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Randomised trial comparing bone remodelling around two uncemented stems using modified Gruen zones

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Abstract: *For assessment of bone remodelling around total hip arthroplasty using dual-emission X-ray absorptiometry (DEXA), a variety of different systems to identify regions of interest (ROI) have been used, making comparisons between stem designs difficult. The Gruen zones are now widely used for this purpose. We present the results of a randomised clinical trial comparing 2 uncemented stem designs with proximal coating, using a modification of the Gruen zones to allow improved representation of the effect of the implant on bone mineral density (BMD) over time.*

DEXA-data were used in a randomised trial with 2 years follow up, comparing the uncemented Symax™ (n=25) and Omnifit® (n=24) stems. The effect on BMD was determined using the 'standard' adapted Gruen zones, and a modification which studied an equal length and position for zones 1 and 7 around both stems, assuring that the same regions in terms of cancellous and cortical bone were compared.

The 'modified' regions of interest give lower BMD values around the Omnifit® than using the 'standard' Gruen zones (3.6 % in zone 7, $p<0.05$). The difference with the Symax™ BMD values, which had been concealed using the standard Gruen zones, became statistically significant in favour of the Symax™ implant.

This adaptation can detect a statistically significant difference in bone preservation in zone 7 between stems that would otherwise not have been revealed. We recommend the use of 'modified' Gruen zones for more valid comparison of remodelling caused by different implant designs.

Key words: *Total hip arthroplasty, DEXA scan, Regions of interest*

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INTRODUCTION

Preservation of periprosthetic bone around hip prostheses is important. Following uncemented total hip arthroplasty (THA), dual energy X-ray absorptiometry (DEXA) has been shown to be a precise and accurate, and a useful tool for assessment of periprosthetic bone remodelling (1-5). However since the introduction of bone densitometry for this purpose, many different classifications of regions of interest (ROI) have been applied, making comparison of BMD results between implant designs difficult. Some of these ROIs were based on implant-related landmarks (2, 6-8), and others on various anatomic landmarks on the femur (1, 4, 9).

An important improvement for standardization of ROIs was the application of the Gruen zones, which were originally designed for analysis of stem loosening on conventional radiographs (10). Since then many authors have adopted these ROIs for bone densitometry around uncemented and ce-

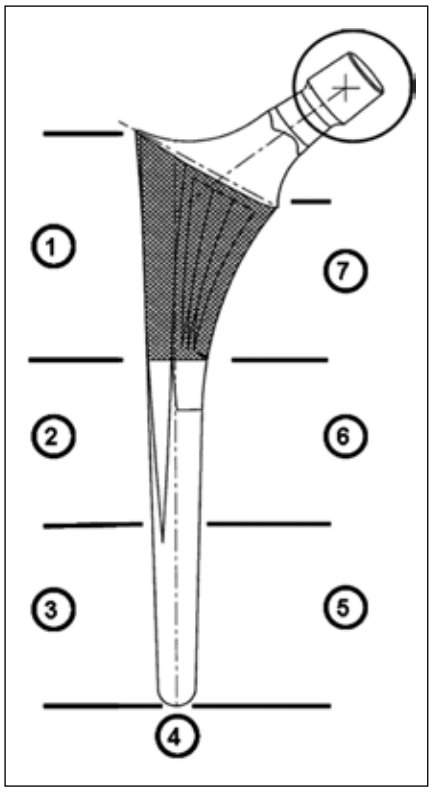

Fig. 1 - *Drawing showing delineation of 'adapted Gruen zones' 1 to 7 in the AP view around an uncemented stem with proximal coating (in this case the Symax™).*

