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Are gingivitis, periodontitis and peri-implantitits associated with autoantibodies- A literature review

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1 ABSTRACT

Introduction: Periodontal disease is one of the most common inflammatory diseases in the world. A possible autoimmune aspect behind the local tissue destruction in periodontal disease, as a result of the invasion of oral pathogens over time has been reported in previous studies, but the correlation is yet unclear. **Purpose:** The aim of this literature review was to shed light on the topic if autoantibodies and autoimmune reactions are associated with gingivitis, periodontitis or peri-implantitis and the progression of these inflammatory diseases. **Material and methods:** A search in the Pubmed database was done resulting in 138 hits. To follow a systematic approach for selecting the studies to include, we used predefined inclusion and exclusion criteria **Results:** 26 articles studying a broad variety of different autoantibodies was included for this literature review. A vast majority of the included studies were of case-control design and, because of the broad variety and different variables and data, we decided that a meta-analysis could not be performed. **Conclusion:** Many studies where results could be compared due to similar comparisons, regarding the incidence of periodontal disease and the prevalence of certain autoantibodies, showed opposite results which makes it hard to reach a conclusion. The main part of the included studies were of small size and therefore more comparable studies are needed to clarify the possible association between periodontal disease and an autoimmune reaction mediated by autoantibodies.

INTRODUCTION

1.1 Anatomy:

The periodontium is the tissue surrounding the teeth, giving structural support and attachment of the teeth. The periodontal ligament, the root cementum, the alveolar bone and the gingiva are the tissues that together build up the periodontium.

Gingiva: The gingiva consists of epithelia and connective tissue structures and covers the alveolar process and the cervical part of the teeth. It can roughly be divided in the free gingiva, the interdental gingiva and the attached gingiva.

The free gingiva is towards the coronal part of the teeth and should under healthy conditions be located 1.5-2mm over the cementoenamel junction of the teeth. The interdental gingiva, also known as the papilla is as the name suggests the gingiva between the teeth.

The attached gingiva is normally located at the same level as the cementoenamel junction and is attached to the alveolar bone and the root cementum through connective tissue fibres.

Tissue fibres constitutes the main component of the gingiva and consists of collagen fibres and functions as the most essential component of the periodontium. The connective tissue also contains fibroblasts, mast cells, resident macrophages, inflammatory cells, vessels and nerves embedded in a matrix consisting of proteoglycans and glycoproteins (e.g. fibronectin, osteonectin). These molecules are vital for normal functions and regulate the structure of the gingiva.

Fibroblasts are the most common connective tissue cell and is responsible for the production of extracellular matrix and collagen together with cementoblasts and osteoblasts. Example of inflammatory cells in the connective tissue are the neutrophilic granulocytes, lymphocytes and plasma cells.

Periodontal ligament: The periodontal ligament is the connective tissue of collagen fibres that connects the root cementum and the alveolar bone. The periodontal ligament is important for the physiological mobility of the teeth and permits forces during masticatory function to be resorbed.

Root cementum: The root cementum is the tissue produced by cementoblasts that covers the root surface of the teeth containing minerals and collagen in a bed of matrix. The periodontal ligaments attach to the root cementum of the teeth. Sharpey´s fibres are located in the cementum and continues as the fibres of the periodontal ligament.

Alveolar bone: The part of the maxillary and mandibular bone that surrounds and supports the teeth. The main component of the organic matrix in the bone consist of collagen type 1 (90%), non fibre- proteins. The dominant inorganic component is hydroxyapatite crystals. The bone is considered as a living organ with the bone cells osteoblasts, osteocytes and osteoclast regulating the bone metabolism (Anaya et al., 2013 chapter 1-2).

1.2 Gingivitis, periodontitis and peri-implantitis.

Periodontal disease can be described as an inflammation of the periodontium and is believed to be caused by an interaction between bacteria in the subgingival biofilm and the host immune system, which results in an inflammatory response which affects the periodontium. Many potential disease modifying factors have been associated with periodontal disease, such as diabetes, smoking, age, genetics etc. Periodontal disease includes different stages and forms, where gingivitis is considered as the first developmental stage with gingival inflammation. Periodontitis is considered a more advanced form of periodontal disease since it includes tissue destruction and thereby loss of tooth-supporting structures such as connective tissue and alveolar bone which can lead to increased mobility and eventually loss of teeth due to inflammation if not treated. (Anaya et al., 2013 chapter 7).

The clinical assessments tools used for diagnostics are probing of the periodontal pockets and radiographic assessment of the marginal bone level. Periodontitis is one of the most common inflammatory diseases in the world with a worldwide prevalence of 20-50% in the global population (Nazir, 2017) and can roughly be divided into chronic periodontitis and aggressive periodontitis. The chronic slower progressing form of periodontal disease is more common among elderly while the aggressive faster progressive form is more common among younger individuals. Studies have shown a strong association between periodontal disease and subgingival bacterial accumulation in the periodontium. Subgingival bacteria, such as *P. gingivalis, T. denticola, T. forsysthia* and *A. actinomycetemcomitans* are strongly associated with periodontal

disease, where *A. actinomycetemcomitans* has a specific association to aggressive periodontitis. These bacteria also have the capacity to interact with the hosts immune system and a strong correlation with the accumulation of B-cells has been observed in periodontal tissue (Mahanonda et al, 2016). However, the presence of the above mentioned bacteria is not synonymous with the manifestation of periodontal disease.

Berglundh et al. suggested that the adaptive immune system plays an important role in the established forms of periodontal disease since they found that B-cells and plasma cells are the predominant immune cells in the periodontal lesion (Berglundh et al, 2011). T-cells, one the other hand, were found in lesser amount and were more rampant accumulated in gingival tissue during the initial stages of periodontal disease (e.g. gingivitis) (Ali et al, 2011).

An autoimmune component of periodontal disease has been suspected for decades but the relationship has not yet been clarified.

