ARTICLE

A Hydroxyapatite Coated Collar Reduces Aseptic Loosening of Cemented Distal Femoral Massive Bone Tumour Prostheses

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Each author certifies that he or she has no commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.

Ethical Review Statement
This document has been uploaded with the submission.

Location of where Work was Performed:
This work was carried out at the John Scales Centre for Biomedical Engineering, Institute of Orthopaedics, University College London, Royal National Orthopaedic Hospital, Stanmore, Middlesex, HA7 4LP.

Abstract
Background: Aseptic loosening of massive bone tumour implants remains one of the major causes of prosthesis failure.

Question: The hypothesis of this study was that an osteointegrated hydroxyapatite (HA) coated collar would reduce the incidence of aseptic loosening around the cemented intramedullary stem in distal femoral bone tumour prostheses.

Methods: Twenty-two patients were pair matched into either; (1) implants with a HA coated ingrowth collar (HA Collar group) and (2) implants without an ingrowth collar (Non-Collar Group). Radiographs obtained throughout the follow-up period were analysed and osteointegration at the shaft of the implant quantified. Cortical bone loss at the bone-shoulder-implant junction was also measured and radiolucent line progression around the cemented stem was scored.

Results: Comparison of the most recent radiographs showed nine out of 11 patients had osteointegrated HA Collars whereas only 1 patient in the Non-Collar group demonstrated osteointegration (p = > 0.05). Results showed a significant increase in cortical bone loss at the bone-shoulder-implant junction in the Non-Collar group when compared with the HA Collar group (p < 0.05). The radiolucent line score quantified around the cemented stem was significantly lower in the HA Collar group when compared with the Non-Collar group (p = 0.001).

Conclusion: Osteointegration at the implant collar resulted in significantly fewer radiolucent lines adjacent to the intramedullary cemented stem and decreased cortical bone loss immediately adjacent to the transection site.

Clinical Relevance: These results suggest that the HA collar may be directly responsible for the reduction of aseptic loosening in patients with this type of implant.

Introduction

Limb-sparing surgery using a massive endoprosthesis has been accepted as the choice of treatment for malignant bone tumours of the distal femur [14, 18]. Longevity of the reconstruction is however a major concern, especially in young and active patients who place high demands on their prostheses [8]. A retrospective study of custom made distal femoral endoprostheses published in 1996, reported aseptic loosening (ASL) as a principle mode of failure with a 67.4% probability of a patient surviving aseptic loosening at 10 years [25]. Young patients in whom a high percentage of the femur has been replaced had the poorest prognosis for survival. Other more recent studies have also reported aseptic loosening as a major complication with loosening rates of distal femoral prostheses between 2.9 and 28.6 % at 4 to 10-years [9-11, 14, 17, 24].

Concerns for successful long-term fixation stimulated advancements in implant design and it has been reported that extracortical bone-bridging and osteointegration at the shoulder of the implant may reduce ASL by improving stress transfer within the cement mantle [20, 23, 3-5]. Aseptic loosening has been reported to initiate with localized cortical bone loss at the bone-shoulder-implant junction where the bone is in direct contact with the shoulder of the implant [1, 2, 26, 27]. Over time, osteolysis increases and cortical bone loss at the bone-shoulder-implant junction is followed by the development and progression of peri-prosthetic bone-cement radiolucent lines that advance along the interface eventually leading to aseptic loosening of the component [1, 2, 26, 27]. The aim of our study was to investigate and quantify extracortical bone growth and the development of radiolucent lines around the cemented interface in implants with and without a circumferential HA coated ingrowth collar at the shoulder of distal femoral bone tumour implants. Our hypothesis was that a HA coated collar would increase osteointegration, reduce cortical bone loss at the bone-shoulder-implant junction and reduce the development of radiolucent lines around the stem.

