quality was used. The onset of peri-implantitis and the pattern of progression was studied by means of estimating a bone loss curve for each

individual implant. To determine the onset of peri-implantitis, the cumulative percentage of implants and patients presenting with estimated bone loss of >0.5 mm, >1.0 mm, >1.5 mm and >2.0 mm at each year (year 1 to year 9) was calculated.

Internal validity

Double assessments were performed to assess internal validity of measurements. In **Study II**, the assessment of early implant loss in patient records was repeated in a total of 50 records. Double assessments revealed an inter- and intraexaminer agreement of 1.0 (Cohen's unweighted *k*). In **Study III**, radiographs of 50 patients were re-measured 6 months after the initial evaluation. The double measurements of marginal bone levels revealed for the inter-examiner comparison a mean measurement error of 0.40 ±0.36 mm (± indicates the standard deviation). For the intra-examiner agreement, the corresponding value was 0.34 ±0.37 mm. Radiographs of implants presenting with bone loss in the range from 1.0 mm to 2.5 mm (n=251) were also re-measured (mean error: 0.25 ±0.33 mm). Averages of the two readings were used for further analysis.

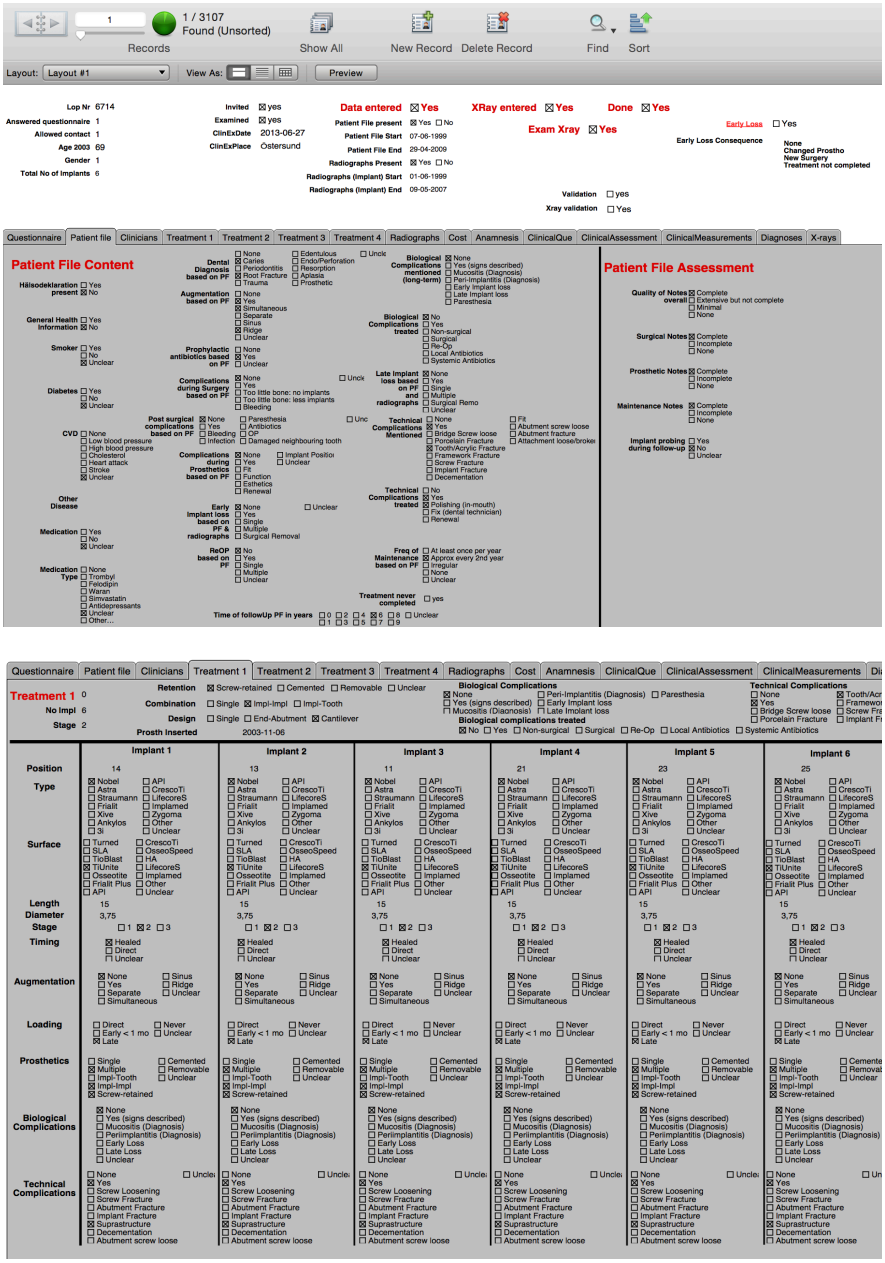
For purposes of calibration, the first 10 patients attending the clinical examination **(Studies II & III)** were seen together by the two investigators performing the majority of clinical examinations.

Data collection and analysis

Each individual was identified by name and unique social security number. Throughout the process of analysis, patients were identified by code numbers and their identity was masked. A digital file containing the key for the masking procedure was stored on a protected computer server. Following the collection of patient records **(Study II)**, personal information regarding clinicians was handled in a similar manner. Clinicians were described by category rather than individually. Contact information for clinicians whose patients attended the clinical examination **(Studies II & III)**, however, was retained. Prior to and following the 9-year examination, clinicians were informed by letter, and radiographs obtained at the examination were provided. No personal information regarding patients or clinicians was used during data analyses.

All information collected from the SSIA registry, the questionnaires **(Study I)**, the patient records and at the clinical examinations **(Studies II & III)** was entered into a specifically designed dataset (FileMaker Pro 12 Advanced, FileMaker Inc., Santa Clara, CA, USA). The individually constructed patient sheets used during the clinical examination (Excel, Microsoft, Redmond, WA, USA) were compatible with the database software, facilitating data transfer. Results from the radiographic analysis were also entered, resulting in one closed dataset (Figure 11).

Figure 11.Screenshots illustrating the database



Upon completion of data entry the database was checked for implausible entries and locked. For purposes of analysis, variables of interest could be exported to appropriate statistical software applications.

