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Impact of systemic diseases and medication on osseointegration

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Relevance of the subject

The serendipitous finding by P.-I. Brånemark that bone tissue can adhere permanently and intimately to an implant surface led to a clinical breakthrough in oral rehabilitation (7). After some pioneering years, excellent results were reached in the edentulous mandible for screw-shaped implants with a well-defined surface geometry: a 99% cumulative success rate cumulative success rate after 15 years (36). In other anatomic locations and in partial edentulism, the results for the same implant system were slightly lower (53). Although medium-term results for some other implant configurations are also good, the results of some are below acceptable levels – below 80% after a few years even in favorable anatomic locations (53). There are many short- or medium-term reports but unfortunately most authors use a self-developed definition of success or confuse survival with success, although several proposals for such definitions have been made (52). Comparison between studies is even more difficult, because the selection criteria for patients lack homogeneity. Indeed, some centers do not tend to recruit patients with a compromised health or unfavorable local bone anatomy. Other centers take in any patient in need of rehabilitation by means of endosseous implants whatever the systemic or local conditions. There are a number of papers dealing with the impact of systemic factors on the outcome of osseointegrated implants but one has to be cautious because it is not possible to collect much information from retrospective studies. The authors either do not give enough insight into the occurrence and nature of the systemic factors among the patients involved (48) or they exclude such patients. It also remains a debated question if some systemic factors compromise the achievement of an intimate bone–implant interface or rather its maintenance over time. It is especially during the healing time, up to abutment surgery, that systemic factors can be most easily identified as risk factors from many other cofactors, which occur after abutment surgery and especially after occlusal loading.

The mean survival age of implants is increasing in both genders. Implant-based treatments are gaining importance but so are the challenges, because of intercurrent systemic factors. Another aspect is the risk of complications due to the surgical treatment itself, which may interfere with the course of the systemic condition.

Age

Aging in mammals and especially humans can be observed from the molecular to the body level. There is, among many observations over time an increase in chromosomal abnormalities and in DNA methylation. We will focus on the properties of bone that are the most relevant for osseointegration. It has been established that the secretion of parathyroid hormone increases with age, both in men and women (10). The cause and result of this, on bone remodeling, remains unknown. There is a decrease of calcitonin and of vitamin D absorption and activation, which can lead to osteopenia and eventually to symptoms of osteomalacia. Because of the increased pH of the stomach fluid, there is a decreased absorption of Ca^{2+} which may lead to osteoporosis and a vitamin B12 deficiency. About half the women older than 65 show evidence of osteoporosis. Elderly men have a decreased testosterone level but it has not been established that this causes osteoporosis at the clinical level, even if evidence exists from animal research (57).

At the histologic level one sees a thinning of the cortical bone and increased trabecular spacing. A

striking characteristic of bone in the elderly, which is of great relevance to the process of osseointegration, is the number of dead osteocytes. Osteocytes have an average life span of 35 years. Eventually, a mineralization of the lacunae around the dead cells and the canaliculae in the vicinity, obliterate the latter. This leads to sclerotic bone, which may appear dense on radiographs but which is brittle.

Another characteristic of bone tissues in the elderly is a reduced vascular supply. This can reduce the oxygen tension, which is a critical factor for bone apposition. The reduced cellularity and reduced vascularity are two factors which may reduce the chances of proper osseointegration.

In a comparative study between groups of younger and older patients (<30, 31–40, 41–50, 51–60, 61–70, >70 years), Bass & Tiplett (4) found success rates above 93% for individual implants (Brånemark system®) in all age groups. When comparing the survival rate of oral implants in medically compromised and healthy patients, Smith et al. (48) investigated age as a covariable. In 24 patients older than 65 years, they found less than 1% implant failure. In a series of more than 200 implants inserted in patients more than 80 years old, Jemt (28) reported a success rate of 96% for an observation time up to 4 years. Using the dental implant registry of about 600 patients at the Department of Veteran Affairs in the USA, which did not distinguish between implant types, implant survival could not be associated with age (56).

In a retrospective study (8), 39 patients above the age of 60 (mean 66 years, varying from 66 to 74 during the duration of the study) were rehabilitated by means of Brånemark system® implants for various types of edentulism and by various prosthetic superstructures. A second group of young individuals (all less than 50 years old at the beginning of the study) was matched for implant length, type of prosthesis, anatomic location, etc. With a follow-up of up to 16 years the study indicated a 92.0% cumulative success rate in the older group vs. 86.5% in the younger group, a difference which was not statistically significant. In a prospective study involving more than 4500 Brånemark system® implants focusing on early failures (19), age again did not seem to play a role.

