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Review Article

The action of anti-resorptive drugs on the survival of total knee and hip arthroplasty

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Abstract

Total knee and hip arthroplasty are major surgical procedures performed in patients with severe osteoarthritis and their incidence has significantly increased in the last 30 years. A number of etiological factors such as low grade infections, stress shielding and degradation products have been, however, shown to endanger the survival of the implants. The prevention of mechanically induced implant loosening has been the aim of many studies investigating, among other things, whether pharmaceutical agents used for the treatment of osteoporosis can positively influence the survival of the arthroplasty implants. We conducted a search of the published literature (PubMed) to identify studies that assessed the effects of anti-resorptive agents (bisphosphonates, denosumab, raloxifene, bazedoxifene, calcitonin) on the outcome and longevity of total arthroplasty of the hip and knee. We found 24 studies for THR, 8 studies for TKR and 2 studies with reference in both hip and knee arthroplasty. Most studies assessed the effects of oral bisphosphonates. Significant difference in BMD is observed after 6 months of postoperative antiosteoclastic therapy with better results and lower revision rate in cemented TKA. Only 2 studies were found assessing the effects of denosumab on implant survival, while no studies were found on SERMs and calcitonin.

Keywords: Antiresorptive agents, Bisphosphonates, Implant survival

Introduction

Total knee and hip arthroplasty are dominant orthopaedic interventions performed in patients with severe osteoarthritis worldwide, whose incidence has been shown to increase for at least the last 2 decades. The classical technique of hip and knee arthroplasty is the combination of hard on soft surface using metallic surfaces of alloy cromium - cobalt (cr-co) avoiding the use of titanium being prone to creating abrasions from wear products[1]. Support of implants can be made with acrylic cement or by using porous material, inducing the biological stabilization of the implant (ingrowth). The placing of rigid and greater size stem in the hip leads to the metaphyseal unload with as consequent the loose of the bone remodeling capacity and its resorption[2]. The basic pattern of bone remodeling is characterized by proximal cortical atrophy, and distal cortical and medullary bone hypertrophy. This phenomenon is more relevant in cementless hip arthroplasty while in cemented implants the stresses are better distributed[4]. The same can happen at the knee in the case of placing a long stem in tibia. The use of implants leads to changes that are dependent on the biocompatibility, wear indicator and the interaction of the industrial characteristics of implant and tissue, gradually leading to bone loss in their interface[2,3]. As a result, aseptic loosening of materials, a consequence of osteolysis, finally occurs, leading to the need to perform a second surgery to replace the loose implants, thereby increasing social and economic burden of the disease in such patients[4,5].

The survival of total hip arthroplasty is affected by the gender, age, type of implants and the skills of surgeon. At higher risk of implant loosening are male patients younger than 40 years who undergo cemented hip arthroplasty[6].

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Regarding total knee prostheses survival the main aggravating factor is the age as younger patients are more active. Other risk factors that affect the durability of TKA are the gender of the patients (better results in women), the type of implant (posterior cruciate ligament retaining or not, posterior stabilized implant, constrained condylar implants, modular and non modular tibial implant), the design of the patellar component, the use of cross-linked or simple polyethylene and the type of fixation (cemented, uncemented and hybrid)[7,8].

Interface is defined as the common border between two materials. It may be a distinct limit, or a zone of interaction between the materials. The interface of bone - implant is a dynamic interactive zone that goes from the phase of genesis (during the implantation of the material) to the healing phase. The micro-movements among them create a fibrous-bone interface[9]. Two are the main mechanisms of bone resorption in the interface bone - implant, as a result of osteoclast activation: a) Stress shielding phenomenon which is due to the different hardness of material in relation to the bone. This phenomenon is most common in femoral prosthesis. The use of acrylic cement offers a better load distribution[10].