For basic analyses, a statistical software package was used (SPSS 21.0; SPSS, Inc., Chicago, IL, USA). Whenever possible and appropriate, patients were chosen as the unit of analysis. Recorded data were expressed in mean values (± standard deviation) and frequency distributions **(Studies I-IV)**. Implant loss **(Study II)** and prevalence of peri-implant health, peri-implant mucositis and peri-implantitis **(Study III)** were assessed on the patient and implant level. In all studies, regression analyses were used to evaluate associations of background information with the outcome variables of interest. All statistical tests were conducted at a significance level of $p<0.05$. The coefficients of the parameter estimates were transformed into ORs. In addition, 95% CIs were calculated.

Logistic regression analyses were used in two of the studies. For purposes of analysis, answers to all questions were transformed into dichotomous data **(Study I)**, summarizing positive and negative answers. Associations of questionnaire data with (i) patient-related, (ii) clinician-related and (iii) therapy-related variables were first analyzed by Chi-square-testing. All statistically significant factors were retained and tested in a multiple logistic regression model for each of the questions. The models were constructed to contain only significant factors. For the factor “clinician”, two categories were established: (i) “general”, if both surgical and prosthetic therapy had been performed by a general practitioner and (ii) “specialist”, if either or both of the procedures had been performed by a specialist.

Logistic regression analysis was also used to identify variables affecting the probability for a patient to be diagnosed with moderate/severe peri-implantitis **(Study III)**. Patient-related variables retrieved from patient records and obtained at the clinical examination were entered as independent factors. For this analysis, the factor "implant brand" was considered a patient-level variable as the use of a combination of implant brands during therapy in 2003/2004 only occurred in 9 individuals. In addition to the three groups of implant brands representing 90% of all implants (S, NB and AT), a fourth group (R) was formed to facilitate analysis. Interaction between independent factors included in the final models was explored, and, in addition to ORs, predicted probabilities were presented.

In **Studies II, III & IV**, the hierarchical structure of the collected data was considered. Factors associated with implant loss **(Study II)**, and moderate/severe peri-implantitis **(Study III)** were explored by multilevel modelling. Two different software packages were used (MLwiN 2.28, Center of Multilevel Modelling, University of Bristol, Bristol, UK and Stata Statistical Software: Release 13, StataCorp LP, College Station, TX, USA). The analyses included the patient at the higher and the implant at the lower level. Patient- and implant-level data were examined for associations with the dependent factors, i.e. early implant loss, late

implant loss and moderate/severe peri-implantitis. Independent factors tested in the analyses are presented in Table 9.

Table 9.Independent factors tested in Studies II & III

Patient	Clinician	Therapy
Gender	Surgical therapy (Clinical setting)	Jaw
Age	Surgical therapy (Clinician)	Location (Anterior vs. posterior)
Smoking	Prosthetic therapy (Clinical setting)	Prophylactic antibiotics
Diabetes	Prosthetic therapy (Clinician)	Implant installation (1- vs. 2-stage)
Cardiovascular diseases	Maintenance therapy (Clinical setting)	Implant installation (Direct vs. delayed)
Periodontal status	Maintenance therapy (Clinician)	Augmentation procedures
		Prosthetic loading (Early vs. delayed)
		Number of implants
		Implant brand
		Implant length
		Implant diameter
		Prosthetic retention
		Prosthetic design
		Distance from prosthetic margin to crestal bone (only Study III)
		Accessibility for cleaning (only Study III)
		Frequency of maintenance therapy

The patient-related factors identified in the logistic regressions analysis in **Study III** were confirmed in the multilevel calculations, in which the factor "implant brand" was considered an implant level variable. Results were expressed as ORs and predicted probabilities, describing outcomes for individual implants.

Parameters were estimated by either Gauss-Hermite quadrature or Markov chain Monte Carlo method with 50,000 simulations.

In a final analysis of the pattern of progression of peri-implantitis, bone loss was chosen as the dependent variable **(Study IV)**. A multilevel model included three levels of analysis: patient, implant and time in function expressed as year. Using the resulting multilevel growth curve, bone loss, including a 95% CI, was estimated for implants and patients over time.

Results

1 Patient-reported outcome measures following implant-supported restorative therapy

The response rate to the questionnaire was 81%. A total of 3,827 completed questionnaires were returned and available for analysis **(Study I)**.

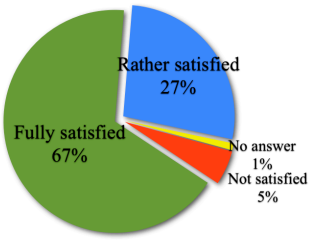
The majority of patients were satisfied with their implant-supported restorative therapy, 6 years after treatment. Over 90% expressed satisfaction with the general and the esthetic results and about two-thirds of all respondents reported that the therapy had improved their chewing ability and self-confidence. A positive perception was also reflected by the fact that more than 80% of subjects considered that the therapy was worth the cost and that, given the same circumstances, they would consider implant therapy again. The majority of patients (79%) reported annual follow-up visits following the completion of restorative therapy.

Figure 12 illustrates the response to selected questions as well as associated factors. Males were more likely to be satisfied esthetically but less likely to attend follow-up visits. Patients in the older age group (65-74 years in 2003) were more positive in general. They expressed a higher degree of satisfaction, greater improvement in terms of chewing and self-confidence and were more likely to consider implant therapy again, if circumstances were similar. They were also more likely to have attended follow-up visits regularly when compared to younger individuals.

Factors related to the clinician performing the therapy also influenced patient-reported outcomes. Individuals treated by specialists were more likely to be satisfied in terms of esthetics and more likely to report improved chewing ability. Patients treated in a private clinical setting were more likely to have received implant therapy within 6 months of tooth extraction when compared to patients in a public setting. Private patients were also more likely to have attended follow-up visits on a regular basis.

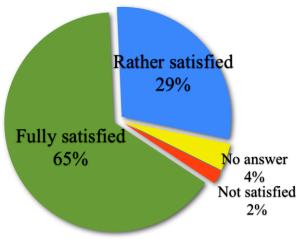
Figure 12.Response to selected questions and associated factors

Are you satisfied with the overall result?



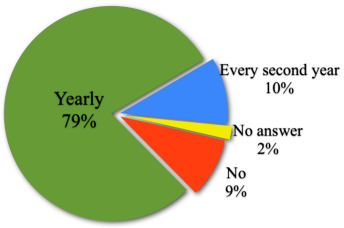
Odds ratio for answering "satisfied"		
Factor	OR	CI (95%)
Age Group (older vs. younger)	2.11	1.54 - 2.88

Are you satisfied with the esthetic result?