Materials and methods

Between 1990 and 2000, 84 primary limb salvage surgeries involving bone tumour resection and reconstruction using a cemented distal femoral endoprosthesis were performed at the Royal National Orthopaedic Hospital (RNOH), Stanmore, United Kingdom. Thirty patients received a cemented distal femoral replacement with a smooth polished metal surface (Non-Collar Group) and 54 patients received a cemented distal femoral replacement with a HA-coated grooved ingrowth collar located at the shoulder of the implant (HA Collar Group). From these two groups, a total of 22 patients were pair-matched (11 matched pairs) and investigated in this study (Table 1). Fourteen patients were female and 8 male and all were matched for age, length of bone resection and length of follow-up, as these factors have been established as independent risk factors for aseptic loosening of distal femoral endoprostheses [25]. The mean age of patients at the time of surgery was 36.1 years

(range, 16 – 66-years). Patients were followed-up at a mean of 7.1-years, (range, 2.3 – 11.7-years). The percentage of bone resected during surgery from each patient was calculated from AP radiographs and a mean of 37.0%, (range, 25 - 59%) of the length of the femur was resected. When the groups were compared, the mean difference in age was 3.7 ± 1.8-years, the difference in follow-up was 2.75 ± 0.53-years and the mean difference in resection length between the two groups was 5.4 ± 1.0%. No significant differences were found when the means of the groups were compared. All surgery was performed for primary bone tumours where osteosarcoma was the most common diagnosis (63.6%) followed by malignant fibrous histiocytoma (13.6%), osteoclastoma (13.6%) and chondrosarcoma (9.1%). None of the implants were revised during the investigative period and each patient received a unilateral implant with 11 inserted into the right leg and 11 into the left.

All prostheses were designed by Stanmore Implants Ltd (Elstree, Hertfordshire, United Kingdom) and manufactured on a customized case-by-case basis. The shaft and intramedullary stem were made from titanium alloy (Ti_6Al_4V) and when indicated, the stem was shaped to follow the natural curvature of the bone. Following resection of the knee joint, all patients in this study were implanted with a SMILES™ rotating hinge total joint made from cast cobalt-chrome-molybdenum alloy. Both the tibial and femoral intramedullary stems were cemented in place. The HA collar was composed of circumferential and longitudinal grooves manufactured 1.5 mm deep, 1.0 mm apart, and 1.0 mm wide. A highly crystalline plasma sprayed hydroxyapatite coating (> 85% crystallinity and 50 μm thick; Plasma Biotal, Derby, United Kingdom) was applied to each collar prior to surgery. In the non-collar group, the shaft at the shoulder of the implant was a smooth polished surface finish.

Where appropriate patients received neoadjuvant chemotherapy and all met the criteria for limb salvage [21]. Patients were given chemotherapy post–surgery and partial weight–bearing was allowed in the first six weeks after surgery, slowly progressing to full weight bearing. After six weeks, patients returned for a period of intensive physiotherapy. All procedures were performed at a single institution and no patients were recalled specifically for this study; all data was obtained from the medical records and post-operative radiographs.

Radiographic Analysis
Radiographic analysis was undertaken by one observer (AS) and measurements (mm ± standard error of mean) made from both the antero-posterior and medio-lateral radiographs taken from each patient beginning immediately post-operatively and at regular intervals throughout their follow-up period. On average, patients attended out-patient clinic three times a year and radiographs were taken on each occasion. The number of radiographs analysed for each patient varied according to length of follow-up, however a mean of 10.09 ± 7.2 (range, 5 – 16) radiographs were analysed per patient in this study.

Each of the radiographs were used to quantify:
  (i)   Extracortical bone growth (maximal bone thickness and length) over the collar,
  (ii)   The presence of radiolucent lines (RL) both (1) around the cemented intramedullary fixation and (2) when interposed between extracortical bone growth and the implant collar.
  (iii) The extent of cortical bone loss immediately beneath the implant shaft.

Extracortical Bone Growth
Results from patients with HA collars were compared with those patients with a smooth metal surface. Maximal extracortical bone thickness, length and all RL measurements were measured and quantified radiographically in four aspects (the medial and lateral aspects on antero-posterior radiographs and the anterior and posterior aspects on lateral radiographs).

Values obtained from A/P and M/L radiographs were averaged and single mean values used for each time-point investigated.

Radiolucent Line Measurements Between Extracortical Bone and the Implant
Radiolucent lines that separated extracortical bone growth at the collar surface were quantified by measuring their mean maximal thickness. Where RLs were present, the implant was considered not ingrown (Figures 1a and b). As above, each collar region was first divided into four quadrants and the presence of a RL quantified in the medial, lateral, anterior and posterior views. A measurement of '0 mm' indicated there were no RLs and the extracortical bone growth had osteointegrated within the collar surface.