The unloaded bone surface is driven in absorption as a result, in accordance with the theory of mechanostat[11], of osteocyte apoptosis which in its turn activates osteoclasts by inducing the expression of RANK-L[12,13]. The expression of sclerostin, inhibitor of bone formation by antagonizing wnt/b-catenin signaling, increases in conditions of unloading while decreases under the action of mechanical loads[14,15]. b) Degradation products which come primarily from polyethylene. These products undergo the process of phagocytosis by macrophages, leading to activation of mediators of inflammation (IL-1B, IL-6, prostaglandins, free radicals, TNF-α) and release of cytokines such as RANK-L, necessary for the differentiation of progenitor cells into osteoclasts[16]. Since bone resorption is a key element of loosening of the implants, it can be implied that the use of anti-resorptive agents may have a protective effect. Antiresorptive drugs that are currently used for the treatment of osteoporosis (bisphosphonates, denosumab, raloxifene, bazedoxifene, calcitonin) have been tested for their potential effect on implant survival. Bisphosphonates, either taken orally (alendronate, risendronate, ibandronate) or intravenously (zolendronate) are potent inhibitors of bone resorption. They have the ability to attach to bone surfaces where bone turnover is more pronounced and their actions consist of: a) inducing osteoclast apoptosis via the attachment to the bone and b) inhibiting the mevalonate pathway, resulting in reduced survival and increased apoptosis of osteoclasts. Denosumab is a human monoclonal antibody (IgG2) against RANKL (with high affinity and specificity) thereby affecting osteoclastogenesis. Preventing interaction RANKL/RANK inhibits the formation, functioning and survival of osteoclasts, reducing to a minimum bone resorption, both compact and trabecular bone. Selective estrogene receptor modifiers (SERMs) such as raloxifene and bazedoxifene are mild antiresorptive agents that act as estrogene agonists concerning their action on bone, while antagonizing the effect of estrogen on the breast and uterus. Salmon calcitonin (CT) has also been used as a mild atiresorptive agent for the prevention and treatment of osteoporosis but its use nowadays is limited. Our aim was to review the current bibliography concerning the potential effects of all the above agents on implant survival in patients undergoing in total knee and hip arthroplasty.

Material and Methods

We conducted a review of the published literature using the Medline database (PubMed). Our inclusion criteria were articles published in the English language, during the last twenty years up to July of 2019, concerning the potential effect of antiresorptive agents, primarily used for the treatment of osteoporosis, on bone implant survival in patients with total hip and or knee replacement. Key words included: antiresorptive agents, bisphosphonates, alendronate, ibandronate, risedronate, denosumab, raloxifene, bazedoxifene, SERMs, calcitonin, hip, knee, implant survival, total arthroplasty survival.

Results

In total, only 20 papers on antiresorptive agents and their effect on BMD and implant survival of total hip and knee arthroplasty were selected for their relevance and scientific quality. We need to clarify that some of the papers included were meta-analyses, so the actual number of studies found to have been performed in the last 20 years is 35. We found no studies assessing the effects of SERM's or calcitonin in the survival of bone implants in patients undergoing hip/knee arthroplasty.

a) Bisphosphonates

The effect of bisphosphonates in patients undergoing hip or knee arthroplasty has been summarized in a meta-analysis by Bhandari et al, which included 6 trials (290 patients), 4 of which were randomized and 2 blind[17]. Five of them studied the action of alendronate (10 mg/day) and one the action of ibandronate (one dose of 90 mg in the fifth postoperative day). Of the 6 trials the four studied the action of bisphosphonates in patients undergoing THA and two the action of bisphosphonates in TKA. The measurements were realized in the distal femur, in the proximal tibia and Gruen femoral zones by DXA. The number of patients in the medication group ranged from 13 to 96 patients. The control group either received calcium (3 studies) or was not given any treatment (3 studies). Common finding of all studies was the reduction of periprosthetic BMD at the third postoperative month in both medication and control groups. However the periprosthetic BMD in the medication group

was preserved at higher levels. The mean periprosthetic BMD difference between the two groups, with favor of the group treated with bisphosphonates, was 3.3% at 3 months (P<0.01), 4.5% at 6 months (p<0.001) and 4.2% at 12 months (P=0.02)[17]. Treatment with BPs had better results, regarding BMD, on cemented hip and knee arthroplasties in relation to uncemented arthroplasties in periprosthetic BMD measurements made by DXA on three, six and twelve months (BMD differences of 0.1%, 5% and 5.4% respectively, significant difference [p<0.001] in twelve months). Enhanced bisphosphonate action was also found in total knee arthroplasty compared with the hip, with differences of BMD in the range of 4.1%, 11.5% and 7.1% (significant difference [p<0.001] only in six months) to the same measurement periods. The periprosthetic BMD was not influenced significantly by the study quality, the bisphosphonate type and its way of administration[17].