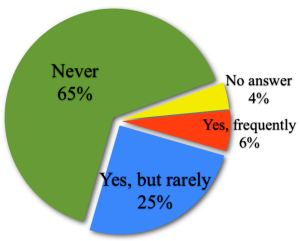
Odds ratio for answering "satisfied"		
Factor	OR	CI (95%)
Gender (male vs. female)	1.46	1.06 - 2.03
Age Group (older vs. younger)	2.07	1.47 - 2.92
Clinician (general practitioner vs. specialist)	0.66	0.47 - 0.94
Location (anterior vs. other)	1.97	1.10 - 3.53

Have you attended regular follow-up visits?



Odds ratio for answering "regular"		
Factor	OR	CI (95%)
Gender (male vs. female)	0.73	0.61 - 0.87
Age Group (older vs. younger)	2.05	1.66 - 2.52
Clinical Setting (public vs. private)	0.59	0.49 - 0.80
Reconstruction (full jaw vs. partial jaw/single)	0.55	0.38 - 0.78
Reconstruction (partial jaw vs. single)	1.52	1.17 - 1.98
Treatment Suggestion (Myself vs. dental professional)	0.76	0.64 - 0.91

Have you experienced any complications?



Odds ratio for answering "yes"		
Factor	OR	CI (95%)
Reconstruction (full jaw vs. partial jaw/single)	1.55	1.15 - 2.08
Reconstruction (partial jaw vs. single)	1.42	1.15 - 1.75

Results demonstrated that the extent of implant therapy did not influence patient satisfaction. More extensive therapy was, however, associated with an increase in chewing ability and self-confidence when compared to implant-supported single crowns. Mandibular restorations were more likely to improve chewing ability when compared to those placed in the maxilla.

In total, 31% of all subjects reported the occurrence of complications related to the implant-supported restorations. Complications were more likely to be reported by individuals provided with more extensive restorations. The written comments indicated a large variation as to what constituted a "complication". Several subjects reported the loss of implants and restorations while others referred to chipping and loosening of composite plugs. Examples of written comments, both positive and complication-related, are presented in Table 10.

Table 10.Examples of written comments in the questionnaire

	Comment
Positive	"I am very happy. The treatment was smooth thanks to my competent dentist."
Positive	"The implant therapy is the absolutely best thing I have ever done. I am perfectly happy."
Positive	"I am very happy with my implant tooth. It helps me chew and it looks good."
Positive	"The result of the treatment is not just good, it is perfect!"
Complication	"My problem, so far, is that the plastic part is not stable. The veneering keeps falling off, which started already after 1 year."
Complication	"The interdental brushes caused some soreness in the gums. Now I use Superfloss instead."
Complication	"One of the teeth fractured in the upper denture. It was repaired and I got my teeth back 4 hours later."
Complication	"My implant fell out after about half a year. 16,000 SEK wasted."
Complication	"The implant operation caused damage in the upper left half of my face. I lost all feeling from my left eye down to the upper lip."
Complication	"A little bit of a tooth recently fractured."
Complication	"Not a good outcome. I rejected the implant and it was removed 3-4 months after installation."

2 Implant loss

A total of 2,765 patient records were assessed for early implant loss **(Study II)**. Early loss was recorded for 121 (4.4%) subjects (Figure 13). Within this group, 102 patients lost 1, 10 lost 2, 4 lost 3, and 5 lost 4 implants. Consequences of early implant loss are illustrated in Figure 14. In total, patients had been provided with 11,311 implants. Of these, 154 (1.4%) were lost prior to the connection of the supraconstruction.

Figure 13.Early and late implant loss

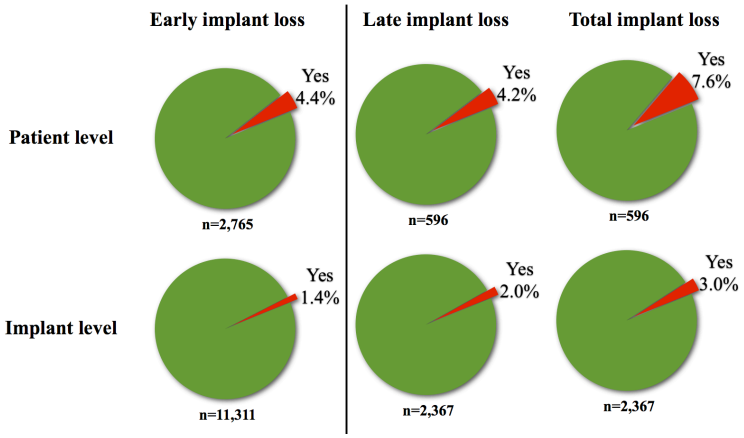
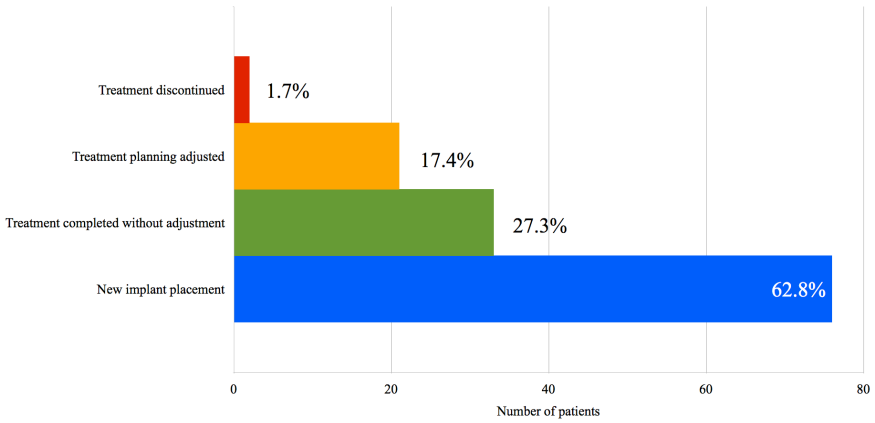


