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REVIEW

The role of FDG-PET in distinguishing between septic and aseptic loosening in hip prosthesis: a review of literature

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Abstract Infection in prosthesis surgery is very dangerous because it changes the patient's prognosis. Differential diagnosis between septic and aseptic loosening is fundamental in order to apply the correct treatment. The correct diagnostic approach is still debated in literature. The aim of this study was to perform a review of literature evaluating positron emission tomography (PET) capacity to distinguish between septic and aseptic loosening in hip prosthesis. Research was done principally among medical archives. Five studies were selected which satisfied the required characteristics, and a weighted average of sensitivity and specificity of the different studies was determined. The fluorodeoxyglucose positron emission tomography (FDG-PET) sensitivity in individuating hip prosthesis infections was 82.8% and specificity was 87.3%. Positron emission tomography based on 2-fluoro-2-deoxy-D-glucose could be a valid option if research is able to find an uptake pattern specific for septic and aseptic loosening.

Résumé Les infections en chirurgie prothétique sont très néfastes car elles peuvent changer le pronostic des patients. Le diagnostic différentiel entre complications septiques ou descellement aseptique est fondamental afin d'avoir un traitement adapté. Le diagnostic différentiel est très discuté dans la littérature. Objectif: Nous avons voulu faire une revue de la littérature afin de mettre en évidence les caractères des descellements septiques ou aseptiques dans les prothèses de hanche. Matériel et méthode: ces travaux ont été réalisés avec Medical Archives. 5 études ont été sélectionnées. Ces articles ont concerné essentiellement les possibilités de diagnostic avec la topographie par émission de protons (PET scan). Résultats: la sensibilité d'utilisation du PET Scan dans les complications infectieuses est de 82,8% et la spécificité de 87,3%. En conclusion: la technique par émission de protons à partir de 2-fluoro-2-deoxy-D-glucose est une option tout à fait intéressante qui permet de faire le diagnostic différentiel entre les descellements septiques ou aseptiques.

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Background

Today, total knee and hip replacement provides good results, assuring pain relief and good function. Prosthesis survival depends on several factors such as surgical technique, prosthesis shape, and loosening risk. New antibiotic therapy protocol decreased infection risk to about 1–4% in first replacement [5–9] and to more then 30% during revision for infection [4, 6, 9].

However, the major complication today is still prosthesis loosening. In order to guarantee a correct approach it is very important to distinguish between septic and aseptic loosening. In septic loosening it is mandatory to heal infection before revision; restoration of normal of inflammatory indices and fine needle aspiration are helpful.

Several tests are able to address diagnosis, but fluorodeoxyglucose positron emission tomography (FDG-PET) is more important than ever because the inflammatory and tumour cells have a high glucose demand. There are

Table 1 Selected prospective studies

Year	Authors	Patients	Gender (M/F)	Hip	Knee	Minimal time from surgery	Minimal follow-up
2001	Zhuang et al. [16]	62		38	36	1 year	1 year
2002	Chacko et al. [2]	32	20/12	41		1 year	9 months
2003	Vanquickenborne et al. [14]	17	8/9	17		2 years	6 months
2004	Stumpe et al. [12]	35	12/23	35		1 years	6 months
2005	Reinartz et al. [11]	63	32/31	92		1 years	9 months

several studies in literature evaluating FDG-PET. In this article the evidence of the use of PET in the differential diagnosis between septic and aseptic loosening is evaluated.

Material and methods

Research was carried out in the following archives:

- PubMed
- Cochrane Musculoskeletal Injuries Group Specialised Register
- Cochrane Register per trias Controllati
- Health Technology Assessment
- EMBASE
- SCOPUS
- CINAHL
- AMED
- DARE
- TRIP

The following keywords were used for the literature search:

- Positron emission tomography
- Painful arthroplasty
- Bone scan
- WBC scintigraphy
- Mobilisation
- Infection

Twenty-five studies were found, and the studies that did not have the following characteristics were excluded:

- Prospective studies evaluating FDG-PET possibility to detect loosening
- PET performed almost one year later then surgery
- Imaging valued by one to two experts, trained in nuclear medicine, not knowing the clinical situation
- A six-month minimum follow-up
- Studies suspected of patient redundancy

The paper of Van Acker et al. [13], considering 21 total knee replacements (TKR), was excluded from this review because of reported false positives, false negatives, true positives, and true negatives for PET–bone scan association. Nevertheless, that study reported a sensitivity (SE) of 100% and a specificity (SP) of 73% for PET alone.

