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GENERAL ORTHOPAEDICS

Biomarkers to discriminate between aseptic loosened and stable total hip or knee arthroplasties: a systematic review

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- *Background:* Loosening is a major cause for failure of total hip and total knee arthroplasties (THAs/TKAs). Preemptive diagnostics of asymptomatic loosening could open strategies to prevent gross loosening. A multitude of biomarkers may discriminate between loosened and stable implants, but it is unknown which have the best performance. The present systematic review aimed to assess which biomarkers have shown the most promising results in discriminating between stable and aseptic loosened THAs and TKAs.
- *Methods:* PubMed, Embase, Web of Science, Cochrane Library, and Academic Search Premier were systematically searched up to January 2020 for studies including THA/TKA and biomarkers 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.
- *Results:* Twenty-eight (three high-quality) studies were included, reporting on a median of 48 patients (interquartile range 28–69). Serum and urine markers were evaluated in 22 and 10 studies, respectively. Tumor necrosis factor α and osteocalcin were significantly higher in loosened compared with stable implants. Urinary N-terminal telopeptide had significantly elevated levels in loosened prostheses.
- *Conclusion:* Several serum and urine markers were promising in discriminating between loosened and stable implants. We recommend future studies to evaluate these biomarkers in a longitudinal fashion to assess whether progression of loosening is associated with a change in these biomarkers. In particular, high-quality studies assessing the usability of these biomarkers are needed.

Keywords: arthroplasty, loosening, biomarkers

Introduction

Aseptic loosening is the leading cause for revision of total hip and total knee arthroplasties (THAs/TKAs) reported in national arthroplasty registries (1, 2). Aseptic loosening may have a multitude of causes including factors related to implant design, surgical technique, and genetic predisposition (3, 4, 5, 6, 7, 8, 9). For the implant-related

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causes, polymer, bone cement, and metal wear particles released due to repetitive motion of the joint can induce inflammation and osteolysis (10, 11, 12). The latter may differ between individuals due to reaction of the foreign body inflammatory response (4, 13). Other mechanisms influencing aseptic loosening such as stress shielding, micromotion, high fluid pressure, and endotoxins have been proposed as well (14, 15, 16, 17).

Ultimately, aseptic loosening can be confirmed intraoperatively, but any diagnostic before extensive revision surgery helps in the decision to perform surgery in patients with complaints of their implant. The presence of pain following THA or TKA could be attributed to various causes and is not specifically indicative of aseptic loosening. Signs of implant loosening include implant migration, radiolucent lines, and cysts, but few other markers are available to diagnose aseptic loosening (17, 18, 19, 20, 21, 22). Besides implant migration, these radiologic signs may only become visible after several years and patients could be asymptomatic up to the point that major revision surgery is required (23, 24). Early identification of loosened implants is important to prevent complications, as late diagnosis could increase the incidence of complications such as fractures with an increased mortality risk following revision surgery as a consequence (25). 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 (26, 27, 28, 29, 30). Further, preemptive diagnostics of implant loosening in asymptomatic patients could not only potentially open strategies to prevent more severe implant loosening by acting as a therapeutic target but also have the potential to monitor disease progression (31).

Implant loosening is a complex mechanism that is controlled by an intricate balance of biomechanical forces and a balance between osteoblasts and osteoclasts. The latter can be quantified by objective biomarkers such as serum and urine markers (11, 32, 33, 34). These biomarkers could provide objective information on biological processes while being minimally invasive and readily available (35). Several studies assessed these biomarkers to discriminate between aseptic loosened and stable implants. However, the number of patients included in these studies was mostly too small to draw any conclusions about the validity of the biomarker to differentiate between aseptic loosened and stable implants. Moreover, a wide variety of biomarkers in THAs and TKAs have been studied, making it difficult to ascertain the most promising biomarkers 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 biomarkers to differentiate between aseptic loosened and stable implants. However, these reviews did not assess the quality of the included studies and also need updating to determine the most promising biomarker (36, 37). Further, these reviews did not identify any validated biomarkers. Therefore, the present systematic review aimed to identify the most frequently studied biomarkers that are able to discriminate between aseptic loosened and stable THAs and TKAs and therefore have the most promising results in differentiating between these groups.

Materials and methods

This systematic review was performed in concordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) 2020 statement and was registered with Prospero (CRD42019133137) prior to the screening of studies (38, 39). No funding was acquired for the present review. Level of evidence: 3a.

Search strategy and selection

The 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 January 30, 2020, without any restriction on publication date. Based on the previous systematic reviews, the current search was composed of three components: (i) THA or TKA (e.g. 'Arthroplasty replacement hip'(Mesh)), (ii) aseptic loosening osteolysis or wear (e.g. 'Osteolysis'(Mesh), 'Prosthesis failure'(Mesh)), and (iii) determinants for aseptic loosening (e.g. 'Biomarkers'(Mesh)); see Appendix A (see the section on supplementary materials given at the end of this article) 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. Inclusion criteria were studies comprising primary THAs and/or TKAs 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 not using biomarkers measured in serum or urine were excluded. Moreover, studies without aseptic loosening as an outcome as well as studies among patients with an infection, tumor 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 (S.H. and P.v.S.). The authors of the studies reviewed 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.). Data extracted were author, title, year of publication, country of the first author, study design,

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specific joint (i.e. THA and/or TKA), and the biomarker used to discriminate between loosened and stable implants. Data on the number of patients in the aseptic loosened and the control group were collected as well as on the percentage of female patients, the mean age of both groups, and the primary diagnosis of the patients. Fixation method and hip weight-bearing surface were collected in THA studies. The outcomes of studies were collected in the original unit including CI, S.E., or S.D., if available. If the S.E. was not reported, it was calculated by dividing the S.D. by the square root of the number of patients included (40). If absolute values were not reported in the text but only in a graph, the values were estimated from the graph. If the same biomarker was reported by three or more studies, results were plotted in a forest plot. Differences in biomarker values 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.