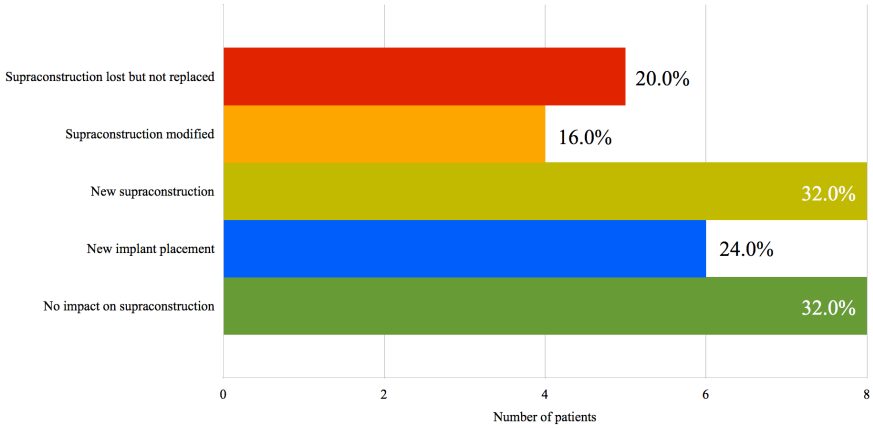
Figure 14.Consequences of early implant loss (121 patients affected)



Twenty-five (4.2%) of the 596 patients attending the 9-year examination had experienced late implant loss (Figure 13). Within this group, 13 patients lost 1, 8 patients lost 2, and 1 patient lost 3 implants. One patient lost 4 and 2 patients lost

5 implants each. Figure 15 illustrates the consequences of late implant loss. The 596 subjects had been provided with 2,367 implants, of which 46 implants (2.0%) were lost following the connection of the supraconstruction.

Figure 15.Consequences of late implant loss (25 patients affected)



Among the 596 patients examined clinically, 45 (7.6%) had experienced implant loss, irrespective of early or late occurrence. A total of 72 implants (3.0%) had been lost (Figure 13).

3 Prevalence of peri-implant health and diseases

The prevalence of peri-implant health and diseases assessed in 427 patients with baseline radiographs is described in Table 11 **(Study III)**. In 98 (23.0%) of the 427 patients, no signs of peri-implant disease were detected, while 137 (32.1%) exhibited only peri-implant mucositis and 192 (45.0%) presented with peri-implantitis. Moderate/severe peri-implantitis was observed in 62 (14.5%) patients. The peri-implant tissues at 620 (39.3%) out of 1578 implants were regarded as healthy, while the mucosae at 947 implants (60%) presented with peri-implant disease. The number of implants with peri-implant mucositis and peri-implantitis was 554 (35.1%) and 393 (24.9%), respectively.

Table 11 also illustrates severity of peri-implantitis: 126 (8.0%) of the 393 implants presented with moderate/severe peri-implantitis. 68 and 36 implants with peri-implantitis presented with bone loss of >3 mm and >4 mm, respectively. The mean bone loss at the 393 implants presenting with peri-implantitis was 1.84 ±1.52 mm. The corresponding value for the 126 implants with moderate/severe peri-implantitis was 3.57 ±1.58 mm. The amount of bone loss at implants with moderate/severe peri-implantitis corresponded to 29.4% of the intraosseous

portion of the implant. A positive correlation between severity of peri-implantitis and proportion of sites with PPD ≥6 mm was observed.

Table 11.Prevalence of peri-implant health and diseases at the 9-year examination (patients and implants with baseline radiographs)

		Patient Level n=427		Implant Level n=1578	
Healthy (No BoP/suppuration)		23.0% (98)	PPD ≥6 mm: 9.4%	39.3% (620)	PPD ≥6 mm: 3.3%
Peri-implant mucositis (BoP/suppuration but no bone loss >0.5 mm)		32.0% (137)	PPD ≥6 mm: 26.3%	35.1% (554)	PPD ≥6 mm: 16.3%
Peri-implantitis (BoP/suppuration & bone loss)	Bone loss >0.5 mm	45.0% (192)	PPD ≥6 mm: 43.2%	24.9% (393)	PPD ≥6 mm: 34.4%
	Bone loss >1 mm	26.9% (115)	PPD ≥6 mm: 53.0%	14.7% (232)	PPD ≥6 mm: 42.4%
	Bone loss >2 mm (Moderate/severe peri-implantitis)	14.5% (62)	PPD ≥6 mm: 71.0%	8.0% (126)	PPD ≥6 mm: 58.7%
	Bone loss >3 mm	10.1% (43)	PPD ≥6 mm: 81.4%	4.3% (68)	PPD ≥6 mm: 69.1%
	Bone loss >4 mm	5.9% (25)	PPD ≥6 mm: 92.0%	2.3% (36)	PPD ≥6 mm: 80.6%
Not accessible for probing		0% (0)		0.7% (11)	

Moderate/severe peri-implantitis was detected in 61 out of 329 patients with >1 implants. The mean number of implants installed in this category of patients was 5.9 ±2.6 and the mean number of implants with moderate/severe peri-implantitis was 2.1 ±1.1. The extent of moderate/severe peri-implantitis was 40.1%. A variation of extent of moderate/severe peri-implantitis was observed between patients provided with different implant brands. Patients with S, NB and R implants presented with an extent of 29.9%, 38.2% and 35.5%, respectively. The extent in patients with AT implants was 61.1%.

The proportion of peri-implantitis among the 699 implants lacking baseline radiographs was 10.9% as based on bone levels of >2 mm apical of a reference landmark together with BoP/SUP.

4 Factors associated with implant loss and peri-implantitis

Results of the different regression analyses revealed that several of the patient-, clinician-, and therapy-related factors displayed in Table 9 were associated with implant loss and moderate/severe peri-implantitis (Table 12).

Two patient-related variables were found to be of significance: periodontal and smoking status. Results in **Study II** demonstrated that implants installed in patients with a history of periodontitis, as reported in patient records, showed significantly higher ORs (3.3) for early implant loss when compared to implants placed in subjects without a history of periodontitis. Similarly, patients presenting with periodontitis at the 9-year examination **(Study III)** were more likely to suffer from moderate/severe peri-implantitis (OR 4.1). Smoking was associated with a higher risk for early implant loss, demonstrated by an OR of 2.3 for implants placed in smokers. Smoking did not influence the risk for late implant loss, neither did it affect moderate/severe peri-implantitis. It was a significant factor in the initial bivariate analysis but not retained in the final model.

Factors related to clinicians were of no statistical significance for implant loss but an association with moderate/severe peri-implantitis was identified. Patients provided with prosthetic therapy performed by general practitioners presented with a higher OR (4.3).

Several therapy-related factors were of importance. Patients with more extensive therapy (≥4 implants placed in 2003/2004) were at higher risk for moderate/severe peri-implantitis (OR 15.1). The extent of therapy was not associated with the risk for implant loss, neither was the factor "jaw of treatment". Implants placed in the mandible, however, were more prone to moderate/severe peri-implantitis (OR 2.0).