A more extensive meta-analysis conducted from Lin et al included 14 studies with follow up up to 72 months and total 671 patients[18]. The number of patients per study ranged from 12 to 96 persons. In 9 trials alendronate orally has been administered, in 2 trials etidronate orally, in 1 trial risedronate orally, in 1 trial pamidronate intravenously and in 1 trial clodronate intramuscularly (doses are not reported). In 9 trials calcium supplementations were also used. In 12 studies, the effect of BPs was evaluated regarding BMD on THA (8 uncemented, 3 cemented and 1 hybrid) and in 2 cemented TKA. The measurements of BMD were performed at the proximal femoral metaphysis, at the distal femur and at the proximal tibia, DXA was performed at the third postoperative month and a reduction of BMD (in both the femur and tibia) was found in both medication and control groups. BMD was found to be higher in the group that received bisphosphonates in relation to the control group in measurements that took place postoperatively at 3 months (percent difference of BMD 2.33%, p<0.01), at 6 months (percent difference of BMD 1.56%, p<0.01), at 12 months (percent difference of BMD 3.89%, p<0.01), at 24-72 months (percent difference of BMD 7.89%, p<0.01) and 18-70 months after the passing of the bisphosphonate treatment (percent difference of BMD 9.4%, p<0.01)[18]. Furthermore the division of the patients into two groups, according to if they were under treatment of first generation BPs or if they received BPs of second and third generation showed statistically important difference (p<0.01) regarding the differences in BMD values between the study group and the control group in measurements carried out at 3, 6, 12 months after surgery. BP's of second and third generation had better results. There were no major differences of BMD between the two groups in longer follow-up , while the results were better in case of continuous and not discontinued treatment as well as in cemented arthroplasties (P<0.05 at 6 and 12 months)[18].

A meta-analysis (by Su Jing et al.) of 6 randomized controlled trials involved 259 patients (men and women almost in equal percentage), 4 trials used 35 mg/week of risedronate, 1 trial used 2,5 mg/day and the last one used 5 mg/day of risedronate (orally).All patients underwent uncemented THA. The follow-up ranged from 6 months to 4 years. After 3 months of medication there was increase of BMD only in Gruen zones 1,2,6,7 compared with the control group (p<0.05) while at 6 and 12 months was observed a significant beneficial effect of oral risedronate on preservation of BMD in all Gruen zones compared with the control group (p<0.05)[19].

In one recent study conducted in Korea, were collected data from the national health insurance service regarding the number of total knee and hip arthroplasties during 2002-2012. Consequently from the total number of patients that underwent total arthroplasty (2002-2012) was registered the amount of patients that underwent revision surgery, until 2016, due to implant loosening. The exclusion criteria were any metabolic disease, the preoperative use of bisphosphonates and the age under 30. The mean age of the patients was 68.8±7 and 59.1±12.6 for TKR and THR, respectively. The patients were considered as BP users if they had received postoperatively at least 1 WHO-defined daily dose of oral bisphosphonate. In both TKA (331,660 patients of whom 88% were female) and THA (56,043 patients of whom 45% were female), the revision rate was significantly lower in BP users (both p<0.001) . The hazard ratio of revision surgery was lower in the patients who received the medication for more than 1 year (p<0.001)[20].

The relationship between bone quality, the probability of implant revision and the influence of the antiresorptive action of bisphosphonates has been investigated by a cohort study which took place in the United Kingdom. The study included patients who underwent total arthroplasty of the knee (18726) or the hip (23269) during the period 1986-2006 and were over the age of 40 years, excluding those who suffered from rheumatoid arthritis or have undergone hip fracture. Women consisted 58.9% of the patients. Patients were divided into two groups, one consisting of people who received oral treatment with bisphosphonates (alendronate, risedronate, ibandronate and etidronate) for a period of not less than six months (at least for six months before the revision) and the other group consisting of those patients who had never received treatment before surgery. The follow-up lasted five years. The average duration of bisphosphonate intake was 3.07 years. It was found that the use of bisphosphonates prolonged the survival of implants and reduced the proportion of patients who underwent new intervention (p=0.047)[21].

In a similar retrospective cohort study in Denmark, with patient selection criteria similar to those of the previously mentioned study (disqualification of individuals under the age of 40 years, sufferers of metabolic diseases or history of hip fracture) the authors reported reduction of the risk of revision surgery at a rate of approximately 59% (statistical significance not reported) in those who received treatment

immediately after the initial surgery. Patients were allocated either as bisphosphonate users (the type of BP and way administration way were not reported), if during the period of time from the initial surgery up to the end of the follow-up, had received medication dose corresponding to that of six months, or as non. Each bisphosphonate user that underwent total arthroplasty accounted for six non-users. The impact of revision among users was 0.75% and 1.05% in first and second year respectively. Among non-users the percentage stood at 1.20% and 2.26% respectively (p<0.0001). Patients with long-term therapy confirmed more the positive relationship between anti-resorptive medication and survival of arthroplasty[22].

