

An Innovative Approach to Dental Implantation in Medically Compromised Patients. Narrow Implants – Yes or No?

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ABSTRACT

Objectives: To locate approaches to diagnosis and treatment in patients suffering from chronic illnesses with the aim of prolonging the lifetime of the dental implants and the rehabilitation that is installed on the implants and to minimize bone absorption around the implant.

Material and methods: This research work was done on the basis of clinical cases. From 2010 to 2015, we treated 370 people whose ages ranged from 31 to 94 years and who suffer from primary or secondary teeth loss. A total of 1113 titanium implants varying in diameter were placed, ranged from 3 mm to 6 mm in diameter. The length of the implants ranged from 5 mm to 18 mm. All patients were divided into two clinical groups based on the presence or absence of chronic illness. The first group of 177 patients had compensated (balanced) chronic diseases. The second group of 193 patients were in good health.

Results: Out of 1113 implants, 1062 survived, which constitutes a success rate of 93.7%. It was found that the greater the diameter of the implant, the more complications occurred around the area of the implant. Complications and rejection of implants were found to be statistically significant for larger diameter implants if the patient had a chronic disease.

Conclusion: The larger the diameter of the implant, the higher percentage of bone absorption in the chronically ill patients, especially during the time frame of 1-6 months. There were also increasing complications with this group around the area of the implants.

DEFINITIONS

1. CT: Three-dimensional computerized tomography x-ray.
2. PAR: Panoramic X-ray.
3. PER: Periapical x-ray.
4. Implantation success- SOI: when the implant was received without over-mobility and without any pain at the implantation site.
5. SCI success: no complications whatsoever.
6. Mucositis (MU): An inflammatory process of the mucosae at the implantation site that was absorbed without any evidence of bone loss.
7. Peri-implantitis (PI): An inflammatory process of the soft tissues that is accompanied by bone recession of the supporting bone at the implantation site.
8. Soft tissues complication (CTC): Fusion during a secondary stretch (fusion complications), hyperplasia, etc.
9. Implant rejection (LOI): During a follow-up, the implant needs to be removed or the implant does not exist.

10. PD: The depth of the periodontal socket at the implantation site.

11. BOP: The bleeding test during the insertion of the probe.

INTRODUCTION

Every medical intervention has its indications and contraindications. In the case of a dental implantation, a number of options exist for patients. There are indications and no contraindications which would be the ideal case, indications, but also contraindications where treatment is possible. No indications, but also no contraindications where we preferably do not treat, and no indications and contraindications where treatment is forbidden. On a practical level, opinions are split regarding indications and contraindications. During the last 20 years attitudes toward contraindications have changed. Contraindications are divided into general and local, absolute and relative, temporary and fixed. Treating with temporary and local contraindications is an inseparable part of the day-to-day treatment with dental implantations. It is important for us to emphasize absolute and relative contraindications. It is also important to state that the more experience accumulated in working with dental implants, the list of absolute contraindications should narrow in favor of the relative contraindications.

Absolute Contraindications

Vascular and hematogenic-organ illnesses at the decompensation stage; central nervous system illnesses; cases of psychiatric disorders (acquired or inherited); malignant disease of different organs and systems before, during, and up until 6 to 12 months after the treatment, as well as illnesses of the immune system, systemic connective tissue diseases, tuberculosis, and unbalanced diabetes.

Relative Contraindications for a Dental Implantation

Local and chronic diseases in a balanced state (compensation), which are efficiently diagnosable and treatable thanks to a wide use of sophisticated equipment that is available today in modern medicine. However, after analyzing the scientific literature of this subject, it is acceptable to claim that the problem of preventing complications in patients suffering from chronic illnesses, which is an imbalance of the implant in the bone, remains actual ^[1]. After studying our own experience and that imparted via scientific articles on the subject of using implants in patients with chronic diseases, we came to the conclusion that there is no single approach for all and that each patient has to be treated on a case-by-case basis ^[2]. Despite the advantages that dental implantation offers, there are obstacles to using this method in patients with chronic illnesses. Furthermore, the quantity and quality of the bone tissue constitutes an important factor that could influence the treatment outcome of flaws in the continuity of the teeth, using the dental implantation ^[3-5]. In non-chronic patients, it has been found that when there is an absence of bone density at the implantation site;

1. Physiological renewal rate and bone rehabilitation decreases, as well as specific weight of the bony structures.
2. Bone growth is delayed around the implant, as well as inhibition of bone-remodeling.
3. There is complete or partial inhibition of the cortical sheath of the compact bone after the implantation.
4. The partial portion of the spongy material increases and likewise growth of primary gross osseous tissue occurs together with perichondrium at the implantation site, (relative and absolute bone recession).
5. There is late yet persistent appearance of blood rich connective tissue (granulation tissue) around and/or on the surface of the implant.

