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Safety of orthopedic implants: implant migration analysis a must

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Citation
Hasan, S. (2024, June 4). *Safety of orthopedic implants: implant migration analysis a must*. Retrieved from https://hdl.handle.net/1887/3762018

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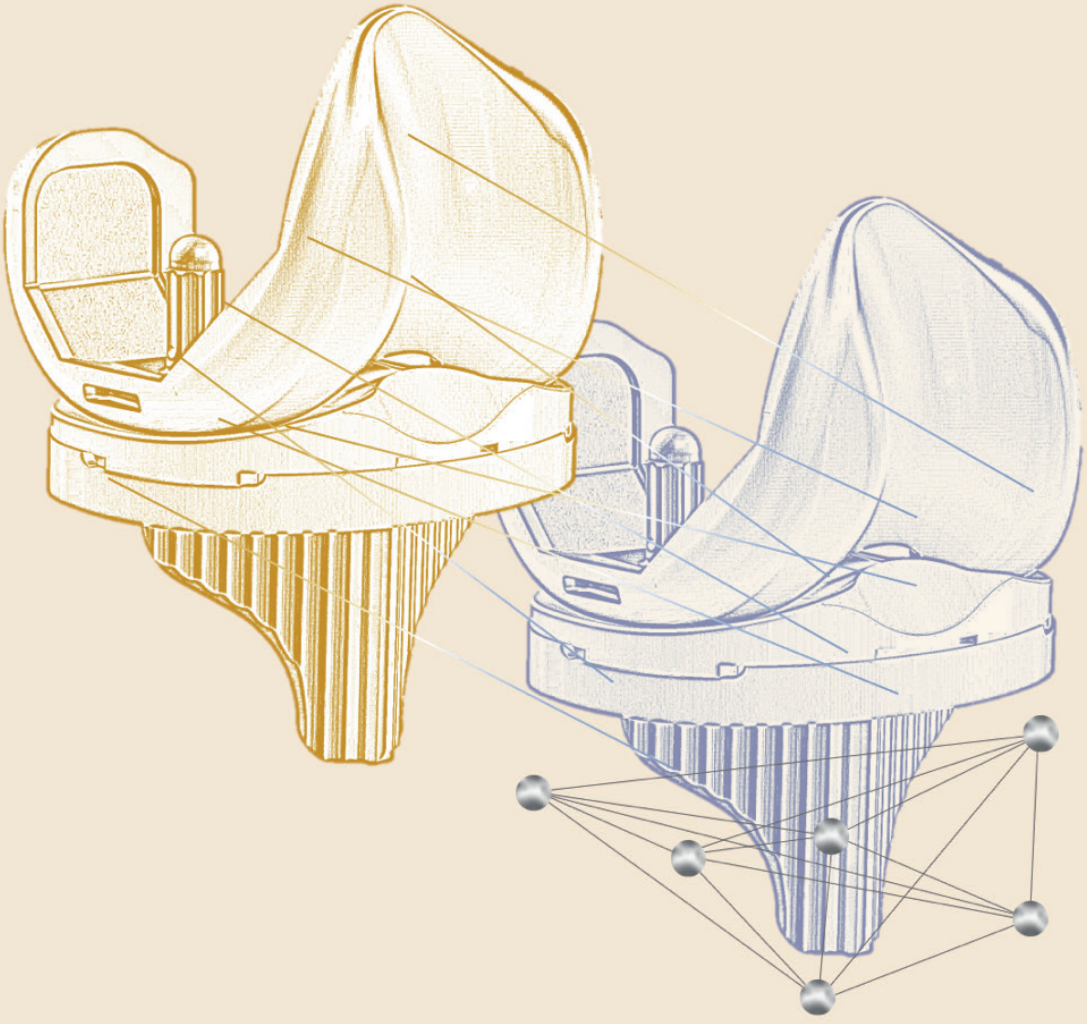
Note: To cite this publication please use the final published version (if applicable).



Chapter III

Bio-markers to discriminate between aseptic loosened and stable total hip or knee implants

A systematic review

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EFORT Open Rev. 2024 Jan 9;9(1):25-39.
doi: 10.1530/EOR-22-0046

Abstract

Loosening is the major cause for failure of total hip and total knee replacements (THRs/TKRs). Pre-emptive diagnostics of asymptomatic loosening could open strategies to prevent gross loosening. A multitude of biological markers may discriminate between loosened and stable implants, but it is unknown which have the best performance. The present systematic review aims to assess which markers have shown the most promising results in differentiating between stable and aseptic loosened THRs and TKRs. PubMed, Embase, Web of Science, Cochrane library and Academic Search Premier were systematically searched up to January 2020 for studies including THR/TKR and markers to assess loosening. Two reviewers independently screened records, extracted data and assessed the risk of bias using the ICROMS-tool to classify the quality of the studies. Thirty-five (five high-quality) studies were included, reporting on a median of 50 patients (range 18–527). Serum, urine, and radiological markers were studied in 22, ten and seven studies, respectively. Tumour necrosis factor α, interleukin1b and osteocalcin were significantly higher in loosened compared to stable implants. Urinary N-terminal telopeptide had significantly elevated levels in loosened prostheses. Radiologically measured migration and radiolucent lines were increased in loosened implants. In conclusion, several serum, urine, and radiological markers were promising in discriminating between loosened and stable implants. We recommend future studies to study these markers in a longitudinal fashion to assess whether progression of loosening is associated with an increase or decrease of these markers. In particular, high-quality studies assessing the usability of these markers are needed.

Keywords: Arthroplasty, Loosening, Markers

Background

Aseptic loosening is the leading cause for revision of total hip and total knee replacements (THRs/TKRs) reported in national arthroplasty registries.[1, 2] Aseptic loosening may have a multitude of causes among which factors related to implant design, surgical technique, and genetic predisposition.[3-5] For the implant related causes, the polymer, bone cement, and metal wear particles released due to repetitive motion of the joint can induce inflammation and osteolysis.[6-8] The latter may differ between individuals due to reaction of the foreign body inflammatory response.[4, 5] Other mechanisms influencing aseptic loosening such as stress-shielding, micromotion, high fluid pressure and endotoxins have been proposed as well.[9-12]

Ultimately, aseptic loosening can be confirmed intraoperatively, but any diagnostic before extensive surgery helps in the decision to perform surgery in patients with complaints of their implant. Even more since the presence of pain of THRs or TKRs is not always associated with a loosened implant. Except implant migration diagnostics, few other markers are available to diagnose aseptic loosening at an early stage in asymptomatic patients.[12, 13] Earlier identification of loosened implants is important to prevent complications as radiological signs only become visible after several years and patients could be asymptomatic up to the point that major revision surgery is required.[14, 15] Furthermore, late diagnosis of loosening could increase the incidence of complications such as fractures with an increased mortality risk after revision surgery as consequence.[16] Although currently no other treatment besides revision surgery is available for aseptic loosened implants, novel treatments such as minimal invasive refixation using cement injection or drugs such as bisphosphonates to prevent bone loss could be viable options in the future.[17-21] Pre-emptive diagnostics of implant loosening in asymptomatic patients could potentially open strategies to not only prevent more severe implant loosening by acting as a therapeutic target, but also has the potential to monitor disease progression.[22]

Implant loosening is a complex mechanism which is controlled by an intricate balance of biomechanical forces and a balance between osteoblasts and osteoclasts. The latter can be quantified by several markers such as serum and urine markers.[7, 23-25] Several studies assessed these markers to discriminate between aseptic loosened and stable implants.[26, 27] However, the number of patients included in these studies was mostly too small to draw any conclusions about the validity of the marker to differentiate between aseptic loosened and stable implants. Moreover, a wide variety of markers in THRs and TKRs have been studied, making it difficult to ascertain the most promising test to discriminate between aseptic loosened and stable implants. Two systematic reviews have previously been conducted, in 2011 and 2014, to assess the feasibility of several markers to differentiate between aseptic loosened and stable implants. However, these reviews did not assess the quality of the included studies and need updating to determine the most promising marker.[26, 27] Therefore, the present systematic review aims to identify the most frequently studied markers which are able to discriminate between aseptic loosened and stable THRs and TKRs, and therefore have the most promising results in differentiating between these groups.