In a survey conducted in Memorial hospital of Taiwan in 96 women, with a mean age of 70 years, who underwent cementless total knee arthroplasty. Women were excluded if they suffered from metabolic disease and were receiving medication or had neuromuscular disorders. Patients were divided into two groups (study and control). In the study group were administrated daily 10 mg of alendronate, from the second post-operative day on and for six months. The average measurement of BMD at the distal end of the femur, decreased by 13.8% in the control group in the first half (p<0.001) and 7.8% in one year (p=0.003). On the study group BMD increased in the first semester by 10% (p=0.010) and 1.9% after twelve months (p=0.049). At the proximal end of the tibia, in the control group, there was a reduction of 6.5% (p=0.002) and 3.6% (p=0.141) in six and twelve months respectively. In the group that received treatment BMD increased by 9.4% (p<0.001) and 5.4% (p=0.032) after six and twelve months respectively[23].

Another randomized controlled study, conducted by Jaroma et al, with a much smaller number of patients, 26 in total (9 male and 17 female, mean age 67 years), but with longer follow - up (seven years) recorded the bone density around implants of total knee arthroplasty in the study group and the control group. At the first group were administered 10 mg/day of alendronate and 500 mg calcium while in the second one only calcium. The treatment lasted 12 months. From the measurements made on DXA, immediately postoperatively, at three and six months, at the first, second, third, fourth and seventh year the authors report increase BMD in the outer part of the tibia metaphysis in the study group in seven years (p=0.002) and a substantially higher rate of BMD throughout all measurements compared to the control group (p=0.024). There were no significant differences in other parts[24].

Similar results were found in another randomized controlled study conducted by Soininvaara et al, in which participated nineteen patients who underwent cemented TKA, with shorter follow-up (one year) and same treatment regimen (10 mg/day of alendronate and 500 mg of calcium in the study group and only calcium in the control group). The patients under treatment with alendronate maintained BMD at the distal femoral (p>0.004) while those who took just calcium showed significant bone loss (p<0.015). There was significant difference, between the study and the control group, in the BMD of the anterior metaphysis (p=0.019), posterior metaphysis (p=0.010), total metaphysis (p=0.024) and diaphysis (p=0.022)[25].

On the other hand, in another double blind randomized study (60 patients, males and females age 50-80) the once weekly, post-operative oral medication with 70 mg of alendronate for six months did not brought any change in bone mineral density around knee implants, in total uncemented arthroplasty, between the two groups (control - study) during the biennial follow-up and not statistically difference was found[26].

In a double blind study, conducted by Hilding et al, in which initially were included 50 patients, aged 60-75 years, the authors assessed the effects of ibandronate administrated i.v as an injection (1mg) on trabecular bone versus placebo (1 mg of saline) to the proximal trabecular bone of the tibia one minute before placing cement in total knee arthroplasty. The study excluded those who were taking bisphosphonates, cortisone or suffered from rheumatoid arthritis or other diseases that affect the bone tissue. Measurements, with radio-stereometric resolution (consists of taking two radiographic films with relative angle 90 degrees between them and processing them with the UmRSA system 4.1 in order to calculate the movement of material in relation to the bone after being both delineated using indicators such as tantalum) were made the first post-operative day and on 6, 12 and 24 months. The authors did not observe cases of material loosening, while there was decrease of mobility (p=0.006)[27].

In a double blind randomized study conducted by Hilding et al the action of clodronate was studied on 50 patients who underwent total knee arthroplasty with cement. Patients under bisphosphonates medication, with rheumatoid arthritis or other illnesses that could affect bone metabolism were excluded. Clodronate was administered orally (1.6 gr/day) versus placebo three weeks before and six months after surgery. The movement of the materials was decreased in radiostereometric measurements (p=0.01) made one year postoperatively. Subsequently, in a relevant study with measurements made at the first post-operative day, at six weeks, at six months, one, two and four years was not found difference at measurements after the first year between the two groups in terms of maximal moving point (p=0.1). Between the two groups there is a difference in rotational movement in four years with a gradual increase from the first year (p=0.04)[28].

