Meniscal problems: to repair and to replace

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Two years follow-up of bone mineral density changes in the knee after meniscal allograft transplantation; results of an explorative study.

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ABSTRACT

Background

A potential chondroprotective effect of meniscal allograft transplantation (MAT) remains still unclear. Subchondral bone mineral density (BMD) and subchondral bone remodelling play important roles in development of osteoarthritis. Evaluation of subchondral BMD after MAT might give more insight in the potential chondroprotective effect. The purpose of our study was to determine early BMD changes in the knee after MAT.

Methods

From 2010 to 2013 twenty-six consecutive patients underwent a MAT. BMD was measured using Dual-energy X-ray Absorptiometry (DXA) scan preoperative and 6 months, 1 and 2 years postoperative. BMD was measured in six regions of interest (ROIs) of tibia and femur (medial, central, lateral) in both treated and healthy contralateral knees.

Results

BMD levels of MAT knees did not significantly change during 2 years follow-up in almost all ROIs. BMD was significant higher in nearly all ROIs in MAT knees at almost all follow-up moments compared to healthy contra-lateral knees. In the healthy contralateral knees BMD slightly, but not statistically, decreased in the first year postoperative, where after BMD normalized to baseline values at 2 years follow-up. BMD levels in all ROIs did not significantly differ between the patients with or without chondropathy at baseline and at 2 years follow-up.

Conclusion

Based on our findings MAT did not show a significant influence on BMD in the first 2 years postoperative. Longer follow-up is necessary to prove the potential chondroprotective effect of MAT using BMD measurements.

INTRODUCTION

Since the first meniscal allograft transplantation (MAT) in 1984,[1] many papers are published in literature regarding different aspects of MAT: indications and contraindications,[2] preoperative graft sizing,[3] methods of graft preservation,[4] surgical techniques,[5] fixation of the allograft,[6] relevance of associated chondral and ligamentous damage,[7] concomitant procedures,[8,9] histologic evaluation,[10] clinical and radiographic outcomes,[11-13] and rehabilitation.[14]

Despite all this research, a chondroprotective effect, as shown in sheep,[15] remains still unclear in humans.[11,16] This may partially be caused of the lack of standardized evaluation methods and the lack of high-quality studies. Nonetheless, MAT seems to provide good clinical results at the short- and long-term, with improvement in knee function and acceptable complication and failure rates.[16]

Concerning the development of osteoarthritis (OA) previous studies suggest that changes in subchondral bone play a key role in the pathogenesis and progression of OA.[17-21] Subchondral bone changes are potentially both a result and a cause of cartilage damage and cartilage loss.[21,22] Even in patients after partial or total medial meniscectomy an increased bone mineral density (BMD) has been seen.[23] The difference in BMD that leads to clinical relevant differences in patients is not known. Some studies have demonstrated that knee OA was associated with lower BMD,[24,25] while another study documented that patients with high tibial BMD had increased joint space narrowing after 1 year.[26] These findings suggest a biphasic process of BMD changes in OA: a reduction in BMD early on followed by an increase during more advanced phases.[27]

We are interested in the effect of MAT on BMD early in the process of OA development. To our knowledge, the effect on BMD of MAT was never investigated using Dual-energy X-ray Absorptiometry (DXA) scans. The purpose of our observational prospective explorative study was to determine BMD changes in the knee after arthroscopic MAT without bone plugs during a 2 year follow-up period and to compare the possible changes with the healthy contralateral knee. Furthermore, we wanted to evaluate if correlations could be found between clinical outcome and BMD findings during follow-up. As MAT can restore mechanical alignment,[28] this might restore biological anatomy as well, so we hypothesized no difference in BMD after 2 years between MAT knees and healthy contralateral knees. We hypothesized that possibly changes in BMD are not related to clinical outcome measured with patient related outcomes measurements (PROMs).

MATERIALS AND METHODS

This study has been approved by the local medical ethical review board (METC number: 15–069) and was registered in the Dutch Trial Register (NTR: NTR5633).

Population

Between March 2010 and October 2013, 26 patients received a cryopreserved non-tissue-antigen-matched and non-irradiated human meniscal allograft. All of the patients were recruited at the outpatient department of the Haaglanden Medical Center (HMC) and were operated by the senior author (EvA). Inclusion criteria were: disabling unicompartmental pain after a (sub)total meniscectomy, patient under the age of 55 years, stable knee joint or stabilized by concomitant anterior cruciate ligament reconstruction (ACLR) and normal knee alignment (5 degrees valgus – 5 degrees varus). Exclusion criteria were: > grade II chondropathy (according to the Outerbrigde classification[29]), PCL insufficiency, abnormal and uncorrected knee or lower limb alignment, complex regional pain syndrome of the knee, arthrofibrosis, muscular atrophy and a history of knee sepsis. Patients with previous operations or signs of chondropathy on the contralateral knee were also excluded. Radiographic measurements and anthropometric parameters (height and weight of the patient) were used to establish the correct size of the graft. All patients gave their written informed consent before participating in this study.

