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ORIGINAL RESEARCH ARTICLE

Value of quantitative serial three phase bone scan for diagnosis of total knee arthroplasty loosening in case of initial equivocal findings

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ABSTRACT

Introduction: The study goal was to determine whether serial quantitative three phase [^{99m}Tc]Tc-MDP bone scintigraphy can provide additional information to accurately predict loosening in symptomatic patients after total knee arthroplasty (TKA) whose initial [^{99m}Tc]Tc-MDP study was not diagnostic.
Methods: We retrospectively include bone scans of 125 patients suffering pain after knee arthroplasty. 52 patients with equivocal image findings on three phase planar bone scintigraphy and inconclusive clinical parameters were candidate for follow up examination. Quantification was performed on delayed planar views of both image series and the ratio of pathological peri-prosthetic tracer uptake to normal bone was evaluated. The change in periprosthetic abnormal to normal bone uptake ratios was analyzed within 6-months interval to assess. Interpretations were validated by clinical follow-ups or revision operation.
Results: Initial quantitative planar analysis in periprosthetic region did not relevantly enhance the diagnostic performance of bone scanning in assessing knee prosthetic loosening. Six months follow-up images improve the diagnostic power of bone scan but it was not statistically significant. However, a threshold of 3.9% rise in periprosthetic abnormal to normal bone uptake ratio of the "tibial plateau" within 6 months markedly improved the performance of three phase [^{99m}Tc]Tc-MDP for the detection of loosening (sensitivity 87%, specificity 89%, p value = 0.002).
Conclusion: Equivocal scintigraphic findings are still a main challenge in management of TKA complications. Follow-up quantitative bone scan improves the diagnostic impact of bone scintigraphy for detection of loosening process in equivocal cases of TKA.

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INTRODUCTION

The number of total knee arthroplasty (TKA) is still growing worldwide [1]. A permanent and stable anchoring of prosthesis native bone is of great importance for proper function and long-term survival. Despite constantly improved surgical techniques and implant materials, complications still occur including aseptic loosening [2-4].

Aseptic loosening as one of the most common complications often requires revision surgery. Revision TKA imposes more economic burden and higher complication rate leading to less favorable outcome and inferior survivorship compared to primary TKA [5]. Since every revision is a major physical and economic burden, it is crucial to improve the diagnosis of aseptic loosening to avoid unnecessary revisions [6].

Definitive loosening is defined as subsidence or progressive radiolucent line wider than 2 mm around the fixation sites [7]. The pathogenesis of aseptic loosening in prosthetic joints is not well understood [8]; many believe to be an inflammatory reaction leading to micromovements in bone/prosthesis interface and osteolysis [9-13].

Over the past decades, several diagnostic procedures have been utilized for the assessment of knee prosthesis complications. Among them were nuclear imaging techniques, providing hybrid data of both anatomical structure and joint metabolism. Although advent nuclear medicine modalities such as [^{18}F]FDG PET/CT with Na[^{18}F]F PET/CT proved their accuracy in loosening diagnosis [14, 15], conventional bone scan is still the most available and the least expensive technique. Hence, three phasic ^{99m}Tc-labelled Methylene diphosphonate ([^{99m}Tc]Tc-MDP) bone scintigraphy is still considered as one of the initial imaging modalities for assessment of painful joint prosthesis [16, 17]. A systematic review and meta-analysis suggest single time bone scintigraphy as one of the most accurate diagnostic methods for detection of aseptic loosening in TKA [18]. Planar bone scan is not specific for loosening differentiation as both focal and diffuse periprosthetic uptake patterns may represent loosening [19]. The impact of SPECT/CT bone scanning for the assessment of loosening of knee prosthesis has been already shown in the literature. Recent studies on [^{99m}Tc]Tc-MDP bone scintigraphy revealed promising diagnostic accuracy by detailed 3D semiquantitative analysis of component position, mechanical and anatomical axes, pattern recognition of the distribution and uptake values [20-25]; however, methods did not gain wide acceptance in clinic and most nuclear medicine practitioners still are used to the conventional visual planar reporting systems.

