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The Role of Genetic Predisposition in Diagnosis and Therapy of Periodontal Diseases in Type 1 Diabetes Mellitus

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1. Introduction

The prevalence of diabetes mellitus (DM) and its probable influence on periodontal disease suggests that DM patients will very likely probably become an increasing proportion of the patient population seen by both general dentists and periodontists. Many investigators have studied the oral manifestations involving periodontitis as a complicating factor in the periodontal therapy of DM patients, whose disease may be more prevalent and more severe and progress rapidly.[1 2 3] Periodontal disease makes chewing difficult or painful, thereby leading to an improper diet. On the other hand, uncontrolled periodontal disease may upset metabolic control of DM.[2]

Until the past 15 years, the management was based on the periodontology model of care, and the aim of these methods was to diagnose the problem and resolve it via treatment. Consequently, repairs were made, but the periodontitis generally recurred or progressed unabated. Disease prevention was not practised. It is clear that the risk of periodontal disease varies greatly from one patient to another.[4-8]

Today many practitioners are providing better and more complete service to their patients because they are beginning to incorporate the principles of the information-intense medical model.[9] Changes in our political and social structure have affected how health care is being managed. With increasing evidence of the influence of periodontal disease on systemic health, dentist and hygienists are taking a more intensive look at the risk factors associated with its onset and progression. Bacteriology, immunology, genetics, and systemic cofactors are often used to determine what is wrong with the patients. Genetic knowledge is an important part of the medical model because it allows for a complete and comprehensive picture of all of the factors contributing to the patient's past, current, and future status.

2. Classification and characterization of periodontal diseases

2.1 Gingivitis

Gingivitis is an inflammatory pathologic alteration affecting the gingival epithelium and connective tissue (Fig.1). Clinical symptoms comprise reddness and swelling of the gingiva, bleeding on probing, and a periodontal pocket deph ≥1mm.

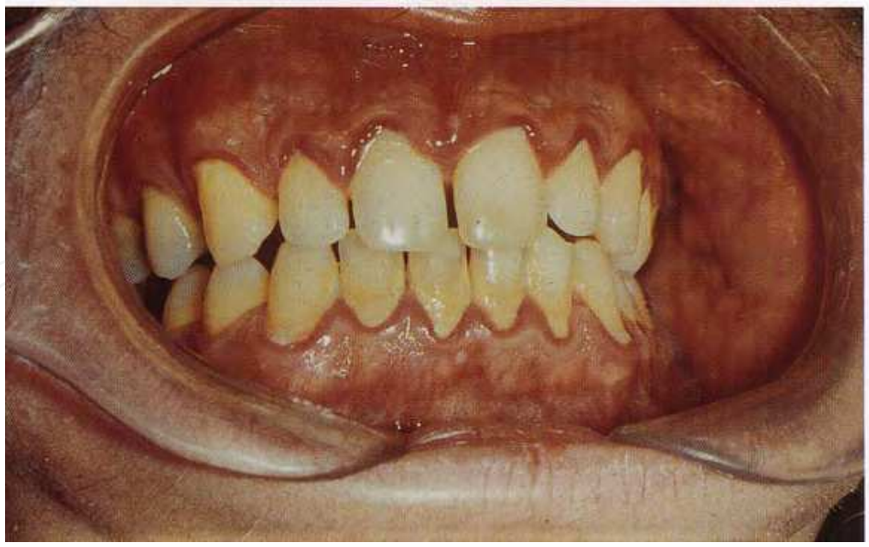


Fig. 1. Gingivitis

Gigivitis is characterized by a subgingival microflora that is slightly shifted in favor of gramm-negativ, anaerobic bacteria without any periodontopathogenic microorganisms. ANUG is the acronym of the acute necrotic ulcerative gingivitis.

2.2 Chronic Adult Periodontitis (AP)

The slowly progressing AP is clinically characterized by persistent loss of attachment, a positive bleeding on probing (BOP), periodontal pockets depths of 1-3 mm, and slight loss of alveolar bone tissue (Fig.2). This is the most common type of periodontitis and generally occurs at the age of 30 years or later. It may be either generalized or limited to molars and/or incisors. The subgingival microbial panel is slightly shifted in favor of gram-negative, anaerobic bacteria with an increased amount of periopathogenic microorganizms.

