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TRIBOCORROSION OF TOTAL JOINT REPLACEMENTS

Are There Biological Markers for Wear or Corrosion? A Systematic Review

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Abstract

Background Identification of biomarkers associated with wear and tribocorrosion in joint arthroplasty would be helpful to enhance early detection of aseptic loosening and/or osteolysis and to improve understanding of disease progression. There have been several new reports since the last systematic review (which covered research through mid-2008) justifying a new assessment.

Questions/purposes We sought to determine which biomarkers have the most promise for early diagnosis and monitoring of aseptic loosening and/or osteolysis related to wear or corrosion in total joint arthroplasty.

Methods We performed a systematic review using MEDLINE and EMBASE databases, covering the period through December 2013, and identified 1050 articles. We restricted

the definition of biomarker to biomolecules and imaging parameters useful for diagnosis and monitoring of disease progression, only including articles in English. We chose 65 articles for full review, including 44 from the original search and 21 from subsequent hand searches. We used the 22 articles in which patients with total joint arthroplasty who had aseptic loosening and/or periimplant osteolysis unrelated to sepsis had been compared with patients with total joint arthroplasty with stable implants. There were 90 comparisons of these two patient populations involving 35 different biomarkers.

Results Diagnostic accuracy was assessed in nine of the 90 comparisons with the highest accuracy found for tartrate-resistant acid phosphatase 5b (0.96), although a separate comparison for this biomarker found a lower accuracy (0.76). Accuracy of > 0.80 was also found for crosslinked n-telopeptide of type I collagen, osteoprotegerin, and deoxypyridinoline. The most studied markers, tumor necrosis factor- α and interleukin-1 β , were found to differ in the affected and control groups in < 30% of the comparisons. Thirty of the 35 biomarkers were studied in four or fewer separate comparisons with nearly half of the biomarkers (17) studied in only one comparison. Many of the comparisons were not able to eliminate a number of confounding variables, and there was only one prospective study.

Conclusions Currently, there are no validated biomarkers for early diagnosis and monitoring of the biological sequelae of wear or tribocorrosion, although there are some promising leads, including markers of bone turnover.

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Introduction

Disease-related molecular biomarkers can be defined as objectively quantifiable molecular parameters that can be

correlated with the presence or risk of a pathological condition [1]. Biomarkers can serve as informative predictors of disease onset in asymptomatic individuals (predictive biomarkers), indicators of disease incidence and progression (diagnostic/progression biomarkers), and measures of response to treatment or surgical intervention (response biomarkers). Our emphasis here is on biomarkers of disease incidence and progression and we, therefore, focused on analysis of tissues that could be collected noninvasively or minimally invasively (eg, by analysis of blood, serum, plasma, urine, synovial fluid, or images). The discovery and development of biomarkers for musculoskeletal disorders represent an active and important area of research, including in osteoarthritis and autoimmune diseases [12]. Given the multifactorial nature of this group of disorders, it is anticipated that biomarker panels have greater potential than individual biomarkers, an argument that would extend to markers of poor implant performance. There currently is no clear consensus on using biomarkers for assessing implant performance and because the only previous systematic review on this topic [19] covered the literature through mid-2008, it seemed appropriate to revisit the literature systematically.

The rationale for biomarker development within the areas of wear and tribocorrosion centers around three main observations. First, the numbers of total joint arthroplasty (TJA) performed annually are increasing rapidly, and it is predicted to reach four million procedures per year in the United States alone by 2030 [15]. Therefore, despite increases in implant performance, many patients are at risk of TJA implant failure. Second, adverse local tissue reactions to implants, including periimplant osteolysis, frequently initiate as clinically silent disorders and remain undiagnosed until substantial bone loss and/or soft tissue damage has already occurred. Sensitive biomarkers would have the potential to complement current followup approaches to enhance early detection of at-risk individuals. Third, there remains a complete lack of approved medical therapies for the treatment of patients with periimplant osteolysis or adverse local tissue reaction to metallic debris. Biomarkers of disease progression would help stratify patient populations for future trials while simultaneously identifying novel therapeutic targets.

In light of these arguments in favor of further biomarker development for implant failure, we have conducted a systematic review of the published literature to determine which biomarkers have the most promise for early diagnosis and monitoring of aseptic loosening and/or osteolysis related to wear or corrosion in TJA.