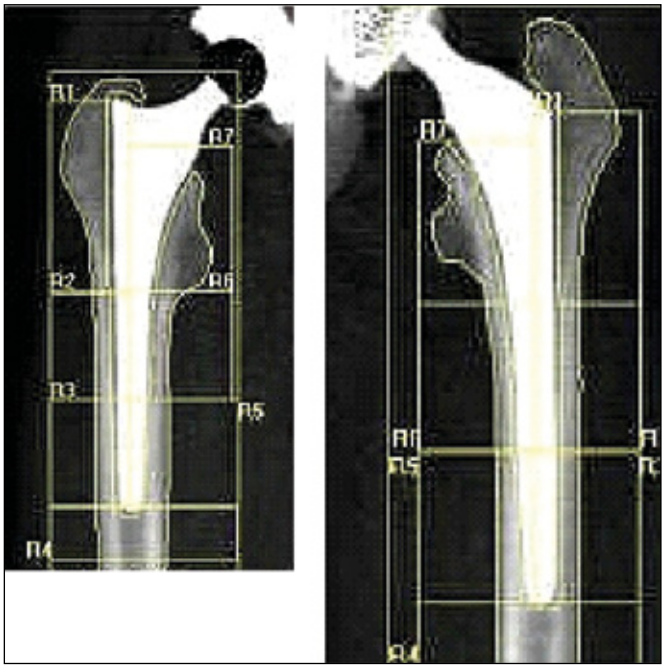

Fig. 2 - *DEXA-pictures of the Symax™ (left) and Omnifit® (right) stems of comparable sizes illustrating how the application of the original (or 'standard') adapted Gruen zones' will result in inclusion of more cortical bone in zone 7 in case of the Omnifit®.*

mented stems (11-22). For uncemented stems with porous or HA proximal coating, these zones were changed to the 'adapted Gruen-zones'; zones 1 and 7 representing the coated area, and zones 2-3 and 5-6 respectively the lateral and medial zones, equally divided around the non-coated part of the stem (Fig. 1). However, for comparing implants with differences in design, stem length and coating-area, using these adapted Gruen-zones may generate spurious conclusions, because compared regions are incomparable in terms of their relative content of cancellous and cortical bone.

Although it is well accepted that bone preservation after stem insertion is mainly driven by biomechanical factors such as stress distribution, the extent of remodelling is also related to the rate of bone metabolism. Cancellous bone is characterised by a higher bone turnover than cortical bone, which is partly due to better vascularisation (23). Therefore, it may be expected that zones that mainly contain cancellous bone will show more postoperative bone loss than zones containing more cortical bone (Fig. 2). This makes comparison of bone density changes between stems with different proximal coating lengths (zone 1 and 7) potentially invalid, because the composition of the compared ROI in terms of cancellous and cortical bone is essentially different (22).

For this reason we performed DEXA-analysis of bone remodelling around two stem designs with different coating length. We compared results using the original 'adapted Gruen-zones' (further referred to as 'standard' zones) with those after adjustment of the ROIs (the 'modified' zones), with the objective of assessing comparable bone areas around both stems. It was hypothesised that there would be a significant difference in DEXA-results in zone 7 between the two methods, which would influence the conclusions of a comparison between two stem designs. We propose 'modified' regions of interest that more correctly attribute remodelling changes to the implant .

PATIENTS AND METHODS

Patient selection

An individually randomised, two group, parallel controlled trial comparing bone remodelling between the uncemented Symax™ (n=25) and the Omnifit®-HA stem (n=24) was performed. The indication for total hip arthroplasty (THA) was osteoarthritis (OA) of the hip in all cases. There were