Methods

This systematic review was performed in concordance with the PRISMA 2020 statement and was registered with Prospero (CRD42019133137) prior to the screening of studies.[28, 29] No funding was acquired for the present review. Level of evidence: 3a.

Search strategy and selection

A search strategy was constructed by an experienced librarian (JS). PubMed, Embase, Web of Science, Cochrane library, and Academic Search Premier were searched for publications up to the 30th of January 2020 without restriction of publication date. Based on the previous systematic reviews, the current search was composed of three

components: THR or TKR (e.g. “Arthroplasty, replacement, hip“[Mesh], “Arthroplasty, replacement, knee”[Mesh]); aseptic loosening, osteolysis or wear (e.g. “Osteolysis”[Mesh], “Prosthesis failure”[Mesh]); and determinants for aseptic loosening (e.g. “Biomarkers”[Mesh], “Risk factors”[Mesh]; see Appendix A for the complete search strategies). Wear was included to prevent missing relevant studies, but studies reporting only wear were excluded during screening.

Two reviewers (SH and PvS) screened all titles and abstracts independently. Any discrepancy was resolved through discussion. A third reviewer was available if consensus could not be reached. Inclusion criteria were studies comprising primary THRs and/or TKRs having both a study group with aseptic loosening (i.e. confirmed during revision surgery) or osteolysis (i.e. confirmed radiologically) as well as a control group with stable implants. Studies were excluded that did not use a marker, defined as a non-operative test used to differentiate between aseptic loosened and stable implants. Moreover, studies without aseptic loosening as outcome as well as studies among patients with an infection, tumour reconstructions or metal-on-metal implants were excluded. In addition, animal studies and in vitro studies were excluded. Studies in English, Dutch, German, and French were eligible for inclusion and were translated by both reviewers (SH and PvS). Authors were contacted if a full-text could not be found.

Data extraction

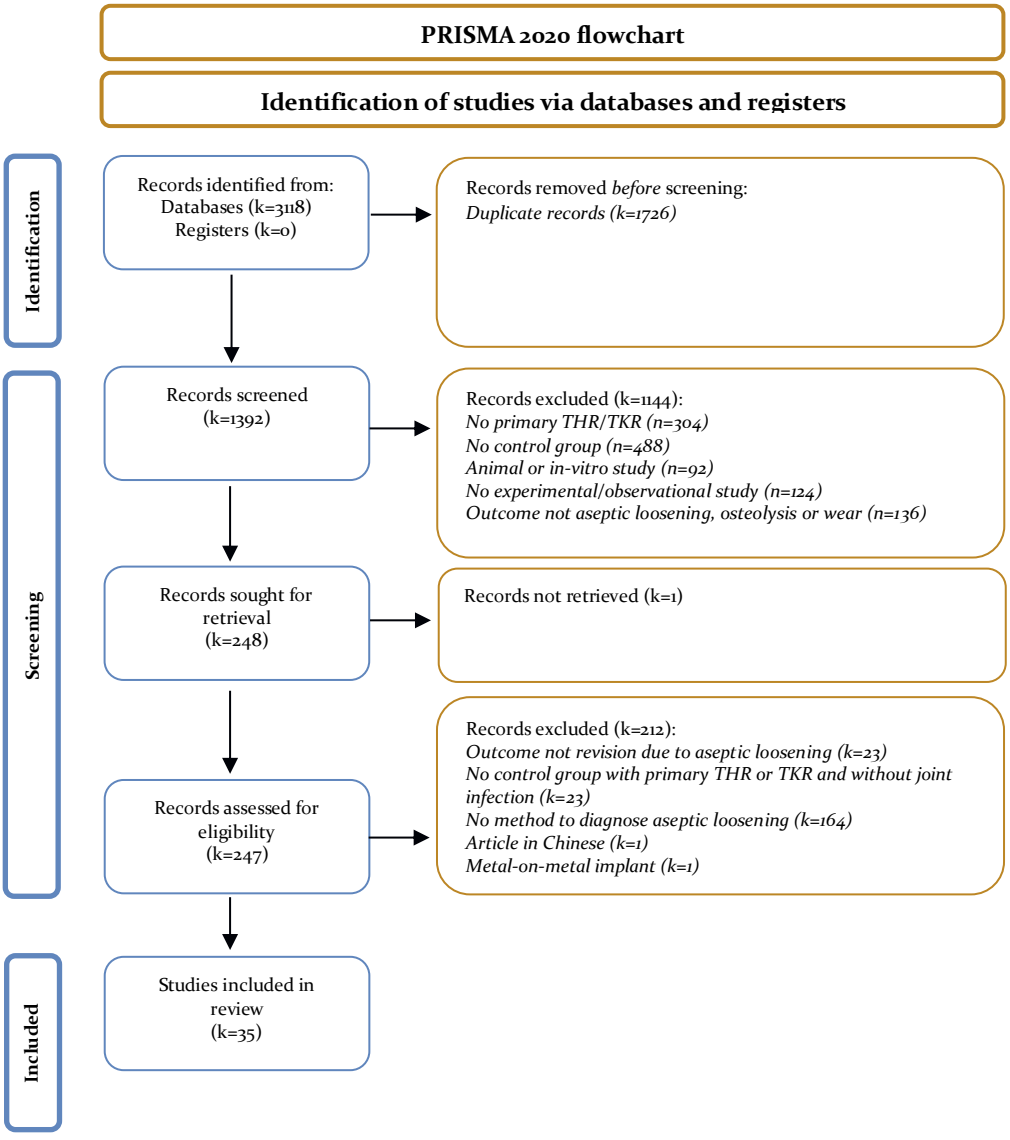
Data were extracted by both reviewers independently using a prespecified SPSS file (IBM SPSS Statistics 26.0; IBM Corp, Armonk, NY, USA). Data extracted were author, title, year of publication, country of the first author, study design, specific joint (i.e. THR and/or TKR) and the marker used to differentiate between loosened and stable implants. The number of patients in the aseptic loosened and the control group were collected as well as the percentage of female patients, the mean age of both groups and the primary diagnosis of the patients. Fixation method and hip bearing was collected only in THR studies. Outcomes of studies were collected in the original

unit including confidence intervals, standard errors (se) or standard deviations (SD), if available. If absolute values were not reported in the text but only in a graph, the values were estimated from the graph. If the same marker was reported by three or more studies, results were plotted in a forest plot. Differences between loosened and stable implants were assessed at diagnosis or before surgery. In case of longitudinal data collection, the final measurement before revision surgery was used and plotted. Data were not pooled because patients, the method of data reporting (e.g. median or mean) and the units of outcomes differed significantly between studies. If the se was not reported, it was calculated by dividing the SD by the square root of the number of patients included.[30]

Assessment of risk of bias

The risk of bias (RoB) was assessed independently by both reviewers (SH, PvS) using the Innovative Tools for Quality Assessment: Integrated Quality Criteria for Review of Multiple Study Designs (ICROMS).[31] The ICROMS comprises seven dimensions with three to six specific criteria per dimension. Every study design must meet a minimum score and mandatory criteria to be included in a review. However, the present review included all studies independent of the ICROMS score and reported the RoB for every study with the rationale that the RoB could be taken into account when weighting study results while excluding studies with high or medium RoB would result in the loss of possibly valuable information. All included studies in the present review were cohort studies for which the specific ICROMS criteria are outlined in appendix B. Studies scoring at least 18 points and fulfilling the mandatory criteria were classified as high quality (HQ) studies. Studies scoring at least 18 points but failing to fulfil the mandatory criteria were classified as moderate quality (MQ) studies. Studies scoring less than 18 points were classified as a low quality (LQ) study. There were no studies that fulfilled all the mandatory criteria but failed to score at least 18 points.

Figure III.I inclusion flowchart. THR = Total hip replacements; TKR = Total knee replacements



Results

Study selection

The search yielded 3118 records. After removing duplicates, 1392 records remained. A total of 1144 records were excluded as 304 did not involve primary THR or TKR, 488 did not have a control group, 92 involved animal or in-vitro studies, 124 did not have an experimental or observational design, and 136 did not use aseptic loosening, osteolysis or wear as outcome, resulting in 248 reports to be assessed for eligibility. One report could not be retrieved. Of the 247 reports, 212 were excluded as 23 did not involve aseptic loosening, 23 did not have a control group with a stable primary THR/TKR without a joint infection, 164 did not involve a marker for aseptic loosening, one comprised metal-on-metal hip implants, and one article was in Chinese, leaving 35 studies to be included [Fig. III.I].

