ON GUIDED BONE REFORMATION IN THE MAXILLARY SINUS TO ENABLE PLACEMENT AND INTEGRATION OF ENDOSSEOUS IMPLANTS.

Clinical and experimental studies

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to enable placement and integration of endosseous implants.
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To myself.
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Abstract

Dental caries and periodontal disease are the major causes for tooth loss. While dental caries commonly involve the posterior teeth in both jaws, the teeth most commonly lost due to periodontal problems are the first and second molars in the maxilla. As a consequence, the upper posterior jaw is frequently edentulous. Implant therapy today is a predictable treatment modality for prosthetic reconstruction of edentulous patient. Insufficient amounts of bone, due to atrophy following loss of teeth or due to the presence of the maxillary sinus, can make it impossible to insert implants in the posterior maxilla.

During the 1970s and 1980s, Tatum, Boyne and James and Wood and Moore first described maxillary sinus floor augmentation whereby, after the creation of a lateral access point, autologous bone grafts are inserted to increase crestal bone height and to create the necessary conditions for the insertion of implants. This surgical procedure requires a two-stage approach and a double surgical site: first, bone is harvested from a donor site and transplanted to the recipient site; then, after a proper healing period of between 4 to 6 months, the implants are inserted. This kind of bone reconstruction, even if well documented, has its limitations, not least in the creation of two different surgical sites and the consequent increased risk of morbidity.

In 2004, Lundgren et al. described a new, simplified technique for the elevation of the sinus floor. The authors showed that by lifting the sinus membrane an empty space was created in which blood clot formations resulted in the establishment of new bone. The implants were placed simultaneously to function as “tent poles”, thus maintaining the sinus membrane in a raised position during the subsequent healing period. An essential prerequisite of this technique is to obtain optimal primary implant stability from the residual bone in the sinus floor. An extremely resorbed maxillary sinus floor, with, for example, less than 2-3 mm of poor quality residual bone, could impair implant insertion.

The aims of the present research project were (i) to evaluate the donor site morbidity and the acceptance level of patients when a bone graft is harvested from the anterior iliac crest, (ii) to evaluate implant stability, new bone formation inside the maxillary sinus and marginal bone resorption around the implants in long term follow up when maxillary sinus floor augmentation is performed through sinus membrane elevation and without the addition of any grafting material, (iii) to investigate new bone formation inside the maxillary sinus, in experimental design, using a resorbable space-maker device in order to maintain elevation of the sinus membrane where there is too little bone to insert implants with good primary stability.

In Paper I, 70 consecutively treated patients were retrospectively evaluated in terms of postoperative donor site morbidity and donor site complications. With regard to donor site morbidity, 74% of patients were free of pain within 3 weeks, whereas 26% had a prolonged period of pain lasting from a few weeks to several months. For 11% of patients there was still some pain or discomfort 2 years after the grafting surgery. Nevertheless, patients acceptance was high and treatment
significantly improved oral function, facial appearance, and recreation/social activities and resulted in an overall improvement in the quality of life of formerly edentulous patients.

In Paper II and III, some differently shaped space-making devices were tested on primates (tufted capuchin - Cebus apella) in two experimental models aimed at evaluating whether a two-stage procedure for sinus floor augmentation could benefit from the use of a space-making device to increase the bone volume and enable later implant installation with good primary stability, without the use of any grafting material. An histological examination of the specimens showed that it is possible to obtain bone formation in contact with both the Schneiderian membrane and the device. In most cases the device was displaced. The process of bone formation indicated that this technique is potentially useful for two-stage sinus floor augmentation. The lack of device stability within the sinus requires further improvement in space-makers if predictable bone augmentation is to be achieved.

In Paper IV, a total of 84 patients were subjected to 96 membrane elevation procedures and the simultaneous placement of 239 implants. Changes of intra-sinus and marginal bone height in relation to the implants were measured in intraoral radiographs carried out during insertion after 6 months of healing, after 6 months of loading and then annually. Computerised tomography was performed pre-surgically and 6 months post-surgically. Resonance frequency analysis measurements were performed at the time of implant placement, at abutment connection and after 6 months of loading. The implant follow-up period ranged from a minimum of one to a maximum of 6 years after implant loading. All implants were stable after 6 months of healing. A total of three implants were lost during the follow-up period giving a survival rate of 98.7%. Radiography demonstrated an average of $5.3 \pm 2.1$ mm of intra-sinus new bone formation after 6 months of healing. RFA measurements showed adequate primary stability (implant stability quotient $67.4 \pm 6.1$) and small changes over time.

In conclusion, harvesting bone from the iliac crest could result in temporary donor site morbidity, but in 11% of patients pain or discomfort was still present up to 2 years after surgery. However, patient satisfaction was good despite this slow or incomplete recovery, as showed by the quality of life questionnaire. Maxillary sinus membrane elevation without the use of bone grafts or bone substitutes results in predictable bone formation both in animal design, where the sinus membrane is supported by a resorbable device, and in clinical conditions, where the membrane is kept in the upper position by dental implants. This new bone formation is accompanied by a high implant survival rate of 98.7% over a follow-up period of up to 6 years. Intra-sinus bone formation remained stable in the long-term follow-up. It is suggested that the secluded compartment allowed bone formation in accordance with the principle of guided tissue regeneration. This technique reduces the risks of morbidity related to bone graft harvesting and eliminates the costs of grafting materials.
Original papers

This dissertation is based on the following papers, which will be referred to in the text by their Roman numerals.


IV. Cricchio G, Sennerby L, Lundgren S. Sinus bone formation and implant survival after sinus membrane elevation and implant placement: a 1- to 6-year follow-up study. Clinical Oral Implant Research accepted for publication 2010
Aims

General aim:
The overall aim of this research project was to evaluate the surgical sequel after augmentation with autologous bone and to assess the possibility of creating bone at the maxillary sinus floor through membrane elevation and the insertion of endosseous implants without the use of bone grafts. A further objective was to evaluate the use of a bioresorbable device instead of endosseous implants.

Specific aims:
To evaluate and compare donor site morbidity and complications when harvesting cortico-cancellous bone grafts from the medial table of the anterior iliac and when harvesting from the superior and lateral table of the anterior iliac crest.

To evaluate the psychological and functional acceptance of prosthetic rehabilitation with iliac crest bone grafts and dental implants.

To histologically evaluate the use of a space-making device for sinus membrane elevation and subsequent bone formation at the maxillary sinus floor in experimental studies.

To evaluate the long-term clinical results of sinus membrane elevation and the simultaneous placement of dental implants.

To radiographically evaluate intra-sinus new bone formation and its long-term stability following sinus membrane elevation.

To evaluate the long-term radiographic marginal bone level at implant sites following sinus membrane elevation.

To evaluate implant stability following sinus membrane elevation.
Introducción

La caries dental y la enfermedad periodontal son las causas principales de pérdida de dientes. Mientras que la caries dental comúnmente afecta dientes posteriores en ambos arcos, los dientes más comúnmente perdidos a causa de problemas periodontales son los primeros y segundos molares en el maxilar (Carlos y Gittelsohn 1965; McCaul et al. 2001; Härkänen et al. 2002; Baquain et al. 2007; Lesolang et al. 2009; Tomasi et al. 2008; Hirshfeld y Wasserman 1978; Mc Fall 1982). Como consecuencia, el arco posterior superior es frecuentemente edéntulo.

La pérdida de dientes resulta en la resorción del proceso alveolar y, consecuentemente, en una reducción del volumen de hueso disponible para la inserción de implantes dentales (Pietrokoski & Massler 1967; Schropp et al. 2003; Pietrokovski et al. 2007). Además, en la maxilar posterior, la pérdida de dientes puede inducir una expansión del seno maxilar, que probablemente es debido a la pneumatización, es decir, la presión positiva del aire durante la respiración (Wehrbein y Diedrich 1992; Sharan y Madjar 2008). La migración del suelo del seno maxilar a una posición inferior, en adición a la resorción del hueso alveolar, puede llevar a una situación donde los implantes dentales no pueden ser insertados (fig. 1).

Varios abordajes quirúrgicos que buscan aumentar el volumen de hueso en la maxilar posterior para la inserción y la integración de implantes dentales han sido propuestos. Tatum (1977, 1986), Boyne y James (1980) y Wood y Moore (1988) fueron los primeros autores en describir un Technique de elevación del suelo del seno maxilar donde se insertan huesos autógenos a través de una ventana de hueso lateral previo a la inserción de los implantes dentales.

El uso de huesos autógenos es considerado el estándar dorado para las procedimientos de aumento de hueso (Burchardt 1987) y debe ser activo en el proceso de osteointegración (Hing 2004). Sin embargo, esto requiere un sitio donador intra- o extraoral para la extracción del hueso, lo que genera un aumento del riesgo de complicaciones y morbilidad. Por este motivo, diferentes materiales de injerto, de origen biológico o sintéticos, son comúnmente utilizados para el aumento del suelo del seno maxilar, por sí mismos o en combinación con huesos autógenos (Smiler & Holmes 1987; Wheeler et al. 1996; Hising et al. 2001; Yildirim et al. 2001; Hallman 2002).

También técnicas alternativas para aumentar el volumen de hueso disponible en la maxilar posterior sin el uso de materiales de injerto se han descrito en la literatura. Por ejemplo, la membrana del seno puede ser elevada a través de un abordaje crestal con osteotomías y mantenida en esa posición mediante la inserción de implantes (Tatum 1986; Summers 1994; Bruschi et al. 1998).

Lundgren et al. (2004) describieron un nuevo Technique de elevación de la membrana del seno usando una ventana de hueso lateral. Los autores mostraron que el simple levantamiento de la membrana del seno y la creación de un espacio vacío en el que se formara un coágulo sanguíneo resultó en la formación de nuevo hueso en acordancia con los principios de la regeneración guiada. Los implantes fueron colocados simultáneamente utilizando una técnica de taladro de tamaño inferior para obtener estabilidad primaria adecuada. Un enfoque similar a este Technique se ha indicado en estudios previos (Brånemark et al. 1984; Ellegaard et al. 1997) y más recientemente investigado por

The sinus membrane elevation technique is dependent on the insertion of implants so as to keep the membrane elevated and to create a space for blood clotting and subsequent bone formation. An obvious limitation is, therefore, the height of the residual crest below the sinus, and the possibility of achieving firm primary implant stability. In fact, primary implant stability is a general determinant for obtaining good results from implant therapy (Albrektsson et al 1981, Lioubavina-Hack et al 2006). Situations with a very limited amount of residual crestal bone at the maxillary sinus floor may lead to inadequate primary implant stability and a restriction in the use of this surgical approach.

![Figure 1](image)

**The Use of Endosseous Implants to Replace Missing Teeth**

Today, the use of dental implants is a well-documented first-choice treatment modality for replacing missing teeth. Historically, osseointegration was developed and scientifically validated by Brånemark and co-workers (1969, 1977), and by Schroeder and co-workers (1976). This international breakthrough and the subsequent international acceptance of the osseointegration technique following the Toronto conference, which was held in 1982 (Zarb). Titanium is the material of choice for dental implants (Brunette et al. 2001) since it has suitable mechanical properties and a well-documented biocompatibility (Albrektsson et al. 2008). The great majority of oral implants are made from commercially pure titanium and produced with a screw-shape design (Henry 2005). The original Brånemark implant had a minimally rough surface due to machining. The titanium surface is highly reactive and, once exposed to air, a thin (2-17 nm) oxide film will immediately form. The properties of this film are thought to be responsible for the material’s
biocompatibility and good biological performance (McCafferty and Wightman 1997, Ellingsen et al 2006). Turned or machined surfaces are less common today and have been replaced by modern moderately rough surfaces implants. These can be produced by blasting, plasma-spraying, etching, oxidation or by a combination of these techniques.

Systematic reviews of long-term follow-up studies have shown that about 95% of the implants are still in function after 5 years when placed in patients with sufficient amount of jaw bone. The survival rates are in general less good when implants are used in conjunction with major bone grafting. (Becktor et al. 2004; Pjetursson et al. 2004; Lambert et al. 2009; Nyström et al. 2009).

**Histological and Biomechanical aspects**

Attainment and maintenance of implant stability are preconditions for successful long-term outcomes. Implant stability is obtained through combination of mechanical stability and bone formation at and around the implants’ surface. Implant stability can be divided into primary and secondary stability. The former is achieved at the time of implant placement and is determined by the density of the bone, the surgical technique and the implant design. Surgical trauma induces a bone-healing response which gradually results in secondary stability. The result of bone healing is an increased amount of bone in contact with the implant surface and an increased bone density, especially for implants placed in cancellous bone. This in turn results in a higher resistance to torque forces due to bone in-growth in surface irregularities. Healing may also result in higher lateral stability, at least for implants placed in low density bone. According to several studies, a certain degree of surface roughness improves the implant’s performance from several points of view (Giordano et al. 2006; Miranda-Burgos 2006; Sul et al. 2006). It has been demonstrated that increased surface roughness results in an increased contact area with bone and consequently better mechanical stability when compared with non-modified machined surfaces.

**The Maxillary Sinus**

**Anatomy and physiology**

The two maxillary sinuses are located laterally to the nose cavity and are often asymmetrical in shape. They are usually very small before the second dentition appears at approximately seven years of age. Until this time, the maxillae contain the tooth buds of the second dentition. After the second dentition eruption is completed, the maxillary sinus develops its final form and size. The maxillary sinus belongs to the paranasal sinus complex and is the largest cavity with a volume of about 15 ml (Becker et al. 1994). From an embryological point of view, the paranasal sinus develops from the lateral nasal wall grooves during the sixteenth week of embryo development (Ten Cate 1994; Bolger 2001).

The maxillary sinus is usually a single chamber, limited by the floor of the orbit superiorly; the hard palate, alveolus and dental portion of the maxilla inferiorly; the zygomatic process laterally; the pterygopalatine fossa posteriorly; and the lateral wall of the nasal cavity, containing the maxillary ostium and the
accessory ostia, medially (Becker et al. 1994; Bolger 2001).

