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Intérêt des biomarqueurs dans le diagnostic précoce des péri-implantites

THÈSE POUR LE DIPLÔME D'ÉTAT DE

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Table des matières

Introduction

La restauration prothétique d'un édentement reste une problématique majeure et en constante évolution dans la dentisterie. Ainsi, l'implantologie a trouvé sa place comme méthode d'excellence pour se rapprocher au mieux d'un organe dentaire naturel. Grâce à cette technique de restauration, les dents adjacentes restent intactes, l'implant possède une bonne biocompatibilité et un biomimétisme permettant d'assurer un confort fonctionnel, esthétique de bonne qualité pour le patient. Cependant, cette restauration prothétique possède une faiblesse concernant son intégration tissulaire. La péri-implantite, infection autour de l'implant liée à une colonisation bactérienne, crée, par le processus inflammatoire, une perte d'attache péri-implantaire (1,2). Cette infection peut aller jusqu'à la perte de l'implant en place par un déséquilibre de la balance bactérienne. La sphère scientifique a donc tenté des alternatives pour améliorer l'intégration tissulaire et éviter ces faiblesses. Des recherches ont été effectué concernant les différent matériaux implantaires applicables (céramique, titane). Il en va également concernant le protocole implantaire pour lequel les phases de chirurgie, implantaire ont vu leur intervalle varier pour comparer le pourcentage de survie selon les protocoles. Il en a été conclu, que la péri-implantite reste très présente concernant les implantations dentaires malgré le choix de matériau le plus biocompatible et un protocole permettant le plus de taux de survie. On en conclut que cette maladie péri-implantaire ne peut être éradiquée et doit être surveillée et contrôlée. Ainsi, une maintenance régulière de cet implant permet de contrôler cette infection (3) et maintenir un résultat esthétique, fonctionnel et biocompatible satisfaisant. A ce jour, cette prévention est basée sur des séances avec le contrôle des paramètres cliniques (profondeur de sondage, saignement au sondage, indice gingival et indice de plaque) et la réalisation de radiographies pour évaluer la valeur de l'alvéolyse osseuse (4-6).

Cependant, au jour d'aujourd'hui, cette infection est détectée lorsqu'elle a déjà progressé et provoqué une destruction osseuse, c'est-à-dire un état avancé de la maladie péri-implantaire car il n'existe à ce jour aucun moyen de détection de la maladie précocément.

Depuis des décennies, la communauté scientifique cherche un moyen de détecter cette maladie infectieuse aux prémices pour prévenir sa progression et éviter les complications péri-implantaires (7).

Depuis les années 1990, l'implication de la réaction inflammatoire dans la maladie parodontale a été étudiée, ce qui a permis de comprendre et d'organiser les soins de support (8,9). Après avoir découvert certains aspects communs entre la parodontite et la péri-implantite, (10,11) notamment sur les bactéries pathogènes, les scientifiques se sont ensuite intéressés au phénomène qui conduit à l'infection, qu'elle soit péri-dentaire ou péri-implantaire (12). La péri-implantite, selon les études, atteint 12 à 43% des implants, chez 28 à 56% des patients, ce qui entraîne alors un taux d'échec qui peut être important et une diminution de la qualité de vie du patient (13-16). L'intérêt de la détection précoce de cette maladie péri-implantaire devient un défi et surtout un objectif afin de réduire le taux d'échec implantaire à court ou long terme. Dans les années à venir, et dès aujourd'hui, la médecine tant à se développer afin de réaliser une thérapeutique personnalisée et plus seulement universelle (17). Cette nouvelle prise en charge permettrait d'inclure les variables de chaque individu qui influent sur le métabolisme et la variation dans l'évolution des pathologies chez chaque patient. Pour se faire, il faut tout d'abord avoir une bonne compréhension de la maladie concernée pour pouvoir juger de la variabilité intra-individuelle.

La compréhension du système inflammatoire péri-implantaire est désormais avancée, depuis l'apparition de ce type de réhabilitation prothétique (18,19) ce qui permet d'envisager de nouveaux outils que ce soit pour la détection ou pour la gestion du traitement. De ce fait, les scientifiques ont pu évaluer l'utilité des biomarqueurs comme outils de diagnostic précoce de la maladie. Ces biomarqueurs possèdent un potentiel de diagnostic conséquent car ils participent aux changements métaboliques qui engendrent les phénomènes inflammatoires permettant de renouveler les tissus ou les composent, ainsi que la défense immunitaire. Dans une démarche d'individualisation de la médecine et de l'évolution de la détection et de la compréhension des fonctions des biomarqueurs, une nouvelle voie est ouverte concernant le diagnostic. Certains sont déjà utilisés comme outils diagnostic dans le domaine de la médecine, c'est le cas pour des pathologies médicales (maladies cardiaques, etc.). C'est grâce à ces avancées que l'on peut espérer pouvoir appliquer ces techniques au domaine de l'odontologie. Il semblerait de par le caractère inflammatoire de la maladie parodontale et péri-implantaire, que les biomarqueurs puissent être utilisés pour détecter précocement la maladie active (20-22).

La sphère de la recherche en odontologie s'est alors intéressée à investiguer différents biomarqueurs en relation avec la maladie péri-implantaire.

Dans l'éventail des biomarqueurs étudiés, les cytokines pro-inflammatoires en font partie. Elles font partie intégrante du système de défense du péri-implant face à l'attaque bactérienne en étant en première ligne. Les biomarqueurs du remodelage osseux font également partie des biomarqueurs étudiés. En effet, ils sont nécessaires durant l'ostéo-intégration implantaire avec le remodelage osseux. Cependant, durant les phases d'inflammation, ils peuvent avoir des niveaux largement augmentés et devenir néfastes pour le péri-implant (23). Les enzymes sont également étudiées. Elles viennent jouer le rôle dans le remodelage tissulaire. Les constituants tissulaires sont évidemment des biomarqueurs qui jouent leur rôle dans le remodelage tissulaire et leurs niveaux pourraient varier en phase d'inflammation. L'ensemble de ces biomarqueurs sont étudiés car ils pourraient être, du fait du processus inflammatoire et de leur fonction, des biomarqueurs valables pour cet usage.

Dans cette recherche de médecine individualisée et de diagnostic précoce, le moyen de diagnostic et la technique envisagée pour l'appliquer fait partie intégrante de la démarche.