Radiolucent Line Score: Cemented Intramedullary Fixation
Radiolucent lines at the cement-bone interface adjacent to the intramedullary stem were quantified from serial routine antero-posterior and medio-lateral radiographs taken throughout the follow-up period. The medial, lateral, anterior and posterior aspects adjacent to the intramedullary stem were each divided into 6 equi-distant zones (Figure 2). When a radiolucent line was observed at the cement-bone interface within a zone, a score of '1' was given. Therefore a maximal score of '12' could be obtained from each radiograph and a total score of '24', would indicate a prosthesis that was surrounded by radiolucent lines along the entire stem in both antero-posterior and medio-lateral radiographs. A score of '0' indicated that no radiolucent lines were measured.

Cortical Bone Loss at the Bone-Shoulder-Implant Junction
The distance that separated bone from the shoulder of the implant located directly above the transection site was measured and quantified over the follow-up time period in each of the 22 patients (Figure 3).

Statistics
Using data obtained from the most recent A/P and M/L radiographs, the Mann-Whitney U test was used for statistical comparison between HA Collar and Non-Collar groups where P values < 0.05 were considered significant (version 10.1; SPSS, Chicago, Illinois). Radiolucent line score and cortical bone loss when measured throughout the follow-up period were univariately assessed for association with osteointegration at the collar using the Spearman Rank coefficient. Mean values ± standard error of mean are presented.

Results
Extracortical Bone Formation
In the HA collar group, 10 out of 11 patients developed extracortical bone growth in at least one of the four quadrants adjacent to the collar. In the Non-Collar Group, 9 out of 11 patients showed bone growth in at least one region. Extracortical formation had occurred in both groups in similar amounts over the follow-up time period investigated. A mean bony length of 7.63 ± 2.58 mm and a mean thickness of 2.85 ± 0.93 mm was measured in patients who received a HA coated ingrowth collar over the 11.7-year follow-up period. This was in comparison to a mean bony length of 6.59 ± 1.85 mm and a mean thickness of 1.47 ± 0.37 mm in patients with no collar. No significant differences were found when the Collar and Non-Collared groups were compared.

Osteointegration of the Collar
When osteointegration of the collar was investigated, results showed that in the HA Collar group, 9 out of the 11 patients demonstrated direct bony ingrowth (as defined by the absence of a radiolucent line) in at least one of the four regions measured. Six out of the 11 patients in the HA Collar group had collars that were osteointegrated in all 4 regions. In the Non-Collar patient group, results showed that only 1 patient demonstrated direct radiological contact in one region of the implant surface (Figure 4).

Overall, significantly thicker radiolucent lines were measured adjacent to the shaft in the Non-Collar group (mean, 1.59 ± 0.35 mm) when compared with the HA collar group (mean, 0.15 ± 0.09 mm) ($p < 0.05$). When the results were separated into the medial, lateral, anterior and posterior regions, no significant differences were found when RL thickness was compared within the Non-Collar and HA collar groups. However, significantly thinner RLs were measured adjacent to the HA coated collars when each of these regions were compared with the Non-Collar group (except in the anterior aspect) (Medial: $p = 0.023$; Lateral: $p = 0.028$ and posteriorly: $p = 0.001$) (Table 2). Over time, results showed that progression of the thickness of the RLs at the bone-collar interface did not increase over the follow-up period in the HA Collar group but did gradually increase in the Non-Collar patient cohort (Figure 5).

Radiolucent Line Score: Intramedullary Stem Fixation
Results demonstrated a significantly lower radiolucent line score adjacent to the cemented intramedullary stem in implants with a grooved HA coated collar (mean 0.58 ± 0.13; range, 0 to 7) when compared with implants in the Non-Collar group (mean 3.80 ± 0.40; range, 0 – 18) ($p = 0.002$) (Figure 6). Results showed that in the HA Collar group and throughout the follow-up period, the score for each of the 11 patients did not rise above '7'. In the non-collar group radiolucent lines was seen to gradually increase over time suggesting that each of the implants in this group of eleven patients were gradually becoming loose as 3 patients scored '18'. In the Non-Collar group and when the RLS was compared over time, a significantly higher RLS was measured in each of the yearly increments when compared with 1-year post operatively (except 2-years) ($p < 0.05$ in all cases). The RLS measured at 10 and 11-years was significantly higher when compared with all other time-points ($p < 0.05$ in all cases). No significant differences in RLS between any of the yearly time-points were found in the HA Collar group.