Assessment of risk of bias

The risk of bias (RoB) was assessed independently by both reviewers (SH and PvS.) using the Innovative Tools for Quality Assessment: Integrated Quality Criteria for Review of Multiple Study Designs (ICROMS) (41). The ICROMS comprises seven dimensions with three to six specific criteria per dimension. Every study design has to 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, considering the rationale that the RoB could be taken into account when weighting study results, whereas 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 fulfill the mandatory criteria were classified as moderate-quality (MQ) studies. Studies scoring less than 18 points were classified as low-quality (LQ) studies. There were no studies that fulfilled all the mandatory criteria but failed to score at least 18 points.

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 THA or TKA, 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 an outcome, resulting in 248 reports to be assessed for eligibility. One report could not be retrieved. Of the 247 reports, 219 were excluded as 171 did not include biomarkers measured in serum or urine, 23 did not involve aseptic loosening, 23 did not have a control group with a stable primary THA/TKA without a joint infection, one comprised metal-on-metal hip implants, and one was in Chinese, leaving 28 studies to be included (Fig. 1).

Risk of bias within studies

Three 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 fulfill the mandatory criteria and were classified as MQ studies. Ten studies scored less than 18 points and were classified as LQ studies (Table 1). The mean ICROMS score was 19 points (S.D. 2.9). Most studies failed to fulfill the mandatory criteria due to not addressing incomplete data. In addition, only a few studies performed a blinded assessment of the outcomes (Table 1).

Study characteristics

Twenty-four studies included only THA and four studies included both THA and TKA. Serum markers were used in 22 studies and urine markers in 10 studies. The number of patients per study ranged from 18 to 160 with a median of 48 (Interquartile range (IQR): 28–69). Two studies used a cohort design, and 26 studies used a case–control design. In the aseptic loosened group, the median number of patients was 25 (IQR: 15–37), and the median number of patients in the control group was 19 (IQR: 12–32). The number of women in each study varied from 10% to 100%. The mean age in the aseptic loosened and control group was 66 years (S.D. 7.1), and 65 years (S.D. 5.7), respectively (Table 2).

Serum markers

Twenty-two out of 28 (78%) included studies used serum markers, of which 3 were HQ, 11 were MQ, and 8 were LQ studies (Table 3).

Five studies assessed tumor necrosis factor α (TNFα). A statistically significant increased TNFα was found in loosened implants in one HQ, one MQ, and one LQ study (42, 43, 44), while no difference between groups was found in one MQ and one LQ study (Fig. 2) (45, 46). 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 3). A statistically significant lower RANKL in loosened implants was found in one MQ study, and no difference

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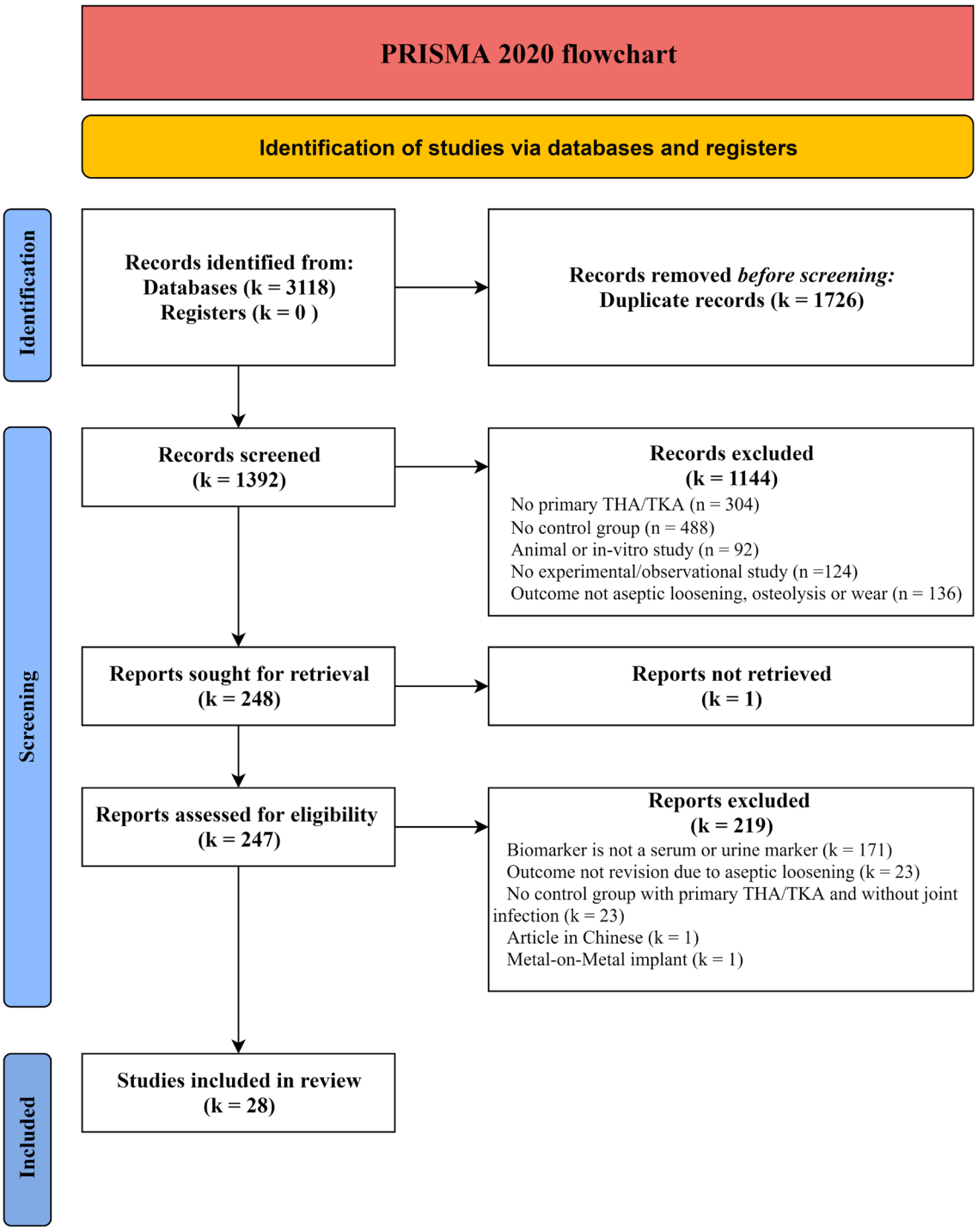

Figure 1

PRISMA 2020 flowchart. THA, total hip arthroplasty; TKA, total knee arthroplasty.

was found in one HQ and two MQ studies (Fig. 3). 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. 4) (42, 45, 47, 48). RANKL and OPG therefore did not seem to show consistent differences between aseptic loosened and stable implants across studies.

