On healing of titanium implants in iliac crest bone grafts

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ABSTRACT

Bone grafts and titanium implants are commonly used for surgical/prosthetic rehabilitation of the atrophic edentulous maxilla. The factors which influence bone graft healing and implant integration are not sufficiently understood.

The aim of this dissertation was to evaluate autogenous bone grafting and delayed placement of titanium endosteal implants for reconstruction of the atrophic maxilla, including the effects of different patient factors on bone graft healing and integration of titanium implants into grafted bone.

A total of 46 patients with severe maxillary atrophy received onlay- (n=35) or interpositional bone grafts (n=11) and 6 mo. later received 341 titanium endosteal implants. All bone grafts were harvested from the iliac crest. All patients received fixed dental bridges and were followed clinically and with radiographical examinations for 3 yr.

In Papers I and II, a total of 68 titanium microimplants were placed and retrieved from the bone grafts at various time points for histological analysis of the bone graft-implant interface. Integration was better after 6 mo. healing than placement in conjunction with bone grafting. Implant integration was similar for the two bone-grafting techniques.

In Papers III and IV, originally including 29 patients and 222 implants, implant stability was measured with resonance frequency analysis (RFA) at placement, abutment connection, after 6 mo. of loading (III) and after 3 yr. of loading (IV). Ten non-grafted patients measured at the same time points were used as controls (III). RFA showed equal implant stability in grafted bone vs. non-grafted bone (III). Stability did not change from the 6-mo. to the 3-yr. control. Cumulative survival was 90% after 3 yr. (21 implants failed). Thirteen implants were lost prior to loading and 8 during functional loading. The group of failed implants showed a lower primary RFA stability than those that remained stable for 3 yr. All patients received and maintained a fixed dental bridge throughout the study.

In Paper V, the graft volume changes (GVC) during the 6-mo. healing period prior to implant placement were studied in 30 patients using computerized tomography. Blood samples were taken from 25 patients in conjunction with bone grafting and were analysed for 13 haematological factors. Bone mineral density (BMD) was measured in 21 patients. Biopsies of the bone grafts were analysed for bone volume fraction (BVF). GVC (loss) was correlated with decreased BMD of the lumbar vertebrae L2-L4. There was no correlation between the haematological factors and GVC. Implant failure was not correlated with BMD, BVF or GVC.

This dissertation shows that surgical/prosthetic rehabilitation of the atrophic edentulous maxilla with autogenous iliac crest bone grafts and delayed placement of titanium implants after 6 mo. of graft healing is effective, reproducible and functional. RFA at placement may be able to predict later implant failure.

**Key words:** Edentulous atrophic maxilla, autogenous bone graft, endosteal implants, microimplants, resonance frequency analysis, implant survival, graft volume changes.
This dissertation is based on the following papers, which will be referred to in the text by their Roman numerals (papers reprinted by kind permission of journal editors):


INTRODUCTION

Background

Tooth loss leads to physiological resorption of the alveolar bone with morphological changes of the alveolar crest as a consequence. These changes can affect the relation between the maxilla and the mandible as well as the facial appearance (Cawood & Howell 1988; Cawood & Howell 1991; Tallgren 2003). For the individual patient tooth loss can lead to both functional and psychological disturbances such as impaired chewing ability (Locker 2002) and decreased self-esteem (Fiske et al 1998). A removable dental prosthesis supported by the residual alveolar crest offers an acceptable solution for many patients, while in others this treatment creates unacceptable functional and/or psychological problems (Trulsson et al 2002). Rehabilitation with a fixed dental prosthesis supported by osseointegrated implants was first described by Bränemark et al (1969) and has radically changed the possibilities for oral rehabilitation of the edentulous patient. Follow-up studies of prosthetic rehabilitation using endosteal implants show this treatment is predictable and offers the individual patient a superior treatment as compared with treatment with removable dentures (Adell et al 1990a; Lekholm et al 1999; Ferrigno et al 2002; Jemt & Johansson 2006). Prosthetic rehabilitation with implants improves health-related quality of life (Heydecke et al 2003), chewing function (Roumanas et al 2003) and esthetics (Cibirka et al 1997).

The degree of resorption in the alveolar process following tooth loss will determine the amount of bone available for placement of implants. In the edentulous maxilla, bone availability for implant placement is limited by the maxillary sinuses, the nasal cavity, the incisal canal and the physiological resorption of bone. To overcome the problem with insufficient bone volume in the atrophic edentulous maxilla, two different strategies can be used. Reconstruction with bone grafts in order to increase the available bone volume or use modified techniques for placing implants in the maxilla. Hallman (2001) reported on a group of patients with insufficient height and width in the alveolar process where narrow implants were placed with a cumulative success rate of 96 % after one year. Another possibility to achieve possibilities for implant placement is exemplified by Becktor et al (2005). The authors reported on 16 maxillary edentulous patients, who had 31 zygomatic implants and 74 additional dental implants placed prior to prosthetic reconstruction. The follow-up period varied from 9 to 69 months with a mean of 46 months. During the follow-up period 3 zygomatic implants had to be surgically removed due to recurrent sinusitis. Three of the 74 additional dental implants failed to integrate and were removed between abutment connection and definitive prosthetic loading. All patients had fixed bridges throughout the study period but postoperative complications with soft tissue and sinusitis occurred frequently. Implant placement in the pterygomaxillary area to support a supraconstruction has been reported by Balshi et al (1999). A cumulative survival rate of 88 % for pterygomaxillary implants was reported.

Treatment of the atrophic maxilla with bone grafts prior to implants is another alternative (Adell 1990b; Nyström 1993a; Lundgren et al 1997; Nyström et al 1997). The requirement for bone grafting prior to implant placement in the edentulous maxilla was radiographically analysed in a population in Malmö city (Petersson et al 1992). A total of 1800 randomly selected people born 1915, 1935, 1945, 1955 or 1960 were offered a clinical and radiological examination of the teeth and jaws. Of the 866 persons who participated 89 individuals were edentulous in the upper jaw and 67 accepted to be examined radiographically. One oral surgeon and one oral radiologist classified the jawbone shape and quality according to
Lekholm & Zarb (1985), the potential number and length of implants, and the need for further radiologic examination. The authors found that 20% of the maxillary edentulous patients would need bone grafting to enable implant treatment. In a radiological study on possible sites for implants in individuals aged between 20 and 70 years, Widbom et al (2000) found that the amount of edentulous maxillae suitable for implant treatment had decreased from 71% in 1983 to 51% in 1993. The authors speculated that the difference could be explained by an increasing number of maxillae with resorbed alveolar process. Although the number of edentulous people in Sweden is decreasing (Wänman et al 2004; Hugoson et al 2005), these findings indicate an increasing need for bone reconstruction procedures prior to implant placement in Swedish patients with edentulous maxillae.

Reconstruction of the edentulous atrophic maxilla prior to implant treatment

The overall goals of reconstructive preprosthetic surgery were presented in 2006 in a consensus report from the International academy for oral and facial rehabilitation (Cawood & Stoelinga 2006). The group declared; “The overall goals of oral and facial rehabilitation are to restore function and aesthetics, preserve the associated structures and contribute to the patient’s perception of improved quality of life (QOL).” With these goals in mind, the planning for reconstruction of the atrophic maxilla should focus on individual patient factors such as the shape of the alveolar process and the 3-dimensional relation between the maxilla and mandible. These factors are determined by the resorption pattern of the alveolar process and maxillary bone following edentulism.

The use of autogenous bone grafts has been the gold standard for reconstruction of the atrophic maxilla prior to implant placement. Reconstruction is also reported with allografts (Olson et al 2000), xenografts (Hallman 2002) or alloplastic materials (Szabó et al 2005; Zijderveld et al 2005) alone or in combination with autogenous bone or venous blood. All patients included in the present dissertation have had their maxillae reconstructed with autogenous bone grafts harvested from the anterior iliac crest.

Harvesting areas for autogenous bone grafts

The choice of bone graft harvesting site is primarily based on the quantity and density of the bone required for the grafting procedure, but the surgeon’s preference is also a factor. For the reconstruction of the atrophic edentulous maxilla both extra- and intra-oral harvesting areas have been described. The harvesting of autogenous bone from extra oral sites creates a second surgical area, which can prolong the operation time and increase the morbidity.

The anterior iliac crest is the most frequently reported harvesting area; it is associated with low morbidity (Arrington et al 1996; Kalk et al 1996; Mischkowsk et al 2006) and can offer a large quantity of bone (Cricchio & Lundgren 2003). Arrington et al (1996) reported of 414 consecutive cases of iliac crest bone graft procedures and divided the complications as minor or major. Major complications were: herniation, vascular injuries, nerve injuries, deep infections, haematomas or iliac wing fractures. Minor complications were: superficial infections, superficial seromas and minor haematomas. Minor complications occurred in 10% and major in 5%. Marx & Morales (1988) compared bone grafting from anterior and posterior iliac crest in conjunction with
reconstruction of mandibular defects and found a reduced morbidity and a greater quantity of bone available from the posterior iliac crest. One disadvantage with the posterior approach is that the patient has to be turned from a supine position to back position during the surgery. The use of intra oral harvesting sites (Jensen et al 1994; Raghoebar et al 2001) limits the surgical procedure to the oral cavity but has its limitation due to the available amount of bone. Intra-oral bone harvesting from the mandible can be done from the symphysis area and the ascending ramus. In a comparison of complications between the two harvesting sites, Clavero & Lundgren (2003) found that harvesting from the symphysis mandibulae was associated with impaired sensory function in the skin innervated from the mental nerve. The authors concluded that the results from the study favoured bone harvesting from the ascending ramus mandibulae. Misch (1997) compared mandibular symphysis bone grafts with bone grafts from ramus mandibulae. The architecture of the bone graft differed with its origin: mainly cortical bone comes from the ramus as compared with mainly corticocancellous bone from the symphysis mandibulae. The ramus donor site resulted in fewer complications.

Donovan et al (1994) and Iizuka et al (2004) reported the outer table of the calvarium harvesting area for reconstruction of the atrophic maxilla. The authors reported a low frequency of donor site morbidity (Donovan et al 1994) and that the postoperative need for additional analgesia was low as compared with bone harvesting from the iliac crest (Iizuka et al 2004). Iizuka et al (2004) also found that the bone resorption was less then the resorption reported from iliac crest. Jakse et al (2001) describe the proximal tibia as bone harvesting area prior to implant placement. Through a bony lid in the medial condyle of the proximal tibia a cancellous bone graft is harvested. Minor swellings and pain were the only postoperative complaints from the patients. The rib graft is another reported harvesting area for reconstruction of the atrophic edentulous maxilla (Köndell 1996).

**Bone grafting techniques for reconstruction of the atrophic edentulous maxilla**

The three main bone grafting techniques reported in the literature are:

1. Grafting to the floor of the maxillary sinus.

Boyne & James (1980) reported on 14 patients in whom the maxillary sinuses were reconstructed with autogenous bone grafts, composite of finely divided cancellous bone and marrow from the iliac crest. Three patients had blade implants placed after initial bone grafting healing. This technique has thereafter been reported in several studies where the grafted bone has been used both as blocks, bone cores and as particulated grafts (Jensen et al 1994; Lundgren 1997; Johansson et al 1999; Wannfors et al 2000; Raghoebar et al 2001; Becktor et al 2004). The technique is used for increasing the bone height in the posterior maxilla, but has its limitation in situations with a thin alveolar process in the posterior maxilla. Perforations of the sinus membrane normally heal without problems, but infections such as sinusitis may occur (Raghoebar et al 1999).
2. Onlay bone grafts where the bone graft is placed on the residual alveolar crest as a veneer graft or saddle graft or both.

Breine & Brånemark (1980) placed tibial bone grafts on the alveolar process in nine patients in order to increase the vertical alveolar bone height. The authors placed implants in the proximal tibia and after 3 months the implants and the surrounding bone was harvested and placed and fixed to the alveolar process using endosteal implants. The onlay grafting technique with horse shoe shaped bone grafts harvested from os ilium with endosteal implants used for the fixation of the graft was first described by Kahnberg et al (1989), Adell et al (1990b) and Nyström et al (1993a). This technique was further developed by several authors (Isaksson & Alberius 1992; Åstrand et al 1996; Van Steenberghhe et al 1997; Widmark et al 2001). The use of onlay grafting and delayed placement of implants was reported by Lundgren et al (1997). By using the technique both the height and width of the alveolar process can be restored. For this technique complications such as wound dehiscence and subsequently graft exposure (Kahnberg et al 1989) and postoperative infections (Bahat & Fontanesi 2001) have been reported.

3. Interpositional bone grafting in conjunction with a Le Fort I osteotomy is a surgical technique with an advancement of the maxillary bone to correct the intermaxillary relation with simultaneous interpositioning of a bone graft to increase the available bone for placement of the implants.

Sailer (1989) was the first to describe the technique with the report of his first 5 patients treated. The technique has its advantage in situations where there are severe sagittal and/or vertical discrepancies between the maxilla and the mandible. Several authors (Isaksson 1994; Krekmanov 1995; Li et al 1996a; Nyström et al 1997; Kahnberg et al 1999; Hallman et al 2005a) have later reported on the same reconstructive technique. The Le Fort I osteotomy with downfracture of the maxilla can result in complications such as fracture of the maxilla (Li et al 1996b), severe bleeding (Lanigan et al 1990), and temporary nerve disturbances (De Jongh et al 1986; Al-Din et al 1996; Boulox & Bays 2000).

In all these described reconstruction techniques the placement of endosteal titanium implants can be performed in the same surgical procedure as the bone grafting (one-stage) or after initial healing of the bone grafts (two-stage). The former has the advantage that it requires a shorter time for the total rehabilitation procedure and reduced number of surgical procedures. Using the latter technique, implants are placed in re-vascularized bone and the position and angulation of the implants can be optimized (Cawood et 1994; Blomqvist et al 1997).

**Bone, bone formation, bone remodelling**

Macroscopically, bone consists mainly of cortical (compact, dense) or cancellous (trabecular) bone. The cortical bone is dense and forms a compact layer outside all skeletal bones. The thickness of the cortical bone varies depending on the location. About 80% of the skeletal mass consists of cortical bone. The cancellous bone is porous, and due to its three-dimensional construction with trabeculae and spicules, the cancellous bone has a surface area
per unit of volume bone that is reported to be between 10 times (Kanis 1994) and 20 times (Buchwalter et al 1995a) greater than cortical bone.

Calcified bone contains organic matrix (about 25%), including cells (2–5%), water (5%) and 70% inorganic mineral, mainly hydroxylapatite (Sommerfeldt & Rubin 2001). The organic part consists of collagen (90%) and non-collagenous proteins (osteocalcin, osteopontin, osteonectin and bone sialoprotein). The organic matrix also contains several growth factors such as transforming growth factor-β family, insulin-like growth factor-1 and -2, bone morphogenetic proteins, and platelet-derived growth factor (Hughes et al 2006).

Mineralized bone can be classified as lamellar (mature) or woven (immature) bone. Woven bone is seen during bone formation; growth and healing. It has an irregular, disorganized pattern of collagen fibre orientation and osteocytes. Woven bone is found, for example, in the temporary callus of healing fractures. It has a rapid rate of deposition and turnover as compared with lamellar bone (Schenk 1994).

Lamellar bone is found in both cortical and trabecular bone. The lamellae run parallel to the trabeculae in trabecular bone and are arranged in osteons in cortical bone. The osteon consists of a Haversian canal in which blood vessels, lymphatic vessels and nerves run. Up to 20 concentric lamellar plates form a cylinder, with a diameter of 200–300 micrometer, around the Haversian canal. Canaliculi containing the cell processes of osteocytes extend in a radial pattern from the central canal. Cement lines define the outer boundary of each osteon. The central osteon canals branch, anastomose and join obliquely oriented vascular canals named Volkmann canals. With this network of canals, ions and fluid can flow freely directly adjacent to the mineralised matrix (Buchwalter et al 1995a; Sommerfeldt & Rubin 2001).

Externally, bones are enveloped by periosteum, except in the regions immediately around and within synovial joints, tendon joints or sesamoid surfaces. The periosteum contributes to the blood supply of the bone. The periosteum consists of a dense outer fibrous layer with fibroblasts, collagen, elastin fibers, nerves, and a microvascular network. The inner “cambium layer” is highly cellular. At skeletal maturity, the inner layer has almost completely disappeared (Buchwalter et al 1995a; Allen et al 2004).

Three different cell types can be found within bone and are involved in bone formation and resorption: the matrix-producing osteoblasts, the osteocytes and the bone-resorbing osteoclasts. The osteoblasts originate from mesenchymal cells and are the cells within bone that lay down the extracellular matrix and regulate its mineralisation. The time interval between extracellular matrix deposition and mineralisation is between 10 and 15 days. The osteoblasts line the bone surface together with their precursors as well as inactive bone lining cells.