The sinus can be divided into smaller cavities by bone septa. The septas are barriers of cortical bone that protrude into the cavity from the floor or the lateral wall of the maxillary sinus (Krennmaier et al. 1999; Velásquez-Plata et al. 2002; Kim et al. 2006; González-Santana et al. 2002). (Fig 2, 3)

The maxillary sinus is lined by a respiratory epithelium. It is pseudo-stratified and columnar–ciliated with globlet cells. The basement membrane is thin and the sub epithelial layer consists of a loose connective tissue, rich in vascularisation and with an epithelium that is densely adherent to the underlying periosteum. (Toppozada et al. 1980; Stierna 2001). The association of epithelium, connective tissues and periostium is collectively called the Schneider membrane (Srouji et al. 2009).

This mucosa lining provides a fundamental and highly complex source of protection for the body, defending it from numerous potentially harmful external influences. The mucociliary apparatus is a significant player in this defensive system thanks to the highly effective functional coupling of secretory film and the cilia of the respiratory epithelium. The cilia in question transport colloidal secretory film from the nasal introitus towards the choana (Becker et al. 1994), pushing mucus, trapped inhaled particles and bacteria along the way at a speed of anything between 3 to 25 mm/min. This significant variation in ciliary beat frequency can be caused by any number of inflammatory substances and the acceleration or deceleration of this function is difficult to predict in clinical situations (Stierna 2001).

The blood supply to the maxillary sinus arrives from the external carotid artery. It is provided mainly by the posterior superior alveolar artery (PSAA) and the infratrochlear artery (IOA), originating from very close to the maxillary artery. Some authors also reported a common origin from a single trunk. These two arteries create an anastomosis inside the maxillary sinus that build up a double arterial arcade, supplying the lateral wall of the antrum and parts of the alveolar process. The PSAA has been found to be in contact with the maxilla and its periosteum (Traxler et al. 1999). It divides into two branches: (i) the gingival branch, suppling the oral mucous membrane in the premolar/molar area and (ii) the dental branch. Both these arteries form anastomoses with the IOA. In particular, an intraosseous anastomosis between the dental branch of the PSAA and the IOA forms the alveolar antral artery. Some other authors use the term alveolar antral artery to indicate the dental branch of the PSAA (Rosano et al. 2009, 2010). This vessel may pose a risk of bleeding during surgery due to its position running along the lateral
wall of the maxillary sinus (Solar et al. 1999; Elian et al. 2005; Flanagan 2005, Mardinger et al. 2007; Ella et al. 2008; Rosano et al. 2010). (Fig 4)

The physiological role of the paranasal sinus is merely speculative and several different functional theories have been suggested. These hypothetical functions can be summarised as: (i) phonetic (resonance, protection from bone conduction of one’s own speech), (ii) respiratory (humidification, buffer pressure changes, local immunologic defense), (iii) olfactory (supply of olfactory mucosa, air reservoir of stimuli), (iv) static (reduce skull weight), (v) mechanical (trauma protection) and (vi) thermal (heat insulation) (Stierna 2001).

The maxillary sinus, arises from, and therefore drain into, the middle meatus delimited by the inferior and middle turbinate. The passageway, from the maxillary sinus to the middle meatus, comprises the maxillary ostium, the ethmoidal infundibulum and the hiatus semilunaris. This complex is also called ostiomeatal complex (Bolger 2001).

The normal patency of the ostiomeatal complex is very important in maintaining the physiological performance of the sinus and in the development of any pathology (sinusitis). Ostial obstruction alters the physiological self-cleaning mechanism of the sinus. Secretion could stagnate and change in composition resulting in the potential development of pathologic conditions (Becker et al. 1994).

The presence of antral pseudocysts or mucocele is another topic that is discussed in regard to maxillary sinus floor augmentation (Fig 5). According to Ziccardi and Betts (1999), the presence of maxillary antral cysts is an absolute contraindication for sinus grafting. However, maxillary sinus cysts comprise a group of lesions whose the nomenclature and pathogenesis have been somewhat controversial (Mardinger et al. 2007). They include sinus mucocele, retention cyst, antral pseudocyst (Soikkonen and Ainamo 1995; Gardner 1984; Gardner and Gullane 1986; Neville et al. 1995; Gnepp 2001) but also as cholesterol granuloma (Karaky et al. 2010). However, whatever the name may be, it would appear that they have no significant clinical relevance. Wang et al. (2007) reported that most retention cysts of the maxillary sinus spontaneously regressed or showed no significant change in size over the long term. These findings suggest that, in the absence of associated complications, “wait and see” may be the appropriate management strategy for these retention cysts. In a case report study, Garg et al. (2000), described how asymptomatic maxillary sinus mucocele was not revealed
until he presented for maxillary sinus grafting and implant placement. Mardinger et al. (2007) reported results from 129 maxillary sinus augmentations where a significant antral pseudocyst was shown before treatment. They concluded that the presence of a pseudocyst in the maxillary sinus is not a contraindication for sinus augmentation. In large lesions and in cases with an unclear diagnosis, further evaluation is needed before sinus augmentation takes place. Kara et al. (2010), in another case report study, concluded that although the presence of antral pseudocysts cannot be a contraindication for sinus augmentation procedures, surgeons may encounter complications, especially in the case of large sinus cysts.

It is well known that tooth loss results in an immediate resorption of the alveolar bone (Pietrokoski & Massler 1967; Pietrokovski et al. 2007; Schropp et al. 2003) (Fig 6). A reduction in bone volume and a subsequent change in the residual bone crest shape can often be observed. It can be speculated that this is also due to a physiological atrophy, which, in turn, is explained by the lack of function and mechanical stimulation of the bone after tooth loss. Furthermore, patients wearing removable prostheses showed a higher rate of bone resorption (Carlsson and Persson 1967; Carlsson et al. 1967; Kelsey 1971; Tallgren 1972; Tallgren 2003; Kovacić et al. 2010) (Fig 7). Other factors are also involved in changes of the bone volume in edentulous areas. For instance, an increased sinus pneumatization following tooth loss has been observed in the posterior maxilla (Fig 8, 9). Sharan and Madjar (2008) measured the superior-inferior difference in the position of the sinus floor position after tooth extraction. They concluded that sinus pneumatization was identified after the extraction of maxillary posterior teeth. The expansion of the sinus was larger following extraction of teeth enveloped by a superiorly curving sinus floor, by extraction of several adjacent posterior teeth, and
by extraction of second molars (in comparison with first molars). Wehrbein and Diedrich (1992) showed that if maxillary sinus pneumatization was present prior to treatment, with more than 30% of root length radiologically protruding into the sinus, clear extension of the basal antrum could be expected. The positive air pressure occurring during breathing inside the maxillary sinus can have an effect on maxillary sinus floor resorption (Asai et al. 2009). It has been speculated that this phenomenon may be the consequence of the alternate balance between positive respiratory air pressure and the atrophy caused by reduced strain from occlusal function.

Surgical techniques for maxillary sinus floor augmentation

General considerations

In the case of surgical procedures involving the maxillary sinus, such as the elevation of the maxillary floor a thorough clinical and radiographic examination should first be obtained. Pre-operative screening to assess any potential pathological conditions in the maxillary sinus should include orthopantomography or computerized tomography. Pathological conditions in the nasal-maxillary complex should be considered a contraindication for sinus floor elevation. Computed tomography can be useful in outlining operative strategies and is a reliable prognosticator of the disease process. It provides objective information about inflammatory sinus disease. Nevertheless, evaluation of sinus disease using CT scans alone lacks sensitivity. Scans are a “picture” of one point in time. Diagnosis of inflammatory sinus disease should be based on CT scan findings, together with
a sinus endoscopy, and an evaluation of patient symptoms and information about associated diseases. All this clinical and radiographic data should be taken in account in the pre-surgical evaluation of the maxillary sinus. Several authors have suggested using the so called “staging approach” to evaluate the sinus conditions. (Joe et al. 2001; Friedman et al. 1990, 1995; Kennedy 1992; May et al. 1993; Lund and Mackay 1993; Gliklich and Metson 1994; Lund and Kennedy 1995, 1997) In particular this kind of approach has also been also suggested by the American Academy of Otolaryngology—Head and Neck Surgery (Rosenfeld et al. 2007; Rosenfeld 2007), the European Academy of Allergology and Immunology, and by the European Rhinologic society (Fokkens et al. 2005; Fokkens et al. 2007a, 2007b).

**Lateral approach with grafting materials**

Tatum (1977, 1986), Boyne & James et al. (1980) and Wood & Moore (1988) were the first authors to describe an augmentation technique for the floor of the maxillary sinus. This technique comprised the creation of an access to the maxillary sinus via a window through the lateral bone wall. A mucoperiosteal trapezoidal flap is raised after a midcrestal horizontal incision along the horizontal portion of the palatal vault, and an anterior and a posterior vertical releasing incision. The anterior incision is made next to the last tooth in the area, while the posterior incision is made in the posterior part of the infrazygomatic crest. The exact location depends on the extent of implant insertion surgery and related bone augmentation. The mucoperiosteal flap is elevated so as to expose the lateral bone aspect of the maxillary sinus. (Fig 10)

The extent of the bone window to the sinus is marked by drilling with a medium size round bur. The holes are then connected to complete the outlining of the bone window (Fig 11). It is important to avoid sinus membrane perforation. According to Wood and Moore (1988), the osteotomy in the superior part of the window should be carried out with a partial thickness approach so as to make the infracture of the window easier. The bone window size is determined by the number of planned implants but should not be too small. A minimum size is required in order to have a comfortable access for dissection of the mucosa and for filling with graft material. On the other hand, it is not necessary to have a too extended window for the case of insertion of more than two implants. Before the window is infractured, the outer margin of the window is dissected free from the

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[Fig 10]

[Fig 11]
sinus membrane in order to avoid tearing of the mucosa at the window infraction (Fig 12). After the window infraction, the sinus membrane dissection is continued (Fig 13). Dissection starts from the inferior part and carries on in anterior and posterior directions. Dissection must be performed carefully in order to avoid sinus membrane perforation. The extension of the dissection to the posterior is related to the number and location of the planned implants. Raghoebar et al. (1993), suggested using a periosteal elevator placed to the posterior/superior part of the created cavity prior to its filling with grafting material. The particulated graft is inserted in the prepared cavity, the periosteal elevator is removed and the mucoperiosteal flap is replaced in position and sutured to cover the window opening.

Several kinds of graft materials have been used for sinus floor augmentation, such as autogenous bone grafts from the iliac crest (Boyne and James 1980; Raghoebar et al. 1993, 1997, 2001a, 2001b), from the mandibular chin (Wood & Moore 1988; Mish et al. 1992; Lundgren et al. 1996; Raghoebar et al. 1997, 2001b) from the mandibular ramus (Misch 1997, 2000; Clavero & Lundgren 2003) or calvarium (Tulasne 1999), as well as bone substitutes by themselves or in combinations with autogenous bone (Smiler & Holmes 1987; Wheeler et al. 1996; Hising et al. 2001; Yildirim et al. 2001; Hallman 2002).

Clinical follow-up studies have shown good results when the maxillary sinus floor is augmented using different grafting materials such as autogenous bone by itself, allografts, bone substitutes or a mixture of the two of them. In a systematic review of the materials of choice for implant placement support, it was reported that implant survival in maxillary sinus augmentation was 92% for implants placed into autogenous and autogenous/composite grafts, 93.3% for implants placed into allogenic/nonautogenous composite grafts, 81% for implants placed into alloplast and alloplast/xenograft materials and 95.6% for implants placed into xenograft materials alone (Aghaloo and Moy 2007). The authors concluded that maxillary sinus augmentation procedures had been well documented, and the long-term clinical success/survival (> 5 years) of implants, regardless of graft material(s) used, compares favorably to implants placed conventionally, with no grafting procedure. Pjetursson et al. (2008), in another systematic review to assess the survival rate of grafts and implants used for sinus floor elevation, reported an estimated annual failure rate of 3.48% translating into a 3-year implant survival rate of 90.1%. When failure rates were analyzed on a patient level, the estimated annual failure rate was 6.04%, translating into 16.6% of the subjects experiencing implant loss over 3 years. They concluded that the insertion of dental implants in combination with
maxillary sinus floor elevation is a predictable treatment method that shows high implant survival rates and low incidences of surgical complications.

Sinus membrane elevation

Lundgren et al. (2004) described a novel technique for maxillary sinus floor augmentation without the use of grafting materials, i.e. the sinus membrane elevation technique. In brief, after a mid-crestal incision and vertical releasing incisions, a mucoperiosteal flap was elevated to expose the sinus wall. The extension of a bone window was marked with a small round bur and the window was cut with a reciprocal microsaw (Fig 14). The inferior margin of the created window was always at least 5 mm above the sinus floor in order to maintain a 3-wall compartment. The saw was tilted to create a tapered osteotomy so as to ensure the stability of the window when it was replaced after surgery. The bone flap was dissected free from the underlying sinus membrane with a dissector and after removal it was kept in saline (Fig 15, 16). If the sinus membrane was perforated during dissection, two holes were made in the sinus wall above the window. The sinus membrane was then sutured to the holes in a superior position. The membrane was elevated by the suture and the perforation was closed. After the insertion of a periosteal elevator into the sinus to protect the elevated membrane, the implant sites were prepared in accordance with an undersize preparation approach and the implants were inserted. The implants were placed simultaneously where adequate primary stability was achieved from the residual bone in the sinus floor, using the technique of undersize drilling (Fig 17, 18). The bone window was then replaced and secured by closure of the oral mucosal flap (Fig 19). The author showed that the mere lifting of the sinus membrane and the creation of a void space in which blood clot formation occurred, resulted in new bone in accordance with the principles of guided tissue regeneration (Dahlin et al. 1988; Nyman 1991) (Fig 20). A similar approach to the sinus has been indicated in earlier studies (Brånenmark et al. 1984; Ellegaard et al. 1997) and further investigated by others (Ellegaard et al. 2006, Palma et al. 2006, Hatano et al. 2007; Thor et al. 2007; Sohn et al. 2008; Borges et al. 2010).