In a 3-year prospective study on overdentures supported by two symphyseal implants (Brånemark system®, IMZ® and ITI®) Meijer and coworkers (41) compared the success rate and several periodontal parameters in two groups of patients (32 and 26 patients each) over 50 years of age (average 44 and 67 years). No difference was observed in implant success between age groups except for a non-significant tendency to have more marginal bone loss in the younger group (1.2 mm vs. 0.8 at 3 years).

From all the data available, one can conclude that age as such, even advanced, does not has an impact on osseointegration or the survival of oral implants afterwards. This should encourage the use of endosseous implants in the elderly. There is an increased risk for bone resorption in edentulous areas over time, and denture wearing can even enhance this process (9).

Young age, although not a risk factor as such, may be a challenge because one has to take into account the reduced bone volume available and the fact that neighboring teeth with their periodontium will further erupt, while endosseous implants maintain their original position. This may lead to occlusal dysharmony (33).

Bone factors

Since the principle of osseointegration is based on intimate bone to implant contact that is achieved during healing and is maintained over the years even under loading, it is logical that bone volume and quality are factors of relevance. While bone volume can easily be assessed by radiographic investigations, preferably in two planes, this is less evident for quality. The latter implies the assessment of several aspects going from vascularity to cellularity and from biomechanical properties to bone turnover. So far, the scientific community has assumed that a certain degree of mineralization is needed to ensure a sufficient stability of the newly inserted implant. Too large micromovements during the initial healing phase may lead to fibrous encapsulation rather than to bone apposition (1). Other aspects of bone have not been investigated in conjunction with endosseous implant placement except for extreme situations such as after radiotherapy, where both cellularity and vascularity are profoundly affected. Poor biomechanical parameters have been considered synonymous with lack of mineralization in the trabecular and/or cortical parts of jaw bone. Below, the underlying pathophysiology will be briefly updated before addressing the few available clinical papers. It is striking that the characterization of bone quality in many clinical environments is not performed according to available techniques. Probable reasons for this are the lack of training of the clinicians involved in this specialized matter, and the fact that the cost of the investigations outweighs

the relatively limited impact on the success rate of endosseous implants.

Osteomalacia

Osteomalacia means a defective mineralization of the organic bone matrix, i.e. collagen. The disorder in adults is often associated with vitamin D deficiency and alimentary deficiencies. Vitamin D deficiency (as in celiac disease, an intestinal malabsorption syndrome) reduces the intestinal uptake and the mobilization of calcium from the bone and thus results in hypocalcemia. This leads to an increased parathyroid hormone (PTH) secretion, which in turn increases the clearance (by the kidneys) of phosphorus. The decrease in the concentration of the phosphorus in the bone fluids prevents a normal mineralization process. This can also result from the intake of antacids or from some renal anomalies (vitamin D-resistant osteomalacia). Serum analysis shows normal calcium but lowered phosphorus and 25-hydroxyvitamin D levels. The radiologic characteristics of bone in osteomalacia are a thinning of the cortices and a decreased density of the trabecular part.

For elderly patients, treatment involves the oral intake of 50,000 IU of vitamin D once a week for 8 weeks. In the case of malabsorption, higher dosages must be considered and possibly a parenteral route. In patients taking anticonvulsants, a daily dose of 1,000 IU is recommended.

The effect of therapy can often be seen in a few months at the radiologic level. An added calcium oral intake is needed if insufficient alimentary doses are noted. One should definitely not provide more phosphorus, which would counteract the uptake of calcium. Osteomalacia related to renal diseases requires a subtle treatment which goes beyond the borderlines of this paper.

No reports could be traced on the clinical relevance of osteomalacia for the outcome of oral implants. It may well be that some osteomalacia patients have been previously categorized in the groups of osteoporosis or ''poor bone quality'', the category IV bone that has been clearly associated with a higher failure rate (20, 27).

Osteoporosis

Osteoporosis can be defined as a reduced weight per volume unit of the bone, without a modified mineral to organic matrix ratio or any anomalies in either. It is a negative balance of bone remodeling which results in a decreased number and diameter of bone trabeculae and a thinner cortex. The bone remodeling is faster in the trabecular part than in the cortices. Radiologically, one will note a decreased density of the inner part before a thinning of the cortices. Since as much as 30% of the bone mass may disappear before it becomes visible on radiographs, techniques other than visual inspection of radiographs, such as dual energy X-ray absorptiometry or dual-photon absorptiometry (25) or quantitative computerized tomography, are mandatory to explore the presence of a clinically relevant osteoporosis. Quantitative computerized tomography is the most generally available method. It measures bone density through a coefficient of linear attenuation. The relationship between mandibular bone density and the bone density of the rest of the skeleton (vertebrae) seems poor (5, 12), which indicates the need to investigate the jaw bone rather than to rely on general bone information.