1.3 Autoimmunity

The definition of autoimmunity is when the immune system targets it´s own structures and molecules, which can lead to local or systemic damage to the host tissue. Autoimmune reactions are believed to occur normally in healthy individuals, but under controlled circumstances. The development of an autoimmune disease is believed to be multifactorial and occurs when the balance of self- tolerance is lost and factors such as genetics, hormones and the environment may contribute to the development of an autoimmune disease. There are multiple pathways for autoimmune reactions to occur, but in this review the focus will be on the humoral pathway, mediated by autoantibodies within the adaptive immune system. Even though T-cells play an important role in the development of autoimmunity, no focus will be laid on the cell-mediated pathway through T-cells (Anaya et al., 2013 chapter 19)

There are studies suggesting that the autoreactive antibodies against self-targets, such as collagen, are a natural part of the physiology. The purpose of these autoantibodies is to ease the clearance of damaged tissue components and dead cells, which occurs in normal healthy tissues as well as in periodontal disease. However, these natural autoantibodies consist of the IgM isotype, while the most common autoantibody isotype against collagen in periodontitis is IgG (Kaur et al, 2017).

1.4 B-cells

B-cells, also known as B-lymphocytes, constitute an important part of the adaptive immune system. They function as antigen presenting cells and are the precursors of plasma cells, which produce antigen-specific antibodies. The antibodies can bind to specific epitopes on antigens (antigenic determinants) to make it possible for phagocytic cells (e.g. neutrophils or macrophages) or complement proteins to become activated and effectively defend against pathogens. The B-cell receptor (BCR) is a surface antibody and is responsible for the recognition and binding of specific antigenic epitopes, which leads to stimulation trough a complicated signalling process that involves receptors, molecules and proteins. The B-cell can develop into antibody secreting plasma cells or memory B-cells.

Both central and peripheral mechanisms are important in B-cell tolerance. To avoid autoreactivity, immature B-cells that have BCRs with a high affinity to self-antigens are deleted or modified through receptor editing, while B-cells with low-affinity autoreactive BCRs can migrate out into the periphery. However, most B-cells that leave the bone marrow are unable to recognize self-antigens. If an immature B-cell recognizes self-antigens in the periphery, the B-cell can be deactivated through apoptosis or anergy mechanisms (Melchers, 2015).

1.5 Infection and autoimmunity

There are evidence suggesting that infections can trigger the development of autoreactive T- and B-cells in some autoimmune diseases. Many autoimmune diseases are related to infections and patients with autoimmune diseases have a higher risk of infections due to treatment of these diseases. Autoantibodies can however also be found in patients with infections but without an established autoimmune disease which could indicate that pathogens may be a factor in the development of these diseases.

To sum it up, there are many possible mechanisms for autoimmune development through infections as known today, but the most important mechanisms for the humoral pathway includes:

Molecular mimicry: Where T- and B-cells are activated through infection but cannot separate self-antigens from infectious agents.

Epitope spreading: Similar self- and pathogen-epitopes.

Chronic infections may also lead to tissue destruction and apoptosis or necrosis of self-tissue cells, which can lead to an enhanced inflammatory response, a possible way for self-antigens to be presented and later on production of autoantibodies (Anaya et al., 2013 chapter 19).

The defence against infection and the development of inflammation includes both the innate and adaptive immune system but due to the subject of this review, we choose to focus on the humoral part of the immune response without diminishing the role of other parts of the immune system in the development of periodontal disease.

The aim of this literature review was to see if autoantibodies and autoimmune reactions are associated with gingivitis, periodontitis or peri-implantitis and the progression of these inflammatory diseases.

2 MATERIALS AND METHODS

2.1 Objective

The purpose of this literature review was to get an overview of the current knowledge about the possible association between autoantibodies and periodontal diseases.

2.2 Ethical Consideration

We have strived to include all articles based on our criteria regarding inclusion and exclusion without impact from our personal views and thoughts and we present our method transparently.

All included data has been extracted from previous studies and all patients involved in the studies were anonymous, so no ethical considerations are necessary regarding patient data.

2.3 Search strategy

The search was conducted in the Pub Med database on the 29th of November 2017 using our keywords gingivitis, periodontitis, peri-implantitis, autoantibodies through free search combined with Mesh-terms.

Search string: (("periodontitis"[MeSH Terms] OR "periodontitis"[All Fields]) OR ("gingivitis"[MeSH Terms] OR "gingivitis"[All Fields]) OR ("peri-implantitis"[MeSH Terms] OR "peri-implantitis"[All Fields] OR ("peri"[All Fields] AND "implantitis"[All Fields]) OR "peri implantitis"[All Fields])) AND ("autoantibodies"[MeSH Terms] OR "autoantibodies"[All Fields]) NOT review

2.4 Inclusion criteria

Based on the lack of therapeutic intervention among studies we choose to set aside the PICO system and SBU:s review templates and choose the following criteria:

- Article that studies the prevalence of autoantibodies, local or in serum, directed against antigens in periodontal tissue directly associated to gingivitis, periodontitis or peri-implantitis
  and/or
- Article that studies the prevalence of autoantigens to autoantibodies (including oral pathogens) in periodontal tissue directly associated with gingivitis, periodontitis or peri-implantitis.

2.5 Exclusion criteria

- Article that only studies correlation between other autoimmune disease (e.g. rheumatoid arthritis or systemic lupus erythematosus), autoantibodies in serum, periodontal tissue or oral pathogens.
- Article not available in English or Swedish.
- Article studying antigens/autoantigens that cannot be found in the oral cavity.

2.6 Processing of articles

Available abstracts from all 138 articles were first read independently by both authors and sorted for full text reading based on our criteria for inclusion and exclusion. In case of disagreement whether an article should be included or excluded both authors discussed the article until an agreement was found. Thirty nine articles were included for full text reading.

After stage 1, both authors read all available 39 full articles and another discussion followed to find complete agreement on which articles should be included. Twelve more articles were excluded after reading and 1 article was unavailable in full text.

Twenty six articles were selected for inclusion. A flowchart describing the article processing is presented in figure 1.

2.7 Data extraction

Due to the broad variety of studied autoantibodies, approaches, co-factors and lack of comparable data, we came to the agreement that a meta-analysis could not be performed as intentionally planned and difficulties were found to present a summarized result.

2.8 Critical evaluation and quality control

In order to evaluate the quality and strength of each included article we used the ”GRADE” evaluation system graded 1-4 presented in figure 2a-b. This template gives a preliminary level of strength based on the study design where case studies has the lowest strength of 1 and randomized controlled trials has the strongest level of evidence at 4. The preliminary strength of case-control starts at 2 and can be heightened or lowered depending on different factors such as study size, confounders, precision etc.