Clinical follow-up studies have shown good results when the maxillary sinus floor is augmented through the mere sinus membrane elevation and without the use of any additional grafting material. (Ellegaard et al. 1997; Lundgren et al. 2004; Ellegaard et al. 2006; Thor et al. 2007; Sohn et al. 2008; Borges et al. 2010).

Crestal approach

As an alternative to the classical maxillary sinus floor augmentation with lateral approach, Tatum and other authors (Summers 1994; Bruschi et al. 1998) have presented a crestal approach. This is a less invasive surgical procedure used to insert implants in insufficient bone volumes in the posterior maxilla. In brief, the maxillary sinus floor is fractured, the sinus membrane is elevated through an implant site with the use of osteotomes and the implants are inserted. This
technique is considered as a valid alternative to the classical lateral approach (Tan et al. 2008). (Fig 21)

The use of Short Implants as an alternative to bone augmentation

The use of short implants can also be considered as a valid alternative to bone augmentation procedure as a means of restablishing a proper masticatory function using osseointegrated implants (Renouard and Nisand 2006).

Pathologies and complications following maxillary sinus floor augmentation

Studies have investigated the consequences of bone augmentation on the health of the maxillary sinus. In a series of studies Timmega et al. (1997, 2001, 2003) used a questionnaire, conventional radiographic examination, and naso-endoscopy and concluded that the augmentation procedure did not have pathological consequences in patients without signs of pre-existing maxillary sinusitis. However, some patients with a predisposition to sinusitis, showed signs of postoperative chronic sinusitis. This is something that requires consideration when evaluating patients for sinus lift procedures.

Griffa et al. (2010), prospectively investigated the mucociliary function during maxillary sinus augmentation in patients without preoperative signs of maxillary sinusitis. Only the detached part of the mucosa at the sinus floor and at the lateral bony window showed the absence of mucociliary function. The authors concluded that maxillary sinus augmentation results in negligible signs of sinus pathology and that mucociliary function is preserved even during the surgical procedure except for the detached area of the Schneiderian membrane.

Sinus membrane perforation can occur during surgery. In 1999 Vlassis & Fugazzotto and 2003 Fugazzotto & Vlassis classified sinus membrane perforations, first in five and later in three classes depending on their position. Class I perforations occur at any point along the superior aspect of the prepared sinus window. Class II occur along the lateral or inferior aspect of the window. Class III occur at any location within the body of the prepared sinus window. Schwarz-Arad et al. (2004) calculated the prevalence of sinus membrane perforation in a study on 70 patients to be 44%. The authors reported that membrane perforations were strongly related to postoperative complications but no relation was found between membrane perforations or postoperative complications and implant survival. Aimetti et al. (2001) evaluated the health of the maxillary sinus in a group of 18 patients who
had undergone maxillary sinus floor augmentation. Endoscopy in sinus with small perforations showed healthy conditions, while cases with large perforations showed signs of sinusitis.

**Autogenous bone harvesting and donor site morbidity**

The first graft material suggested for the reconstruction of bone defects was autogenous bone. Van Meekren, already in 1682 reported success after transplanting canine skull bone to a calvaria defect (Rogers 1930; Chase and Herndon 1955; Prolo and Rodrigo 1985; Cutting et al. 1990).

As already noted, autogenous bone is considered the gold standard graft for bone reconstruction (Burchardt 1987). Theoretically, autogenous bone possesses the prerequisite properties for the successful incorporation of a grafting material, thanks to it being both osteoconductive and osteoinductive (Urist 1965, 1980).

The limitations of using autogenous bone grafts concern the size of the donor site and risks of morbidity due to demanding surgery. Factors to be taken into account when choosing the donor site are the amount of bone required, the type (cortical vs. cancellous) of bone needed, the recipient site, and the expected biological behaviour (neovascularization and resorption) (Goldenberg & Stevensson 1987; Körloff et al. 1973; Gord et al. 1998; Johansson et al. 2001).

Donor sites can be i) extraoral or ii) intraoral. The iliac crest, the calvaria, the ribs and the tibia are the most commonly described extraoral donor sites in the literature (Nystrom et al. 1993, 1997; Kondell et al. 1996; Lundgren et al. 1997; Tuslane 1999). These sites can provide a sufficient amount of bone for reconstructing totally edentulous jaws. The anterior iliac crest is the most commonly used extraoral donor site, particularly when both cortical and cancellous bone is required (Fig 22).

The medial or internal table of the ilium is often described in the literature as a preferable site, owing to its easy accessibility and its low morbidity, especially when only cancellous bone is harvested. (Bloomquist and Turvey 1992) The medial table has a thin cortical plate compared with the superior or lateral border of the iliac crest (Fig 23, 24). The area of the lateral iliac crest where the medial gluteus muscle inserts is called the tubercle, and the cortical bone has a high density and thickness. This area can be chosen when large amounts of cortical bone are needed. The disadvantage of harvesting bone from the superior or lateral border of the iliac crest is interference with the insertion of the gluteal muscles and the inherent risk of gait disturbance. Excessive amounts of bone harvested from the superior or lateral part of the
iliac crest can also result in a change in appearance of the hip contour. Several authors have focused on the risk of donor site morbidity when harvesting from these extraoral sites (Marx & Morales 1988; Arrington et al. 1996; Kalk et al. 1996; Marchena et al. 2002; Mischkowska et al. 2006).

Intraoral sites can be used in case of smaller localised bone defects, where smaller bone grafts are needed. The proximity between donor and recipient sites, the reduced operative time and the chance to avoid general anaesthesia are obvious advantages of intraoral bone grafting. Several different intraoral donor sites have been suggested: mandibular symphysis, mandibular ramus, infrasygomatic crest and maxillary tuberosity (Mish et al. 1992; Lundgren et al. 1996; Misch 1997, 2000; Nkenke et al. 2001, 2002; Raghoebbar et al. 2001; Joshi 2004; Booij et al. 2005; Kainulainen et al. 2005; Proussaefs 2006; Lundgren & Sennerby 2008; Soehardi et al. 2009; Weibull et al. 2009). These sites require a double intraoral surgical site and present a risk of post-surgical morbidity. Mandibular symphysis and ramus are the two most investigated sites. The ascending mandibular ramus is considered as the first choice due to lower rates of morbidity (Clavero & Lundgren 2002, Raghoebbar et al. 2007). (Fig 25, 26)
Histological aspects of maxillary sinus floor augmentation

Autogenous bone grafts and endosseous implants

Revascularization of the grafted bone is a prerequisite for successful healing and incorporation. This can be achieved by (i) re-establishing microcirculation through microanastomosis with existing blood vessels and (ii) osteoclastic resorption followed by ingrowth of new vessels (Urist 1980; Goldenberg & Stevensson 1987). Necrotic bone is incorporated into newly formed bone, resorbed by osteoclasts and replaced with mature lamellar bone. It is easy to understand that revascularization is faster in cancellous bone grafts than in cortical ones due to the porous morphology of the former. Moreover, cancellous bone grafts lose more volume than cortical bone during healing. Rigid fixation of the bone graft is important to avoid mobility and consequent fibrous soft tissue formation (Philips & Rahn 1988, 1990; Lin et al. 1990). Another surgical approach is the use of vascularized bone grafts. This technique is mainly used for maxillary reconstruction after ablation of tumours (Rohner et al. 2003; Jaquiéry et al. 2004).

Lundgren et al. (1999) studied integration of titanium microimplants in autogenous bone blocks in the maxilla in 10 patients with severely resorbed maxillae who where treated with iliac cortico-cancellous bone grafts and titanium implants in a two-stage procedure. The authors histologically analysed the bone graft–titanium microimplant interface after six and twelve months of healing for a simultaneous approach and after six months for a delayed approach. Histomorphometrical analyses showed a higher degree of bone–implant contact and more bone filling the implant threads in the delayed approach using microimplants. They speculated that this was probably due to the partly revascularized grafted bone found in the delayed approach being better able to respond to the surgical trauma, resulting in interfacial bone formation. The authors concluded that a delayed approach when using free autogenous bone grafts and titanium implants for reconstruction of the severely atrophied maxilla, is to be preferred in order to obtain a higher degree of implant osseointegration.

Bone substitutes and endosseous Implants

In order to simplify bone reconstruction by avoiding donor site surgery, the use of bone substitute is obviously an attractive alternative. Several bone substitutes of biological and synthetic origins are available on the market. Biological ones can be allografts, i.e. from other humans or xenografts, i.e. from other species than humans. Fresh or untreated allograft are limited in use due to the presence of antigens, which may affect the immune response and trigger an inflammatory response and rejection. The antigens responsible for this immune response are the soluble proteins originating from the allograft. The one with the highest antigenic properties is a hydrophobic glycopeptide (HGP) (Urist et al. 1975). When in contact with a bone matrix, it starts to produce mononuclear leukocytes and fibrous connective tissue instead of progenitor cells, thus blocking the bone’s morphogenetic activity. Efforts have been made to eliminate these antigens, while trying at the same time to maintain the osteoinductive properties of the allografts. Frozen or freeze-dried, mineralised or demineralised, demineralised dentin and
autolysed antigen-extracted allogenic bone (AAA) are examples of allografts with extracted antigens. Obviously, this kind of treatment results in that the allograft losing its osteoinductive properties.

Pinholt et al. (1990) showed, in a rat model that demineralised and lyophilized dentin and bone could induce new bone formation. In other studies this induction property has not been demonstrated (Pinholt et al. 1991, 1992; Lohmann et al. 2001).

In 1988, Jensen and Sennerby compared histologies from 12 microimplants retrieved from patients treated for maxillary sinus augmentation using autogenous bone or radiated mineralised cancellous allografts and a one stage implant approach. After 6 and 12 months, varying amounts of bone/allografts were present in loose connective tissue. Histological specimens showed a great amount of non-viable allograft particles and in most of cases an absence of any relationship between viable bone and the implant surface that was most in contact with the connective tissue. On the contrary, autogenous bone graft specimens showed viable lamellar bone mixed with normal marrow tissue and the presence of normal bone morphology.

Xenografts are derived from the bone tissue of animals. As with allografts, proteins are extracted for reasons of immunological safety. As a consequence, the osteoinductive properties disappear and the graft can only work as an osteoconductive scaffold. The healing of xenografts follows the same principles as those for allografts. The most widely used xenograft is a bovine derivated hydroxyapatite (BHA). In a series of clinical investigations including x-rays, histology and RFA measurements, Hallman et al. (2002, 2004) obtained good results using BH alone or in combination with autologous bone. Histological specimens after six months and three and five years showed a good healing pattern, new bone formation after six months, BH particles embedded in dense lamellar bone after 3 years and no difference between implants in augmented bone or in residual alveolar bone only after five years. The use of BH, autogenous bone alone or an 80:20 mixture of the two showed similar results at histomorphometrical analysis with implants inserted from 6 to 9 months after the augmentation procedure. Light microscopy showed a similar degree of osseointegration in all three situation. One of the major issues to have been considered in the use of these materials is the ability of the receiving body to absorb bone substitutes and replace them with newly formed bone. That’s a very discussed topic. Some authors suggest that BHA is resorbable, some others that is slowly degraded, some others that is phagocytatable and yet others that is not resorbable (Klinge et al. 1992; Berglundh & Lindhe 1997; Schlegel & Donath 1998; McAllister et al. 1999; Piattelli et al. 1999; Schwartz et al. 2000; Valentini et al. 2000; Yildirim et al. 2001; Karabuda et al. 2001; Hallman 2002; Taylor et al. 2002; Sartori et al. 2003; Schlegel et al. 2003; Tadjoedin et al. 2003; Hallman & Thor 2008; Perrotti et al. 2009a 2009b).

In a recent study, Mordenfeld et al (2010) showed that deproteinezed bovine bone (DPBB) was well integrated in lamellar bone, with no significant sign of changes in particle size after 11 years.

Implant materials or synthetically derived alloplasts, have osteoconductive properties only. The most common examples are hydroxyapatite, bioglass, tricalciumphosphate (TCP), calcium sulphate (plaster of Paris) and polymers. They
differ considerably from a structural, chemical, mechanical and biological point of view, and can be divided in two groups: resorbable and not resorbable. HA and bioactive glass belong to the not resorbable group. TCP and calcium sulphate belong to the resorbable one. Tricalcium phosphate is the most commonly used alloplast material and maybe the most documented one. Its major limit is its rapid resorption rate. Calcium sulphate has been used in craniofacial surgery for more than 100 years (Dresdman 1892), and De Leonardis & Pecora (2000) were the first to use it for sinus floor augmentation in implant dentistry. The volume of the grafted material can decrease very quickly reducing the original size and creating unfavourable condition for correct implant management (Hallman and Thor 2008).

In a randomised controlled study, Lindgren et al. (2009) compared bone formation around microimplants placed at the time of maxillary sinus augmentation, using synthetic biphasic calcium phosphate (BCP) or deproteinized bovine bone (DBB). They showed that new bone formation and bone-to-implant contact was found to be equivalent. The number of DBB particles in contact with newly formed bone was higher than the BCP ones. The same author, in a 1-year prospective clinical and radiographic trial published in (2010), compared the two materials. He concluded that, after 1 year of functional loading, similar results were found for implants placed after sinus augmentation using the two different materials.

**Sinus membrane elevation and endosseous implants**

As previously discussed, the mere elevation of the sinus membrane results in bone formation at the floor of the maxillary sinus. In an experimental study by Palma and co-workers, machined and oxidised endosseous implants were placed in conjunction with sinus membrane elevation using the replaceable bone window technique (Lundgren et al. 2004). One sinus was filled with autogenous bone grafts and served as a control for the elevated side where no grafts were used. Histology was performed after 6 months of healing. Two machined implants had been lost. Histology showed bone formation around the implants at both sides with no apparent differences. The lifted sinus membrane lined the new bone and the apex of the implant with no signs of inflammatory infiltrates or irritation. The surface-modified oxidized implants showed more direct bone-implant contacts than the machined ones irrespective of treatment.