One distinguishes between type I osteoporosis, associated with menopause and characterized by a negative bone turnover in the trabecular part, and type II osteoporosis, which equally occurs in aged (over 70 years) men and women and which is associated with loss of bone mass in both the cortical and trabecular part (like the jaw bone). Type I osteoporosis is therefore associated with fractures of the vertebrae and type II osteoporosis with fractures of the femoral neck. No anomalies of either calcium or phosphorus are found in blood tests, not even of alkaline phosphatase, which is a marker enzyme with osteoblastic activity. On the other hand, signs of increased bone loss are seen in urine, showing an increased level of calcium and pyridinoline.

Epidemiologic data clearly show that osteoporosis is increasing among the elderly male population, and 50% and more of the female population above 65 years old. In the US alone, more than 10 million women are suffering from osteoporosis type I. From experiments in animals, it appears that estrogen deficiency leads to a reduction of bone mineral density in loaded bones (31). There are indications from study in sheep that alveolar bone mineral density may be an early diagnostic tool of osteoporosis, as are some salivary concentrations of interleukin (IL)-6 and osteocalcin (31).

The treatment of osteoporosis (37), both preventive and curative, unfortunately does not get the attention it deserves. If the installation of endosseous implants is considered in the presence of signs of osteoporosis, a treatment should be considered even if it appears that fracture healing is impaired. The biomechanical characteristics of osteoporotic bone do not offer the same stability to osseointegrating

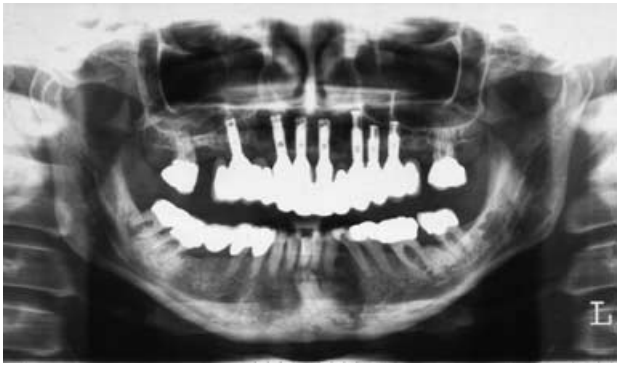

Fig. 1. Osteoporotic bone with lacunae in a 61-year-old woman treated by hormone replacement therapy. (In the mandible, other abnormalities can be detected.)

implants, being similar to the Lekholm & Zarb (35) type IV bone, in which a decreased success rate has been clearly demonstrated. The success rate of implants in osteoporotic bone has hardly been investigated.

In menopausal women, estrogens, which are known to retain calcium, can be added as a hormonal substitution therapy (22). In a recent study investigating the effect of estrogen replacement therapy postmenopausal women not taking estrogen replacement therapy had nearly twice the maxillary implant failure rate (13.6%) compared to other groups (8.1%, 6.3%, 6.3%, and 7.6%, respectively, for postmenopausal women plus estrogen replacement therapy, premenopausal women, men <50 years and men >50 years) (2). An alternative in estrogen-deprived women is an added daily calcium intake of 1,500 mg. To enhance calcium uptake, a supplementary dose of vitamin D (1000 IU/day) is also recommended.

Therapeutic approaches for established osteoporosis involve prescription of biphosphonates and calcitonin. Biphosphonates (such as alendronate or tiludronate) are inhibitors of bone resorption. The usual dose is 10 mg/day, which should be prescribed for months and which can efficiently increase the bone mineral density (45). The patients should be instructed not to take any calcium-rich food (milk) ahead of or after the intake of the biphosphonates. Biphosphonates should also be taken while standing and with ample water to avoid risk of esophagitis.

Calcitonin, a polypeptide normally secreted by the thyroid gland, inhibits bone resorption and alters the calcium metabolism. There are synthetic forms derived from salmon (salcalcitonin) which can be applied parenterally, or through a nasal spray (200 IU/day corresponding to one spray in each nare), which is advocated for 4 weeks. The treatment can be reinstated after some interruption. A side effect of the spray is nasal congestion.