Cortical Bone Loss at the Bone-Shoulder-Implant Junction
Results showed that significantly more cortical bone loss at the bone-shoulder-implant junction occurred in the Non-Collar group (mean 1.07 ± 0.11 mm; range, 0.0 - 8.5mm) when compared with those implants in the HA Collar group (mean 0.39 ± 0.05; range, 0.0 – 2.0 mm) ($p < 0.05$). Cortical loss remained constant over the follow-up period in the HA Collar group (Figure 7), but appeared to gradually increase in the Non-Collar group over time, however no significant correlation was found.

Extracortical Bone Thickness at the Collar
When divided into the medial, lateral, antero- and posterior aspects, results showed that in both groups, predominantly more bone growth had occurred in the medial and posterior regions of the implant when compared with the anterior and lateral regions (Tables 3 and 4). When extracortical bone thickness in all four regions was combined and results compared over time, significantly increased extracortical thickness was measured adjacent to the shaft of the implant at 6-years when compared with bone growth 1-year post-operatively ($p = 0.043$) in the Non-Collar group. In the HA Collar group, no significant differences were found between time-points suggesting that bone formation occurred earlier in this group.

Extracortical Bone Length at the Collar
When extracortical bone length was compared, results showed that increased amounts of bone growth had occurred in the medial and posterior regions of the implant when compared with the anterior and lateral regions (Tables 5 and 6). At 6 and 4-years post surgery, extracortical bone length was significantly higher when compared with bone growth 1-year post-operatively ($p < 0.05$ in both cases) in the HA Collar group. In the Non-Collar group, no significant differences were found.

Correlation of Extracortical Bone and Radiolucent Lines
A significant correlation was found where increased follow-up time in the Non-Collar group was associated with an increase in the thickness of radiolucent lines found adjacent to the shaft of the implant ($p < 0.05$). No other significant correlations were found with radiolucent lines in the HA collar group or in any of the data investigated. Results in the Non-Collar group showed a stronger correlation over time with RLS measured along the stem-cement interface ($p = 0.071$) compared with the HA Collar group where less correlation was evident ($p = 0.745$).

Discussion
Aseptic loosening of the intramedullary stem remains one of the major causes of distal femoral prosthesis failure. The only identifiable risk factors reported in the literature are age, bone resection length and time of follow-up [25]. In our study, 22 patients with a distal femoral massive bone tumour prosthesis were retrospectively pair matched according to age, resection length, follow-up time, and tumour diagnosis. Eleven patients had DFRs inserted with a circumferential HA coated ingrowth collar located at the shoulder of the implant and the other eleven patients had no collar present and instead a polished titanium alloy surface. All of these patients had the same prosthetic design. In theory, osteointegration of extracortical bone growth to the implant surface at the shoulder of the implant may be associated with a more advantageous biomechanical environment and improved stem fixation [3-5, 20, 23]. Therefore in this study we hypothesized that the HA coated ingrowth collar would increase osteointegration and reduce the development of radiolucent lines, aseptic loosening and improve survivorship. Our results showed that over the mean 7.1-year follow-up period, 9 of the 11 HA Collars were radiographically osteointegrated whereas only 1 patient in the Non-Collar group had integrated. We can accept our hypothesis that a greater radiolucent line score was measured adjacent to the cemented fixation in the HA Collar group when compared with to patients with implants without a collar. For the non-collared group, this RLS increased over time indicating progression towards loosening of the stem. None of the implants in the HA Collar group developed progressive radiolucent lines. No implants in either group were revised during the investigative period, however results showed that implants in all patients in the Non-Collar group were gradually becoming aseptically loose.

A secondary question asked was whether the presence of the HA Collar would reduce the onset of aseptic loosening by preventing cortical bone loss at the bone-shoulder-implant junction. Several studies have reported that the loosening sequence in cemented massive bone tumour implants begins with osteolysis of cortical bone at the implant-bone junction [1, 2, 26, 27]. Osteolysis then slowly progresses along the bone-cement interface culminating in aseptic loosening of the implant.   In our study, results showed increased cortical loss at the shoulder of the implant in patients without HA collars. Although no significant trend was found, cortical loss remained consistently low in the HA collar group but gradually increased in the Non-Collar group over time.