The new bone was probably formed according to the principle of guided tissue regeneration (GTR). GTR was developed by Nyman and Karring (1979) and deals with the regeneration of a desired tissue in a a secluded space created using a barrier membrane (Karring et al. 1980, 1984; Nyman et al 1980, 1982a, 1982b, 1989; Gottlow et al. 1984, 1986). The initial studies published in the early 80s, focused on the regeneration of periodontal tissues around teeth. Dahlin et al (1988) tested the biological principle for regeneration of critical bone defects in a rat model. This method was later called guided bone regeneration (GBR) (Dahlin et al. 1989, 1990; Seibert & Nyman 1990; Nyman 1991). In order to create and maintain a space, barrier membranes made of a variety of different materials and with different features have been used. The following factors are important
for a good clinical outcome: membrane stability, barrier function duration, size of membrane perforations enhanced access of bone and bone-marrow-derived cells to the area for regeneration, ample blood fill of the space and prevention of covering soft tissue dehiscence.

Barrier membranes can be divided in two groups: non-resorbable and resorbable membranes. The most common non-resorbable membranes are made of polytetrafluoroethylene (PTFE) and expanded PTFE (ePTFE). These membranes can also be reinforced with a titanium skeleton that make them more rigid. Today, resorbable membranes are the first choice in GBR, the obvious main advantage being that they need not be removed with a second surgical intervention. In contrast, some authors reported better results using ePTFE membranes compared to the bioresorbable ones (Simion et al. 1997; Ito et al. 1998; McGinnis et al. 1998; Mellonig et al. 1998). Materials used for the fabrication of membranes belong to the group of natural or synthetic polymers. The most common ones are collagen or polyglycolide and/or polylactide or copolymers (for review see Hutmacher et al. 1996).

Several authors also reported good results in clinical studies where bone was augmented with GBR to enable implant placement (Lazzara 1989; Becker and Beker 1990; Buser et al. 1990; Nyman et al. 1990; Wachtel et al. 1991; Dahlin et al. 1991, 1995; Jovanovic and Spiekermann 1992; Lang et al. 1994).
Materials and methods

Clinical studies

Paper I

Patients

70 consecutively treated patients were retrospectively evaluated with regard to postoperative donor site morbidity, complications and the outcome of the oral rehabilitation. The patients, who were recruited from referrals to the Department of Oral & Maxillofacial Surgery, Umeå University, Sweden, were evaluated by means of a quality-of-life questionnaire.

Surgery

Surgery was performed under general anesthesia. All patients received prophylactic preoperative penicillin G. In the case of a penicillin allergy, clindamycin was given.

In 30 patients the corticocancellous bone graft was taken from the medial table of the iliac crest, whereas in 40 patients the bone graft was harvested from the superior and lateral part of the iliac crest (Fig 23, 24). The skin incision started 3 to 4 cm medial to the iliac crest following the skin lines in the posterolateral direction over the crest 3 to 4 cm behind the superoanterior iliac spine; the incision was not extended beyond the lateral border of the iliac crest. The dissection proceeded in the subcutaneous fat layer until the aponeurosis between the abdominal and gluteal muscles was identified. The direction of the incision was then changed to follow the iliac crest in a posterior direction, and the dissection was carried out in contact with bone. The fascia lata was dissected in a careful manner, ensuring that it was kept intact for an optimal adaptation at the time of wound closure. After the exposure of the superior surface of the iliac crest, the following dissection was made in accordance with the kind of bone graft that was to be harvested: (i) anteromedial bone graft harvesting. The dissection of the fascia lata was extended along the medial surface uncovering the planned harvesting area. (ii) Superolateral bone graft harvesting. The dissection of the fascia lata was extended further along the superolateral border of the iliac crest close to the insertion of the gluteus muscles. Depending on the resorption class (Cawood and Howell classification) to be reconstructed, the dissection could be extended in the lateral direction to include the thick cortical bone at the lateral border where the medial gluteus muscles insert (Fig 27). This means that some of the muscle
fibers of the gluteus muscles need to be stripped off the bone margin. In another Cawood and Howell class situation, the tubercle is used for the anterior maxillary reconstruction, resulting in a further release of the muscle fibers in the bone margin. The graft was outlined with a sagittal or reciprocal saw. After the osteotomies were completed, the graft was harvested with a straight osteotome (Fig 28). The wound was closed in layers; the closure of the first layer, the fascia lata, was carefully readapted to avoid marrow bone bleeding into the surrounding soft tissue. An activated vacuum drain was positioned between the fascia lata and the muscles and kept in place as long any bleeding occurred. The skin was closed with continuous intracutaneous sutures using a resorbable material. A pressure dressing was left in place for 24 hours.

**Quality-of-life questionnaire**

Retrospective evaluation was performed with the aid of a questionnaire sent to the patients no less than 2 years after the reconstructive surgery. The time span of 2 years was chosen to ensure that all the treatment was completed, to avoid the risk of bias stemming from patient-doctor dependence and to be able to classify any neurosensory disturbance as permanent.

**Statistics**

To analyse the difference between the two harvesting techniques regarding pain and gait disturbance a life analysis in which life expectancy is time to painless has been chosen. Since the exact times when the pain ceases is missing the lifespans are interval censored (Logrank test for interval censored data).

To analyse if the oral function improved significantly through rehabilitation McNemar’s chi-square test has been used.
Paper IV

Patients

A total of 84 consecutive patients were subjected to 96 maxillary sinus membrane elevation procedures and the simultaneous placement of 239 implants. Twelve patients were subjected to bilateral augmentation while 72 underwent unilateral surgery. Patients were recruited from referrals to the Department of Oral & Maxillofacial Surgery, Umeå University, Sweden and a private practice in Palermo, Italy. The patients were clinically and radiographically followed at the time of implant placement, at abutment connection, after 6 months of loading and then annually up to 6 years of loading.

Inclusion criteria

The inclusion criteria were; (i) need for implant treatment in the maxillary premolar or molar area and a residual bone height of 7 mm or less, (ii) healthy maxillary sinuses as assessed from the radiographic and clinical examinations, (iii) and the possibility of achieving adequate primary stability in the residual bone.

Implants

Thirteen mm long implants were used in most sites, although in some cases shorter implants were used to avoid tension in the membrane or if a minor perforation had occurred.

A total of 239 Brånemark System, TiUnite implants were inserted. Of these implants, 205 were MKIII 3.75 mm in diameter; nine were MKIII 5 mm in diameter and were used in the first molar position; additionally, 25 were Brånemark System TiUnite Groovy implants 3.75 mm in diameter. Of the 239 implants, 50 were inserted entirely in residual bone and the remaining 189 protruding into the maxillary sinus. Out of these 189, 179 were protruded at least 4 mm in the created sinus compartment, 8 mm on average with a range 4 - 13 mm. Abutment connection surgery was performed in 78 patients. In 6 patients abutments were inserted simultaneously with the implant surgery.

Surgery

The surgical procedure was performed with local anaesthesia and conscious sedation.

The surgical technique used has been described previously (Lundgren et al. 2004). In brief, after a mid-crestal incision and vertical releasing incisions, a mucoperiosteal flap was elevated to expose the lateral sinus wall. The extension of a bone window was marked with a small round bur and the window was cut with a reciprocal microsaw (Aesculap, B Braun Melsungen Ag, Melsungen, Germany) under continuous saline irrigation (Fig 14). The saw was tilted in order to make a tapered osteotomy, thus ensuring the stability of the window when it was replaced after surgery. The bone flap was dissected free from the underlying sinus membrane with a dissector and after removal it was kept in saline (Fig 15, 16). The sinus membrane was elevated in order to create a secluded compartment for the implants.
(Fig 20). If a small sinus membrane perforation (approximately <5 mm) occurred during the dissection procedure, the elevation was extended in all directions until it was possible to lift the membrane without tearing, so as to let the perforation close by itself (Fig 29, 30) and/or to keep it away from the implant tip (Fig. 31). In the case of a larger perforation, that would not close by itself, one or two small holes were drilled with a round bur above the window and the membrane was lifted and sutured to the holes to close the perforation (Fig 32, 33) After the elevation was complete, instruments were removed from the prepared cavity. In order to obtain a correct primary implant stability, implant site preparation was performed as follows: planned implant positions were marked with a pilot bur. In the implant positions the residual bone crest was perforated with a 2mm-diameter twist drill, thus avoiding interference with the dissected membrane.

Further preparation for the implants depended on the thickness (height) of the residual bone. If the bone thickness (height) was 5 mm or more with a good density, a 2/3 mm pilot drill was used for the outer 1 mm of bone preparation. Then a 2.85 mm-diameter twist drill was used for final preparation of the residual bone. If the bone height was less than 5 mm or of low density, a 2.85 mm twist drill or 2.8/2.4 mm step twist drill was used directly after the 2 mm twist drill. The selection of the final drill diameter was decided with the aim of obtaining adequate primary stability for the healing of the implants. Dental implants were placed into the obtained space with the aim of maintaining the sinus membrane in the elevated position. During implant insertion, the elevated membrane was inspected through the window. None of the implants studied presented any vertical or horizontal mobility at the end of the surgery. The final drill used depended on the available thickness and density of the residual bone. Due to the limited residual bone, a countersink bur was not used. The same under-preparation concept, aimed at obtaining the right primary stability, was used in the case of wide implants (5 mm in diameter). All the twist drills, used for implant site preparation, were manufactured by Nobel Biocare (Nobel Biocare AB, Gothenburg, Sweden). The bone window was repositioned and if necessary secured with the aid of cyanoacrylate tissue glue (Fig 34) (Indermil, Henkell Corporation, Germany).

The patients were kept on an antibiotic regimen in the form of 1 gr amoxicillin twice daily for at least 7 days postoperative and instructed to refrain from blowing their nose.

Radiographic analysis

Intraoral and panoramic radiographs and computerized tomograms (CTs) were taken prior to surgery and used as baseline radiographs.

Radiographic follow-up examinations were performed with intraoral radiographs within 2 weeks after surgery (baseline), after 6 month of healing, after 6 months loading and thereafter annually. A second CT was performed in 40 patients after 6 months of healing.

Measurements of newly formed bone and marginal bone levels were performed in digitised radiographs using a specific software (DBSWIN, Dürr Dental AG, Bietigheim-Bissingen, Germany). All radiographs were calibrated based on the known length of the specific implant that was found to be the most
perpendicular implant in the radiograph. The apical and marginal bone levels were measured at mesial and distal aspects of each implant by using the implant/abutment junction as a reference point (Fig 35). From the radiograph, the bone level at the apical as well as the marginal aspect of the implants were calculated twice, by two different examiners, for each radiograph in 10 patients randomly chosen.

In order to find out if the relative length of the implant protruding into the secluded space in the maxillary sinus affected the amount of new bone formation, implants were divided in two sub-groups: (i), implants protruding 4 to 8 mm into
the sinus and (ii), implants protruding 8.1 to 13 mm into the sinus.

In the pre- and post-surgical CT measurement of bone height, calculations were made in the sections between each of the implants or posterior to the most posterior implant (Fig 36).

**Resonance frequency analysis**

Implant stability was measured after 6 months of healing and after 6 months of loading with RFA (Ostell TM, Integration Diagnostics AB, Göteborg, Sweden). On these occasions, a transducer was attached to each implant and measurements were taken in implant stability quotient (ISQ) units.

**Statistics**

A linear mixed model (SPSS Inc., Chicago, IL, USA) was used for correlation analysis of implant protrusion into the maxillary sinus and new bone (NB). Implant protrusion into the sinus was used as a fixed factor, while the patient was used as a random factor. Comparisons of ISQ values between implants placed entirely in residual bone, anterior to the maxillary sinus, and implants protruding into the sinus cavity were performed using the linear mixed model as well. The patient was used as a random factor while the ISQ value was used as a fixed factor. To evaluate the individual differences in the repeated measurements of apical bone level (Abl) and marginal bone level (Mbl) from the 10 randomly selected patients, a Gage repeatability and reproducibility study was performed (Fig 37). The level of significance was 0.05. In the analysis before the decision regarding
which statistical methods should be use, no relevant deviation for assumption for normality was found.

**Experimental studies, paper II and III**

**Animals and anaesthesia**

In papers II and III, a total of 14 tufted capuchin primates (Cebus apella) underwent bilateral sinus membrane elevation surgery after the extraction of the three premolars and the first molar on both sides of the maxilla to create an edentulous area. A bioresorbable space-making device was placed below the elevated membrane on the sinus floor with or without the insertion of an oxidized implant protruding into the created space. In paper II, the bioresorbable space-making device, about 6 mm wide and 6 mm in height, was placed below the elevated membrane on the sinus floor; an oxidized implant (Nobel Biocare AB, Gothenburg, Sweden) was installed in the residual bone, protruding into the created space at one side while the other side was left without an implant. Four animals were sacrificed after 6 months of healing. The remaining four animals received a second implant in the side with a space-making device only and followed for another 3 months before sacrifice (Fig 38, 39). In paper III, a modified resorbable space-making device only was inserted in each maxillary sinus. The animals were euthanatised after 6 months.

In papers II and III, before surgery, the animals were kept in individual cages, with water and food ad libitum. For all procedures involved in the study, the primates were first sedated with ketamine hydrochloride (Ketamin™, Cristalia Produtos Químicos Farmacêuticos Ltd., Campinas, Brazil), 10 mg/kg body weight administered intramuscularly. Prior to surgery or any animal manipulation, general anesthesia was obtained using pentobarbital sodium (Abbott Laboratories North Chicago, Chicago, IL, USA), in a dosage of 30 mg/kg. The anesthesia was supplemented by local administration of 2% mepivacaine HCI with 1:100,000 epinephrine (DFL Ltd., Rio de Janeiro, Brazil). Prior to surgeries, the animals received dental prophylaxis and all the surgical sites were washed with 0.12% chlorhexidine gluconate solution (Periogard™, Colgate-Palmolive Ltd., São Paulo, Brazil). The surgeries were performed under sterile conditions.
Space-making devices

In paper II, all eight animals received a space-making device made from polylactide acid 70% and polyethylene glycol 30% (polylactide 70/30, Radi Medical System AB, Uppsala, Sweden), approximately 6 mm wide and 6 mm high (Fig 40).