The literature review for this research was completed in June 2007 with the selection of five prospective studies as summarised in Table 1.

The research made by Zhuang et al. [16] was a prospective study performed on 62 patients having 38 total hip replacements (THR) and 36 TKRs. All patients complained of painful prosthesis. In three cases FDG-PET was performed shortly before the first year after the surgery, but this is an insignificant limit. In 43 patients final diagnosis was done through microbiological and histological tests after surgery; in the remaining patients it was done at the first year follow-up.

The study by Chacko et al. [2] was based on 32 patients having 41 painful hip prostheses. FDG-PET was performed

Table 2 FDG-PET results

Authors	PT	THR	TP	TN	FP	FN	SE	SP	AC
Zhuang et al. [16]	62	38	9	25	3	1	90.0%	89.3%	89.5%
Chacko et al. [2]	32	41	11	28	1	1	91.7%	96.6%	95.1%
Vanquickenborne et al. [14]	17	17	7	7	2	1	87.5%	77.8%	82.3%
Stumpe et al. [12]	35	35	3	21	5	6	33%	81%	68.6%
Reinartz et al. [11]	63	92	31	56	3	2	94.0%	95.0%	95.0%

FDG-PET fluorodeoxyglucose positron emission tomography, *PT* patients, *THR* total hip replacement, *TP* true positive, *TN* true negative, *FP* false positive, *FN* false negative, *SE* sensitivity, *SP* specificity, *AC* accuracy

at least one year after surgery. Final diagnosis was done after revision in 28 cases and at nine months follow-up in the other 13.

The study by Vanquickeborne et al. [14] was done on 17 patients with THR, ten first implants and seven revisions. FDG-PTE bone scan and $^{99\,m}$Tc-labelled WBC scintigraphy were performed almost two years after surgery. Final diagnosis was based on microbiological and histological tests after surgical revision in 11 patients and at six months follow-up in the remaining six cases.

Stumpe et al. [12] performed FDG-PET and bone scan in 35 patients having hip prostheses after almost one year postsurgery. In 26 cases, diagnosis was made by referring to surgery results, in the other nine patients at six-month follow-up.

The study of Reinartz et al. [11] was made on 63 patients having 93 hip prostheses, 64 of which were painful. FDG-PET and bone scan were performed. Definitive diagnosis was carried out on the surgery results in 36 cases and at nine-month follow-up in the other cases.

The studies mentioned above identified 209 patients, 223 hip prostheses, and 36 knee prostheses. All knee prostheses were examined by Zhuang et al. [16] in 2001. As already mentioned, data reported by Van Acker et al. [13] were not included.

Results

The FDG-PET sensitivity in identifying hip prosthesis infections was found to be 82.8%; this is the weighted average of sensitivity of the different studies. Nevertheless, the result is influenced by the data of Stumpe et al. that reported an SE of 33% in 35 cases; without this contribution, SE would have been higher then 92% (SP was 87.3%). These results are reported in Table 2.

Discussion

Love et al. [8] showed the first patient statistic case in 2000, with 18 females and four males, and a total of 11 THR and 15 TKR. They found out that FDG-PET had an SP of 47% in identifying the infection, therefore declaring it useless. They affirmed that infection is characterised by high metabolic activity and that aseptic loosening shows an intermediate metabolic activity.

In 2001, Van Acker et al. [13] studied 21 patients affected by painful knee prostheses. Bone scan, $^{99\,m}$Tc-labelled WBC scintigraphy and FDG-PET were performed. The authors agreed that a focal uptake is common within the first 36 months from the surgery and it is not an indication of infection. To have infection a focal or diffuse uptake must be localised at the bone–prosthesis interface; other localisations are not specific and may be due to synovitis as well. They reported an SE of 100 and an SP of 53% for $^{99\,m}$Tc-labelled WBC scintigraphy. If the results are the same as that given from the bone scan, the SP reaches 93%, achieving better than PET (SE 100%, SP 75%, PPV 60%).

In 2002, Zhuang et al. [15] performed FDG-PET at three, six, and 12 months after surgery in nine volunteers having THR; this study suggested that uptake near the neck and head prosthesis is normal while it is not present at the bone–metal interface. One year earlier, the same group demonstrated how a high uptake near the neck was related to aseptic loosening. Chacko et al. [2] found an SE of 91.7% and an SP of 96.6% using as infection criteria an uptake in bone–prosthesis interface, postulating that an uptake in the soft tissue surrounding the femoral neck could be related to aseptic loosening.