Study design

All patients were clinically evaluated preoperatively and during a minimum follow-up of 2 years. Accordant to our standard care patients were asked to complete questionnaires. Questionnaires included the Knee injury and Osteoarthritis Outcome Score (KOOS),[30] International Knee Documentation Committee subjective knee form (IKDC)[31] and Tegner activity score.[32] All questionnaires were filled in at baseline (preoperative) and 6 months, 1 and 2 years postoperative, except for the Tegner activity score. This score was not completed at 6 months postoperative, because of the rehabilitation protocol. During these follow-up moments a DXA scan was performed in the Erasmus Medical Centre, Rotterdam.

BMD measurement

BMD measurement was performed as described by van Meer et al.[33] In short, a Lunar Prodigy scanner (GE Lunar Corp., Madison, WI, USA) was used with “the spine protocol”. The lower extremity was fixed in a plastic device and the knee was slightly flexed (10 degrees). The positioning laser light was used to position the centre of the scanner arm 8 cm below the tibial tubercle. This resulted in anteroposterior views. Contours of the femur and tibia were outlined by placing anatomical landmark points using the freely available active shape model toolkit software package (Manchester University, Manchester, UK).

With these landmark points, six regions of interest (ROIs) were extracted: medial, central, lateral in the tibia, and medial, central and lateral in the femur. Anatomical landmark point placing for all DXA scans was done by one person (DA). The height and placement of the regions were based on reference lines between landmark points that indicated the medial and lateral sides of the tibia and femur (Figure 1). In the tibia, the regions run from the lower point of these lines up to a point 30% beneath the top of the line. This was to assure that the regions were positioned below the subchondral bone. In the femur, the bottom of the regions was positioned 10% of the length of the reference line above the lowest point, while the top was placed at 50%. The regions in the femur were positioned such that the medial and lateral ROIs were placed inside the respective condyles. The most lateral and medial border of the ROIs in the tibia and femur were positioned parallel to the outline of the tibia and femur, at a distance from the outline of 5% of the width of the bone. The area without bone in the central region of the femur, which interfered with the femoral notch, was excluded from BMD analysis.

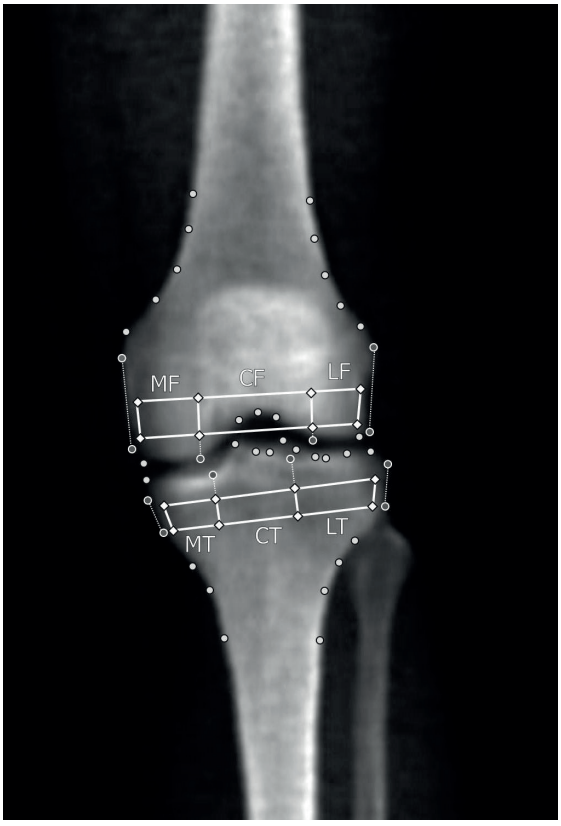

Figure 1. Determination of six regions of interest (ROIs) by using landmark points. 1: medial tibia (MT), 2: central tibia (CT), 3: lateral tibia (LT), 4: medial femur (MF), 5: central femur (CF), 6: lateral femur (LF). (Published with permission of B.L. van Meer)

Surgical technique

The meniscal allograft was delivered on the donor tibia plateau and was dissected leaving the posterior and anterior meniscal ligaments intact, no bone block was used. Fiberwire sutures 2.0 (Arthrex, Naples, Florida) were placed through the posterior and anterior meniscal ligament. Another two sutures were placed at the posterior and anterior horn. The MAT was performed arthroscopically using one tibia tunnel. Needling of the remnant of the peripheral rim was performed to provide blood at the attachment site. A FlipCutter (Arthrex, Naples, Florida) was used to create an inside-out socket in the tibia plateau with the same diameter as the posterior horn attachment. There through a passing suture was brought intra articular and taken out of the joint through a posterior portal. On this suture a second passing suture was attached extra articular and both were pulled through the anterior arthrotomy opening, resulting in a passing suture through the tibia tunnel and one through the posterior portal. The posterior sutures of the donor meniscus were fixed to the passing sutures and the graft was gradually pulled into the joint. The posterior horn suture was fixed over an anteriorly placed button on the tibial cortex. By pulling the suture through the portal tension on the meniscus was adjusted. The posterior side of the allograft was attached with two or three all inside meniscal repair systems (Fast-fix, Smith & Nephew, Memphis, Tennessee). Using meniscal repair needles (Arthrex, Naples, Florida) with two or three inside out meniscal sutures the middle part of the allograft was fixed. Using a self-punching SwiveLock anchor (Arthrex, Naples, Florida) the anterior horn suture was fixed to the tibia plateau. The arthrotomy wounds were closed after the knee was arthroscopically inspected for the final time.