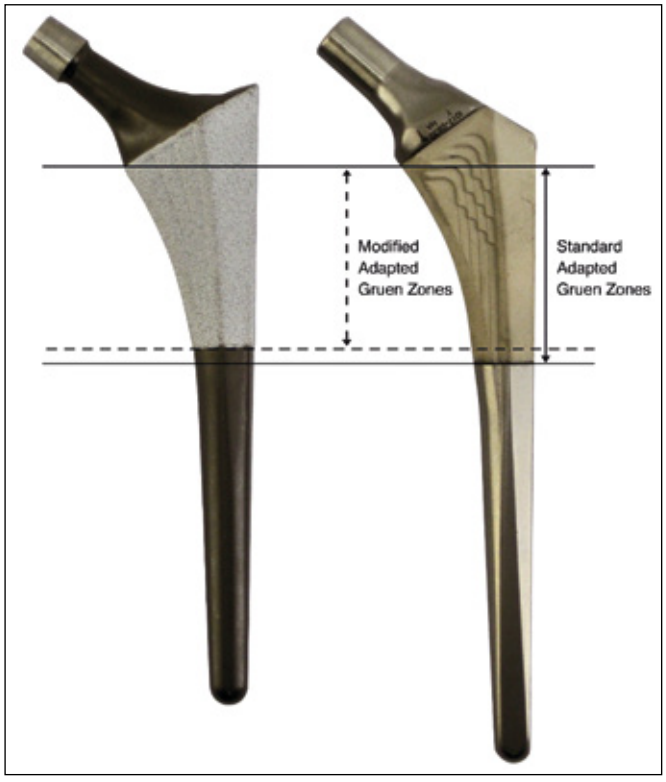

Fig. 3 - *Illustration of the Symax™ (left) and Omnifit® (right) illustrating the small difference in coating length between comparable stem sizes. Good comparison of bone remodelling in zone 7 makes adjustment of the 'standard adapted Gruen zones' around the Omnifit® to the 'modified adapted Gruen zones' necessary.*

no fractures and no cases of osteonecrosis of the femoral head. Exclusion criteria were a history of hormonal therapy, any medication or illness known to affect bone metabolism, and a body mass index (BMI) higher than 35 kg/m^2. After obtaining signed informed consent, participants were allocated at random to the type of prosthesis by sequentially drawing sealed opaque envelopes stipulating choice of implant. The surgeon was unaware of the content and sequence of the envelopes (allocation concealment).
The original trial was approved by the local Medical Ethics Committee and performed at the Orthopaedic department of the Maastricht University Medical Centre (registration nr. 02-072). It was carried out in line with the Seoul amendment (2008) of the Helsinki declaration.

Implants

The Symax™ stem (Stryker® EMEA, Montreux, Switzerland) is forged from Ti6Al4V alloy. It features a proximal plasma-sprayed, commercially pure (CP) Titanium coating, and a biomimetic electrochemically deposited BONIT® HA coating (proprietary to DOT GmbH, Rostock, Germany) (24, 25). Distally the stem is treated with the Dotize® surface process, which reduces protein adsorption and consequently distal bone apposition and osseointegration (26-28).
The Omnifit® HA stem (Stryker®, Mahwah, New Jersey, USA) is made of the same alloy, has a macrotextured surface and a plasma-spray HA-coating on the proximal 40 % of the stem (Fig. 3).

Surgical protocol and postoperative management

All operations were performed by 2 experienced orthopaedic surgeons (R.t.B. and R.G.) according to identical and standardised orthopaedic procedures using the posterolateral approach without osteotomy of the greater trochanter. Patients were treated with 24 hours intravenous antibiotic prophylaxis (Augmentin®), DVT prophylaxis with low molecular weight heparin (Fraxiparin®) for 6 weeks and prophylaxis against heterotopic ossification with non-steroidal anti-inflammatory medication (Indocid®) for 14 days. Full weightbearing was allowed from day 1.

DEXA protocol and regions of interest

The primary outcome measure was periprosthetic BMD from baseline to 2 years follow up. In the first postoperative week the baseline BMD measurement was performed with the fan-beam Hologic QDR 4500A densitometer (Hologic Inc., Waltham, MA, USA) with exact positioning of the leg by stabilizing rotation using standard knee and foot support devices. A dedicated software programme was used for removal of the metal hip stem area. Quality control of the densitometer was executed through daily automatic self-calibration. There was no significant drift during the study period. All DEXA-scans were made by the same experienced independent analyst.
Follow-up evaluations were performed at 6 weeks, 3 months, 6 months, 1 year and 2 years. Analysis of the raw scans was carried out by one member of the research group (R.H.) who was not part of the surgical staff and blinded for clinical and radiographic results.
When comparing implant sizes, the HA-coating is somewhat longer on the Omnifit®-stem than on the Symax™ (Fig. 3). Bone density around the Symax™ was analysed

in one way. BMD around the Omnifit® was assessed in two ways. The 'standard' Gruen zones define the length of Gruen zones 1 and 7 by the length of HA coating, resulting in different lengths for these zones according to prosthesis selection. Using 'modified' Gruen zones, zones 1 and 7 around the Omnifit® are identical in length to those of the size-matched Symax™. In this way comparable bone areas were analysed for both stems. Gruen zones 2 to 6 were equally divided around the rest of the stem (Fig. 3). The appropriate matching of Symax™ and Omnifit® sizes was confirmed with templating on the preoperative X-ray.