Search Strategy and Criteria

A search of MEDLINE (1946 through December 2013) and EMBASE (1991 through December 2013) was performed in

early January 2014 using the following strategy: (“biological markers” OR “marker” OR “biomarker”) AND (“arthroplasty” OR “joint replacement” OR “hip replacement” OR “knee replacement” OR “shoulder replacement” OR “ankle replacement”), yielding 1050 articles (Fig. 1). We reviewed all of the abstracts and eliminated papers not written in English, in which the marker was metal levels in body fluids, where genotype was used to predict implant failure, where aseptic loosening or osteolysis was not mentioned, or where only animal models were used. We excluded studies about metal ion levels because these are direct markers of implant degradation but not biological markers. We did not consider studies in which genotype was used to predict failure because genotype does not change in response to implant degradation. Review articles and case reports also were excluded.

Our inclusion criterion was that the abstract needed to explicitly state or imply that one of the study groups included a group that had aseptic loosening or periimplant osteolysis and that the control group included patients with implants. Using these criteria, we eliminated 1006 papers, leaving 44 articles for review. We also performed a hand search using the references cited in papers that were reviewed and the “cited by” function on PubMed to identify 21 additional papers. Thus, 65 papers were fully reviewed. Of these, 43 were excluded because of the criteria already outlined or because the control group did not include subjects who had an implant placed. Thus, in the 22 papers included in the systematic review, the “test” group was usually stated to have aseptic loosening or periimplant osteolysis and the “control” group was usually stated to have stable implants or no osteolysis. A previous systematic review through July 2008 [19] included 13 of these 22 papers and five additional papers that did not meet our inclusion criteria. In four papers in the previous review, the control subjects did not have placement of an implant and in one paper, there was no specific mention of implant loosening or periimplant osteolysis. Our study included nine papers not in the previous review, six of which were published in 2009 or more recently.

From these 22 articles, we constructed a database in which each record represented a specific biomarker in which there was a comparison between a test group with aseptic loosening and/or periimplant osteolysis with a control group in which the implant was stable or in which there was no osteolysis. We found 90 such comparisons spread over 35 biomarkers (see Table 1 for biomarker abbreviations and synonyms).

Two reports are of particular interest. In the only prospective longitudinal study in the systematic review, Li et al [17] found that the bone resorption marker, C-terminal telopeptide of type I collagen (CTX-1), was elevated at 6, 12, and 24 months after total knee arthroplasty (TKA) in subjects classified as having potentially unstable implants

Fig. 1 Outline of search strategy. Note that most of the papers initially identified in the search did not meet the inclusion and exclusion criteria.

compared with patients with stable implants based on radiostereometric analysis (RSA) to classify the patients. These authors also found that osteocalcin (OC) was elevated at 12 months in the patients with potentially unstable implants, but procollagen I C-terminal propeptide (PICP) was not different between the two groups. Using a unique statistical approach in which a panel of markers was studied, He et al [10] compared serum levels of interleukin-1 β (IL-1 β), crosslinked n-telopeptide of type I collagen (NTx), osteoprotegerin (OPG), PICP, receptor activator of nuclear factor kappa-B ligand (RANKL), and tumor necrosis factor- α (TNF- α) among patients with late aseptic loosening, early aseptic loosening, and stable implants. Although none of the individual markers showed between-group differences, a statistical analysis in which all six markers were included showed a difference between patients with late aseptic loosening and those with stable implants and a nearly significant difference between patients with early aseptic loosening and patients with stable implants.

Results

Ten of the 90 comparisons included sensitivity and specificity for diagnosis calculations (Table 2). Sensitivity ranged from 33% to 92% and specificity ranged from 65% to 100%. The best reported accuracy was 0.96 in a comparison of patients with aseptic loosening to patients with stable implants using serum TRAP-5b [16]. For this study sensitivity was 83% and specificity was 92% [16]. Another

study of TRAP-5b found a much lower accuracy (0.76) for this marker [28]. NTx has been studied in three comparisons with accuracy ranging from 0.64 to 0.85, sensitivity ranging from 33% to 82%, and specificity ranging from 72% to 100% [29, 30, 35] (Table 2). OPG [8] and deoxypyridinoline (DPYD) [30] also had accuracies > 0.80 (Table 2).