Three MQ and two LQ studies assessed interleukin 1 beta (IL-1β) (Table 3). A statistically significant higher IL-1β concentration was found in the loosened group in one MQ

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Table 1 Risk of bias. A score of 0 (did not fulfill the criterion), 1 (unclear if the criterion is fulfilled), or 2 (did fulfill the criterion) could be given to every criterion.

Study	Year	1A*	2E*	3E	3F	3G*	4C*	5B	6C	7A	7B	7C	7D	7E	ICROMS score
Low RoB/HQ															
Chaganti *et al.* (42)	2013	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Trehan *et al.* (55)	2017	2	2	0	2	2	2	2	2	2	2	2	2	2	24
Morakis *et al.* (53)	2011	2	2	0	2	2	2	2	2	2	0	2	2	2	22
Moderate RoB/MQ															
Hundric-Haspl *et al.* (43)	2006	2	2	0	2	2	0	2	2	2	2	2	2	2	22
Ovrenovits *et al.* (57)	2015	2	2	0	2	2	0	2	2	2	2	2	1	2	21
Savarino *et al.* (73)	2010	2	0	2	2	1	2	2	2	2	0	2	2	2	21
Ross *et al.* (31)	2018	2	2	0	2	0	2	1	2	2	2	2	1	2	20
Lawrence *et al.* (58)	2015	2	2	0	2	2	0	2	2	2	0	2	2	2	20
Streich *et al.* (50)	2003	2	2	0	2	2	0	2	2	2	0	2	2	2	20
Antoniou *et al.* (65)	2000	2	1	0	2	2	0	2	2	2	1	2	2	2	20
Friedrich *et al.* (48)	2017	2	2	0	2	2	0	2	0	2	2	2	1	2	19
He *et al.* (45)	2013	2	2	0	2	2	0	1	2	2	0	2	2	2	19
Streich *et al.* (63)	2009	2	2	0	2	2	0	2	2	1	0	2	2	2	19
Wilkinson *et al.* (52)	2003	2	2	0	2	2	0	2	2	1	0	2	2	2	19
Witzleb & Menschikowski (66)	2001	2	1	0	2	1	0	2	2	2	1	2	2	2	19
Granchi *et al.* (47)	2006	2	0	0	2	2	0	2	2	2	0	2	2	2	18
Moreschini *et al.* (49)	1997	2	2	0	2	2	0	2	2	2	0	2	2	0	18
Kreibich *et al.* (74)	1996	2	2	0	2	2	0	2	2	2	0	2	2	0	18
High RoB/LQ															
Roato *et al.* (56)	2010	2	1	0	0	2	0	2	2	2	0	2	2	2	17
von Schewelov *et al.* (64)	2006	2	1	0	2	2	0	2	1	1	2	2	0	2	17
Schneider *et al.* (51)	1998	2	2	0	2	2	0	1	2	2	0	2	2	0	17
Tang *et al.* (54)	2016	2	1	0	2	2	0	2	2	2	0	2	2	0	17
Wu *et al.* (44)	2009	2	0	0	2	1	0	2	2	2	0	2	2	2	17
Cenni *et al.* (61)	2003	2	0	0	2	2	0	2	0	2	0	2	2	2	16
Granchi *et al.* (62)	2000	2	0	0	2	2	0	2	2	2	0	2	2	0	16
Fiorito *et al.* (46)	2003	2	0	0	2	2	0	1	2	2	0	2	2	0	15
Schneider *et al.* (59)	1997	2	1	0	2	1	0	1	2	1	0	2	2	0	14
Pellengahr *et al.* (67)	2001	2	1	0	2	1	0	2	0	2	0	0	2	0	12

The studies with an ICROMS score ≥18 and which fulfilled the mandatory criteria were classified as low RoB/high quality. The studies with an ICROMS ≥18 points but did not still fulfill the mandatory criteria were classified as moderate RoB/moderate quality. The studies with an ICROMS <18 points and which did not fulfill the mandatory criteria and were classified as high RoB/low quality.
*****Indicates mandatory criteria and these criteria are in bold.
ICROMS, Integrated Quality Criteria for Review of Multiple Study Designs; HQ, high quality; LQ, low quality; MQ, moderate quality; RoB, risk of bias.

and one LQ study (43, 44), while no difference between groups was found in another MQ and LQ study (45, 46). In one MQ study, IL-1β was detectable in four out of nine patients with aseptic loosened implants, and detectable in one out of 13 patients with stable implants (Fig. 5) (49). Interleukin 1 (IL-1) was used in one HQ study which found comparable levels between loosened and stable implants (42). 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. 6) (42, 46, 50). Other interleukins studied were interleukin 2R, interleukin 8, and interleukin 11 (Table 3). IL-1β might discriminate between loosened and stable implants, but evidence supporting the use of other interleukins is 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 3). No difference in any of these biomarkers was found between patients with loosened versus stable implants, indicating poor usability of these biomarkers to identify patients with aseptic loosening (45, 49, 51, 52).

Osteocalcin was compared between aseptic loosened and stable implants in one HQ, one MQ and one LQ study (Table 3). The osteocalcin was statistically significantly higher in the aseptic loosened group in the HQ and LQ study (51, 53) while no difference was found in the MQ study (52). 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

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Table 2 Study characteristics.