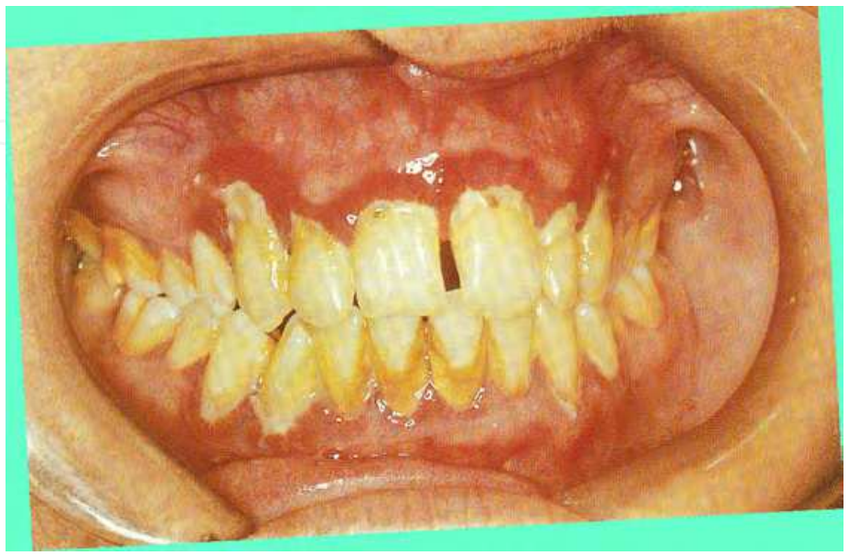


Fig. 2. Periodontitis (loss of alveolar bone tissue)

2.3 Refractory marginal periodontitis

Refractory or therapy-resistant AP shows a progressive loss of attachment even with diligent mechanical therapy and positive compliance of the patients. This type of periodontitis is characterized by a progressive loss of supporting tissue even if treated thoroughly. In most cases the lesions compromise more than one tooth and are infected by high concentration s of periodontal pathogens. After a massive degradation of supporting tissue the affected teeth are often lost (Fig.3).

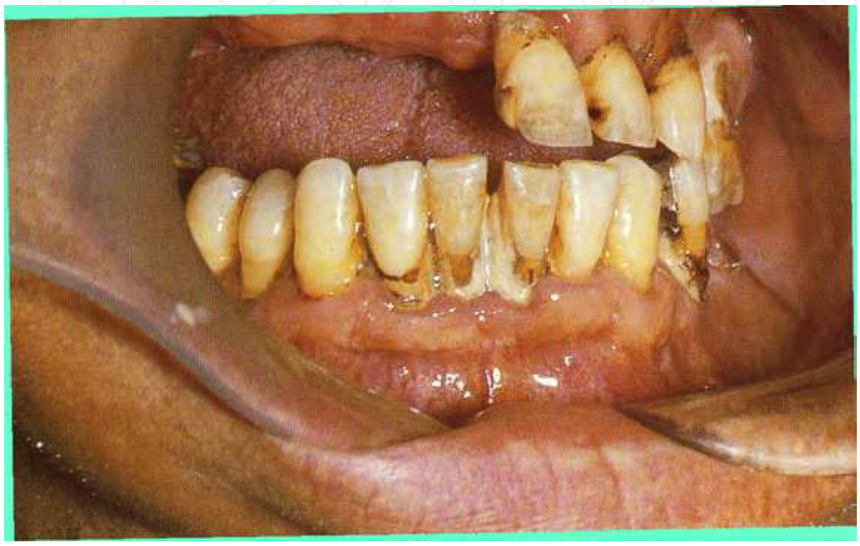


Fig. 3. Periodontitis (degradation of supporting tissue the affected teeth are often lost)

2.4 Localised Juvenile Periodontitis (LJP)

This type usually affects healthy adolescents at the age of 10 to 20 years. It is distinguished by a severe, but localized loss of bone tissue combined with the development of deep pockets at the first molars and/or the incisors. *Actinobacillus actinomycetemcomitans* is considered to be the marker pathogen for LJP.

2.5 Rapidly Progressive Periodontitis (RP)

RPP is mostly seen in patient's at the age of 20 to 35 years. The patients medical history frequently shows a prior LJP. This form of periodontitis is generalized and progresses intermittently with severe loss of bone tissue, gingival bleeding and acute inflammation.The subgingival oral microflora is characterized by a high concentration of periodontal pathogens.

3. The oral cavity ecosystem

The human oral cavity accomodates about 50 billion bacteria belonging to about 400 different species.[10] The various habitats are occupied by microbial populations specifically adapted to their enviroments.

The deep periodontal lesion is a unique eco-system within the oral cavity providing particular living conditions. It is the only place within the oral cavity not being flushed by saliva. Instead is filled with crevicular fluid. Moreover, the acigen concentration decreases progressively with pocket depth creating optimal growth conditions for anaerobic bacteria.[1]

These bacteria lack the enzymes necessary to detoxify oxigen radicals resulting in a severely reduced growth or even death in the presence of oxigen. Dispite the great variety of the microbial flora only a fraction of the bacterial species is etiologically connected to the development of periodontitis. The flora of a healthy sulcus usually consists of aerobic grampositive cocci and rods. These bacteria known as „beneficial flora" show no pathogenic potential but, by their presence, are able to prevent the colonization is progressing the microbial spectrum is shifted in favor of anaerobic gram-negative rods.