The problem of limited research in this area becomes evident when the markers are ranked by total number of comparisons (Table 3). The most studied biomarkers include the inflammatory markers TNF- α and IL-1 β , both of which have been used in 11 comparisons with only three (27%) and two (18%) of the comparisons, respectively, finding a difference between the affected group and the control group. For the most studied bone turnover marker, NTx, only 50% of the comparisons (four of eight) found differences. All of the remaining markers have been examined in five or fewer comparisons (Table 3). The biomarkers were most commonly studied in plasma or serum (64 comparisons; Table 4) followed by peripheral blood cells and urine (11 comparisons each; Tables 5, 6) and synovial fluid (four comparisons; Table 7). There were no imaging biomarkers that met inclusion and exclusion criteria. The details of the comparison groups (Tables 4–7) show that length of followup in the affected and control groups often differed by years and the number of subjects studied never exceeded 52 in each group with the sample size often being much smaller. Implant composition and other characteristics of the populations studied such as age and sex distribution were often not as comparable as one

Table 1. Biomarker abbreviations, synonyms, and alternate abbreviations

Abbreviation	Biomarker	Synonyms, alternate abbreviation
BAP	Bone-specific alkaline phosphatase	BSAP, bone ALP, BALP
CD	Cluster of differentiation or cluster of designation cell surface molecule	
CRP	C-reactive protein	
CTX-1	C-terminal telopeptide of type I collagen	CrossLaps, CTX, collagen type-1 crosslinked C-telopeptide
DPYD	Deoxypyridinoline	DPD, D-Pryilinks
GM-CSF	Granulocyte-macrophage colony-stimulating factor	
HA	Hyaluronic acid	Hyaluronan, hyaluronate
IL-1 β	Interleukin-1 beta	
IL-6	Interleukin-6	
IL-8	Interleukin-8	
IL-11	Interleukin-11	
MMP-1	Matrix metalloproteinase-1	MMP1
NTx	Crosslinked n-telopeptide of type I collagen	NTX, NTX-1, NTx1, collagen-type I N-telopeptide
OC	Osteocalcin	OC, bone gamma-carboxyglutamic acid-containing protein (BGLAP)
OPG	Osteoprotegerin	Osteoclastogenesis inhibitory factor (OCIF), tumor necrosis factor receptor superfamily member 11B (TNFRSF11B)
PGE2	Prostaglandin E2	Dinoprostone
PICP	Procollagen I C-terminal propeptide	Collagen I propeptide, carboxyterminal propeptide of type I procollagen, carboxy-terminal propeptide
PIIINP	Procollagen III C-terminal propeptide	Collagen III propeptide, aminoterminal propeptide of type III procollagen
PINP	Procollagen I N-terminal propeptide	Collagen I propeptide, aminoterminal propeptide of type I procollagen, Amino-terminal propeptide
PYD	Pyridinoline	PD, hydroxylslypyridinoline
RANKL	Receptor activator of nuclear factor kappa-B ligand	Tumor necrosis factor ligand superfamily member 11 (TNFSF11), TNF-related activation-induced cytokine (TRANCE), osteoclast differentiation factor (ODF)
sIL-2r	Soluble interleukin-2 receptor	CD25 antigen, interleukin-2 receptor alpha CE
TGF- β	Transforming growth factor beta	
TNF- α	Tumor necrosis factor alpha	Cachexin, cachectin
TRAP-5b	Tartrate-resistant acid phosphatase 5b	TRACP 5b

would hope. None of the studies directly addressed the issue of differentiating between type of wear debris or corrosion product and biological marker profile.

Discussion

In the decades to come, clinicians may need to screen a very large number of patients for the sequelae of wear and tribocorrosion after TJA. As TJA use increases, so does the pool of patients at risk for failure, and so there is a pressing need for well-validated biomarkers and medical therapies for these conditions. To address the biomarker issue, we have asked the question “which biomarkers have the most promise for early diagnosis and monitoring of aseptic loosening and/or osteolysis related to wear or corrosion in

TJA?” Although the original motivation for this review was to identify biomarkers for wear or corrosion, nearly all of the studies in the literature were directed at assessing aseptic loosening and/or osteolysis and only by implication wear or corrosion. We found that although there are some promising biomarkers for aseptic loosening/osteolysis, these are not yet directly validated as biomarkers of wear or corrosion. Our sense is that advancements in this field have not been rapid and many of the concerns and unanswered questions discussed in a review published in 2008 [4] remain today. For instance, it is still not possible to correlate wear and corrosion of specific materials with particular biomarkers.