''Poor'' bone quality

Because of the special clinical settings in which patients receive implants, and which may vary from a university hospital to a general dentist's clinic, many patients with osteoporosis or osteomalacia are not properly diagnosed. The clinician, with sometimes limited training in detecting bone diseases, will notice a poor degree of mineralization of the jaw bone or will experience a limited resistance by tactile assessment while drilling. This type of jaw site fit into the category of quality IV bone according to the Lekholm & Zarb classification (35). All studies indicate that the failure rate is greater in type IV bone (16, 19, 27).

It has been demonstrated from a study on *ex vivo* human preparations that the cutting resistance during implant installation correlates well with the bone density as assessed by microradiography (20).

From animal experiments (30) it has been ascertained that the healing time before loading implants in less dense bone should be extended. Thus, the measuring of the countertorque at implant installation is relevant. Poor bone quality may also encourage, for these special indications, the use of more ''active'' surfaces than the classical machined c.p. titanium surface, which was used in the above-mentioned papers.

Diabetes mellitus

Diabetes mellitus is a common endocrine disorder, which is normally subdivided into type I and type II. Type I and type II diabetes mellitus are to many synonymous with insulin-dependent (IDDM)- and non insulin-dependant (NIDDM). This is not really the case, since type II diabetes patients may become completely insulin dependent to avoid ketoacidosis. Therefore, in a more updated classification, type I refers to an autoimmune etiology (whatever be the trigger) and type II to a non-autoimmune etiology. In both categories there may be patients who are insulin dependent, or not.

It is well established that diabetic patients are more prone to healing complications of even clean wounds (23, 40). For extraction wounds, unbalanced diabetes leads to delayed wound healing (14).

Uncontrolled diabetes in rats hinders bone formation around endosseous implants placed in the tibia

(39, 50). In a rat model in which diabetes was induced, plasma-sprayed implants were installed in the femur bone (18). It appeared that insulin therapy was able to improve the histometric parameters around those implants (18).

In a similar study reported earlier by the same group (43), it was reported that histometrically the same quantity of bone was formed around implants in experimentally induced diabetic rats as in the control rats, although there was a very significant reduction of the surface of bone-to-implant contact ($P < 0.0001$).

In diabetes type II patients, the survival of implants was significantly lower than in non-diabetic patients ($P = 0.02$) (42). Nevertheless, if the patient was considered the independent variable, the significance level became marginal ($P = 0.05$). Antimicrobial therapy seemed to reduce the implant failure rate (42).

In a prospective study in 89 type II diabetic patients receiving Brånemark implants in the symphyseal area, the cumulative success rate after 5 years was only about 88% globally (44). The duration of diabetes was a significant predictor for implant failure ($P < 0.025$) (43). The cumulative success rate for this implant type has been known to reach 99% after 15 years in the symphyseal area (36).

In another prospective study (42) in 663 patients (2887 implants) a model assuming independence showed that significantly more failures occurred in type II diabetes ($P = 0.02$). The use of preoperative antibiotics and postoperative chlorhexidine rinses improved the outcome, again suggesting a risk factor of infectious complications.

It should be noted that, in one retrospective study, an increased incidence of postoperative paraesthesia was reported (four of five patients) (15). This may be due to the delayed healing or to a neural deficit related to the diabetes.

Sjögren's disease is an autoimmune disorder, which affects all exocrine glands (explaining the xerostomia and xerophthalmia) and collagen-containing tissues (explaining the rheumatoid arthritis). Less than half a percent of the population is affected, and the disease often remains undiagnosed. It can also be seen as a complication of an already established connective tissue disease such as sclerodermia or lupus erythematosus disseminatus.

Unhappily, except for one (6), three (46) and eight case reports (26) nothing is known about the impact of Sjögren's disease. In the first study (6), one patient showed an impressive marginal bone loss while the two others were uneventful. The affected patient had implants placed in both jaws, was a smoker and received corticoids and chemotherapy, features which may explain the abnormal bone loss. In the absence of any significant further data, one can only encourage the use of osseointegrated implants in xerostomic patients who often experience, because of the dryness, prosthesis retention problems.

Developmental disorders of the skin

Developmental disorders of the skin include a large series of rare ectodermal anomalies which are characterized by hypohydrosis, skeletal deformities and often mental retardation (47). It may involve hypodontia or anodontia and aggressive forms of juvenile periodontitis, which often lead to a need for the use of oral implants (32). Since retention of dentures may be a problem due to the extremely thin jaw bone ridges. Zygomatic implants may be a solution for maxillary rehabilitation (3).