The marker pathogens of periodontitis belong to the group of obligatory anaerobic, black pigmented Bacteroides species as *Porphyromonas gingivalis* and *Prevotella intermedia* as well as *Bacteroides forsythus, Treponema denticola, and Actinobacillus actinomycetemcomitans*.[11,12] A strict correlation of the alveolar pocket depth and presence of periodontopathogens could be proven by several clinical studies.[13,14,15]

Several metabolites produced by the periodontitis-associated pathogens either destroy the sorrounding periodontal tissue or inactivate the humoral host defense system. The most important virulence factors produced by the three marker pathogens *P. gingivalis*, *P. intermedia* and *A. actinomycetemcomitans*.[14]

4. Aetiology of periodontitis

The development of plaque is considered to be the primary cause of periodontitis. Especially at the gingival margin plaque hardens to tartar resulting in a mechanical irritation. Exotoxins produced by the plaque bacteria diffuse into adjacent tissue and give rise to reddening and swelling -the typical clinical characteritics- of gingivitis. After professional removal of plaque and dental calculus a healthy periodontium is quickly restored indicating that gingivitis is a reversible condition. In case no professional removal of the dental calculus is performed the infection will progress and a periodontitis becomes established showing the typical clinical characteristics like bleeding on probing (BOP), increasing pocket deph and loss of alveolare bone tissue.[11]

At the age play a roule development of periodontitis[16], and the age of 40 far more teeth are lost by periodontitis than by caries.

Periodontitis associated bacteria are found in low concentration even in the healthy sulcus. Therefore, additional factors must exist that determine the onset and the progress of disease. In case of an impaired immune system e.g. by stress, medication, hormonal imbalances, diabetes or smoking the pathogens utilize the selective advantages for prompt proliferation leading to the establishment of an manifest infection of the periodontium.[17-20]

5. Genetic component to periodontitis

For approximately the past 15 years, dental researchers have been focusing on dental plaque. Clinicians have made treatment decisions as though the plaque-disease interrelationship was quantitative: the more plaque, the more bacteria, the more inflammation, the more disease. However, clinical experience demonstrates that not all people respond the same way to similar accumulations of plaque. There are patients with a lot of plaque who have moderate and advanced disease. Some types of plaque simply are more virulent than others. However, clinical experience demonstrates that not all people respond the same way to plaque accumulations. Because so much variability respond to plaque, and respond to treatment. Some type of plaque symply are more virulent than

others. In adults, these bacteria routinely colonize the teeth when tooth cleaning is not performed on a regular basis. Although bacteria are essential for the initiation of periodontitis, there is currently no mechanism for determing the clinical trajectory of the disease for individual patients, i.e., differentiating those patients who will have a mild to moderate form of disease and respond well to simple professional care from those who are likely to develop a more severe periodontitis that demands extensive therapy and results in tooth mobility. Individual differences in disease progression are dramatic and are often not predictable by currently known mechanisms.

Identification of a risk factors may explain why individual patients do not respond uniformly to standard treatment. For example, a patient who is a heavy smoker may not heal as soon or as well as expected after treatment. Patients react differently to bacterial stimulation. This is a result not only of the type and amount of bacteria but also of the underlying genetic characteristics of the patient's immune system.The cytokines tumor necrosis factor alpha(TNFά) and interleukin 1 (IL-1) are key mediators of the inflammatory process and modulate the extracellular matrix components and bone which comprise the periodontal tissues.The genes encode pro-inflammatory proteins (IL 1A and IL-1B producing IL-1 ά and IL-1β). Several genetic polimorphisms have been described in the genes of the IL-1 cluster and, in case control studies, associations have been reported with increased severity of several chronic inflammatory diseases.

The genetic risk of developing periodontitis has been investigated by studying families and populations as well as twin.[21-26] The studies conducted on twins have reported a significant genetic component explaining the variation in clinical attachment loss, probing depth and gingivitis. An association between the severe chronic form of the disease and a composite genotype in the interleukin IL-1ά and IL-1β genes has been reported.[21] However, this association was found only in non-smokers. Other authors have subsequently investigated the IL-1ά - IL-1β genotypes with a chronic form of periodontitis with different results.[27,28]

The genetics influence resistance on periodontal disease has been determined from a wide variety of sources.[29-32] Genotype positive patients had significantly more clinical expression of inflammation, as determined by bleeding on probing. In healthy patients 46.7 % of genotype positive patients had bleeding as compared with only 8.6% of genotype-negative patients.[32,33] Their results from genetic susceptibility testing have the real potential to improve patient management. Many of the genetic markers for common disease involve polymorphisms in gene sequences involved in cytokine biological activity. Researchers know that in healthy subject IL-1 plays a very important role in inflammation and the expression of periodontitis. Patients with this genotype progress more rapidly toward severe periodontitis and have statistically significant increased inflammation.[32] It has been established that this genotype occurs in approximately 30% of most of the populations that have been tested for this genotype.