Study	Joint	Fixation method	Assessment method	Indication studied‡	Number of patients*		Mean age, years	
					LG	CG	LG	CG
Low RoB/HQ								
Chaganti *et al.* (42)	Hip	Mixed fixation	Serum markers	Aseptic loosening	15 (5)	13 (4)	70	71
Trehan *et al.* (55)	Hip	Mixed fixation	Serum markers	Aseptic loosening	20 (9)	10 (6)	68	63
Morakis *et al.* (53)	Hip	Cemented	Serum markers	Osteolysis	12 (12)	12 (12)	72	73
Moderate RoB/MQ								
Hundric-Haspl *et al.* (43)	Hip, Knee	NR	Serum markers	Osteolysis	50 (40)	50 (43)	65	62
Ovrenovits *et al.* (57)	Hip	Uncemented	Serum markers	Aseptic loosening	10 (NR)	10 (6)	NR	60
Savarino *et al.* (73)	Hip	NR	Serum markers	Aseptic loosening	27 (23)	19 (15)	69	62
Ross *et al.* (31)	Hip	Mixed fixation	Urine markers	Osteolysis	16 (7)	11 (4)	56	61
Lawrence *et al.* (58)	Hip	Cemented	Serum markers Urine markers	Osteolysis	26 (7)	24 (8)	73	74
Streich *et al.* 50)	Hip	Mixed fixation	Serum markers	Aseptic loosening	23 (10)	23 (12)	65†	67†
Antoniou *et al.* (65)	Hip	NR	Urine markers	Osteolysis	21 (3)	8 (0)	54	67
Friedrich *et al.* (48)	Hip, knee	NR	Serum markers	Aseptic loosening	51 (33)	21 (13)	68	64
He *et al.* (45)	Hip	Mixed fixation	Serum markers	Aseptic loosening	31 (18)	19 (10)	66	61
Streich *et al.* (63)	Hip	Uncemented	Urine markers	Aseptic loosening	52 (26)	52 (26)	65†	63†
Wilkinson *et al.* (52)	Hip	Cemented	Serum markers Urine markers	Osteolysis	23 (6)	26 (8)	73	75
Witzleb & Menschikowski (66)	Hip, knee	Mixed fixation	Urine markers	Aseptic loosening	58 (42)	67 (48)	68	68
Granchi *et al.* (47)	Hip	Mixed fixation	Serum markers	Osteolysis	36 (23)	33 (20)	65	58
Moreschini *et al.* (49)	Hip	Mixed fixation	Serum markers	Osteolysis	9 (7)	13 (8)	63	62
Kreibich *et al.* (74)	Hip	Uncemented	Serum markers	Aseptic loosening	14 (5)	14 (7)	51	54
High RoB/LQ								
Roato *et al.* (56)	Hip	Mixed fixation	Serum markers	Aseptic loosening	15 (NR)	15 (NR)	76	75
von Schewelov *et al.* (64)	Hip	Mixed fixation	Urine markers	Aseptic loosening	33 (19)	127 (76)	50	61
Schneider *et al.* (51)	Hip	Mixed fixation	Serum markers Urine markers	Aseptic loosening	50 (27)	50 (29)	70	68
Tang *et al.* (54)	Hip	NR	Serum markers	NR	26 (12)	26 (10)	59	59
Wu *et al.* (44)	Hip	Mixed fixation	Serum markers	Aseptic loosening	43 (24)	16 (12)	67	61
Cenni *et al.* (61)	Hip	Mixed fixation	Serum markers	NR	23 (15)	15 (9)	69	58
Granchi *et al.* (62)	Hip	NR	Serum markers	NR	13 (9)	11 (5)	64†	44†
Fiorito *et al.* (46)	Hip	Uncemented	Serum markers	Osteolysis	8 (4)	10 (2)	62	66
Schneider *et al.* (59)	Hip	Mixed fixation	Serum markers Urine markers	Aseptic loosening	37 (22)	30 (17)	70	64
Pellengahr *et al.* (67)	Hip, knee	NR	Urine markers	Aseptic loosening	35 (24)	34 (20)	68	67

‡A study group had aseptic loosening if this was confirmed preoperatively and osteolysis if this was confirmed radiographically; *The values in parentheses are number of female patients; †Indicates median value.
CG, control group; HQ, high quality; LG, loose group; LQ, low quality; MQ, moderate quality; NR, not reported.

only one study (Table 3) (42, 43, 44, 46, 49, 50, 54, 55, 56, 57, 58, 59, 60, 61, 62).

Urine markers

Ten out of 28 studies (36%) included urine markers, of which 6 were of MQ and 4 were of LQ (Table 4).

Urinary 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 (31, 63, 64). One MQ study compared aseptic loosened acetabular cups to stable cups, and aseptic loosened femoral stems to stable stems, and found that the NTX was higher in the aseptic loosened groups, but this difference only reached statistical significance in the femoral group (52). Higher NTX levels of loosened implants was found in one MQ and one LQ study (51, 65). Overall, NTX thus tended to be higher in aseptic loosened implants (Fig. 7).

Urinary C-terminal telopeptide (CTX) was assessed in three MQ studies (Table 4). αCTX was statistically higher in loosened implants in one MQ study (31), while no difference between groups was found in another MQ study (58). One study did not specify whether α- or β-crosslaps were assessed but found no difference in CTX between groups (63). Evidence supporting the use of urinary CTX to assess aseptic loosening was thus limited.

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Table 3 Serum marker results. Some studies did not report the unit of the outcome.