Another genetically determined skin disease is the rare hyperkeratosis palmo-plantaris, also called Papillon-Lefèvre syndrome (47). In a case report of a patient with Papillon-Lefèvre syndrome, successful implantation was reported (51). Papillon-Lefèvre syndrome also shows an aggressive periodontitis, which makes this observation even more relevant.

Thus, based on case reports (13, 17, 32, 49) it seems that ectodermal dysplasias and hyperkeratosis palmo-plantaris do not constitute contraindications for the placement of oral implants.

Sclerodermia

Only one case report is available reporting on the impact of sclerodermia on osseointegration (29). In our personal experience, limited to one patient rehabilitated in both jaws with full fixed prostheses on Brånemark system implants, no particular drawbacks were encountered. The 11 implants were all successfully integrated and remained stable for over more than 15 years (Fig. 2). If the treatment had not been performed in due time, before the lips were more severely affected, as is now the case, the treatment would have become impossible.

Crohn's disease

In a recent retrospective study (51) of all 399 patients treated in our department over 3 consecutive years and observed up to 1 week after the second stage

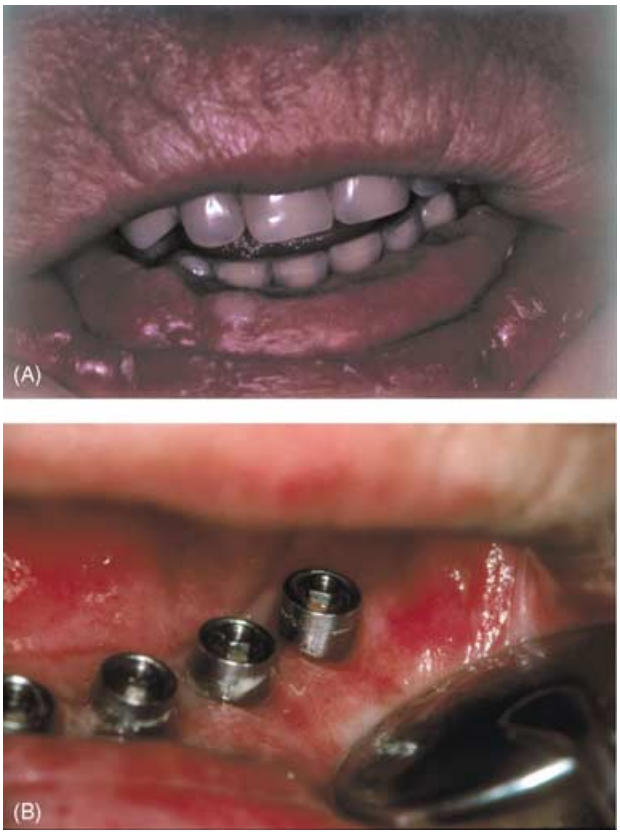

Fig 2. (A) A 60-year-old lady suffering from sclerodermia (see lips). This led to a vestibuloplasty with a skin graft performed by a plastic surgeon. (B) Intraorally, the soft tissues seemed healthy even if the lips could hardly be pulled away.

surgery, the influence of systemic and local factors was evaluated. All patients were treated with Brånemark system implants. Of the three patients with Crohn's disease, implant failure occurred in two. Because of the limited number and the association with other factors, a final conclusion cannot be drawn at this time, but caution is indicated when implants are planned in such patients. The circulating antigen–antibody complexes in Crohn's disease may lead to autoimmune inflammatory processes in several parts of the body, including the bone–implant interface during the healing phase. Factors associated with the disease, such as medication or malnutrition, may also play a role in respect to implant placement.

Parkinson's disease

Parkinson's disease is a chronically progressive neurologic disorder caused by neurodegeneration, leading to a reduction of the dopaminergic nigrostriatal neurons. The disease results in rigidity of the limbs, tremor and bradykinesia. The oro-pharyngeal musculature is often affected, leading to problems with speaking, chewing and swallowing. Implants can increase the patients' comfort in cases of (partial) edentulism. Heckmann and co-workers (24) investigated three patients with Parkinson's disease who were treated with implants in the interforaminal region as retention units for an overdenture. Patient comfort, as assessed by a questionnaire, was judged to be greatly improved. Body weight and, as assessed by the gastrointestinal scale, chewing ability improved in all three patients. Diseases affecting motor skills can profit from implant-retained overdentures. In contrast, full fixed prosthetic dentures should not be considered because of the difficulty of effective cleaning.