3 RESULTS

3.1 Selection of articles included in the review

The original search was done on the 29th of November 2017, using our keywords *gingivitis, periodontitis, peri-implantitis* and *autoantibodies* through free search combined with Mesh-terms which generated 138 individual articles. Using our inclusion and exclusion criteria, this number was reduced to 26.

3.2 Anti-collagen autoantibodies

Eight of the included articles presented results regarding the association of autoantibodies targeting collagen.

3.2.1 Patients with periodontitis

Two studies found significantly increased levels of anti-collagen type I antibodies in sera from periodontitis patients. The first study included 39 patients with mild to severe chronic periodontitis, which were compared to 22 healthy controls, (Hirsch et al, 1988). The other study compared 20 patients with chronic periodontitis to 10 healthy controls (Sugawara et al, 1992). In contrast, another study found no significant association between the presence of anti-collagen type I antibodies and periodontitis when

comparing 13 patients with periodontitis and healthy controls (number of healthy controls not specified) (Rajapakse & Dolby, 2004).

Two studies found significantly higher serum levels of anti-collagen type I among patients with aggressive periodontitis compared to patients with chronic periodontitis. One of these studies included 22 patients with aggressive periodontitis, 18 with chronic periodontitis and 10 healthy controls (De-Gennaro et al, 2006). The other smaller study included 5 patients with aggressive periodontitis, 5 with chronic periodontitis and 5 healthy controls. No autoreactivity against collagen type I was found among the healthy controls (Koutouzis et al, 2009).

One study including 18 patients with gingivitis, 14 with chronic periodontitis and 25 with aggressive periodontitis (no healthy controls) showed that serologic antibodies from the patients with aggressive periodontitis binds to collagen type I and collagen type III, compared to those with chronic periodontitis or gingivitis where no binding was shown (Hendler et al, 2010).

Three of the included studies found higher local levels of anti-collagen type I in tissues, as compared to that in autologous sera. Two of these studies presented a statistically significant difference; The first study included 15 patients with chronic periodontitis in which they compared gingival tissue to autologous sera (Anusaksathien et al, 1992). The other study included 13 patients with chronic periodontitis where they compared gingival crevicular fluid (GCF) to autologous sera (Rajapakse & Dolby, 2004) The third study found a prevalence of autoantibodies targeting both collagen type I and type III in periodontal tissue while none of these were found in sera. The latter study included 39 patients with moderate to severe chronic periodontitis and the authors did not present a statistical analysis (Hirsch et al, 1988).

One study of 20 patients with periodontitis found no significant difference in anti-collagen type I antibodies when comparing GCF and autologous sera (Sugawara et al, 1992).

3.2.2 Patients with periimplantitis

In contrast to that in periodontitis patients, no significant difference was found when comparing the levels of anti-collagen type I antibodies in 21 patients with periimplantitis to 21 patients with healthy implants (Papi et al, 2017). However, comparing 21 patients with peri-implantitis to 21 patients with implants, but without

active inflammation, it was found that periimplantitis patients had a significantly higher level of anti-collagen type III antibodies (Papi et al, 2017). Anti-collagen type IV antibodies were only found in periimplantitis patients but the difference was not statistically significant (Papi et al, 2017).

3.3 Other extracellular matrix autoantibodies

Seven of the selected articles investigated the prevalence of other autoantibodies directed against extracellular matrix proteins other than the more frequently studied collagen proteins.

3.3.1 Anti-desmosomal antibodies

A study including 10 patients with periodontitis and 20 healthy controls showed increased local (GCF) levels of IgG autoantibodies against desmosomal proteins among patients with periodontitis, compared to healthy controls. In addition, a majority of the periodontitis patients also had increased IgG autoantibodies against desmosomal proteins when comparing sera of periodontitis patients with that of healthy controls. GCF from periodontally inflamed sites also showed greater IgG autoreactivity compared to autologous healthy sites which supports the theory of a local autoimmune reaction. No differences were found in the specificity of these IgG autoantibodies against desmosomal proteins when comparing periodontitis patients and healthy controls (Govze & Herzberg, 1993).

3.3.2 Anti-β1-adrenoreceptor (AR) peptide IgG

A study including 25 patients with chronic periodontitis and 20 healthy controls found that serum IgG from chronic periodontitis bound significantly more to fibroblast cells compared to serum IgG from healthy controls, where IgG from chronic periodontitis patients increased the production of proinflammatory mediators while IgG from healthy controls did not. Anti-β1-AR peptide IgG was identified to be the autoantibody that led to the overexpression of these proinflammatory mediators (Sterin-Borda et al, 2009a). The same authors later showed that the immune reactivity to gingival fibroblast cells was significantly higher in sera from patients with chronic periodontitis compared to healthy controls and that these autoantibodies decreased the DNA-synthesis by an inhibitory effect on the fibroblast cells, an effect found to be dose-related (Sterin-Borda et al, 2009b).

3.3.3 Anti-laminin (LM) and anti-fibrinogen (FN)

Two articles investigated the presence in sera of anti-laminin (anti-LM) and anti-fibrinogen (anti-FN) antibodies. The first showed a significantly higher prevalence of seropositivity to anti-FN and anti-LM among patients with aggressive periodontitis compared to chronic periodontitis in a study of 22 patients with aggressive periodontitis and 18 with chronic periodontitis (no healthy controls were included)(De-Gennaro et al, 2006).

The later study compared 21 patients with periimplantitis to 21 healthy controls with implants. Anti-FN was absent in both groups while anti-LM was found in both groups but without a significant difference (Papi et al, 2017).

3.3.4 Anti- CL

A study including 32 patients with local aggressive periodontitis, 87 patients with generalized aggressive periodontitis, 129 patients with chronic periodontitis and 163 healthy controls, found a significantly higher prevalence of anti-CL (β-2-glycoprotein I-dependent anticardiolipin) in generalized periodontitis patients, as compared to patients with local periodontitis. Patients positive for anti-CL showed significantly higher pocked depth and attachment loss compared to anti-CL negative patients. No significant difference in prevalence of anti-CL or anti-β2GPI IgG antibodies was found when comparing patients with local aggressive periodontitis and healthy controls (Schenkein et al, 2003)

3.4 Rheumatoid arthritis (RA)-associated antibodies

Thirteen of the included articles investigated the association between periodontal disease and rheumatoid arthritis associated autoantibodies. Seven articles investigated the association between periodontal disease and rheumatoid factor (RF) and seven of the articles investigated the association with anti-citrullinated protein antibody (ACPA) or anti- cyclic citrullinated peptides (anti-CCP).