Schweizer et al. designed SPECT/CT study to differentiate symptomatic from asymptomatic patients and found pattern recognition as the key to distinguish the two groups [26]; Klett et al. primarily analyzed the diagnostic efficacy of SPECT/CT bone scan in all symptomatic patients [17]. This study is specifically designed to assess symptomatic patients whose general quantitative planar and visual SPECT/CT reports were inconclusive [27, 28].

Bone scintigraphy displays variable radiotracer accumulation around an asymptomatic prosthesis; almost 90% of tibial components reveal high bone uptakes for up to several years as a consequence of fixation type as well as TKA orientation and alignment. Nevertheless, it has been suggested that an asymptomatic knee prosthesis follows a reduced periprosthetic uptake pattern over time in serial bone scintigraphies [27, 29, 30]. These two raised the basis of current study whether dynamic uptake changes offer additional diagnostic value to the static radioactivity ratios in distinguishing intact from loosened prosthesis.

This quantitative descriptive study addressed the issue whether there are any definable cut-off values in bone uptake ratios over time for predicting loosening in implanted knee joints.

METHODS

Study population

This study is a monocentric retrospective study on 3-phase [^{99m}Tc]Tc-MDP bone scintigraphy. A total number of 125 patients were consecutively included for investigation with inclusion criteria of (a) patients with unclear clinical presentations after TKA complaining discomfort without definite clinical/radiological diagnosis, (b) equivocal visual findings on planar 3-phase [^{99m}Tc]Tc-MDP bone scintigraphy with SPECT/CT and exclusion criteria of (a) positive history of documented infection, trauma and/or bone fracture in the area of the knee prosthesis, (b) history of previous revision surgery, (c) reaching definite diagnosis of loosening via the first bone scan with SPECT-CT and clinical findings, and (d) negative three phase bone scan for loosening.

52 patients with equivocal findings were selected for serial bone scintigraphy. Demographic data such as age, gender, diagnosis before and after bone scintigraphy and 6 months clinical follow-up were recorded.

The study was carried out in accordance with the Helsinki Declaration compiled with the provisions of data Protection Act in Austria and has been approved by institutional ethics committee with the approval research number of EK 39/14. Informed

consent was obtained within the setting of clinical examination.

[^{99m}Tc]Tc-MDP three phase bone scintigraphy with SPECT/CT

Bone scintigraphy was performed as a three phase scan by injection of 500–750 MBq ^{99m}Tc-labelled Methylene diphosphonate by the use of a dual headed SPECT/CT gamma camera (Symbia T16, Siemens, Erlangen, Germany) equipped with a low energy, high resolution collimator. Scintigraphy consists of anterior and posterior planar images of the knees region in the perfusion phase (immediately after injection), the blood pool phase (1 to 5 min after injection) and the whole body delayed metabolic phase (2 h after injection). Scan speed was 10 cm/min. Knee SPECT/CT was performed three hours after radioactivity injection with matrix size of 128× 128, angle step of 32 and time per frame of 25 s.

The traditional concept of interpretation was applied. Tibial component was considered loose in case of any tracer activity seen along the bone-prosthetic interface outside of the joint space or focal increased tracer uptake detected at the tip of tibial component and at contralateral tibial tray. Loosening of the femoral component was also diagnosed via increased uptake near the posterior aspects of the condyles, adjacent to the bone prosthesis interface. Besides, loosening was diagnosed if the CT component showed periprosthetic lucency greater than 2mm in width with irregular margins at the site of increased bone uptake. In case of inconclusive results of the first referral, including both planar and SPECT/CT studies, the orthopedic surgeon has requested a 6 month follow-up evaluation. The impact of SPECT/CT bone scanning for the assessment of loosening of knee prosthesis has been already shown in the literature [20]. Therefore, we only focused on quantitative analysis of planar images. Quantitative analysis was performed for both studies by manually defining rectangular regions of interest (ROIs) on periprosthetic tibia plateau and a reference region on ipsilateral or contralateral tibial diaphysis (sparing any focus of increased activity in tibia) (Figure 1). Uptake ratio was measured by dividing the geometric mean of the [^{99m}Tc]Tc-MDP uptake in anterior and posterior views of tibia plateau by the geometric mean of tibial diaphysis as the background activity. The follow up ratio was then compared to the primary value; besides, the percent of changes in bone activity over time was calculated. Change in percentage was calculated by subtracting the initial ratios from follow-up values divided by the initial figures, illustrated as a percent. The thresholds for uptake ratios of each study, initial and follow-up, were determined whether they can classify loosening versus intact prostheses. Final diagnosis was made according to the surgical findings and active 6 months clinical and radiological follow-up by treating orthopedic surgeon expert in revision TKA. Gold standard was clinical impression of the referring orthopedist who included all clinical, radiological and scintigraphic findings. Loosened implants undergone revision surgery within 3 months after the second scan. In those labeled as non-loosening, the clinical follow-up and other findings guides the orthopedist to other diagnoses or the alleviation of symptoms eventually confirmed non-loosening.