Mononuclear cells derived from stem cells present in haematopoetic tissues can proliferate and differentiate into mononuclear osteoclast progenitor cells which enter the circulation and accumulate on the periosteum or endosteum. Osteoclast precursors can be stimulated to further differentiate and fuse to form multinucleated osteoclasts. The osteoclast differentiation and activation process is dependent upon close interactions with surrounding stromal cells/osteoblasts and influenced by systemic or local factors (Lerner 2004). The activated osteoclasts attach to fully mineralised bone and start the resorption process at sites called Howship’s lacunae (Sommerfeldt & Rubin 2001). The osteoclasts participate in conversion of immature woven bone into mature lamellar bone and in the continuous remodelling process which replace mature lamellar bone.
Osteoblasts which become entrapped in their own calcified matrix, change their phenotype and develop into osteocytes. The osteocytes account for 90% of all cells in the skeleton and remain connected with other entrapped osteocytes and with bone-lining cells (Sommerfeldt & Rubin 2001). The function for the osteocytes in the adult bone can be to regulate bone formation/bone resorption in orders to adapt to loading.

In embryogenesis, two types of bone formation/modelling are observed:

A. Intramembraneous formation occurs when mesenchymal cells differentiate directly into osteoblasts and then proceed to form bone by mineralisation of an organic matrix membrane. This process forms the facial bones and the vault of the skull.

B. Endochondral formation occurs when mesenchymal cells proceed via chondrocytes, which form cartilaginous templates for the future bones. The long bones, pelvis, vertebrae and the base of the skull are formed with enchondral formation (Hing 2004).

Thereafter, the bones are continuously remodelled throughout life, and the remodelling process is dependent on the interactions of the two cell lines: the mesenchymal osteoblastic lineage and the haematopoietic osteoclastic lineage (Raisz 1999). The remodelling of bone takes place in “bone multi-cellular units” (BMUs). The osteoclasts resorb a given volume of bone and the Howship’s resorption lacunae are filled with new bone from osteoblasts. The BMUs exist on the surface on cortical/trabecular bone as well as in the Haversian canals of cortical bone, but are more frequent in trabecular bone. Under normal conditions $1-2 \times 10^6$ BMUs are present in the adult skeleton (Lerner 2004). The bone resorption starts by dissolution of the inorganic components, mainly hydroxylapatite, crystal, and then the bone matrix is degraded. The inorganic and organic matrix is transported through the osteoclast which allows the osteoclast to keep close contact to the bone (Lerner 2000).

During the first year of life the rate of the remodelling of the skeleton approaches 100 per cent. But the rate declines to about 10 per cent per year in late childhood and continues at approx. the same rate, or more slowly, throughout life (Buchwalter et al 1995b).

**Bone healing**

Bone is unique in its ability to heal via the formation of new bone. All other vertebrate tissues heal by replacement with scar tissue. The repair process recapitulates the pathway of normal embryonic development of bone (Hing 2004). The cortex, the periosteum, the bone marrow, and the external soft tissue are involved in the repair process (Ozaki et al 2000; Dimitriou et al 2005).

Fracture healing can be divided into direct (primary) and indirect (secondary) fracture healing. Direct fracture healing (primary cortical fracture healing) occurs when there is anatomical reduction of the fracture. In order to restore mechanical continuity the cortex reestablishes new Haversian systems by formation of discrete remodelling units known as “cutting cones”. Vascular endothelial cells and perivascular mesenchymal cells provide the osteoprogenitor cells which will become osteoblasts. During this process, little or no periostal response is noted.

Indirect (secondary fracture healing) involves a combination of intramembranous and enchondral ossification with the subsequent formation of a callus. The intramembranous ossification involves a direct bone formation from osteoprogenitor and undifferentiated
mesenchymal cells from the periosteum. A callus, histologically described as a “hard callus” is then formed. Endochondral ossification involves the recruitment, proliferation and differentiation of undifferentiated mesenchymal cells into cartilage, which later calcifies and will be replaced by bone. The periosteum and external soft tissues contribute to the healing by producing an early “soft callus” (Dimitriou et al 2005).

After a fracture, the damage to the bone and the surrounding soft tissues forms a haematoma. The osteocytes nearest the to the fracture die, which leads to a local necrosis around the fracture. Macrophages remove tissue debris and fibroblasts synthesize extracellular matrix. Inflammatory cells release growth factors and cytokines; mesenchymal stem cells are recruited from bone marrow and periosteum. The mesenchymal stem cells proliferate and differentiate into osteoprogenitor cells. This leads to thickening of the periosteum and production of collars of external fracture callus around the fracture site. The osteoprogenitor cells that lie closest to undamaged bone differentiate into osteoblasts and form osteoid. The osteoid calcifies rapidly into bone. Osteoprogenitor cells lying farther away become chondroblasts and form cartilage. Angiogenesis is induced and almost as soon as the cartilage has been formed and the fracture site is stabilized it is replaced by woven cancellous bone via endochondral ossification. The uncalcified material is resorbed and new bone is deposited on the remaining spinicules of calcified tissue. The woven bone is remodelled into lamellar bone and normal bone marrow in the cancellous regions. Cortical bone is repaired by filling the spaces between the trabeculae with successive layers of bone (Frost 1989; Hing 2004).

**Autogenous bone graft healing**

The use of the autogenous bone graft for bone grafting procedures is described as “the gold standard” for bone grafting (Burchardt 1987), and the bone graft “should not only replace missing bone but also encourage osseointegration in the alveolar process by acting as a scaffold for guided bone growth into the graft” (Hing 2004).

Several different factors are important for the incorporation of the bone graft. The surgical technique was studied by Albrektsson (1980a). In a study on tibial grafts in rabbits he found that graft removed with minimal trauma showed a faster remodelling and a shorter revascularization time than a traumatized bone graft. The rate of revascularization of the bone graft is also dependent upon the architecture of the bone graft. A cortical bone graft is densely packed as compared with a cancellous bone graft. Albrektsson (1980b) found that the revascularization was faster in cancellous rabbit tibial bone than in cortical rabbit tibial bone. The revascularization in the cancellous bone graft was completed after 20 days, under special conditions due to end-to-end anastomoses between the vessels in the graft and the host. The vascular ingrowth into cortical bone followed the pre-existing Haversian and Volkmann canals, and the revascularization could be completed in 60 days.

The revascularization of the bone graft is also dependent on the vascular supply in the host area (Cutting et al 1990). Gordh (1998) studied the survival of onlay bone grafts in adult rats and found that the integration of the graft was excellent after exposure of the marrow of the host bed.

The importance of rigid fixation of the bone graft in order to maintain volume has been studied in sheep by Philips & Rahn (1988) and in rabbits by Lin et al (1990). Both groups of authors concluded that the rigid fixation of the bone graft was positive for volume
maintenance. The orientation of a bone graft can affect the integration, especially in situations with unicortical bone grafts. A cancellous bone graft is more porous than a cortical bone graft. If a unicortical bone graft is used as an onlay bone graft the cancellous part should be oriented against the recipient bed. Gordh (1998) found a “superior” integration of unicortical onlay bone grafts in adult rats when the marrow of the bone graft was in contact with the recipient bed.

The micro-architecture (relative cortical and cancellous composition) of the bone graft has greater importance for bone graft maintenance than the bone graft origin (Donovan et al 1993; Ozaki & Buchman 1998). On the other hand, Finkelmann et al (1994) compared samples from calvarial bone with samples from the iliac crest and vertebral body in 10 men at autopsy. The authors found significantly higher concentrations of growth factor IGF-II and TGF-β in calvarial bone and concluded that the increased concentrations of growth factors could lead to higher capacity for bone repair and graft retention.

Factors that affect the general bone metabolism also affect the healing of autogenous bone grafts. Several hormones are involved in the general bone metabolism. Parathyroid hormone and 1,25-dihydroxy vitamin D are two major calcium-regulating hormones. Calcitonin, growth hormone, glucocorticoids, thyroid hormone, estrogen and androgen are other examples of hormones which affect bone metabolism. Examples of diseases that affect bone metabolism are: hyperparathyroidism, hyperthyroidism, Pagets disease, osteoporosis and osteopetrosis (Raisz 1999).

The autogenous bone grafts are believed to stimulate new bone formation via three basic principles. *Osteogenesis* (1) - the autogenous bone graft consists of surviving bone-forming cells from the surface of the bone graft. A cancellous bone graft with its large surface area can provide such viable cells. *Osteoconduction* (2) - the bone grafts provide the three-dimensional structure which promotes healing of the bone tissue. *Osteoinduction* (3) - mesenchymal cells from the host are recruited to differentiate into osteoblasts under the influence of diffusible bone morphogenetic proteins (BMPs) (Goldberg & Stevenson, 1987). These three principles work more or less in concert. More than 20 BMPs have been identified. Examples of other growth factors found in bone are: transforming growth factor-beta (TGF-beta), Insulin-like growth factor-1 and -2 (IGF-1 and -2) and platelet-derived growth factor (PDGF) (Hughes et al 2006).

Goldberg & Stevenson (1987) described the different phases of cancellous bone grafting in dog: Hemorrhage and inflammation occur rapidly after bone grafting, and the bone graft becomes necrotic even if a few osteocytes survive and produce new bone. The necrotic bone is invadedged by host granulation tissue. The cancellous bone graft revascularizes early, which brings osteoblast precursors and osteoclasts to the graft. Bone graft resorption and new bone formation proceeds in parallel. Mesenchymal cells migrate into the graft and differentiate into osteoblasts and begin to produce new bone. In 3 months most of the original spongiosa is replaced by new bone. Osteoconduction is characterized by ingrowth of sprouting capillaries. Osteoblasts line the edges of the dead trabeculae and deposit osteoid on the dead bone. Haemopoietic cells accumulate within the transplanted bone and form a new, viable bone marrow. The graft is usually completely resorbed and replaced by viable new bone after six months.

Goldberg & Stevenson (1987) also described the different phases for cortical bone grafting in the canine: The early inflammatory changes are similar to those described for cancellous bone grafting. The rate of revascularization is slower and complete revascularization may not occur until 2 months after surgery. The vascular penetration results from peripheral osteoclastic
resorption and vascular infiltration of Haversian canals. The incorporation starts with resorption and appositional new bone formation proceeds slowly. Cortical bone grafts will remain an admixture of necrotic and viable bone.

Integration of titanium implants in bone

Implant stability in the bone at the time for placement, is one of the most important factors for osseointegration (Meredith 1998; Marco et al 2005; Raghavendra et al 2005). Zarb & Albrektsson (1991) defined the term osseointegration as “a process whereby clinically asymptomatic rigid fixation of alloplastic materials is achieved, and maintained, in bone during functional loading”. In situations with reduced implant stability, micromotions can occur which increase the risk for fibrous healing instead of osseointegration. The stability results from direct contact between the surrounding bone and the surface of the implant and can be divided into primary and secondary stability (Sennerby & Roos 1998). The former is achieved at implant surgery and is determined by the implant design, the surgical technique and the density of the bone. In the situation with reconstruction of the atrophic edentulous maxilla with autogenous bone grafts and titanium implants, the surgeon has several possibilities to improve the primary stability of the implant. One can increase the density of the bone graft with high contents of cortical bone (Cricchio & Lundgren 2003). An adapted preparation technique with reduced drill diameter can also be used; it will induce compression and thereby increase implant stability. Secondary stability is achieved after primary healing and is determined by the primary stability, bone formation, and remodelling in the interface between the implant and the surrounding bone. The surgeon has the possibility to improve the bone remodelling and bone formation in the interface by a prolonged healing time for the implant (Friberg 1999a).

The healing mechanisms behind osseointegration of an implant placed in bone are very similar to the mechanisms of bone fracture repair (Marco et al 2005). The bone tissue response to unloaded, screw-shaped titanium implants has been studied in several animal studies (Sennerby et al 1993a; Masuda et al 1997). After the implant is placed in the bone, it will be surrounded be a mixture of bone fragments, fibrin clot and red blood cells. During the first week mesenchymal cells and multinuclear giant cells are present in the area around the implant. After 7 days newly formed woven bone develops from the endosteal surfaces towards the implant. Newly formed woven bone is also found as solitary islands within the implant threads. The amount of bone increases and approaches the implant surface to fill the threads, and signs of remodelling of the woven bone are seen after 28 days for rats (Masuda et al 1997). For rabbits the remodelling process is seen after 6 weeks and is completed after 90 days (Sennerby 1993a).

When studying the interface between the titanium implant and the surrounding bone by transmission electron microscopy an unmineralized or partly mineralised zone is found. Sennerby et al (1992a, 1993b) studied titanium implants in rabbit tibia and found a 100 – 400 nm thick amorphous unmineralized layer which separated the implant from the surrounding bone. The authors also found a 100-nm wide electron dense line (lamina limitans) present at the border between the mineralised bone and the non-calcified amorphous layer. The findings with the amorphous layer and the lamina limitans-like line are also found in studies on the interface from implants placed in humans (Sennerby et al 1991). These ultrastructural studies indicate that the stability of the implant is mainly biomechanical.

There are not many clinical histological studies on the healing of titanium implants in autogenous bone grafts. Nyström et al (1993b) reported on a patient who died four months
after reconstruction of the atrophic edentulous maxilla with autogenous onlay bone graft and
titanium implants. Histological evaluation of the retrieved implants and surrounding bone
revealed incorporation of the bone graft but only minimal degrees of direct bone contact
with the titanium although all implants were clinically stable. Piattelli et al. (1997) reported on
a mandibular discontinuity case reconstructed with a nonvascularized iliac block graft.
Seventeen months later three titanium implants were placed in the reconstructed mandible.
After 10 months of loading one implant was retrieved and prepared for histologic
examination. Newly formed mature compact bone was seen in contact with the implant
surface. Jensen & Sennerby (1998) studied the healing of titanium microimplants placed in
grafted maxillary sinuses. Particulate autogenous bone grafts were compared with radiated
mineralized cancellous allografts. The use of particulate bone grafts resulted in the formation
of more viable bone than the use of an allograft. Normal bone formation and remodelling
occurred in the autograft specimens, whereas a mixed morphologic picture of nonviable bone
particles and connective tissue together with minor bone formation was seen in the allograft
specimens. The authors found the technique with microimplants to be a useful model for the
histological evaluation of the sinus graft-implant interface.

**Non-invasive test methods for assessment of implant stability and osseointegration**

In the clinical situation it is of interest to assess the biomechanical properties of the
bone/implant interface. Manual rotational stability testing, the Periotest® technique,
resonance frequency analysis (RFA) and insertion torque measurements are examples of non-
destructive intraoral testing methods. RFA and Periotest® have been suggested to assess
implant stability. Insertion torque measurements have been used for assessment of bone
density (Friberg et al 1999b; Johansson et al 2004), but the technique only assesses conditions
at the time of implant placement. Radiographs are useful for evaluation of marginal bone
levels and the periimplant tissue (Stridh 1985a). The clinical status of the marginal bone level
and the periimplant tissue can indicate if the implant is osseointegrated or not (Stridh 1985b).
A high positive predictive value for the identification of implant instability has been seen in
connection with the Brånemark implant system (Gröndahl & Lekholm 1997). On the other
hand, Nyström et al (1996) reported on a group of patients reconstructed with autogenous
bone grafts and titanium implants. Only three of 26 failing implants could be radiographically
diagnosed as non-integrated.

For evaluation of rotational stability of the implant the surgeon can use a screwdriver placed
on the cover screw or on the abutment and apply clockwise rotational force. If the implant is
stable and not associated with pain the implant can be considered as osseointegrated
(Albrektsson et al 1986).