Implant-related factors were also identified, as short implants (<10 mm) were more likely to be lost prior to prosthesis connection (OR 3.8) when compared to longer implants. In addition, certain implant brands were associated with a higher risk for implant loss as well as peri-implantitis. Not only did S implants show the lowest rates of early implant loss, they also presented with lower rates of moderate/severe peri-implantitis when compared to NB, AT and R implants. In terms of late loss, S implants showed significantly lower rates than R implants. Finally, a higher OR (2.3) for moderate/severe peri-implantitis was observed for implants with a reduced distance (≤1.5 mm) from the prosthetic margin to the crestal bone as measured in baseline radiographs.

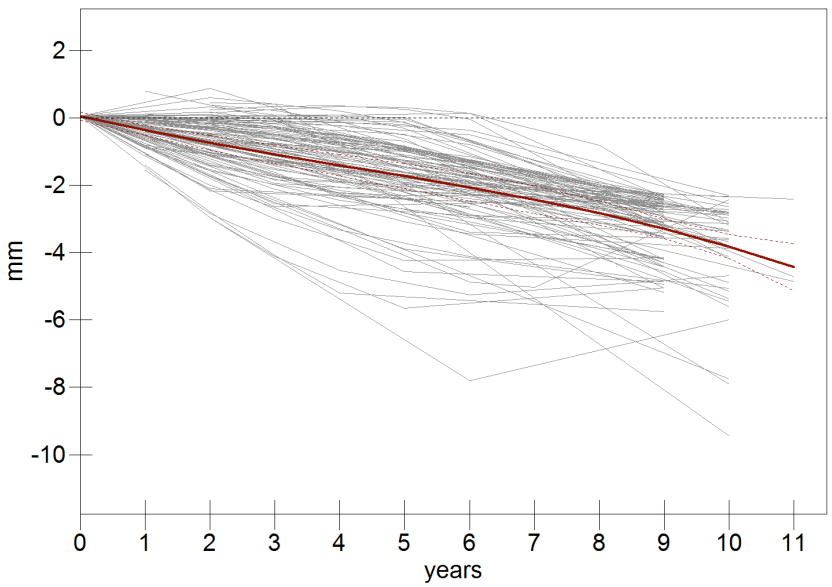
Table 12.Factors associated with implant loss and moderate/severe peri-implantitis (OR and 95% CI)

Factor		Implant loss		Moderate/severe peri-implantitis	
		Early Implant level	Late Implant level	Implant level	Patient level
Periodontitis	No	1	-	1	1
	Yes	3.29 (1.69-6.42)	-	6.54 (2.39-17.91)	4.08 (1.88-8.86)
Smoking	No	1	-	-	-
	Yes	2.32 (1.03-5.24)	-	-	-
Prosthetic therapy	Specialist	-	-	1	1
	General Practitioner	-	-	5.79 (1.87-17.94)	4.27 (1.76-10.41)
Number of implants placed	<4 implants	-	-	1	1
	≥4 implants	-	-	10.84 (3.32-35.37)	15.09 (6.17-36.88)
Jaw of treatment	Maxilla	-	-	1	-
	Mandible	-	-	2.02 (1.11-3.69)	-
Implant length	≥10 mm	1	-	-	-
	<10 mm	3.78 (2.15-6.64)	-	-	-
Implant brand	S	1	1	1	1
	NB	1.94 (1.02-3.69)	6.13 (0.47-80.51)	5.58 (1.86-16.71)	3.77 (1.60-8.87)
	AT	2.10 (1.03-4.30)	5.23 (0.28-99.38)	8.20 (2.27-29.60)	3.55 (1.29-9.77)
	R	7.79 (3.69-16.47)	58.15 (2.35-1435.92)	4.14 (0.90-18.99)	5.56 (1.70-18.24)
Distance from prosthetic margin to crestal bone at baseline	>1.5 mm	-	-	1	-
	≤1.5 mm	-	-	2.29 (1.21-4.34)	-

5 Onset and pattern of progression of peri-implantitis

The mean number of radiographic measurements for the 105 implants was 4.1 (range: 3-7) and the mean bone loss at the 9-year examination was 3.5 ±1.5 mm. During the building of the growth curve model **(Study IV)**, a statistically significant association between time and bone loss was observed. The initial linear model estimated an annual bone loss of 0.38 mm per implant. Extending the growth model by introducing a polynomial term significantly improved the model and reduced the variance on the lowest level (time) by 64% and 91% when compared to the linear and empty models, respectively. The final model demonstrated that bone loss did not follow a linear pattern but accelerated over time as illustrated in Figure 16. Results of the estimation of bone loss for all implants are also illustrated.

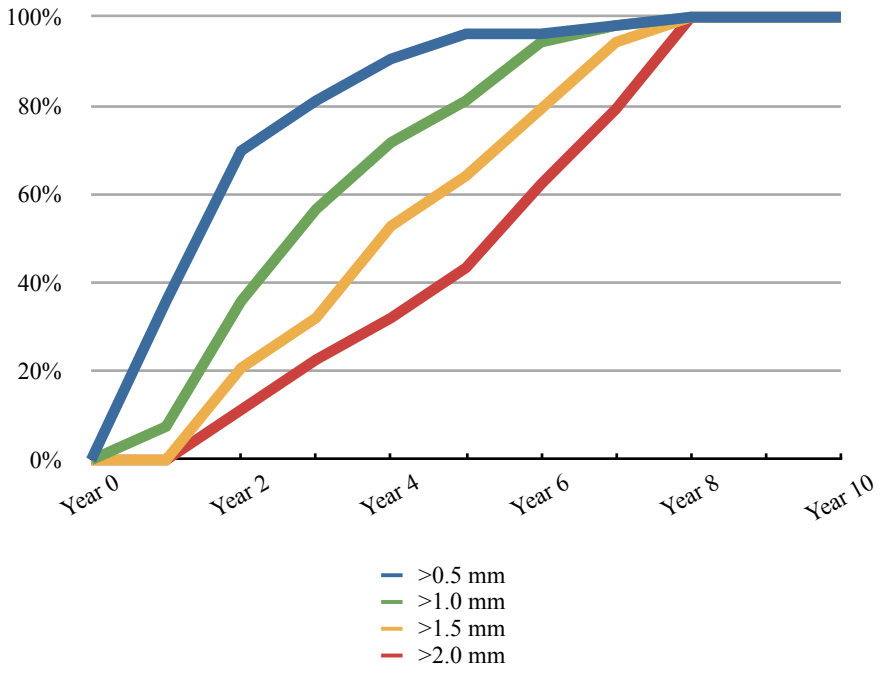
Figure 16.Estimated pattern of bone loss for each implant diagnosed with moderate/severe peri-implantitis at the 9-year examination (n=105, implants with ≥3 radiographic measurements); the red regression line indicates the mean estimated bone loss over time including the 95% CI