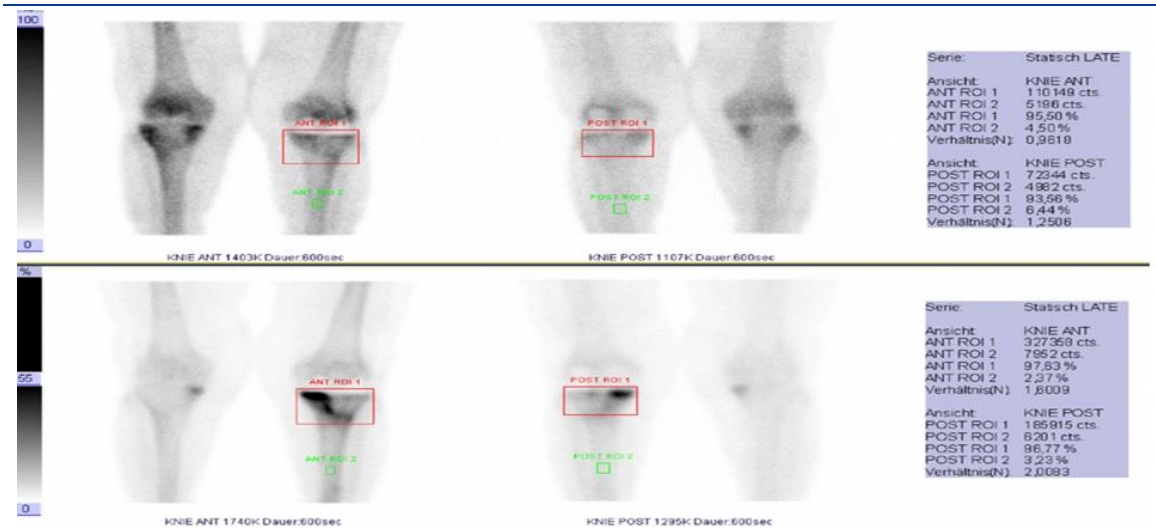

Fig 1. Quantitative assessment of periprosthetic tibial plateau: example of drawing the reference region of interest (ROI) on tibial plateau and ipsilateral tibial diaphysis (as reference for physiologic bone uptake): [^{99m}Tc]Tc-MDP planar scintigraphy (upper row: primary imaging, lower row: six months follow-up). Drawing ROI on periprosthetic tibia plateau; reference ROI on ipsilateral tibial diaphysis: anterior planar views (left), posterior planar views (right). Both visual and quantitative assessment of the peri-prosthetic uptake show increasing pattern, which was approved as loosening

Statistical analysis

Statistical analysis was performed using SPSS, version 26.0 (SPSS Inc. and LEAD Technologies) by a professional statistician. For all analysis, Paired T-tests were used to compare both primary and 6 months follow-up uptake ratios, and the maximum ratios of loosened and intact prostheses were analyzed in each group to find a cut off point for differentiating the two categories. Besides, the difference in percentage of the two ratios was also analyzed for finding a suitable cut off point. An area under receiver operating characteristic curves was drawn in order to find a value that could differentiate loosening from non-loosening. The suitability of ratios for the determination of loosening is analyzed by means of receiver operating characteristic (ROC) curves. TKA loosening confirmation was eventually achieved via surgical reports or active clinical follow-up.