In paper III, all six animals received modified shaped space-making devices, either H-shaped or star-shaped (Fig 41). The device was warmed up to 50°C in saline solution to shape it to the sinus floor anatomy and introduced into the maxillary sinus cavity in order to maintain the sinus membrane elevated (Fig 42, 43).

Surgery

In paper II, all eight animals received a space-making device, which was introduced into the maxillary sinus cavity in order to maintain the sinus membrane in an elevated position (Fig 44). One dental implant, was placed into the obtained space at one side (Fig 45). After 6 months of healing, four animals received a second
implant in the other sinus, which in the previous surgery had been implanted with the space-making device only (two-stage procedure). These implants were installed with no care for membrane elevation. In paper II, one dental implant, 3.75 mm in diameter and 8.5 mm in length (MKIII TiUnite, Brånemark System™, Nobel Biocare AB, Gothenburg, Sweden), was placed into the obtained space in the maxillary sinus.

In paper III, all six animals received modified space-making devices with two different shapes in order to maintain the sinus membrane elevated. (Fig 46)

The removed bone window was then repositioned and stabilized, always using with n-butyl-2 cyanoacrylate tissue glue (Indermil™, Henkel AG & Co. Düsseldorf Germany). (Fig 47)

**Radiography**

In paper II, all animals were subjected to coronal computed tomography (CT) scanning (Toshiba XvisionTM, Tokyo, Japan) after 6 months of healing to evaluate new bone formation.

**Resonance frequency analysis**

In paper II implant stability was measured at implant insertion and after 6 and 9 months of healing with RFA (OstellTM, Integration Diagnostics AB,
Göteborg, Sweden). On these occasions, a transducer was attached to each implant and measurements were taken in implant stability quotient (ISQ) units.

**Sacrifice and Specimens Post-Processing**

In paper II, four animals were sacrificed 6 months after the first surgery, and another four animals with the additional implants were sacrificed 9 months after the initial surgery. Overall, four one-stage implants were evaluated at 6 months, four one-stage implants were evaluated at 9 months, and four two-stage implants were evaluated at 3 months.

In paper III, all six animals were sacrificed after 6 months of the initial maxillary sinus surgery.

All the animals were anaesthetized with pentobarbital sodium associated with analgesics to undertake vascular perfusion with paraformaldehyde. The maxilla was retrieved en bloc and the surrounding soft tissues were detached. The specimens were trimmed and immersed in 4% paraformaldehyde in 0.1 M in sodium phosphate buffer (pH 7.4).

**Histological Preparation and Assessments**

All the specimens were dehydrated in a series of ethanol embedded in hard-grade acrylic resin (LR WhiteTM, London Resin Company Ltd, Berkshire, England) and polymerized in dry heat oven at 60°C under vacuum environment. The plastic blocks were mounted on glass slides.

In paper II, two buccal-palatine sections were taken from each implant (Microslice 2TM, Ultratec Inc., Santa Ana, USA).

In paper III, three buccal-palatine sections (anterior, central, and posterior) were taken from each sinus (Microslice 2TM, Ultratec Inc., Santa Ana, CA, USA). Only the central ground sections were examined.

All sections were stained with toluidine blue/pyronin-Y method and examined under a Leica DMLBTM microscope (Leica Microsystems Wetzlar GmbH, Wetzlar, Germany), equipped with a Leica Digital Camera DFC 300FX (Leica Microsystems Wetzlar GmbH).

**Histometric Analysis**

In paper II, histometric measurements were carried out using X10 object lenses and a coupled Leica QwinTM V3 software (Leica Microsystems Wetzlar GmbH, Germany). The analyses comprised measurements of the degrees of bone-implant contact and bone area both expressed in percentage.

**Statistics**

In paper II and III, no statistic tests were applied because of the low number of animals. In paper II, descriptive data were presented in plot charts with group means.
Results

Clinical studies

Paper I
Clinical findings

The complications found as a consequence of surgery can be summarised as follows (Fig 48):

_Minor complications_ - Minor complications at the donor site included hematomas, seromas, infections, and temporarily decreased skin sensitivity. Nine patients experienced minor hematomas, one a minor seroma, and one a minor superficial infection. The seroma was evacuated by aspiration. Hematomas did not require any treatment other than observation, and the infection was treated only with a change of wound dressings. Nine patients had decreased sensitivity on the lateral part of the thigh, corresponding to innervation of the lateral femoral cutaneous nerve branches. The sensitivity returned to normal within 1 to 6 months. Two patients had a minor change in hip contour, mainly owing to skin cicatrices rather than a change in bone contour.

_Major Complications_ - Three major complications were recorded in three patients: one iliac wing fracture and two neurologic injuries. The iliac wing fracture occurred 2 weeks post-operatively while the patient was lifting a heavy object; this resulted in an audible crack and profound pain. The fracture was treated nonsurgically and healed without sequelae. One patient experienced a burning sensation and tenderness in the buttocks starting immediately postoperatively and lasting for 4 weeks. Another patient had a postoperative gait disturbance, tenderness, and discomfort; these subsided somewhat in the first 3 months, but the tenderness and discomfort were still a problem after 2 years.

<table>
<thead>
<tr>
<th>COMPLICATIONS</th>
<th>MINOR (20)</th>
<th>MAJOR (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>hematomas, seromas, infections (9)</td>
<td></td>
<td>iliac wing fracture (1)</td>
</tr>
<tr>
<td>hematomas, seromas, infections with</td>
<td></td>
<td>neurologic injuries (2)</td>
</tr>
<tr>
<td>change in hip contour (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>decrease sensitivity (9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Quality-of-life questionnaire

Regarding donor site morbidity, 74% of the patients were pain-free within 3 weeks, whereas 15% patients had a prolonged postoperative period of pain lasting from a few weeks to several months, and 11% still had some pain or discomfort 2 years after the grafting surgery. For gait disturbance the figures were similar: 79% of the patients had no problem 3 weeks postoperatively; in the eight patients who still had pain after 2 years, three also experienced gait problems (Fig 49). When comparing the anteromedial harvesting technique with the superolateral technique, 17% had persistent pain for more than 3 weeks in the anteromedial group compared with 34% in the laterosuperior group (Fig 50). For gait disturbance the corresponding figures were 17% and 25%, respectively (Fig 51). In total, 44% of patients reported the need to use a cane or a crutch during the first post-operative week (37% for the

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anteromedial Group (n = 30)</td>
</tr>
<tr>
<td>Postoperative pain</td>
<td></td>
</tr>
<tr>
<td>For 2 d</td>
<td>8</td>
</tr>
<tr>
<td>For 4 d</td>
<td>1</td>
</tr>
<tr>
<td>For 1 wk</td>
<td>6</td>
</tr>
<tr>
<td>For 2 wk</td>
<td>5</td>
</tr>
<tr>
<td>For 3 wk</td>
<td>5</td>
</tr>
<tr>
<td>Prolonged (&gt; 3 wk)</td>
<td>5</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td></td>
</tr>
<tr>
<td>For 2 d</td>
<td>9</td>
</tr>
<tr>
<td>For 4 d</td>
<td>0</td>
</tr>
<tr>
<td>For 1 wk</td>
<td>6</td>
</tr>
<tr>
<td>For 2 wk</td>
<td>4</td>
</tr>
<tr>
<td>For 3 wk</td>
<td>6</td>
</tr>
<tr>
<td>Prolonged (&gt; 3 wk)</td>
<td>5</td>
</tr>
<tr>
<td>Support needed (cane, crutch)?</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>19</td>
</tr>
<tr>
<td>Yes</td>
<td>11</td>
</tr>
<tr>
<td>Exceeded expectations?</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>4</td>
</tr>
<tr>
<td>Yes</td>
<td>26</td>
</tr>
<tr>
<td>Would recommend?</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>Yes</td>
<td>28</td>
</tr>
</tbody>
</table>

Fig 49

Fig 50

41
anteromedial group vs 50% for the superolateral group). The difference between the two harvesting techniques regarding pain and gait disturbance was not statistically significant. The reconstructive treatment was better than expected for 86% of the patients, and 94% felt they would consider recommending the treatment to a close friend or relative. (Fig 49)

Paper IV
Clinical findings

Eighty-three (83) patients were followed for at least 1 year and up to 6 years after implant loading. One patient was lost to follow up after 3 years of loading. The implant survival rate was 98.7% as three of 239 implants failed in three different patients. Two failures occurred during prosthetic procedures before loading and one within the first year of loading. Two additional implants became rotationally mobile after connection surgery during prosthetic treatment. They recovered stability after an additional 2 months of healing. All 50 implants placed entirely in the residual bone were stable during the follow-up period (100%). Of the remaining 189 inserted implants, 179 protruded a minimum of 4 mm into the sinus cavity. A total of 11 perforations (11.5%) occurred during the elevation of the sinus membrane: six minor (<5 mm) and five major perforations (>5 mm). All but one implant inserted in the sinuses with membrane perforation (n = 25) were stable at the end of the follow-up period.

Radiographic findings

The average residual bone height in the lowest part of the maxillary sinus before implant/sinus membrane elevation surgery was 3.8 mm ± 1.6 (SD). The average residual bone height, calculated in all implant sites, was 5.7 mm ± 2.3 (SD). The calculated height of the intra-sinus new bone (NB), was 10.9 ± 2.2 mm on average after 6 months of healing, 11.5 ± 2.3 mm after 6 months of loading, 11.3 ± 2 mm after 1 year, 11.6 ± 2 mm after 2 years, 10.9 ± 2.6 mm after 3 years, 11 ± 3.3 mm after 4 years, 9.7 ± 2.4 mm after 5 years and 12.2 ± 1.9 mm on average after 6 years (Fig 52, 53). NB was significantly higher for group (ii), implants protruding more than 8 mm in the sinus cavity, after 6 months healing (P ≤ 0.009), after 6 month loading (P ≤ 0.010), after 1 year of loading (P ≤ 0.003) and after 2 years of loading (P ≤ 0.028) (Fig 54, 55). The sample size was too small from the third to
the sixth year follow-up for statistical analyses. It was not possible to perform bone measurements in all intra-oral radiograms for three main reasons: (i) the degree of bone mineralization was too low to detect the new bone level in the sinus (Fig 56) (ii) distortion of the film leading to deformation of the radiographic image (iii) difficult to visualise the apical part of the implant on the intraoral radiographic film. The average bone level as measured in the CTs was 5.9 mm ± 2.2 (SD) at baseline (n = 60) and 11.2 mm ± 2.5 (SD) after 6 months of healing (n = 65). Thus, the average NB was 5.2 mm ± 2.2 (SD).

The average marginal bone level (Mbl), measured from the implant/abutment junction (A/F), was +0.4 mm ± 0.9 (SD) after implant surgery, −0.3 mm ± 1.2 (SD) at abutment connection, −1.3 mm ± 0.7 (SD) after 6 months, −1.5 mm ± 0.8 (SD) after 1 year, −1.5 mm ± 0.6 (SD) after 2 years, −1.0 mm ± 1.8 (SD) after 3 years, −1.6 mm ± 0.6 (SD) after 4 years, −1.0 mm ± 0.8 (SD) after 5 years and −1.6 mm ± 0.7 (SD) after 6 years. (Fig 57,58)

To calculate measurement system error in radiographic analysis, data from

<table>
<thead>
<tr>
<th>Time</th>
<th>Bone level</th>
<th>S.D.</th>
<th>Range</th>
<th>N of measurements</th>
<th>N of patients</th>
<th>N of implants</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.4 mm</td>
<td>±1.0</td>
<td>-2.3 / 5.3</td>
<td>299</td>
<td>84</td>
<td>239</td>
</tr>
<tr>
<td>6 month heal</td>
<td>-0.3 mm</td>
<td>±1.3</td>
<td>-3.3 / 4.3</td>
<td>308</td>
<td>84</td>
<td>239</td>
</tr>
<tr>
<td>6 month load</td>
<td>-1.3 mm</td>
<td>±0.8</td>
<td>-3.5 / 2.6</td>
<td>230</td>
<td>84</td>
<td>237</td>
</tr>
<tr>
<td>1 yr load</td>
<td>-1.5 mm</td>
<td>±0.9</td>
<td>-4.0 / 1.5</td>
<td>263</td>
<td>84</td>
<td>236</td>
</tr>
<tr>
<td>2 yr load</td>
<td>-1.5 mm</td>
<td>±0.6</td>
<td>-2.9 / 1.1</td>
<td>117</td>
<td>44</td>
<td>110</td>
</tr>
<tr>
<td>3 yr load</td>
<td>-1.0 mm</td>
<td>±1.8</td>
<td>-3.3 / 4.6</td>
<td>44</td>
<td>22</td>
<td>49</td>
</tr>
<tr>
<td>4 yr load</td>
<td>-1.6 mm</td>
<td>±0.7</td>
<td>-3.5 / 0.0</td>
<td>28</td>
<td>13</td>
<td>31</td>
</tr>
<tr>
<td>5 yr load</td>
<td>-1.0 mm</td>
<td>±0.8</td>
<td>-1.8 / 0.8</td>
<td>12</td>
<td>11</td>
<td>26</td>
</tr>
<tr>
<td>6 yr load</td>
<td>-1.6 mm</td>
<td>±0.7</td>
<td>-2.6 / 0.4</td>
<td>20</td>
<td>6</td>
<td>14</td>
</tr>
</tbody>
</table>
10 randomly selected patients were used for analysis. A total of 259 measurements (121 for intra-sinus bone formation and 138 for MB resorption) of the implant to bone border on the radiograms were performed once by two different observers. The part-to-part variation between the measurements on the individual implants was estimated at 3.275. For reproducibility, the difference between the two observers was estimated at 0.224 while the intra-individual variation between the repeated measurements was estimated at 0.572. The measurement system variation was estimated at 0.796 (0.224 + 0.572) and the total variation at 4.071 (3.275 + 0.224 + 0.572). Thus, the measurement system variation was 19.6 % out of the total variation.