Ainsi, la recherche se focalise sur le principe d'un outil de diagnostic simple et non invasif, afin de détecter une maladie péri-implantaire avant même l'apparition de signes cliniques et ainsi permettre sa stabilité et sa bonne ostéo-intégration tout en favorisant le confort du patient.

L'objectif de cette revue de littérature sera d'évaluer l'intérêt des biomarqueurs dans le diagnostic précoce des péri-implantites. On étudiera les différentes biomarqueurs étudiés ainsi que les techniques de prélèvement effectuées. Cette étude pourrait alors conclure sur le potentiel de ces biomarqueurs en tant que diagnostic précoce des péri-implantites.

Interest of biomarkers in the early diagnosis of peri-implantitis

E. Gontier, X. Struillou, A. Soueidan, F. Perez, C. Verner

Introduction : The area of comprehensive and preventive care is leading the scientific community to look at new tools that would allow early diagnosis of diseases such as peri-implantitis. Biomarkers would provide a non-invasive diagnostic tool to detect early peri-implantitis. We will study the interest of biomarkers in the early diagnosis of peri-implantitis.

Material and methods : We performed a systematic review including 48 high level evidence articles (RCT, meta-analysis, systematic review) and compared the different biomarkers studied and the method used by each study. The majority of the studies were cross-sectional with a sample of crevicular fluid obtained by strip paper and analysed by ELISA.

Results : The most studied biomarkers are bone biomarkers, enzymes, cytokines, tissue constituents and hormones.

Discussion : The biomarkers that seem to be the most promising are bone biomarkers (OPG, RANK, RANKL, OC), cytokines (IL-1) and enzymes (metalloproteinases). Indeed, the majority of investigations carried out on them show significantly different levels of biomarkers between healthy and early peri-implantitis. This encourages the idea that they could be used as a diagnostic tool for early peri-implantitis.However, as most studies are cross-sectional, prospective studies with larger sample sizes are needed to increase the reliability and level of evidence for the use of these biomarkers as early diagnostic tools for peri-implantitis.

INTRODUCTION

Peri-implantitis, an infection around the implant linked to bacterial colonization, creates, through the inflammatory process, a loss of peri-implant attachment (1,2). This infection can go as far as the loss of the implant in place. However, regular maintenance of this implant helps to control this infection (3). To date, this prevention is based on sessions with control of clinical parameters (probing depth, bleeding on probing, gingival index and plaque index) and taking X-rays to assess the value of bone alveolysis (4–6).

However, this infection is detected when it has already progressed and caused bone destruction, that is to say an advanced state of peri-implant disease.

For decades, the scientific community has been looking for a way to detect this infectious disease early to prevent its progression and thus avoid peri-implant complications (7).

Since the 1990s, the involvement of inflammatory reaction in periodontal disease has been studied, which has led to an understanding and organized supportive care (8,9). After discovering some common aspects between periodontitis and peri-implantitis, (10,11) in particular on pathogenic bacteria, the scientists then became interested in the phenomenon that led to the infection, whether peri-dental or peri-implant (12). The peri-implantitis, according to studies, reaches 12 to 43% of implants, in 28 to 56% of patients, which then leads to a failure rate that can be significant and a decrease in quality of life for the patient.(13–16) Thus, the interest in early detection of this peri-implant disease becomes a challenge and above all an objective in order to reduce the rate of implant

failure in the short or long term. In fact, in addition, we are now aiming for personalized medicine and no longer just universal (17).

The peri-implant inflammatory system is now a little better understood, since appearance of this type of prosthetic rehabilitation (18,19). As a result, scientists have been able to assess the usefulness of biomarkers as tools for early diagnosis of the disease. This is the case for other medical pathologies (heart disease, etc.) and therefore seems to be an applicable means for periodontal and in particular peri-implant diseases (20–22).

The studies evaluated pro-inflammatory cytokines, biomarkers of bone remodelling (necessary however for osteo-integration but harmful if present in excess (23)), enzymes, tissue constituents, which could be, due to the inflammatory process, biomarkers valid for this use.

As for the means of diagnosis, the research then focuses on the principle of a simple and non-invasive diagnostic tool, in order to detect peri-implant disease even before the appearance of clinical signs and thus allow its stability and good osteo-integration.

The aim of this literature review will be to assess the interest of biomarkers in the early diagnosis of peri-implantites.

MATERIEL AND METHODS

We carried out a bibliographic search in order to select the articles to made our systematic review. Thus, on the PubMed database, we used as keywords:

Keywords	results
Peri implant crevicular fluid	281 results, 117 retained
MeSH : gingival crevicular fluid/biomarkers/peri implantitis	18 results, 15 retained
MeSH : biomarkers/periimplantitis	42 results, 31 retained
MeSH : dental implant/mucositis/biomarkers	3 results, 2 retained
MeSH : Interleukin-1beta/periimplantitis	34 results, 16 retained
MeSH : tnfalpha/peri implantitis	26 results, 11 retained
MeSH : factor, transforming growth/periimplantitis	0
MeSH : cytokines/periimplantitis	99 results, 49 retained

Table 1 : MeSH for bibliographic search

We then made a selection by inclusion and exclusion criteria by selecting according to the titles:

Inclusion criteria	Exclusion criteria
Peri-implant	Cardiovascular disease
Peri-implantitis	Obese/body fat patient
Levels	Stress
Cytokines	Smoking
Biomarkers	Treatment
Interleukines (6,8,10,12,17,23,33)	Chirurgical treatment
Enzymes/ metalloproteases/MMP-8/ collagenase 2	Bacterial diversity
Gene expression	Antibiotic
Bone loss	Probiotic therapy
Resorption	Laser therapy
Remodelling	Photobiomodulation therapy
Healthy or not implant	Oncological disease
Cellular population	Prostheses
Cathepsine K	Bar or ball retained mandibular overdenture
RANK/RANKL/OPG	Full arch prostheses
Aspartate aminotransferase	Influence of platform switching
Biological response	Effect of restoration marging
Peri-implant crevicular fluid	Orthodontics
Gingival crevicular fluid	Orthodontic mini-screw
Calprotectin	Comparison loaded/non loaded
Collagen	Treatment of peri-implant disease
CD14, TNFalpha, TGFbeta	Effects of nano-hydroxyapatite
Microbiological host response	Antiseptic gel
CyPA Emmprim	Oxidized surfaces
Saliva	Dogs
Diagnostic tool	Mouse
Prostaglandines	Manual VS sonic toothbrushing
Human beta defensines	Wound healing
Trem/PGLYRP1	Comparison flapless and flap surgery
Vascular endothelial growth factor	Enamel matrix derivative
RCT/ Meta-analyse/revue systematic	

Table 2 : inclusion and exclusion criteria

Thus, according to the research: a total of 549 articles were identified and then, after elimination of duplicates, there remained in the end 335

articles. After study by title (according to exclusion criteria), 214 were retained. After sorting by inclusion criteria, 56 articles remained (including articles from references linked to RCT articles).