RESULTS

During the initial part of the study, among 125 patients examined by [^{99m}Tc]Tc-MDP bone scintigraphy, those who had definite imaging or clinical diagnosis were excluded from the study. The remaining population of 52 patients (16 men, 36 women; mean age 69±9 years, range 45-88 years) exhibiting inconclusive clinical/imaging findings, still suspected to have loosening were selected for serial 6months follow-up scan with [^{99m}Tc]Tc-MDP bone scintigraphy.

The primary bone [^{99m}Tc]Tc-MDP uptake ratios ranged between 0.9 and 2.66 and could not be used to differentiate the patients. The ROC curve was drawn with an area under the curve of 0.52 in initial images (AUC = 0.52); the ROC curves found no striking predictive threshold values. Initial uptake ratios reveal weak predictive characteristics, sensitivity 50% and specificity 57% for loosening detection (optimal cut-off value 1.55, AUC 0.52). Among the delayed images, figures show loosening prediction enhancement with sensitivity 71% and specificity 79% (cut-off 1.53, AUC 0.79) (Tables 1, 2 and 3).

Table 1. Measurment of tibial plateaue to background [^{99m}Tc]Tc-MDP uptake ratio in patients finally diagnosed as loosening

	Age	Gender	Initial ratio	Follow-up ratio	Change ratio
1	59.00	m	1.56	2.30	0.47
2	72.00	m	0.95	1.05	0.11
3	66.00	w	2.09	3.45	0.65
4	73.00	w	1.36	1.48	0.09
5	74.00	m	1.34	1.35	0.00
6	63.00	w	1.76	1.98	0.13
7	63.00	w	1.70	2.02	0.19
8	84.00	w	1.11	1.80	0.62
9	77.00	m	1.56	2.03	0.30
10	62.00	w	1.88	2.28	0.21
11	59.00	w	2.10	2.50	0.19
12	59.00	w	1.60	4.30	1.69
13	75.00	w	1.13	1.20	.06
14	62.00	w	1.66	1.69	0.02
15	77.00	w	1.39	1.47	0.05
16	73.00	m	1.58	1.60	0.01
17	79.00	w	1.26	1.37	0.09
18	59.00	w	0.97	1.12	0.15
19	60.00	m	1.50	1.65	0.10
20	71.00	m	1.51	1.58	0.04
21	62.00	w	1.47	1.66	0.13
22	75.00	w	1.10	1.55	0.41
23	63.00	w	2.03	2.20	0.08
24	74.00	w	1.62	2.39	0.48

Results show that loosened knee prostheses had strong correlation with increased bone tracer uptake over time. A comparison of the bone ratios reveals a statistically significant increase in patients finally diagnosed as loosening (p value =0.002), while there is a meaningful decrease in the data of patients who were eventually labeled as non-loosening (p value =0.001). Change in uptake ratios within 6 months could clarify the diagnosis with a sensitivity of 87% and a specificity of 89% in patients with equivocal primary findings (Table 3).

The change of the values was analyzed and a valuable cut off value was identified to predict the loosening state of a prosthesis via the pattern of changes in uptake ratios. Therefore +3.9% change in ratio seem to be acceptable as a switch from equivocal to definite loosening diagnosis. The area under the curve was 0.94 with this cutoff value providing sensitivity of 87% and a specificity of 89%.

Table 2. Measurment of tibial plateaue to background ratio in patients finally diagnosed as non-loosening

	Age	Gender	Initial ratio	Follow-up ratio	Change ratio
1	64.00	m	1.78	1.50	-0.16
2	75.00	m	1.05	1.00	-0.05
3	85.00	w	1.25	1.01	-0.19
4	80.00	w	1.62	1.69	0.04
5	70.00	w	1.55	1.30	-0.16
6	61.00	w	1.68	1.68	0.00
7	75.00	m	1.58	1.20	-1.00
8	75.00	w	1.15	1.11	-0.04
9	76.00	w	1.75	1.43	-0.18
10	62.00	w	1.30	1.10	-0.15
11	66.00	w	1.38	1.05	-0.24
12	88.00	m	1.36	1.21	-0.11
13	80.00	w	1.50	1.38	-0.08
14	73.00	w	1.77	1.38	-0.22
15	74.00	w	1.07	1.05	-0.02
16	74.00	w	0.90	0.85	-0.06
17	78.00	m	1.74	2.07	0.19
18	57.00	m	1.82	1.66	-0.09
19	61.00	w	1.17	1.21	0.03
20	45.00	w	1.55	1.39	-0.10
21	56.00	w	1.75	1.51	-0.14
22	65.00	w	1.18	1.20	0.02
23	75.00	w	2.66	1.75	-0.34
24	65.00	w	1.30	1.12	-0.14
25	57.00	w	1.60	1.30	-0.19
26	72.00	m	1.68	1.57	-0.06
27	67.00	m	1.49	1.48	-0.01
28	79.00	m	1.61	1.21	-0.25