The major limitation of this review is that most of the studies were conducted to determine if biomarkers reflected the end stage of the disease state. Thus, there is very

Table 2. Sensitivity, specificity, and accuracy for biomarkers to detect aseptic loosening or osteolysis (see Table 1 for abbreviations)

Biomarker	Effect	Implant	Groups compared (test versus control)	Test time from implantation (years)	Control time from implantation (years)	Number of test subjects	Number of control subjects	Tissue	Sensitivity	Specificity	Accuracy	Reference
NTX	Elevated	THA	Aseptic loosening versus stable implants	9.6	9.1	50	50	Urine	82%	87%	0.85	[30]
NTX	Elevated	THA	Aseptic loosening versus stable implants	12.6	12.6	23	26	Urine	71%	72%	0.70	[35]
NTX	Elevated	THA	Osteolysis versus stable implants	9.6	2.1	21	18	Serum	33%	100%	0.64	[29]
TRAP-5b	Elevated	THA	Aseptic loosening versus stable implants	9.7	3.7	12	12	Serum	83%	92%	0.96	[16]
TRAP-5b	Elevated	THA	Aseptic loosening versus stable implants	5.2	8.8	27	19	Serum	67%	89%	0.76	[28]
DPYD	Elevated	THA	Aseptic loosening versus stable implants	8.2	7.8	52	52	Urine	54%	96%	N/R	[32]
DPYD	Elevated	THA	Aseptic loosening versus stable implants	9.6	9.1	50	50	Urine	83%	83%	0.83	[30]
OPG	Elevated	THA	Aseptic loosening versus stable implants	9.3	2.7	36	33	Serum	92%	75%	0.85	[8]
Oc	Elevated	THA	Aseptic loosening versus stable implants	9.6	9.1	50	50	Serum	69%	65%	0.67	[30]
PYD	Elevated	THA	Aseptic loosening versus stable implants	9.6	9.1	50	50	Urine	41%	98%	0.38	[30]

Table 3. Summary of biomarker findings (see Table 1 for abbreviations and Tables 4–7 for details of each comparison)

Marker	Total number of comparisons	Proportion of comparisons showing a difference	No effect	Elevated	Depressed	Tissue	Marker category
TNF- α	11	27.3%	8	3		Serum/plasma or synovial fluid	Inflammatory
IL-1 β	11	18.2%	9	2		Serum/plasma or synovial fluid	Inflammatory
NTx	8	50.0%	4	4		Serum/plasma or urine	Bone turnover
IL-6	5	60.0%	2	3		Serum/plasma	Inflammatory
PICP	5	20.0%	4		1	Serum/plasma	Bone turnover
DPYD	4	50.0%	2	2		Urine	Bone turnover
CTX-I	4	25.0%	3	1		Serum/plasma or urine	Bone turnover
OC	3	66.7%	1	2		Serum/plasma	Bone turnover
OPG	3	33.3%	2	1		Serum/plasma	Bone turnover
RANKL	3	33.3%	2		1	Serum/plasma	Bone turnover
CD14 ⁺ CD16 ⁺ cell number	2	100.0%		2		Pb	Inflammatory
IL-8	2	100.0%		2		Serum/plasma	Inflammatory
TRAP-5b	2	100.0%		2		Serum/plasma	Bone turnover
CD4+ (% or cell number)	2	50.0%	1	1		Pb	Inflammatory
CD8+ (% or cell number)	2	50.0%	1	1		Pb	Inflammatory
CRP	2	50.0%	1	1		Serum/plasma	Inflammatory
Marker Panel	2	50.0%	1	1		Serum/plasma	Inflammatory and bone turnover
BAP	2	0.0%	2			Serum/plasma	Bone turnover
CD2+ (%)	1	100.0%		1		Pb	Inflammatory
CD22+ (%)	1	100.0%		1		Pb	Inflammatory
CD25+ (%)	1	100.0%		1		Pb	Inflammatory
Hyaluronic Acid	1	100.0%		1		Serum/plasma	Inflammatory (connective tissue degradation or macrophage activation)
OPG/RANKL	1	100.0%		1		Serum/plasma	Bone turnover
Osteoclastogenesis	1	100.0%		1		Pb	Bone turnover
PYD	1	100.0%		1		Urine	Bone turnover
CD35+ (%)	1	0.0%	1			Pb	Inflammatory
Elastase	1	0.0%	1			Serum/plasma	Inflammatory (connective tissue degradation or granulocyte/macrophage activation)
GM-CSF	1	0.0%	1			Serum/plasma	Inflammatory (connective tissue degradation or granulocyte/macrophage activation)
IL-11	1	0.0%	1			Serum/plasma	Inflammatory
MMP-1	1	0.0%	1			Serum/plasma	Inflammatory
PGE2	1	0.0%	1			Serum/plasma	Inflammatory
PIIINP	1	0.0%	1			Serum/plasma	Inflammatory (connective tissue degradation or macrophage activation)
PINP	1	0.0%	1			Serum/plasma	Bone turnover
sIL-2r	1	0.0%	1			Serum/plasma	Inflammatory
TGF- β	1	0.0%	1			Serum/plasma	Mechanism
totals	90	41.1%	53	35	2		