Rehabilitation

The rehabilitation period started with 3 weeks of partial weight bearing (25%) with mobilization on crutches with a limit of 60º of flexion. After the first three weeks partial weight bearing was allowed till 50% and knee flexion to 90º. From week 9 till 12 the knee was progressively loaded more and flexed until 120º. During week 13 – 24 postoperative patients were allowed to progressively train their knees. When the knee had 80% of its former strength back, the patients were allowed to exercise and move without restrictions. However, it was advised to avoid high-impact activities and contact sports.

Reproducibility

Test-retest for placing landmark points was assessed. Landmark points were placed in 25 scans of randomly chosen patients from the study from van Meer et al[32] to determine interobserver agreement. Intraobserver agreement was determined by placing landmark points twice in 25 randomly chosen patients from this study with a time interval of two weeks.

Statistical analysis

All statistical analyses were performed with the use of SPSS (version 22.0, SPSS Inc, Chicago, IL). The statistical significance was set at alpha of <0.05. Data was tested for normality with the Shapiro-Wilk test. Normally distributed data is presented in mean and standard deviation (SD), non-normally distributed data is presented in median and interquartile range (IQR). The reproducibility of the DXA scan measurements was assessed by determining the intraclass correlation coefficient (ICC; two-way random effects model, absolute agreement). The strength of examiner agreement was defined according to the guidelines of Landis and Koch.[34] Linear mixed model analyses (repeated covariance type: compound symmetry) were applied to analyse differences in BMD levels regarding time of measurement, side and compartment and to evaluate changes in KOOS, IKDC and Tegner scores. Correlation between Tegner activity score and BMD was analysed using Pearson's correlation.

RESULTS

Baseline patient characteristics are shown in Table 1. One patient missed DXA scan at 6 months and 1 year follow-up because of pregnancy. Logistical problems were the reason for missing two other DXA scans (one at 6 months and one at 2 years follow-up). So 100 of a potential 104 DXA scans (96%) were available for evaluation.

Table 1. Patient characteristics. Data are presented in median and inter quartile range (IQR) unless otherwise indicated, n = number, ACL = anterior cruciate ligament, MAT = meniscal allograft transplantation.

Baseline characteristics	**n = 26**
Gender (female) – n (%)	15 (58)
Age (years)	39 (26 – 45)
BMI (kg/m^2)	24.3 (21.8 – 25.9)
Compartment (medial) – n (%)	10 (39)
Chondropathy – n (%) - Grade 0 - Grade 1	 12 (46) 14 (54)
No. of operations previous to MAT	3 (2 – 4)
No. of concomitant ACL reconstructions – n (%) medial / lateral - n	4 (15) 3 / 1
Interval between (sub)total meniscectomy and MAT (months)	29 (18.5 – 61.8)

Reproducibility

Interobserver agreement for landmark point placing was excellent (ICC = 0.826 to 0.976). Intraobserver agreement for landmark point placing ranged from good to excellent (ICC = 0.757 to 0.980).

BMD changes

The BMD levels of the MAT knees did not significantly change during the 2 year follow-up in almost all ROIs. A significantly decrease (P = 0.002, 95% CI = 0.74 – 0.92) in BMD was only seen at the central tibia (CT) 6 months postoperative compared to baseline for medial MAT knees. In lateral MAT knees no significant changes in BMD during follow-up was seen. In contrast, several BMD changes were seen in the compartments of healthy contralateral knees. After 6 months, a significant decrease in BMD was seen in all ROIs, except the medial femoral (MF) compartment. From this point, BMD gradually increased after 1 and 2 years follow-up, but never reached baseline level (Table 2).

The BMD levels in all ROIs at all time points were significantly higher in the MAT knee than the BMD levels of the contralateral healthy knee (Table 2).

BMD levels in all ROIs did not significantly differ between the patients with or without chondropathy at baseline and at 2 years follow-up. Baseline BMD levels in the MAT knees were higher for both patients with (grade 1) or without (grade 0) chondropathy compared to the healthy contralateral knees (Table 3).

Table 2. Bone mineral density levels (g/cm^2) of the knee after meniscal allograft transplantation (MAT) and in the contralateral healthy knees based on Linear Mixed Model analyses (medial versus lateral MAT).