Table 3. Overall comparison of diagnostic efficacy of single versus serial bone scan for the diagnosis of loosening

	Cut off ratio	Sensitivity	Specificity
Initial study	1.55 (AUC = 0.52)	50%	57%
Follow-up study	1.53 (AUC= 0.79)	71%	79%
Serial difference	3.9%↑(AUC= 0.94)	87%	89%

When analyzing mean ratios of initial and follow-up scan, the percentage changing ratios of the loosening group appear to be 36% greater than when no loosening is set (mean percent change in loosening group (26%±36%), mean percent change in non-loosening group (−13%±20%) (Tables 1 and 2, Figures 2 and 3).

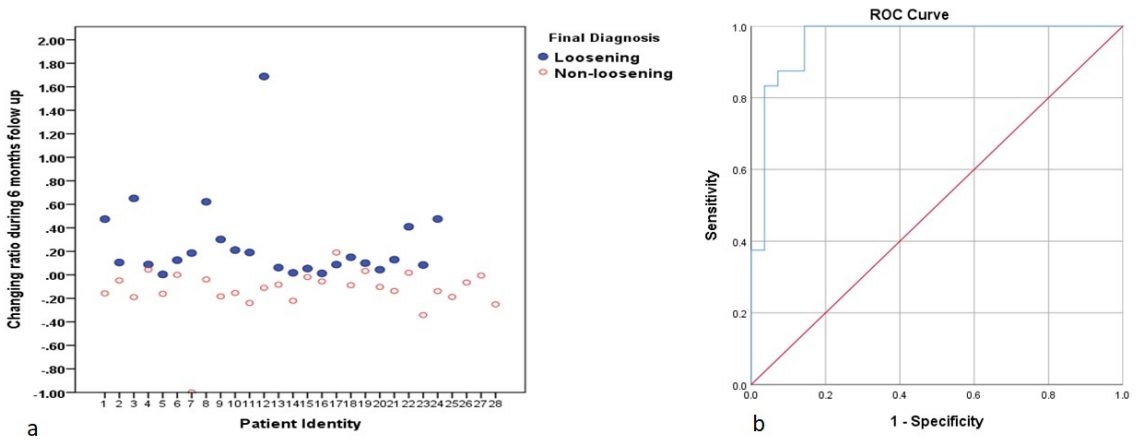

Fig 2. Schematic presentation of changing ratios during 6 months follow up in all patients