3.4.1 Rheumatoid factor (RF)

3.4.1.1 Higher levels/frequency of RF in sera among periodontitis patients compared to controls

Three articles presented results supporting an autoimmune response through an association between RF and periodontitis. Only one study, which included 171 patients with periodontitis and 65 healthy controls, reported a significantly higher level of RF

among the periodontitis patients (The & Ebersole, 1991). Another study, which included 22 patients with periodontitis and 22 healthy controls, reported a three times higher mean RF-titer level among periodontitis patients compared to the healthy controls, although a similar prevalence was found among the two groups (De Nardin et al, 1991). A more recent experimental study showed that RF-levels increased after inducing experimental periodontitis in rats, a difference however not reaching statistical significance. That study also found that rats with induced RA plus experimental periodontitis (n=10) had a higher level of RF in sera compared to rats with induced RA alone (n=10). Alveolar bone loss was significantly higher in rats with experimental periodontitis+RA compared to controls (n=10), RA and EP. RA did not lower the alveolar bone significantly alone, but EP showed higher alveolar bone loss then RA and controls but lower then experimental periodontitis+RA (Correa et al, 2017)

Three articles did not find any significant differences regarding seropositivity or RF levels in sera between periodontitis patients and healthy controls. These three articles included studies of 29 patients with chronic periodontitis which were compared to 53 healthy controls (Hirsch et al, 1989), 114 patients with periodontitis compared to 36 healthy controls (Janssen et al, 2015) and 113 patients with periodontitis compared to 36 healthy controls (Janssen et al, 2017).

3.4.1.2 Local production?

One study found higher local levels of RF and RF-secreting cells in gingival biopsies compared to autologous sera among 12 RF-positive patients with periodontal disease (no statistical significance provided). The same study found no significant correlation between RF secreting cells in gingival biopsies and RF levels in sera (Hirsch et al, 1989).

3.4.1.3 Reports correlating severity of disease and levels of RF

Two articles investigated a possible correlation between severity of periodontitis and the levels of RF but none of them found a significant association between RF seropositivity or RF levels and severity of periodontitis. (Janssen et al, 2015) (De Nardin et al, 1991).

3.4.2 Anti-citrullinated protein antibody (ACPA)

Seven articles provided results regarding ACPA, which are antibodies targeting post-translational modified (through citrullination) self-proteins.

One study reported significantly higher levels of ACPA in sera in a study of 96 patients with periodontitis and 98 healthy controls (de Pablo et al, 2014). A recent experimental study presented results showing an increase of ACPA-levels after inducing experimental periodontal disease in rats, however still not reaching significant differences (Correa et al, 2017).

One study including 29 patients with periodontitis and 11 healthy controls found that 9 out of 11 anti-CCP-positive GCF samples came from periodontitis patients, but the result did not reach statistical significance. They did however find a significantly higher level of the autoantigen CCP in periodontitis-samples compared to healthy control samples (Harvey et al, 2013).

Three studies measured the presence or heightened levels of autoantigens associated with ACPA/anti-CCP and other post-translational modified proteins. One study including 15 periodontitis patients and 6 healthy controls showed that 80% of periodontitis-samples had elevated levels of citrullinated proteins compared to 33% of healthy periodontal tissue. (Nesse et al, 2012). Another study including 29 patients with different forms of periodontitis and 11 healthy controls showed that periodontitis samples had a significant higher level of CCP compared to healthy controls (Harvey et al, 2013). The third study including 6 patients with mild to moderate periodontitis and 3 healthy controls showed an increased immunostaining of citrullinated, carbamylated and MMA-modified proteins in periodontitis tissue that increased with the severity of disease while healthy control samples showed an insignificant amount of staining. (Bright et al, 2018)

Four studies, 114 periodontitis patients vs 36 healthy controls (Janssen et al, 2015), 65 periodontitis- patients vs 59 healthy controls (Reichert et al, 2015), (Kharlamova et al, 2016), 113 periodontitis patients vs 36 healthy controls (Janssen et al, 2017), presented no significant differences of anti-CCP levels or prevalence in sera between periodontitis patients and healthy controls. One study without controls found that 5% of Periodontitis patients were seropositive to anti-CCP (Mikuls et al, 2009)

Two earlier mentioned studies reported no significant differences in ACPA levels or prevalence between periodontitis and healthy controls (Janssen et al, 2015; Reichert et al, 2015)

3.4.3 Reports correlating severity of periodontal disease and levels of ACPA/anti-CCP

One article investigated the correlation between these autoantibodies and severity of periodontitis and found a borderline correlation with anti-CCP seropositivity (Janssen et al, 2015).

3.5 Other autoantibodies associated with periodontal disease

3.5.1 Anti-carbamylated protein antibodies

One study included results regarding anti-carbamylated protein antibodies. They reported no significant difference in anti-CarP-levels in sera of 114 patients with periodontitis as compared with that in 36 healthy controls. However, they found a significant correlation between anti-CarP seropositivity and severity of periodontal disease (Janssen et al, 2015).

3.5.2 Antinuclear antibody (ANA)

Two articles investigated the levels of ANA and one study found that 9 out of 29 periodontitis patients (31%) showed increased levels of ANA, as compared to 2 of 22 healthy controls (9%) (De Nardin et al, 1991). The other study found no difference in seropositivity to anti-citrullinated H3 when comparing 113 periodontitis patients to 36 healthy controls. Only one of the 15 gingival tissue samples from the periodontitis patients had antibodies that bound to citrullinated histone H3 (Janssen et al, 2017).

3.5.3 Anti-neutrophil cytoplasmic antibodies (ANCA)

One included article studied the prevalence of anti-neutrophil cytoplasmic antibodies (ANCA) in sera of 30 patients with periodontitis and 20 healthy controls. They found a significantly higher prevalence of these antibodies among periodontitis patients compared to healthy controls. Among ANCA-positive periodontitis patients, 33.3% showed autoreactivity against proteinase 3 (Novo et al, 1997).