Although the level of osteointegration differed in our two groups, our study showed that similar and consistent amounts of extracortical bone had grown over the shoulder of the implant. The major difference was the osteointegration of the shaft due to the use of the HA collar.   No significant differences were found when the length and thickness of extracortical bone was compared in the two groups. The regional difference found in bone formation adjacent to the shaft of the prosthesis in both groups may be associated with high compressive loads found medially and posteriorly at the shoulder of massive bone tumour implants with higher tension measured in the anterior and lateral planes [25, 23]. A radiographic study has also shown increased bone density and remodeling in areas of high compression at the shoulder of proximal femoral and distal femoral prostheses with bone resorption in areas of high tension [13, 23, 25].

Methods to enhance the osteointegration of bone to the shoulder of massive bone tumour prostheses have been investigated and a number of different ingrowth surfaces assessed with varying amounts of extracortical growth reported [5, 12, 16, 26]. Tanzer et al. [22] reported that radiographic extracortical bone growth adjacent to porous coated collars in 20 bone tumour patients at a mean follow-up of 2.3-years did not correlate with osteointegration to the implant surface when investigated histologically. In this retrieval study no osseointegration was demonstrated. A recent study [6] reported the histological evaluation of 4 distal femoral replacements with a HA grooved ingrowth collar and 4 implants with a smooth titanium alloy surface finish and results showed that ingrowth with direct bone-implant contact was seen in all patients with a HA collar. As similarly reported in Tanzer's study [22], no bone-implant contact was seen in the non-collar group and all of the extracortical bone formed was separated from the implant surface by a relatively thick layer of fibrous tissue. In this current study, we report on osteointegration to the HA collar following radiographic analysis and it is possible that histological osteointegration may not have occurred in all patients despite the radiographic appearance. However, a radiolucent line between the extracortical bone and the shaft of the implant in the Non-Collar group was clearly evident in all cases except one. The importance of osteointegration at the shoulder has been recognized and a number experimental studies have investigated methods to enhance extracortical bone formation these include the use of BMP's [19] and the use of stem cells [7, 15].

Our study had limitations. Firstly, it was a retrospective analysis where variation was minimized by pair-matching patients. However patient variations in height, weight, activity level and dose of chemotherapy were not accounted for and a further limitation was the small sample size investigated. However, further variations were minimized as all implants were of a similar design, made by a single manufacturer and all surgical techniques and patient care were consistent as patients were treated at a single institution.

In conclusion, this study demonstrated that a grooved HA coated ingrowth collar located at the shoulder of cemented distal femoral massive prostheses resulted in significantly fewer radiolucent lines adjacent to the intramedullary cemented stem and decreased cortical bone loss immediately adjacent to the transection site. These results suggest that the HA collar may be directly responsible for the reduction of aseptic loosening possibly due to load transfer from the shoulder to the cortical bone surrounding the intramedullary stem reducing aseptic loosening.

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Figure Legends

Figure 1a: An A/P radiograph of a Non-Collared implant 2.8-years post surgery. The white arrows show a clear radiolucent margin separating the newly formed extracortical bone growth with the implant surface. This collar was considered not ingrown. The red arrows indicate the radiolucent lines that are present at the cement-bone interface within the stem fixation.

Figure 1b: An A/P radiograph of the pair matched HA coated collared implant 1.1-years post surgery. The white arrows show bone integration within the grooves with direct contact with the implant surface. This collar was considered ingrown.

Figure 2: An antero-posterior radiograph demonstrating the dividing lines that created 6 zones along the medial and lateral intramedullary stem length respectively. A maximal score of 12 would indicate the presence of a radiolucent line in all 12 of the divided zones. Twelve zones were also assessed on medial-lateral radiographs.

Figure 3: An Medial-Lateral radiograph of an implant in the Non-Collar group at 1.2 years post surgery showing cortical 'loss' adjacent to the implant shoulder.

Figure 4: [A] An A/P microradiograph from a patient in the Non-Collar group at 3.6-year follow up, showing radiolucent lines separating the implant surface and bony pedicle. [B] An A/P microradiograph from a pair matched patient in the HA Collar group at 1-year follow up, showing osteointegration of the collar.

Figure 5: A graph showing the thickness (mm) of radiolucent line measured between the extracortical bone pedicle and implant shaft in the HA Collar and Non-Collar groups over the study period.

Figure 6: A graph showing the radiolucent line score measured along the cemented stem in both the HA Collar and Non-Collar groups over the study period.

Figure 7: A graph showing the amount of cortical bone loss measured adjacent to the implant shoulder in the HA Collar and Non-Collar groups over the study period.