In this way, chronic diseases and general diseases damage the entirety of the histochemical properties of different tissues (the base) at the area of implantation - a phenomenon that constitutes a risk factor during the implantation procedure and in forecasting the outcome of the proposed surgery ^[6,7]. There is therefore a great deal of interest in understanding the subject of implantations for chronic patients, including the choice of implant, in order to ensure the maximal bone mass and to preserve the bone's rehabilitation ability at the area of the implantation.

Goal of the Research

To locate approaches of diagnosis and treatment for patients suffering from chronic illnesses with the aim of prolonging the lifetime of the implant and the rehabilitation installed on the implant and to minimize bone absorption around the implant.

MATERIALS AND RESEARCH METHODS

This research work was done on the basis of clinical cases. From 2010 to 2015, we treated 370 patients whose ages ranged from 31 to 94 years and who suffer from primary or secondary teeth loss. Of the 370, 174 were men, (47.03%) and 196 were women, (52.97%). A total of 1113 titanium implants were used which had three different geometries with varying style of threads. "Unique" style implants made up the majority, (799; 70%), "Perfect" style implants were next, (204; 18.3%) and "Prima" style implants the remaining, (130; 11.7%), all from DMi Innovative Technology Limited, Holon, Israel. The diameter of the implants ranged from 3 mm to 6 mm. The length of the implants ranged from 5 mm to 18 mm. An implantation was done in the case of a

complete lack of teeth in one of the jaws: 32 patients received 336 implants (30.2%); in scenarios involving 2 or more teeth that were missing in one jaw, 132 were implanted with 528 implants (47.4%). In the event of a missing tooth or the removal of one tooth per jaw: 206 patients were implanted with 249 implants (22.4%). All surgical tools, abutments and parts of prostheses, were manufactured by "DMI Innovation Technology Ltd. All patients went through the standard diagnosis: A history was taken, lab tests were performed, jaw structure and bite were examined, and localized oral cavity imaging scans were studied, CT, PAR, and PER as necessary. All patients were divided into two clinical groups based on their general symptoms of their chronic illness: the first group of 177 patients had compensated (balanced) chronic diseases. The second group of 193 patients were in good health. Each group had six sub-groups, according to the diameter of the implant. The first group included patients with a balanced chronic disease (diabetes, renal or cardiac insufficiency, cardiovascular diseases, tuberculosis, hepatitis C, HIV, psoriasis, mucosal tissue diseases and patients suffering from general chronic gingivitis or who receive immunosuppressive drugs. The pre-operational preparation stage, as well as the stage of surgery in all groups, was done by the conventional method. The implantation was performed according to the mono-phasic or bi-phasic method, in addition to a direct method of implantation that was performed at the exact location of the extracted tooth with immediate loading. All implants were performed using a bi-cortical fixation method to the extent that was possible. In all groups, according to the need, a directed reconstruction of the jaw bone was done (bone augmentation). After 1-6 months, rehabilitation of the teeth on top of the implants was done (permanent or removable). In all treatment stages, a follow up was done regarding the bone around the implant. Valuation of the parameters that characterize the quality of connection between bone and implant, such as the measure of the implant's stability, was done by examining the state of the bone around the implant using PAR, PER, and CT scans. Comparison was done of the scans prior to the operation or the unveiling of the implant, before, and after installing the rehabilitative structure and during follow up visits.