The analysis regarding the onset of peri-implantitis demonstrated that, with a threshold for estimated bone loss of >0.5 mm, 52% and 66% of implants were identified at years 2 and 3, respectively. At year 5, 89% of implants presented with estimated bone loss of >0.5 mm. Using the >1 mm threshold for estimated bone loss, the proportions of implants detected at years 2, 3 and 5 were 31%, 47% and 73%, respectively. The corresponding calculations for patients diagnosed with

moderate/severe peri-implantitis at the 9-year examination are illustrated in Figure 17. A total of 81% and 96% of subjects presented with ≥1 implants with estimated bone loss of >0.5 mm at years 3 and 5, respectively. Estimated bone loss of >1 mm was calculated for 57% of patients at year 3 and 81% at year 5.

Figure 17.Cumulative percentage of subjects diagnosed with moderate/severe peri-implantitis at the 9-year examination: different levels of bone loss by year (n=53)



Main Findings

In a randomly selected patient cohort provided with implant-supported restorations under conditions found in everyday dental practice, it was found that:

- the overall patient satisfaction was high but influenced by (i) age and gender of the patient, (ii) the extent of restorative therapy and (iii) the training of the clinician performing the treatment **(Study I)**.

- implant loss occurred in 7.6% of all patients over a follow-up of 9 years; patient and implant characteristics influenced the outcome **(Study II)**.

- 14.5% of all patients exhibited moderate/severe peri-implantitis, and several patient- and implant-related characteristics were identified as risk indicators **(Study III)**.

- progression of peri-implantitis occurred in a non-linear, accelerating pattern, and, in the majority of cases, the onset of the disease had occurred early **(Study IV)**.

Concluding remarks

In the current series of studies the effectiveness of implant therapy was described. Different relevant outcomes were considered and they were assessed in a large and randomly selected patient sample.

Evaluation of effectiveness

Effectiveness of an intervention is defined as the outcome of therapy under everyday conditions (e.g. Berglundh and Giannobile, 2013) and is ideally evaluated in large-scale field studies (e.g. Nallamothu et al., 2008). This approach provides data different from those obtained in small-scale, randomized controlled clinical trials. While RCTs usually entail higher levels of internal validity, the external validity of such research may not always be guaranteed (Grimes and Schulz, 2002b).

Implant therapy in general practice

Swedish authorities started to reimburse implant therapy in 1986, but only if treatment was performed by trained specialists. At the end of the 90s, these restrictions were abandoned. Our data, originating from a patient cohort treated with implants in 2003/2004, indicated that a significant proportion of implant-supported restorations in Sweden were performed by general practitioners. At the time, 27% of all surgical and 76% of all prosthetic procedures were carried out in general practice. The corresponding proportions today are not known. However, it may be speculated that implant therapy, over the last decade, has become even more established in general practice. It should also be kept in mind that, on an international level, implant therapy may very well be performed in general practice to an even higher degree than it is in Sweden.

Discrepancy between clinical research and clinical reality

Existing clinical research on dental implants is almost exclusively based on conveniently selected patient samples treated in single centers by specially trained clinicians (for review, see Tables 2-4). The discrepancy between such research and the clinical reality is noteworthy and may present a concern for the interpretation of available data, i.e. external validity. Results from the present project are therefore of particular significance as (i) different categories of patients, (ii) different categories of clinicians and (iii) different types of implant-supported restorations were included. The external validity of the data generated may be considered as high, and, therefore, the findings may be of relevance to clinicians but also to policy makers.

Representative patient sample

The subjects included in the present series of studies were identified in a registry kept by the SSIA in Stockholm, Sweden. Registry studies are suitable for obtaining data on effectiveness of a device or a treatment modality (Dreyer et al., 2010). By allowing wide inclusion criteria, patients with multiple confounding complications, wide age ranges, various socioeconomic backgrounds and differing healthcare attitudes are included. Research based on registries is common in Sweden. Emilsson et al. (2015) identified 103 healthcare registries that had applied for financial support to the Swedish authorities in 2012. The authors reported that completeness of these registries was high as the majority included ≥80% of target populations. All Swedish citizens are eligible for financial support for dental care, including implant-supported restorative therapy. It is unlikely that large groups of patients received implant therapy outside of the SSIA reimbursement system, and it is therefore assumed that the SSIA registry used in the present series of studies also reflects a high degree of completeness.

Although healthcare registries around the world are common and research utilizing such registries is frequently performed, only few studies have been carried out on the use of dental implants. Antalainen et al. (2013) used an implant registry from Finland to assess the occurrence of loss among 198,538 dental implants placed between 1994 and 2012. In addition to information on implant loss, the registry included basic background information such as gender, jaw of treatment, implant brand and implant length. When comparing the number of implants that were sold in Finland from 2008 to 2010 to those registered during the same period, a marked discrepancy was noted. Thus, only 76% of all implants sold were included in the registry, suggesting that reporting of relevant therapy and associated complications by the clinicians was incomplete. In this context it should be observed that the registry kept by the SSIA did not depend on reports from clinicians or patients. On the contrary, it relied on applications for reimbursement of implant-support restorative therapy submitted by clinicians to two central units of the SSIA located in Lund and Stockholm, Sweden. This further strengthens the validity of the patient selection for the current studies.

The registry kept by the SSIA is different from the healthcare registries referred to by Emilsson et al. (2015), as no data on outcome of treatment is recorded. While details regarding the planned and reimbursed therapy are outlined, no information on implant loss, peri-implantitis or background variables, e.g. smoking, are available. This necessitated additional collection of data, and, for this purpose, a questionnaire was used, patient records were evaluated, and clinical examinations were performed. Patient inclusion was initially based on response to the questionnaire. Non-responders were not considered in the following parts of the project. Although the response rate was high (81%), a certain degree of selection bias may have been possible as questionnaire responders have been shown to

differ from background populations. Females and older subjects generally respond to a higher degree than males and younger subjects (Ronckers et al., 2004; Rönmark et al., 2009). Seltzer et al. (1974) observed that smokers were slower to respond to mailed questionnaires and also presented with a lower overall response rate. Rönmark et al. (2009), in a questionnaire study on respiratory health including 29,218 subjects, reported an overall response rate of 62%. In this study, smokers were underrepresented among responders and, therefore, the authors suggested that extrapolation of results to non-responders was not possible. In the present study, non-response and non-attendance also occurred at the stages of collection of patient records and clinical examination. However, no systematic selection bias could be detected in the analysis.