4 Discussion

Our search generated a broad variety of articles. Twenty-four of the studies were observational case-control studies except one experimental study and one case study. No interventional studies were found in this search. Many of the included studies measured different types of autoantibodies and the types of results varied among the articles studying the same autoantibody due to different comparisons. This made it hard

to present a summarized result. The variables could be different types of antibodies, autoantigens, different media (serum, gingival tissue, periodontal tissue) and the results comprised of different comparisons of these mediums between the different study groups.

The included articles studied the broad variety of autoantibodies and only three of these different groups of antibodies were studied in more than three articles (figure 3). These more frequently studied group of autoantibodies associated with the periodontal diseases gingivitis or periodontitis or peri-implantitis were anti-collagen, rheumatoid factor and anti-CCP. Anti- CCP is said to be a subgroup of ACPA- antibodies (Ioan-Facsinay et al, 2011).

4.1 Anti-collagen autoantibodies

4.1.1 Local or systemic production of anti-collagen autoantibodies

Three out of 4 studies provided significant results supporting a local autoimmune response by anti-collagen antibodies comparing local samples to autologous sera in patients with chronic periodontitis and one found no significant difference. Overall these results suggest that an autoimmune response in chronic periodontitis and the production of autoantibodies occurs in the periodontal tissue, although all 4 studies provided a low to limited grade of evidence due to study design, size of study, not considering all clinical variables and co-founders etc. (Anusaksathien et al, 1992; Hirsch et al, 1988; Rajapakse & Dolby, 2004; Sugawara et al, 1992).

4.1.2 Systemic autoimmune response.

Two out of 3 articles found a significantly higher level of anti-collagen type I in sera among patients with periodontitis compared to healthy individuals. This data suggests that periodontitis is associated with the production of autoantibodies targeting collagen. However it cannot be excluded that another yet undiagnosed autoimmune disease is the underlying cause of anti-collagen type I in these patients. While these results do not explain where the autoantibodies were produced, measuring the systemic levels of autoantibodies targeting collagen might work as a diagnostic tool for detecting periodontal disease. However, one study by Rajapakse et al presented data showing no significant difference compared to matched controls. The two studies supporting the association did not have age-matched controls which might affect the results. In

addition, all three studies provides low to limited evidence and differ in clinical variables such as smoking and small size of study which lowers the strength of evidence.(Govze & Herzberg, 1993; Hirsch et al, 1988; Rajapakse & Dolby, 2004; Sugawara et al, 1992).

4.1.3 Gingivitis, chronic periodontitis, aggressive periodontitis and peri-implantitis.

Three articles comparing aggressive periodontitis to chronic periodontitis all showed significant results indicating a stronger association of autoreactivity to collagen in patients with aggressive periodontitis. However, all these 3 articles presented different kinds of support, where one showed higher prevalence (De-Gennaro et al, 2006), another showing higher levels (Koutouzis et al, 2009) and the third showing higher affinity to collagen. This latter study also showed that the antibodies from chronic periodontitis and gingivitis serum showed no affinity to collagen. (Hendler et al, 2010).

The only article in this review studying implants found a significant association between periimplantitis and the prevalence of anti-collagen antibodies. This study provided a low grade of evidence due to size of study and study design, although describing clear criteria's for inclusion, exclusion and evenly matched controls. More studies are needed to strengthen the level of evidence (Papi et al, 2017).

4.2 Rheumatoid arthritis (RA)-associated antibodies

4.2.1 Rheumatoid factor (RF)

4.2.1.1 Local or systemic production of RF?

RF is the autoantibody targeting Immune complexes, and is believed to cause an enhanced immune response through activation of the complement system and inflammatory mediators (Tan and Smolen, 2016). Only one article (Hirsch et al, 1989) showed results supporting a local production of autoantibodies by higher levels of RF and RF-secreting cells in gingiva compared to sera in patients with chronic periodontitis. The grade of evidence however is considered as limited due to the small size of the study, lacking statistical analysis and case-control design which is considered

as limited. More studies are needed to strengthen the support of a local production of these autoantibodies and the association with periodontitis.
Another study (Correa et al, 2017) showed that RF-levels increased after inducing experimental periodontitis in rats but not enough to be of statistical significance and the animal model with experimental periodontitis is hard to compare to the human forms of periodontitis.

4.2.1.2 Systemic response (periodontitis serum vs healthy control serum)

Three out of 5 articles showed data suggesting that chronic periodontitis don't have a significant association with RF. Two of them were however based on the same study groups by the same main author of a quite larger study population compared to similar studies. These studied also adjusted for different variables giving the results a strengthened but still limited grade of evidence (Janssen et al, 2015; Janssen et al, 2017). The third study by (Hirsch et al, 1989) further strengthens this results although being a smaller study of case-control design with limited evidence.
Two out 5 articles however gave the opposite result suggesting a correlation between systemic RF and chronic periodontitis (De Nardin et al, 1991) not a significance prevalence but finding three times higher mean titer levels of RF among the patients witch chronic periodontitis in a study with a limited grade of evidence, moderate sized group and matched healthy controls and consideration for clinical variables however strengthens this result. The other study supporting this association was a the study by (The & Ebersole, 1991) who found significant higher levels in serum from patients with 3 different forms of periodontitis compared to healthy controls. This study provided limited evidence due to lack of information of the control group although it was a large study involving many subjects with each form of periodontitis (localized aggressive periodontitis, generalized aggressive periodontitis and chronic periodontitis).

4.2.2 Anti-citrullinated protein antibodies (ACPA) and anti- cyclic citrullinated peptides (anti-CCP).

4.2.2.1 Local: (periodontitis tissue vs healthy control tissue)

The only study on human models found no significant correlation between local anti-CCP positivity in gingival tissue and chronic periodontitis although most of the positive samples (82%) came from the periodontitis patients and the autoantigen CCP was found

in significantly higher levels among periodontitis- samples. The grade of evidence is low due to study size although following precise criteria for inclusion and exclusion (Harvey et al, 2013).