Statistical Calculations and Data Processing

Statistical calculations of each of the study's parameters were performed according to the implant's diameter in all groups. Grades were given at the following time spans: From 1 to 6 months post implantation and until the assembly of the rehabilitation on top of the implants. Then from 36 to 60 months post-implantation and rehabilitation. The statistical processing was done using the following parameters: 1-MU, 2-PI, 3-CTC, 4-LOI, 5-SOI, 6-SCI. The numerical data that was received went through analysis using "variation" and "alternative" statistics that matches a relatively small number of the study samples. The mean was calculated for each parameter [8]. All statistics were done according to the ISO14155:2011 standard (CRF).

RESULTS

After 3 to 5 years post implantation, 370 patients remained. Out of 1113 implants in the first stage (1-6) months, 1087 survived to be loaded in fixed rehabilitation (97.7%). For the next observation period (after the loading of the implants) out of the 1087 remaining implants, 1062 survived (97.7%).

The general grade in all groups and treatment stages: Out of 1113 implants, 1062 survived, which constitutes a success rate of 93.7%. In terms of patients with chronic diseases, out of 500 implants, 469 survived (96.7%). The overall success rates were not different from the scores received in other studies [Becker et. al. 1997, p. 9-15]. The implantation success rates in both groups were checked at various stages (Table 1).

The percentage of the implantation complications in both groups was also checked and at both the first stage (Figures 1 and 2) and at the second stage (Figures 3 and 4), it was found that the bigger the diameter of the implant, the more complications occurred around the area of the. At the presence of a chronic disease, the degree of complications upon increasing the diameter was more statistically significant compared to the healthy patients. Significant differences were found with the peri-implantitis complication (Figure 5).

Table 1. The percentage of implantation successes by implant's diameter.

Group 1	Number of implants	130/130	104/105	106/110	71/75	40/45	31/35
	The remained/installed						
Stage 1	SOI success	100%	99.1%	96.4%	94.7%	88.9%	88.6%
	SCI success	98.5%	97.6%	90.9%	84.3%	83.8%	74.3%
Group 2	Number of implants	92/92	88/89	168/170	138/140	65/68	53/54
	The remained/installed						
Stage 1	SOI success	100%	98.9%	98.8%	98.6%	95.6%	98.1%
	SCI success	99.5%	96.9%	97.5%	95.4%	84.2%	89.3%
Group 1	Number of implants	130/130	103/104	102/106	66/71	38/40	30/31
	The remained/installed						
Stage 2	SOI success	100%	99%	96.2%	93%	95%	96.8%
	SCI success	91.2%	91.1%	84.2%	83.8%	78.1%	79%

Group 2	Number of implants	91/92	87/88	166/168	134/138	63/65	51/53
	The remained/installed						
Stage 2	SOI success	98.9%	98.9%	98.1%	97.1%	96.9%	96.2%
	SCI success	95.9%	95.7%	94.0%	94.4%	91.1%	89.6%

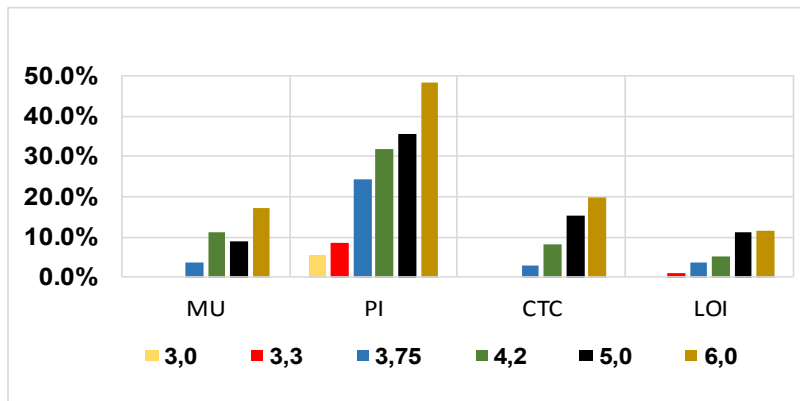


Figure 1. Complications as a result of implantation in patients suffering from chronic diseases, in relation to the implant's diameter, within a time frame of 1-6 months.