**Resonance frequency analysis**

The average ISQ value for all implants was 67.4 ± 6.1 (SD) at placement (n = 181), 66.4 ± 5.2 (SD) after 6 months of healing (n = 195) and 66.6 ± 3.6 (SD) after 6 months of loading (n = 142). There were no significant differences at any time point between implants entirely inserted in residual bone and those elevating the sinus membrane. (Fig 59)

<table>
<thead>
<tr>
<th>RFA</th>
<th>mean ISQ value</th>
<th>S.D.</th>
<th>n of measurements</th>
<th>n of patients</th>
<th>n of implants</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>67.5</td>
<td>±6.1</td>
<td>181</td>
<td>84</td>
<td>239</td>
</tr>
<tr>
<td>6 month heal</td>
<td>66.5</td>
<td>±5.2</td>
<td>195</td>
<td>84</td>
<td>239</td>
</tr>
<tr>
<td>6 month load</td>
<td>66.5</td>
<td>±3.6</td>
<td>142</td>
<td>84</td>
<td>237</td>
</tr>
</tbody>
</table>

**Experimental studies, paper II and III**

**Surgery**

In paper II, in one animal the sinus membrane elevation procedure caused extensive rupture of the membrane in both sides because of the presence of several septas. In eight cases, small membrane perforations (less than 1.0 mm) occurred without major clinical complications.

In paper III, Sinus membrane perforations occurred in 5 out of 12 treated sinuses. All of them could be considered minor perforations (less than 2 mm) and were treated by folding the membrane in, as a consequence of elevation, before the device was installed.

**Post surgical findings**

In paper II, the postoperative period was uneventful and the animals were healthy throughout the follow-up time. One implant was found mobile and was removed after 6 months of healing. All other implants maintained their stability during the entire experimental period.

In paper III, the postoperative period was uneventful, and the animals were healthy
throughout the follow-up time.

During examination of the anatomical specimens we found that the space-making devices were displaced from their original positions in the sinuses. (Fig 60)

Radiographic findings

In paper II, CT examination was not able to demonstrate the presence of mineralised bone after 6 month of healing.

Resonance frequency analysis

In paper II, implant stability measurements revealed firm primary stability for both simultaneous and delayed placement of the implants, 66.0 (standard deviation [SD] ± 4.7, n = 8) versus 67.0 (SD ± 1.2, n = 4). The follow-up measurements of the simultaneously placed implants showed a slight decrease of stability to 65.4 ISQ (SD ± 4.9, n = 7) after 6 months and 64.7 ISQ (SD ± 3.1, n = 3) after 9 months. The delayed implants showed a more marked drop to 60.3 ISQ (SD ± 5.6, n = 4). (Fig 61)

<table>
<thead>
<tr>
<th>animal</th>
<th>RFA</th>
<th>One-stage</th>
<th>Two-stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>baseline</td>
<td>6 months</td>
<td>9 months</td>
</tr>
<tr>
<td>1</td>
<td>70</td>
<td>68</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>62</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>70</td>
<td>64</td>
</tr>
<tr>
<td>4</td>
<td>74</td>
<td>56</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>67</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>66</td>
<td>66</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>61</td>
<td>lost</td>
<td>lost</td>
</tr>
<tr>
<td>8</td>
<td>62</td>
<td>69</td>
<td>-</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>60.4 (4.7)</td>
<td>65.4 (4.9)</td>
<td>64.7 (3.1)</td>
</tr>
</tbody>
</table>

Histological findings

The devices seemed well tolerated by the surrounding tissues, as no signs of inflammatory reaction could be detected in any of the cases. No signs of material resorption were noticed during the whole experiment.

The repositioned bone flaps were found in position and well-healed in all specimens. There were no signs of remaining tissue glue or adverse tissue reactions such as infiltrate of inflammatory cells at these sites. (Fig 62)

In paper II, in the group with space-making device only, no or only minor bone formation could be observed under the devices. As shown in figure 63, after 6 month of healing, an empty space in the center of the sinus and isolated segments of the space-making device were the main histological findings. The tip of legs from the devices were found partially bone integrated in the sinus walls.

In the group with space-making device and simultaneous implant placement
(one-stage procedure), as shown in figure 64, the sinus membrane was always captured outlining the implant surface and a process of new-bone formation could be seen bridging the implant and the sinus membrane. The space between the implant surface and the sinus membrane seemed to create the required conditions for new-bone deposition after 6 (Fig 65) as well as 9 months (Fig 66). In some areas, the bone was also found in direct contact with the device’s outer surface as a consequence of a close proximity with an intact sinus membrane. (Fig 67)

In the group with space-making device and delayed implant placement (two-stage procedure), for the implants installed 6 months after space-making device installation, the implants became osseointegrated solely at the residual bone. Part of the implants was immersed in fibrous tissue (Fig 68) after 3 months of healing.

The quantitative analyses (histomorphometric measurements) of the
implants showed lower degrees of bone contacts and bone area filling the threads for the two-stage implants compared to the one-stage implants.

In paper III, invariably, the Schneiderian membrane was found in intimate contact with mineralized tissue (Fig 69). New bone formation was a common finding in all sinuses irrespective of the type of device. As a general rule, trabecular bone originating from the sinus periphery was projected into the center (Fig 70) in the vast majority of the cases. The trabeculae exhibited different stages of bone deposition, typically a mature pattern outlined by newly formed bone, or newly formed bone surrounding fat cells (Fig 71). Even in regions where the soft tissue predominated, mineralized islands (Fig 72) could be captured, indicating an ongoing and diffuse process of bone formation within the sinus cavity. An important histological finding in many specimens was the presence of marrow-like tissue in the center of the sinus, characterised by a loose connective tissue and the presence of vessels, fat cells, and hemopoietic cells close to forming trabeculae (Fig 73). The device’s surface was frequently found separated from the bone tissue by a thin layer of soft tissue featuring foreign-body giant cells and macrophages (Fig 74) in close proximity with the device.
Bone augmentation of the maxillary sinus floor was first described by Tatum (1977, 1986), Boyne & James (1980) and Wood & Moore (1988).

These authors, after the creation of a lateral bone window for the access to the maxillary sinus and the lifting of the Schneider membrane, suggested the use of autologous bone graft. Several other authors have documented the use of autologous bone as grafting material. Initially, the donor sites were mainly suggested as extraoral; iliac crest (Kahnberg et al. 1989; Ellis 1991; Nyström et al. 1993, 1997; Raghoebarg et al. 1993; Lundgren et al. 1997), calvaria (Tuslane 1999), and tibia (Marchena et al. 2002). Obviously, an approach requiring a second surgical site makes it far more invasive. A second extraoral surgical site necessarily requires general anesthesia and hospitalization of the patient, with a significant increase in economic and biological costs (Marx & Morales 1988; Arrington et al. 1996; Kalk et al. 1996; Marchena et al. 2002; Mischkowski et al. 2006). For this reason, in the case of local bone reconstructions, such as those for sinus floor elevation, authors started to suggest the use of intraoral donor sites (Wood & Moore 1988; Lundgren et al. 1996; Misch 1997; Nkeke et al. 2001, 2002).

Thanks to ease of accessibility and the availability of large bone quantities, the iliac crest is one of the most commonly used extraoral sources of bone for reconstruction in the maxillofacial region. Both cancellous and corticocancellous grafts can be obtained from this donor site with moderate morbidity. Complications specific to the ilium donor site include gait and/or neuro-sensory disturbances, the formation of seromas, trauma to the abdomen, fracture of the ilium, and hernia. In a retrospective review of 414 consecutive orthopaedic patients in whom bone was harvested from the anterior or posterior ilium, Arrington and colleagues found an incidence of major complications in 6%. The complications regarded vascular injuries, nerve injuries, deep infections, deep hematomas, iliac wing fractures, and donor defect hernias.

In paper I, we compared two different iliac crest harvesting techniques with focus on the donor site morbidity and the rate of complications. The classical anteromedial technique (Blomquist & Turvey 1992) was compared to a lateral-superior harvesting approach to iliac crest. The latter technique was chosen in order to have access to cortico-cancellous grafts with a higher portion of cortical bone. (Fig 23, 24)

Bone resorption in the initial healing of iliac crest bone grafts was found to be pronounced (Johansson et al. 2001). A mean resorption rate of 47% was found in the first 6 month of healing using bone harvested from the anterio-medial site. A latero-superior approach, with a main cortical graft component, might lead to less resorption in the graft healing period (Nyström et al. 1995).

However, the lateral-superior approach adds the risk of more invasive surgery
as a larger area of the iliac crest is exposed in order to obtain mainly cortical bone.

We found that three patients had major complications: one iliac wing fracture and two neurologic injuries. The iliac wing fracture occurred in a patient in whom the bone was harvested using the anteromedial approach, with a large corticocancellous bone block harvested, leaving a thin residual rim of the external surface attached to the gluteal muscles. The fracture of the thin rim was verified by radiography. This complication could probably have been avoided by stripping off the most superior positioned middle gluteal muscle fibers attached to the thin bone rim.

One of the two patients with a neurologic complication had a burning sensation in the buttocks that lasted for 4 weeks. The complication was probably caused by an injury of the lateral cutaneous branches of the subcostal and iliohypogastric nerves, following excessive soft tissue retraction in the area of the tubercle. The pain was intense in the immediate postoperative 4 weeks but subsided during the following 6 months. This patient was referred to a pain clinic, and she was offered local anaesthetic and corticosteroids to block the nerve. She decided to refrain from any further treatment, and at present she is fully recovered.

According to Marx and Morales (1988), the lateral cutaneous branches of the subcostal and iliohypogastric nerves are the most frequently damaged nerves during iliac crest bone harvesting owing to retraction injury in the tubercle area.

The second patient with a neurologic complication had a long-term gait disturbance. The persisting symptoms were most pronounced when the patient was taking long walks and when she was driving the car. This patient was also referred to a pain clinic as well as an orthopaedic clinic. Except for radiologic and physical examinations, she only underwent repeated nerve blockings with a local anaesthetic in combination with corticosteroids in the insertion area of the femoral quadriceps muscle. The patient was temporary relieved of the symptoms; however, she still complains of the problem but has refused any further invasive intervention.

Both patients with neurologic complications had undergone bone harvesting using the superolateral approach.

Twenty patients (29%) experienced minor complications. Eleven of the patients had hematomas, seromas, or superficial infections. Nine patients had a temporarily decreased sensitivity on the lateral part of the thigh (Fig 48). These 20 patients were equally distributed between the anteromedial and the superolateral groups. Marx and Morales reported that 38% of their patients who underwent the anterolateral approach to the iliac crest experienced temporary decreased skin sensitivity. Donor site morbidity can be divided into short-term, temporary, or prolonged complications, depending on the duration of the morbidity. The majority of our patients were without pain or gait disturbance within 3 weeks (short term); temporary morbidity lasted from 4 weeks to several months. Eight of our patients experienced some pain for 2 years or longer (prolonged), and among these patients, three also reported gait problems. None of the patients reported persistent gait problem without pain. There was an increased tendency of temporary donor site pain and gait disturbance in cases of superolateral harvesting compared to those of anteromedial harvesting (Fig 49), but for the prolonged complications (2+ yr), there was no difference between the groups.
Marx and Morales found that 42% of their patients who had bone harvested from the anterior ilium via a lateral approach experienced gait disturbance on the tenth day; this corresponds to short-term morbidity in the present study. They also found that after 8 weeks, 16% experienced gait disturbance, which is similar to the 21% temporary morbidity in the present study. One could expect the anteromedial approach to produce less pain and gait disturbance than the laterosuperior approach due to the different amounts of bone harvested. On the other hand, surgical trauma per se can cause soreness in the surrounding soft tissue resulting in temporary donor site morbidity. Marx and Morales found much less gait disturbance and pain of shorter duration with posterior iliac crest bone harvesting compared with anterior iliac crest bone harvesting. In the present study, the tendency in the difference in duration of pain and gait disturbance between the different approaches to the anterior iliac crest is not statistically significant (Fig 49, 51). Regarding major and minor complications, there was no difference between the two groups.

Many factors are important when considering treatment outcomes of the rehabilitation process from an edentulous situation (wearing a removable denture) to one involving endosseous implants and a fixed bridge. Morbidity of the donor site is one. Other factors of importance are the patient’s degree of disability from the edentulous situation and the psychological and social impact of oral rehabilitation. Quality of life is an expression of this phenomenon. The vast majority of the patients felt that the treatment results were better than expected and that the impact of rehabilitation on their quality of life was strong. Oral dysfunction with regard to speech, chewing, mouth opening capacity, and eating was reported by the majority of the patients prior to treatment. The oral function improved significantly through rehabilitation. In addition, the absence of teeth had negatively affected the facial appearance and recreation/social activities for the majority of the patients, and the rehabilitation resulted in an improvement in the quality of life for the vast majority. (Fig 75)

Other authors used questionnaire to investigate morbidity and patient satisfaction after autologous bone harvesting and reconstruction (Kalk et al. 1996; Stellingsma et al. 2003). Kalk et al retrospectively evaluated the morbidity of bone harvesting from the inner table of the anterior iliac crest and patient satisfaction after treatment. Donor sites were evaluated using the following three methods: a survey of the medical record, a mail-in questionnaire, and a standardised physical examination. The questionnaire contained multiple choice questions about duration and severity of postoperative pain at the donor site, meteorotropism, sensory loss, use of crutches, duration of subjective rehabilitation, the patient’s perception of the surgical scar, comparison between postoperative symptoms at the donor and recipient sites, and the patient’s acceptance of the procedure. Pain severity was graded on a visual analog scale (0 representing no pain, 10 representing severe pain). According to 13% of the patients, the postoperative course was in accordance with their expectations, 71% stated that the postoperative course was better than expected, and 16% said that it was worse than expected. Postoperative pain at the donor site was experienced by 32 patients. In 15 patients the pain lasted less than a month and in nine patients the pain lasted for 1 to 3 months. To estimate the subjective acceptability of the bone harvesting, the patients were requested to
judge the procedure using a number between 0 and 10, with 0 indicating “very bad experience” and 10 “no problems at all.” The judgment averaged 8.4. The time from harvesting to evaluation ranged from 1 to 4 years.