ROI		Baseline (T0)	6 months (T1)	1 year (T2)	2 years (T3)
Medial MAT		n = 10 Mean (SD, 95% CI)	n = 10 Mean (SD, 95% CI)	n = 10 Mean (SD, 95% CI)	n = 10 Mean (SD, 95% CI)
MT	MAT	0.93 (0.16, 0.87 – 0.99)	0.92 (0.15, 0.86 – 0.98)	0.92 (0.15, 0.86 – 0.98)	0.92 (0.18, 0.86 – 0.98)
	Healthy	0.88 (0.16, 0.81 – 0.94)	0.83 (0.21, 0.77 – 0.90)*	0.83 (0.16, 0.77 – 0.90)	0.86 (0.16, 0.80 – 0.92)
P value[#]		**<0.001**	**<0.001**	**<0.001**	**<0.001**
CT	MAT	0.86 (0.18, 0.80 – 0.93)	0.85 (0.18, 0.79 – 0.92)*	0.86 (0.17, 0.79 – 0.92)	0.85 (0.18, 0.78 – 0.91)
	Healthy	0.84 (0.16, 0.78 – 0.90)	0.75 (0.17, 0.69 – 0.82)*	0.77 (0.15, 0.70 – 0.83)	0.79 (0.16, 0.73 – 0.86)
P value[#]		**<0.001**	**0.016**	**<0.001**	**0.031**
LT	MAT	0.89 (0.15, 0.83 – 0.95)	0.89 (0.15, 0.83 – 0.94)	0.88 (0.16, 0.82 – 0.94)	0.88 (0.15, 0.82 – 0.94)
	Healthy	0.86 (0.13, 0.80 – 0.92)	0.78 (0.15, 0.72 – 0.84)*	0.79 (0.14, 0.73 – 0.85)	0.81 (0.15, 0.75 – 0.87)
P value[#]		**<0.001**	**<0.001**	**<0.001**	**<0.001**

Table 2. Bone mineral density levels (g/cm^2) of the knee after meniscal allograft transplantation (MAT) and in the contralateral healthy knees based on Linear Mixed Model analyses (medial versus lateral MAT). (*continued*)

ROI		Baseline (T0)	6 months (T1)	1 year (T2)	2 years (T3)
MF	MAT	1.12 (0.16, 1.05 – 1.20)	1.12 (0.17, 1.04 – 1.19)	1.08 (0.16, 1.00 – 1.16)	1.11 (0.16, 1.04 – 1.19)
	Healthy	1.04 (0.16, 0.97 – 1.12)	0.99 (0.19, 0.91 – 1.06)	0.98 (0.19 ,0.90 – 1.05)	0.99 (0.18, 0.92 – 1.07)
P value#		**<0.001**	**<0.001**	**<0.001**	**<0.001**
CF	MAT	1.37 (0.20, 1.3 – 1.45)	1.35 (0.21, 1.27 – 1.42)	1.36 (0.16, 1.29 – 1.44)	1.38 (0.20, 1.29 – 1.44)
	Healthy	1.34 (0.17, 1.27 – 1.42)	1.23 (0.28, 1.16 – 1.31)*	1.22 (0.20, 1.15 – 1.30)	1.24 (0.22, 1.15 – 1.30)
P value		**0.020**	**<0.001**	**0.001**	**<0.001**
LF	MAT	1.14 (0.20, 1.06 – 1.22)	1.14 (0.18, 1.06 – 1.22)	1.15 (0.19, 1.07 – 1.23)	1.15 (0.16, 1.07 – 1.23)
	Healthy	1.12 (0.18, 1.05 – 1.20)	1.00 (0.20, 0.92 – 1.08)*	1.06 (0.30, 0.98 – 1.14)	1.11 (0.22, 1.03 – 1.19)
P value#		**<0.001**	**<0.001**	**<0.001**	**0.005**
Lateral MAT		n = 16 Mean (SD, 95% CI)	n = 14 Mean (SD, 95% CI)	n = 15 Mean (SD, 95% CI)	n = 16 Mean (SD, 95% CI)
MT	MAT	0.89 (0.14, 0.82 – 0.96)	0.89 (0.14, 0.82 – 0.96)	0.89 (0.15, 0.82 – 0.97)	0.90 (0.15, 0.83 – 0.97)
	Healthy	0.82 (0.13, 0.75 – 0.90)	0.80 (0.13, 0.72 – 0.87)*	0.80 (0.14, 0.73 – 0.87)	0.81 (0.12, 0.73 – 0.88)
P value#		**<0.001**	**<0.001**	**<0.001**	**<0.001**
CT	MAT	0.83 (0.15, 0.75 – 0.92)	0.83 (0.16, 0.75 – 0.91)	0.83 (0.16, 0.75 – 0.92)	0.83 (0.17, 0.75 – 0.91)
	Healthy	0.81 (0.16, 0.73 – 0.90)	0.73 (0.15, 0.65 – 0.82)*	0.74 (0.14, 0.66 – 0.82)	0.77 (0.130, .69 – 0.85)
P value#		**0.030**	**<0.001**	**<0.001**	**0.005**
LT	MAT	0.88 (0.16, 0.80 – 0.96)	0.88 (0.16, 0.8 – 0.96)	0.88 (0.16, 0.80 – 0.96)	0.88 (0.17, 0.80 – 0.96)
	Healthy	0.85 (0.15, 0.77 – 0.93)	0.77 (0.14, 0.69 – 0.85)*	0.79 (0.19, 0.71 – 0.87)	0.81 (0.14, 0.73 – 0.89)
P value#		**<0.001**	**<0.001**	**<0.001**	**<0.001**
MF	MAT	1.08 (0.18, 0.99 – 1.17)	1.09 (0.19, 1.00 – 1.18)	1.05 (0.17, 0.96 – 1.14)	1.07 (0.15, 0.98 – 1.16)
	Healthy	0.96 (0.18, 0.87 – 1.05)	0.94 (0.19, 0.84 – 1.03)	0.93 (0.19, 0.83 – 1.02)	0.93 (0.18, 0.84 – 1.02)
P value#		**<0.001**	**<0.001**	**<0.001**	**<0.001**
CF	MAT	1.35 (0.17, 1.26 – 1.44)	1.31 (0.20, 1.22 – 1.41)	1.35 (0.20, 1.25 – 1.44)	1.36 (0.18, 1.26 – 1.45)
	Healthy	1.33 (0.17, 1.24 – 1.43)	1.22 (0.20, 1.12 – 1.31)*	1.23 (0.19, 1.13 – 1.31)	1.24 (0.16, 1.14 – 1.33)
P value#		**0.047**	**<0.001**	**<0.001**	**<0.001**
LF	MAT	1.14 (0.18, 1.04 – 1.24)	1.11 (0.16, 1.01 – 1.21)	1.14 (0.21, 1.03 – 1.24)	1.15 (0.19, 1.05 – 1.26)
	Healthy	1.12 (0.24, 1.02 – 1.23)	0.98 (0.17, 0.88 – 1.09)*	0.99 (0.18, 0.89 – 1.10)	1.09 (0.22, 1.00 – 1.19)
P value#		**<0.001**	**0.001**	**<0.001**	**0.020**