Table 4. Biomarkers in serum or plasma (see Table 1 for abbreviations)

Biomarker	Effect	Implant	Groups compared (test versus control)	Test time from implantation (years)	Control time from implantation (years)	Number of test subjects	Number of control subjects	Tissue	Reference
BAP	None	THA	Aseptic loosening versus stable implants	9.6	9.1	50	50	Serum	[30]
BAP	None	THA	Aseptic loosening versus stable implants	12.6	12.6	23	26	Serum	[35]
CRP	None	THA	Osteolysis versus no osteolysis (long-term)	> 10	> 10	6	10	Serum	[11]
CRP	Elevated	THA	Osteolysis versus no osteolysis (short-term)	> 10	4.1	6	5	Serum	[11]
CTX-I	None	THA	Aseptic loosening versus stable implants	9.7	3.7	12	12	Serum	[16]
CTX-I	Elevated (trend)	THA	Aseptic loosening versus stable implants	12.6	12.6	23	26	Serum	[35]
CTX-I	Elevated	TKA	Potentially unstable versus stable (RSA)	0.5, 1, 2	0.5, 1, 2	15	25	Serum	[17]
Elastase	None	THA	Aseptic loosening versus stable implants	8.6	8.4	23	23	Serum	[31]
GM-CSF	None	THA	Aseptic loosening versus stable implants	8.6	8.4	23	23	Serum	[31]
HA	Elevated	THA	Aseptic loosening versus stable implants	5.4	5.6	9	13	Serum	[20]
IL-1 β	None	THA	Late aseptic loosening versus stable implants	17	5	17	13	Plasma	[10]
IL-1 β	None	THA	Early aseptic loosening versus stable implants	5	5	7	13	Plasma	[10]
IL-1 β	None	THA	Osteolysis versus no osteolysis (long-term)	> 10	> 10	6	10	Serum	[11]
IL-1 β	None	THA	Osteolysis versus no osteolysis (short-term)	> 10	4.1	6	5	Serum	[11]
IL-1 β	None	THA	Osteolysis versus stable implants	6.5	4.9	8	10	Serum	[6]
IL-1 β	Elevated	THA, TKA	Aseptic loosening versus stable implants	10	11	50	50	Plasma	[13]
IL-1 β	None	THA	Aseptic loosening versus stable implants	5.4	5.6	9	13	Serum	[20]
IL-1 β	None	THA	Aseptic loosening versus mechanical loosening	9.7	7.2	43	30	Plasma	[36]
IL-1 β	Elevated	THA	Aseptic loosening versus stable implants	9.7	2.2	43	16	Plasma	[36]
IL-6	None	THA	Osteolysis versus stable implants	6.5	4.9	8	10	Serum	[6]
IL-6	None	THA	Aseptic loosening versus stable implants	8.6	8.4	23	23	Serum	[31]
IL-6	Elevated	THA	Osteolysis versus no osteolysis (long-term)	> 10	> 10	6	10	Serum	[11]
IL-6	Elevated	THA	Osteolysis versus no osteolysis (short-term)	> 10	4.1	6	5	Serum	[11]
IL-6	Elevated	THA	Osteolysis versus stable implants	12.3	5.4	28	24	Serum	[33]
IL-8	Elevated	THA, TKA	Aseptic loosening versus stable implants	10	11	50	50	Plasma	[13]
IL-8	Elevated	THA	Osteolysis versus stable implants	12.3	5.4	28	24	Serum	[33]
IL-11	None	THA	Osteolysis versus stable implants	6.5	4.9	8	10	Serum	[6]
Marker panel*	Different	THA	Late aseptic loosening versus stable implants	17	5	< 31	< 19	Plasma	[10]
Marker panel*	Different (trend)	THA	Early aseptic loosening versus stable implants	5	5	< 15	< 19	Plasma	[10]
MMP-1	None	THA	Osteolysis versus stable implants	6.5	4.9	8	10	Serum	[6]
NTX	Elevated	THA	Osteolysis versus stable implants	9.6	2.1	21	18	Serum	[29]
NTX	None	THA	Late aseptic loosening versus stable implants	17	5	29	14	Plasma	[10]
NTX	None	THA	Early aseptic loosening versus stable implants	5	5	7	14	Plasma	[10]
OPG	Elevated	THA	Aseptic loosening versus stable implants	9.3	2.7	36	33	Serum	[8]