Risk of bias within studies

Five studies scored at least 18 points on the ICROMS quality assessment score, fulfilled the mandatory criteria, and were classified as HQ studies. Fifteen studies scored at least 18 points but did not fulfil the mandatory criteria and were classified as MQ studies. Fifteen studies scored less than 18 points and were classified as LQ studies [Table III.I]. The mean ICROMS score was 18 points (SD 3.1). Most studies failed to fulfil the mandatory criteria due to not addressing incomplete data. In addition, only a few studies performed a blinded assessment of the outcomes [Table III.I].

Study characteristics

Thirty studies included only THR, four studies included both THR and TKR, and one study included only TKR. Markers used in these studies were serum markers (n = 22), urine markers (n = 10), radiological markers (n = 7) or skin markers (n = 1). The

Table III.I

Author	Year	1A*	2E*	3E	3F	3G*	4C*	5B	6C	7A	7B	7C	7D	7E	ICROMS score
Chaganti[32]	2013	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Trehan[45]	2017	2	2	0	2	2	2	2	2	2	2	2	2	2	24
Streit[58]	2016	2	2	0	2	2	2	2	2	2	2	2	1	2	23
Morakis[43]	2011	2	2	0	2	2	2	2	2	2	0	2	2	2	22
Kobayashi[60]	1997	2	2	2	1	2	2	2	2	2	0	2	2	0	21
Hundric-Haspl[33]	2006	2	2	0	2	2	0	2	2	2	2	2	2	2	22
Ovrenovits[47]	2015	2	2	0	2	2	0	2	2	2	2	2	1	2	21
Savarino[68]	2010	2	0	2	2	1	2	2	2	2	0	2	2	2	21
Ross[22]	2018	2	2	0	2	0	2	1	2	2	2	2	1	2	20
Lawrence[48]	2015	2	2	0	2	2	0	2	2	2	0	2	2	2	20
Streich[40]	2003	2	2	0	2	2	0	2	2	2	0	2	2	2	20
Antoniou[55]	2000	2	1	0	2	2	0	2	2	2	1	2	2	2	20
Friedrich[38]	2017	2	2	0	2	2	0	2	0	2	2	2	1	2	19
He[35]	2013	2	2	0	2	2	0	1	2	2	0	2	2	2	19
Streich[53]	2009	2	2	0	2	2	0	2	2	1	0	2	2	2	19
Wilkinson[42]	2003	2	2	0	2	2	0	2	2	1	0	2	2	2	19
Witzleb[56]	2001	2	1	0	2	1	0	2	2	2	1	2	2	2	19
Granchi[37]	2006	2	0	0	2	2	0	2	2	2	0	2	2	2	18
Moreschini[39]	1997	2	2	0	2	2	0	2	2	2	0	2	2	0	18
Kreibich[69]	1996	2	2	0	2	2	0	2	2	2	0	2	2	0	18

Table III.I continued

Author	Year	1A*	2E*	3E	3F	3G*	4C*	5B	6C	7A	7B	7C	7D	7E	ICROMS score
Roato[46]	2010	2	1	0	0	2	0	2	2	2	0	2	2	2	17
von Schewelov[54]	2006	2	1	0	2	2	0	2	1	1	2	2	0	2	17
Schneider[41]	1998	2	2	0	2	2	0	1	2	2	0	2	2	0	17
Stromberg[61]	1996	2	1	0	2	1	2	1	2	2	0	2	2	0	17
Mont[70]	1995	2	2	0	1	2	2	0	2	2	0	2	2	0	17
Tang[44]	2016	2	1	0	2	2	0	2	2	2	0	2	2	0	17
Wu[34]	2009	2	0	0	2	1	0	2	2	2	0	2	2	2	17
Cenni[51]	2003	2	0	0	2	2	0	2	0	2	0	2	2	2	16
Granchi[52]	2000	2	0	0	2	2	0	2	2	2	0	2	2	0	16
Gil-Albarova[62]	1992	2	1	0	1	2	0	2	2	2	0	2	2	0	16
Fiorito[36]	2003	2	0	0	2	2	0	1	2	2	0	2	2	0	15
Krismer[59]	1996	2	1	0	2	1	2	1	0	2	0	2	2	0	15
Schneider[49]	1997	2	1	0	2	1	0	1	2	1	0	2	2	0	14
Steinbeck[71]	2014	0	0	0	2	0	0	2	0	2	2	2	2	0	12
Pellengahr[57]	2001	2	1	0	2	1	0	2	0	2	0	0	2	0	12

Table III.I Risk of bias (RoB) table. A score of 0 (i.e. did not fulfil the criteria), 1 (i.e. unclear if criteria is fulfilled), or 2 (i.e. did fulfil the criteria) points could be given to every criterion. * indicates the mandatory criteria and these criteria are dark coloured. The green highlighted studies have an ICROMS score ≥18, and fulfil the mandatory criteria, and were therefore classified as low RoB/high quality. The grey highlighted studies have an ICROMS ≥18 points, but do not fulfil the mandatory criteria, and were therefore classified as moderate RoB/moderate quality. The red highlighted studies have an ICROMS <18 points, and do not fulfil the mandatory criteria, and were therefore classified as high RoB/low quality. ICROMS = Integrated Quality Criteria for Review of Multiple Study Designs.

Table III.II

Author	Year	Joint	Fixation method	Assessment method	Study group with aseptic loosening or osteolysis	Number of patients (female) in loose group	Number of patients (female) in control group	Age loose group, mean in years	Age control group, mean in years
Chaganti[32]	2013	Hip	Mixed fixation methods	Serum markers	Aseptic loosening	15 (5)	13 (4)	70	71
Trehan[45]	2018	Hip	Mixed fixation methods	Serum markers	Aseptic loosening	20 (9)	10 (6)	68	63
Streit[58]	2016	Hip	Mixed fixation methods	Radiography	Aseptic loosening	9 (3)	73 (40)	53	56
Morakis[43]	2011	Hip	Cemented	Serum markers Radiography	Osteolysis	12 (12)	12 (12)	72	73
Kobayashi[60]	1997	Hip	Mixed fixation methods	Radiography	Aseptic loosening	41 (24)	486 (332)	50	60
Hundric-Haspl[33]	2006	Hip & Knee	NR	Serum markers	Osteolysis	50 (40)	50 (43)	65	62
Ovrenovits[47]	2015	Hip	Uncemented	Serum markers	Aseptic loosening	10 (NR)	10 (6)	NR	60
Savarino[68]	2010	Hip	NR	Serum markers	Aseptic loosening	27 (23)	19 (15)	69	62
Ross[22]	2018	Hip	Mixed fixation methods	Urine markers	Osteolysis	16 (7)	11 (4)	56	61
Lawrence[48]	2015	Hip	Cemented	Serum markers Urine markers	Osteolysis	26 (7)	24 (8)	73	74
Streich[40]	2003	Hip	Mixed fixation methods	Serum markers	Aseptic loosening	23 (10)	23 (12)	65[median]	67[median]
Antoniou[55]	2000	Hip	NR	Urine markers	Osteolysis	21 (3)	8 (0)	54	67
Friedrich[38]	2017	Hip & Knee	NR	Serum markers	Aseptic loosening	51 (33)	21 (13)	68	64
He[35]	2013	Hip	Mixed fixation methods	Serum markers	Aseptic loosening	31 (18)	19 (10)	66	61
Streich[53]	2009	Hip	Uncemented	Urine markers	Aseptic loosening	52 (26)	52 (26)	65[median]	63[median]
Wilkinson[42]	2003	Hip	Cemented	Serum markers Urine markers Radiography	Osteolysis	23 (6)	26 (8)	73	75
Witzleb[56]	2001	Hip & Knee	Mixed fixation methods	Urine markers	Aseptic loosening	58 (42)	67 (48)	68	68
Granchi[37]	2006	Hip	Mixed fixation methods	Serum markers	Osteolysis	36 (23)	33 (20)	65	58
Moreschini[39]	1997	Hip	Mixed fixation methods	Serum markers	Osteolysis	9 (7)	13 (8)	63	62
Kreibich[69]	1996	Hip	Uncemented	Serum markers	Aseptic loosening	14 (5)	14 (7)	51	54