ROI = region of interest. MT: medial tibia, CT: central tibia, LT: lateral tibia, MF: medial femur, CF: central femur, LF: lateral femur. SD = standard deviation. 95% CI = 95% Confidence Interval. * = significant difference between baseline and 6 months follow-up. # = P value for bone mineral density levels between MAT and healthy knees for each time interval.

Table 3. Bone mineral density levels (g/cm^2) of the knee after meniscal allograft transplantation (MAT) and in the contralateral healthy knees based on Linear Mixed Model analyses (for grade 0 versus grade 1 chondropathy) at baseline and at 2 years follow-up.

ROI	Baseline (T0)		2 years (T3)	
Medial MAT	Mean (SD, 95% CI)		Mean (SD, 95% CI)	
Grade of chondropathy	0	1	0	1
MT MAT	0.94 (0.16, 0.88 – 0.97)	0.92 (0.15, 0.86 – 0.99)	0.93 (0.15, 0.86 – 0.97)	0.95 (0.18, 0.90 – 1.01)
Healthy	0.87 (0.15, 0.80 – 0.93)	0.85 (0.19, 0.79 – 0.90)	0.83 (0.16, 0.77 – 0.90)	0.85 (0.16, 0.79 – 0.92)
P value#	<0.001	<0.001	<0.001	<0.001
CT MAT	0.86 (0.17, 0.81 – 0.93)	0.88 (0.16, 0.80 – 0.94)	0.86 (0.15, 0.80 – 0.93)	0.89 (0.18, 0.83 – 0.95)
Healthy	0.84 (0.15, 0.79 – 0.91)	0.75 (0.15, 0.68 – 0.82)	0.77 (0.15, 0.71 – 0.83)	0.79 (0.16, 0.72 – 0.88)
P value#	<0.001	<0.001	<0.001	<0.001
LT MAT	0.89 (0.16, 0.83 – 0.96)	0.91 (0.16, 0.86 – 0.98)	0.87 (0.16, 0.81 – 0.93)	0.89 (0.15, 0.82 – 0.93)
Healthy	0.83 (0.14, 0.81 – 0.92)	0.80 (0.15, 0.76 – 0.86)	0.78 (0.14, 0.70 – 0.82)	0.82 (0.14, 0.75 – 0.87)
P value#	<0.001	<0.001	<0.001	0.016
MF MAT	1.14 (0.17, 1.06 – 1.20)	1.10 (0.16, 1.03 – 1.18)	1.12 (0.16, 1.05 – 1.20)	1.13 (0.17, 1.05 – 1.19)
Healthy	1.02 (0.16, 0.96 – 1.12)	0.99 (0.18, 0.91 – 1.05)	0.99 (0.19 ,0.90 – 1.06)	0.99 (0.17, 0.92 – 1.08)
P value#	<0.001	<0.001	<0.001	<0.001
CF MAT	1.38 (0.20, 1.30 – 1.46)	1.35 (0.19, 1.28 – 1.42)	1.34 (0.16, 1.28 – 1.42)	1.36 (0.20, 1.27 – 1.43)
Healthy	1.33 (0.17, 1.28 – 1.42)	1.25 (0.28, 1.15 – 1.31)	1.25 (0.20, 1.16 – 1.33)	1.24 (0.19, 1.14 – 1.28)
P value#	<0.001	<0.001	<0.001	<0.001
LF MAT	1.10 (0.19, 1.06 – 1.19)	1.14 (0.17, 1.05 – 1.22)	1.12 (0.17, 1.07 – 1.20)	1.09 (0.16, 1.02 – 1.20)