After a complete study of the articles, 8 articles could be excluded.

This left 48 articles for the systematic review.

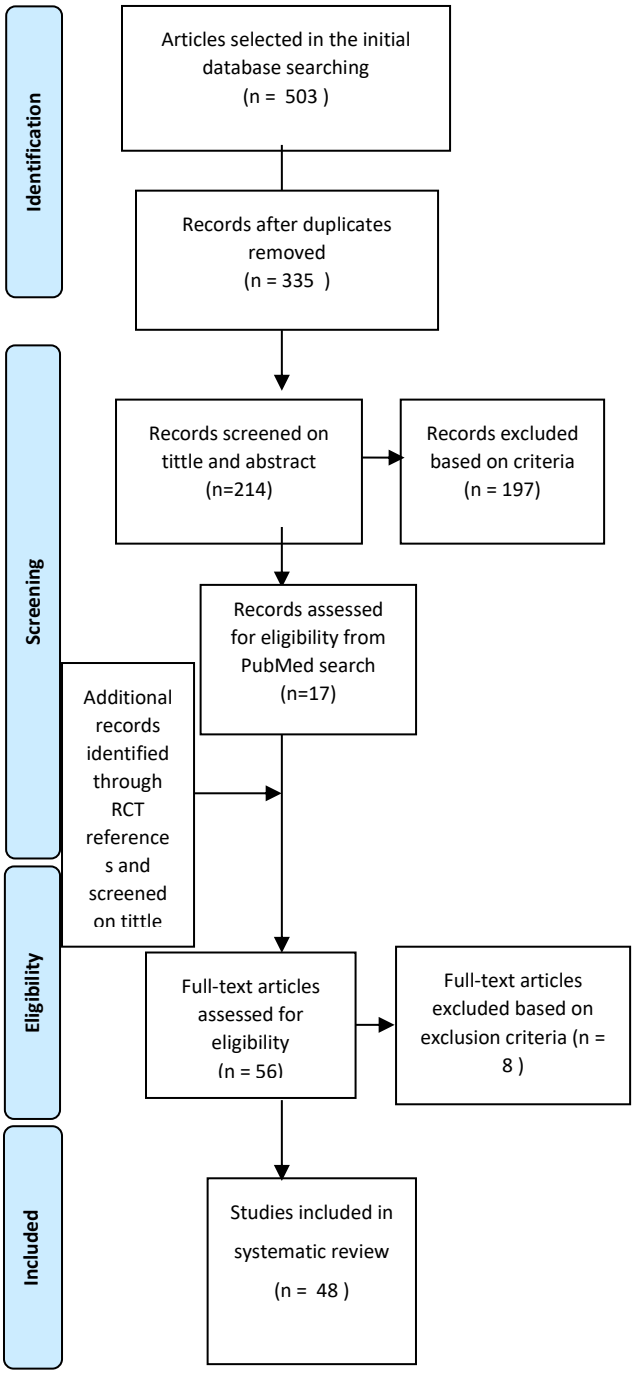

Figure 1 PRISMA schema

We then produced a table of articles to compare the articles according to the type of study, the sampling, the results and the clinical benefit of the results.

For the biomarkers assessed, the studies investigated:

o Aminotransferase (enzyme): ASAT/ALAT

o TNF Alpha-308A (necrosis factor, activation for inflammation)

o Bone loss biomarkers: RANKL/OPG/SRANKL (signaling pathway regulating osteoclasts)

o Osteoporotegerin (soluble receptor binding to RANKL to differentiate osteoclasts)

o RANKL: receptor activator of nuclear factor kappa-B ligand (ligand involved in bone metabolism by activating Ob and Oc)

o RANK (transmembrane protein activating Oc differentiation)

o C-telopeptide (bone remodeling marker, when accelerated collagen degradation)

o Collagenase 2 (enzymes released during bacterial pathogenesis, after cytokine release)

o Myeloperoxidase (oxydorductase active when bacterial infection)

o Cytokines: interleukin 1B, interleukin 6, interleukin 34, TNFa (protein involved in inflammation and acute phase reaction)

o CSF-1 (macrophage colony stimulation factor)

o prostaglandin E2 (proinflammatory)

o Metalloprotease matrix: 25 and 26, 8, 7 (responsible for the proteolysis of the extracellular matrix)

o Elastase (catalyzes the hydrolysis of elastin, elastic fiber that determines the mechanical properties of connective tissue with collagen)

o alpha2-macroglobulin (blood plasma protein involved in the fibrinolytic proces

o Alkaline phosphatase (present in bone)

o Sclerotin (protein)

o TWEAK (biomarker by monocyte and macrophage)

o Osteoporosin (bone tissue adhesion protein linking hydroxyapatite to bone cells)

o Lamina-5 gamma-2 (major protein constituent of the basal blade)

o Collagenase 2 (MMP8) (connective tissue collagen cleavage enzyme)

o Osteocalcin (protein hormone, non collagen, bone specific, secreted by osteoblasts in favor of CA^{2}+fixation)

o Deoxypyridinoline (collagen bypass molecule released during bone resorption)

The types of studies are case-control studies (22), randomized clinical trials (12), meta-analyses (5) and systematic reviews (5), and cross-sectional studies (4).

However, the sample of studies often remains limited (samples of fewer than 30 patients or systematic reviews of fewer than 30 articles for 19 studies).

To measure the data, for the majority of studies, the samples were taken by periostrip and then analysed by ELISA or qPCR (this last especially for enzymes).

Results:

We have created a table to provide better legibility regarding the criteria (article reference, type of study, population, method, result) for each article. We then detail, by type of biomarker, the results obtained. (Table 3).

Type of Bias:

-of selection:

Some studies have selection biases such as inclusion in the population of a patient with rheumatoid arthritis. However, this disease is an inflammatory disease that could then alter the results for the investigation of inflammatory factors in this study. (24). A change in the results may also be made by including smokers and non-smokers in a study, which may also change the inflammation and composition of the vesicular fluid (25). The age of the patients can also influence the inflammatory phenomenon and thus the amount of biomarkers present at the peri-implant sampling sites (26). For example, some samples have allowed the inclusion of patients with risk factors that influence inflammation (27).