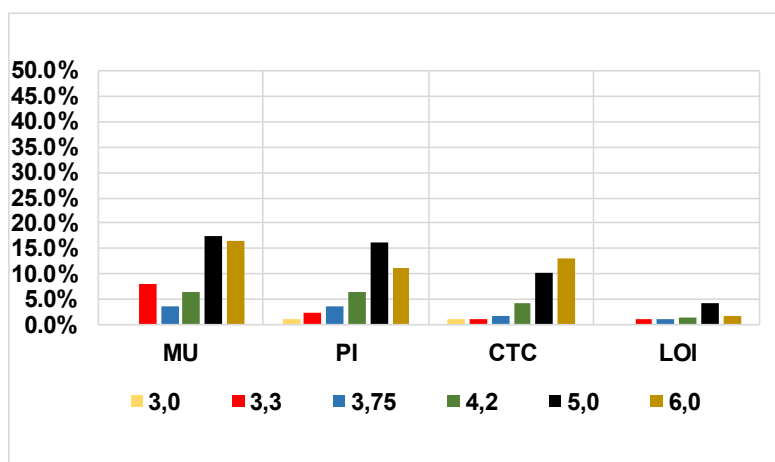


Figure 2. Complications as a result of implantation in healthy patients, in relation to the implant's diameter within a time frame of 1-6 months.

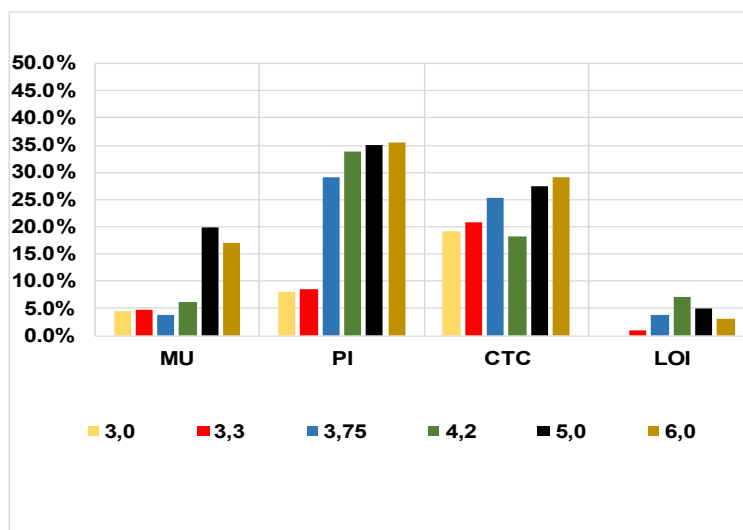


Figure 3. Complications as a result of implantation in patients suffering from chronic diseases, in relation to the implant's diameter within a time frame of 36-60 months.

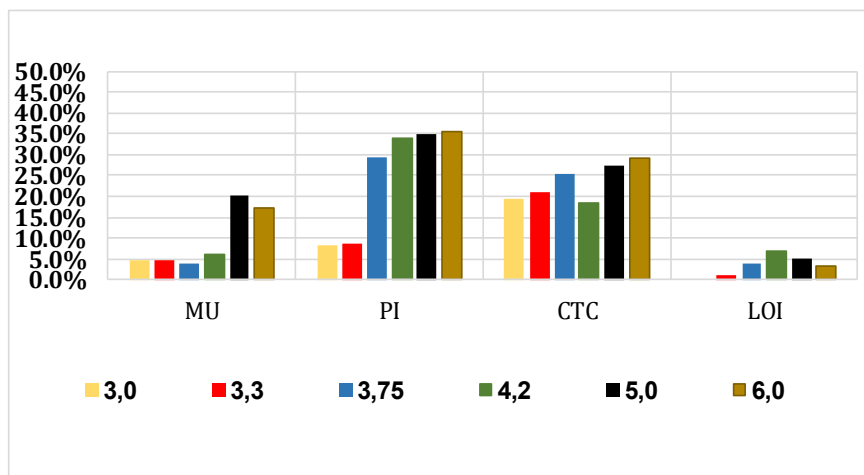


Figure 4. Complications as a result of implantation in healthy patients, in relation to the implant's diameter within a time frame of 36-60 months.