Cardiovascular diseases

The term cardiovascular disease is not really meaningful, as it may refer to extremely different pathologies, from aneurysm to heart infarction. Nevertheless, this cluster of diseases has been investigated in a retrospective study, which only superficially documents the anamnesis and clinical examination (34). In a group of 39 patients who were compared with 109 patients with other types of diseases and 98 healthy individuals, no significant differences were noted. Although the methodology does not allow any firm conclusion, it appears that cardiovascular diseases do not constitute a serious challenge to osseointegration.

Hematologic diseases

Leukemias

Anomalies in hematopoiesis can lead to a large variety of blood disorders. Pluripotential stem cells in the bone marrow evolve into a series of cells, from erythrocytes to eosinophils, which are found in the circulating blood. Red blood cell and/or hemoglobin disorders can be genetic (sickle cell disorder) or the result of insufficient/imbalanced alimentary uptake (iron deficiency anemia). There are also a variety of myeloid leukemias due to neoplastic cells, which infiltrate bone marrow, blood and many other tissues. Acute leukemia, where hereditary and environmental factors have been implicated, is characterized by lymphadenopathies, hepato- and splenomegaly, anemia thrombocytopenia and a high leukocytosis

(>15,000/ml). Patients are treated by chemotherapy, platelet and blood transfusion to achieve remission. Postremission therapy includes autologous or allogenic bone marrow transplantation. Death sometimes occurs because of infection complications such as oral candidosis.

A case report (11) shows that even in a patient treated successfully with an allogenic bone marrow transplantation for chronic myelogenous leukemia it was possible to achieve osseointegration (in the symphyseal area) and maintain the implant for years.

Chronic myeloid leukemia affects men slightly more than women. The etiology remains largely unknown but radiation has been shown to be relevant. The clinical picture evolves slowly, sometimes very discretely. White blood cell counts are elevated, with a large fraction of immature cellular forms, and there are increased numbers of thrombocytes. The treatment consists of allogenic bone marrow transplantation followed by chemotherapy or interferon therapy, which as a side effect provokes lethargy, or at least some neurologic side effects.

Other hematologic disorders are lymphoid cell malignancies such as lymphocytic leukemias and non-Hodgkin lymphoma. The latter can have a spontaneous remission or must be treated by chemotherapy. There are several other malignancies of the white blood cells like Hodgkin's disease and aggressive lymphomas, the relevance of which in terms of implant placement is unknown.

Platelet and coagulation anomalies

It is evident that osseointegration is dependent on the formation of a normal blood clot, which leads to an organized fibrin clot, allowing an uneventful migration of bone cells to the implant surface. Thrombocytopenia, which can result from a series of disorders, especially from drug intake, will jeopardize a normal blood clotting. One patient with thrombocytopenia was treated with oral implants (unpublished data). Not only did a serious hematoma develop even though transfusion had been given preoperatively, and three out of four implants failed. Besides thrombocytopenia, there are a number of blood platelet anomalies like von Willebrand's disease.

In addition to platelet disorders, any coagulation anomaly, from blood vessel wall anomalies to hemophilia, is a challenge to any surgery and to the achievement of a proper osseointegration in particular. Unfortunately the clinical relevance of these hypotheses remains obscure. Nevertheless, only a specialized team should place implants in patients with coagulation abnormalities.

Medications

Phenytoin

The antiepileptic drug phenytoin is known to provoke gingival enlargement in the presence of plaque, and thus in edentulous areas because of the plaque-carrying prosthesis, which is in intimate contact with the underlying gingiva (38). Gingival overgrowth may also happen around transgingival/mucosal abutments in the presence of plaque accumulation. Resection of the soft tissue can be performed by gingivectomy for limited overgrowths or by flap surgery when larger volumes are involved. With the latter technique, no connective tissue is exposed to the oral environment. No data are available for oral implants in patients receiving phenytoin.

Calcium-channel antagonists

Dihydropyridines, calcium-channel blockers for hypertension and cyclosporine have gingival overgrowth as a common side-effect. The gingival overgrowth does not appear to be plaque-related. Here, too, data concerning the risk of gingival overgrowth in patients rehabilitated by means of implants are lacking.

Cyclosporine has a more challenging effect on osseointegrated implants, namely its well documented effect of accelerating bone turnover and provoking a negative bone balance (21).

Conclusions

Most systemic contraindications are relative. Since several of these patients are the ones most in need of oral rehabilitation following implants, one should evaluate both assets and liabilities.

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