The Periotest® technique (Schulte & Lukas 1993) uses a metal probe accelerated by an
electromagnet. The contact duration of the probe on the implant is measured by an
accelerometer and contact time is then related to implant mobility. However, the Periotest®
approach results in widely different data, and individual measurements have failed to reveal
whether an implant is osseointegrated or not (Albrektsson et al 2003).
Aparicio et al (2006) summarized the knowledge about the resonance frequency analysis (RFA). The RFA technique for implant stability measurement was first described by Meredith and co-workers (1996). The earlier versions of the technique made use of an L-shaped transducer that could be screwed to an implant or its abutment and excited over a range of frequencies, typically from 5 to 15 kHz. The response of the beam was analysed by a frequency-response analyser. At the first flexural resonance of the beam, a marked change in the amplitude and in the phase of the received signal was seen. The resonance frequency was identified in a plot of the frequency (Hz) against the amplitude (V) values. A prototype instrument has been used by the research group in a number of studies giving the results in Hz. One drawback with the technique was that each transducer had its own fundamental resonance frequency (RF) and that the RF of the same implant varied between transducers. In addition, a linear relation was found between abutment length and RF, and measurements with different transducers and of implants with different abutment lengths had to be calibrated before entering statistical analyses. Osstell™ (Integration Diagnostic AB, Göteborg, Sweden) was the first commercial version of the RFA technique and used transducers calibrated by the manufacturer. In order to compensate for abutment length, this had to be registered before performing measurements. RF measurements were now given in ISQ (Implant Stability Quotient) with values from 1 to 100, which were based on the underlying and calibrated RF of the transducer. Today is a wireless version of the technique available and makes use of an aluminium peg attached to an implant or abutment (Mentor™, Integration Diagnostic AB, Göteborg, Sweden). The peg is excited and the RF measured electromagnetically in ISQ units.

Early developmental work in vitro showed that RF was determined by the stiffness of the bone-implant complex as demonstrated by performing repeated measurements of implants placed in self-curing resin (Meredith et al 1996). The authors also found a linear relationship between exposed implant heights in an aluminium block, which indicated that vertical implant placement, marginal bone loss and abutment height influence RF. Meredith et al (1997) performed a longitudinal study with measurements of 56 implants in the maxilla of 9 patients and demonstrated an increase of implant stability from placement to abutment connection for all but two implants, which were judged as failed. The authors also performed measurements of 52 implants in 9 patients after at least 5 years in function in the maxilla, and found a significant relation between effective implant length (abutment length + bone loss) and RF. The data indicated an increase in stiffness of the bone-implant complex with time, except for the failed implants. Friberg et al (1999c) reported on a correlation between cutting resistance and primary RF values for maxillary implants. Repeated measurements indicated that all implants, irrespective of initial stability, reached similar RF values at abutment connection and after 1 year of loading. This could also be demonstrated as an inverse correlation between cutting torque and change of RF values from placement to abutment connection. RF values showed small changes over a 15-week period of time when implants were placed with one-stage technique in dense mandibular bone (Friberg et al 1999d). A small and significant decrease of stability was observed, which marginal bone loss and an increased effective implant length could explain.

The Osstell™ technique has demonstrated higher stability in mandibular bone as compared with maxillary bone (Balleri et al 2002; Barewal et al 2003; Bischof et al 2004; Balshi et al 2005; Becker et al 2005; Myiamoto et al 2005; Östman et al 2006). A correlation has been observed between bone quality (Lekholm & Zarb index 1985) and ISQ values by some investigators (Bischof et al 2004; Balshi et al 2005; Östman et al 2006), but not by others (Zix et al 2005). Myiamoto et al (2005) observed a strong correlation between cortical thickness, as
judged from CT scans, and initial ISQ values for 225 screw-shaped implants placed in upper
and lower jaws. Based on RFA measurements of 905 consecutive screw-shaped implants,
Östman et al (2006) reported that, apart from the factors discussed above, also gender,
implant diameter, and anterior/posterior position influenced primary stability. Interestingly,
Östman et al (2006) found decreasing stability with increasing implant length. This may be
explained by the fact that long Bränemark® implants have a reduced diameter in the coronal
direction to reduce friction heat. A similar observation was made by Miyamoto et al (2005).
The findings from Zix et al (2005) on measurements of maxillary ITI® implants confirmed
higher stability in male than in female patients. However, according to Bischof et al (2004),
implant position, implant length, implant diameter and vertical position did not affect the
ISQ values of 106 ITI® implants placed in mandibular and maxillary bone.

It has been observed that implants with low stability show a greater increase in stability with
time than implants with high stability (Friberg et al 1999c; Friberg et al 1999d; Barewal et al
2003; Nedir et al 2004; Becker et al 2005), indicating that differences in stability between
implants will diminish with time. This may be due to the fact that a similar bone density is
reached with time as a result of bone formation and remodelling.

For implants placed with one-stage surgery and immediately loaded implants an initial
decrease of implant stability is reported, which seems to recover within 2 to 3 months
(Barewal et al 2003; Glauser et al 2004; Balshi et al 2005). This most likely reflects a decrease
of the stiffness of the bone-implant complex as a result of remodelling.

As discussed above, correlations between effective implant length and RF values indicate that
the technique may be able to detect or discriminate between small changes of the marginal
bone height of the implants. In a recent clinical study by Turkyilmaz et al (2006), a correlation
was seen between marginal bone loss around mandibular implants and change of stability
from implant placement to the 6-month check-up. Consequently, increased bone loss
resulted in decreased ISQ values. However, no such correlation was observed between the 6-
month and the 12-month follow ups. The authors speculated that the effect of bone loss was
compensated for by increased interfacial stiffness as a result of bone formation and
remodelling.

**Follow up**

The use of well defined criteria for success is important for long-term evaluation of the
outcomes of reconstruction with autogenous bone grafts and endosteal implants. The
implants can basically be judged as either stable or mobile. A mobile implant is not
osseointegrated according to the definition and should be removed. Remaining implants
would then be classified as survivals. Albrektsson et al (1986) defined five criteria for implant
success:

1. An individual, unattached implant is immobile when tested clinically.
2. A radiograph does not demonstrate any evidence of peri-implant radiolucency.
3. Vertical bone loss is less than 0.2 mm annually following the implant's first year of
   service.
4. The individual implant performance can be characterized by an absence of
   persistent and/or irreversible signs and symptoms such as pain, infection,
   neuropathy, paresthesia or violation of the mandibular canal.
5. Thus, in the context of the 4 criteria above, a successful rate of 85% at the end of a five-year observation period and an 80% rate at the end of a ten-year period should be the minimum criteria for success.

A stable implant which meets all five criteria is judged as successful. A stable implant not meeting one or several criteria is classified as a survival. Albrektsson & Zarb (1993) further developed the classification of the implants into four categories: successes, survivals, unaccounted for and failures. Roos et al (1997) discussed the methods for evaluation and suggested that surviving implants should be classified into three success grades dependent upon the extent of the clinical and radiographic examinations.

**Implant failure and clinical consequences**

Single implant failures are more frequently seen than multiple losses after maxillary reconstruction (Lundgren et al 1997; Nyström et al 1997). In a situation where eight endosteal implants are placed after healing of the bone graft, a single implant failure will not have any consequence on the possibility of making a fixed bridge. Multiple implant failures are usually clustered in a few patients, both in grafted (Johansson et al 1999; Nyström 2004) and non-grafted maxillae (Jemt & Häger 2006). For the individual patient multiple implant failure is a severe clinical problem because it can preclude the possibility for a fixed bridge in the maxilla.

Failures can be classified as early or late failures (Esposito et al 1998a). Early failures appear prior to loading and are mainly caused by surgical trauma, infections or loading during healing. Late failures appear after loading of the implant and are mainly caused by excessive load on the implant/bone interface, peri-implant infection or technical problems. The consequences of early failures are dependent upon the localization and number of failing implants and have to be evaluated for the individual patient. Late failures may lead to reduced extension or even removal of the fixed prosthetic construction, which would require placement of new implants in order to attach the prosthetic construction at a later time.

Reconstruction of the edentulous atrophic maxilla with autogenous bone grafts in conjunction with or prior to, implant placement creates a situation in which the implant is placed in grafted bone and the long-term result are dependent upon the possibility of achieving osseointegration. In the literature, placement of titanium implants after initial healing of the bone grafts (Lundgren 1997; Nyström et al 1997) seems to result in higher implant survival than simultaneous placement (Adell et al 1990b; Nyström et al 2004). The literature also describes different bone grafting techniques prior to/in conjunction with implant placement (Jensen et al 1994; Krekmanov 1995; Åstrand et al 1996; Neyt et al 1997; Nyström et al 1997; Wannfors et al 2000). For better understanding of the healing process of titanium implants in bone grafts there is a need for controlled clinical investigations using histological and histomorphometrical analyses of the bone graft-titanium interface. With these analyses, it would be possible to evaluate the impact of timing of placement, length of healing period, and the impact of different bone grafting techniques. Achievement and maintenance of implant stability is essential for the long-term success of oral implant treatment. The situation with implant placement in a maxilla reconstructed with bone grafts constitutes a complex healing situation and involves revascularization and incorporation of the bone graft as well an integration of the implants.
At present it is not known whether implants in a bone-grafted maxilla will become as stable as implants placed in a non-grafted maxilla, and how stability changes over the long-term.

The reasons for multiple implant failures are important to identify in order to understand the background mechanisms and to avoid failures in future patients. Both local and systemic factors may significantly influence the outcome with implants in grafted bone. For instance, the vitality and density of the bone graft per se may affect the bone graft incorporation process and the integration of implants. It is also likely that factors related to the systemic bone metabolism affect on the healing and remodelling of the bone graft in the recipient site.

In non-grafted situations implant failure has been reported to occur more often in situations with low bone density and reduced volumes (Herrmann et al 2005). Reduced implant survival has been reported for shorter implants than longer (Sennerby & Roos 1998). Thus, with a reduced volume and density of the bone graft during healing, the risk for implant failures may increase.

It would be of interest to find prognostic factors for prediction of the outcome of a planned reconstruction of the atrophic edentulous maxilla. One reason for clustering of implant failures in a few patients may be related to general osteopenia/osteoporosis which then may serve as a significant prognostic indicator. Osteopenia/osteoporosis can be diagnosed with bone mineral density (BMD) measurements using dual energy absorptiometry (Kanis et al 1994). Blomqvist et al (1996) used BMD for analysing factors of implant failure in a group of reconstructed patients with multiple implant failures and found a correlation. The structure of the bone graft can also be examined with histomorftometry in biopsies (Blomqvist et al 1998; Pejrone et al 2002). The mineralised bone area can be expressed in bone volume fraction as a measurement of bone density which may serve as another prognostic indicator. During the initial healing of the bone graft, three-dimensional changes appear (Nyström et al 1995; Reinert et al 2003) which can be evaluated with computer tomography (CT) (Nyström et al 1995; Honma et al 1999; Johansson et al 2001a). Measurements of haematological factors, such as markers of enzymatic activity in bone metabolism or products released during bone formation/bone resorption (Thorsen 1996), may also serve as prognostic indicators.
**AIMS**

The general aim of the present dissertation was to evaluate the clinical outcome of surgical/prosthetic reconstruction of the atrophic edentulous maxilla with autogenous iliac crest bone grafts and delayed placement of titanium implants.

Specific aims were:

- to histologically study the influence of timing of placement and length of healing period on the integration of titanium microimplants in iliac crest bone grafts. (Papers I & II).

- to histologically compare the integration of titanium microimplants in onlay bone grafts with integration in interpositional bone grafts (Paper II).

- to monitor the development of implant stability in grafted and non-grafted maxillae using repeated resonance frequency analysis (RFA) measurements (Papers III & IV).

- to investigate if there is a correlation between RFA measurements and implant failure (Papers III & IV).

- to evaluate implant survival after 6 months and 3 years of functional loading (Papers III & IV).

- to evaluate the density of iliac crest bone grafts at the time of implantation and the dimensional changes after the 6-month graft healing period (Paper V).

- to investigate if there exists any correlation between patient related factors and implant failure (Paper V).
MATERIALS AND METHODS

Patients
Papers I – V included a total of 46 consecutive patients (31 females and 15 males) with a mean age of 57 years (range 44 – 73) at the time of bone-grafting surgery. The patients were referred for reconstruction of their edentulous atrophic maxilla with autogenous bone grafts and delayed placement of endosteal implants. In addition, 10 patients previously treated with implant-supported prostheses in their edentulous maxilla without bone grafts were used as a reference group in Paper III.

The patients were preoperatively evaluated with clinical and radiographic examinations. The radiographic examinations included orthopantomograms, lateral cephalograms and intraoral radiographs. The amount of available bone at each planned implant site was assessed with help of lateral tomographs and six to eight oblique parasagittal tomograms perpendicular to the tangent to the maxillary arch (Philips-Massiot polytome with hypocycloid movement). The resorption pattern was classified according to Cawood & Howell (1988), in the vertical and bucco-palatal dimensions using a transparent template corresponding to a 10-mm long implant with a regular platform (Fig. 1).

Figure 1. The bone dimension in the planned implant site was evaluated with a transparent template corresponding to an implant placed over the radiograph.

Bone grafting was considered if the dimensions of the available residual crest were less than 4 mm in width and 10 mm in height in the majority of the planned implant sites for the individual patient. The patients were included in the study if their general health did not prevent general anaesthesia. Smokers were advised to refrain from or reduce their smoking and were offered a stop-smoking program.

In all studies autogenous bone grafts from the anterior iliac crest were used as grafting material. One patient included in Papers III - V had complementary bone graft from mandibular ramus due to extensive local resorption in the graft surface.

The harvesting of autogenous bone from the iliac crest was performed under general anaesthesia and followed the technique described by Cricchio & Lundgren (2003). The skin incision followed the skin lines in a posterolateral direction with start 3 – 4 cm medial to the
iliac crest. Using blunt and sharp dissection through the subcutaneous fat layers, the aponeurosis between the abdominal and gluteal muscles was exposed. The superior surface of the iliac crest was exposed after a sharp dissection through the periosteum following the crest. The dissection was carried out with great attention to avoid laceration of the fascia lata. Different techniques for harvesting the bone grafts in corticocancellous blocks was performed dependent upon the resorption pattern in the maxilla. The graft was outlined with a sagittal saw and the graft was harvested with a straight osteotome. The donor site was closed in layers with special attention to the first layer; the fascia lata. This layer was sutured close to avoid marrowbone bleeding. An activated vacuum drainage was positioned between the fascia lata and the muscles until the patient was mobilized. The skin incision was closed with continous intracutaneous resorbable sutures.

Two surgical techniques were used for reconstruction of the atrophic alveolar process in the maxilla:

A. Interpositional bone graft in conjunction with a Le fort I osteotomy was performed in 11 patients (Fig. 2).

Figure 2. Diagram of the interpositional bone-grafting technique. Printed with permission from Quintessence Publishing Co Inc.

The Le Fort I osteotomy was performed with a technique according to the orthognatic surgical concept using a vestibular incision. The buccal wall of the maxillary sinus and the nasal aperture were exposed, and osteotomies were performed of the nasal septum and lateral and medial walls of the maxillary sinus. The maxilla was then down fractured and mobilised, and sinus membrane in the sinus recesses was removed. The harvested bone was then adjusted to fit into the nasal cavity and sinus recesses. After checking the horizontal and sagittal relation to the mandible the maxilla was secured to the midface with titanium miniplates. The soft tissue incision was thereafter closed with sutures.

B. The reconstruction was carried out using a buccal onlay bone graft together with nasal floor inlay-graft in 35 patients (Fig. 3).

Figure 3. Diagram of the onlay bone-grafting technique. Printed with permission from Quintessence Publishing Co Inc.
All 35 patients had onlay grafting in the anterior maxilla. In 24 patients the posterior maxilla was also reconstructed using onlay bone grafts. The remaining 11 patients had their posterior maxillae reconstructed with maxillary sinus antral graft only. The cortico-cancellous bone blocks were adjusted and secured to the alveolar process with titanium mini-screws with a width of 2 mm. In order to stretch the flap over the graft, and to avoid tension on the incision, a horizontal periosteal incision was made in the labial flap and closed with sutures.

Either benzyl-penicillin (3 g x 3) or, in the case of allergy to penicillin, clindamycin (600 mg x 3) was given parenterally immediately preoperatively and for the following 24 hours. All patients were hospitalised 2 – 3 days postoperatively, and given phenoxymethyl-penicillin (1 g x 3) or clindamycin (300 mg x 3) for the 7 days following the operation. Analgetics (paracetamol or non-steroidal anti-inflammatory drugs) were prescribed 7 to 10 days postoperatively.

In Papers I – V a total of 341 Brånemark® System implants (290 Standard® implants and 51 selftapping MK II®, Nobel Biocare AB Göteborg, Sweden), 10 – 18 mm in length and 3.75 mm in diameter, were placed in accordance with the two-stage surgical protocol for the Brånemark® System implants after six months of bone grafting. After exposure of the alveolar process the fixation material was removed. The implants were placed without pretapping with a final drill diameter of 2.85 mm. The patients in the reference group in Paper III were provided with 75 implants using the same surgical technique but with a final drill diameter of 3.00 mm.