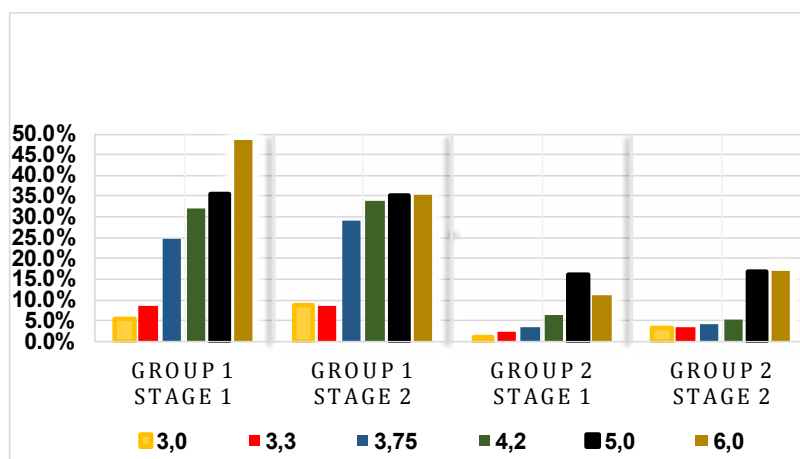
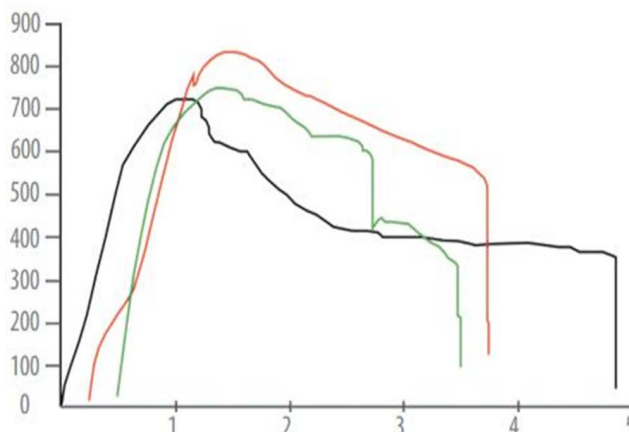


Figure 5. Comparison of the periimplantitis intervention between chronically ill and healthy patients in all treatment stages.