Another study provided the opposite result in rat models and showed that the levels of ACPA increased in gingival tissue after inducing experimental periodontitis but not enough to be of statistical significance. These results are interesting but it is uncertain how these results can be transferable to human models (Correa et al, 2017)

Nesse et al. found that 80% of periodontal tissue from the studied chronic periodontitis patients had elevate levels of citrullinated proteins which in comparison to 33% of the healthy individuals in the study gives support that local citrullination of proteins occurs and these citrullinated proteins can function as possible autoantigens for ACPAs (Nesse et al, 2012). The study was however to small which gives a low level of evidence.

4.2.2.2 Systemic response (periodontitis serum vs healthy control serum)

Five out of 6 included studies did not find a significant difference in anti-CCP or ACPA- levels or prevalence in sera comparing aggressive or chronic periodontitis to healthy controls. Kharlamova et al. did not even find detectable levels in the reasonably large study group with periodontitis (Kharlamova et al, 2016). All together these results suggest, with a moderate level of evidence, that periodontitis do not relate to the systemic prevalence or production of these autoantibodies.

One article giving opposite result found significant higher serum levels of the ACPA anti- Cep-1 in patients with moderate to severe periodontitis in a moderately large study with a younger control group but adjusting the results for age (de Pablo et al, 2014).

Correa et al found that induced experimental periodontitis in the earlier mentioned rat models lead to increased levels of ACPA in sera although not enough to be of statistical significance (Correa et al, 2017; de Pablo et al, 2014; Janssen et al, 2015; Janssen et al, 2017; Kharlamova et al, 2016; Reichert et al, 2015).

4.3 Other extracellular matrix antibodies.

4.3.1 Anti-b1-AR peptide IgG

Two articles by the same author and same population presented significant results supporting an autoimmune response against human fibroblasts associated with chronic periodontitis. The study design, narrow population and the lack of information around

the studied patients, for example if they had undergone periodontal treatment, gives the results a limited level of evidence (Sterin-Borda et al, 2009a; b).

4.3.2 Anti- desmosomal antibody

The results by Govze and Hertzberg supports an association between periodontitis and increased autoreactivity against desmosomal components, but the article only describe the age intervals in the two compared groups so it´s uncertain if the mean age differs and affects the results. The study design and size thus gives the results a low level of evidence (Govze & Herzberg, 1993).

4.3.3 Anti- laminin (Anti- LM) and Anti- fibronectin (Anti-FN)

No significant association was found between peri-implantitis and these autoantibodies in a relatively small case-control study with limited value due to clear criteria in study methods. (Papi et al, 2017)

However, the association of these autoantibodies was shown to be stronger in relation to aggressive periodontitis as compared to chronic periodontitis in a small case-control study with low level of evidence (De-Gennaro et al, 2006).

These two studies gives little support that the prevalence of these antibodies contributes to the disease. More studies of aggressive periodontitis should be done comparing with healthy controls to evaluate the importance of results in the latter study. However this result could suggest that these autoantibodies could be used as a marker do differentiate between these two types of periodontitis.

4.3.4 Anti-neutrophil cytoplasmic antibodies (ANCA)

Only one case-control study shows an association between ANCA and chronic periodontitis but the result has a low level of evidence due to study design and more studies are needed to strengthen this result (Novo et al, 1997).

4.3.5 Anti-cardiolipin (Anti-cl)

One large case-control study of good quality showed that generalized forms of periodontitis has a significantly higher association with these autoantibodies and the

presence correlates with the severity of periodontitis. More studies are needed to strengthen this result. (Schenkein et al, 2003)

4.4 Other autoantibodies associated with periodontal disease

4.4.1 Anti-carbamylated protein antibodies

One relatively larger study of case-control design showed no correlation between anti-CarP and chronic periodontitis (Janssen et al, 2017). Another study however showed that gingival tissue from periodontitis contained more carbamylated proteins which are potential targets for these autoantibodies, but in a study so small it fails to contradict the previous stronger result with higher but still limited level of evidence (Bright et al, 2018).

4.4.2 Anti-nuclear antibodies (ANA)

Two relatively large case-control studies gave little support that these autoantibodies can be significantly associated with periodontitis, despite that one of the two (De Nardin et al, 1991) showed that increased levels of these autoantibodies can be seen more commonly among periodontitis patients. However, the lack of information regarding the studied population gives this low level of evidence and the difference seen did not reach statistical significance.

5 CONCLUSION:

This search of the literature resulted in a broad variety of studies, which gave a too limited material to perform a meta-analysis. Almost all of the included studies can in someway be classified as case-control studies which according to “GRADE” evaluation system gives a limited level of evidence. The results from these articles, suggesting the occurrence of autoimmunity in these periodontal diseases, gave little strength due to the critical evaluation of our combined search results. Furthermore, most of the data found are hard to combine for analyses of higher strength of evidence. In studies where the results could be compared due to same similar study structures, regarding incidence of periodontal disease and the prevalence of certain autoantibodies, opposite results were found which makes it hard to come to a conclusion. Almost all studies were of small size and further studies must be done with the same study design so data can be

extracted for direct comparison to strengthen the support of these results. If an association between autoantibodies and periodontal disease could be confirmed more precisely, strategies could be designed to target these autoantibodies to treat periodontal disease. In addition, autoantibodies could also be used for diagnostics and classification of periodontal disease. Such ambitions could be of extra importance since some studies suggest that the levels of association may differ between the different forms of periodontal disease and the presence of autoantibodies.