Roato[46]	2010	Hip	Mixed fixation methods	Serum markers	Aseptic loosening	15 (NR)	15 (NR)	76	75
von Schewelov[54]	2006	Hip	Mixed fixation methods	Urine markers	Aseptic loosening	33 (19)	127 (76)	50	61
Schneider[41]	1998	Hip	Mixed fixation methods	Serum markers Urine markers	Aseptic loosening	50 (27)	50 (29)	70	68
Stromberg[61]	1996	Hip	Cemented	Radiography	Aseptic loosening	NR (NR)	42 (34)	NR	63
Mont[70]	1995	Knee	Uncemented	Radiography	Aseptic loosening	30 (21)	30 (21)	55	55
Tang[44]	2016	Hip	NR	Serum markers	NR	26 (12)	26 (10)	59	59
Wu[34]	2009	Hip	Mixed fixation methods	Serum markers	Aseptic loosening	43 (24)	16 (12)	67	61
Cenni[51]	2003	Hip	Mixed fixation methods	Serum markers	NR	23 (15)	15 (9)	69	58
Granchi[52]	2000	Hip	NR	Serum markers	NR	13 (9)	11 (5)	64^{median}	44^{median}
Gil-Albarova[62]	1992	Hip	Cemented	Skin test	Aseptic loosening	26 (15)	8 (5)	60	58
Fiorito[36]	2003	Hip	Uncemented	Serum markers	Osteolysis	8 (4)	10 (2)	62	66
Krismer[59]	1996	Hip	NR	Radiography	Aseptic loosening	NR (NR)	NR (NR)	NR	NR
Schneider[49]	1997	Hip	Mixed fixation methods	Serum markers Urine markers	Aseptic loosening	37 (22)	30 (17)	70	64
Steinbeck[71]	2014	Hip	Uncemented	Tissue	Aseptic loosening	16 (5)	2 (2)	64	67
Pellengahr[57]	2001	Hip & Knee	NR	Urine markers	Aseptic loosening	35 (24)	34 (20)	68	67

Table III.II Study characteristics. A study group had aseptic loosening if this was confirmed peroperatively, and osteolysis if this was confirmed radiographically. The green highlighted studies have an ICROMS score ≥18, and fulfil the mandatory criteria. The grey highlighted studies have an ICROMS ≥18 points, but do not fulfil the mandatory criteria. The red highlighted studies have an ICROMS <18 points, and do not fulfil the mandatory criteria. NR = Not reported. ICROMS = Integrated Quality Criteria for Review of Multiple Study Designs. References are cited using superscript.

number of patients included ranged from 18 to 527 with a median of 50 (Interquartile range (IQR) 28 - 75). In the aseptic loosened group, the median number of patients was 26 (IQR 15 - 37; range 8 - 58), and the median number of patients in the control group was 20 (IQR 12 - 36; range 2 - 486). The number of women in each study varied between 10%-100%. The mean age in the aseptic loosened and control group was 64 years (SD 7.5), and 64 years (SD 5.8), respectively [Table III.II].

Serum markers

Twenty-two out of 35 (63%) included studies used serum markers of which three were HQ, 11 were MQ and eight were LQ studies [Table III.III].

Five studies assessed tumour necrosis factor α [TNFα; Table III.III]. A statistically significant increased TNFα was found in loosened implants in one HQ, one MQ, and one LQ study,[32-34] while no difference between groups was found in one MQ and one LQ study [Fig. III.II].[35, 36] Aseptic loosened implants thus seemed to have higher TNFα compared to stable implants.

Four studies assessed receptor activator kappa-B ligand (RANKL) and osteoprotegerin (OPG) [Table III.III]. A statistically significant lower RANKL in loosened implants was found in one MQ study, and no difference was found in one HQ and two MQ studies [Fig. III.III]. A statistically significant higher OPG concentration in the aseptic loosened group was found in one MQ study, while the three other studies (one HQ and two MQ) found no difference between both groups [Fig. III.IV].[32, 35, 37, 38] RANKL and OPG therefore did not seem to be different for aseptic loosened and stable implants.

Three MQ and two LQ studies assessed interleukin-1b (IL-1b) [Table III.III]. A statistically significant higher IL-1b concentration was found in the loosened group in one MQ and one LQ study,[33, 34] while no difference between groups was found in another MQ and LQ study.[35, 36] In one MQ study, IL-1b was detectable in four out of nine patients with aseptic loosened implants, and detectable in one out of thirteen

patients with stable implants [Fig. III.V].[39] Interleukin-1 (IL-1) was used in one HQ study which found comparable levels between loosened and stable implants.[32]

Table III.III

Serum markers	Aseptic loosened group				Stable group			Quality
	Mean	Unit	SD		Mean	Unit	SD	
TNFα	7.1[median]	pg/mL	11.6	>	1.5[median]	pg/mL	1.3	HQ[32]
	32.7	pg/mL	32.4	>	22.9	pg/mL	18.7	MQ[33]
	32.2	pg/mL	50.6	=	15.9	pg/mL	7.4	MQ[35]
	37	pg/mL	18.1	>	8.1	pg/mL	5.5	LQ[34]
	4.32	pg/mL	5.2	=	3.84	pg/mL	1.13	LQ[36]
TNF mRNA	No difference			=	No difference			LQ[44]
TNFbeta	23175	pg/mL	8873	=	21120	pg/mL	13657	LQ[36]
IL-1	0.4	pg/mL	0.37	=	0.29	pg/mL	0.34	HQ[32]
IL-1b	3.7	pg/mL	5.5	>	1.5	pg/mL	2	MQ[33]
	1.75		1.44	=	0.97		0.29	MQ[35]
	Detectable in 4/9 patients			=	Detectable in 1/13 patient			MQ[39]
	9.1	pg/mL	3.9	>	6.4	pg/mL	4.1	LQ[34]
	2.15	pg	1.37	=	2.26	pg	0.89	LQ[36]
IL-2r	469	µ/mL	155	=	515	µ/mL	160	MQ[40]
IL-6	8.9	pg/mL	13.2	=	3.5	pg/mL	0.7	HQ[32]
	4.0	pg/mL	5.3	=	4.1	pg/mL	6.1	MQ[40]
	2.86	pg/mL	1.95	=	4.58	pg/mL	4.02	LQ[36]
IL-8	14.7	pg/mL	9	>	8.1	pg/mL	4.7	MQ[33]
IL-11	0	pg/mL		=	1.22	pg/mL	2.57	LQ[36]
OPG	7.9	pmol/L	3	=	7.5	pmol/L	2.2	HQ[32]
	No difference			=	No difference			MQ[38]
	26.7		19.9	=	24.1		5.2	MQ[35]
	4198	pg/mL	286	>	2397	pg/mL	1632	MQ[37]
RANKL	19.1	pmol/L	23.9	=	44.8	pmol/L	55	HQ[32]
	No difference			=	No difference			MQ[38]
	109.3		212.7	=	189		86.1	MQ[35]
	1483.0	pg/mL	1179	<	3312	pg/mL	2211	MQ[37]
RANKL mRNA	7.4 times higer in AL group			=	7.4 times higher in AL group			LQ[44]
hsCRP	1.86	mg/dL	4.76	=	0.24	mg/dL	0.19	HQ[32]
GM-CSF	3.97	pg/mL	5.33	=	Not detectable	pg/mL		MQ[40]
Elastase	58.91	ng/mL	46.78	=	56.56	ng/mL	44.95	MQ[40]
NTX	25.671		27.528	=	20.192		4.962	MQ[35]
	27.22	nM BCE	5.15	>	19.53	nMB CE	6.32	HQ[43]
PICP	-1251.864		308.54	=	-1444.529		169.25	MQ[35]
	107.5	ng/mL	70.4	=	82.2	ng/mL	32.8	LQ[41/49]
PINP	No difference			=	No difference			MQ[42]
PIIINP	No difference			=	No difference			MQ[39]
CCL18	66	nM		=	78	nM		HQ[45]
CHIT1	98	nM		>	39	nM		HQ[45]
CTX	0.56	ng/mL	0.2	>	0.27	ng/mL	0.14	HQ[43]
βCTX								
Femoral loosening	0.43[median]	ng/mL	31-0.56[IQ]	=	0.33[median]	ng/mL	22-0.48[IQ]	MQ[42]
Acetabulur loosening	0.45[median]	ng/mL	23-0.57[IQ]	=	0.33[median]	ng/mL	29-0.45[IQ]	MQ[42]
OC	28.9	ng/mL	10.38	>	18.66	ng/mL	5.05	HQ[43]
	No difference			=	No difference			MQ[42]
	Higher			>	Lower			LQ[41/49]
Osteoclastogenesis	134		64	>	22		21	LQ[46]
Osteoclasts rate, day 7	23.4	%	5.3	>	3.4	%	0.5	LQ[44]
Osteoclasts rate, day 14	82.5	%	14.7	>	17.7	%	5.6	LQ[44]
Osteoclasts rate, day 21	92.8	%	20.6	>	32.1	%	9.3	LQ[44]
Bone erosion rate day 14	43.40	%		>	12.90	%		LQ[44]
Bone erosion rate day 21	88.40	%		>	31.60	%		LQ[44]
CD4+ (%)	Higher			>	Lower			LQ[46]
CD8+ (%)	Higher			>	Lower			LQ[46]
CD11a								MQ[47]
Lymphocytes	1140.9		885.4	=	1086.4		456	
Monocytes	1901.5		1269	=	2637.4		3064.7	
Granulocytes	1344.2		1259.9	=	812.3		318.4	