-Measurement:

Despite the precautions taken for the collection of peri-implant crevicular fluid or gingival crevicular fluid, it is nevertheless possible that these samples are polluted by saliva, which would change the results regarding biomarker levels.

A heterogeneity in the definition of peri-implantitis (criteria taken into account) leads to a variation in the results, particularly for meta-analyses, which then highlight results that take into account studies with variable measurement parameters.

Our systematic review was thus has been achieved with this bias that we tried to limit at best by selecting studies of high level of evidence to reduce its effect. It is then possible to get rid of it by implementing a double investigator or even setting up a questionnaire which allows investigators to have guidelines for the selection of articles (28).

Results (table 3)

reference	biomarkers	type of study	sampling	clinical method	analysis	results
Hall J et Al., 2011	TRAP, DKK-1, OPG, CatK, OC	randomized clinical trial	7 healthy patients, 7 patients with clinical signs of peri-implantitis	PICF sampling with paper strip and capillary tube	qPCR	identical levels for HI VS MU and HI VS PI. Diff in 1 patient
Hall J et Al., 2015	plasminogen system: interleukins 1Beta, 8, tPA, PAI-2, TRAP, CathepsineK	case control study	75 patients: HI (25), MU (25), PI (25)	PICF sampling with paper strip and capillary tube	qPCR	significantly higher levels interleukin 1B and 8 for group PI, significantly higher levels tPA and PAI-2 for MU group, no significant difference for TRAP and cathepsinK
Dereka X et al., 2012	Interleukins 1,2,6 and TNFalpha, TGFB1	systematic review	7 articles	database search	2 independant readers	between IL1 / 2/6, TNFa, TGFB1 and loss early bone PI: no evidence of association; 2/3 of studies associating PI and IL1 genotype = IL1RN (intron 2), IL1A (-889), IL1B (+3954): corr between>infection and PI destruction
Paolantonio M et Al., 2000	aspartate aminotransferase	case control study	81 patients: 27 HI, 27 MU, 27 PI	PICF sampling with endodontic paper strip	spectrophotometry	Significant difference in activity of AST between HI and PI and MI and PI. Correlation of AST activity with PDP / BOP / PO

Table 3

Mo Y-Y et Al., 2016	Tumor necrosis factor alpha G-308A	meta-analysis	6 studies	database search (PubMed, Embase, Cochrane) since 2015, july	Odd's-ratio	No significant correlation between TNFα-G308A polymorphism and IP risk
Lachmann et Al., 2007	Interleukins 1A-889 and IL-1B+3954	cross-sectional study	29 implants at 29 patients	PICF sampling with paper strip + RX + clinical parameters (attachment, probing depth)	ELISA method	the effect of irrelevant genotypes on differences in peri-implant sites of inflammation
Talo Yildirim T et Al., 2017	Interleukin 1B	randomized clinical trial	40 patients in 2 groups: group "1 surgical step" and group "2 surgical steps"	PICF sampling with paper strip and recording of clinical parameters	ELISA method	no significant difference between group 1 and 2
Rakic M et Al., 2012	RANKL/RANK/OPG	case control study	70 patients: 23 PI, 25 HI, 22 with periodontitis severe chronic	PICF sampling with paper strip and recording of clinical parameters	ELISA method	significant difference in PI VS HI and correlation between parameters clinical and biomarker levels sauf chez PI
Arikan F et Al., 2011	C-telopeptide, sRANKL/OPG and albumine	case control study	18 implants: 12 PI = 21 implants, 16 HI patients = 21 implants	PICF sampling with paper strip and clinical parameters (PI/PD/BOP)	ELISA method	significant difference in sRANKL / OPG concentrations
Faot F et Al., 2015	Interleukins 1B/4/6/10/12/17 and TNFa	meta-analysis	articles since 1966 to 2013, october	Taken into account cross-sectional studies and prospective	software for determine the prevalent biomarker	interleukin 1b: the most studied, then TNFa. IL-1b and TNFa: significant difference between PI and HI

Xu L et Al., 2008	collagenase, metalloprotease-8	case control study	10 healthy implants, 19 with periodontitis and peri-implantitis	PICF sampling with paper strip	Volume determination by tampons containing proteases + measurement of collagenase activity by DNP-synthetic and western-blot	collagenase: difference sign in MU VS HI; MMP-8: higher activity in severe PI VS periodontitis chronique
Al Ghazal L et Al., 2017	Interleukins 1B/6/8/10/12 and TNFa and clinical parameters	randomized clinical trial	18 patients: control group (curettes) and test group (perio airflow)	PICF sampling with paper strip (per 3 month during 12 month)	ELISA method	identical clinical results between the 2 techniques, Interleukin 6: only cytokine correlated with BOP
Fiorellini JP et Al., 2000	aminotransferase	cross-sectional study	59 implants at 20 patients	PICF sampling with paper strip + recording of clinical parameters (PDP,GI,BOP)	ELISA method	Difference between parameters clinical periodontics and higher levels of AST per site
Liskmann S et Al., 2016	myeloperoxidases	cross-sectional study	24 patients	PICF sampling with paper strip and recording of clinical parameters	ELISA method	correlation between higher levels of MPO and BOP and when IG> 1mm and PDP> 3 mm
Duarte PM et Al., 2016	9 different osteogenesis cytokines, pro-inflammatory and anti-inflammatory et chemokines	systematic review	18 articles	database search Medline and Embase (since 1990 to 2015, march)	ELISA method	Inflammatory cytokine levels, osteogenesis cytokines and chemokines: limited interest in PI detection compared to pro-inflammatory cytokines
Gomes AM et Al., 2018	9 biomarkers including interleukin 1b and interleukin 6	systematic review	6 articles	database search PubMed/Medline/ Web of science/ cochrane library	ELISA method	IL-1b: significantly lower for HI, + correlation between IL-6 and PI