The placement was performed under local anaesthesia (20 mg/ml lidocain, 12.5 µg/ml adrenaline ASTRA AB), with antibiotic prophylactics used for seven days (phenoxymethyl-penicillin or, in case of penicillin allergy, clindamycin) and conscious sedation. In Paper III the initial stability was manually tested by the surgeon during placement of the cover screw. The decision for the length of healing time was based on the initial stability for the implant. If one or more implants could be rotated together with the cover screw using a manual screwdriver, a prolonged healing time of 8 months was selected. For stable, non-rotating implants, the healing time was 6 months. The abutment connection, 6 to 8 months later, was performed under local anaesthesia and conscious sedation.

After the reconstructive surgery new removable dentures were fabricated and could be worn from the eighth postoperative week. During the 6-month healing period after the grafting procedure the patients were recalled for individual check ups and, if necessary, the dentures were relined with a soft-tissue relining material. After the implants were placed the dentures were again adjusted and relined with a soft-tissue material. In the patients for whom a metal-ceramic bridge was planned, a temporary all-acrylic bridge was fabricated and delivered immediately after abutment connection. The temporary bridge was used for four to eight weeks. The temporary bridge was fabricated with short cantilevers or without cantilevers and with flat cusps in order to achieve a gentle occlusion. The permanent metal-ceramic bridges (Procera Implant Bridge®) were produced according to normal procedures described in the manual provided from the company. In the situation where a bridge in titanium-acrylic material was planned, no temporary bridge was used. Patients who had lost one or more implants were evaluated by the surgeon together with the restorative dentist, regarding the need for supplementary implants. Several factors, e.g., the position of the remaining implants, the dentition in the opposing jaw, loading, functional habits and cantilever length, played an important role in determining whether additional implants should be installed. If so, a temporary bridge was fabricated that was reinforced with Kevlar threads, and ordinary gold
cylinders were used in the acrylic material. The temporary bridge was then used for the additional healing period of approx. 6 months, and thereafter the supplementary implants were placed. The patients with no need for supplementary implants were judged as patients without lost implants. After delivery of the final bridge the patients were instructed in oral hygiene and an individual recall program was set up.

**Study outlines for the present dissertation**

In Papers I and II a total of 23 patients had microimplants placed in the bone graft and retrieved for histological processing with light microscopic analysis and histomorphometry.

In Papers III and IV the implant survival, changes of marginal bone level and evaluation of implant stability with resonance frequency analysis (RFA) were evaluated in 28, out of 29, patients after 6 months and after 3 years of functional loading. In Paper III, the RFA measurements were compared with those made in a reference group of 10 non-grafted patients.

In Paper V the degree of resorption for onlay bone grafts in 30 patients was radio graphically estimated with computer tomography and correlated to bone volume fraction from 46 patients, bone mineral density from 21 patients, haematological factors from 25 patients and implant stability according to resonance frequency analysis in 18 patients. The implant survival was evaluated prior to loading and after a follow up period of a minimum of 3 years for 46 patients. Possible correlations between the aboved mentioned factors and implant failures were analysed. The study design in the present dissertation is summarised in table 1.

**Table 1. Study design used in the present dissertation.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Paper I (No. of patients)</th>
<th>Paper II (No. of patients)</th>
<th>Paper III (No. of patients)</th>
<th>Paper IV (No. of patients)</th>
<th>Paper V (No. of patients)</th>
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<td>23</td>
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<td>Histomorphometry iliac crest</td>
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<td>Bone mineral density</td>
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<tr>
<td>Haematology</td>
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<td>25</td>
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</table>
Microimplants (Papers I and II)
A total of 68 screw-type turned microimplants were placed in the bone graft in 23 patients (Fig. 4).

**Figure 4.** Microimplant at the time for placement in onlay bone graft.

The microimplants had a 5-mm long threaded section, which was 2 mm in diameter, and a slotted head. In 3 patients, 3 additional microimplants were placed in the residual alveolar ridge. Placement of the microimplants: at the bone grafting surgery, a 1.6-mm twist drill was used to prepare two microimplant sites in grafted bone only. The microimplants were placed with a small screwdriver, as in the case for self-tapping screws, until the head reached the surface of the bone graft, but with no contact with the residual alveolar ridge. During drilling and implant placement there was copious irrigation with sterile saline.

At the time of implant placement (6 months later), 1 microimplant was retrieved together with the surrounding bone tissue using a trephine drill (inner diameter 3.1 mm) and an additional microimplant was placed in the healed graft. The remaining 2 microimplants were retrieved at the third surgery (abutment connection) a minimum of 6 months later. In this way, a model for simultaneous placement with 6 months of healing (1), simultaneous placement with 12 to 14 months of healing (2), and delayed placement with 6 to 8 months of healing (3) could be analysed histologically (Table 2).

<table>
<thead>
<tr>
<th>0 months</th>
<th>6 months</th>
<th>12 – 14 months</th>
<th>Healing time for Microimplants</th>
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<td>Implant placement</td>
<td>Abutment connection</td>
<td>0 - 6 months simultaneous</td>
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<tr>
<td>Placement of one microimplant</td>
<td>Retrieval</td>
<td></td>
<td>0 – 12/14 months simultaneous</td>
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<tr>
<td>Placement of one microimplant</td>
<td>Retrieval</td>
<td></td>
<td>6 – 12/14 months delayed</td>
</tr>
</tbody>
</table>

**Bone volume fraction (Paper V)**
For the evaluation of the bone volume fraction at the donor site, biopsies were taken from the internal table of the anterior crest of the iliac bone with a 3 mm trephine bur at the same time as the bone grafting surgery was performed (Fig. 5).
The received specimens were fixed by immersion in 4% buffered formaline solution, later dehydrated in a graded series of ethanol and finally embedded in plastic resin (Technovit® A 7210 VCL; Kulzer & Co, Hanau, Germany). According to a technique described by Donath & Breuner (1982), sections were cut and ground to a thickness of approximately 10 µm by means of exact cutting and grinding equipment (Exact Apparatbau, Norderstedt, Germany). The ground sections were stained with 1% toluidine blue and 1% purpurin-G.

Examination, photography, and histomorphometrical measurements were carried out using a Leitz Orthoplan microscope (Wetzlar, Germany) (objectives 1.6x to 40x, with a ability to zoom in up to 2.5x when needed) equipped with a Leitz Microvid Morphometric System and connected to a personal computer (IBM, New York, NY). The measurements were performed at 6x and 10x magnification. The morphometrical measurements of the microimplants included measuring of the degree of bone – implant contact and expressed as percentage of the total distance from the lowest point of the implant head to last apical thread. The bone area within the treads was calculated as the area of bone within each thread divided by the total thread area. A mean was calculated for each specimen based on measurements in all threads. Calculations were also made of new and grafted bone in the biopsies and expressed as a percentage of newly formed bone in the biopsy area. The total bone area was calculated as the area of bone divided by the total biopsy area minus the area occupied by the implant. Mean values and standard deviations (SD) were calculated. Figure 6 exemplifies the registrations of bone-implant contact and bone area within in threads. For biopsies without microimplants the calculations comprised of total bone area in the biopsy and proportions of new and grafted bone.

Figure 5. Biopsy from iliac crest.

Figure 6. Calculation of bone-implant contact and area of bone within threads.
Resonance frequency analysis (Papers III - V)

The resonance frequency analysis (RFA) technique was first described by Meredith and co-workers (1996) and has been developed since then. In brief, the first versions consisted of a transducer, a custom-designed frequency response analyser and a portable laptop computer. The transducer is an L-shaped cantilever beam, which was connected to the implant perpendicular to the bone crest via a screw attachment. A piezoelectric crystal on the vertical of the L-shaped beam was then used to stimulate the implant/transducer complex across a frequency range of approximately 2 to 15 kHz in steps of 25 Hz. A second piezoelectric crystal on the opposite side of the beam was used as the receiving element to detect the response of the beam. The resonance frequency is seen as a peak in a frequency-amplitude plot.

In Paper III 28 of the 29 grafted patients were measured on three occasions: after implant placement, at abutment connection, and after 6 months of functional loading. Ten patients with edentulous but non-grafted maxillae served as the control group. The resonance frequency was recorded as the peak amplitude for each implant. As different transducers have different fundamental resonance frequencies, they were calibrated using aluminium blocks with predetermined resonance frequencies. An implant stability quotient (ISQ) value (Integration Diagnostics Ltd, Sävedalen, Sweden) based on the underlying resonance frequency, was calculated for each measurement. The ISQ is presented as a value from 1 (lowest stability) to 100 (highest stability) and represents a standardised unit.

In Paper IV resonance frequency analysis (RFA) was performed in 25 patients to measure implant stability after 3 years of loading (Fig. 7) using an Osstell™ instrument (Integration Diagnostics AB, Göteborg, Sweden).

Figure 7. Resonance frequency registration at the time of the three-year follow up.

Mean ISQ values were calculated for each patient and time point. Mean values were also calculated for anterior and posterior implants for each patient and time point (Paper IV). Anterior implants were defined as implants placed in positions 12, 11, 21, or 22 (Position according Federation Dentaire International, FDI). Posterior implants were defined as implants placed posterior to positions 12 or 22. Mean ISQ values were also calculated for the different implant lengths at implant placement. Additionally placed implants and implants with angulated abutments were not included in the analyses.

In paper V, the correlation between graft volume change and stability according to RFA at the time for implant placement was analysed in 18 patients.
Marginal bone height (Paper IV)

Intraoral radiographs at bridge delivery (baseline) and after 1, 2 and 3 years of loading were used to evaluate the marginal bone level. The parallel technique was used to avoid distortion in the radiographs. The distance from the implant/abutment junction (reference point) to the most coronal point (marginal bone level), where the marginal bone meets the implant, was measured on both sides of each implant. Mean values were calculated for each patient and time. The registrations were made with a loupe with a magnification factor of 7 and a scale in tenths of millimetres. The distance over 5 threads was measured and divided by the real distance of 3.0 mm, thus revealing the variation in magnification in the radiographs. The resulting magnification factor for each implant and examination was used to transform the measured radiographic changes of bone level into real bone loss.

Graft volume change (Paper V)

For evaluation of the onlay bone graft volume change during initial healing, radiographic examinations used contiguous computer tomography (Fig. 8) (Philips Tomoscan LX Plus) and was performed in 30 patients (21 women/9 men, mean age 58, range 44 – 73).

Figure 8. Radiographic examination using contiguous computer tomography.

The distance between the axial slices was 1.5 mm and parallel to the hard palate with the first slice inferior to the alveolus/bone graft and the last slice superior to the alveolus/bone graft. The radiographic film was optically transferred into a computer. The area was calculated with help of a semi-automatic software; Image Access Analysis and a personal computer (Compaq Prolinea 4/33 s) and expressed in mm$^2$. The volumes of the plotted areas were calculated by adding the sums of the plotted areas and multiplying them by the thickness of the sections, $V^{\text{mm}} = \text{sum of plotted areas} \times \text{thickness of the section}$ (Uschida et al 1998, Johansson et al 2001a) and expressed in cm$^3$ (Fig. 9).
\[ \Delta h = dS \times \Delta h \]

\[ V = \Sigma dS \times \Delta h \]

Figure 9. Diagram showing the method used for measuring the onlay bone graft volume (from Uchida et al 1998).

The procedure was performed within three weeks after bone grafting (Fig. 10) and was repeated after six months of bone graft healing (Fig. 11).

Figure 10. Axial slice post grafting.  
Figure 11. Axial slice after six months of bone graft healing.

The resorption was calculated as the volume of the onlay bone graft after six months of healing divided with the volume of the onlay bone graft directly after the grafting procedure and expressed in per cent.

Haematological analyses (Paper V)

Selected blood samples were collected from 25 patients (18 women/7 men, mean age 57, range 48 – 73) in addition to the reconstructive surgical procedure and were analysed according to the parameters described in Table 3. The collected blood samples were centrifuged and the sera were analysed by standard methods at the Umeå University Hospital Department of Clinical Chemistry. In a first classification based on normal ranges, the results were classified as within/over/ or below normal ranges.
Table 3. Haematological parameters analysed in 25 patients.

<table>
<thead>
<tr>
<th>Haematologic factor</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-PTH</td>
<td>pmol/L</td>
</tr>
<tr>
<td>S-Albumin</td>
<td>g/L</td>
</tr>
<tr>
<td>S-TSH</td>
<td>mU/L</td>
</tr>
<tr>
<td>S-Osteocalcin</td>
<td>μg/L</td>
</tr>
<tr>
<td>S-Cortisol</td>
<td>nmol/L</td>
</tr>
<tr>
<td>S-Testosteron, total</td>
<td>nmol/L</td>
</tr>
<tr>
<td>S-Testosteron, free</td>
<td>% of total</td>
</tr>
<tr>
<td>S-Estradiol</td>
<td>pmol/L</td>
</tr>
<tr>
<td>S-IGFBP3 [Insulin-like growth factor binding protein-3]</td>
<td>mg/L</td>
</tr>
<tr>
<td>S-Phosphate</td>
<td>mmol/L</td>
</tr>
<tr>
<td>S-IGF-1 [Insulin Like Growth Factor]</td>
<td>μg/L</td>
</tr>
<tr>
<td>S-Calcitriol [1,25(OH)2-cholecalciferol]</td>
<td>ng/L</td>
</tr>
<tr>
<td>S-ICTP [Carboxy-terminal telopeptide of type I collagen]</td>
<td>μg/L</td>
</tr>
</tbody>
</table>

Bone mineral density (Paper V)

In 21 patients (15 women/6 men, mean age 59, range 50 - 73) the bone mineral density (g/cm²) (BMD) was measured through dual energy x-ray absorptionsmetry (Lunar DPX-L, Lunar Co, Wisconsin, USA) with program version 4.6e (Voltage 76 kVp, current 150 μA, medium collimation, sample size 4.8 x 9.6, sample interval 1/32, scan width 576 mm, scan length 1958 mm). Results were obtained from whole body (Fig. 12), femoral neck (Fig. 13) and lumbar vertebrae L2 – L4 (Fig. 14) and expressed as T-score.

Figure 12. Bone mineral density of total body.

Figure 13. Bone mineral density of femoral neck.

Figure 14. Bone mineral density of vertebrae L2-L4.
Implant survival and failure (Papers III – V)

After delivery of the bridge, follow-ups were performed after 1, 2 and 3 years of function (Papers I – V). For patients in Papers III and IV the bridges were removed for stability tests of the individual implants after 6 months and 3 years of functional loading (Fig. 15).

Figure 15. Fixed bridge removed exposing the individual implants at the three-year follow-up.

In Papers III and IV implant survival was calculated based on registered implant failures. Stability tests of individual implants were performed at abutment surgery and after 6 months and 3 years of loading. In paper V implant failures were registered prior to bridge loading and after a minimum of three years of loading. At the three-year follow-up 17 of the patients were routinely checked up without removal of the bridge. Implant failures were registered on a patient basis.

Literature survey (Paper IV)

A survey of the literature without limitation regarding year of publication was conducted using the National Library of Medicine computerised bibliographic databases MEDLINE and PubMed, with links to related articles. The search words used were: edentulous maxilla, bone graft, reconstruction, titanium implants and their combinations. The reference lists in the collected papers were used to further expand the survey. The following inclusion criteria were applied:

1. The study had to have been published in English, or had an English abstract, in a refereed journal.
2. The study must include patients with edentulous maxillae or, in studies with mixed total/partial edentulism, it should be possible to discern which.
3. The reconstructions in the patients should be with free autogenous bone grafts.
4. The reconstruction technique should be identifiable.
5. The number of placed and failed implants in grafted bone should be defined.
6. The minimum follow-up period should be 12 months, calculated after implant placement for all patients in the study.
7. In cases with multiple reports on the same patient/implant material, the most recent study with the longest follow up was analysed.
Statistics

The SPSS software package (versions 10.0 and 13.0; SPSS Inc., Chicago IL, USA) were used for all statistical analyses.

Microimplants (Papers I and II): In Paper I the Wilcoxon signed rank test and Spearman correlation Test were used. In Paper II the Students t-test for paired observations was used for comparing 1-stage and delayed implant placement. The paired t-test was also used for comparing microimplants placed in the residual alveolar crest, with those placed simultaneously with grafting, and retrieved after 6 months The Students t-test for unpaired observations was used to compare the two bone grafting techniques.

Resonance frequency analysis (Papers III and IV): For analysis of RF values, all statistical tests were based on the patient as a unit except in cases of comparison between successful and failed implants. The Wilcoxon signed rank test for paired data was used for comparison of changes in ISQ between the four registrations and in the comparison between anterior and posterior implants. For comparison of ISQ values between grafted and non-grafted patients and reconstruction techniques the Mann-Whitney U-test was used. For comparison of successful vs. failed implants, registered at the time of placement, and mobile vs. clinically stable implant, the Mann-Whitney U-test was used both on a patient level and for the individual implant. For analysis of the correlation between ISQ value at implant placement and implant length a Spearman rank test was used. For comparison of stability between placement and abutment connection a regression analysis was used.