Table 4. continued

Biomarker	Effect	Implant	Groups compared (test versus control)	Test time from implantation (years)	Control time from implantation (years)	Number of test subjects	Number of control subjects	Tissue	Reference
OPG	None	THA	Late aseptic loosening versus stable implants	17	5	29	12	Plasma	[10]
OPG	None	THA	Early aseptic loosening versus stable implants	5	5	14	12	Plasma	[10]
OPG/RANKL ratio	Elevated	THA	Aseptic loosening versus stable implants	9.3	2.7	36	33	Serum	[8]
Osteocalcin	Elevated	TKA	Potentially unstable versus stable (RSA)	1	1	15	25	Serum	[17]
Osteocalcin	Elevated	THA	Aseptic loosening versus stable implants	9.6	9.1	50	50	Serum	[30]
Osteocalcin	None	THA	Aseptic loosening versus stable implants	12.6	12.6	23	26	Serum	[35]
PGE2	None	THA	Osteolysis versus stable implants	6.5	4.9	8	10	Serum	[6]
PICP	None	TKA	Potentially unstable versus stable (RSA)	0.5, 1, 2	0.5, 1, 2	15	25	Serum	[17]
PICP	Depressed	THA	Osteolysis versus stable implants	9.6	2.1	21	18	Serum	[29]
PICP	None	THA	Late aseptic loosening versus stable implants	17	5	18	11	Plasma	[10]
PICP	None	THA	Early aseptic loosening versus stable implants	5	5	13	11	Plasma	[10]
PICP	None	THA	Aseptic loosening versus stable implants	9.6	9.1	50	50	Serum	[30]
PIINP	None	THA	Aseptic loosening versus stable implants	5.4	5.6	9	13	Serum	[20]
PINP	Elevated (trend)	THA	Aseptic loosening versus stable implants	12.6	12.6	23	26	Serum	[35]
RANKL	Depressed	THA	Aseptic loosening versus stable implants	9.3	2.7	36	33	Serum	[8]
RANKL	None	THA	Late aseptic loosening versus stable implants	17	5	20	18	Plasma	[10]
RANKL	None	THA	Early aseptic loosening versus stable implants	5	5	9	18	Plasma	[10]
sIL-2r	None	THA	Aseptic loosening versus stable implants	8.6	8.4	23	23	Serum	[31]
TGF- β	None	THA	Osteolysis versus stable implants	6.5	4.9	8	10	Serum	[6]
TNF- α	None	THA	Late aseptic loosening versus stable implants	17	5	29	11	Plasma	[10]
TNF- α	None	THA	Early aseptic loosening versus stable implants	5	5	9	11	Plasma	[10]
TNF- α	None	THA	Osteolysis versus no osteolysis (long-term)	> 10	> 10	6	10	Serum	[11]
TNF- α	None	THA	Osteolysis versus no osteolysis (short-term)	> 10	4.1	6	5	Serum	[11]
TNF- α	None	THA	Osteolysis versus stable implants	6.5	4.9	8	10	Serum	[6]
TNF- α	Elevated	THA, TKA	Aseptic loosening versus stable implants	10	11	50	50	Plasma	[13]
TNF- α	None	THA	Aseptic loosening versus mechanical loosening	9.7	7.2	43	30	Plasma	[36]
TNF- α	Elevated	THA	Aseptic loosening versus stable implants	9.7	2.2	43	16	Plasma	[36]
TNF- α	None	THA	Osteolysis versus stable implants	12.3	5.4	28	24	Serum	[33]
TRAP-5b	Elevated	THA	Aseptic loosening versus stable implants	5.2	8.8	27	19	Serum	[28]
TRAP-5b	Elevated	THA	Aseptic loosening versus stable implants	9.7	3.7	12	12	Serum	[16]

* Combination score based on IL-1 β , NTx, OPG, PICP, RANKL, and TNF- α .