Lira-Junior R et Al., 2019	CSF-1 and Interleukin 1b and 34	case control study	43 patients: 20 with MU and 23 with PI	PICF sampling with paper strip + recording of clinical parameters (PI/BOP/PDP)	ELISA method	no significant difference for IL-1B and IL-34, Significantly higher CSF-1 in PICF at PI VS MU
Panagakos FS et Al., 1996	Interleukin-1b	case control study	50 implants at 13 patients: 3 groups: HI, Early PI, Advanced PI	PICF sampling with paper strip+ recording of clinical parameters (PDP,GI,BOP)	ELISA method	Presence of IL-1b in PICF and levels correlated with increased attachment loss
Yalçn S et Al., 2005	Prostaglandin E2	randomized clinical trial	48 implants: 24 for a group of witnesses, 24 "case" implants	PICF sampling with paper strip+ recording of clinical parameters (PI/PD/GI)	ELISA method	Significant difference in case vs. control group for PGE2 levels and clinical parameters
Aboyoussef H et Al., 1998	prostaglandin E2 and metalloprotease and interleukin 1b	case control study	29 patients: healthy group = 37 and affected group of PI early = 37	PICF sampling with paper strip	ELISA method	Significant difference between HI and PI interleukin 1b + levels no significant difference in levels prostaglandin E2
Salvi GE et Al., 2004	settings biochemical and clinics	systematic review	articles before 2003, august	MEDLINE search	analysis assisted by computer	assess peri-implant health essential by evaluating clinical parameters and radiographic
Mogi M et Al., 2004	RANKL and OPG	case control study	132 patients: Group severe periodontitis = 47, periodontitis group moderate = 58, group periodontitis mean = 28 and group healthy = 28	PICF sampling with endodontic paper strip (Offenbacher's method)	ELISA method	significantly greater difference of RANKL in GCF of periodontitis, and significantly lower level of OPG

Plagnat D et Al., 2002	Elastase, alpha-2 macroglobulin, alkaline phosphatase	case control study	11 implants at 8 patients = PI symptoms, 11 implants at 7 patients = HI	PICF sampling with paper strip of 2 sites per implant	ELISA method	Detection of the 3 mediators in most sites, correlation of the 3 mediators with clinical parameters, significantly greater difference of ALP and EA for PI
Yakar N et Al., 2019	Sclerotine, TWEAK, RANKL and OPG	case control study	91 patients: group PO = 22, group PI = 27 and healthy group = 17	PICF et GCF sampling with paper strip+ recording of clinical parameters and RX	ELISA method	significant difference for biomarkers in PI and PO VS HI, correlation between parameters biochemical and clinical and biomarkers; TWEAK: significant for PI and PO Sclerotin: significant for PI
Alkan EA et Al., 2016	prostaglandin E2	randomized clinical trial	24 sockets: EDM group and Bio-oss group	PICF sampling with paper strip à JO, M1 et M3 post intervention	ELISA method	to M1: significant difference PGE2 VS JO in EDM VS Bio-oss group at M3: no significant difference
Slotte C DDS et Al., 2012	Interleukin 1b, TNFa, osteocalcin, alkaline phosphatase, cathepsine K, TRAP	randomized clinical trial	18 patients: Test group = 9 implants with immediate restoration by bridge, 9 implants loaded at +3 months	PICF sampling with paper strip (J2/14/28/90) + recording of clinical parameters	PCR	correlation of TNFa, ALP, IL1b and OC with clinical parameters (the strongest correlation for TNFa on D2 and D14)
Sharma CGD et Al., 2006	Osteopontin	case control study	45 patients: 3 groups: HO, G, PO chronic	GCF sampling with paper strip	ELISA method	Positive correlation between levels osteopontin and loss of attachment clinical
Lu H-K et Al., 2006	OPG/RANKL and gp130 and Interleukin 6	case control study	95 sites on 20 patients with periodontitis chronic generalized divided into 4 groups according to BOP and PDP	GCF sampling with paper strip and samples tissue	ELISA method	significant difference of RANKL in GCF for PO, positive correlation between RANKL and Interleukin 6 No correlation between OPG/RANKL and severity of the disease

Kao RT et Al., 1995	Interleukin 1Beta	case control study	24 patients: Healthy group = 12, peri-implantitis group = 12	PICF sampling with paper strip	ELISA method	Increased levels interleukin 1b multiplied by 3 in sites with peri-implantitis vs healthy
Ataoglu H et Al., 2002	Interleukin 1b and TNFalpha and neutrophile elastase	cross-sectional study	42 implants at 14 patients	PICF sampling with paper strip + recording of clinical parameters (PI/PD/GI)	ELISA method+ substrat spécifique pour l'élastase neutrophile	correlation between levels enzymes and GI / PDP; positive correlation between IL-1b and neutrophil elastase activity in progressive PI
Rakic M et Al., 2019	RANKL/OPG	case control study	252 implants at 126 patients : 3 groups HI/MU/PI	PICF sampling with paper strip + recording of clinical parameters	ELISA method	the detection of biomarkers of bone remodeling make it possible to demonstrate the presence of peri-implant bone resorption for the PI group, however, additional studies are needed to support these results
Kivelä-Rajamäki M et Al., 2003	Lamina-5 gamma-2 and collagenase2(MMP8)	case control study	13 patients: groups HI and PI (72 sites)	PICF sampling with paper strip + recording of clinical parameters+ RX	Western blot for MMP8 and lamina	low levels of MMP8 and lamina in sites with non-active IP and high presence in MU; high levels of MMP8 and lamina correlated with disease activity
Kivelä-Rajamäki M et Al., 2003	MMP7 (matrilysin-1) and MMP8 (collagenase 2)	case control study	72 samples of PICF on 13 patients. 2 groups: HI and PI	PICF sampling with paper strip + recording GI + bone resorption (between A-1 and OJ)	Western blot for detection of MMP7 and 8	Levels of MMP7 and MMP8 in PICF significantly higher in PI VS MU + correlation with the index gingival
Karoussis IK et Al., 2003	clinical parameters and radiographic	randomized clinical trial	112 patients, group A = 21, ATCD periodontitis; group B = 91, no ATCD periodontitis	recording of clinical parameters and bone level per year during 10 years		significantly higher risk implant failure when ATCD periodontitis