Arabmotlagh et al. studied, in a prospective randomized study, the femoral BMD variation (at seven Gruen zones) in patients who received post-operatively (cementless THA) alendronate. The study included initially 57 patients with 49 of them evaluated at sixth year. The patients (mean age 64) who formed the study group were divided into two sub-groups. One group received 10 mg/day of alendronate for ten

weeks and the other group 20 mg/day for five weeks. BMD measurements on DXA were performedin all Gruen zones at the sixth post-operative year. In Gruen zones 5 there was observed a significant increase of BMD in the control group, at the sixth post-operative year, comparing with BMD values of the same group at the first postoperative year (4.2 and 3.5%, respectively; p=0.04). In Gruen zone 5 there was a significant difference of BMD value in the group under 20 mg/day of alendronate six years after the operation comparing to the BMD value at the first postoperative year (4.2 and 3.5%, respectively; p=0.04). Comparing the bone density in the first year and after six years there was no significant difference in the rest Gruen zones. After six years the bone loss was significantly smaller in zones 6 and 7 in the patients of the drug groups compared to the control group (p=0.05 and p=0.04 for the 10 mg/day and 20 mg/day alendronate groups respectively)[29].

Venesmaa et al. studied the effect of alendronate administrated in the dose of 10 mg/day with 500 mg/day of calcium supplements (study group) comparing to the control group which received only 500 mg/day of calcium. The medication was administered from the first post-operative day. The study enrolled 13 patients (men and postmenopausal women) who underwent uncemented THA and were followed-up for 6 months. Measurements were made in all Gruen zones using DXA at the third post-operative week and at three and six months after surgery. In the alendronate group the BMD ranged from 5.1% of decrease (-5,1%) to +3.8% (of increase) while in the control group the decrease ranged from -4.4% to -19.6%. In the proximal metaphysis (Gruen zone 1 and 7) and in total periprosthetic regions (Gruen zones 1 to 7) there was a significant BMD difference between the two groups (p=0.019 for both)[30].

Another randomized double blind study which enrolled 31 patients assessed the action of etidronate on femoral implants of cemented THA. Patients with diseases that affect bone metabolism or those with previous intake of bisphosphonates, calcium, vitamin D, androgen and estrogen were excluded. In the study group were administrated 400 mg/day of etidronate for two weeks (cyclic therapy) followed also by the administration of calcium (260 mg/day) for the next twelve weeks. Consequently the authors evaluated the periprosthetic BMD, by DXA, in all Gruen zones and in proximal femur at 1 week, three weeks, 3, 6, 12 months. There was not recorded any significant difference of mean value of BMD between the study and the control group in total periprosthetic area (p=0.645 at 1 week, p=0.792 at 6 weeks, p=0.402 at 3 months, p=0.118 at 6 months, p=0.246 at 12 months). In both groups there was registered a significant mean bone loss[31].

A randomized placebo-controlled trial conducted on 49 postmenopausal women who suffered by degenerative hip arthritis and underwent uncemented total hip arthroplasty was conducted by Aro et al. The patients had not received antiosteoporotic treatment during the preoperative period. The authors studied the effect of zoledronic acid i.v on periprosthetic BMD (at the proximal femur). In both medication and control groups were administered supplementations of calcium and vitamin D. The BMD measurements were carried out the third post-operative day, and after 3, 6, 12 and 48 months. The administration of a single dose of 5mg of zoledronic acid i.v in the fifth post-operative day retained the periprosthetic bone mineral density in Gruen zone 7 significantly higher compared to the placebo group (p=0.006). Higher BMD was also retained in Gruen zone 6 by 10% compared to the placebo group at the fourth post-operative year while a decrease of BMD in zone 1 and increase in zone 4 in both groups on measurements made with the DXA method were found on the fourth postoperative year. No statistical significance (p=0.79) was found between the study and placebo group regarding the prosthesis migration[32].

b) Denosumab

Only 2 studies were found in human subjects assessing the effects of denosumab on the survival of implants. In the first study[33] fifty patients (30 women and 20 men) eligible for cemented total knee arthroplasty were randomized in two groups. The authors excluded patients under treatment with bisphosphonates or other medication that could affect bone metabolism. In the study group (10 men and 15 women), patients were administered one dose of 60 mg of denosumab s.c at the day of surgery and one additional dose after six months. The implant stability was estimated with radiostereometric analysis in six, twelve and twenty-four months. From the measurements the authors reported substantial statistic difference, in favour of the study group, at twelve (p=0.01), six and twenty four months (p=0.02 for both) but not during the period between the first and the second year. In total knee arthroplasty, chosen as primary treatment, denosumab reduces by one third the migration and by extension the material loosening, without this relationship being linear[33].