Healthy	1.02 (0.18, 0.92 – 1.11)	1.03 (0.20, 0.92 – 1.08)	1.06 (0.25, 0.91 – 1.16)	1.01 (0.19, 0.94 – 1.09)
P value#	<0.001	<0.001	<0.001	<0.001
ROI	Baseline (T0)		2 years (T3)	
Lateral MAT	Mean (SD, 95% CI)		Mean (SD, 95% CI)	
Grade of chondropathy	0	1	0	1
MT MAT	0.90 (0.15, 0.84 – 0.96)	0.93 (0.15, 0.87 – 1.00)	0.89 (0.15, 0.83 – 0.96)	0.90 (0.16, 0.84 – 0.99)
Healthy	0.83 (0.13, 0.73 – 0.90)	0.84 (0.17, 0.78 – 0.91)	0.81 (0.16, 0.74 – 0.90)	0.82 (0.13, 0.77 – 0.92)
P value#	<0.001	<0.001	<0.001	<0.001
CT MAT	0.85 (0.14, 0.80 – 0.92)	0.87 (0.16, 0.80 – 0.96)	0.83 (0.15, 0.76 – 0.93)	0.88 (0.18, 0.80 – 0.96)
Healthy	0.80 (0.15, 0.72 – 0.90)	0.78 (0.14, 0.65 – 0.81)	0.74 (0.14, 0.69 – 0.83)	0.81 (0.16, 0.74 – 0.89)
P value#	<0.001	<0.001	<0.001	<0.001
LT MAT	0.88 (0.16, 0.81 – 0.95)	0.89 (0.17, 0.80 – 0.98)	0.88 (0.16, 0.80 – 0.94)	0.90 (0.16, 0.83 – 0.95)
Healthy	0.83 (0.15, 0.75 – 0.91)	0.80 (0.16, 0.75 – 0.88)	0.81 (0.14, 0.72 – 0.85)	0.83 (0.14, 0.77 – 0.90)
P value#	<0.001	0.017	<0.001	<0.001
MF MAT	1.09 (0.18, 1.01 – 1.19)	1.11 (0.16, 1.01 – 1.20)	1.13 (0.17, 1.01 – 1.20)	1.13 (0.16, 1.03 – 1.18)
Healthy	1.03 (0.17, 0.96 – 1.14)	0.97 (0.18, 0.90 – 1.03)	1.00 (0.18 ,0.91 – 1.02)	0.99 (0.17, 0.90 – 1.05)
P value#	0.002	<0.001	<0.001	<0.001
CF MAT	1.35 (0.18, 1.23 – 1.44)	1.35 (0.17, 1.25 – 1.44)	1.35 (0.18, 1.25 – 1.43)	1.34 (0.18, 1.24 – 1.43)
Healthy	1.29 (0.17, 1.23 – 1.42)	1.24 (0.16, 1.14 – 1.31)	1.23 (0.19, 1.13 – 1.33)	1.24 (0.19, 1.14 – 1.30)
P value#	<0.001	<0.001	<0.001	<0.001
LF MAT	1.13 (0.17, 1.03 – 1.19)	1.12 (0.16, 1.01 – 1.22)	1.13 (0.17, 1.07 – 1.20)	1.15 (0.18, 1.02 – 1.22)
Healthy	1.00 (0.19, 0.90 – 1.06)	1.03 (0.18, 0.94 – 1.09)	1.02 (0.18, 0.92 – 1.11)	1.05 (0.22, 0.98 – 1.13)
P value#	<0.001	<0.001	<0.001	0.006

ROI = region of interest. MT: medial tibia, CT: central tibia, LT: lateral tibia, MF: medial femur, CF: central femur, LF: lateral femur. SD = standard deviation. 95% CI = 95% Confidence Interval. # = P value for bone mineral density levels between MAT and healthy knees.

All time points and all knees (MAT or healthy) showed significant higher BMD levels in the femur compared to the tibia in each compartment (medial, central and lateral).