		Aseptic loosened group		Stable group			
Serum markers	**Study**	Mean	S.D.	Mean	S.D.	**Outcome**	**Quality**
TNFα, pg/mL	(42)	7.1†	11.6	1.5†	1.3	>	HQ
	(43)	32.7	32.4	22.9	18.7	>	MQ
	(45)	32.2	50.6	15.9	7.4	=	MQ
	(44)	37	18.1	8.1	5.5	>	LQ
	(46)	4.32	5.2	3.84	1.13	=	LQ
TNF mRNA	(54)	ND		ND		=	LQ
TNFbeta, pg/mL	(46)	23175	8873	21120	13657	=	LQ
IL-1, pg/mL	(42)	0.4	0.37	0.29	0.34	=	HQ
IL-1b, pg/mL	(43)	3.7	5.5	1.5	2	>	MQ
	(45)	1.75	1.44	0.97	0.29	=	MQ
	(49)	DT in 4/9**		DT in 1/13‡		=	MQ
	(44)	9.1	3.9	6.4	4.1	>	LQ
	(46)	2.15	1.37	2.26	0.89	=	LQ
IL-2R, μ/mL	(50)	469	155	515	160	=	MQ
IL-6, pg/mL	(42)	8.9	13.2	3.5	0.7	=	HQ
	(50)	4.0	5.3	4.1	6.1	=	MQ
	(46)	2.86	1.95	4.58	4.02	=	LQ
IL-8, pg/mL	(43)	14.7	9	8.1	4.7	>	MQ
IL-11, pg/mL	(46)	0		1.22	2.57	=	LQ
OPG, pmol/L	(42)	7.9	3	7.5	2.2	=	HQ
	(48)	ND		ND		=	MQ
	(45)	26.7	19.9	24.1	5.2	=	MQ
pg/mL	(47)	4198	286	2397	1632	>	MQ
RANKL, pmol/L	(42)	19.1	23.9	44.8	55	=	HQ
	(48)	ND		ND		=	MQ
	(45)	109.3	212.7	189	86.1	=	MQ
pg/mL	(47)	1483.0	1179	3312	2211	<	MQ
RANKL mRNA	(54)	↑7.4 times‖		↑7.4 times‖		=	LQ
hsCRP, mg/dL	(42)	1.86	4.76	0.24	0.19	=	HQ
GM-CSF, pg/mL	(50)	3.97	5.33	NTDT		=	MQ
Elastase, ng/mL	(50)	58.91	46.78	56.56	44.95	=	MQ
NTX	(45)	25.671	27.5282	20.192	4.962	=	MQ
nM BCE	(42)	27.22	5.15	19.53	6.32	>	HQ
PICP	(45)	−1251.864	308.539	−1444.529	169.247	=	MQ
ng/mL	(51), (59)	107.5	70.4	82.2	32.8	=	LQ
PINP	(52)	ND		ND		=	MQ
PIIINP	(49)	ND		ND		=	MQ
CCL18, nM	(55)	66		78		=	HQ
CHIT1, nM	(55)	98		39		>	HQ
CTX, ng/mL	(53)	0.56	0.2	0.27	0.14	>	HQ
βCTX, ng/mL							
Femoral loosening	(52)	0.43†	0.31–0.56‡	0.33†	0.22–0.48‡	=	MQ
Acetabular loosening	(52)	0.45†	0.23–0.57‡	0.33†	0.29–0.45‡	=	MQ
OC, ng/mL	(53)	28.9	10.38	18.66	5.05	>	HQ
	(52)	ND		ND		=	MQ
	(51), (59)	Higher		Lower		>	LQ
Osteoclastogenesis	(56)	134	64	22	21	>	LQ
Osteoclast rate, %							
Day 7	(54)	23.4	5.3	3.4	0.5	>	LQ
Day 14	(54)	82.5	14.7	17.7	5.6	>	LQ
Day 21	(54)	92.8	20.6	32.1	9.3	>	LQ
Bone erosion rate, %							
Day 14	(54)	43.40		12.90		>	LQ
Day 21	(54)	88.40		31.60		>	LQ
CD4+ (%)	(54)	Higher		Lower		>	LQ
CD8+ (%)	(54)	Higher		Lower		>	LQ
CD11a	(57)						MQ

(Continued)

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Table 3 Continued.

		Aseptic loosened group		Stable group			
Serum markers	**Study**	Mean	S.D.	Mean	S.D.	**Outcome**	**Quality**
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	=	
CD11b	(57)						MQ
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	(57)						MQ
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+, %	(44)	22.4	10.6	15.8	5.7	>	LQ
CD14++ CD16−, %	(44)	68.7	11.3	75.4	5.4	=	LQ
CD14+ CD16+, %	(44)	13.7	7.5	9.2	5.6	>	LQ
CD18	(57)						MQ
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 (%)	(56)	ND		ND		=	LQ
CD62L	(57)						MQ
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 (%)	(56)	ND		ND		=	LQ
TRAP-5β, U/L	(73)	4.23	1.38	2.73	0.78	>	MQ
	(58)	4.17		3.44		>	MQ
ICTP, ng/mL	(58)	7.04		5.15		>	MQ
Bone ALP, U/L	(52)	ND		ND		=	MQ
	(51), (59)	123.8	42.5	110.4	28	=	LQ
MCP-1	(54)	Higher		Lower		=	LQ
Hyaluronic acid, µg/L	(49)	779.3	475.8	112.9	42.5	>	MQ
Cobalt, nmol/L	(74)	22.1	28.8	6.4	2.2	>	MQ
	(62)	5.9	1*	4.5	0.6*	=	MQ
Chromium, nmol/L	(74)	21.1	29.7	16.9	9.7	=	MQ
	(62)	8.0	1.3*	5.3	0.7*	>	MQ
Sclerostin	(58)	ND		ND		=	MQ
DKK-1	(58)	ND		ND		=	MQ
Calcium, mmol/L	(51), (59)	2.32	0.226	2.36	0.112	=	LQ
Creatinine, mmol/mL	(51), (59)	7.69	6.5	8.76	4.85	=	LQ
D-dimer, ng/mL	(61)	132	21*	42	8.5*	>	LQ
PAI-1, U/mL	(61)	2.3	1.1*	8.1	1.8*	>	LQ
PDGF-AB, ng/mL	(61)	2.4	0.35*	1.9	0.23*	=	LQ
Protein C, %	(61)	108	4*	114	6.6*	=	LQ
Antithrombin III, %	(61)	99	2.2*	101	2.0*	=	LQ
PGE2, pg/mL	(46)	1330	1097.44	2021	1.046	=	LQ
MMP-1, pg/mL	(46)	3.69	1.75	4.1	1.44	=	LQ
PHA	(62)	5.3	0.8*	4.9	0.9*	=	MQ
AIM-V	(62)	62.8	4.7*	28.3	3.5*	>	MQ

If the outcome was significantly higher in the aseptic loosened group, the study was marked with >; If the outcome was significantly lower, the study was marked with <; If no difference between both groups was found, the study was marked with =.