Literature survey (Paper IV): For comparison between the different bone grafting techniques Chi-square tests were used.

Implant survival (Paper IV): In Paper IV a life table was used to calculate the cumulative survival rate. The associations between gender, smoking, length and position of implant, resorption of the planned implant position, the reconstruction technique and implant failure were evaluated by unconditional logistic regression to estimate odds ratios and corresponding 95 % confidence intervals. The effect of each factor was assessed both in univariate analysis and after adjustment for the other factors considered.

Graft dimensional changes (Paper V): In univariate analysis the effects of gender, body mass index (BMI), smoking, glukocorticoid medication, bone volume fraction (BVF), bone mineral density (BMD) of total body, femoral neck, vertebrae L2-L4 (expressed as T-score) on graft volume change were assessed by the Kruskal Wallis test. The correlation between haematological factors and graft volume change was analysed by Pearson correlation test. The associations between early and late implant failures and graft volume change, implant stability expressed in implant stability quotient (ISQ), BVF, BMI, smoking, gender, glucocorticoid medication, BMD for total body femoral neck and L2-L4 were evaluated by unconditional logistic regression to estimate odds ratios (OR) and corresponding 95 % confidence intervals (CI). The correlation between graft volume change and ISQ was tested with Pearson correlation test.

All significance tests were two-tailed and the level of significance was set to $p \leq 0.05$. 

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RESULTS

Microimplants (Papers I and II)

No severe complications were seen in any of the 23 patients who received titanium microimplants. Sixty-five of the 68 microimplants placed in grafted bone were clinically stable when tested with a forceps. All of the three microimplants placed in residual alveolar ridge were stable. The removal of the microimplant together with surrounding bone graft resulted in bleeding from the retrieval site.

All specimens contained a central section of microimplant and various amounts of bone and soft tissue. Differences in the biopsies were seen between microimplants with respect to different time schedules of placement and retrieval.

The 6-month specimens of simultaneous microimplants had a more immature appearance as compared with the two other groups. Various amounts of cortical and cancellous bone, mostly grafted bone, surrounded each microimplant. Both bone resorption and subsequent formation of new bone, within and on the surface of the grafted bone, were evident in all specimens. The implant surface was only occasionally in contact with newly formed bone. Most of the newly formed bone had a lamellar appearance, although areas of woven bone were sometimes observed. The soft tissue components consisted of loose connective tissue rich in vessels, sinusoids and cells. Thus, the morphology of the connective tissue resembled that of bone marrow. The morphology of the tissue surrounding implants placed simultaneously and retrieved after 12 to 14 months (Figure 16) resembled that of the tissue surrounding the microimplants placed after a 6-month postgrafting healing period. The bone had a mature appearance, with lamellar bone, and secondary osteons were present. Grafted bone could still be distinguished. Active bone formation could still be observed. There were no apparent differences between the microimplants retrieved from interpositional bone grafts and those retrieved from onlay/inlay bone grafts.

Figure 16. Light micrograph of a specimen placed simultaneously with grafting and allowed to heal for 12 months. Mature lamellar bone (LB) is seen adjacent to and in contact with the implant (I) surface. The nonmineralized tissue consisted of a loose connective tissue (LCT) rich with cells and vessels (toulidine blue; bar = 200 μm)
Bone-implant contact. In Paper I the bone-implant contact was significantly higher (p<0.05) with delayed placement of titanium microimplants than for simultaneously placed microimplants with 6- and 12-months of healing (Fig. 17). These findings, with a significantly greater (p=0.05) bone-implant contact between delayed- vs. simultaneously-placed microimplants, were confirmed in Paper II.

![Figure 17](image1.png)

**Figure 17.** Results from morphometrical measurements of degree of bone-implant contact (Paper I). *p<0.05 as compared with the other groups. 0-6 and 0-12 months indicate simultaneous placed microimplants, 6-12 months indicate delayed placement of microimplants.

Bone area within threads. There was a significant difference (greater) (p<0.05) bone area within the threads of delayed-placement microimplants as compared with simultaneously-placed microimplants when bone area within the implant threads was analysed in paper I (Fig. 18). However, in Paper II, with analysis from 23 microimplants, no significant differences were found.

![Figure 18](image2.png)

**Figure 18.** Results from morphometrical measurements of bone area within implant threads (Paper I). *p<0.05 as compared with other groups. 0-6 and 0-12 months indicate simultaneous placed microimplants, 6-12 months indicate delayed placement of microimplants.

Amount of newly formed bone. In papers I (Fig. 19) and II the delayed placement of titanium microimplants resulted in significantly higher (p<0.05) amounts of newly formed bone as compared with simultaneously-placed microimplants.
Interpositional vs. onlay bone grafting. In Paper II the focus was on differences in bone-implant contact, bone area within threads and amount of newly formed bone between interpositional- and onlay/inlay bone-grafting technique. No significant differences were found between the grafting techniques (Table 4).

Table 4. Comparison between interpositional and onlay bone/inlay grafting techniques (Mean + SD)

<table>
<thead>
<tr>
<th></th>
<th>Interpositional (n=8)</th>
<th>Onlay/Inlay (n=15)</th>
<th><em>p</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone implant contact</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>14.6±8.2</td>
<td>20.8±17.6</td>
<td>0.270</td>
</tr>
<tr>
<td>B</td>
<td>28.4±16.7</td>
<td>23.2±8.8</td>
<td>0.467</td>
</tr>
<tr>
<td>C</td>
<td>37.7±20.5</td>
<td>25.2±1.5</td>
<td>0.214</td>
</tr>
<tr>
<td>Bone area within threads</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>22.1±9.2</td>
<td>25.2±17.9</td>
<td>0.585</td>
</tr>
<tr>
<td>B</td>
<td>33.5±16.7</td>
<td>24.0±9.0</td>
<td>0.198</td>
</tr>
<tr>
<td>C</td>
<td>41.8±22.3</td>
<td>28.1±17.6</td>
<td>0.221</td>
</tr>
<tr>
<td>New bone area</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>57.5±7.1</td>
<td>63.2±9.0</td>
<td>0.115</td>
</tr>
<tr>
<td>B</td>
<td>67.3±9.1</td>
<td>60.2±8.6</td>
<td>0.143</td>
</tr>
<tr>
<td>C</td>
<td>75.3±12.3</td>
<td>66.3±14.3</td>
<td>0.163</td>
</tr>
</tbody>
</table>

*p* values represent interpositional vs. onlay/inlay
A = simultaneous load, 6-month healing; B = simultaneous load, 12 – 14 month healing; C = delayed load, minimum 6-month healing. Healing refers to the healing period between implant placement and removal.

Grafted vs. non-grafted residual alveolar ridge. In Paper II, three microimplants placed in the residual alveolar ridge and retrieved after 6 months showed significantly greater mean values for bone area within threads and amounts of newly formed bone than microimplants placed in interpositional bone grafts using the simultaneous technique and retrieved after 6 months from the same patient (Table 5).
Table 5. Comparison between microimplants placed in residual alveolar ridge and interpositional bone graft (Mean + SD)

<table>
<thead>
<tr>
<th></th>
<th>Residual alveolar ridge (n=3)</th>
<th>Interpositional (n=3)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone implant contact</td>
<td>49.3±18.3</td>
<td>21.7±7.1</td>
<td>0.112</td>
</tr>
<tr>
<td>Bone area within threads</td>
<td>58.0±13.7</td>
<td>25.7±11.0</td>
<td>0.003</td>
</tr>
<tr>
<td>New bone area</td>
<td>75.0±8.0</td>
<td>56.5±10.9</td>
<td>0.009</td>
</tr>
</tbody>
</table>

*P values represent residual alveolar ridge vs. interpositional bone grafts

Resonance frequency analysis (Papers III and IV)

All statistical tests were performed on the patient as the unit except for the analysis of successful vs. failed implants in paper IV. In that paper statistical tests were performed both on the patient level and for the individual implant.

Grafted vs. non-grafted maxillae. When comparing the ISQ values for the grafted and non-grafted patients at three different ISQ registrations in Paper III, a non-significant difference was seen (Fig. 20). In the grafted maxillae, a statistically significant difference (p=0.045) was found between abutment connection (ISQ 60.2±6.9) and loaded implants (62.5±5.2). For normal maxillae, a significant difference (p=0.022) was found between implant placement (ISQ 58.5±4.7) and loaded implants (63.0±5.6).

Figure 20. Comparison of implant stability in grafted and normal (non-grafted) maxillae (Paper III). Statistically significant differences were found in the grafted maxillae between abutment connection and loaded implants (p=0.045) and for normal maxillae between implant placement and loaded implants (p=0.022). No significant differences were found when comparing the two techniques.

Change of stability for implants placed in grafted maxillae (Paper III). When comparing the change of stability from placement to abutment connection (Fig. 21), implants with low primary stability according to ISQ-value increased ISQ-value more than implants with high primary stability (p=0.004).
Interpositional vs. onlay bone grafting. There was no significant difference in ISQ values between implants which were placed in interpositional bone graft as compared with those placed in onlay bone graft in Paper III (Fig. 22).

Stable vs. rotation-mobile implants. In Paper III, implants’ rotational stability, or instability, was analysed. In fifteen of the 28 grafted patients the primary stability of 20 implants (9%) was judged as low due to rotational mobility at the time of placement. The clinically stable implants had a significantly higher ISQ value than the rotation-mobile implants (p=0.020).

Longitudinal follow up in grafted maxillae. In Paper IV, resonance frequency registrations were performed on 190 out of 192 implants at the time of implant placement. Two implants were impossible to measure because the transducer could not be positioned due to lack of space. The mean ISQ for the implants at placement was 61.9±9.5, and it was 61.8±5.5 (N.S.) after 3 years of loading (Fig. 23). There was a significant increase (p=0.05) in the ISQ value between the abutment connection (60.2±7.3) and the measurement after 6 months of bridge loading (62.5±5.5). However, that difference was no longer present at the three-year follow-up.
Successful vs. failing implants. ISQ values at the time for placement were compared both with the patient as the unit and as individual implants in the analysis of successful and failing implants (Paper IV). The mean ISQ for patients with successful implants at the time of placement was 61.0±9.4 as compared with 55.9±11.1 for failed implants (p=0.11). When comparing individual implants the mean ISQ at placement for 170 successful implants was 62.6±11.1 as compared with 54.9±11.1 for 20 failed implants (p=0.004). There was a significant difference between successful and failed implants only when individual implants were compared (Fig. 24).

Anterior vs. posterior implants. In Paper IV a comparison of ISQ values was performed between anterior- and posterior-placed implants (Fig. 25). Significant differences were found when comparing anterior and posterior placements of implants at the first and last registrations, respectively (p=0.019, p=0.024). For posteriorly-placed implants there was a significant increase when comparing the ISQ value at the abutment connection with that after 6 months of loading (p=0.032) and after 3 years of loading (p=0.026).
Figure 25. Paper IV, comparison between ISQ values for anteriorly and posteriorly placed implants. Significant differences were found when comparing anteriorly and posteriorly placed implants at the first and last registration (p=0.019, p=0.024). For posteriorly placed implants there was a significant increase when comparing the ISQ value at the abutment connection with the 6 months of loading (p=0.032) and 3 years of loading (p=0.026).

**Implant length.** There was a significant difference (p<0.001) in ISQ value at the time of implant placement when 10 and 13 mm (n=97) implants were compared with 15 and 18 mm (n=93) implants in Paper IV (Fig. 26).

**Marginal bone height (paper IV)**
At base-line registration (bridge delivery) the mean value for the marginal bone level was 1.9 ± 0.4 mm apical to the reference level (implant/abutment junction). The marginal bone level was 2.0±0.3 mm at the one-year follow up, 2.2±0.5 mm at the two-year follow up and 2.2±0.4 mm apical to the reference level at the three-year follow-up. The change in marginal bone level from baseline to the three-year follow-up was 0.3±0.3 mm. Figure 27 shows the change in marginal bone level during the study.
Graft volume change (Paper V)

The volumes of the onlay bone grafts immediately after surgery and after 6 months of healing, as measured in repeated CT radiographs, are shown in Figure 28. The average decrease in onlay bone volume after 6 months was $37\% \pm 10.2$ (range 16 – 59).

Haematological analyses (Paper V)

In the first classification based on normal ranges, serum-IGFBP3 was the only haematological parameter that differed from the normal range with 19 out of 24 (79%) samples over the normal range.

Bone mineral density (Paper V)

The bone mineral density (BMD) data for 21 patients showed that 16 patients had a T-score $\geq -1$ when the total body was analysed. BMD of femoral neck showed that 8 patients had a T-score $\geq -1$ and 9 patients had a T-score $>-1$ when vertebrae L2-L4 was analysed.
Bone volume fraction (Paper V)

Biopsies taken from the internal plate of the anterior iliac crest at the time of bone grafting were used for bone volume fraction (BVF) analysis. The mean value for the mineralized bone volume fraction was 32% ±11.2 (range 15 – 74), Figure 29.

Figure 29. The bone volume fraction in 46 biopsies from internal table, crista iliaca.

Different factors’ effects on graft volume change. Univariate analysis of the effect of different factors on graft volume change is shown in Table 6. Of all factors assessed, only BMD L2-L4 was significantly associated with graft volume change (p=0.017).

Table 6. Univariate analyses of different factors and their correlations with graft volume change. (*p<0.05, 1: Kruskal Wallis test, 2: Pearson correlation test)

<table>
<thead>
<tr>
<th>Factor</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>0.8591</td>
</tr>
<tr>
<td>Body mass index (categorized into 2 groups: &lt; 25, 25+)</td>
<td>0.7031</td>
</tr>
<tr>
<td>Smoking (yes/no)</td>
<td>0.1311</td>
</tr>
<tr>
<td>Glucocorticoid medication (yes/no)</td>
<td>0.9481</td>
</tr>
<tr>
<td>Bone volume fraction (categorized into 2 groups: &lt; 29%, ≥ 29 %)</td>
<td>0.0721</td>
</tr>
<tr>
<td>Bone mineral density of total body (T-score categorized into 2 groups: T-score ≥ -1 or &lt; -1)</td>
<td>0.1261</td>
</tr>
<tr>
<td>Bone mineral density of femoral neck (T-score categorized into 2 groups: T-score ≥ -1 or &lt; -1)</td>
<td>0.8521</td>
</tr>
<tr>
<td>Bone mineral density of vertebrae L2-L4 (T-score categorized into 2 groups: T-score ≥ -1 or &lt; -1)</td>
<td>0.0171</td>
</tr>
<tr>
<td>S-PTH (pmol/L)</td>
<td>0.2272</td>
</tr>
<tr>
<td>S-Albutinin (g/L)</td>
<td>0.5841</td>
</tr>
<tr>
<td>S-TSH (mU/L)</td>
<td>0.3002</td>
</tr>
<tr>
<td>S-Osteocalcin (μg/L)</td>
<td>0.0612</td>
</tr>
<tr>
<td>S-Cortisol (mmol/L)</td>
<td>0.3952</td>
</tr>
<tr>
<td>S-Testosteron, total (nmol/L)</td>
<td>0.7702</td>
</tr>
<tr>
<td>S-Testosteron, free (% of total)</td>
<td>0.8172</td>
</tr>
<tr>
<td>S-Estradiol (pmol/L)</td>
<td>0.6712</td>
</tr>
<tr>
<td>S-IGFBP3 [Insulin-like growth factor binding protein-3] (mg/L)</td>
<td>0.8552</td>
</tr>
<tr>
<td>S-Phosphate (mmol/L)</td>
<td>0.0792</td>
</tr>
<tr>
<td>S-IGF-1 [Insulin Like Growth Factor] (μg/L)</td>
<td>0.2922</td>
</tr>
<tr>
<td>S-Calcitriol [1,25(OH)2-cholecalciferol] (ng/L)</td>
<td>0.5882</td>
</tr>
<tr>
<td>S-ICTP [Carboxy-terminal telopeptide of type I collagen] (μg/L)</td>
<td>0.0682</td>
</tr>
</tbody>
</table>
Correlation between graft volume change and implant stability. No correlation was found between graft volume change and ISQ (Pearson correlation test, p=0.865).

Individual implant survival and failure (Papers III - IV)

The preoperative resorption in the alveolar process for the original 29 patients is shown in Table 7. The time the maxilla had been edentulous varied from 1 to 46 years (median 34 years).

Table 7. The preoperative status of resorption in the alveolar process for 222 planned implant sites, classification according to Cawood & Howell (1988). The question mark indicates no preoperative radiological examination.