Table III.III continued

CD11b								MQ[47]
Lymphocytes	9.5		5	=	12.4		10	
Monocytes	346.3		256	=	263.6		127.4	
Granulocytes	416.5		174.9	>	149.1		99.6	
CD11c								MQ[47]
Lymphocytes	5.1		1	=	6.6		5.5	
Monocytes	409.7		242.3	>	116.1		188.4	
Granulocytes	228		74	>	98.2		77.1	
CD16+	22.4	%	10.6	>	15.8	%	5.7	LQ[34]
CD14++CD16-	68.7	%	11.3	=	75.4	%	5.4	LQ[34]
CD14+CD16+	13.7	%	7.5	>	9.2	%	5.6	LQ[34]
CD18								MQ[47]
Lymphocytes	56.4		45.5	<	278.8		129.5	
Monocytes	122.2		81.5	<	1026.9		512.2	
Granulocytes	60.8		20.3	<	423.7		223.5	
CD25 (%)	No difference			=	No difference			LQ[46]
CD62L								MQ[47]
Lymphocytes	21	10.9		=	33.4		13	
Monocytes	71.3	43.5		=	88.7		33.2	
Granulocytes	88.1	61.4		=	124.3		39.2	
CD69 (%)	No difference			=	No difference			LQ[46]
TRAP-5b	4.23	U/L	1.38	>	2.73	U/L	0.78	MQ[68]
	4.17	U/L		>	3.44	U/L		MQ[48]
ICTP	7.04	ng/mL		>	5.15	ng/mL		MQ[48]
Bone ALP	No difference			=	No difference			MQ[42]
	123.8	U/L	42.5	=	110.4	U/L	28	LQ[41/49]
MCP-1	Higher			=	Lower			LQ[44]
Hyaluronic acid	779.3	ug/L	475.8	>	112.9	ug/L	42.5	MQ[39]
Cobalt	22.1	nmol/L	28.8	>	6.4	nmol/L	2.2	MQ[69]
	5.9		1^{SEM}	=	4.5		0.6^{SEM}	MQ[52]
Chromium	21.1	nmol/L	29.7	=	16.9	nmol/L	9.7	MQ[69]
	8.0		1.3^{SEM}	>	5.3		0.7^{SEM}	MQ[52]
Sclerostin	No difference			=	No difference			MQ[48]
DKK-1	No difference			=	No difference			MQ[48]
Calcium	2.32	mmol/L	0.226	=	2.36	mmol/L	0.112	LQ[41/49]
Creatinine	7.69	nmol/ml	6.5	=	8.76	nmol/ml	4.85	LQ[41/49]
D-dimer	132	ng/mL	21^{SEM}	>	42	ng/mL	8.5^{SEM}	LQ[51]
PAI-1	2.3	U/mL	1.1^{SEM}	>	8.1	U/mL	1.8^{SEM}	LQ[51]
PDGF-AB	2.4	ng/mL	0.35^{SEM}	=	1.9	ng/mL	0.23^{SEM}	LQ[51]
Protein C	108	%	4^{SEM}	=	114	%	6.6^{SEM}	LQ[51]
Antithrombin III	99	%	2.2^{SEM}	=	101	%	2.0^{SEM}	LQ[51]
PGE2	1330	pg/mL	1097.4	=	2021	pg/mL	1.046	LQ[36]
MMP-1	3.69	pg/mL	1.75	=	4.1	pg/mL	1.44	LQ[36]
PHA	5.3		0.8^{SEM}	=	4.9		0.9^{SEM}	MQ[52]
AIM-V	62.8		4.7^{SEM}	>	28.3		3.5^{SEM}	MQ[52]

Table III.III Serum markers results table. Some studies did not report the unit of the outcome. If the outcome was significantly higher in the aseptic loosened group, the study was marked with > in green. If the outcome was significantly lower, the study was marked with < in red. If no difference between both groups was found, the study was marked with = in yellow. Numbers in superscript refer to the reference list.
SD = standard deviation; SEM = standard error of the mean; HQ = high quality study; MQ = medium quality study; LQ = low quality study

Figure III.II Mean serum TNFα in the aseptic loosened and control group. Differences were assessed at diagnosis of loosening or before revision surgery. The blue, round shaped point estimates represent the AL groups and the yellow, diamond shaped point estimates represent the control groups. Error bars represent 95% confidence intervals. TNFα = tumour necrosis factor α; AL = aseptic loosening; HQ = High quality; MQ = Moderate quality; LQ = Low quality.

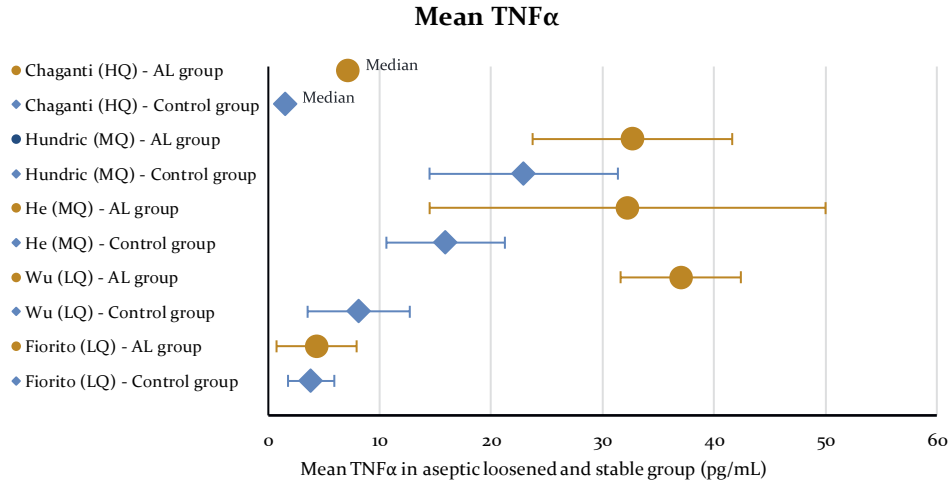


Figure III.III Mean serum RANKL in the aseptic loosened and control group. Differences were assessed at diagnosis of loosening or before revision surgery. The blue, round shaped point estimates represent the AL groups and the yellow, diamond shaped point estimates represent the control groups. Error bars represent 95% confidence intervals. *value displayed is the true value divided by 10. RANKL = receptor activator factor kappa-B ligand; AL = aseptic loosening; HQ = High quality; MQ = Moderate quality.