†Median values; *S.E.M. values; ⁋7.4 times higher in AL group; ‡IQR values; **Detectable in 4 out of 9 patients; ⁑Detectable in 1 out of 13 patients.

AIM-V, unstimulated peripheral blood mononuclear cell; ALP, alkaline phosphatase; CCL18, CC chemokine ligand 18; CD, cluster of differentiation; CHIT1, chitotriosidase; CTX, C-terminal telopeptide; DKK-1, dickkopf-1; GM-CSF, granulocyte–macrophage colony-stimulating factor; hsCRP, high-sensitivity C-reactive protein; HQ, high-quality study; ICTP, carboxy terminal telopeptide of type 1 collagen; LQ, low-quality study; MCP-1, monocyte chemoattractant protein-1; MMP-1, matrix metalloprotease-1; MQ, moderate-quality study; ND, no difference; NTDT, not detectable; NTX, cross-linked N-telopeptide of type 1 collagen; OC, osteocalcin; OPG, osteoprotegerin; PAI-1, plasminogen activator inhibitor-1; PDGF-AB, platelet-derived growth factor; PGE2, prostaglandin E2; PHA, phytohemoagglutinin; PICP, procollagen type I C-terminal peptide; PIIINP, procollagen type III N-terminal peptide; PINP, procollagen type I N-terminal peptide; TRAP-5b, tartrate-resistant acid phosphatase-5b.

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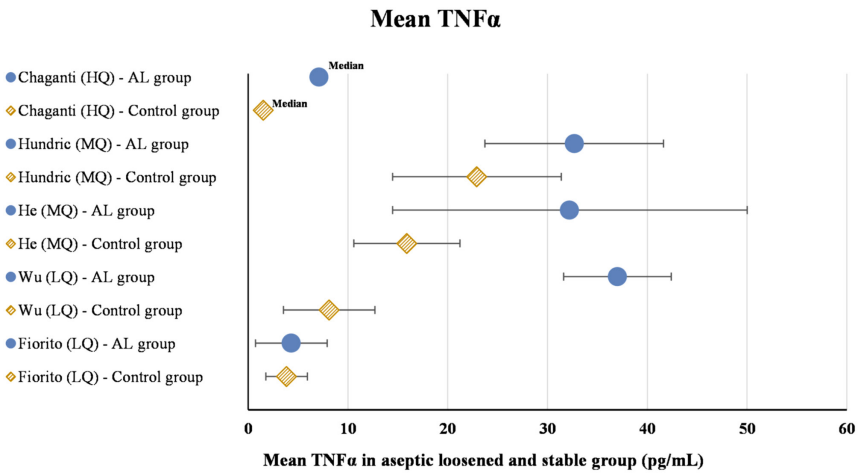

Figure 2

Mean serum TNFα in the aseptic loosened and control groups. 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% CIs. AL, aseptic loosening; LQ, low quality; MQ, moderate quality; TNFα, tumor necrosis factor α.

Urinary deoxypyridinoline (DPD) was compared between aseptic loosened and stable implants in four MQ studies and one LQ study (Table 4). A lower DPD concentration of loosened implants compared to stable implants was found in one MQ study (31), no difference between groups was found in two MQ studies (52, 66), and a higher DPD concentration of loosened implants was found in one MQ study (63). 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 (67). These results suggest poor usability of DPD as a biomarker to assess aseptic loosening (Fig. 8).

Discussion

Biomarkers 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 serum and urine markers were used as a proxy for implant–bone stability. Serum markers were most frequently studied. For that matter, TNFα, IL-1β, and osteocalcin were elevated in patients with aseptic loosening of a primary THA or TKA in most studies. Urinary NTX was the only urine marker found in our review to discriminate between aseptic loosened and stable implants.

A higher concentration of the serum markers TNFα, IL-1β, and osteocalcin in aseptic loosened implants was found in several studies, but a few studies did not detect a difference. Further fundamental research may help to understand the role of these biomarkers in the mechanism resulting in aseptic loosening and osteolysis. TNFα and IL-1β play an important role in the inflammation, and especially TNFα has been shown to induce osteolysis *in vivo* (68). Schwarz *et al.* compared mice that overproduce TNFα with mice that had a defective TNFα signaling pathway and found that the mice that overexpressed TNFα showed increased osteolysis, whereas the defective mice showed little osteolysis (68). Osteocalcin, on the other hand, is secreted by osteoblasts and plays an important role in bone formation (69). A recent murine study assessed osteocalcin and implant loosening in a longitudinal fashion and found a correlation between serum osteocalcin and implant fixation (70). The present review suggests that an increased serum TNFα, IL-1β, and osteocalcin level could be indicative for aseptic loosening. Interestingly, the biomarkers serum CTX and PINP are frequently used in osteoporosis to assess bone

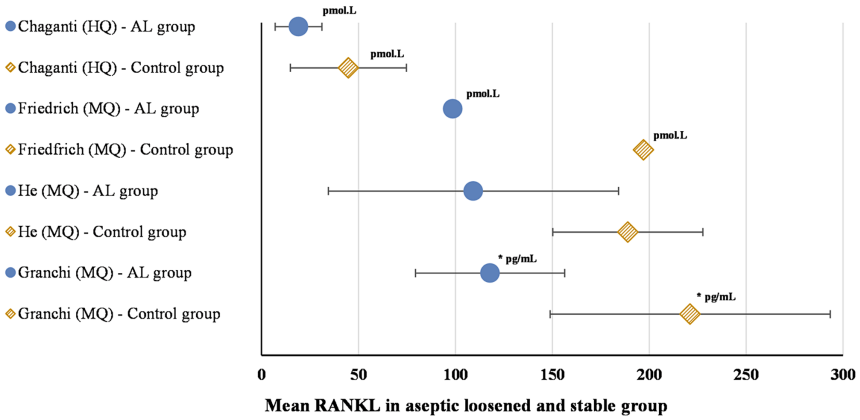

Figure 3

Mean serum RANKL in the aseptic loosened and control groups. 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% CIs. *Value displayed is the true value divided by 10. AL, aseptic loosening; HQ, high quality; MQ, moderate quality; RANKL, receptor activator of nuclear factor kappa-B ligand.