<table>
<thead>
<tr>
<th>Classification of alveolar process (Cawood &amp; Howell 1988)</th>
<th>No. of planned implant sites</th>
<th>Per cent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>IV</td>
<td>67</td>
<td>30</td>
</tr>
<tr>
<td>V</td>
<td>111</td>
<td>50</td>
</tr>
<tr>
<td>VI</td>
<td>25</td>
<td>11</td>
</tr>
<tr>
<td>?</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>222</td>
<td>100</td>
</tr>
</tbody>
</table>

Individual implant failures. Twenty-five of the original 29 patients fulfilled the 3-year follow up (Paper IV). Implant survival was calculated based on registered implant failures. A total of 20 of the 192 implants failed during the follow-up period, giving a survival rate of 90% after a minimum follow up of 3 years. Twelve of the failures happened prior to loading and were classified as early failures. Six out of 18 (30%) of the implants classified as having low primary stability at placement were lost during the treatment time. The distributions of the failures among the patients is shown in Table 8.

Table 8. Distribution of implant failures with regard to patients.

<table>
<thead>
<tr>
<th>No. of failures</th>
<th>No. of patients</th>
<th>No. of implants</th>
<th>No. of early failures</th>
<th>No. of late failures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>5</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>20</td>
<td>12</td>
<td>8</td>
</tr>
</tbody>
</table>
The locations for placed and failed implants with regard to tooth position are shown in Table 9. The distribution of implants with regard to length and failure are shown in Table 10.

**Table 9. Distribution of placed and failed implants with regard to tooth position. Position according Federation Dentaire International (FDI).**

<table>
<thead>
<tr>
<th>Position (FDI)</th>
<th>No. of placed implants</th>
<th>No. of failed implants</th>
<th>Percent failed</th>
</tr>
</thead>
<tbody>
<tr>
<td>15/25</td>
<td>43</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>13/23</td>
<td>49</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>12/22</td>
<td>50</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>11/21</td>
<td>50</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>192</td>
<td>20</td>
<td>10</td>
</tr>
</tbody>
</table>

**Table 10. Distribution of implants with regard to length and failure.**

<table>
<thead>
<tr>
<th>Implant length</th>
<th>10 mm</th>
<th>13 mm</th>
<th>15 mm</th>
<th>18 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of placed implants</td>
<td>23</td>
<td>76</td>
<td>85</td>
<td>8</td>
</tr>
<tr>
<td>Number of failed implants</td>
<td>7</td>
<td>9</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Percent failure</td>
<td>30</td>
<td>12</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

Sixty-one implants were placed in men and one implant (2%) failed. For women, 19 out of 131 implants (14%) failed. One out of 29 implants (3%) failed in patients where interpositional bone grafts had been used for reconstruction. Nineteen out of 163 implants (12%) failed of those placed in onlay/inlay bone grafts. Two of eight smokers (25%) lost an implant during the follow-up period as compared with eight out of 17 non-smokers (47%).

Table 11 shows odds ratios (ORs) with 95% confidence intervals (CIs) for gender, smoking, implant length and position, resorption in planned implant position (FDI) and reconstruction technique. In univariate analysis significant differences were found for gender, implant length, implant position and resorption in planned implant position. However, only gender and resorption remained significant after adjustment for the other factors. All patients received and maintained a fixed bridge throughout the three-year follow up. However, at the three-year follow-up visit 4 of 6 implants were unstable in one patient and suggested to be removed. The patient refused removal of the implants at that time so the bridge was inserted again without removal of the implants.
Table 11. Odds ratio (OR) and 95% confidence intervals (CI) for gender, smoking, implant length and position, resorption of planned implant position and reconstruction technique.

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR</th>
<th>95% CI</th>
<th>OR(^1)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>10.18</td>
<td>1.33-77.90</td>
<td>8.22</td>
<td>1.04-64.95</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>0.48</td>
<td>0.15-1.50</td>
<td>0.42</td>
<td>0.12-1.24</td>
</tr>
<tr>
<td>Length of implant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-18 mm</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-13 mm</td>
<td>4.29</td>
<td>1.38-13.35</td>
<td>2.51</td>
<td>0.69-9.14</td>
</tr>
<tr>
<td>Position of implant (FDI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15/25,13/23,12/22</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11/21</td>
<td>2.61</td>
<td>1.01-6.75</td>
<td>2.05</td>
<td>0.69-6.12</td>
</tr>
<tr>
<td>Resorption of planned implant position</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-5</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>5.56</td>
<td>1.93-16.07</td>
<td>3.91</td>
<td>1.13-13.48</td>
</tr>
<tr>
<td>Reconstruction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interpositional</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onlay/inlay</td>
<td>3.69</td>
<td>0.48-28.73</td>
<td>2.66</td>
<td>0.30-23.70</td>
</tr>
</tbody>
</table>

\(^1\) OR from a multiple logistic regression analysis with gender, smoking status, length of implant, position of implant, crista resorption and reconstruction technique included as explanatory
A life table including all the originally placed implants (n=222) in 29 patients is shown in Table 12. A cumulative survival rate of 90% was seen after 3 years of loading.

**Table 12.** Life-table for all originally placed implants (n=222) in 29 patients.

<table>
<thead>
<tr>
<th>Time intervals</th>
<th>No. of entering implants</th>
<th>No. of failed implants during each interval</th>
<th>No. of dropouts</th>
<th>Survival rate within group (%)</th>
<th>Cumulative Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>222</td>
<td>13</td>
<td>0</td>
<td>94.1</td>
<td>94.1%</td>
</tr>
<tr>
<td>2</td>
<td>209</td>
<td>4</td>
<td>8</td>
<td>98</td>
<td>92.3%</td>
</tr>
<tr>
<td>3</td>
<td>197</td>
<td>4</td>
<td>21</td>
<td>97.9</td>
<td>90.3%</td>
</tr>
<tr>
<td>4</td>
<td>172</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Intervals
1: Placement to abutment surgery
2: Abutment surgery to six months of loading
3: Six months of loading to 3 years of loading
4: > 3 years

**Implant failure registered on patient basis (Paper V)**

In all 46 patients, rotation stability of each implant was manually tested at the abutment connection. Mobile implants were classified as failures and removed. Implant failure was registered on a patient basis. A total of 15 patients had one or more implant failure prior to loading, classified as early failures. Forty-two out of 46 patients were followed a minimum of 3 years after loading of the implants. Four patients were dropouts due to: death (n: 1), moving out from the area (n: 2) and refusal to participate in the study (n: 1). In addition, six patients out of 42 had to remove one or more implants during the three-year follow-up and those patients were classified as late failures.
Tables 13 and 14 shows odds ratios (ORs) with 95% confidence intervals (CIs) for the association between early and late implant failures and graft volume change (GVC), implant stability expressed as Implant Stability Quotient (ISQ), bone volume fraction (BVF), body mass index (BMI), smoking, gender, glucocorticoid medication, bone mineral density (BMD) for total body, femoral neck and L2-L4 (categorized into T-score \(\geq -1.0\) or \(< -1\)). No significant differences were found.

**Table 13. Risk of implant failure prior to loading according to different factors.**

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. of individuals</th>
<th>No. (%) of failures</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GVC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\leq 37.6)%</td>
<td>15</td>
<td>3 (20.0%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>(&gt;37.6)%</td>
<td>15</td>
<td>7 (46.7%)</td>
<td>3.50</td>
<td>0.69-17.71</td>
</tr>
<tr>
<td><strong>ISQ</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\leq 61.7)%</td>
<td>14</td>
<td>6 (42.9%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>(&gt;61.7)%</td>
<td>14</td>
<td>2 (14.3%)</td>
<td>0.22</td>
<td>0.04-1.39</td>
</tr>
<tr>
<td><strong>BVF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\leq 29)%</td>
<td>23</td>
<td>7 (30.4%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>(&gt;29)%</td>
<td>23</td>
<td>8 (34.8%)</td>
<td>1.22</td>
<td>0.36-4.19</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\leq 25)</td>
<td>19</td>
<td>5 (26.3%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>(&gt;25)</td>
<td>27</td>
<td>10 (37.0%)</td>
<td>1.65</td>
<td>0.46-5.96</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>31</td>
<td>12 (38.7%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15</td>
<td>3 (20.0%)</td>
<td>0.40</td>
<td>0.09-1.70</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15</td>
<td>4 (26.7%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>31</td>
<td>11 (35.5%)</td>
<td>1.51</td>
<td>0.39-5.90</td>
</tr>
<tr>
<td><strong>Glucocorticoid medication</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>43</td>
<td>14 (32.6%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3</td>
<td>1 (33.3%)</td>
<td>1.04</td>
<td>0.09-12.41</td>
</tr>
<tr>
<td><strong>BMD Total body</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\geq -1.0)</td>
<td>16</td>
<td>4 (25.0%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>(&lt; -1.0)</td>
<td>5</td>
<td>2 (40.0%)</td>
<td>2.00</td>
<td>0.24-16.61</td>
</tr>
<tr>
<td><strong>BMD Femoral neck</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\geq -1.0)</td>
<td>8</td>
<td>3 (37.5%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>(&lt; -1.0)</td>
<td>13</td>
<td>3 (23.1%)</td>
<td>0.50</td>
<td>0.07-3.44</td>
</tr>
<tr>
<td><strong>BMD L2-L4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\geq -1.0)</td>
<td>9</td>
<td>2 (22.2%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>(&lt; -1.0)</td>
<td>12</td>
<td>4 (33.3%)</td>
<td>1.75</td>
<td>0.24-12.64</td>
</tr>
</tbody>
</table>
Table 14. Risk of implant failure after a minimum follow up of 3 years according to different factors.

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. of individuals</th>
<th>No. (%) of failures</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GVC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤37.6%</td>
<td>14</td>
<td>5 (35.7%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>&gt;37.6%</td>
<td>14</td>
<td>8 (51.1%)</td>
<td>2.40</td>
<td>0.52-10.99</td>
</tr>
<tr>
<td><strong>ISQ</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤61.7%</td>
<td>13</td>
<td>8 (61.5%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>&gt;61.7%</td>
<td>13</td>
<td>3 (23.1%)</td>
<td>0.19</td>
<td>0.03-1.03</td>
</tr>
<tr>
<td><strong>BVF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤29%</td>
<td>21</td>
<td>9 (42.9%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>&gt;29%</td>
<td>22</td>
<td>12 (54.5%)</td>
<td>1.60</td>
<td>0.48-5.34</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤25</td>
<td>18</td>
<td>7 (38.9%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>&gt;25</td>
<td>25</td>
<td>14 (56.0%)</td>
<td>2.00</td>
<td>0.58-6.87</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>30</td>
<td>16 (53.3%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13</td>
<td>5 (38.5%)</td>
<td>0.55</td>
<td>0.14-2.06</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15</td>
<td>5 (33.3%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>28</td>
<td>16 (57.1%)</td>
<td>2.67</td>
<td>0.72-9.87</td>
</tr>
<tr>
<td><strong>Glucocorticoid medication</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>40</td>
<td>20 (50.0%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3</td>
<td>1 (33.3%)</td>
<td>0.50</td>
<td>0.04-5.97</td>
</tr>
<tr>
<td><strong>BMD total body</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥-1.0</td>
<td>14</td>
<td>5 (35.7%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>&lt; -1.0</td>
<td>4</td>
<td>2 (50.0%)</td>
<td>1.80</td>
<td>0.19-16.98</td>
</tr>
<tr>
<td><strong>BMD femoral neck</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥-1.0</td>
<td>8</td>
<td>3 (37.5%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>&lt; -1.0</td>
<td>10</td>
<td>4 (40.0%)</td>
<td>1.11</td>
<td>0.16-7.51</td>
</tr>
<tr>
<td><strong>BMD L2-L4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥-1.0</td>
<td>8</td>
<td>2 (25.0%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>&lt; -1.0</td>
<td>10</td>
<td>5 (50.0%)</td>
<td>3.00</td>
<td>0.40-22.71</td>
</tr>
</tbody>
</table>
A total of 23 publications (Adell et al. 1990b; Isaksson & Alberius 1992; Donovan et al. 1994; Isaksson 1994; Jensen et al. 1994; Misch & Dietsh 1994; Jemt & Lekholm 1995; Krekmanov 1995; Li et al. 1996a; Köndell et al. 1996; Åstrand et al. 1996; Cutilli et al. 1997; Lundgren et al. 1997; Neyt et al. 1997; Nyström et al. 1997; Van Steenberghe et al. 1997; Johansson et al. 1999; Wannfors et al. 2000; Raghoetbar et al. 2001; Widmark et al. 2001; Nyström et al. 2002; Becktor et al. 2004; Sjöström et al. 2005) met the criteria listed. In four papers (Jensen et al. 1994; Lundgren et al. 1997; Becktor et al. 2004; Sjöström et al. 2005) three, two, and two different patient groups were described and analysed as separate patient groups. This resulted in 28 separate patient groups within which a total of 556 patients with edentulous maxillae could be identified. In the 28 patient groups the number of patients varied between 1 and 75, with a mean of 20 patients per group. Gender was reported in 21 of the patient groups: two thirds of the patients were women (66%). The patient groups had a mean age at the time of the bone graft of 54 years (range 46 – 63). In patients where the reconstruction was performed with onlay or sinus inlay together with additional techniques classification was made according to the bone-grafting technique that was employed for the majority of the implants. The use of the onlay bone-grafting technique, alone or with additional sinus inlay or sinus inlay together with nasal inlay, was described in 50% of the patient groups (Adell et al. 1990b; Isaksson & Alberius 1992; Donovan et al. 1994; Jensen et al. 1994; Misch & Dietsh 1994; Jemt & Lekholm 1995; Köndell et al. 1996; Åstrand et al. 1996; Lundgren et al. 1997; Neyt et al. 1997; van Steenberghe et al. 1997; Widmark et al. 2001; Nyström et al. 2002; Sjöström et al. 2005). Sinus inlay alone or with nasal inlay was reported in eight groups (Jensen et al. 1994; Lundgren et al. 1997; Johansson et al. 1999; Wannfors et al. 2000; Raghoetbar et al. 2001; Becktor et al. 2004) and an interpositional bone-grafting technique was reported in six groups (Isaksson 1994; Krekmanov 1995; Li et al. 1996a; Cutilli et al. 1997; Nyström et al. 1997; Sjöström et al. 2005). The anterior iliac crest was described as the donor site in 75% of the groups (21 groups). Other donor sites mentioned were posterior iliac crest (two groups), mandibular symphysis (two groups) and calvarium, lateral sinus wall and rib, one group for each.

In fifteen out of 28 patient groups the implants and the bone graft were placed simultaneously, one stage technique (Adell et al. 1990b; Isaksson & Alberius 1992; Isaksson 1994; Jensen et al. 1994; Jemt & Lekholm 1995; Krekmanov 1995; Li et al. 1996a; Köndell et al. 1996; Åstrand et al. 1996; van Steenberghe et al. 1997; Johansson et al. 1999; Nyström et al. 2002; Becktor et al. 2004). In nine patient groups, the implants were placed in a later procedure (Donovan et al. 1994; Cutilli et al. 1997; Lundgren et al. 1997; Neyt et al. 1997; Nyström et al. 1997; Becktor et al. 2004; Sjöström et al. 2005), and in four patient groups some implants were placed using a one-stage technique and some a two-stage technique (Misch & Dietsh 1994; Wannfors et al. 2000; Raghoetbar et al. 2001; Widmark et al. 2001). The healing time between bone grafting and implant placement in the two-stage technique varied between 3 and 7 months with a majority having 6 months of healing. The minimum follow-up time ranged between 12 and 60 months with a mean of 22 months and median of 13 months. A total number of 2965 implants were included in the 28 patient groups (range 6 – 326, mean per group 106, median 92). During the follow-up time a total of 490 implant failures were reported which gave a survival rate of 83% for all reported patients after a minimum of 12 months.
The number of placed implants, failed implants and survival rate (per cent) for the three different grafting techniques are shown in Table 15. No significant differences were found between the grafting techniques.

**Table 15.** Number of placed implants, failed implants and survival rate for onlay, sinus inlay and interpositional bone-grafting techniques

<table>
<thead>
<tr>
<th></th>
<th>Number of placed implants</th>
<th>Number of failed implants</th>
<th>Survival rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onlay bone grafting</td>
<td>1407</td>
<td>223</td>
<td>84%</td>
</tr>
<tr>
<td>Sinus inlay bone grafting</td>
<td>1074</td>
<td>190</td>
<td>82%</td>
</tr>
<tr>
<td>Interpositional bone grafting</td>
<td>484</td>
<td>77</td>
<td>84%</td>
</tr>
</tbody>
</table>

Table 16 shows the number of placed implants, failed implants and survival rate when the material was divided into three different groups with respect to treatment sequences. A significant difference was found between one-stage and two-stage techniques in favour of the delayed technique (Chi-square test, *p*=0.039).