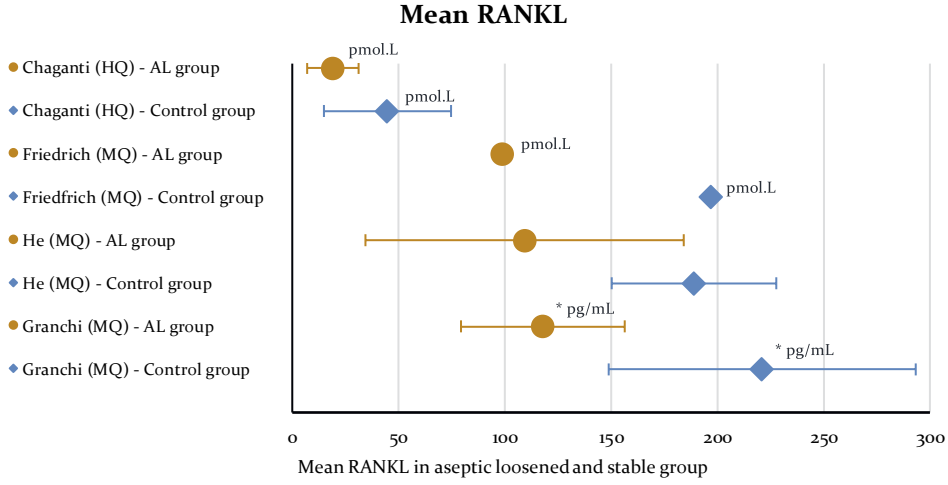


Figure III.IV Mean serum OPG in the aseptic loosened and control group. Differences were assessed at diagnosis of loosening or before revision surgery. The blue, round shaped point estimates represent the AL groups and the yellow, diamond shaped point estimates represent the control groups. Error bars represent 95% confidence intervals. *value displayed is the true value divided by 100. OPG = osteoprotegerin; AL = aseptic loosening; HQ = High quality; MQ = Moderate quality.

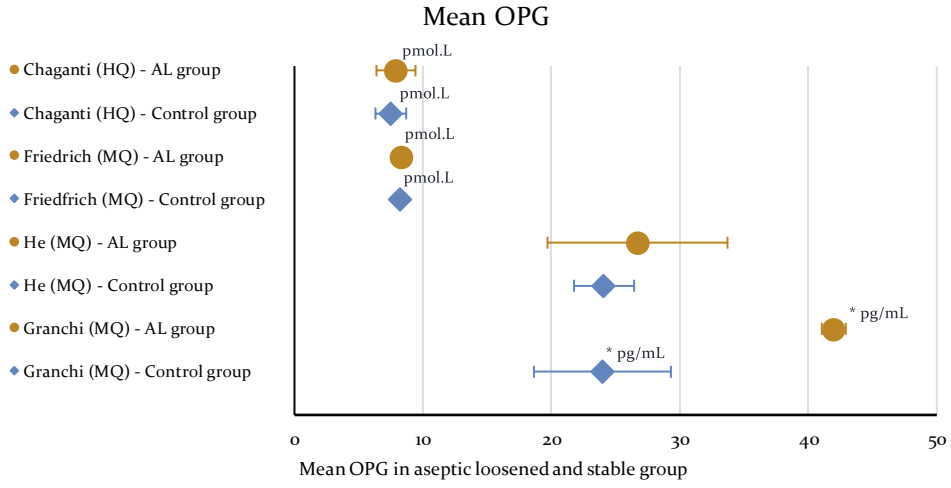


Figure III.V Mean serum IL-1b in the aseptic loosened and control group. Differences were assessed at diagnosis of loosening or before revision surgery. The blue, round shaped point estimates represent the AL groups and the yellow, diamond shaped point estimates represent the control groups. Error bars represent 95% confidence intervals. IL-1b = interleukin-1b; AL = aseptic loosening; MQ = Moderate quality; LQ = Low quality.

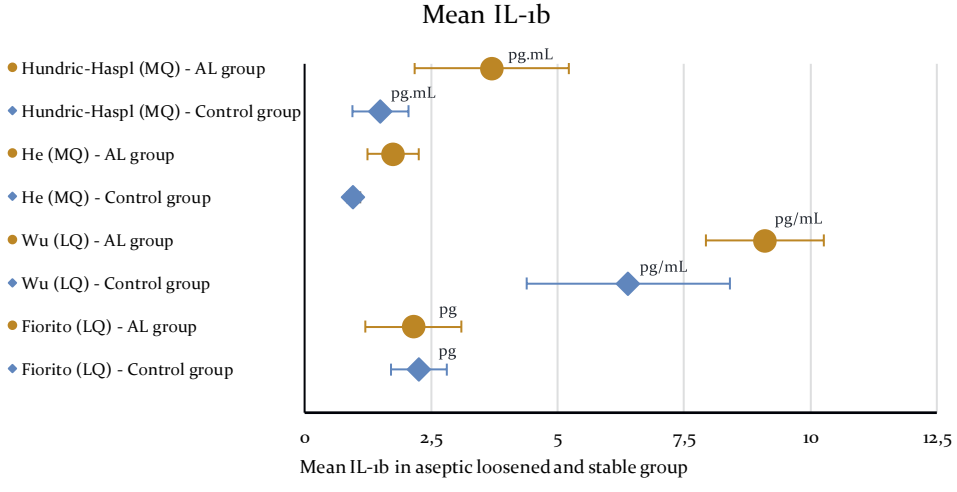
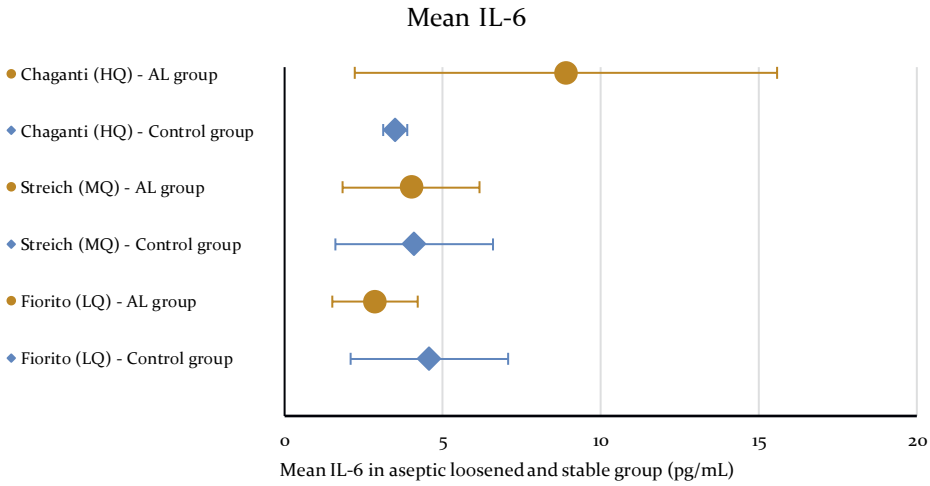


Figure III.VI Mean serum IL-6 in the aseptic loosened and control group. Differences were assessed at diagnosis of loosening or before revision surgery. The blue, round shaped point estimates represent the AL groups and the yellow, diamond shaped point estimates represent the control groups. Error bars represent 95% confidence intervals. IL-6 = interleukin-6; AL = aseptic loosening; MQ = Moderate quality; LQ = Low quality.



Interleukin-6 was studied in one HQ, one MQ and one LQ study, and none of these studies found a difference between both groups [Fig. III.VI].[32, 36, 40] Other interleukins studied were interleukin-2r, interleukin-8, and interleukin-11 [Table III.III]. Evidence showing whether interleukin levels can discriminate between loosened and stable implants is thus limited.

Procollagen type I C-terminal peptide (PICP), procollagen type I N-terminal peptide (PINP), and procollagen type III N-terminal peptide (PIIINP) were examined in two studies (one MQ, one LQ), one MQ study, and one MQ study, respectively [Table III.III]. No difference in any of these markers was found between patients with loosened versus stable implants, indicating poor usability of these markers to identify patients with aseptic loosening.[35, 39, 41, 42]

Osteocalcin was compared between aseptic loosened and stable implants in one HQ, one MQ and one LQ study [Table III.III]. The osteocalcin was statistically significantly higher in the aseptic loosened group in the HQ and LQ study[41, 43] while no difference was found in the MQ study.[42] Osteocalcin might thus have the potential to discriminate between loosened and stable implants.