Preoperative and (one and two year) postoperative DEXA scanning was also performed of the AP-lumbar spine, to detect abnormal systemic bone metabolism during study follow-up. The preoperative lumbar scan served as a baseline measurement for comparison.

Radiological and clinical evaluation

Anteroposterior (AP) pelvis and lateral radiographs of the involved hip were taken at the same follow-up as the DEXA-scans, following a standard protocol. They were scored according to Engh's criteria for implant ingrowth (29). Clinical results and physical activity were assessed using the Harris Hip Score (HHS).

Statistics

Longitudinal BMD results per Gruen zone are expressed as relative values with the immediate postoperative DEXA measurement of the operated femur being the reference value (baseline), set at 100 %. Absolute and relative BMD values are described by their means and standard deviations, demographic parameters by mean and range. Deviations from the normal distribution were tested by the Kolomogorov-Smirnov test. Since no deviations could be observed, the unpaired Student's t-test for 2 independent samples was used for comparing the Symax™ and Omnifit® group for all ROIs. For the Omnifit®, differences between the 'standard' and the 'modified' Gruen zones were tested per region with the paired t-test. Differences with one-sided p-values equal or lower than 0.05 were considered statistically significant. Microsoft Office Excel 2003 (Microsoft Corporation, Redmond, Washington, USA) and SPSS software 15.0 for Windows (SPSS Inc., Chicago, Illinois, USA) was used for data analysis.

RESULTS

Demographic details and initial lumbar BMD (preoperative) between patient groups showed no important differences (Tab. I). There was no difference in level of physical activity among patients postoperatively according to HHS recordings.

At one year follow-up all stems showed radiological evidence of stable bone ingrowth (29), and none of the patients complained of hip pain at the final evaluation. At two years the lumbar spine BMD did not show a decrease when compared to the start of the study (t_0) in either group. Due to a deviation of protocol and based on anatomical considerations, one patient received a Symax™ instead of an Omnifit®. This same patient was withdrawn from the study because of an intra-operative fracture requiring revision and preventing full weightbearing. All other patients consequently had all their scans performed during the entire follow-up and within the predefined timeframe. All patients who underwent randomization received the treatment to which they were originally allocated (intention to treat principle).

Results of absolute and relative BMD around the Omnifit® were different dependent on the use of 'standard' or 'modified' Gruen zones (results are shown in Table II and graphically represented in Figure 4). For the Omnifit®, absolute BMD was consistently lower at every follow-up using the 'modified' zones instead of the 'standard' zones. In ROI-1 this difference varied between 0.16 g/cm^2 (=1.5%) at 6

TABLE I - PATIENT CHARACTERISTICS AND BASELINE DEMOGRAPHIC DATA

	Omnifit (24)	**Symax (25)**
Age at operation in yrs, mean (range)	60.4 (39-71)	60.2 (46-72)
Weight in kg, mean (range)	78.5 (60-96)	82.2 (54-105)
Body Mass Index in kg/m^2, mean (range)	27.2 (22-32)	27.8 (22-37)
Sex: Male (%)	15 (62.5 %)	12 (48 %)
Baseline BMD spine:		
normal	16 (66.6 %)	17 (68.0 %)
osteopenic	7 (29.2 %)	7 (28.0 %)
osteoporotic	1 (4.2 %)	1 (4.0 %)

Values are given as mean (and range) or frequencies (and percentage).