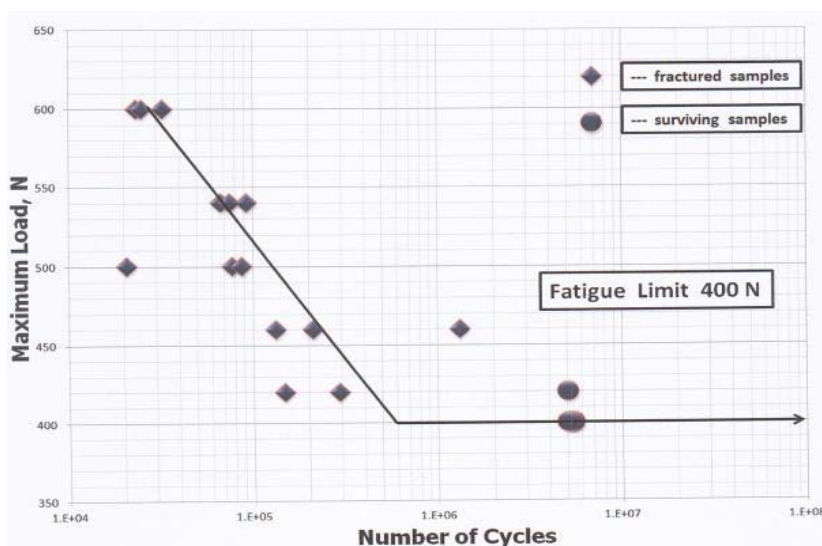
DISCUSSION

As the research shows, in the presence of chronic illnesses there is a direct link between the implantation complications and the diameter of the implant. The complications decrease around the implant in conjunction with the smaller diameters. This association was also registered during the initial part of the implantation (Figure 1), and during the second phase of the implantation (Figure 3). In our opinion, there is a direct link to the quality and the mass of the bone at the implantation site in comparison to the trauma that is caused to the bone as a result of the size of the drilling. The more that the general bone mass at the area of the implantation decreases (in the context of the preparation of the bony-implantation site that matches the implant) in healthy patients, thus, all of the characteristics of the physiological bone rehabilitation and its renewed growth are diminished [7]. In cases of patients suffering from chronic and general diseases the morphological-histological-chemical characteristics of the tissues (the base) are suppressed at the area of the implantation. This fact constitutes a negative factor, which acts against the implantation process. Therefore, the most important condition for implantation is keeping a maximal bone mass around the implantation. In order to maintain this condition, one should minimize trauma and loss of bone. After minimal bone intervention, a narrow implantation site is created, which matches only narrow implants. Other researchers share this opinion [9,10]. Naturally, the narrower the diameter of the implant is, thus it's physical and mechanical characters are damaged. The main test that can be used to check the strength of the implant and the load which is possible to be put on osteo-integrated implant is a stress-fracture test [11]. In order to do this test, the narrowest and longest implant that is connected to the abutment at the greatest angle is chosen. The implants with the abutment are placed on a special base, and a directed load is operated against them, using planned force. The research was held according to the international regulation standard ISO 14801-2007. A stress-fracture study that was done using static load, showed high measures of strength: from N 751 and up until N 838 (Graph 1). In conditions of reciprocal loading, the measure was N 400 (Graph 2). The limit of the accepted measurement for a stress fracture under reciprocal loading of no less

than 5,000,000 cycles, is about N200 [12-14]. Narrow implants of the "Unique" type are of highly resistant to stress fractures, which allows their wide use in all areas of the upper and lower jaws, and enables them to be loaded comparable to regular implants.



Graph 1. A study of stress fractures using statistical loading on "Unique" implants with a 3 mm diameter and a 25° angular titanium made abutment.



Graph 2. A study of stress fractures using dynamic loading on "Unique" implants with a 3 mm diameter and a 25° angular titanium made abutment.

Recommendations for the Need for Dental Implants in Patients Suffering From Chronic Diseases

When a dental implantation is being planned in patients who suffer from chronic diseases: narrow implants must be used. Crowns should be united to one bridge in order to prevent over-loading.

Choosing the method of performing the implantation does not affect its success. The basic requirement is to cause minimal trauma while preserving the bone mass at the area of the implantation. Therefore, first and foremost, use of a new and sharp bone-drill is recommended. The number of drills used should be minimal in order to keep the maximal amount of cortical bone at the ridge of the supporting bone (alveolar bone), since the cortical bone does not entirely renew itself. But, this number should be enough in order to create the bony implantation site for the implant. The drilling process of the bony implantation site needs to be done according to the following method:

1. Using a marking drill in order to mark the drilling spot. It is desirable not to flatten the alveolar ridge to keep the ridge's cortical bone.
2. Using a pilot drill with a 2 mm diameter, drilling the length of the designated implant.

D4 Type of Bone

Entering into a depth of 4-6 mm with a 2.8 mm diameter drill and implanting a "Unique" implant with a 3 mm diameter or entering with a countersink drill with a 3.2 mm diameter and implanting a "Unique" implant with a 3.3 mm diameter (there is also a possibility to install a "Perfect" implant with a 3.75 mm diameter).

D3 Type of Bone

Entering with a 2.8 mm drill into the depth of the implant that we are going to install (in the case of a cortical fixation of an implant up to the cortical bone) and implanting a "Unique" implant with a 3.0 mm diameter, or entering with a 2.8 mm diameter drill all along its length with a countersink drill of a 3.2 mm diameter and implanting a 3.3 mm "Unique" implant (there is also a possibility of installing a "Perfect" 3.75 mm diameter implant).

D2 Type of Bone

Entering with a 2.8 mm drill into the depth of the implant that we are about to place (in the case of cortical fixation of the implant up to the cortical bone) and implanting a 3.0 mm diameter "Unique" implant, or entering with a 3.2 mm diameter drill all the length of the implant, with a countersink drill of a 3.2 mm diameter and implanting a 3.3 mm diameter "Unique" implant.

D1 Type of Bone

Entering with a 2.8 mm drill into the depth of the implant that we are about to implant and additionally entering with a 3.2 mm diameter drill all the way until a length of half of the implanted implant is reached. Implanting a 3.0 mm diameter "Unique" implant or entering with a 3.8 mm diameter drill enough to reach the length of the implant with a countersink drill of a 3.2 mm diameter and implanting a 3.3 mm diameter "Unique" implant.