Stumpe et al. [12], in a study on THR, obtained a low SE, perhaps because of a severe diagnostic criteria used (SE 33%, SP 81%).

Mumme et al. [10] conducted an important study where triple-phase bone scan was compared with FDG-PET in 50 patients having painful prostheses to differentiate septic from aseptic loosening. They found an SE of 91% and an SP of 92% (accuracy of 91%), without correlation to cement use, pointing out five uptake categories:

Pattern I: No uptake in interface bone-prosthesis
Pattern II: Uptake surrounding femoral neck
Pattern III: Uptake localised in the area surrounding the femoral neck and in a part of the bone–acetabular cup and/or I and VII Gruen's zones
Pattern IVa: Uptake in the area surrounding the femoral neck and in the totality of the bone–femoral cup interface, without compromising peri-prosthetic soft tissue
Pattern IVb: Uptake localised in the neck area and in most of the bone–stem interface without compromising periprosthetic soft tissue
Pattern IVc: IVa plus IVb
Pattern V: Uptake in bone–prosthesis interface and in periprosthetic soft tissue

Patterns I, II, and III are not associated with loosening, pattern IV should be associated with aseptic loosening, and in pattern V there should be infection.

As already pointed out by Zhuang et al. [16], Mumme affirmed nonspecific uptake was related to prosthesis components causing a reactive inflammatory process with granulation tissue production. That tissue, between bone

and prosthesis components, should be responsible for aseptic loosening. The same group affirmed it is not possible to distinguish aseptic from septic loosening basing on standardised uptake value (SUV); it has to be considered an auxiliary criteria. The same year they published a prospective study carried out among 63 patients [11] where an SE of 95% and an SP of 94% were confirmed in differentiating septic from aseptic loosening [10].

Conclusions

Clinical signs, blood tests, and X-ray are not able to distinguish septic from aseptic loosening.

Fine needle aspiration is characterised by an SE of 67% [7] and a low negative predictive value (Magnunson 1988) [3, 7]. Furthermore, several authors demonstrated that this has to be performed exclusively where a high suspicion level or an increased VES and CRP are present in order not to expose the patient to infection risks [11].

Nuclear medicine techniques have a high SE but a lower SP; bone scan, using TC99-bisphosphonate, is a bone metabolism marker with an SE of 100% but a very low SP (30%) [1]. The use of $^{99\,m}$Tc-labelled WBC scintigraphy allows partial avoidance of this problem, achieving an SP of 86% and gold standard status [1].

Nevertheless, it has several other problems including high cost, dangers related to blood manipulation, and a longer procedure.

Positron emission tomography based on 2-fluoro-2-deoxy-D-glucose could be a valid option if research is able to find an uptake pattern specific for septic and aseptic loosening.

In the literature there are two principal opinions. The first affirms septic and aseptic loosening are not characterised by a topographic specific pattern so that differentiation has to be done exclusively on quantity of radiodrug uptake, being higher in septic form [8, 13]. The second opinion, sustained by the majority of the authors, hypothesises that radiodrug localisation in bone–prosthesis interface is a characteristic of septic loosening. Therefore the presence of an osteolytic area visible through X-ray with PET negative, or partially positive, should be related to aseptic mobilisation [2, 10, 15, 16].

The use of such diagnostic criteria increases SP for PET in detecting septic loosening, but with a consequent decrease of SE.

While waiting for new prospective studies, $^{99\,m}$Tc-labelled WBC scintigraphy is still today the gold standard especially when associated with bone scan. The potential value of FDG-PET is confirmed because it offers several benefits above traditional methods: good accuracy, a faster procedure, lower cost, as well as lower contamination risk for technicians because they do not have to come in contact with the patient's blood.

SE and SP reported in selected studies confirms PET importance as tomorrow's principal test to approach painful hip prosthesis.

For knee prosthesis, the study by Zhuang et al. [16] is the only one in the literature reporting specific data (SE 90.0%, SP 89.3%), but it contrasts with the data reported by Van Acker et al. [13] (SE 100%, SP 73%). New studies are necessary to identify normal and pathological patterns in knee prostheses.

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