Arawaka H et Al., 2012	matrix metalloprotease 8	randomized clinical trial	76 implanted patients between 1990 and 2000, 12 excluded: rest 64. 2 groups: control = HI and severe peri-implantitis	PICF sampling with paper strip + recording of clinical parameters	Western-blot	MMP8 associated with severe peri-implantitis
Güncü GN et Al., 2008	myeloperoxidase	randomized clinical trial	220 peri-implant sites and natural teeth: 109 implants and 111 natural teeth	PICF and GCF sampling with paper strip + recording of clinical parameters	spectrophotometry	MPO levels significantly higher for MU and PI VS HI, positive correlation between MPO and gum index
Murata M et Al., 2002	ostéocalcin, deoxypyridinoline and interleukin 1beta	case control study	34 implants at 16 patients: group 1 = PI (6 patients) group 2 = MU (8 patients) group 3 = HI (20 patients)	PICF sampling with paper strip + recording of clinical parameters (PD, GI, PI)	ELISA method	Significantly osteocalcin levels senior staff at MU VS HI, Interleukin 1b significantly higher at PI VS MU and HI No detection of deoxypyridoline
Arikan F et Al., 2008	osteoprotegerin	case control study	86 implants at 39 patients: 3 groups= HI/MU/PI	PICF sampling with paper strip + recording of clinical parameters (PI/BOP/PD/GI) according to criteria by Mombelli	ELISA method	correlation between OPG levels and PICF + IG / BOP volume, no correlation with PDP and IP
Alassy H et Al., 2019	Interleukin 1beta, TNFa, MMP8	meta-analysis	71 articles	Pub-Med database of the US National Library of Medicine, for articles published up to October 2019	use of Endnote ™ then summarized in a BM table (bone biomarkers, pro-inflammatory cytokines and enzymes)	increased levels of bone biomarkers in PI VS HI however no results significant for cytokines pro-inflammatory
Sharma et Al., 2007	osteopontin	case control study	40 patients: 4 groups: healthy group, gingivitis, chronic periodontitis, periodontitis treated at 6-8 weeks	GCF sampling with paper strip + recording of clinical parameters	ELISA method	OP levels significantly higher in GCF of sites with periodontal destruction, significant decrease in OP after periodontal treatment, positive correlation between OP in GCF and plasma

Jepsen S et Al., 1996	NPE (neutral proteolytic enzyme)	randomized clinical trial	25 patients at 54 implants	PICF sampling with paper strip + recording of clinical parameters (PD,GI,BOP), to OM and 6M	Periocheck	significant difference for the index of plate and NPE between progressive PI and implant condition stabilized
Javed F et Al., 2011	cytokines pro-inflammatory	meta-analysis	50 articles, 180 patients, since 1994 to 2010, july			pro-inflammatory cytokine levels in PICF significantly higher in PICF of peri-implantitis
Nicu et Al., 2012	OPG/RANKL	randomized clinical trial	14 patients: with ATCD periodontitis. 78 implants: 2 groups = 39 TiU and 39 Tur	PICF sampling with paper strip + recording of clinical parameters+ RX	PCR for biofilm and ELISA method for OPG / RANKL	no significant difference between clinical, biochemical parameters and microbiological between surfaces Tur and TiU implants
Prati AJ et Al., 2013	TGF/OC/PTH/OP	randomized clinical trial	40 patients: IM group (setting charge at + 72h) and group NL (no in immediate charge)	PICF sampling with paper strip to +7J/15/30/60/90/120 and recording of clinical parameters (BOP/PD)	Level analysis by Luminex Assay	early detection of biomarkers for IM VS NL group, no significant difference between clinical parameters and demographic
Wohlfahrt JC et Al., 2014	MMP8, IL-6, OPG/OC/OP/PTH/TNFa and leptin/adinopectin/ insulin	case control study	32 patients (control group and test group)	PICF sampling with paper strip + recording of clinical parameters	ELISA method and Luminex Assay	significant difference of MMP8 / IL6 / OPG / leptin / adinopectin at M12, correlation + between decrease in IL6 / MMP8 / insulin and decrease in PDP, no significant difference for bone biomarkers in the Test VS control group
Bielemann AM et Al., 2018	52 biomarkers : the most studied are interleukin 1 / TNFa and nitric oxide	systematic review	30 prospective studies	database search (pubmed, embase, scopus, cochrane library, web of science)	2 independent readers, sorting by type of study, demography, analysis and results of types and biomarker levels	difficult to assess the performance of biomarkers to obtain a system data based on PICF volume and concentration of biomarkers (heterogeneity of studies)

Nomura T et Al., 1998	metalloproteases (MMP8, TIMP)	case control study	31 patients = healthy group (10), gingivitis group (10), periodontitis group (11)	GCF sampling with paper strip	ELISA method and for collagenase : SDS-page	MMP8: most metalloprotease present in GCF of G and PO, significantly higher levels of TIMP-1 and collagenase in G / PO, 87% correlation between parameters clinics and composition of the GCF
Ghassib I et Al., 2019	Interleukins 1b/6, TNFa and MMP8	meta-analysis	90 articles	search(pubmed, embase, cochrane library) since 2018,march. 2 independent	standardized analysis with 95% confidence interval, randomization model for each cytokine	IL1 levels: 6 / MMP8 significantly higher at MU VS HI and PI VS H

Discussion

Bone Biomarkers

The study of bone biomarkers is one of the privileged path by scientists because it is this bone remodeling that will be in negative balance during peri-implantitis and responsible for the loss of the implant.

The most studied bone biomarkers are OPG and RANKL. Thus, osteoprotegerin shows a correlation between its levels and clinical parameters (gingival index and bleeding on probing) but not pocket depth (17,29–31). This significant difference between peri-implantitis and healthy peri-implant would thus allow us to estimate that OPG may be a marker that could be used as a diagnostic tool (32–34). These differences in the levels of OPG and RANKL also occur in cases of periodontitis compared to healthy periodontitis (29). Moreover, some studies show that there is a significant increase in implant failure when the patient has a history of peri-implantitis (35).

Some studies present a significant difference of OPG levels between the healthy and peri-implantitis groups (36). On the other hand, a study comparing the presence of these biomarkers at the level of peri-implantitis surface differences makes it possible to specify that there would be no significant difference between the levels of RANKL and OPG (37). Besides this, osteocalcin is part of other biomarkers that show significant differences between patients with mucositis and with healthy peri-implant surfaces (38) and the latter could then be a potential biomarker for use as a diagnostic tool (39). OPG and osteocalcin show identical levels between healthy and peri-implantitis patients in several studies (24,30) , which contrasts with previous results.

As for osteopontin (40), in cases of periodontitis, presents significantly higher levels in the gingival crevicular fluid as well as a positive correlation between its local level and the loss of clinical attachment in cases of periodontitis (41). However, these results are to be taken with precaution because they concern cases of periodontitis and there is a lack of studies concerning cases of peri-implantitis to claim that osteopontin is valid as a diagnostic tool for peri-implantitis.