TABLE II - PERIPROSTHETIC BMD AROUND OMNIFIT® (N=24) AND SYMAX™ (N=25) STEM DURING 2 YEAR PROSPECTIVE FOLLOW-UP

BMD Omnifit standard adapted Gruen zones

	post-op	6 weeks	3 months	6 months	1 year	2 years
ROI 1	1.04 ± 0.17	1.02 ± 0.16	0.98 ± 0.18	0.94 ± 0.17	0.92 ± 0.17	0.90 ± 0.18
	100.0%	98.1%	94.2%	90.4%	88.5%	86.5%
ROI 2	1.70 ± 0.27	1.69 ± 0.28	1.64 ± 0.27	1.64 ± 0.28	1.63 ± 0.26	1.64 ± 0.26
	100.0%	99.4%	96.5%	96.5%	95.9%	96.5%
ROI 3	1.69 ± 0.18	1.66 ± 0.21	1.62 ± 0.22	1.65 ± 0.19	1.68 ± 0.19	1.70 ± 0.21
	100.0%	98.2%	95.9%	97.6%	99.4%	100.6%
ROI 4	1.78 ± 0.21	1.77 ± 0.21	1.76 ± 0.23	1.76 ± 0.21	1.77 ± 0.25	1.78 ± 0.23
	100.0%	99.4%	98.9%	98.9%	99.4%	100.0%
ROI 5	1.73 ± 0.26	1.72 ± 0.27	1.72 ± 0.28	1.72 ± 0.27	1.77 ± 0.29	1.77 ± 0.23
	100.0%	99.4%	99.4%	99.4%	102.3%	102.3%
ROI 6	1.65 ± 0.24	1.63 ± 0.26	1.62 ± 0.27	1.64 ± 0.28	1.66 ± 0.29	1.68 ± 0.28
	100.0%	98.8%	98.2%	99.4%	100.6%	101.8%
ROI 7	1.20 ± 0.23	1.13 ± 0.20	1.06 ± 0.21	1.02 ± 0.20	0.99 ± 0.20	1.00 ± 0.22
	100.0%	94.2%	88.3%	85.0%	82.5%	83.3%

BMD Omnifit modified adapted Gruen zones

	post-op	6 weeks	3 months	6 months	1 year	2 years
ROI 1	0.89 ± 0.17	0.86 ± 0.16	0.83 ± 0.17	0.80 ± 0.17	0.79 ± 0.17	0.78 ± 0.19
	100.0%	96.6%	93.3%	89.9%	88.8%	87.6%
ROI 2	1.67 ± 0.28	1.64 ± 0.26	1.60 ± 0.27	1.61 ± 0.28	1.60 ± 0.28	1.61 ± 0.27
	100.0%	98.2%	95.8%	96.4%	95.8%	96.4%
ROI 3	1.70 ± 0.18	1.66 ± 0.22	1.62 ± 0.21	1.65 ± 0.19	1.68 ± 0.19	1.69 ± 0.20
	100.0%	97.6%	95.3%	97.1%	98.8%	99.4%
ROI 4	1.78 ± 0.22	1.77 ± 0.21	1.75 ± 0.22	1.74 ± 0.21	1.78 ± 0.25	1.78 ± 0.24
	100.0%	99.4%	98.3%	97.8%	100.0%	100.0%
ROI 5	1.72 ± 0.25	1.72 ± 0.26	1.70 ± 0.27	1.67 ± 0.39	1.77 ± 0.29	1.76 ± 0.23
	100.0%	100.0%	98.8%	97.1%	102.9%	102.3%
ROI 6	1.60 ± 0.27	1.60 ± 0.28	1.57 ± 0.29	1.59 ± 0.30	1.61 ± 0.31	1.64 ± 0.30
	100.0%	100.0%	98.1%	99.4%	100.6%	102.5%
ROI 7	1.16 ± 0.23	1.08 ± 0.20	1.01 ± 0.21	0.97 ± 0.20	0.93 ± 0.20	0.93 ± 0.22
	100.0%	93.1%	87.1%	83.6%	80.2%	80.2%