Stellingsma et al. (2003) carried out a study on patients’ satisfaction and psychosocial aspects for three different edentulous mandible rehabilitation modalities by means of a questionnaire. In this prospective, comparative study, jaw edentoulism were treated with transmandibular implants according to Bosker (1991), augmentation of the mandible followed by four endosseous implants and the insertion of four short endosseous implants. Denture satisfaction, psychosocial aspects and experiences during the surgical phase were assessed with a battery of questionnaires before treatment and 12 months after placement of the new overdenture. Differences amongst the three groups were not significant. However, in terms of discomfort and pain during the surgical phase as well as the length of this phase (at least 6 months), the least favourite option of the three modalities studied was augmentation using an autologous bone graft from the iliac crest, followed by the insertion of four endosseous implants 3 months later.
In paper I, Quality-of-life questionnaires were delivered to patients two years after grafting surgery. This time span was decided to be sure that any presence of pain or discomfort at the time of questionnaire could be considered permanent. On the other hand, it may be considered that questionnaire delivered after such a long time can create a time bias.

In the protocol used today for iliac crest bone grafting, a careful selection of patients are made prior to surgery; obesity, spinal and/or hip pain/tenderness are exclusion factors. Less invasive surgical technique based on minimal incision in the skin and subcutaneous tissue, followed by the tunnel dissection technique for access to the cortico-cancellous graft area, result in a reduction of the morbidity. The vast majority of patients subjected to iliac crest harvesting surgery are able to walk on the first post-operative day.

Other authors, as noted above, investigated the morbidity of intraoral donor sites.

Intraoral donor sites have to be considered a more limited source of autologous bone compare to extraoral sites. Nevertheless, the amount of bone that can be harvested is enough for local reconstruction, such as for maxillary sinus floor augmentation.

There are two principal intraoral sources of bone; the chin and the mandibular ramus.

It is preferable to harvest bone from the mandibular ramus rather than the mandibular symphysis as the former results in fewer complications, less morbidity, no facial contour changes and easier postoperative care. Patient satisfaction for retromolar bone harvesting is between 8.5 and 9.3 on a 10-point scale, and all patients stated that they would be willing to repeat the procedure when necessary (Raghoebar et al. 2007). It is also possible to obtain enough bone from the mandibular ramus for bilateral maxillary sinus augmentation, though it is difficult to obtain enough bone for the procedure when harvesting from the mandibular symphysis (Clavero and Lundgren 2003). It is also reported that the amount of bone harvested from the mandibular symphysis is directly proportional to the rate of morbidity and complications, whilst the volume of bone harvested from the mandibular ramus does not seem to be related to the morbidity or complications experienced (Clavero and Lundgren 2003). The ascending mandibular ramus is considered as the first choice, due to fewer consequence of morbidity (Clavero & Lundgren 2003; Raghoebar et al. 2007).

Even if autologous bone grafts are considered the gold standard for bone reconstruction, the need for a source of bone to harvest with the risk of an increased morbidity, prompted researchers to look for other solutions. The use of bone substitute that eliminate donor site morbidity-related risks was further investigated.

In a systematic review, Pjetursson et al. (2008) concluded that maxillary sinus floor augmentation using a lateral approach and various grafting materials is a well-documented procedure with good clinical outcomes.
Other authors have suggested and documented that the mere elevation of the maxillary sinus membrane at the time of implant insertion is a successful approach for bone reformation and implant survival, both in preclinical (Palma et al. 2006) and clinical studies (Ellegaard et al. 1997, 2006; Lundgren et al. 2004; Hatano et al. 2007; Thor et al. 2007; Sohn et al. 2008; Borges et al. 2010). In paper IV, 96 maxillary sinuses in 84 consecutive patients treated with mere membrane elevation, confirmed these results. Radiographic evidence of bone formation and a high implant survival rate were observed during 1–6 years of loading after sinus membrane elevation and placement of dental implants without the use of any adjunctive grafting materials. In a long-term follow-up, Ellegaard et al. (2006) described a technique in which, after traditional lateral access to the sinus, the created bone window was rotated inwards and the implants were inserted without the use of any additional material. The authors showed a survival rate of 98.1%, 91% and 85.4% after 1, 5 and 10 years, respectively, for implants inserted using a two-stage submerged approach and a corresponding survival rate of 98.5%, 88.7% and 79.9% for implants inserted using a one-stage non-submerged approach. Borges et al. (2010) in a prospective, controlled and randomised clinical study evaluated whether sinus membrane elevation and simultaneous placement of dental implants without autogenous bone graft can create sufficient bone support to allow implant success after 6 months post-surgically. The authors performed the sinus elevation bilaterally in 15 patients in a split-mouth design. They compared the mere sinus membrane elevation (test side) with membrane elevation and intra-oral autogenous bone graft. They found no statistically significant difference in new bone formation between the two groups. A significant positive correlation was found between the protruded implant length/bone gain. In addition, absence of sinusitis was correlated with implant survival.

In the meta-analysis by Pjetursson et al. (2008) the survival rate of rough surface implants, as used in the present study, ranged from 96.3% to 99.8% after 3 years of follow-up, which is similar to the results of the present study, i.e. 98.7% after 1–6 years. Interestingly, they found the lowest failure rate in studies where a membrane was used to cover the lateral window defect. The repositioning of the removed lateral bone flap as presented in this dissertation may have contributed to the good results by creating a closed compartment with better healing condition compare to the use of a barrier membrane. In a recent study, Sohn et al. (2010) further supported this theory. Through a histomorphometric analysis in rabbits, the authors compared sinus membrane elevation without bone grafts and repositioned lateral bone window (test group) with sinus membrane elevation with additional anorganic bovine grafts where the lateral bone window was substituted with a resorbable collagen membrane (control group).

After 1 week of healing, they found new bone formation starting not only from the elevating membrane but also from the floor of the replaced bony window in test group. This bone formation increased throughout the experimental period. They concluded that the replaceable bony window can work as an autologous barrier and accelerates new bone formation early in the healing phase compared with the collagen membrane over a bone graft in the maxillary sinus.

The implant failures in paper IV occurred after second-stage surgery, two during the prosthetic procedures and one within the first year of loading. This
indicates that the implants were insufficiently integrated and sensitive both to mechanical manipulation during prosthetic treatment and to loading (Esposito et al. 1998). Another two implants, in paper IV, became rotationally mobile during prosthetic treatment and were left to heal for an additional 2 months, thereafter both re-gained stability and successfully supported a fixed bridge throughout the study. This phenomenon is supported by an experimental study by Ivanoff et al. (1997), who reported that previously rotationally mobile implants reached the same level of stability after a period of healing as control implants.

The amount of the measured intra-sinus new bone (NB) should be considered within the limits related to the radiographic technique. Intra-oral radiograms transform a 3-D reality into a 2-D projection. For this reason, some information can be missed. In particular, it can be difficult to identify the new level of the intra-sinus NB in some radiograms taken in the early follow-up period due to the low level of mineralization. (Fig 56)

Nevertheless, intra-sinus bone formation was a constant finding at all implant sites and amounted, on average, to 5.3 mm 6 months after implant surgery. There was a positive correlation between the amount of bone formation and the implant length in the maxillary sinus, i.e. the higher the sinus membrane elevation, the more bone was created (Fig 54, 55). This is in line with the findings of Thor et al. (2007). They found more bone in sites with 2.0–5.5 mm of residual bone than in sites with more bone and drew the conclusion that this was due to longer implant length present in sinuses with less residual bone. In an experimental study, Sung-Han et al. (2008) placed an implant bilaterally in the maxillary sinus of six adult female mongrel dogs. The implants protruded alternatively 4 or 8 mm into the maxillary sinus after sinus membrane elevation. The authors found that the length of implant protrusion into the sinus cavity after sinus membrane elevation was not related to the height of new bone in the sinus. Their results may be related to the surgical technique used.

In paper IV, the average height in the thinnest part of the maxillary sinus floor before surgery was 3.8 mm with a range from 0.5 to 7 mm. All patients except for three had a residual crest of 6 mm or less. These three patients belonged to the first group of 10 patients where the inclusion criteria was 7 mm of residual bone or less, due to the concern of achieving sufficient primary implant stability.

Lundgren et al. in 2004, describing the technique of sinus membrane elevation, proposed a limit in the minimal residual crestal bone height in order to obtain implant primary stability. Therefore, this technique may not be considered useful in case of very resorbed sinus floor, less than 2-3 mm.

For this reason our group decided to investigate the use of a resorbable space-making device as an alternative to endosseous implants for maintaining the maxillary sinus membrane in the elevated positioning in cases where bone height was not sufficient to achieve primary stability for the implants.

In two patients we tested a device, made of polydioxanone (PDS). Six months later new bone formation was detected. The amount of new bone formation was less than expected in relation to the level of membrane elevation and the device was found to be completely resorbed. (Fig 76, 77, 78)

We decided to test space-making devices made with a polymer with slower resorption compared to PDS, in experimental study designs. The material chosen
was polylactic acid 70/30.

The histology from paper II showed an inflammatory-free tissue response and even some direct bone formation on the polymer material after 6 months of healing. However, it was obvious that the device used in the present study did not fulfill its purpose, as the membrane was found beneath the device in most of the histological sections. The reason for this finding may lie in a postoperative displacement of the device during the early stages following implantation. It could also be due to the configuration of the device resulting in a closed cage (Fig 40, 44) interfering with the physiologic exchanges between the sinus membrane and the blood clot during the following healing phases.

As a consequence, this may have resulted in a rupture of the original membrane. Nevertheless, in all cases except one, with or without sinus membrane perforation at the end of elevation surgery, the membrane could be histologically observed below the device.

The process of bone formation in the sinus cavity seemed to differ dramatically among the experimental sites. The use of the space-making device alone resulted in no or only minor signs of bone formation after 6 months of healing, even in cases where the sinus membrane was intact. When the device and the implant were placed at the same stage, the process of bone formation seemed to extend from the membrane towards the implant surface, resembling the outcomes previously reported by our group (Palma et al 2006). Differently, the two-stage procedure, where implant placement into the sinus was performed through the membrane, resulted in very few bone-to-implant contacts and no bone formation on the surface of the membrane, whereas membrane elevation always resulted in bone formation. Altogether, these data may suggest that the fresh coagulum delivered during sinus elevation surgery in the presence of rough titanium surface forms an important combination to enhance bone proliferation (Thor et al 2007). The so-called bone contact osteogenesis theory that has been widely described and confirmed in a number of studies supports this speculation (Palma et al. 2006; Davies 2003; Salata et al. 2007).

The outcomes of this first pre-clinical study (paper II) indicated that the lack of stabilization of the device underneath the Schneiderian membrane was a crucial factor for the unfavourable results. Another aspect to take into account is the fact that the space-making device did not meet the expected biological functions. The consistency of the material was rather rigid and this made the device resistant to fine re-shaping. The device’s surface was smooth and the legs large in width, a feature that increased the contact area with the sinus membrane. Considering the strong scientific evidence that the sinus membrane exhibits osteoinductive properties (Palma et al. 2006; Gruber et al. 2004; Srouji et al. 2009, 2010), the use of this device – to a certain extent – could hinder this effect.

The outcomes of paper II suggested: 1) material is needed that can be shaped depending on the sinus floor’s anatomical variations; and 2) the legs of the device should be permeable for cell and fluid exchange between the inner compartment of the sinus and the membrane. These modifications were developed by our group in order to accomplish our purpose.

In paper III, the results from the use of the modified device, corroborated with previous reports suggesting osteoinductive properties of the Schneiderian...
membrane (Gruber et al. 2004; Palma et al. 2006; Srouji et al. 2009, 2010). The sinus membrane elevation surgery triggered bone formation between the membrane and the secluded space in the sinus cavity.

A comparison between the outcomes results of paper II and from paper III revealed that the biomechanical modifications of the device resulted in improved biological performance: bone formation was evident.

On the other hand, the problem of keeping the space-making device in a stable position in the sinus recurred in paper III. This deserves further analysis as it may be the key factor for more predictable bone formation. The ideal space-making device may need anchorage to the neighbouring bone walls if it is to remain stable. The size of the sinus cavity in primates such as tufted capuchin primates is rather small. This anatomical condition made it difficult to achieve a correct stability of the device.

The small size of sinuses in primates and the presence of a high number of bone septa increased the risk of sinus membrane perforation during its dissection (and during the insertion of the space-making device into the sinus). Indeed, perforation of the membrane was obvious in some cases, but it was treated by folding the membrane inward, before the device was installed. In paper III, even in the cases of membrane perforation, bone formation could be seen within the sinus if one of the device’s leg was maintain the membrane in an elevated position. The capacity of the sinus membrane for self-repair was shown by Forsgren and colleagues.

A N-butyl-2-cyanoacrylate glue was used in these experimental studies to stabilise the replaced bone window after the insertion of the space-making device. Previous experimental studies have shown the possibility of using cyanoacrylate for oral hemostasis, fixation of soft and hard tissues, and closing sinus membrane perforation with low toxicity (Greer 1975; Amarante et al. 1995; Choi et al. 2006; Inal et al. 2006; Harper & Ralston 1983; Ahn et al. 1997; Shermak et al. 1998). Good clinical results using cyanoacrylate in osteosynthesis fixation of mandibular fractures were also reported (Mehta et al. 1987). An intact lateral sinus wall was found in the retrieved specimens of these two studies, which indicates that the cyanoacrylate glue did not interfere with the bone healing process. A recent experimental study by our group confirmed good bone tissue healing when cyanoacrylate glue was used for onlay bone graft fixation (de Olivera Neto et al. 2010).

The results of these preclinical studies indicated that the concept of creating new bone with a space-making device to maintain the sinus membrane elevated can be explained by the principles of guided-bone regeneration (Dahlin et al. 1988; Nyman 1991). However, further studies are required to establish a protocol for space-making devices with improved stability inside the maxillary sinus with the aim of obtaining clinically applicable results.