After the success of the implantation, each patient suffering from a chronic illness should be offered a conservative preservative treatment plan.

1. Medicines for treating general chronic illnesses- should be taken before and after the implantation surgery (except blood-thinners, which ought to be stopped 5-7 days prior to the implantation surgery, and should be re-administered a day after it). Alternatively, the family physician should be consulted with regard to therapeutic alternatives.
2. Antibiotics treatment – Augmentin should be administered a day or two prior to the surgery (500 mg 3 times a day, or 875 mg twice daily), and be continued some 7-10 days afterwards. If additional bone rehabilitation treatments are required, then Metronidazole should be added into the regimen (250 mg 4 times a day) for duration of 5-7 days.
3. For reducing swelling after the implantation, Dexamethasone (2 mg) should be administered (must be coordinated with the family physician) in the following manner: on the first day post-operation, 2 mg 5 times a day, on the second day- 2mg 4 times a day, on the third day 2 mg 3 times a day, on the fourth day 2 mg twice a day, and on the fifth day one dose of 2 mg.
4. Solid foods should be avoided for 15-20 days after the implantation, while trying to eat high-caloric foods for 2-3 months after the implantation (in order to give the body energy strength and therapeutic energy).
5. Frequent soft-tissue follow-ups are recommended around the implant in order to diagnose the condition of the osseous and soft tissues. They should be performed after the implantation and before the rehabilitation – at least once a month. After the rehabilitation, at least once every three months.
6. Implantation- supportive therapies, according to the severity of the complications around the implant ^[15].

Approach Number 1

Suitable for the starting conditions when there are sediments on the gums and BOP, but when the PD is 3 mm or less. In this case, the patient should be reminded of the importance of oral cavity hygiene and encouraged to adhere to the hygiene. A mechanical cleaning is done using a non-metallic grater (in order to avoid scratching the abutments, which will cause a greater formation of calcification) teeth polishing is done using a rubber ring with a paste that does not cause harm to the tooth.

Approach Number 2

When PD reaches 4.5 mm, a mechanical cleaning is done using a non-metallic grater, polishing using a rubber ring with a paste that does not cause harm to the tooth, and the most important thing is that- an antiseptic treatment is administered using a Chlorhexidine Digluconate solution, usually in a form of mouth-wash, 0.1-0.2% of the substance, about 10 ml for a duration of 30 seconds, or locally using a gel of Chlorhexidine (0.2%), also in a form of focal wash and/or Periochip that works by extended release ^[16].

Approach Number 3

When PD surpasses 5 mm, an x-ray should be performed in addition to the clinical examination. Continue with a treatment that is similar to approach number 2, and additionally a general therapy is prescribed, for instance, Augmetin (500 mg 3 times a day or 875 mg twice a day) is prescribed for 7-10 days with Metronidazole (250 mg 4 times a day) for 5-7 days. Local treatment could be combined with a local antibiotic treatment while controlling the mechanism of the drug's release- for 10 days. For example: strings dipped in Minocycline. Antibiotics can be used topically or systematically. After exhausting approaches 1, 2 and 3 a surgical approach could be considered 4 ^[17].

Approach Number 4

Together with a surgical per-implantitis treatment, a general anti-bacterial treatment should be combined, and purification and cleaning of the outer area of the implant that is revealed or substituting of the crown of the implant (Prefix of a modular implant) or changing the entire implant^[18]. If we choose rehabilitative treatment, the use of membrane should be examined separately and together with implanting bone pieces in order to catalyze regeneration and/or substitutions for the bone material. If the condition around the implant is not suitable for the bone reconstruction approach, then an alternative of changing the implant should be examined.

CLINICAL CONCLUSIONS

Marginal bone absorption around the implant remains low, starting from 0.15 mm (medially) and up until 0.35 mm (distally) while narrow implants were used in the two groups, but the larger the diameter of the implant, the higher percentage of bone absorption grew in the chronically ill patients, especially during the time frame of 1-6 months, and reached 48.5% in implants with a 6 mm diameter (**Figures 1 and 3**). The rate of complications and soft-tissue changes in patients with chronic diseases was more significant in comparison to the healthy individuals. This is mainly due to their general health condition. In the first stage, in patients with chronic illnesses due to the poor physiological and healing capabilities of their bodies, and in the second stage due to the large amounts of medicines taken, which causes drug side-effects such as hyperplasia of the edge of their gums around the implant. In the clinical study it was found that complications or the lack of them at the healing stage after the surgery are dependent on the general somatic condition of the patient. In both stages, it was demonstrated that as the diameter of the implants increased, so does the complication around the area of the implant.