Nagoya et al studied the effect of denosumab in twenty female patients of mean age 80.8 who underwent uncemented THA. The patients were separated in two equal groups. In the study group the patients received one dose of 60 mg of denosumab sc within 7-14 days postoperatively and another similar dose in six months. Both groups received 0,75 μg/day of an active form of vitamin D. The authors reported that denosumab significantly increased BMD only at Gruen zone 7 (p=0.04) after 6 months and 1 year of treatment[34].

Discussion

Many studies have previously shown reduction of BMD on anatomical areas of the prosthesis placement in patients undergoing arthroplasty of the hip and/or knee. Several clinical studies have been conducted in order to investigate the action of drugs with antiresorptive action on material

preservation of total knee or hip arthroplasty from aseptic loosening that will lead to revision surgery. Most of these studies mainly assessed the effects of alendronate which was administrated orally daily (10 mg) or weekly (70 mg), while only a small number of studies was performed with other bisphosphonates (risedronate, ibandronate, etidronate, clodronate, zoledronate) and only 2 studies focused on denosumab. Most of these studies excluded patients with a pre-operative use of antiresorptives or who suffered from bone metabolic diseases that affect the bone quality. In most studies, patients were not divided into groups according to gender, and only two studies were carried out exclusively in postmenopausal women. Thus, the results of the post-operative stability of the materials cannot be correlated with the changes occurring after menopause. The median age of patients ranged from 64 to 75, while only in the two cohort studies the age range was wider, including patients older than 40 years. The total number of patients who participated in each study (excluding cohort studies) was limited. The active drug group and the control group ranged each from 19 to 96 individuals, a number quite small in order to draw safe conclusions on the action of the antiresorptive medication and the stability of the prosthesis of total knee and hip arthroplasty. Also the follow-up ranged from 1 to 7 years, with the most common monitoring duration to be 1-2 years. Thus, the limited number of patients and the short period of follow up are restrictive factors in the extraction of absolute and safe conclusions. In two cohort studies in England and Denmark[21,22], including all patients aged over 40 years who underwent total knee or hip arthroplasty and received bisphosphonates more than 6 months, there was a statistically significant difference concerning the survival of the arthroplasty implants. The post-operative administration of 10 mg of alendronate daily for at least 6 months, with or without concomitant administration of calcium supplementation, resulted in the preservation or limited loss of BMD and the stabilization of the implants of cemented total arthroplasty (knee or hip). In the case of administration of 70 mg/week of alendronate in patients treated with uncemented TKA, there was no significant difference between the drug and the control groups. Ibandronate was also found to stabilize bone implants when injected into the bone peri-operatively[27]. Also, the administration of two doses of denosumab (immediately after surgery and in 6 months) in patients undergoing TKA led to a significant increase in the bone density of the study group ($p=0.01$) in the first postoperative year. In cementless total hip arthroplasty, alendronate was found to significantly increase BMD ($p<0.05$) whereas the action of denosumab was different in each of the 7 Gruen zones. The most beneficial action of denosumab was considered to be in zones 6 and 7.

Among common findings on measurements performed in the third pos-toperative month is the decrease of periprosthetic BMD in both the study and the control groups in cemented arthroplasties. However bone loss was found in a number of studies to be lower in the bisphosphonate group. Also better results of the antiresorptive medication have been observed in cemented compared to uncemented arthroplasties. Furthermore, bisphosphonates administered for longer periods have been found to exert better results on preserving BMD in the periprosthetic region or to the restriction of bone loss. In the case of cyclic administration of etidronate in cemented THA there was not any significant diference of mean BMD in the study and the control groups while the bone loss in both groups was significant.

Conclusions

The post-operative administration of bisphosphonates has been found in numerous studies to exert a positive effect on the preservation and the minimum loss of BMD around the implants of cemented total knee arthroplasty. In uncemented TKA this positive action has not been observed. In patients who underwent total hip replacement and bisphosphonates, reduction of bone loss around the implant and of the risk of aseptic loosening was noted by some authors[35]. This decrease was in direct relation to the kind of treatment (bisphosphonates of second and third generation were more effective) as well as with the surgical technique chosen (with cement or without cement implants)[18,17]. It has been suggested that cement and metal particles can affect the osteoclasts formation and activation inducing cytokine release by osteoblasts, macrophages, marrow-cells and T-lymphocytes[34,41]. Denosumab and bisphosphonates seem to have similar positive effect on periprosthetic BMD preservation or increase and the avoidance of aseptic loosening. The maximum bone loss occurs during the first post-operative semester while maximum results of antiresorptive action have been observed to be obtained within the year of its administration.

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