Observational research

The present research is observational and not interventional. By definition, observational research can only identify risk indicators of disease, while the identification of risk factors requires prospective and controlled trials (Hill, 1965). Several statistically significant associations between potential risk indicators and disease were identified in **Studies II & III**. In a commentary on the limitations of observational epidemiology, Grimes & Schulz (2012) presented several historical examples of supposed associations which were later refuted by interventional research. The authors refer to the inherent risk for bias in observational research, including selection, information, and confounding bias, as the reason for erroneously reported associations that are not based on actual causation. As a consequence, it was suggested that weak correlations demonstrated in observational research with ORs not exceeding 3 should be disregarded, irrespective of statistical significance. Stronger associations merit further investigation. In the present research, efforts were taken to minimize bias in all categories (selection, information, confounding). Several of the identified risk indicators demonstrated a magnitude of association that put them in the "zone of potential interest" (Grimes and Schulz, 2012). Ideally, findings from observational research should be used to appropriately design controlled trials in order to confirm or refute associations. Such research, however, is yet to be performed for dental implants. Rocchietta & Nisand (2012) reviewed the available evidence regarding risk factors/risk indicators in the field and found that virtually all data were based on observational studies. There is obvious need for future research and present results may help in its design. It should also be noted that, while RCTs remain the gold standard in clinical research (Grimes and Schulz, 2002a), they are not always feasible. Due to ethical considerations, certain potential risk factors cannot be studied in a prospective fashion as that may entail neglect of patient care. Two such examples are smoking and periodontal status. Both may require intervention and are, therefore, often studied in observational research.

Outcome measures

Outcome measures considered in the present research included (i) PROMs, (ii) implant loss and (iii) peri-implantitis. These, among others, were identified as areas of interest for research on dental implants (Tonetti and Palmer, 2012; Berglundh and Giannobile, 2013). Two important fields, however, have not been considered: technical complications and questions related to health economics. These issues will be the object of future research, using the patient sample of the current studies. Therefore, not all aspects of the effectiveness of implant dentistry were covered in the present thesis. Furthermore, the present evaluation of effectiveness of implant therapy did not consider any success criteria. In addition to implant survival, success criteria have been the most frequently described outcome in studies on implant therapy. In a systematic review, Needleman et al. (2012) reported that, while 60% of all studies used implant survival as the primary outcome, 16% reported on success criteria. In these studies, the definition of success was based on clinical and radiographic criteria and was often used as a composite outcome. The most commonly used criteria were suggested by Albrektsson et al. (1986) and included (i) absence of implant mobility, (ii) absence of radiographic peri-implant radiolucency, (iii) marginal bone loss <0.2 mm annually following the first year of function and (iv) absence of pain and signs of infections. Needleman et al. (2012) described a considerable heterogeneity among criteria used, but virtually all authors included a time-associated condition in their definitions of success, i.e. annual bone loss not exceeding a certain dimension. This is different from case definitions used in studies on periodontitis, where "function time" or age was not considered (Savage et al., 2009). Hence, the classification of success or failure of implant-supported restorations according to Albrektsson et al. (1986) requires not only the collection of soft tissue and bone loss data but, in addition, calculation of function time. Consequently, a certain magnitude of crestal bone loss at year 3 following installation could identify failure, while the same amount of bone loss after 5 years may very well fulfill the success criteria. The patient, however, may present with the same degree of biological complication at both time points. Hence, the fact that success criteria include a time aspect makes them unsuitable for use in everyday clinical practice. Rather, the absence or presence of any complication, regardless of the time point of occurrence, is of interest to the patient and the clinician. This reflects the recommendations for future research proposed at the 8th EWoP (Tonetti and Palmer, 2012).

Needleman et al. (2012) also reported that outcomes in terms of implant loss and treatment success were mostly reported on the implant level, while information on the patient level was less common. This supports the conclusion by Berglundh et al. (2002), who in a systematic review stated that, if at all reported, the occurrence of biological complications was exclusively expressed on the implant level. Results of the assessments of implant loss **(Study II)** and moderate/severe peri-

implantitis **(Study III)** demonstrated that the proportion of affected patients was higher than the proportion of affected implants. While 3% of all implants were lost, 7.6% of all patients, or 1 out of 13, lost at least one implant over a time period of 9 years. Similarly, 8% of all implants presented with moderate/severe peri-implantitis at the 9-year examination, while 14.5%, or 1 out of 7, of all patients were diagnosed with moderate/severe peri-implantitis. The differences between implant and patient level data are explained by the fact that patients were frequently provided with multiple implants, and, that not all implants within the same individual were necessarily affected by the biological complication. These findings emphasize the importance of considering patient level data in the reporting of biological complications of dental implant therapy as implant level data may underestimate the problem. Even though we assessed outcomes on the implant level in **Studies II & III**, we focused and reported on the proportion of affected patients. Inter-dependency of data, as described by Herrmann et al. (1999), was considered by using multilevel statistical techniques in **Studies II-IV**.

Interpretation of odds ratios

In **Studies I-III**, outcomes of the factor analyses were presented as ORs. The use of ORs to describe associations between factors and outcomes is common and well established in observational research. Thus, major studies exploring risk indicators of cardiovascular diseases (e.g. Kim et al., 2012; Nelson et al., 2015) and cancer (e.g. D'Souza et al., 2007; Nishihara et al., 2013) expressed their findings in such a fashion. It should be noted that clinicians are not necessarily used to interpret results in terms of odds, as thinking in terms of risks is more intuitive. Risk expresses the probability that an event will occur, while odds expresses the probability that a particular event will occur against the probability it will not occur (Sinclair and Bracken, 1994). The OR compares the odds of an event in an exposed group (e.g. smokers) with the odds in the non-exposed group (e.g. non-smokers). This entails that OR and risk ratios are similar for rarely occurring events, but they may differ significantly for more common events. In addition, the unit of analysis should be considered. In **Study II**, ORs were calculated for the single implant, while in **Study III** ORs were calculated for patients and implants. To facilitate the interpretation of our findings in **Study III**, we converted ORs to predicted probabilities.