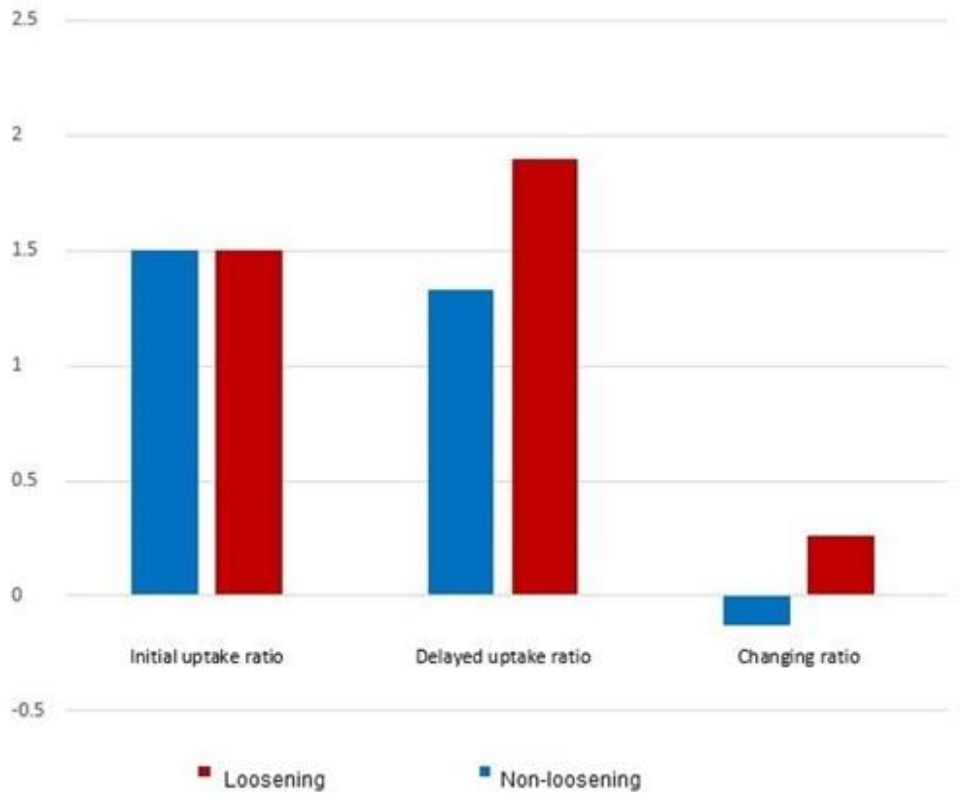

Fig 3. Initial, delayed and changing in mean planar [^{99m}Tc]Tc-MDP uptake ratios in the loosening vs. non-loosening groups

DISCUSSION

Loosening of a prosthesis is not a yes/no differentiation. It is an ongoing progressive process. Findings of this study successfully supported the diagnostic efficacy of serial [^{99m}Tc]Tc-MDP bone scintigraphy in diagnosing TKA loosening.

Increase uptake pattern in favor of loosening, although rather intuitive and predictable, has not been reported as a cutoff value in previous literature. Our investigation found 3.9% increase in bone tracer uptake ratios over time a good predictor to diagnose loosening (p value =0.002), while significant decrease was noticed in others eventually labeled as non-loosening (p value =0.001).

Diagnostic SPECT/CT patterns in favor of loosening in bone scan have been previously surveyed, as follows:

Many scientists have studied quantitative [^{99m}Tc]Tc-MDP uptake patterns of knee joints after TKA [24, 26, 31, 32]. Images were analyzed by means of three-dimensional quantification and anatomically subdivision on SPECT/CT with high diagnostic accuracy. A review by Adesanya et al. declared that SPECT and SPECT/CT will improve the image quality and sensitivity of bone scan-based assessment in painful prosthetic joints [16]. A recent study by Hirschmann et al. on component positions of 100 knee prostheses, analyzed with 3-D SPECT/CT reconstructed images [24]. They quantitate pathologic uptake on the basis of intensity ratios (comparing femoral shaft) and found [^{99m}Tc]Tc-MDP uptake patterns via delicate anatomical localization utilizing segmental computerized tomography information. Finally, they clarified that SPECT/CT using their specific algorithm provides more clinical diagnostic values than planar [^{99m}Tc]Tc-MDP bone scan images. Present study focused on quantitative analysis regardless of SPECT-CT findings; SPECT-CT is not available in all nuclear medical centers; and the interpretation is more sophisticated.

Regarding cut-off values, Awengen et al. identified thresholds for each femoral, tibial and patellar regions in asymptomatic knees after bilateral total knee arthroplasty. A ratio of the BTU intensity and the reference region of more than 2.5 in femoral regions and more than 5 in tibial and patellar regions was considered as a pathology [23].

Klett et al. studied 31 cemented knee prostheses in tibial components [17]. In agreement with our study, Klett et al. applied the tibial/femur uptake ratios as a useful quantitative parameter to interpret bone scan images. The authors divided the tibia plateau to medial and lateral regions in their quantitative retrospective analysis and analyzed the bone uptake ratios. Femoral diaphysis was selected as the reference. They found threshold of 5 for tibia/femur ratio with a maximum specificity and threshold of 3.3 for maximum sensitivity. We added an extra quantitative measurement of the bone uptake after 6 months interval. Our study design differs with Klett et al. investigation in some other ways; regardless of the prosthesis type, we evaluated the patients with equivocal [^{99m}Tc]Tc-MDPSPECT/CT bone scan findings in two temporal phases while Klett and his colleagues primarily analyzed the diagnostic efficacy of SPECT/CT bone scan in all symptomatic patients [17].