Parallel to the experimental studies reported in paper II and III, we gained more and more clinical experience with the technique of sinus membrane elevation and simultaneous placement of implants. As a consequence, it was possible to insert implants with a sufficient primary stability also in sites where the residual bone
height was even less than 1 mm (Fig 79, 80, 81, 82). It seems that the minimal requirement for achieving primary stability is the presence of a cortical bone layer. In all of the 96 consecutively treated maxillary sinuses, sufficient implant stability was obtained without the need to carry out conventional sinus elevation using bone graft or bone substitute. In the present study, we used three different implant types. According to the manufacturer, two types can be classified as Regular Platform, 3.75mm in diameter, and one type as Wide Platform, 5 mm in diameter. The first two regular platform types differ in terms of surface configuration and outer shape design. In the situation of minimal height of the residual crest, there was no space to submerge the implant head, which in some cases, resulted in an early cover screw exposure (Fig 83). None of the early exposed implants failed during
the follow-up period. Nevertheless, in some cases, it was noted that if a cover screw exposure occurred during the post-surgical six month healing period after sinus membrane elevation surgery, an increased marginal bone resorption was observed. (Fig 84, 85)

The amount of bone mineralization, detected in the radiographs, seemed to increase with time. In general, NB was more easily distinguished after 1 year and later than on the earlier radiographs. It seemed that the longer the follow-up period, the easier it was to identify the new sinus floor level (Fig 56). This phenomenon is most likely related to ongoing bone formation and remodelling, resulting in a denser, more radiopaque bone with time (Schenk 1994). According to Wolff’s law (Wolff 1892; Treharne 1981), bone changes its microscopic texture as a reaction to functional demands. New mineral apposition could therefore occur as a physiological reaction to functional implant loading (Romanos et al. 2003; Degidi et al. 2005). Owing to the absence of any radiographic methodology for evaluating changes in bone mineralization, this kind of findings require further investigations.

The use of a crestal approach for sinus floor augmentation in conjunct with implant placement has been described by several authors (Tatum 1986; Summers 1994; Bruschi et al. 1998). With this technique the maxillary sinus floor is fractured and the membrane carefully elevated through the use of osteotomes where after the implant is inserted. In a multicenter study, Rosen and co-workers (1999) reported that the implant survival rate dropped from 96% in sites with 5 mm bone height or more to 85.7% in sites with 4 mm or less. Ferrigno et al. (2006) reported an implant survival rate of 94.8% for 588 implants in 323 patients with a residual bone height between 6 and 9 mm. This technique could be considered for situations where an appropriate residual bone height is already present at baseline.
and only a minor augmentation of the sinus floor has been accomplished. In such cases, the use of short implants alone may be considered as an alternative for the rehabilitation of the posterior maxilla, as reported by Renouard and Nisand (2005).

With a traditional lateral approach to the maxillary sinus, the bone wall is rotated inside the sinus, interposing the elevated sinus membrane and the apical part of the implants. This is different to the technique of the present study, where the sinus membrane is in direct contact with the implants and the blood clot. In this situation, the sinus membrane may play a more direct role in the healing process. Gruber et al. (2004) concluded, in an in vitro study, that the sinus mucosa contains mesenchymal progenitor cells and cells committed to the osteogenic lineage, which can respond to BMP-6 and BMP-7 through an increase in their osteogenic differentiation. Kim et al. in 2009, analyzed human maxillary sinus membrane specimens collected from orthognathic surgery patients and cultured in an incubator. Their results suggest that there are multipotent mesenchymal stem cells (MSCs) in human maxillary sinus membrane tissue, which can be differentiated into osteoblasts under osteogenic induction. Srouji et al. (2009, 2010) confirmed that a genuine osteogenic potential is associated with the human maxillary sinus membrane. They reported that the histological analysis of in vivo subcutaneous transplants of human maxillary sinus Schneiderian membrane (hMSS) derived cells in athymic nude mice showed evidence of bone trabecula formation at an ectopic transplantation site. The authors concluded that the maxillary sinus membrane can contribute to the development of successful sinus augmentation techniques, in both in vitro and in vivo assays (2009). They also reported that, after subcutaneous transplantation of the folded sinus membrane with or without additional fibrin clot, new ectopic bone formation was detected. The close relationship between NB and the elevated sinus membrane sustained by the implant without the use of any grafting material has been histologically evaluated by Palma et al. (2006). Thus, the sinus membrane seems to play an important role in the bone healing process after elevation, thanks both to its osteogenic properties and its function as a barrier membrane protecting the blood clot after surgery. On the other hand, Scala et al. (2010) in a study on primates, investigated early healing after elevation of the maxillary sinus floor and simultaneous implant installation without the use of grafting materials. The authors applied a lateral access to the sinus where the osseous window was fractured along the osteotomy lines and rotated into the sinus cavity. The healing was histologically investigated after 4, 10, 20 and 30 days, in the area posterior to the implants. The authors found at days 4, 10 and 20 that newly formed bone originated from the sinus walls and septa, while there was no evidence of participation of the Schneiderian membrane in this process. Only specimens from 30 days of healing partly showed the sinus mucosa in direct contact with the newly formed bone. The present study illustrates that bone formation started from the residual walls and septa of the sinus, and that the Schneiderian membrane did not participate in the early phase of bone formation. The authors did not exclude the possibility that the sinus mucosa may be involved in bone formation in a later stage of healing. In their previous described study on rabbits, Sohn et al. (2010) histologically analysed bone healing phases 1, 2, 4, 6 and 8 weeks after sinus membrane elevation. They found new bone formation at the floor of the replaced bony window and at the elevated sinus membrane already after 1 week. This new
bone formation increased throughout the experimental period. More new bone formation was seen on the surface of the elevated sinus membrane and the floor of the repositioned bony window than at the central area of the augmented sinus. From this observation, the sinus membrane indicates its osteoinductive capacity, and this result corresponds with other previously described studies. The authors also interestingly underlined significantly higher and faster new bone formation in sinuses that had undergone sinus membrane elevation without bone graft (test side) compared to those that were augmented with additional anorganic bovine grafts (control group). One may speculate that the absence of additional grafting materials in test group can reduce the overall healing time, thus reducing the second phase in the healing of the wound (cleansing phase).

The influence of sinus membrane perforation on implant survival rate in sinus floor augmentation procedures has been reported in two studies, Ardekian et al. (2006) reported no statistically significant influence of membrane perforation on implant survival rate, which was 94.4% in the perforation group and 93.9% in the control group. Similarly, Karabuda et al. (2006) obtained an overall survival rate of 95.9% and concluded that there was no statistically significant difference between implants placed in conjunction with sinus membrane perforation areas and non-perforated sites. In paper IV, six minor perforations (<5 mm) and five major perforations (>5 mm) occurred. Of the 25 implants inserted in the sinuses with membrane perforation, only one failed, giving a survival rate of 96% for implants in perforated sites. The six minor perforations were left to heal, while the five major perforations were sutured to the adjacent bone wall. Bone formation was observed in all perforated sites. These results were confirmed in papers II and III, in which minor membrane perforation seemed to have no consequence on the NB. The sinus membrane has good healing potential, as shown by Forsgren et al. (1993), who demonstrated complete regeneration of the membrane after its removal. In the studies by Ardekian and Karabuda all the sinus membrane perforations were treated with the positioning of a resorbable collagen membrane in order to close the perforation. In papers II, III and IV all minor perforations were left to heal by themselves without the use of any additional treatment or device. As no graft material was used there was no risk of graft material replacement through the perforation, something which could initiate sinus inflammation.

The average marginal bone (MB) loss from placement to abutment connection was 0.7 mm. Another 0.7– 1.3 mm was lost during functional loading with a small difference from 1 year and onwards, indicating that MB resorption occurred mainly after implant exposure surgery and during the first year of loading (Fig 57, 58). This pattern of MB loss is in accordance with previous studies (Naert et al. 2001; Engquist et al. 2002; Åstrand et al. 2004; Lekholm et al. 2006 and Nyström et al. 2009). In a review of the literature it should be noted that MB loss was evaluated from the day of implant placement, while many studies use abutment connection or prosthesis connection as their baseline. If recalculating the results of the present study, the bone loss from abutment connection to the annual check-ups was between 0.7 and 1.3 mm, a level that is within the range of what has been reported before on the same implant design (Lekholm et al. 2006). We were not able to demonstrate any significant correlation between cover screw exposure and marginal bone loss even though this seems to be a risk factor of relevance in
clinical situations.

In paper II, the RFA measurements revealed high primary implant stability in both simultaneous and delayed approaches. The delayed implants showed a marked drop of almost 7 ISQ units during 3 months, which probably reflected unfavourable healing, as observed with histology. The simultaneously placed implants showed bone formation and a high stability was maintained throughout the study.

In paper IV, the RFA measurements confirmed that firm stability was achieved at implant placement with a mean ISQ value of 67, which is regarded as a high degree of stability and even considered as sufficient for immediate loading (Östman et al. 2005, 2008; Sennerby & Meredith 2008). The technique measures lateral stability and is sensitive to the density of the bone at the marginal portion of the implant. In the present studies, the residual crest consisted of dense cortical bone and reduced final drill diameters were used to ensure good stability, a feature that may explain the high values. Follow-up measurements showed no change of stability, which is expected when starting from such a high ISQ level as 67 (Sennerby & Meredith 2008).

In most cases, traditional sinus floor augmentation techniques consider a two-stage approach, first bone augmentation and then implant insertion. The above-described sinus membrane elevation technique is a one-stage approach procedure, which could reduce both the number of surgical events and the total treatment time.

Future research should focus on further simplifying the sinus membrane elevation technique and on obtaining a better understanding of the healing mechanisms.

Notwithstanding the small amounts of bone below the maxillary sinus, firm primary stability was frequently obtained in the cases where membrane elevation was used. The insertion torque value often rose to over 30 Ncm and the ISQ value was frequently more than 65. Such levels of insertion torque and ISQ values have previously been accepted as being high enough to allow for early/immediate loading of the implant (Östman et al. 2005, 2008; Sennerby & Meredith 2008). Early loading would obviously be advantageous for the patient and would also simplify the technique. Moreover, it can be speculated that early functional loading may positively influence bone formation in accordance with Wolf’s law (Fig 86). Even if early/immediate loading is not used, a one-stage surgery protocol could probably be used, thus reducing the number of surgical interventions to one. With healing abutments connected to the implants it would also be possible to monitor the development of stability by ISQ measurements. Other authors have suggested and tested a protocol for implants placed in healed sites whereby the implants were restored when the ISQ value reached 65 or higher (Bornstein et al. 2009). The one-stage surgery approach would also eliminate the problem of exposed cover screws and subsequent marginal bone resorption, which was observed in paper IV of the present thesis.

Another aspect that requires further investigation are the healing mechanisms and role of the sinus membrane on bone formation during the early healing phase.
As previously discussed, several authors have demonstrated the osteogenic potential of the maxillary sinus membrane (Gruber et al. 2004; Palma et al. 2006; Kim et al. 2009; Srouji et al. 2009, 2010). On the other hand, in a study on primates, Scala et al. (2010) reported that the sinus membrane is not involved in new bone formation during the first 20 days after surgery. They found that new bone originates from the sinus wall and from septa.

The influence of sinus membrane perforation on new intra-sinus bone formation would also be an interesting subject for further investigation. Most studies on sinus membrane perforations state that it is necessary either to close the perforation before continuing with the sinus augmentation procedure by suturing the membrane or to use resorbable membranes. In this thesis, perforations less than 5 mm was not treated in anyway. In spite of this, no negative influence on the clinical outcome could be seen. It is possible that the regenerative potential of the sinus membrane is so great that at least small perforations will heal spontaneously. However, further specific investigations are required.
Aims

The overall aim of this research project was to evaluate the surgical sequel after augmentation with autologous bone and to assess the possibility of creating bone at the maxillary sinus floor through membrane elevation and the insertion of endosseous implants without the use of bone grafts. A further objective was to evaluate the use of a bioresorbable device instead of endosseous implants.

To evaluate and compare donor site morbidity and complications when harvesting cortico-cancellous bone grafts from the medial table of the anterior iliac and when harvesting from the superior and lateral table of the anterior iliac crest.

To evaluate the psychological and functional acceptance of prosthetic rehabilitation with iliac crest bone grafts and dental implants.

To histologically evaluate the use of a space-making device for sinus membrane elevation and subsequent bone formation at the maxillary sinus floor in experimental studies.

To evaluate the long-term clinical results of sinus membrane elevation and the simultaneous placement of dental implants.

To radiographically evaluate intra-sinus new bone formation and its long-term stability following sinus membrane elevation.

To evaluate the long-term radiographic marginal bone level at implant sites following sinus membrane elevation.

To evaluate implant stability following sinus membrane elevation.
Conclusions

When harvesting a large amount of unicortical corticocancellous bone blocks from the superolateral site of the iliac crest using a “peel-off technique”, morbidity and complication rates do not differ significantly when compared to those of the traditional anterior medial approach.

Oral rehabilitation using maxillary reconstruction with bone grafts from the iliac crest and endosseous implants significantly improved oral function, facial appearance and recreation/social activities and resulted in an overall improvement in the quality of life of formerly edentulous patients.

The device used in this study did not trigger any important inflammatory reactions; when the sinus membrane was elevated, bone formation was constantly found to occur; and an ideal space-making device should be stable and capable of elevating the membrane so as to ensure an exchange between the membrane and the secluded space.

Maxillary sinus membrane elevation and the simultaneous placement of implants without using bone grafts or bone substitutes results in predictable bone formation with a high implant survival rate of 98.7% during a follow-up period of one to 6 years after loading.

Intra-sinus bone formation was a constant finding at all implant sites and amounted, on average, to 5.3 mm 6 months after implant surgery. There was a positive correlation between the amount of bone formation and the implant length in the maxillary sinus, i.e. the higher the sinus membrane elevation, the more bone was created.

The average MB loss from placement to abutment connection was 0.7mm. Another 0.7–1.3mm was lost during functional loading with a small difference from 1 year and onwards, indicating that MB resorption occurred mainly after implant exposure surgery and during the first year of loading.

The RFA measurements confirmed that firm stability was achieved at implant placement with a mean ISQ value of 67. This stability was maintained after six months of healing and after six months of loading.
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