Findings

Patient-reported outcome measures

Results from the assessments of PROMs **(Study I)** indicated a high degree of patient satisfaction with implant-supported restorations. These findings are in agreement with reports from studies covering similar periods of follow-up (Pjetursson et al., 2005; Simonis et al., 2010). Thus, it may be concluded that the large majority of patients are satisfied with long-term outcomes of implant

therapy. It is noteworthy that the perception of patients treated under everyday conditions was similar to perceptions described in studies on cohorts treated in specialist clinics.

Implant loss

The proportion of patients experiencing implant loss reported in **Study II** is in general agreement with the few studies presenting patient level data following different follow-up periods. Roos-Jansåker et al. (2006a), after 9 to 14 years, and Jemt et al. (2014), after 1 to 28 years, both recorded implant loss in 10.1% of patients. Balshe et al. (2009) found that 8.6% of patients had lost at least one implant after 2 to 7 years of follow-up. It is noteworthy that the proportion of implant loss in the present patient cohort (7.6%) compares favorably to results reported in above-mentioned studies, all describing patient samples treated in specialist clinics. On the other hand, the one registry study published (Antalainen et al., 2013) reported lower numbers of implant loss (3.1% of patients affected) than the present cohort study. This discrepancy between the study from Finland and the present findings may be related to the validity of the data in the Finnish registry. It also supports the concept that registry studies should be complemented by clinical examinations for validation.

The level of training of the surgeon has been discussed as an important factor for failure rates in implant dentistry. Albrektsson et al. (2012) stated that, when experienced, well-trained clinicians are involved in the therapy, the collective rate for implant loss and peri-implantitis over 10 years is expected to be below 5% on the implant level. In the present patient cohort, the level of clinical training (specialist vs. general practitioner) did not influence the odds for implant loss or peri-implantitis. In fact, 22% of all patients in the present sample received (surgery) their implants in a general practice setting, and implant loss in this subgroup was not different from outcomes in patients treated in specialist clinics. In the analysis of risk indicators of implant loss, we included a multitude of potential factors. While we controlled for the extent of therapy, augmentation, number of implants, etc., we were not able to adjust for the inherent complexity of each individual case. It may be assumed that more complicated clinical situations were handled by more experienced clinicians. Therefore, the observed lack of differences between categories of clinicians may have been confounded by the complexity of cases not considered in the statistical analysis.

Peri-implantitis

While almost 50% of all patients presented with clinical and radiographic signs of peri-implantitis at the 9-year examination, a subgroup of 14.5% was diagnosed with moderate/severe peri-implantitis **(Study III)**. Moderate/severe peri-implantitis entailed, in addition to soft tissue inflammation, a crestal bone loss exceeding 2 mm. These affected implants (8% of all implants) had, on the

average, lost 29% of their bone support. The overall estimate of peri-implantitis, including inflammation and crestal bone loss >0.5 mm, on the patient level (45%) was considerably higher than results obtained from a recent meta-analysis presented by Derks & Tomasi (2015). The authors reported a weighted mean patient prevalence of 22% (95% CI: 14–30%). This lower proportion of peri-implantitis is in agreement with our findings on the prevalence of moderate/severe peri-implantitis. Furthermore, it was stated in the review that the case definitions for peri-implantitis applied in the different studies influenced the reported disease prevalence. We used the radiographic thresholds suggested by Koldsland et al. (2010; 2011) and found similar proportions of overall and moderate/severe peri-implantitis.

Eke et al. (2012; 2015) reported that 8% of all adults above the age of 30 exhibited signs of advanced periodontitis (≥2 interproximal sites with ≥6 mm attachment loss and ≥1 interproximal sites with ≥5 mm PPD). The corresponding value for moderate/severe peri-implantitis in the present project was 14.5%. In this context it should be realized that, even though the prevalence of the two diseases - periodontitis and peri-implantitis - appears similar, important histopathological differences between the two disorders exist (Berglundh et al., 2011; Carcuac and Berglundh, 2014).

The results of **Study IV** were generated from a statistical model and indicated that the majority of patients diagnosed with moderate/severe peri-implantitis at the 9-year examination showed early signs of crestal bone loss already after 3 years. This may indicate that bone loss, as part of peri-implantitis, may start early following implant placement and, if not treated, may progress over time. This is in general agreement with findings presented by Fransson et al. (2010) and Cecchinato et al. (2014) but stands in apparent contrast to results by Koldsland et al. (2010), who identified groups exhibiting different levels of disease severity but no differences in mean follow-up time.

Consequences of complications

It is obvious that the consequences of a complication, rather than the diagnosis itself, may be the primary concern of the patient. Results from **Study II** demonstrated that early and late implant loss entailed potentially severe consequences for the majority of patients, ranging from changes in treatment planning to complete loss of applied restorations. Health economics of implant loss and peri-implantitis were not analyzed in the current studies, but it may be assumed that costs associated with complications were high, both for the patient, for the clinician and providers of health insurance. Zitzmann et al. (2013) compared the cost-effectiveness of tooth-supported 3-unit restorations and single implants in the anterior dentition. The implant-supported solutions were found to be more cost-effective in a probability model based on an average observation

period of 4 years. Results from **Studies III & IV** indicated that peri-implantitis is common and that its onset and progression may be time-dependent. Therefore, the 4-year observation period in the study by Zitzmann et al. (2013) may have underestimated the effects of peri-implantitis, particularly the costs related to its treatment. In two separate 10-year reports, Roccuzzo et al. (2012; 2014) calculated the need for invasive treatment of peri-implantitis in patient cohorts treated in a private specialist clinic. Surgical therapy and/or the use of systemic antibiotics were considered necessary in 11% to 67% of all patients, depending on the periodontal classification of the subjects. Data from the SSIA registry in Stockholm indicated that, while approximately 15,000 subjects received implants in Sweden annually over the last three years (2012-2014, Table 1), around 2,000 were, on an annual basis, treated surgically for peri-implantitis during the same time period (data from SSIA register, based on reimbursed surgeries with associated diagnosis of peri-implantitis). It may, again, be assumed that associated costs were high, and that consequences of peri-implantitis also, from a patient point of view, may be severe and, at times, dramatic.

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Appendix

I. Derks J, Håkansson J, Wennström JL, Klinge B, Berglundh T (2015). Patient-reported outcomes of dental implant therapy in a large randomly selected sample.
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IV. Derks J, Schaller D, Håkansson J, Wennström JL, Tomasi C, Berglundh T (2015). Peri-implantitis - onset and pattern of progression.
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