Table 5. Biomarkers in urine (see Table 1 for abbreviations)

Biomarker	Effect	Implant	Groups compared (test versus control)	Test time from implantation (years)	Control time from implantation (years)	Number of test subjects	Number of control subjects	Reference
CTX-I	None	THA	Aseptic loosening versus stable implants	8.2	7.8	52	52	[32]
DPYD	Elevated	THA	Aseptic loosening versus stable implants	8.2	7.8	52	52	[32]
DPYD	None	THA, TKA	Aseptic loosening versus stable implants	Not specified	Not specified	36	33	[24]
DPYD	Elevated	THA	Aseptic loosening versus stable implants	9.6	9.1	50	50	[30]
DPYD	None	THA	Aseptic loosening versus stable implants	12.6	12.6	23	26	[35]
NTX	None	THA	Osteolysis versus stable implants	3.5	6.1	33	127	[34]
NTX	None	THA	Aseptic loosening versus stable implants	8.2	7.8	52	52	[32]
NTX	Elevated	THA	Aseptic loosening versus stable implants	9.6	9.1	50	50	[30]
NTX	Elevated	THA	Osteolysis versus stable implants	8.8	2.4	11	8	[2]
NTX	Elevated	THA	Aseptic loosening versus stable implants	12.6	12.6	23	26	[35]
PYD	Elevated	THA	Aseptic loosening versus stable implants	9.6	9.1	50	50	[30]

Table 6. Biomarkers in synovial fluid (see Table 1 for abbreviations)

Biomarker	Effect	Implant	Groups compared (test versus control)	Test time from implantation (years)	Control time from implantation (years)	Number of test subjects	Number of control subjects	Reference
IL-1 β	None	THA	Aseptic loosening versus stable implants	9.8	2.8	26	12	[22]
IL-1 β	None	THA	Loosened type II or III versus loosened type I	Not specified	Not specified	Not specified	Not specified	[22]
TNF- α	None	THA	Aseptic loosening versus stable implants	9.8	2.8	38	12	[22]
TNF- α	Elevated	THA	Loosened type II or III versus loosened type I	Not specified	Not specified	Not specified	Not specified	[22]

Table 7. Biomarkers in peripheral blood (see Table 1 for abbreviations)

Biomarker	Effect	Implant	Groups compared (test versus control)	Test time from implantation (years)	Control time from implantation (years)	Number of test subjects	Number of control subjects	Reference
CD14 ⁺ CD16 ⁺ cell number	Elevated	THA	Aseptic loosening versus stable implants	9.7	7.2	43	30	[36]
CD14 ⁺ CD16 ⁺ cell number	Elevated	THA	Aseptic loosening versus stable implants	9.7	2.2	43	16	[36]
CD2+ (%)	Elevated	THA	Aseptic loosening versus stable implants	7	10	26	8	[7]
CD22+ (%)	Elevated	THA	Aseptic loosening versus stable implants	7	10	26	8	[7]
CD25+ (%)	Elevated	THA	Aseptic loosening versus stable implants	7	10	26	8	[7]
CD35+ (%)	None	THA	Aseptic loosening versus stable implants	7	10	26	8	[7]
CD4+ (%)	None	THA	Osteolysis versus stable implants	7	10	26	8	[7]
CD4+ cell number	Elevated	THA	Aseptic loosening versus stable implants	12	4	15	15	[26]
CD8+ (%)	None	THA	Osteolysis versus stable implants	7	10	26	8	[7]
CD8+ cell number	Elevated	THA	Osteolysis versus stable implants	12	4	15	15	[26]
Osteoclastogenesis	Elevated	THA	Aseptic loosening versus stable implants	12	4	15	15	[26]

little evidence that biomarkers can provide early warning of these often occult pathologies. A second limitation is that we did not include animal studies in which biomarkers of aseptic loosening/osteolysis were studied [14, 18, 21, 27] because only two of these studies included stable and loosened implants [18, 27]. These two studies showed dramatic increases in serum CTX-1, OPG, cathepsin K, and PINP and depression of serum OC. We also eliminated many papers examining synovial fluid markers because the control subjects were often healthy subjects or patients who were at the end stage of a disease such as osteoarthritis, rheumatoid arthritis, or osteonecrosis but had not yet had an implant. Another limitation is that not all studies had control groups matched to the failure groups on the basis of age, sex, duration of implant placement, and type of implant. Some of these confounding factors could account for inconsistencies between reports.