In addition to these more frequently studied serum markers, over 40 other serum markers were studied by only one study [Table III.III].[32-34, 36, 39, 40, 44-52]

Urine markers

Ten out of 35 studies (29%) included urine markers of which six were of MQ and four were of LQ [Table III.IV].

N terminal telopeptide (NTX) was assessed in six studies. NTX was assessed in a longitudinal fashion in one MQ study and this MQ study did not find a difference at any time point between the loosened and stable group, nor did two other MQ studies.[22, 53, 54] One MQ study compared aseptic loosened acetabular cups to stable cups, and aseptic loosened femoral stems to stable stems, and found that the

Table III.IV Urine markers results table. Some studies did not report the unit of the outcome. If the outcome was significantly higher in the aseptic loosened group, the study was marked with > in green. If the outcome was significantly lower, the study was marked with < in red. If no difference between both groups was found, the study was marked with = in yellow. Numbers in superscript refer to the reference list.
95%CI = 95% Confidence Interval; SD = Standard deviation; IQR = interquartile range; RoB = risk of bias; HQ = High quality study; MQ = Moderate quality study; LQ = Low quality study.

Urine markers	Aseptic loosened group				Stable group			Quality
	Mean	Unit	95%CI		Mean	Unit	95%CI	
NTX	No difference			=	No difference			MQ[22]
	73[median]	nmol/mmol creatinine		>	25[median]	nmol/mmol creatinine		MQ[55]
	51.4	nmol/mmol creatinine		=	53	nmol/mmol creatinine		MQ[53]
Femoral loosening	61	nm BCE/mM creatinine	40.9-72.1	>	39.9	nm BCE/mM creatinine	27.0-52.7	MQ[42]
Acetabular loosening	62.3	nm BCE/mM creatinine	32.0-72.1	=	42.8	nm BCE/mM creatinine	28.1-53.2	MQ[42]
	34	nM BCE/nM	12[SD]	=	29	nm BCE/nM	15[SD]	LQ[54]
	96	nmol/mmol creatinine		>	40	nmol/mmol creatinine		LQ[41]
αCTX	Higher			>	Lower			MQ[22]
	0.61[median]	ng/mL		=	0.63[median]	ng/mL		MQ[48]
βCTX	No difference			=	No difference			MQ[22]
CTX (NS)	94.3[median]	nmol/mmol creatinine		=	67.0[median]	nmol/mmol creatinine		MQ[53]
DPD	Lower			<	Higher			MQ[22]
	9.17[median]	nmol/mmol creatinine		>	5.72[median]	nmol/mmol creatinine		MQ[53]
	8.2	nmol/mmol creatinine		=	8.2	nmol/mmol creatinine		MQ[56]
Femoral loosening	61.0	nmol/mM creatinine	40.9-72.1	=	39.9	nmol/mM creatinine	27.0-52.7	MQ[42]
Acetabular loosening	62.3	nmol/mM creatinine	32.0-72.1	=	42.8	nmol/mM creatinine	28.1-53.2	MQ[42]
Male	7.8	nmol/mmol creatinine		=	5.8	nmol/mmol creatinine		LQ[57]
Female	8.6	nmol/mmol creatinine		=	10.1	nmol/mmol creatinine		LQ[57]
IL-6	Higher			>	Lower			MQ[22]
IL-8	No difference			=	No difference			MQ[22]
OPG	No difference			=	No difference			MQ[22]
PYR	No difference			=	No difference			MQ[22]
PYD	Higher			>	Lower			LQ[41]
DPYD	Higher			>	Lower			LQ[41]

NTX was higher in the aseptic loosened groups, but this difference only reached statistical significance in the femoral group.[42] Higher NTX levels of loosened implants was found in one MQ and one LQ study.[41, 55] Overall, NTX thus tended to be higher in aseptic loosened implants [Fig. III.VII].

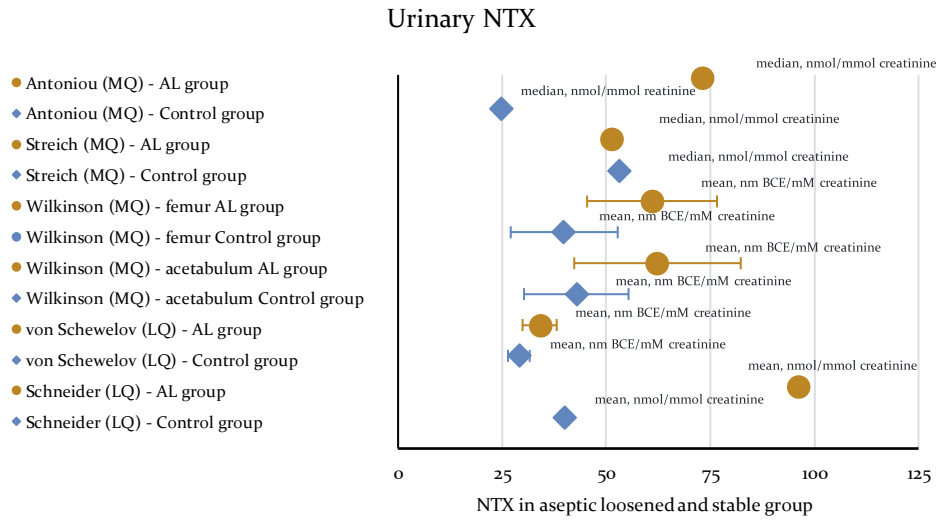
Urinary C terminal telopeptide (CTX) was assessed in three MQ studies (Table III.IV). αCTX was statistically higher in loosened implants in one MQ study,[22] while no difference between groups was found in another MQ study.[48] One study did not specify whether α- or β-crosslaps were assessed but found no difference in CTX between groups.[53] Evidence supporting the use of urinary CTX to assess aseptic loosening was thus limited.

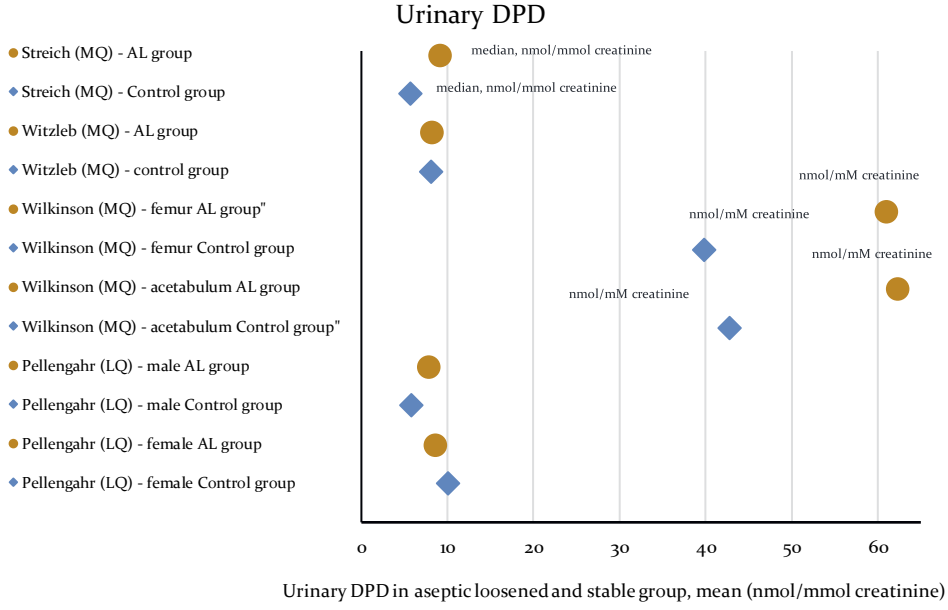
Urinary deoxypyridinoline (DPD) was compared between aseptic loosened and stable implants in four MQ studies and one LQ study [Table III.IV]. A lower DPD concentration of loosened implants compared to stable implants was found in one MQ study,[22] no difference between groups was found in two MQ studies,[42, 56] and a higher DPD concentration of loosened implants was found in one MQ study.[53] One LQ study separated male and female patients and found a higher DPD in male patients with aseptic loosened implants, but a lower DPD in female patients with aseptic loosened implants compared to male and female patients with stable implants, respectively.[57] These results suggest poor usability of DPD as a marker to assess aseptic loosening [Fig. III.VIII].