**Table 16.** Number of placed implants, failed implants and survival with respect to sequence of treatment.

<table>
<thead>
<tr>
<th></th>
<th>Number of placed implants</th>
<th>Number of failed implants</th>
<th>Survival rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One-stage technique</td>
<td>1500</td>
<td>317</td>
<td>79%</td>
</tr>
<tr>
<td>Two-stage technique</td>
<td>740</td>
<td>91</td>
<td>88%</td>
</tr>
<tr>
<td>One- and two-stage techniques</td>
<td>725</td>
<td>82</td>
<td>89%</td>
</tr>
</tbody>
</table>
DISCUSSION

Patients
The patients in Papers I - V were all referred to the Department of Oral & Maxillofacial surgery, Umeå University, for reconstruction of their edentulous atrophic maxillae with autogenous bone grafts and endosteal implants. The patients had previously been investigated at the Department of Prosthetic Dentistry, where the decision for bone reconstruction prior to rehabilitation with a fixed implant-supported bridge was taken. Patients were excluded from bone reconstructive surgery if their general health status could be jeopardized by the use of general anaesthesia. A total of 31 women and 15 men with a mean age of 57 years at the time for the bone-grafting procedure were consecutively included. The patients had been edentulous in the maxilla for 34 years (median time). The reasons for removal of the maxillary teeth were not individually analysed. In the literature survey, Paper IV, the ratio between men and women was also found to be 2:1.

Prior to the reconstructive surgery, the amount of maxillary residual alveolar bone was evaluated in 29 patients in the planned implant sites (Papers III and IV). The results indicated that 61% of the planned implant sites had a class V or VI resorption according to Cawood & Howell (1988) and that only eight% of the planned implant sites had a class III resorption. A transparent template corresponding to an implant with 10 mm length and four mm width was placed for evaluation of tomographic sections on the implant site. The template was used without consideration of angulation or intermaxillary relation. The preoperative evaluation results indicated severe bone resorption of the jaw bone. Nyström et al (1996) performed the same preoperative classification of the alveolar process and found that 13 out of 156 planned implant sites (8%) in 26 patients were suitable for implant therapy with an implant of 7 mm length.

Smokers were advised to refrain from, or reduce, their smoking and were offered a stop-smoking program. Smoking did not exclude any patient from the treatment. Fifteen patients were current smokers at the time for bone grafting.

Surgical techniques
All patients in the present studies were given antibiotics at the time for bone grafting and implant placement for the initial healing period of 7-10 days. Esposito et al (2003) analysed the effects of antibiotics for prevention of complications in dental implant treatment. The authors found that there is not appropriate scientific evidence to recommend or discourage the use of prophylactic systematic antibiotics. All patients were prescribed paracetamol and/or non-steroid anti-inflammatory drugs (NSAIDs) 7 to 10 days postoperatively. The influence of NSAIDs in bone healing was discussed by Aspenberg (2005) who suggested that Cox inhibitors could be detrimental in fractures of long bone shaft fractures, when bone grafting was required or when healing was impaired.

The selection of reconstruction technique was based on evaluation of the intermaxillary relation and the volume and shape of the maxillary alveolar process. To reduce interoperator
variability the same surgeon was responsible for the planning and performance of the bone grafting procedure and the implant placement and abutment connection.

The patients were treated with one of two reconstruction techniques: eleven patients were subjected to interpositional bone graft in conjunction with a Le Fort I osteotomy (Nyström et al 1997), whereas 35 patients were reconstructed with buccal onlay bone grafts together with nasal floor inlay-grafts (Lundgren et al 1997). All 35 patients had onlay bone grafting in the anterior maxilla. In 24 patients the posterior maxilla was also reconstructed using onlay bone grafts, while 11 patients had their posterior maxillae reconstructed with maxillary sinus antral grafting only. The literature survey in Paper IV identified three main techniques for the reconstruction: interpositional bone grafting in conjunction with a Le Fort I osteotomy, onlay bone grafts where the bone graft is placed on the residual alveolar crest as a veneer graft or saddle graft or both, and grafting to the floor of the maxillary sinus.

Grafting to the floor of the antral maxillary sinus alone is not useful in the atrophic edentulous maxilla if there is a need for reconstruction of the alveolar process. All patients in this dissertation were class IV to VI according to Cawood and Howell (1988) with a need for alveolar reconstruction in the anterior maxilla to facilitate optimal prosthetic rehabilitation. The use of onlay bone grafting as an alternative to sinus inlay grafting in the reconstruction of the posterior maxilla has the advantage of restoring the transversal widths. This technique favours the direction of the posterior implants and excludes maxillary sinus surgery. According to Cawood & Howell (1988) resorption in the posterior maxilla is both vertical and horizontal from a buccal aspect, which will create a maxillary dental arch with diminishing transversal width. The interpositional bone grafting in conjunction with a Le Fort I osteotomy is a surgical technique with an advancement of the maxillary bone to correct the intermaxillary relation with simultaneous interpositioning of a bone graft to increase the available bone for placement of the implants. This correction of the intermaxillary relation facilitates the placement of the implants in favourable positions and angulations and allows the fabrication of an implant-supported prosthesis that is acceptable esthetically and phonetically (Nyström et al 1997). The correction of the sagittal relation is also limited due to the fact that the vertical dimension has to be restored. The sagittal advancement of the maxilla has been reported to 4 – 5 mm (Hallman et al 2005a), 5 mm± 3 mm (Nyström et al 1997) and 4 mm (Stoelinga et al 2000). Freihofer et al (1989) discussed the technique with a Le Fort I osteotomy with interpositional bone grafts for 16 maxillary edentulous patients and concluded that the improvement of intermaxillary relationship was more important than the relapse of 1 – 2 mm. Relapses of 1 – 2 mm have also been reported by Nyström et al (1997) who concluded that small relapses seem to have no significant impact if implants are placed after initial healing of the bone graft. In Paper IV the impact of the two bone grafting techniques was analysed in univariate and multivariate analyses. Both analyses showed a non-significant difference for the risk for implant failure between onlay bone grafting and interpositional bone grafting. The literature survey also showed a non-significant difference in implant survival between interpositional bone grafting and onlay bone grafting. No analysis was performed of the impact of simultaneous vs. delayed placement of the implants in the different reconstruction techniques.

**Bone graft**

The selection of bone harvesting area is mainly related to the amount of bone graft needed and thereby the architecture of the donor site. However, factors such as tradition and
previous experience, surgical skill of the surgeon and risk for complications are also important. All patients in Papers I – V were reconstructed with bone graft harvested from the anterior iliac crest as corticocancellous blocks. The literature survey in Paper IV also identified the anterior iliac crest as the most used harvesting site. However, Hall et al (1990) reported in a comparative anatomical study between the anterior and posterior iliac crest that the posterior iliac crest offered more than twice as much cancellous bone as the anterior one. Nkenke et al (2004) compared anterior iliac bone grafting with posterior iliac bone grafting and focused on the superficial sensory function of the skin, gait disturbances and pain level. The authors found that bone grafting from the posterior iliac crest resulted in less complications than from the anterior iliac crest. One disadvantage with the posterior approach is that the patient has to be turned during the operation.

The technique used in this dissertation for anterior iliac crest bone harvesting has been described by Cricchio & Lundgren (2003). The bone harvested from the iliac crest contains large amounts of cortical bone. Animal studies indicate that the micro-architecture, cortical vs. cancellous, can be more important for bone graft maintenance than the embryogenic origin, i.e. enchondral vs intramembranous. (Donovan et al 1993; Ozaki & Buchman 1998).

Lee et al (1994) found that osseointegration for implants was faster in corticocancellous bone blocks than in particulated bone grafts in a dog model. One reason for the difference, according to the authors, could be that the preparation of particulated bone grafts is more traumatic than preparation of a corticocancellous block. The bone graft should preferably be placed on the alveolar crest with the cancellous part towards the alveolar crest, and a perforation of the graft as well as the recipient bed will probably improve the bone incorporation of the onlay graft (Gordh 1998; De Carvalho et al 2000). All bone grafts in the present study were fixed with rigid fixation using titanium screws and lag-screw technique for onlay bone grafting. Titanium plates were used in the interpositional bone grafting situation.

Soft tissue dehiscence and exposure of the bone graft are reported as factors that can jeopardize the graft (Nyström et al 2004). To minimize the risk of soft tissue dehiscence a horizontal periostal incision was made at the time the mucoperiosteal flap was raised. With this technique the soft tissue flap is lengthened to avoid tension and minimize the risk for soft tissue dehiscence and graft exposure. To minimize the risk for traumatisation of the soft tissue the patients were informed to not wear a removable prothesis during eight weeks following surgery. Of the 46 reconstructed patients, one patient had an extreme resorption of the anterior portion of the bone graft and had to be regrafted with a mandibular ramus bone graft prior to implant placement.

**Graft volume change**

In paper V, the onlay bone graft volume was shown to be reduced by 37 % during the first 6 months of bone graft healing. In a comparable study in 10 patients, Johansson et al (2001b) found a volume change of 47 % during the 6-month initial healing period. The difference between the studies might be due to different bone harvesting techniques. The onlay bone grafts in Paper V were harvested from the superolateral part of the iliac crest (Cricchio & Lundgren 2003), which offers a bone graft with a large amount of cortical bone. In the present dissertation, biopsies where taken from the internal plate of the anterior iliac crest at the time for bone grafting for the investigation of individual variation in bone volume fraction. No correlation was found between bone volume fraction and graft volume change. Other studies have shown that bone grafts containing more cortical bone are more resistant to resorption than grafts containing more cancellous bone (Donovan et al 1993; Alonso et al
In spinal fusion surgery, smoking is reported to have a negative effect on bone graft healing (Glassman et al 2000). The mechanism behind the smoking effect is probably related to the inhibition of early revascularization of cancellous bone grafts (Daftari et al 1994). Hollinger et al (1999) wrote that nicotine in tobacco causes peripheral vasoconstriction, tissue ischemia, decreases oxygen tension and depresses osteoblast activity. Riebel et al (1995) studied in a rabbit model the influence of nicotine on the revascularization of cancellous iliac crest bone grafts and reported that nicotine decreased the vascular ingrowth. It can be speculated that this inhibition also has an impact on the graft volume change. However, smoking was not correlated to graft volume change in Paper V.

Prior to bone reconstructive surgery of the present patients, 13 bone metabolic factors were analysed. Only S-IGFBP3 differed, with a majority of the samples above the normal range. IGFBP3 is a binding protein for serum insulin-like growth factor-I (IGF-I) (Banerjee & Clayton 2006). Silha et al (2003) found in a study on mice that an increased level of S-IGFBP3 indicated increased osteoclast number, increased bone resorption and impaired osteoblast proliferation. The result could indicate ongoing bone resorption in the present patients, but the statistical analysis did not verify a correlation between graft resorption and this factor. Twelve factors were within normal from the first classification based on normal ranges.

Parathyroid hormone, thyroid hormone, androgen, estrogen, S-Cortisol and S-Calciitrol are involved in the systematic regulation of bone remodelling (Raisz 1999). Osteocalcin is a noncollagenous bone matrix protein synthesized by osteoblasts and is a sensitive marker for bone turnover and bone formation (Thorsen 1996; Reinhardt et al 2004). Insuline-Like Growth Factor-1 (IGF-1) is involved in regulation of the osteoblast (Hughes 2006). S-ICTP (carboxy-terminal telopeptide of type I collagen) is released from collagen during breakdown and used as a marker for bone resorption (Reinhardt et al 2004). Regulation of bone metabolism as well as fracture healing is a complex process (Raisz 1999; Lerner & Lundberg 2002; Dimitriou et al 2005; Niu & Rosen 2005), and the statistical analysis could not verify a correlation between graft volume change and the evaluated haematological factors. However, a non-significant correlation was found for S-osteocalcin and S-ICTP and might indicate a reduced bone remodelling.

Three patients were on steroid medication at the time for bone grafting surgery but any impact on the graft volume change was not observed.

Analysis of the relation between bone mineral density (BMD) measurements and bone graft volume change showed a significant association with BMDs of vertebrae L2-L4. BMD measurements showed different results in different parts of the body of the same patients, which is also supported by the findings of other authors (Kanis et al 1994). However, not all patients were evaluated with BMD, which limited the statistical analysis and conclusions. Analyses of BMD have not proved that the jaw bone is affected in case of osteoporosis, but jawbone responds to osteoporotic treatments similar to other sites in the skeleton, which would indicate that jawbone is susceptible to osteoporosis (Lerner 2006). The situation with reconstruction of the atrophic edentulous maxilla is complex, since the bone graft will be incorporated with the alveolar process through a healing process. The early phases of bone graft healing have many aspects in common with fracture healing (Burchardt 1987). The fracture mechanism in patients with osteoporosis is not different from that of healthy objects. However, because the structural and material properties of the cortical and trabecular bone, fixation strength will be affected, which can affect the healing (Chao et al 2004). The importance of rigid fixation for bone graft volume maintenance is well described (Philips &
Rahn 1988; Lin et al 1990), and in the situation of bone reconstruction to the alveolar process the rigid fixation will probably enhance the healing and reduce the graft volume resorption.

**Microimplants**

The microimplant technique was used as a model for the evaluation of the bone graft-titanium interface. The microimplants did not interfere with the ordinary implant treatment and were well accepted by the patients. The retrieval of the microimplant together with the surrounding bone caused bleeding from the reconstructed alveolar process, indicating revascularization of the bone graft. The histomorphometric and histological analyses of the microimplants showed that the delayed placement resulted in better integration of the microimplants as compared with the simultaneous technique. In the former situation, the graft will be partly revascularized and will contain regenerated bone and bone marrow at the time of microimplant placement. The regenerative capacity of bone is determined by the presence of vessels, bone marrow and vital bone surfaces. In the delayed placement situation, the surgical trauma will most likely stimulate an immediate healing response, which is in contrast to implant placement simultaneously with bone grafting where the implant will be placed in a practically non-viable bone. The clinical outcome with implant survival was analysed in the literature survey in Paper IV. In the comparison between one-stage and two-stage surgery there was a significant difference between the implant survival rates favouring the two-stage technique. However, in situations with one-stage surgery, implants can achieve integration and remain stable. In the literature survey the implant survival rate was 79% for one-stage surgery after a minimum follow-up period of 12 months. This result can probably be attributed to sufficient integration in the recipient bone. Jemt & Lekholm (1995) found that the survival rate of short implants placed in patients with severe maxillary bone resorption without bone grafts was only somewhat higher compared to that in patients treated with bone grafts and implants in a one-stage procedure over a 5-year period.

The bone graft-titanium interface was analysed for differences between interpositional bone grafts and onlay bone grafts. The results indicated a similar integration between the two bone grafting techniques. The blood supply in the host area is essential for bone grafting (Cutting et al 1990) and bone healing (Dimitriou et al 2005). The interpositional bone grafting technique after a Le Fort I osteotomy is a more invasive surgical technique than the onlay bone grafting technique, which can affect the blood supply to the host area. This can explain the tendency for lower mean values for microimplants placed simultaneously with interpositional bone grafts and retrieved after 6-months of healing. However, the microimplants allowed to heal for 12 months and those placed after initial healing of the bone grafts showed similar or higher mean values, which would indicate that the maxillary blood supply was restored after the Le Fort I osteotomy. The literature survey in Paper IV found a non-significant difference in implant survival between interpositional and onlay bone grafting techniques.

The bleeding from the biopsies indicated revascularization of the bone graft, but one can speculate if the bleeding itself indicates an optimal capacity for implant integration. In comparison between one-stage and delayed placement of microimplants, the results from the simultaneously placed microimplants indicated that 6 or even 12 months were too short healing time for optimal integration in bone grafts. The comparison between microimplants placed in residual alveolar crest and microimplants placed in bone grafts and retrieved after 6
months showed that the microimplants in residual alveolar crest had significantly higher values.

The histomorphometric analysis as well as the histological analysis was performed in one section per specimen. One can speculate if this section was representative for the entire specimen. Serial sectioning had probably resulted in a more accurate analysis of the bone-implant interface. However, the ground sectioning technique used in the present study does not allow serial sections of such thin implants. The thickness of the sections was about 10 μm, which gives accurate measurements according to Johansson & Morberg (1995) who found that morphometrical parameters could be overestimated for sections over 30 μm. Moreover the purpose of the morphometrical measurements in the present study was to compare three groups of microimplants rather than describing the true degrees of bone contacts and bone areas.