to be continued

TABLE II - CONTINUED

BMD Symax adapted Gruen zones						
	post-op	**6 weeks**	**3 months**	**6 months**	**1 year**	**2 years**
ROI 1	0.96 ± 0.17	0.95 ± 0.18	0.92 ± 0.19	0.89 ± 0.18	0.87 ± 0.19	0.87 ± 0.19
	100.0%	97.9%	94.8%	91.8%	89.7%	89.7%
ROI 2	1.74 ± 0.29	1.71 ± 0.31	1.67 ± 0.30	1.65 ± 0.29	1.67 ± 0.29	1.68 ± 0.30
	100.0%	98.3%	96.0%	94.8%	96.0%	96.6%
ROI 3	1.76 ± 0.21	1.70 ± 0.21	1.70 ± 0.20	1.69 ± 0.22	1.73 ± 0.20	1.73 ± 0.19
	100.0%	96.6%	96.6%	96.0%	98.3%	98.3%
ROI 4	1.85 ± 0.22	1.82 ± 0.21	1.82 ± 0.23	1.84 ± 0.21	1.87 ± 0.21	1.89 ± 0.21
	100.0%	98.4%	98.4%	99.5%	101.1%	102.2%
ROI 5	1.77 ± 0.22	1.74 ± 0.22	1.72 ± 0.23	1.76 ± 0.23	1.80 ± 0.24	1.83 ± 0.24
	100.0%	98.3%	97.2%	99.4%	101.7%	103.4%
ROI 6	1.66 ± 0.18	1.63 ± 0.20	1.62 ± 0.20	1.64 ± 0.20	1.67 ± 0.21	1.71 ± 0.20
	100.0%	98.2%	97.6%	98.8%	100.6%	103.0%
ROI 7	1.29 ± 0.20	1.22 ± 0.18	1.17 ± 0.19	1.13 ± 0.21	1.12 ± 0.22	1.11 ± 0.22
	100.0%	94.6%	90.7%	87.6%	86.8%	86.0%

Presenting absolute values per ROI, with standard deviation, and expressed as percentage of baseline reference. For the Omnifit® both 'standard' and 'modified' Gruen zones are analysed (see Fig. 3 and text).

TABLE III - P-VALUES OF DIFFERENCES IN BMD BETWEEN THE SYMAX™ AND THE OMNIFIT® USING 'STANDARD' AND USING 'MODIFIED' ZONES

	6 weeks	**3 months**	**6 months**	**1 year**	**2 year**
Symax versus Omnifit standard	0.47	0.26	0.28	0.10	0.20
Symax versus Omnifit modified	0.38	0.08	0.11	0.01	0.04

weeks, and 0.12 g/cm^2 (=1.1%) at 2 years. In ROI-7 the difference in BMD was 0.05 g/cm^2 (=1.1 %) at 6 weeks, and 0.07 g/cm^2 (= 3.1%) at 2 years ($p \leq 0.05$). As can be expected, in the more cortical areas this effect was much smaller. In ROI-2 differences varied between 1.2 % (6 wks.) and 0.1 % (2 yrs.), for ROI-6 this was -1.2 % and -0.7 %, for ROI-3 this was 0.6 % and 1.2 %, for ROI-4 this was 0 % and 0 %, and for ROI-5 this was -0.6 % and 0 %. All these differences are not statistically significant.

The difference in BMD between Symax™ and Omnifit® became more evident using the 'modified' Gruen zones. For ROI-1 the difference increased from 1.3% at 6 weeks to 2.1% at 2 years, and for ROI-7 the difference increased from 1.5% at 6 weeks (p=0.38) to 5.8% at 2 years (p=0.04). At 2 years the difference between the groups in zone 7 was 2.7% (p=0.20) using the 'standard' zones and became 5.8 % by adapting the 'modified' zones (p=0.04). The results show consistently higher BMD values for the Symax™. The differences in zone 7 became statistically significant from one year onward (Tab. III).