In medial MAT knees, BMD levels were significant higher in the lateral femoral (LF) compartment compared to the medial femoral (MF) compartment. No significant difference was found in BMD levels between medial tibial (MT) and lateral tibial (LT) compartments in medial MAT knees. In the femoral compartments no significant difference in BMD level was found comparing medial and lateral in lateral MAT knees. A significant increased BMD level was found in the medial compartment of the tibia (MT) in lateral MAT knees. No significant differences in BMD were found between both femoral and tibial compartments in the healthy contralateral knees.

Only 4 patients had a concomitant ACLR, 3 patients in combination with medial MAT and 1 in combination with lateral MAT. This number was too small to draw any statistical conclusions about the influence of ACLR on BMD of tibia and femur.

Patient Related Outcome Measurements

A significant improvement in KOOS score compared to baseline was found for all subtypes at all follow-up moments. After 1 year a significant deterioration in KOOS score was found for two subtypes: Sports and Recreation and Quality of Life. The other 3 KOOS items remain on the same level. IKDC score also significantly improved during follow-up compared to baseline. A small increase in Tegner activity score was found, but this was not significantly different (Table 4).

Table 4: Patient Related Outcome scores. Data are presented in mean, standard deviation (SD) and 95% Confidence Interval (95% CI) unless otherwise indicated.

	Baseline Mean (SD, 95% CI)	6 months	1 year	2 years
KOOS Symptoms	55 (16.1, 47.9 – 62.9)	72 (21.7, 62.1 – 81.3)*	77 (13.5, 70.9 – 83.1)*	78 (12.1, 72.4 – 84.0)*
KOOS Pain	50 (18.0, 41.2 – 58.1)	78 (18.0, 65.6 – 85.5)*	82 (17.1, 74.2 – 89.8)*	85 (12.1, 79.4 – 91.0)*
KOOS ADL	63 (21.0, 53.5 – 73.2)	84 (15.7, 77.3 – 91.2)*	78 (14.0, 71.8 – 84.3)*	93 (9.5, 88.5 – 97.7)*
KOOS S&R	26 (21.7, 15.4 – 36.4)	44 (32.2, 29.7 – 58.3)*	82 (17.0, 75.1 – 90.2)*	61 (27.2, 47.8 – 74.0)*#
KOOS QoL	28 (11.7, 10.7 – 44.6)	54 (20.0, 45.5 – 63.2)*	89 (16.3, 81.8 – 96.2)*	64 (16.7, 56.0 – 72.2)*#
IKDC	47 (16.2, 39.7 -55.9)	65 (15.3, 56.7 – 73.6)*	71 (14.0, 63.3 – 79.4)*	75 (14.7, 67.4 – 82.6)*
Tegner (median, IQR)	2 (1.0 – 3.0)	N/A	3 (2.3 – 3.8)	4 (2.0 – 5.0)

ADL = activity in daily living, S&R = sports and recreation, QoL = quality of life. N/A = not applicable. * significantly different from baseline (p<.05), # significantly different from 1 year (p<.05).

We did not find a significant relationship between the Tegner activity score and the BMD levels at 1 and 2 year follow-up in the MAT knees in all ROIs, neither we did find a significant correlation between Tegner activity score and BMD levels in all ROIs in the healthy contralateral knees.

DISCUSSION

Subchondral bone is thought to play a key role in the pathogenesis of OA.[35] Structural changes in subchondral trabecular bone are associated with cartilage loss in OA and these changes are both a result and a cause of cartilage loss.[20,22,36] Investigating BMD after MAT could give more insight in the potential chondroprotective effect of MAT.

This explorative study showed that BMD in the knee after MAT does not change substantially in the first two years after surgery. Because this study is the first to report about BMD changes after MAT we could not compare our results to previous findings regarding BMD and MAT. It is generally known that a decrease in load or physical activity is related to a decrease in BMD.

All patients were rehabilitated according to a standard protocol. Complete weight bearing was prohibited for at least 6 weeks. Hereafter, patients were only allowed to exercise and move without restrictions when the knee had 80% of its former strength back, which usually took a few months. This period of lesser physical activity might explain the decrease in BMD in the healthy knee. Because of reduced weight bearing and disuse BMD in the MAT knee can be expected to be even more decreased. BMD levels did not increase in the MAT knees over time. BMD levels in MAT knees were higher than BMD levels in healthy knees, but stayed the same, while the values in healthy knees decreased. It should be taken into account that the observed difference in BMD levels between MAT knees and healthy knees is due to the decrease in BMD levels of the healthy knees, more than due to the unchanged BMD levels of the MAT knees. This raises questions about the comparability between BMD levels between a MAT knee and a healthy knee, even in the same patient.