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7 Figures:

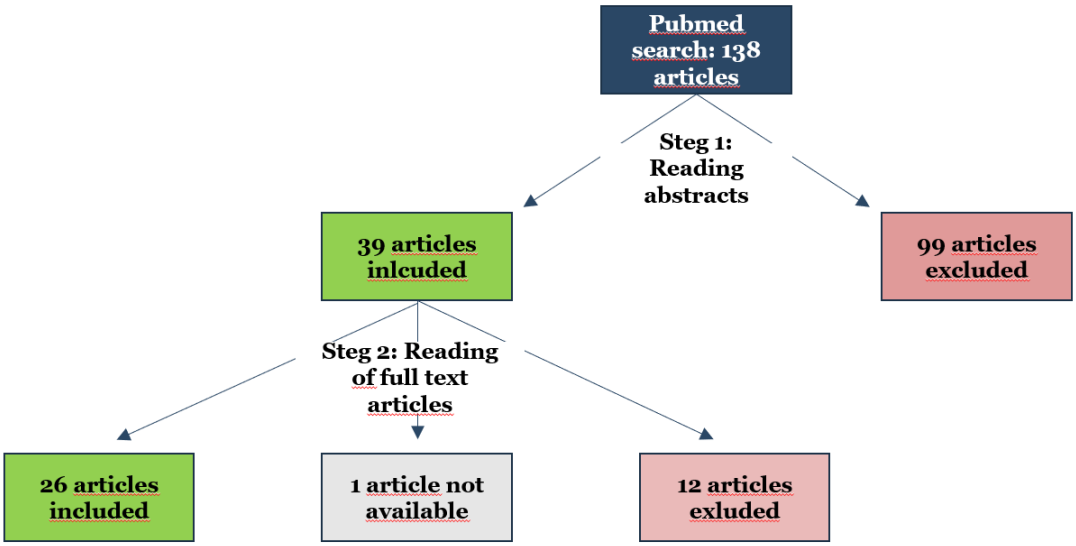

Figure 1 *Flowchart over search, inclusion and exclusion.*

Article	Study design	Study Population	Controls	Level of evidence (GRADE): 1 to 4	GRADE factors +/-
Anusaksathien. Autoimmunity to collagen in adult periodontal disease: immunoglobulin classes in sera and tissue.	Cross sectional study/ Case study	Chronic periodontitis (n=15)	No controls	1	Minus: Study design. Small study. No controls
Correa: Periodontitis increases rheumatic factor serum levels and citrullinated proteins in gingival tissues and alter cytokine balance in arthritic rats.	Experimental study	Experimental periodontitis and experimental arthritis (EP+RA) (n = 10) Experimental arthritis (RA) (n = 10) Experimental periodontitis (EP) (n = 10)	Controls (N = 10)	2	
De Nardin: Humoral Immunity of Older Adults with Periodontal Disease to Porphyromonas gingivalis	Case control study	Chronic periodontitis (n=62)	Healthy controls (n=22)	2	
de Pablo: The autoantibody repertoire in periodontitis: a role in the induction of autoimmunity to citrullinated proteins in rheumatoid arthritis?	Case control study	Moderate to severe periodontitis (n=96)	Healthy controls (n=98)	2	
De-Gennaro LA. Autoantibodies directed to extracellular matrix components in patients with different clinical forms of periodontitis.	Case control study	Aggressive periodontitis (n=22) Chronic periodontitis (n=18)	Healthy controls (n=10)	1	Minus: Small study
Govze Y, Serum and gingival crevicular fluid anti-desmosomal antibodies in periodontitis.	Case control study	Periodontitis (n=10)	Healthy controls (n=20)	1	Minus: Confounders (age). Small study
Harvey GP: Expression of peptidylarginine deiminase-2 and -4, citrullinated proteins and anti-citrullinated protein antibodies in human gingiva	Case control study	Chonic periodontitis (n=29)	Healthy controls (n=21, n=11 included)	2	Plus: Confounders
Hendler A. Involvement of autoimmunity in the pathogenesis of aggressive periodontitis.	Case control study?	Aggressive periodontitis (n= 25) Chronic periodontitis (n= 14) Gingivitis (n= 18)	Controls with RA (n=12)	1	Minus: Confounders
Hirsch HZ. Autoimmunity to collagen in adult periodontal disease.	Case control study (Unknown if matched controls)	Chronic periodontitis (n=39)	Healthy controls (n=22)	1	Minus: Confounders, Study quality.
Hirsch: Local Production of IgA- and IgM-Rheumatoid Factors in adult periodontal disease	Case control study	Moderate to severe chronic periodontitis (n=29)	Healthy controls (n=53)	2	
Jansen KMJ: Rheumatoid arthritis–associated autoantibodies in non–rheumatoid arthritis patients with mucosal inflammation: a case–control study	Case control study	Chronic periodontitis (n=114)	Healthy controls (n=36)	2	
Janssen KMJ: Autoantibodies against citrullinated histone H3 in rheumatoid arthritis and periodontitis patients	Case control study	Severe periodontitis (n=113)	Healthy controls (n=36)	2	
Kharlamova: Antibodies to Porphyromonas gingivalis Indicate Interaction Between Oral Infection, Smoking, and Risk Genes in Rheumatoid Arthritis Etiology	Case control study	Chronic periodontitis (n=65),	Healthy controls (n=59)	2	