Uptake ratio in our study in symptomatic patients ranged between 0.9 and 2.66 in initial [^{99m}Tc]Tc-MDP bone scan and calculation methods were consistent with findings described by Soininvaara et al. [30] except for different reference area selection; they draws ROI on femur SPECT views but we insert the background ROI on tibia.

This study found enhanced predictive values of component loosening in the region of the tibial plateau at a cut-off of 1.55 (AUC = 0.52) in early and 1.53 (AUC = 0.79) in six-month images. In our study, the tibia to background uptake ratio in the initial bone scan did not reveal a reasonable cut off to differentiate loosening. Delayed scans though revealed prediction enhancement, did not provide remarkable diagnostic efficiency. These findings were in complete accordance with earlier publications opposing the application of bone scans in loosening gnosis reporting accuracies of 50-70% diagnosis [33, 34]; although, regarding the high values of negative results, bone imaging still represents the initial screening test [27]. Knowing the limitations of bone scintigraphy, this survey specifically take into account the post-operative bone remodeling process, following the uptake ratios of equivocal cases for a time course of 6 months.

In spite of high diagnostic value of a negative bone study, the positive uptake around the prosthesis was not actually specific by means of planar three phase bone scan in visual interpretation [27, 28], although recent SPECT- CT studies find recognition patterns improving the specificity [23, 26, 35].

Previously, the interpretation of bone tracer uptake values was reported to be dependent to the examiner's experience, needing a close interplay between an orthopedic implant-experienced nuclear medicine physician and the treating surgeon; however, serial scan provides quantitative cut-off values for interpretation regardless of the examiner experience and completely in concordance with final clinical diagnosis.

Test accuracy could be optimized reaching maximum specificity using changing threshold of 20 % and maximum sensitivity with changing threshold of 0.2% in 6 months serial bone scan. To avoid unnecessary revision surgeries, high specificity rather than high sensitivity is required; therefore, the maximum specificity threshold of 20% can best be used in this case.

The change in ratio of +3.9% to be used as a switch from equivocal to definite loosening diagnosis is optimal considering the mean changing ratios in each group (mean percent change in loosening group 26%±36%, mean percent change in non-loosening group -10%±11%) and also considering the acceptable pattern of decreased post-surgical bone remodeling with time in intact prostheses.

Study results deal with ratio cutoffs rather than pure quantitative values, changing ratios are independent of single values and we surpass the limitation to present a reproducible value for other institutions. The camera was qualified with European quality control standards. The standard dose was administered to all patients. The scanner was same for serial scans in this study. Indeed, the changing ratio also seems to be independent of scanner type and protocol.

There were 4 patients without clear evidence of loosening demonstrating increasing uptake ratios with time, negatively affecting the scan specificity; they were supposed to suffer from superimposed traumatic or degenerative changes leading to increase in radiotracer uptake ratios over time.

Several limitations of the present study have to be acknowledged. Limited number of patients; however, all cases belong to inconclusive category in initial clinical, scintigraphic and radiological assessments. Another limitation was non-availability of follow-up evaluations in cases with definite loosening diagnosis in initial evaluations.

Regarding the small sample size, this study did not intend to analyze other post-surgical complications including septic joint diseases, patellofemoral problems or maltracking. The retrospective nature and disregarding SPECT/CT

quantifications was the other limitation. According to high diagnostic power of SPECT/CT in quantitative interpretation, future studies can better compare the performance of quantitative serial planar versus quantitative initial SPECT/CT.

CONCLUSION

Post-surgical serial bone scans (initial and 6months follow-up) point out a potential additional criterion to differentiate between loosened and intact prostheses in equivocal cases. Allowing an uncertainty of 5%, we found threshold of 3.9% for the changes in tibial uptake ratios to differentiate between loosened and intact prostheses. Hence, the results of this study help to differentiate disease-specific from patient-specific uptake values; and further improve the diagnostic accuracy of TKA loosening in patients with equivocal clinical findings and undetermined primary [^{99m}Tc]Tc-MDP bone scan images.

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