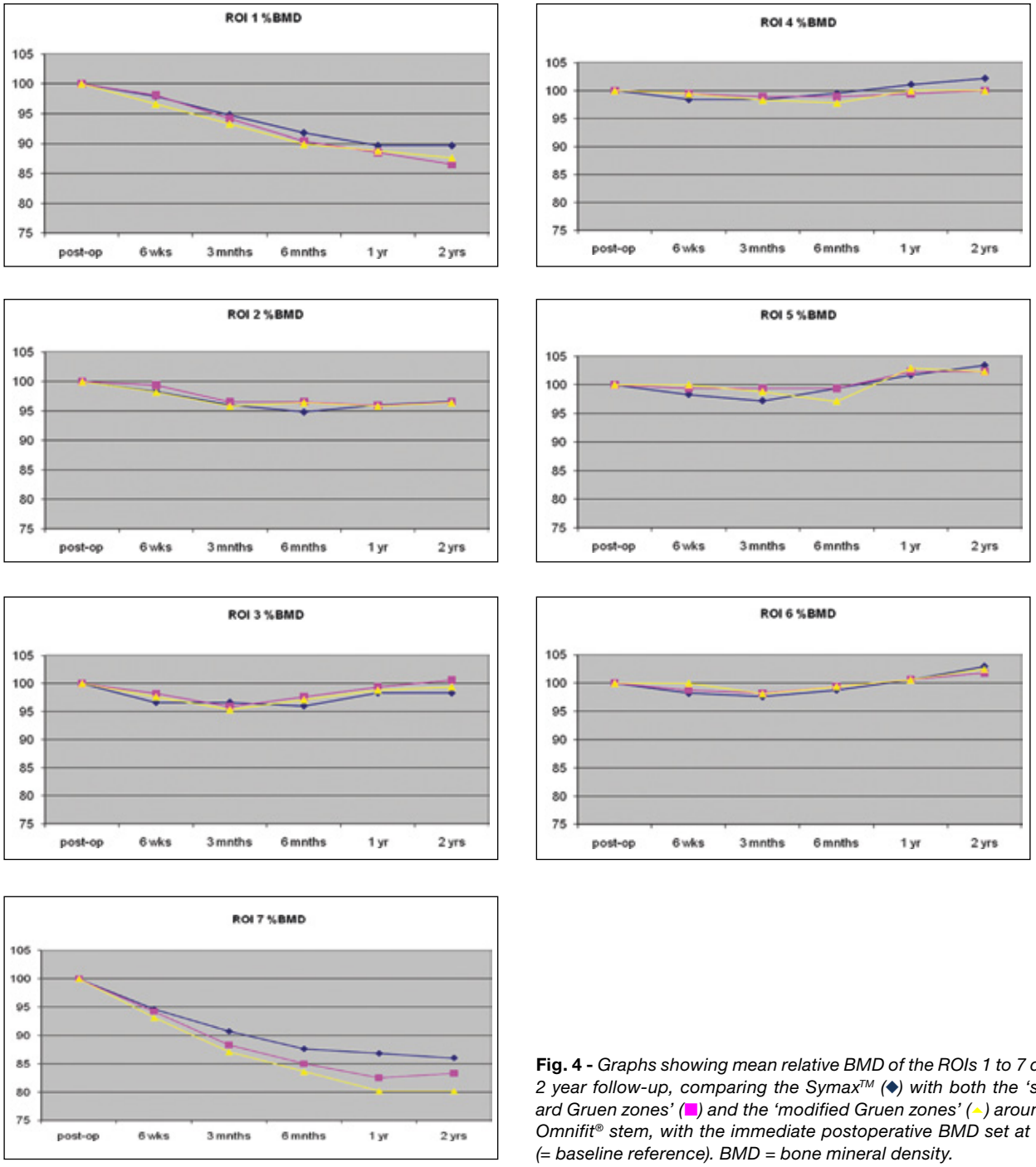

Fig. 4 - *Graphs showing mean relative BMD of the ROIs 1 to 7 during 2 year follow-up, comparing the Symax™ (◆) with both the 'standard Gruen zones' (■) and the 'modified Gruen zones' (▲) around the Omnifit® stem, with the immediate postoperative BMD set at 100% (= baseline reference). BMD = bone mineral density.*