Figure 2a *Study design, studied subjects and controls.*

Article	Study design	Study Population	Controls	Level of evidence (GRADE): 1 to 4	GRADE factors +/-
Koutouzis T. Autoreactivity of serum immunoglobulin to periodontal tissue components: a pilot study.	Pilot study (case control study)	Chronic periodontitis (n=5) Local aggressive periodontitis (n=5)	6 periodontally healthy extracted teeth and tissue surrounding	1	Minus: Small study. Study quality. Confounders.
Mikuls: Antibody responses to Porphyromonas gingivalis (P. gingivalis) in subjects with rheumatoid arthritis and periodontitis	Case control study	RA (n=78), Mild to severe chronic periodontitis (n=39)	Healthy controls (n=40)	2	
Nesse W: The periodontium of periodontitis patients contains citrullinated proteins which may play a role in ACPA (anti-citrullinated protein antibody) formation	Case control study	Chronic periodontitis (n=15) RA (n=4)	Healthy controls (n=6)	1	Minus: Confounders (age). Small study.
Novo E. A possible defective estimation of antineutrophil cytoplasmic antibodies in systemic lupus erythematosus due to the coexistence of periodontitis: preliminary observations.	Case control study	Periodontitis (n=30) (+SLE n=30)	Healthy controls (n=20)	1	Minus: Confounders
Papi P. Peri-implantitis and extracellular matrix antibodies: A case-control study.	Case control study?	Peri implantitis (n=21)	Healthy dental implant patients (n=21)	2	
R. Bright: Gingival tissue, an extrasynovial source of malondialdehyde-	Case control study	Mild periodontitis (n=3) Moderate periodontitis (n=3)	Healthy controls (n=3)	1	Minus: Small study
Rajapakse PS. Evidence for local production of antibodies to auto and non-self antigens in periodontal disease.	Case control study	Periodontitis (n=13)	Healthy controls (n=13) (Not clearly specified)	1	Minus: Confounders. Study quality. Small study.
Reichert: Association of levels of antibodies against citrullinated cyclic peptides and citrullinated α-enolase in chronic and aggressive periodontitis as a risk factor of Rheumatoid arthritis: a case control study	Case control study	Generalized Chronic periodontitis (n=89), Generalized aggresvie periodontitis (n=51)	Healthy controls (n=89)	2	
Schenkein HA. Anti-cardiolipin antibodies in sera from patients with periodontitis.	Case control study	Local aggressive periodontitis (n=32) Genereal aggressive periodontitis (n=87) Chronic periodontitis (n=129)	Healthy controls (n=163)	2+	Positive: Confounders. Large study.
Sterin- Borda L. Circulating beta(1) Adrenergic Autoantibodies from Patients with Chronic Periodontitis Interact with Gingival Fibroblasts.	Case control study	Chronic periodontitis (n=25)	Healthy controls (n=20)	2	
Sterin-Borda L. Autoantibodies to beta 1-adrenoceptors in human chronic periodontitis induce overexpression of fibroblast CD40 and trigger prostaglandin E2 generation.	Case control study	Chronic periodontitis (n=25)	Healthy controls (n=20)	2	
Sugawara M. Detection of, and anti-collagen antibody produced by, CD5-positive B cells in inflamed gingival tissues.	Case control study (Partially matched)	Periodontitis (n=20)	Healthy controls (n=10) (not age-matched)	1	Minus: Confounders (age). Small study
The J: Rheumatoid Factor (RF) Distribution in Periodontal	Case control study	Localized aggressive periodontitis(n=57), Generalized aggressive periodontitis (n=57), Chronic periodontitis (N=62)	Healthy controls (n=65)	2	

Figure 2b *Study design, studied subjects and controls.*

Autoantibody	Autoantigen	Localization GT= gingival tissue, PT= periodontal tissue, S= serum, GCF= Gingival crevicular fluid	References
Anti- collagen	Collagen	GT, PT, S GT, S GT, S, GCF S, Granulation tissue S GT, S, PT S S	(Hirsch et al, 1988) (Anusaksathien et al, 1992) (Sugawara et al, 1992) (Rajapakse & Dolby, 2004) (De-Gennaro et al, 2006) (Koutouzis et al, 2009) (Hendler et al, 2010) (Papi et al, 2017)
Anti- fibronectin	Fibronectin	S S	(De-Gennaro et al, 2006) (Papi et al, 2017)
Anti- laminin	Laminin	S S	(De-Gennaro et al, 2006) (Papi et al, 2017)
Rheumatoid factor (RF)	IgG- Fc	GT, PT, S S S S S S GT, S	(Hirsch et al, 1989) (The & Ebersole, 1991) (De Nardin et al, 1991) (Mikuls et al, 2009) (Janssen et al, 2015) (Correa et al, 2017) (Janssen et al, 2017)
Anti- cyclic citrullinated peptide (Anti- CCP)	Citrullinated proteins and peptides	GT, GCF S S S GT, S	(Harvey et al, 2013) (de Pablo et al, 2014) (Janssen et al, 2015) (Reichert et al, 2015) (Janssen et al, 2017)
Anti citrullinated protein antibodies (ACPA)	Citrullinated proteins and peptides	S GT, S GT, S	(Kharlamova et al, 2016) (Correa et al, 2017) (Janssen et al, 2017)
Anti- desmosomal antibodies	Desmosomal components	S, GCF	(Govze & Herzberg, 1993)
Anti-b1-AR peptide IgG	b1-adrenoceptors (b1-AR) on fibroblasts	GT, S GT, S	(Sterin-Borda et al, 2009) (Sterin-Borda et al, 2012)
Antineutrophil cytoplasmic antibodies (ANCA)	Proteinase 3	S	(Novo et al, 1997)
Anti-carbamylated protein antibodies (anti- CarP)	Carbamylated proteins	S	(Janssen et al, 2015)
Anti-nuclear antibodies (ANA)	Proteins inside the nucleus of cells	S	(De Nardin et al,) (Janssen et al, 2017).
Anti-CL (b-2-glycoprotein I-dependent anticardiolipin)	Cardiolipin	S	Schenkein et al, 2003
Anti-CEP-1 (ACPA)	citrullinated α-enolase peptide 1	S	(Reichert et al, 2015)
Anti citrullinated histone H3 (ACPA)	Citrullinated histone H3	GT, S	(Janssen et al, 2017)
Not mentioned in article	Vimentin	GT, S, PT, Extracted teeth	(Koutouzis et al, 2009)
Not mentioned in article	Spectrin	GT, S, PT, Extracted teeth	(Koutouzis et al, 2009)
Not mentioned in article	Filamin	GT, S, PT, Extracted teeth	(Koutouzis et al, 2009)
Not mentioned in article	Actin	GT, S, PT, Extracted teeth	(Koutouzis et al, 2009)
Not mentioned in article	Laminin	GT, S, PT, Extracted teeth	(Koutouzis et al, 2009)
Not mentioned in article	Keratin	GT, S, PT, Extracted teeth	(Koutouzis et al, 2009)
Not mentioned in article	Tubulin	GT, S, PT, Extracted teeth	(Koutouzis et al, 2009)
Not mentioned in article	HSP	GT, S, PT, Extracted teeth	(Koutouzis et al, 2009)
Not mentioned in article	Lipoprotein	GT, S, PT, Extracted teeth	(Koutouzis et al, 2009)
Anti- MCV	Not mentioned in article	S	(de Pablo et al, 2014)
Anti-REP-2	Not mentioned in article	S	(de Pablo et al, 2014)
Anti- cit-vim (ACPA)	Not mentioned in article	S	(de Pablo et al, 2014)
Anti-cit-fib (ACPA)	Not mentioned in article	S	(de Pablo et al, 2014)
Anti- rep-1	Not mentioned in article	S	(de Pablo et al, 2014)
Anti-vimentin	Not mentioned in article	S	(de Pablo et al, 2014)
Anti- fibrinogen	Not mentioned in article	S	(de Pablo et al, 2014)

Figure 3 *Overview of studied antibodies, antigens and biopsies.*

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