However, in spite of these results contributing to the fact that bone biomarkers can be used as diagnostic tools, complementary studies with larger samples and prospective studies should be useful to confirm this hypothesis.

Cytokines

The most studied cytokine for the diagnosis of peri-implantitis is interleukin 1 (42). This pro-inflammatory cytokine, detected in the peri-implant sulcus, could be a lead as a tool in the early detection of peri-implantitis. Thus, levels of interleukin 1 are increased in some studies (28,38,43–47). A correlation of IL-1 levels with clinical parameters (48)as well as with the significant decrease in clinical attachment levels (49) are highlighted. There is also a correlation between IL-1 levels and elastase levels in cases of progressive peri-implantitis (50). On the other hand, studies show a lack of correlation between interleukin-1 levels and early bone loss in cases of peri-implantitis (51). Others do not show a significant difference of interleukin-1 levels between different peri-implant stages (26,52–55), between two interleukin genotypes (56) and finally between two periodontal treatments (25).

Next, we will focus on TNF-alpha. Few studies present a significant difference of its levels between healthy and affected peri-implant (42) or a correlation with clinical parameters (48) because the majority of the studies concerning the evaluation of this biomarker do not show evidence allowing to consider the use of this biomarker as a diagnostic tool (28,36,50,51,54,55). There is also an absence of significant difference of TNFa levels between two periodontal treatments (25) as well as an absence of correlation between TNFa polymorphism and risk of peri-implantitis (57).

Concerning interleukin 6, the results seem more mixed. Indeed, some studies claim significant differences in levels between healthy and affected peri-implant (28,44) as well as a positive correlation between their level and RANKL levels (31), and with bleeding on probing (25) and decreased pocket depth (36). On the other hand, insignificant results for interleukin 6 levels were also demonstrated (42,53) as well as a lack of correlation with early bone loss (51). Interleukin-6 therefore does not appear to be a biomarker with significant validity for use as a diagnostic tool.

Other cytokines have also been studied (interleukins 2/4/8/10/12/17/34) and interleukin-8 is the only cytokine concerned by a possible significant difference (43) while the others do not show a significant difference in its levels between healthy and affected peri-implant (26,42,51).

Thus, the cytokines that could be considered as potential diagnostic tools would be interleukin 1, others such as interleukin 6 and 8 lack evidence for their use, and, finally, TNFa and interleukin 2/4/10/12/17/34 would not present convincing results.

Tissue constituents

The tissue constituents studied include laminina-5-gamma-2, prostaglandin E2 and deoxypyridoline.

For lamina, there was a correlation between its levels and disease activity as well as low levels in non-active peri-implantitis sites (58). For prostaglandin E2, levels of this biomarker show a significant difference between healthy and diseased peri-implant (59) as well as a positive correlation with clinical parameters. Levels would also be increased using two different regeneration techniques (increased levels in EDM compared to bio-oss) (60). In contrast to this, one study reports levels with no difference between healthy and diseased states (45). As for deoxypyridoline, this biomarker was not detected at significant levels in gingival crevicular fluid in the pathological state of peri-implantitis compared to the healthy state (38). These studies demonstrate the potential of prostaglandin E2 for the detection of peri-implantitis, however prospective studies and larger samples would be useful to determine whether this biomarker would indeed be valid as an early diagnostic tool for peri-implantitis. Laminin could be a diagnostic tool however there is a lack of evidence to determine its usefulness.

Hormones

Hormones present in gingival crevicular fluid could also be biomarkers that would allow early detection of peri-implantitis. Thus, few papers, such as for tissue constituents, report data on hormone levels. Results show a potential for leptin and adinopectin (increase of their levels in peri-implant crevicular fluid at 12 months of implantation) (36) as well as an early detection of TGFBeta during implantation (39). Insulin may also show promise as it is positively correlated with an increase in peri-implant crevicular fluid and a decrease in pocket depth (36). However, especially concerning TGFBeta, another study creates the contradiction due to the non-significant difference of its levels in the peri-implant crevicular fluid (51). Thus, hormones could have a potential in the early diagnosis of peri-implantitis, however due to the lack of studies on these biomarkers and their potential, it is, at present, not possible to have a reliable opinion on their use.

Enzymes

Enzymes are among the most studied biomarkers concerning the potential of early diagnosis tools for peri-implantitis.

Thus, the most studied enzymes are metalloproteases (17,30,48,49). Most of the studies concerning them show a significant difference in their levels between healthy peri-implant and peri-implantitis (27,28,36,54,58,61,62). Nevertheless, some studies contrast with these results (45,54). However, metalloproteases seem to be biomarkers that could be useful as diagnostic tools for early peri-implantitis.

Other enzymes such as elastases, alkaline phosphatase (63); cathepsin K (43) and myeloperoxidase (64) show significantly higher levels in the crevicular fluid of the affected peri-implant compared to the healthy peri-implant. Furthermore, one study reports a significant correlation between the levels of these enzymes and clinical parameters (48) as well as for aminotransferase (65,66) and myeloperoxidase (67). These results suggest that these enzymes could be a lead as early diagnostic tools and merit further investigation.

Neutrophil elastase has also been involved in a study of correlation levels. Thus, levels of neutrophil elastase are correlated with levels of interleukin 1 in the case of progressive peri-implantitis (50).

The neutral proteolytic enzyme could also be a useful enzyme as a potential diagnostic tool for

early peri-implantitis as it shows a significant positive correlation between its level and the decrease in MMP8 levels as well as pocket depth (36). There is also a correlation between its levels and the plaque index in the healthy peri-implant compared to the diseased peri-implant. (68).

It can therefore be concluded that the enzymes have, according to the studies currently available, a high potential for their use in the early diagnosis of peri-implantitis. However, studies with a larger sample and prospective will be necessary to confirm the hypotheses proposed in these initial studies.

Inflammatory markers

Few markers of inflammation have been studied and the results seem to be moot. Thus, there are significant differences in CSF-1 and TWEAK levels between healthy and affected implants (26,33). There is also a correlation that has been demonstrated between levels of alpha-2-macroglobulin and clinical parameters (63). On the other hand, a study shows that there is no significant difference in the levels of C-telopeptide (34). The results therefore seem insufficient to conclude whether or not the inflammation markers detected in the crevicular fluid are useful as early diagnostic tools. Thus, studies with larger samples and over the longer term could shed light on the possibility or otherwise of using these biomarkers for diagnosis. Nevertheless, it does not seem possible, on the basis of these few studies, to envisage using these biomarkers as early diagnostic tools for peri-implantitis.