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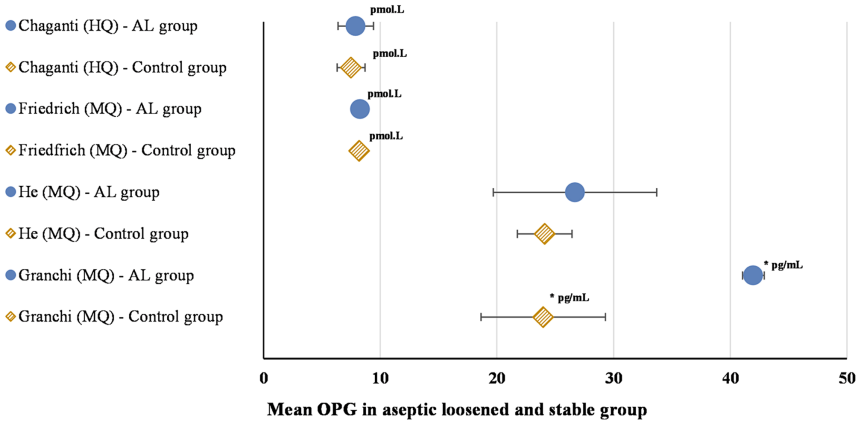

Figure 4

Mean serum OPG in the aseptic loosened and control groups. 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% CIs. *Value displayed is the true value divided by 100. AL, aseptic loosening; HQ, high quality; MQ, moderate quality; OPG, osteoprotegerin.

formation and resorption, but the number of included studies assessing these markers in the present review was limited (71). We recommend future studies to further assess whether these markers could discriminate between stable and loosened implants.

In contrast to the many serum markers studied, only a few urine markers were studied, of which NTX, CTX, and DPD were the most popular. Urinary NTX showed the most promising results in discriminating between aseptic loosened and stable implants (Fig. 7), whereas urinary DPD showed conflicting results and seemed to have the least discriminative ability. This finding was supported by a canine study which assessed urinary CTX, NTX, and DPD (72). This canine study concluded that urinary NTX was the most discriminatory bone resorption marker in focal malignant osteolysis (72). In the first 6 months, urinary NTX appeared to be elevated in all patients following THA or TKA, but levels returned to normal thereafter, making these biomarkers potentially usable to identify loosening after 6 months (60). 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 arthroplasty (31). However, none of the other included studies found a difference in CTX between groups. More studies are needed to further investigate whether NTX and possibly also CTX urine markers can discriminate between aseptic loosened and stable implants.

Currently, radiological assessment of an implant is most used in clinical practice to identify aseptic loosening. Radiolucent lines, cysts and migration are suggestive for loosening (19, 20, 21, 22). However, most of these characteristics may become visible only at an advanced stage of osteolysis. Other diagnostics such as radiostereometric analysis (RSA) could be used to assess implant loosening at an earlier stage. This technique measures micromotion, and high initial migration or continuous migration measured with RSA is suggestive for early aseptic loosening of an implant (17, 18). Although RSA has the ability to identify patients at risk for aseptic loosening as early as 1 or 2 years after the primary surgery, this technique is costly. Second, RSA needs tantalum markers to be inserted in the periprosthetic bone. Therefore, other more accessible methods such as serum 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 even 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 emphasizes the need for well-designed studies to assess the ability of these biomarkers 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 the primary outcome,

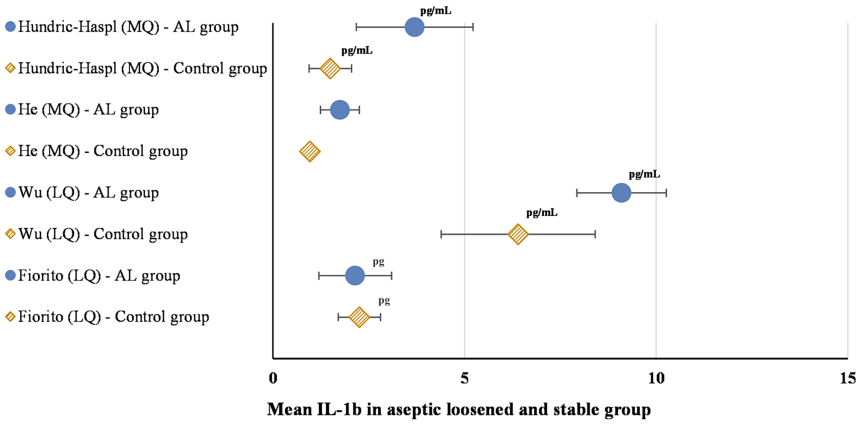

Figure 5

Mean serum IL-1β in the aseptic loosened and control groups. 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% CIs. AL, aseptic loosening; IL-1β, interleukin 1 beta; LQ, low quality; MQ, moderate quality.

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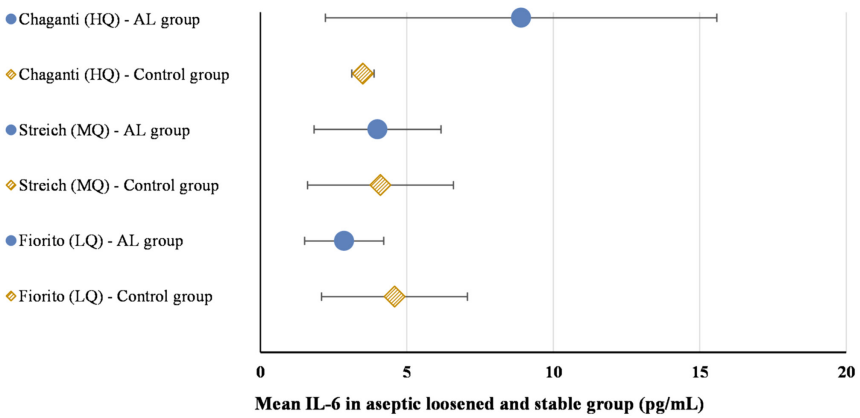

Figure 6

Mean serum IL-6 in the aseptic loosened and control groups. 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% CIs. AL, aseptic loosening; IL-6, interleukin 6; LQ, low quality; MQ, moderate quality.