Only patients with chondropathy grade ≤ 1 were included in this study. Despite this strict selection criterion, patients in this state of maximal slightly chondropathy, might already have subchondral bone changes resulting in higher BMD. It is known that as cartilage area decreases in the medial joint, bone volume fraction and trabecular thickness in the medial tibia increases,[20] leading to an increased BMD. An increased BMD in both medial and lateral compartment in MAT knees in patients with grade 1 chondropathy compared to the patients without chondropathy can be explained by the slight reduction in cartilage condition and its effect on subchondral bone. However, even in the selection of MAT patients without chondropathy on index surgery or on preoperative MRI a higher

BMD was found. This emphasizes that subchondral bone changes can occur in patients without clinical or radiological signs of OA and also in patients after (sub)total meniscectomy. This is in accordance with the results of the study of Petersen,[23] which showed an increased bone mineral density (BMD) and a specific distribution of BMD in the cortical of the subchondral plates and below in the trabecular bone in the medial compartment after partial or total medial meniscectomy in patients with isolated medial meniscal tears.[23]

The difference in BMD between tibia and femur is in concordance with other studies[33] and is probably physiological. The possibility of patella overlap, giving erroneous measurements of the femoral ROIs should also be taken into account.[37]

Regarding subchondral bone changes one would expect higher BMD levels in the affected compartment. Nonetheless, we could not demonstrate higher BMD in the affected compartment of a MAT knee compared to the non-affected compartment in the same MAT knee. A good explanation was not found. It might be the limb alignment that could play a role here. Although, all our patients have a normal aligned knee before surgery, varying between 5 degrees of valgus and 5 degrees of varus. Because of the axial loading BMD levels could be higher in the medial compartment, in a slightly varus aligned knee a higher BMD even in a lateral MAT knee. In vivo studies are needed to see if mechanical anatomy and mechanical function will restore after MAT.

Differences in BMD between compartments were not found in healthy knees, where we assume mechanical anatomy and mechanical function are normal. In healthy knees BMD in medial compartment compared to lateral compartment in the both femur and tibia were the same (e.g. BMD in medial femoral compartment compared with lateral femoral compartment). In this study three patients had a concomitant ACLR during medial MAT and one patient during lateral MAT. As mentioned before, this number was too small to draw any statistical conclusions about the influence of ACLR on BMD of tibia and femur. However, in the first 6 months we found a significantly decrease in BMD for the central tibial compartment in the group of 10 patients having a medial MAT. The influence of a drilled tunnel in the tibia on BMD, especially on BMD changes of the central tibial compartment, was not described in other studies. One could imagine that drilling a hole in the tibia and removing trabecular and cortical bone would give a decrease in bone mass and a decrease in BMD level at this specific site. This might be an explanation for the significantly decrease in BMD in the central tibial compartment in the group of patients where one-third had a concomitant ACLR. Nevertheless, after 6 months BMD levels of the central tibia compartment were equal the BMD levels of the other compartments. Probably, a 6 months period is long enough to restore BMD and for incorporation of the anterior cruciate ligament (ACL) graft.

Patient related outcome improved during the first two years after MAT as seen in many other studies.[12] Nonetheless, in our study patients score worse on recreation and sports after 1 year. A possible reason is that patients might still have too much complaints of their

knee which force them to stop practising sports or renounce recreational activities. This could negatively influence their quality of life, especially in this young patient population, but can help them to function on the same level in activities of daily living (ADL) with the same scores on pain and symptoms like 1 year before.

The overall improvement found in PROMS does not seem to have a relation with BMD levels, since they do not improve. Any literature on clinical influence of BMD changes is not available. Longer follow-up in a bigger group of patients could give some more insight on this topic.

This study has some limitations. First, this is the first study describing BMD level changes after MAT. Baseline or normal values of BMD, clinical relevance of BMD levels and BMD level changes after MAT are not clear yet. Second, the study population consists of 26 patients, which is relatively small. The group of patients having a concomitant ACLR was even smaller. This makes it difficult to draw strong conclusions on the influence of ACLR on BMD. Third, a follow-up time of 2 years might be too short to show any changes in the subchondral bone, especially concerning a long-term process such as developing OA. Fourth, with the lack of any former studies examining the influence of MAT on BMD levels, a power analysis was not possible. At last, there is some heterogeneity among this patient population (left versus right (dominant versus none dominant side), lateral versus medial MAT and ACLR versus intact anterior cruciate ligament (ACL), which has influence on the power of this study. More studies are needed to investigate BMD changes after MAT to investigate the potential chondroprotective effect of MAT. A longer follow-up in a larger group of patients is needed to see whether BMD remains stable or changes over time more than two years after MAT and to see if BMD measurement can be a suitable tool to prove a chondroprotective effect of MAT.

In conclusion, this study is the first prescribing BMD changes after MAT. The results show that BMD levels differ after MAT compared to the healthy contralateral knee and do not change over time after 2 years of follow-up. The difference in BMD between healthy and operated knees can be explained by subchondral bone changes which already occurred as the initial step of the development of OA. This explorative study is a base for further research on BMD in MAT patients and might contribute to a better understanding of the clinical good results of MAT.

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