CONCLUSIONS

We found that there is a very impressive list of counter-indications for teeth implantation, only a portion of which negate implantation. Neither the presence of chronic diseases, nor age, constitute complete contraindications for performing the implantation. These contraindications can only limit the use of different types of implants, or to cause the doctor to watch for several recommendations in the implantation procedure; In most cases, early preparation, treating the patient (local and systemic), complete diagnosis of the patient's dental status, correct choice of the type and size of the implant, usage of non-invasive and non-traumatizing techniques as much as possible and to prepare the site of the osseous implantation, will determine optimum outcome. Also important is the presence of a skilled medical crew to avoid many complications or diminish their influence so that a successful dental implantation can be performed. Diminishing biological and technical risks during the implantation stages is dependent not only upon the doctor who constructs the rehabilitation, but also with the surgeon and his choice of how many implants must be performed in one jaw, within the context of the general condition of the patient.

REFERENCES

1. Shibli JA, et al. Histological comparison between implants retrieved from patients with and without osteoporosis. *Int J Oral Maxillofac Surg.* 2008;37:321-327.
2. Mushayev I, et al. Practical dental implantology. Method pos. 2008;500.
3. Becker W, et al. Osteoporosis and implant failure: an exploratory case-control study. *J Periodontol.* 2000;71:625-631.
4. Becker AR, et al. Osteoporosis risk factors in female dental patients. A preliminary report. *J Indiana Dent Assoc.* 1997;76:15-19.
5. Dedov I, et al. Osteoporosis: pathogenesis, diagnosis, print sipyprofilaktikiilecheniya. Method pos dlyavrachey M. 1999;62.
6. Agazade AR, et al. Histomorphometric and quantitative histo-chemical analysis of periimplantation zone in patients with different bone mineral density within dental implantation. *Vestnik Rossiiskoi akademii meditsinskikh nauk's.* 2014;3:19-23.
7. Roberts WE, et al. Bone physiology and metabolism in dental implantology: Risk factors for osteoporosis and other metabolic bone diseases. *Implant Dent.* 1992;1:11-21.
8. Unkerov V, et al. Mathematical and statistical processing of medical research. SPb MMA. 2011;318.
9. Arisan V, et al. Evaluation of 316 narrow diameter implants followed for 5-10 years: a clinical and radiographic retrospective study. *Clin Oral Implants Res.* 2010;21:296-307.
10. Sohrabi K, et al. How successful are small-diameter implants? A literature review. *Clin Oral Implants Res.* 2012;23:515-525.
11. Lee CK, et al. Evaluation of test protocol variables for dental implant fatigue research. *Dent Mater.* 2009;25:1419-1425.
12. Bathias C. There is no infinite fatigue life in metallic materials. *Fatigue and Fracture of Engineering Materials and Structures.* 1999;22:559-565.

13. Quek CE, et al. Load fatigue performance of a single-tooth implant abutment system: effect of diameter. *Int J Oral Maxillofac Implants*. 2006;21:929-936.
14. Shemtov-Yona K, et al. Effect of dental implant diameter on fatigue performance. Part I: mechanical behavior. *Clin Implant Dent Relat Res*. 2014;16:172-177.
15. Lang NP, et al. Biological complications with dental implants: their prevention, diagnosis and treatment. *Clin Oral Implants Res*. 2000;11:146-155.
16. Heitz-Mayfield, et al. Antimicrobial treatment of peri-implant diseases. *Int J Oral Maxillofac Implants* 2004;19:128-139.
17. Schou, et al. Surgical treatment of peri-implantitis. *Int J Oral Maxillofac Implants*. 2004;19:140-149.
18. ISO 14801. Fatigue test for endosseous dental implants. Geneva: International Organization for Standardization. 2007.