Biomarkers with known connection to inflammation and bone turnover are of particular interest based on their likely involvement in the molecular pathogenesis of periimplant osteolysis. Thus, it is somewhat surprising that the proinflammatory cytokines TNF- α , IL-6, and IL-1 β were not strongly implicated by this review. However, the apparent insensitivity of these proinflammatory markers may reflect their transient, but early, involvement with relatively minor roles at end-stage disease when the majority of the reviewed studies were conducted. Markers of bone resorption (NTx, DPYD, and pyridinoline [PYD]) did tend to be elevated in patients with aseptic loosening or osteolysis (six of 10 comparisons). Serum IL-8, and TRAP-5b were elevated in all four comparisons involving these markers, and the distribution of immune-related peripheral blood cell types appears to be consistently affected, indicating that genuine biomarkers for aseptic loosening/periimplant osteolysis do exist and encourage future studies.

One main conclusion from this systematic review is that many candidate biomarkers remain unvalidated because the findings of different studies do not corroborate each other. Principal causes of this inconsistency include problems with the control groups and the lack of prospective studies. Thus, careful selection of control populations, ideally representing well-matched patients with nonproblematic implants of equivalent design, should be emphasized as a key component of future studies. Perhaps even more important is the need for prospective studies so that change in markers over time in the same subject can be studied, thereby minimizing the effect of interindividual variation.

We chose to exclude studies in which the marker was levels of metal ions in body fluids or in which the genotype was identified as a risk factor for development of osteolysis. The metal ion level studies merit separate review and do not meet the definition of a biological marker. The

genotype studies were reviewed recently [5] and were eliminated because our main interest was in biomarkers of disease incidence and progression and, thus, we focused on biomarkers that could change in response to disease pathogenesis.

An implication of this review is that biomarker panels may have significantly greater potential to differentiate disease status or progression than individual biomarkers. This makes sense from a theoretical point of view given that implant failure is likely a highly multifactorial disorder involving multiple cell types and signaling pathways as well as significant contributions from host genetic factors. The value of biomarker panels is highlighted by the article by He et al [10] that showed increased capacity of combined analysis of several biomarkers over each biomarker considered in isolation. This promising study suggests that future studies focusing on panels should be emphasized.

Within this regard, opportunities remain for more advanced hypothesis-based biomarker discovery initiatives as well as for more “unbiased” studies where multiple molecules are screened in an attempt to discover completely novel biomarkers. Because studies clarify the basic biological mechanisms underlying poor implant performance, the scope of potential pathway-focused biomarker panel investigations will increase. These may include pathways involving inflammatory activation of myeloid cells, osteoclast generation, and activation as well as key pathways within mesenchymal cell populations such as Wnt/beta catenin signaling [3, 9, 23, 25]. Biomarker discovery efforts centered on these important pathways that are likely dysregulated during implant failure may help drive our understanding of the molecular pathophysiology of implant failure, generate new potential biomarkers, and guide therapeutic strategies.

Clearly, longitudinal studies are needed. Indeed, the one longitudinal study included in this review showed that the bone resorption marker, CTX-1, was elevated early in patients undergoing TKA suspected to have loosened implants [17] and we recently also found that this marker was elevated early in a rat model [27]. A major challenge in longitudinal studies in patients is stratification into aseptic loosening/osteolysis and control groups, which can only occur long after initiation of the study because of the normal etiology of the disease. Thus, it would be of great value to have an early, independent marker of implant loosening as has been proposed in RSA [17]. Well-defined animal models would also be helpful because the discovery cycle can be greatly shortened, it is easier to include appropriate controls, longitudinal studies can be more easily performed, the effects of different challenge agents (eg, polyethylene particles versus corrosion products) can be studied, and marker levels can be related to well-defined stages of disease progression.

In conclusion, we believe that the goal of establishing useful biomarkers of implant performance, specifically wear and corrosion, is achievable but not yet fully realized. Published studies have failed to fully validate potential biomarkers, a shortcoming that probably can be attributed to issues of selection of appropriate controls. The importance of continued efforts in this direction is clear. TJA rates are increasing, driving establishment of increasing groups of individuals at risk of poor implant performance and failure, yet early detection methodologies and therapeutic options are lacking. Optimization of future biomarker discovery and validation efforts should take into consideration careful control for implant materials and ensuring that the time since implantation is consistent in the study groups. Approaches in which tests of specific pathways and biomarkers and in which multiple biological molecules are screened are both needed. These studies are likely to lead to the discovery of novel pathways and point to biomarkers that can help diagnose impending implant failure long before clinical signs and symptoms appear.

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