DISCUSSION

As a result of the modification of Gruen zones we observed a difference in BMD around the Omnifit® between the original ('standard') and the 'modified' Gruen zones varying between 0 and 3.1 % in ROI 1 and 7, being higher using the 'standard' zones. Because the more distal zones are mainly cortical, their relative compositions do not change much when using the 'modified' Gruen zones. Consequently there is no clear difference in BMD between the two methods in zones

2 to 6. The improved preservation of bone stock around the Symax™ stem compared to the Omnifit® became clearer using 'modified' zones, and also statistically significant. This difference was not revealed using the 'standard' zones.

The difference between the Symax™ and Omnifit® in proximal coating length, and consequently the difference in length of zone 1 and 7 using 'standard' zones, is small. Nevertheless the effect on BMD results is evident, and emphasises the value of the modification. In case of larger differences in coating length this phenomenon might be even more important because the 'standard' zones might reveal more prominent differences in proximal BMD. This would (superficially) suggest remodelling differences between the implants, but in fact would simply represent incomparable ROIs. A clear example of this is seen in the study of Rahmy et al (22). He compared a Mallory Head (MH) (Biomet, Warsaw, Indiana, USA) with an Anatomique Benoist Girard (ABG) (Stryker, Newbury, UK), both uncemented stems made of titanium alloy with a proximal HA coating. The authors mainly attributed the difference in remodelling to design-related loading patterns. However the large stem and coating length in combination with the use of 'standard' Gruen zones as an important cause for the relatively small bone loss around the MH (- 6.2 % versus – 16.5 % for the ABG), was not recognised. Because of the length of the proximal coating on the MH stem, the adapted Gruen zones 1 and 7 are much larger compared to the same ROIs around the shorter ABG stem. As a result these larger ROIs contain more cortical bone, which undergoes less remodelling and therefore suggests better preservation of bone stock. In their study it remains unclear whether prosthetic properties or the choice of ROIs contributes most to the apparent difference in remodelling between the compared implants.

In our study there were no differences in lumbar spine BMD between the implant groups at the start of the study and at 2 years follow-up, illustrating that differences in bone remodelling between the groups could not be explained by metabolic bone disease in either group, or by difference in age-related bone density changes.

Bone remodelling can be considered as a surface phenomenon, as the remodelling cycle is initiated by osteoclastic removal of bone from the bone surface. Therefore, the remodelling potential of bone is dependent on the amount of internal pore surface in the bone for bone apposition or resorption, as observed by Martin et al (30). This may explain why cancellous bone tends to remodel more extensively than cortical bone, and stress shielding will have more effect in the proximal metaphysis than in the diaphysis of the femur (31). At the same time the cancellous bone in Gruen zones 1 and 7 is characterised by better vascularisation responsible for higher bone metabolism, and consequently stronger remodelling effects (23). Muller et al (21) discriminated between quantitative bone loss, expressed as relative change of bone mineral content (BMC) compared to the initial value at operation, and qualitative bone changes, to stress the geometrical adaptations in terms of bone volume and shape. The first, also called 'internal remodelling', is responsible for changes in periprosthetic bone density (BMD), and can be compared with what is measured in most other studies. It can be considered as the way in which cancellous bone reacts to loading, explaining the changes in Gruen zones 1 and 7. Qualitative modelling or 'external modelling' represents structural bone changes that mainly take place in cortical bone. They are recognised as adaptations in bone area (like cortical hypertrophy) without a change in BMD, seen in zones 2 to 6.

It can be argued that for correct comparison of periprosthetic bone remodelling, the regions of interest should be exclusively related to anatomic landmarks on the femur, independent of implant or coating dimensions (1, 4, 9), leading to fixed sizes of ROIs for all compared stems. However, this would prevent assessment of the remodelling effects of bioactive coatings, applied to variable parts of the surface. Whether bone adaptations are due to implant specific characteristics can only be judged if Gruen zone differences, caused by unequal stem or coating lengths, are taken into account but not allowed (on their own) to determine the zones of comparison.

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