Conclusion:

The detection of early peri-implantitis by sample collection of crevicular fluid would make it possible to manage implant maintenance in a simplified and early manner. The longevity of implant treatments and the desire to reduce the rate of peri-implantitis and in particular implant failure (5 to 10% of implants).

This systematic review highlights that the most studied biomarkers in the early detection of peri-implantitis are biomarkers of remodelling as well as cytokines in particular interleukin 1. Thus, bone biomarkers such as OPG, RANKL, OC, OPG and interleukins are promising biomarkers for early peri-implantitis. In the second line, enzymes such as metalloproteases are studied and present a lot of evidence.

Concerning tissue constituents, hormones and inflammatory markers, there are still not enough studies and too many mixed results to conclude their relevance.

At least some biomarkers stand out. For example, one study shows that leptin and adinopectin are hormones that could be studied further. In terms of inflammatory markers, CSF-1 and TWEAK could also be studied more closely. However, these are only ways of study because too few studies have found that these biomarkers could be used as a biomarker for the early diagnosis of peri-implantitis.

These studies are promising, but for the most part they are cross-sectional studies which only allow a comparison at a time T.

The hope of being able to quickly detect and treat early peri-implantitis would prevent the terminal outcome of this disease, which is implant failure. The interest of biomarkers in the early diagnosis of peri-implantitis then seems to be a potential lead in the early and non-invasive management of peri-implantitis. This is part of the global and personalised management of each patient and for whom maintenance remains an obligation concerning implant prosthetic restoration.

Nevertheless, these potential tools are still to be explored and require more evidence before they can be considered for daily and routine practice.

Thus, future biomarker studies in early detection could be done with a large sample, to have a large power of results, in longitudinal studies, with specific PICF sample collection protocols, as well as a common definition for reproducible criteria concerning, initially, the categorisation of patients according to peri-implant state.

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Conclusion

Pour conclure sur cette étude concernant l'intérêt des biomarqueurs dans le diagnostic précoce des péri-implantites, il semblerait que certains biomarqueurs aient un potentiel concernant leur utilité. La détection des péri-implantites précoces par le prélèvement du fluide créviculaire permettrait de gérer la maintenance des implants de manière simplifiée et précoce afin d'augmenter la longévité des traitements implantaires, la volonté de réduire le taux de péri-implantite et surtout d'échec implantaire (5 à 10% des implants).

Cette revue systématique met en évidence que les biomarqueurs les plus étudiés dans la détection précoce de la péri-implantite sont les biomarqueurs du remodelage ainsi que les cytokines en particulier l'interleukine 1. Ainsi, les biomarqueurs osseux tels que OPG, RANKL, OC et les interleukines sont des biomarqueurs prometteurs pour la péri-implantite précoce. En deuxième ligne, des enzymes telles que les métalloprotéases sont étudiées et présentent de nombreuses preuves.

En ce qui concerne les constituants tissulaires, les hormones et les marqueurs inflammatoires, il n'y a pas encore un nombre assez conséquent d'études et des résultats mitigés (significatifs pour certaines études, non significatifs pour d'autres) pour conclure à leur pertinence.

Parmis ces résultats, certains biomarqueurs se distinguent. Par exemple, une étude montre que la leptine et l'adinopectine sont des hormones qui pourraient être étudiées avec plus d'intérêt. En ce qui concerne les marqueurs inflammatoires, le CSF-1 et le TWEAK pourraient également être étudiés avec des études sur du plus long terme et de plus grands effectifs. Cependant, ce ne sont que des pistes d'étude car trop peu d'études ont montré que ces biomarqueurs pourraient être utilisés pour le diagnostic précoce de la péri-implantite.

Ces études sont prometteuses, mais il s'agit pour la plupart d'études transversales qui ne permettent qu'une comparaison à un instant T.

L'espoir de pouvoir détecter et traiter rapidement une péri-implantite précoce permettrait d'éviter l'issue terminale de cette maladie, à savoir l'échec de l'implant. L'intérêt des biomarqueurs dans le diagnostic précoce de la péri-implantite semble alors être une piste potentielle pour une prise en charge précoce et non invasive de la péri-implantite. Celle-ci s'inscrit dans la prise en charge globale et personnalisée de chaque patient et pour lequel la maintenance reste une obligation concernant la restauration prothétique implantaire.

Néanmoins, ces outils potentiels restent à explorer et nécessitent davantage de preuves avant d'être considérés dans la pratique quotidienne et de routine. On peut tout de même envisager une pratique au fauteuil simplifiée grâce au prélèvement de liquide creviculaire par papier strip que la plupart des études appliquent. Cet outil serait non invasif et confortable pour le patient.

Ainsi, les futures études de biomarqueurs dans la détection précoce pourraient être réalisées avec un large échantillon, pour avoir une grande puissance de résultats, dans des études longitudinales, avec des protocoles spécifiques de collecte d'échantillons de PICF, ainsi qu'une définition commune de critères reproductibles concernant, dans un premier temps, la catégorisation des patients en fonction de l'état péri-implantaire.
Il semblerait que détecter précocement la maladie péri-implantaire et donc augmenter le taux de survie implantaire devienne une éventualité pour l'avenir de la thérapeutique implantaire.

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RESUME
Les biomarqueurs constitueraient un outil de diagnostic non invasif pour détecter les péri-implantites précoces. Nous allons étudier l'intérêt des biomarqueurs dans le diagnostic précoce de la péri-implantite.
Nous avons réalisé une revue systématique incluant 48 articles de haut niveau de preuve (RCT, méta-analyse, revue systématique) et comparé les différents biomarqueurs étudiés et la méthode utilisée pour chaque étude. La majorité des études étaient transversales avec un échantillon de fluide créviculaire obtenu par papier strip et analysé par méthode ELISA.
Les biomarqueurs les plus étudiés sont les biomarqueurs osseux, les enzymes, les cytokines, les constituants tissulaires et les hormones.
Les biomarqueurs qui semblent les plus prometteurs sont les biomarqueurs osseux (OPG, RANK, RANKL, OC), les cytokines (IL-1) et les enzymes (métalloprotéinases). Cependant, comme la plupart des études sont transversales, des études prospectives avec des échantillons plus larges sont nécessaires pour augmenter la fiabilité et le niveau de preuve de l'utilisation de ces biomarqueurs comme outils de diagnostic précoce de la péri-implantite.

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