Radiological markers

Seven out of 35 studies (20%) used radiological markers to compare aseptic loosened and stable implants of which three were HQ, one was MQ, and three were LQ studies. Migration was assessed in two HQ studies and one LQ study using EBRA-FCA (one HQ and one LQ study)[58, 59] or conventional radiographs (one HQ study).[60] Migration was higher in the loosened group compared to the stable group in all three studies and could thus be used a marker to discriminate between loosened and stable implants.

Figure III.VII and III.VIII. Mean urinary NTX and DPD in the aseptic loosened and control group. Differences were assessed at diagnosis of loosening or before revision surgery. The blue, round shaped point estimates represent the AL groups and the yellow, diamond shaped point estimates represent the control groups. Error bars repr esent 95% confidence intervals. NTX = N-terminal telopeptide; DPD = deoxypyridinoline; AL = aseptic loosening; MQ = Moderate quality; LQ = Low quality.





Bone Mineral Density (BMD) was compared in one HQ and one MQ study. The BMD was measured at the lumbar spine,[43] around the cup,[42] around the femoral component,[42] and at different locations of the tibia.[43] The BMD did not differ at the lumbar spine (HQ study) and did not differ around the cup (MQ study) between groups. The BMD around the femoral components was significantly lower in the aseptic loosened group (MQ study). The BMD at 4%, 14%, and 38% of the tibial length measured from the distal tibial end was assessed in one HQ study.[43] This study found that the BMD was lower at 14% of the tibial length and at 38% of the tibial length, only the cortical BMD was significantly lower in the aseptic loosened group. The usability of BMD as a marker to discriminate between aseptic loosened and stable implants was thus limited.

Lytic lesions and radiolucent lines were compared between both groups in a HQ study which found a significant increase in lytic lesions and radiolucent lines in the aseptic loosened group.[60] Demarcation of bone-cement and progressive radiolucency at the tip of the cement was analysed in a LQ study using conventional anteroposterior and lateral radiographs at one year follow-up, and found that loosened stems showed significantly more demarcation of bone-cement and progressive radiolucency at the tip of the cement compared to stable stems.[61] Lytic lesions, radiolucent lines and demarcation of bone-cement were suggestive for aseptic loosening.

Skin markers

Skin markers were assessed in one LQ study in patients with loosened and stable cemented THRs, and a higher reaction to polymethylmethacrylate bone cement was found in patients with loosened implants, indicating that a lymphocyte-mediated immune response was induced in loosened cemented implants.[62] Skin markers might be able to discriminate between loosened and stable implants but only one study using this marker was included in the present review.

Discussion

Serological, urine and radiological markers for aseptic implant loosening of total hip and total knee implants were evaluated for their ability to discriminate between well fixed and loosened implants. Both serological and urine markers are used as a proxy for implant-bone stability. Serum markers were most frequently studied. For that matter, TNFα, IL-1b, and osteocalcin were elevated in patients with aseptic loosening of a primary THR or TKR in most studies. Urinary NTX was the only urine marker found in our review to discriminate between aseptic loosened and stable implants. In radiological studies, migration was most frequently studied and aseptic loosened implants migrated more in all studies compared to stable implants. Beside migration, radiolucent lines surrounding the stem or to a lesser extent the socket were suggestive for aseptic loosening.

A higher concentration of the serum markers TNFα, IL-1b, and osteocalcin in aseptic loosened implants was found in several studies but a few other studies did not detect a difference. Other fundamental research may help to understand the role of these markers in the mechanism resulting in aseptic loosening and osteolysis. TNFα and IL-1b play an important role in the inflammation and especially TNFα has shown to induce osteolysis in vivo.[63] Schwarz et al. compared mice that overproduce TNFα with mice that had a defective TNFα signalling pathway and found that the mice that were overexpressed to TNFα showed an increased osteolysis, whereas the defective mice showed little osteolysis.[63] Osteocalcin on the other hand is secreted by osteoblasts and plays an important role in the bone formation.[64] A recent murine study assessed osteocalcin and implant loosening in a longitudinal fashion and found a correlation between serum osteocalcin and implant fixation.[65] The present review suggests that an increased serum TNFα, IL-1b, and osteocalcin level could be indicative for aseptic loosening.

In contrast to the many serum markers studied, only a few urine markers were studied of which NTX, CTX and DPD were most popular. Urinary NTX showed the

most promising results in discriminating between aseptic loosened and stable implants [Fig. III.VIII], whereas urinary DPD showed conflicting results and seemed to have the least discriminative ability [Fig. III.IX]. This finding was supported by a canine study which assessed urinary CTX, NTX and DPD.[66] This canine study concluded that urinary NTX was the most discriminatory resorption bone marker in focal malignant osteolysis.[66] In the first 6 months, urinary NTX appears to be elevated in all patients following THR or TKR, but levels return to normal hereafter making these markers potentially usable to identify loosening after 6 months.50 Interestingly, Ross et al. found that preoperative αCTX had the highest accuracy in identifying patients at risk for aseptic loosening, suggesting that at risk patients could be identified prior to the primary joint replacement surgery.[22] However, none of the other included studies found a difference in CTX between groups. Future studies should further investigate whether NTX and CTX urine markers can discriminate between aseptic loosened and stable implants.

Currently, radiological assessment of an implant is the most used in clinical practice to identify for aseptic loosening. Radiolucent lines, cysts and migration are suggestive for loosening. However, most of these characteristics become only visible at an advanced stage of osteolysis. The present review found three studies using migration of which two used EBRA-FCA and one study used measurements on conventional radiographs. Other tests such as radiostereometric analysis (RSA) can measure micromotion, and high initial migration or continuous migration measured with RSA is suggestive for early aseptic loosening of an implant.[12, 13, 67] Although RSA has the ability to identify patients at risk for aseptic loosening as early as one or two years after the primary surgery, this technique is costly. Secondly, RSA needs tantalum markers to be inserted in the periprosthetic bone. Therefore, other more accessible serological and urine markers could be valuable to identify patients at risk for aseptic loosening as these are readily available and have the potential to track disease progression or to function as a target for future treatment.

Several limitations of this review should be noted. First, only a limited number of the included studies were of good methodological quality (HQ). The lack of HQ studies emphasises the need for well-designed studies to assess the ability of these markers to discriminate between loosened and stable implants. Three specific RoB scoring criteria were frequently lacking in the included studies which were a blinded assessment of primary outcome, the assessment of incomplete data, and the reporting of limitations. Although blinding may not always be possible, future studies should clearly assess missing data, eligible patients, excluded patients, and the limitations of their study. Second, there was significant variability between studies in the methods used to measure serum and urine markers, and in the reporting of the outcomes which limited the ability to pool data. This was mostly due to a difference in the units of measurement and due to succinct reporting of outcomes with some studies only reporting whether there was a difference accompanied with p-value but without absolute numbers or a figure. We recommend future studies to report their results uniformly to allow between study comparisons and to report absolute numbers of their outcome. Third, the present systematic review included studies which used markers to assess loosened and stable implants following the search strategy from two previously conducted systematic reviews.[26, 27] Studies that did not use the term marker (or a related term) were thus not included, which may explain that only one study on skin markers was found, but searching for every individual marker or test was unfeasible considering the large number available. Last, several markers were assessed by only a single study. As some of these markers were significantly different between aseptic loosened and stable implants, we recommend future studies to assess these possible markers of aseptic loosening.

The present review examined several markers in their ability to identify implants with osteolysis and aseptic loosening in THRs and TKRs. Especially serum TNFα, IL-1b and osteocalcin showed a promising role in discriminating between loosened and stable implants and urinary NTX as one of the few urine markers. Moreover,

migration was the most frequent radiological marker, which was increased in loosened implants in all studies with an increased incidence of radiolucent lines being another marker. We therefore recommend future studies to study these serum, urine, and radiological markers in a longitudinal fashion to assess whether progression of loosening is associated with an increase or decrease of these markers. In particular, high-quality studies assessing the usability of these markers are needed.

Acknowledgements

None

Appendix A and B accessible digitally

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