Table 4 Urine marker results. Some studies did not report the unit of the outcome.

		Aseptic loosened group		Stable group			
Study	**Urine markers**	Mean	95% CI	Mean	95% CI	**Outcome**	**Quality**
(31)	NTX, nmol/mmol creatinine	ND		ND		=	MQ
(65)		73*		25*		>	MQ
(63)		51.4		53		=	MQ
(52)	Femoral loosening, nm BCE/mM creatinine	61	40.9–72.1	39.9	27.0–52.7	>	MQ
(52)	Acetabular loosening, nm BCE/mM creatinine	62.3	32.0–72.1	42.8	28.1–53.2	=	MQ
(64)		34	12†	29	15†	=	LQ
(51)	nmol/mmol creatinine	96		40	>		LQ
(31)	αCTX	Higher		Lower		>	MQ
(58)	ng/mL	0.61*		0.63*	=		MQ
(31)	βCTX	ND		ND		=	MQ
(63)	CTX (NS), nmol/mmol creatinine	94.3*		67.0*		=	MQ
(31)	DPD, nmol/mmol creatinine	Lower		Higher		<	MQ
(63)		9.17*		5.72*		>	MQ
(66)		8.2		8.2		=	MQ
(52)	Femoral loosening, nmol/mM creatinine	61.0	40.9–72.1	39.9	27.0–52.7	=	MQ
(52)	Acetabular loosening, nmol/mM creatinine	62.3	32.0–72.1	42.8	28.1–53.2	=	MQ
(67)	Male, nmol/mmol creatinine	7.8		5.8		=	LQ
(67)	Female, nmol/mmol creatinine	8.6		10.1		=	LQ
(31)	IL-6	Higher		Lower		>	MQ
(31)	IL-8	ND		ND		=	MQ
(31)	OPG	ND		ND		=	MQ
(66)	PYD	ND		ND		=	MQ
(51)		Higher		Lower		>	LQ
(51)	DPYD	Higher		Lower		>	LQ

If the outcome was significantly higher in the aseptic loosened group, the study was marked with >; if the outcome was significantly lower, the study was marked with <; if no difference between both groups was found, the study was marked with =.
*Median values; †S.D. values.
CTX, C-terminal telopeptide; DPD, free deoxypyridinoline; DPYD, deoxypyridinoline; HQ, high-quality study; IQR, interquartile range; LQ, low-quality study; ND, no difference; MQ, moderate-quality study; NTX, cross-linked N-terminal telopeptide of type 1 collagen; OPG, osteoprotegerin, PYD, pyridinoline; RoB, risk of bias.

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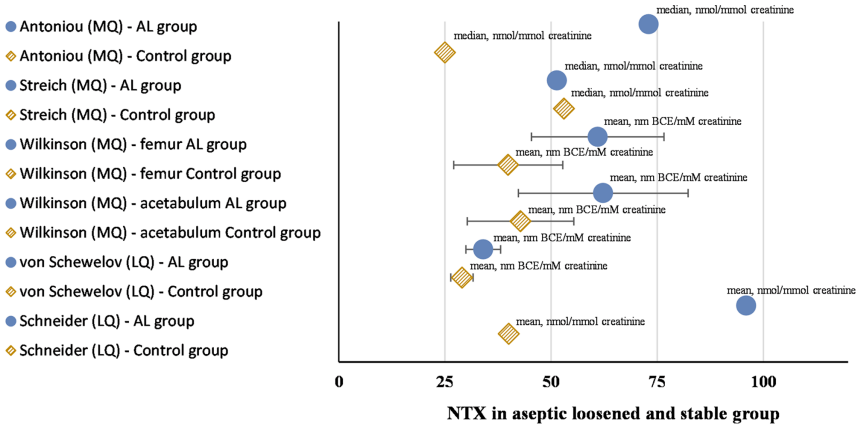

Figure 7

Mean or median urinary NTX in the aseptic loosened and control groups. 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% CIs. AL, aseptic loosening; LQ, low quality; MQ, moderate quality; NTX, N-terminal telopeptide.

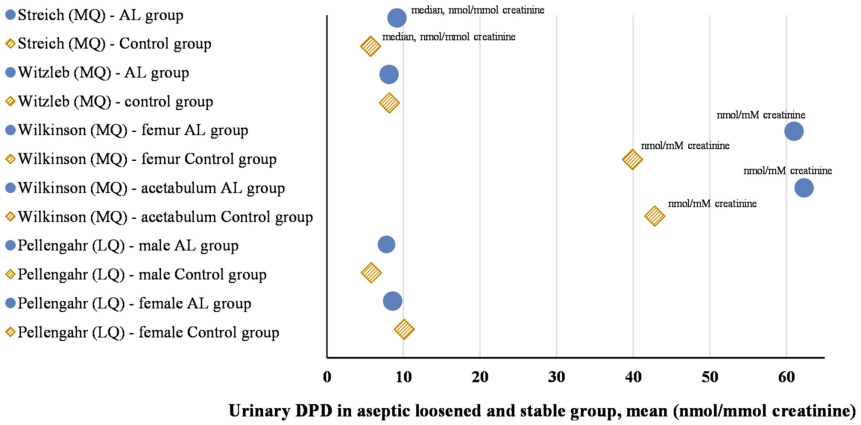

Figure 8

Mean urinary DPD in the aseptic loosened and control groups. 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% CIs. AL, aseptic loosening; DPD, deoxypyridinoline; LQ, low quality; MQ, moderate quality.

the assessment of incomplete data, and 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. Lastly, we did not perform a diagnostic accuracy study. In the future, this approach could be used for promising biomarkers.

Conclusions

The present review examined several markers in their ability to identify implants with osteolysis and aseptic loosening in THAs and TKAs. Especially serum TNFα and osteocalcin showed a promising role in discriminating between loosened and stable implants and NTX as one of the few urine markers. We therefore recommend future studies to study these serum and urine 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.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EOR-22-0046.

ICMJE Conflict of Interest Statement

There is no conflict of interest that could be perceived as prejudicing the impartiality of the study reported.

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