### Resonance frequency analysis (RFA)

The resonance frequency registrations were easy to perform without any side effects for the patients. Meredith et al (1996) have found the error to be less than 1 % with a repeatability of resonance frequency measurements which is in line with Nedir et al (2004) who found a repeatability of 1.14 %.

In Paper III a comparison of the stability, as measured with RFA, was performed between the grafted and non-grafted maxilla. At the time for implant placement, implants placed in grafted bone showed a tendency for higher stability as compared with implants placed in non-grafted maxillae. The difference in ISQ values at the first registration was probably an effect from the difference in final drill diameter. In the grafted situation the final drill diameter was 2.85 mm whereas it was 3.0 mm in the non-grafted situation. The same effect can be obtained by using a tapered implant design. O'Sullivan et al (2000) found a higher primary stability for tapered implants in comparison with cylindrical implants when both where placed in soft bone (type IV according to Lekholm & Zarb 1985). The reduced drill diameter or a tapered implant will create high compression stresses when placing the implant. In the grafted situation the stability decreased between implant placement and abutment connection. This is probably due to mechanical stress relaxation as well as some demineralisation of the interfacial bone in response to the compressive loading. This finding with initial decrease of implant stability is also found in studies on one-stage and immediately-loaded implants (Glauser et al 2005; Balshi et al 2005). The results from Paper III indicated that the stability of implants placed in bone grafts became as stable as implants placed in a non-grafted maxilla after 6 months of loading. The results from Paper III also showed that implants with a high initial stability had a reduced stability during healing and that implants with low initial stability according to RFA had an increased stability during healing. Nedir et al (2004) and Becker et al (2005) also report this finding. Friberg et al (1999c) found that the implants placed in maxillary bone reached similar levels of stability after one year of loading irrespective of the initial stability. That result indicates that differences in stability between implants will diminish with time. This may be due to the fact that similar bone density is reached with time as a result of bone formation and remodelling. In Paper III there was a significant increase in ISQ value between the abutment connection and the 6-month follow up. In Paper IV a three-year follow-up was performed for implants placed in bone grafts with a non-significant difference between the two last RF registrations. There was a significant difference between anteriorly and posteriorly placed implants at the first and last registration.
This finding is in contrast to Bischoff et al (2004) who found a non-significant difference between anteriorly and posteriorly placed implants at the time of placement and after 12 weeks of healing. Baller et al (2002) found a non-significant difference between anteriorly and posteriorly placed implants when stability registrations with RFA were performed on 45 implants after 1 year of loading. The same non-significant difference between anterior and posterior placed implants was found in the RF-registrations at the abutment connection and the 6-month follow-up. At the six-month and three-year follow up there was an increase in stability for posterior placed implants. One can speculate whether the change in stability is due to the fact that the implants were loaded.

The impact of implant length was evaluated in Paper IV. A significantly higher ISQ value at the time for implant placement was found for 15- and 18-mm long implants as compared with 10- and 13-mm implants. This result would indicate that implant length correlates to the ISQ value. This finding is in contrast to Bischof et al (2004) where no correlation was found. Östman et al (2006) reported a decreased ISQ value for increasing implant length. This finding could be explained by the fact that long Bränemark® implants have a reduced diameter in the coronal direction to reduce friction heat. Miyamoto et al (2005) also found a negative correlation between implant length and resonance frequency. The authors found a positive correlation between cortical thickness and resonance frequency. They concluded that the initial stability at the time for implant placement is more influenced by cortical thickness than by implant length. That conclusion can explain the difference between the ISQ value between interpositional and onlay bone grafting at the time for implant placement in Paper III. In the interpositional bone grafting situation, the alveolar process of the residual maxilla has a higher cortical bone content than for onlay bone grafting where the implants are placed into the grafted bone which is being remodelled.

Can the RF value at the time for implant placement serve as an indicator for the risk of implant failure? As found in Paper III and by other authors (Barewal et al 2003; Glauser et al 2004; Balshi et al 2005) the implant stability decreases during the initial healing period. Glauser et al (2004) performed monthly RF registrations during the first three months of implant healing for 81 immediate-loaded implants. The RF value at the time for placement did not differ between 72 implants that remained stable and 9 implants that failed during the study. A significant difference between failing implants and implants that remained stable was evident at the RF-registration after one month. The lower the ISQ value after one month of immediate loading, the higher was the risk for future failure. For instance, there was an 18.2 % risk for failure if ISQ levels were between 49 to 58.

Friberg et al (1999d) reported on 75 one-stage implants in the edentulous mandible. One implant showed decreasing RF values from 2 to 15 weeks when clinical mobility was evident. In another patient three of five implants showed a dramatic drop in RF value from 2 to 6 weeks postoperatively, when the implants were loaded with a relined denture. After unloading of the implants two showed increasing RF values. The results from Friberg et al (1999d) indicate that RF measurements can identify failing implants and that failure may be avoided by unloading. On the other hand, with a single RF registration at the time for implant placement there is risk of missing a failing implant with a high initial ISQ value. In a study comparing immediately loaded ITI® implants and implants loaded after 3 months of healing Nedir et al (2004) concluded that the RFA technique was not a reliable tool to identify mobile ITI® implants. However, implant stability could be reliably determined for implants with an ISQ above 47.
In Paper IV the ISQ values were evaluated both on a patient level and for individual implants. There was a non-significant difference when comparing the ISQ value for implants that remained stable to the implants that failed. On the other hand, in the comparison for the individual implants there was a significant difference in ISQ value between failing implants and implants that remained stable throughout the follow-up period of three years. From the results in Papers III and IV one can speculate that implants with high ISQ values during follow-up are successfully integrated, while low and decreasing ISQ values may be a sign of ongoing disintegration and/or marginal bone loss. Therefore, the ISQ value at the time of placement can probably serve as an indicator of the level of risk for implant failure. The prognostic value of RFA has yet to be established in prospective clinical studies (Aparicio et al., 2006), and ISQ levels should be calibrated for each implant system (Ersanli et al., 2005).

**Implant failure**

The result from the three-year follow-up in Paper IV showed that the cumulative survival rate was 90% when analysing the individual implants. In the literature survey the implant survival rate was 88% after a minimum follow-up period of 1 year for the two-stage technique. The 90% survival rate is comparable to the results in long-term follow-up studies on implants placed in non-grafted maxillae (Adell et al., 1990; Ferrigno et al., 2002). All patients in Paper IV were provided with a fixed bridge at the time for the three-year follow-up. During the three-year follow-up, one patient with 5 late implant failures was identified. That patient was offered removal of the implants and the bridge but refused at that time. The patient was later re-operated. In Paper IV, 12 of 20 implant failures occurred prior to loading for patients who fulfilled the three-year follow-up. A multivariate analysis of factors that could explain implant failures showed a significantly increased risk for women. This is in line with the findings from other studies. For instance, Schliephake et al. (1997) studied 137 patients who were reconstructed with bone grafts prior to or in conjunction with implant placement. The only factor of prognostic relevance was gender with a significantly worse prognosis for women. Nyström et al. (2004) reported on a 10-year follow-up of patients reconstructed with onlay bone grafts and implants placed in a one-stage procedure. The total group of 30 patients was divided in a development group of 10 patients and a routine group of 20 patients. The 10-year implant survival rate was 72.8% for the whole group, 50.9% for the development group and 83.1% for the routine group. In the total group there was a significant difference between women and men with higher implant failure rate for women. In the multivariate analysis a class VI resorption (Cawood & Howell, 1988) prior to reconstruction was significantly associated with implant failure. The class VI resorption indicates a resorption to basal bone, which creates a reconstruction both on height as well as width.

In the material included in Papers I – V, 14 out of 21 patients lost one implant; three patients lost two implants and three patients lost three implants. All patients, but one, were provided with and continued to use an implant-supported bridge in spite of the failures. One patient with 5 implant failures lost the bridge after 3 years of loading. The patient was later re-operated and provided with a new fixed bridge. In Paper V, implant failures were registered on patient level instead of the individual implant. Fifteen of 21 patients with implant failures had the implant failure prior to loading. Six patients had to remove one or more implants from bridge delivery up to 3 years of loading. Implant failures prior to loading or at the time for the three-year follow-up did not correlate to any of the investigated factors. The effect of smoking on implant failure was evaluated both in Paper IV and V. In Paper IV the
association between smoking and individual implant survival was estimated with odds ratios and confidence intervals but no association was found. Also in Paper V, where implant failures were registered on a patient level basis, no association was found. Several authors have discussed the effect of smoking on implant failure (Bain and Moy 1993; Vehemente et al 2002; Chuang et al 2002), and all found that smoking negatively affects the implant survival rate. Vehemente et al (2002) and Chuang et al (2002) analysed the same patient material of 677 patients with Bicon® dental implants placed in two different ways. Vehemente et al (2002) analysed one randomly selected implant from each patient whereas Chuang et al (2002) analysed all 2349 implants placed in 677 patients. Kan et al (1999) found that smoking negatively affected the implant survival rate in patients with grafted maxillary sinuses. Peleg et al (2006) analysed 2132 implants placed in grafted sinuses with a one-stage technique with different graft materials and found no significant difference in implant survival between smokers and non-smokers. The authors speculated that patients who abstained from smoking prior to surgery and 10 days afterward could avoid complications that are frequently observed in smokers. Hallman et al (2005b) reported a three-year follow-up on patients where a sinus floor augmentation with 80:20 mixtures of deproteinized bovine bone and autogenous bone was used for reconstruction of the maxillary sinuses. The authors found a correlation between implant failure and smoking. From the literature smoking seems to negatively affect implant survival for non-grafted situations, while the impact of smoking on the grafted patient receiving implants is not conclusive.

In a review, the impact of general health on implant failure was discussed by Esposito et al (1998b). The authors summarized that there are only a few studies analysing success rates of implants in relation to systemic conditions and that there is a need for well-designed prospective follow-up studies. Chuang et al (2002) performed an analysis of risk factors for implant failure in 677 patients who had 2349 implants placed. In the analysis of the impact of general health for implant failures they found that 99 % of the patients were healthy or had a mild systemic disease and that general health did not have an impact on implant failure.

Resonance frequency (RF) measurements at the time of implant placement showed a tendency toward lower values for future failing implants than implants that remained stable throughout the follow-up at the patient level, but the difference was not statistically significant. However, when using the implant as a unit, a significant difference could be established. Thus, the findings indicate that implants with low stability at placement are more prone to failure.

The analysis of the marginal bone level indicated a change of the marginal bone level of 0.3±0.3 mm from bridge loading to the three-year follow-up. No radiographic examination was performed at the time for implant placement, which precluded the analysis of the change for the marginal bone level during the initial healing period prior to bridge loading. Åstrand et al (2004) reported a steady state of the marginal bone level after three years of loading in the majority of cases provided with ITI® dental implants and Brånemark® implants placed in partially edentulous maxillae. Nyström et al (2004) found a stable marginal bone level after 3 years in a 10-year follow up of grafted patients. The possibility of identifying failing implants in radiographs seems difficult in the grafted situation. Nyström et al (1996) reported on 30 patients reconstructed with onlay bone grafts and endosteal implants in a one-stage surgery, only 3 of 26 failed implants showed an absence of osseointegration in the radiographs. Johansson et al (1999) found several implant failures that were completely unexpected because no peri-implant radiolucency was seen. These findings indicate the importance of manual tests of each individual implant for the evaluation of osseointegration. Esposito et al (1998a) concluded that “radiographic examination together with implant mobility test seems
to be the most reliable parameters in the assessment of the prognosis for osseointegrated implants”.

Post-dissertation protocol

The goal for development of the present protocol for surgical/prosthetic reconstruction of the atrophic edentulous maxilla ought to be to further increase the predictability and to shorten the treatment period. With the present protocol, reconstruction with bone grafts and placement of implants is a procedure that takes at least 1 year. Another goal is to reduce the discomfort of not being able to wear prosthesis after grafting. Moreover, negative side-effects of the surgical procedures per se should be reduced to a minimum.

The superolateral technique of bone harvesting from the iliac crest used in the present dissertation has been further refined and larger amounts of cortical bone can be harvested without increased morbidity (Cricchio & Lundgren 2003).

With the knowledge from the histomorphometric analysis all reconstruction procedures of the edentulous atrophic maxilla in our department are preformed in two stages. A period of 6 months is used for healing of the autogenous iliac crest bone graft after which the titanium implants are placed. Although 6 months of bone-graft healing is believed to be necessary, the time of implant healing may be reduced. In a study on mini-pigs Zechner et al (2003) compared osseous healing characteristics of three different implant types. Comparison of the bone-implant contact during the first 12 weeks of implant healing was made between anodically modified implants, machined implants and hydroxyapatite (HA)-coated implants. The surface-modified implants had a higher bone-implant contact as compared with the machined-surface implants during the follow-up period. Ivanoff et al (2003) compared screw-typed turned microimplants with oxidized microimplants in a study on 20 edentulous patients. The patients had one turned and one oxidized microimplant placed in the alveolar crest. After 3 to 6 months healing the microimplants were removed together with the surrounding bone. The oxidized microimplants showed higher bone-implant contact and bone area within threads. Hallman et al (2005a) reported on 22 patients who had their atrophic edentulous maxilla reconstructed with interpositional bone graft in conjunction with a Le Fort I Osteotomy. They compared turned Bränemark System® implants (Nobel Biocare AB, Göteborg, Sweden) with Astra Tech implants with a blasted titanium surface (Tioblast®, Astra Tech AB, Mölndal, Sweden). The authors found no difference in implant survival and marginal bone level between the two implant systems after 5 years of loading. Brechter et al (2005) reported on 47 patients reconstructed with six different reconstructive procedures. A total of 200 oxidized titanium implants (Mk III, TiUnite™, Nobel Biocare AB Göteborg, Sweden) were placed and the implant survival rate was 98.5% after a mean follow-up period of 30 months.

All implants in Papers I – V were placed with a modified surgical technique with reduced drill diameter. Albreksson (2001) concluded that focus should be on the surgical and prosthetic skills and not only on modifications on the implant surface. In the planning of the number of implants, the patients have received eight implants in onlay bone grafts and six in interpositional bone grafts. In patients that received eight implants, removal of one implant will not affect the possibility of making a fixed bridge. In the material included in Papers I – V, 14 out of 21 patients with implant failures lost one implant, three patients lost two implants each and three patients lost three implants each. For all these patients the use of an implant-supported bridge could be continued. Only in one patient with five implant failures
did the supraconstruction have to be removed and the patient re-operated and provided with a new bridge.

A second possibility for shortening the treatment time is to reduce the bone-graft healing time. Raghoebar et al (2003a) reported on 10 maxillary edentulous patients that were reconstructed due to a severe resorption (Class V-VI according to Cawood & Howell 1988). The healing time between bone grafting and implant placement was 3 months. Sixty-eight endosseous implants were placed with one-stage implant placement technique and were loaded after 2 months. Implant survival rate after 1 year was 96%.

A third way to reduce the reconstruction treatment period is to provide the patient with a fixed temporary bridge immediately after implant placement. The temporary bridge will also splint the implants immediately to reduce the risk of micro motion during healing. This will shorten the time the patient has to be without a fixed supraconstruction and will eliminate the use of a removable prosthesis. Stability measurements with RFA may be used to judge if it is possible to provide the patient with a bridge immediately after the implant placement. The results from the use of early (Raghoebar et al 2003b) and immediate loading (Chiapasco & Gatti 2003) of implants placed in the edentulous mandible have shown that there is a possibility to load the implants early. Also reports on early or immediate loading of implants placed in the edentulous non-grafted maxilla show encouraging results (Fischer and Stenberg 2004; Bergkvist et al 2005; Östman et al 2005). This concept might be used in the treatment of the bone-graft reconstructed edentulous maxillae. However, this requires prospective controlled studies.
CONCLUSIONS

- Placement of titanium microimplants in iliac crest bone grafts after an initial healing period of 6 months results in better integration than when placing microimplants simultaneously with the bone grafts.
- There are no differences in bone integration of microimplants when placed in onlay bone grafts or interpositional bone grafts.
- Implants placed in the grafted maxilla after an initial healing period of 6 months achieve a similar stability as implants placed in non-grafted maxillae.
- Low primary implant stability as measured with RFA is a risk factor for implant failure in the grafted maxilla.
- The cumulative survival rate for implants placed in the grafted maxilla after an initial healing period of 6 months is 90% after 3 years of loading.
- The volume decrease of iliac crest bone grafts in the maxilla during an initial healing period of 6 months is significantly correlated with BMD of the lumbar vertebrae L2-L4.
- Implant failure does not correlate with factors such as BMD, bone graft density and change of bone graft volume.
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