Cells from people with a positive genotype produced up to four times more IL-1 in response to the same bacterial challenge.[34] Because IL-1 in high concentrations is involved with destruction of tissues, this increased IL-1 response may explain the more rapid progression of periodontal disease in genotype-positive patients when faced with a bacterial challenge in their plaque. For patients with this genetic susceptibility to periodontitis, tooth loss was be minimized by good plaque control and definitive periodontal therapy.[35]

6. Genetic test for susceptibility to periodontal disease

Two polymorphisms within the IL-1 gene cluster show a close association with periodontitis. One polymorphism is located at position -899 of the Interleukin 1ά gene, the other at position +3953 of the Interleukin 1β gene.[32,36] Within both polymorphisms allele 1 harbors a cytidin c, whereas allele 2 carries a thymidin (T) at the respective position. Allele 2 of the +3953 polymorphism of the IL-1β gene leads to an alteration of the corresponding protein resulting in an overproduction of IL-1β.[37] This overproduction of IL-1 seems to override the feedback mechanisms which normally limit inflammation resulting in the development of massive gingival pockets and degradation of periodontal tissue. These data allow a risk assessment, defining a patients as PRT-positive or PRT negative, the presence of periodontitis risk alleles at positions IL-1ά-889 and IL-1β +3953.

6.1 Genotyp^{R} PRT test

With the Genotyp^{R} PRT test (Hain Lifescience) the base composition and allelic combination of the two IL1 loci can be analysed. The test is a molecular biological assay based on the identification of gene loci associated with an elevated risk in developing periodontitis by means of highly specific DNA probes. It is based on the analysis of nucleic acids, there is no need for viable bacteria to perform the test and no special precautions are required during transport. A detailed sequence analysis has to be performed by additional examinations. The Genotyp^{R} PRT test is not a diagnostic test for periodontal disease. It is rather a test determing the patient's genetic susceptibility to developing severe, generalized periodontitis in the future and helps to plan a comprehensive therapy. Processing and interpretation of the test is performed in clinical laboratories from a buccal swab containing cells of the mucous membrane of the patient's cheek.

7. Indications for microbiological testing of the subgingival flora

It is generally accepted that periodontitis is initiated by the establishment of a specific subgingival bacterial flora. Some of the marker pathogens belong to the group of obligatory anaerobic, black pigmented *Bacteroides species* such as *Porphyromonas gingivalis* and *Prevotella intermedia.* In addition, the bacterial species *Actinobacillus actinomycetemcomitans* (*Haemophilus a.*), *Bacteroidea forsythus,* and *Treponema denticola* play a pivotal role in the initiation of periodontal disease (Table 1).

Strong evidence for etiology	**Moderate evidence for etiology**
Actinobacillus actinomycetemcomitans	Campylobacter rectus
Porphyromonas gingivalis	Eubacterium nodatum
Bacteroides forsytus	Fusobacterium nucleatum
	Prevotella intermedia
	Peptostreptococcus micros
	Streptococcus intermedius-complex
	Treponema denticola

Table 1. Specific Bacteria Associated with Periodontal Disease (Annals of Periodontology 1:928,1996)

7.1 MicroDent^R test

Like Genotyp^R PRT the microDent^R test is a molecular biological diagnostic device. Since it is based on the analysis of nucleic acids, there is no need for viable bacteria to perform the test and no special precautions are requireed during transport. The microDent^R test a highly sensitive and highly specific molecular bological PCR-DNA-probe method. Due to the high specificity of the PCR, any potential contamination of the probe by concomitant flora has no influence on the test results.

A defined cut-off ensures that every positive test result is of clinical relevance and that bacterial concentrations present in a healthy sulcus lead to a negative result. Sampling is performed from the gingival pocket with strile paper points. These marker species can be detected with the microDent^R test: *Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Bacteroides forsythus, Treponema denticola.*

Periodontopathogenic bacteria activate inflammatory mechanisms within the local periodontal tissue throught the production of toxins and other metabolites. The degree of this response depens on the general health and immunologic state of the patients. Besides that, exogenic risk factors such as haevy smoking, stress and medication can negatively influence the progression of periodontal disease. Patients who in addition are PRT-positive suffer from an overproduction of IL-1 leading to a significantly increased immunologic response to the presence of periodontopathogenic bacteria. This individuals therefore are at an even higher risk for developing severe disease and losing teeth. Knowledge of the IL—1 genotype, the bacterial load, and possible additional risk factors allow for the prediction of the patient's future periodontal status including the risk of further tooth loss.

8. Risk factor influence on periodontitis in type 1 DM

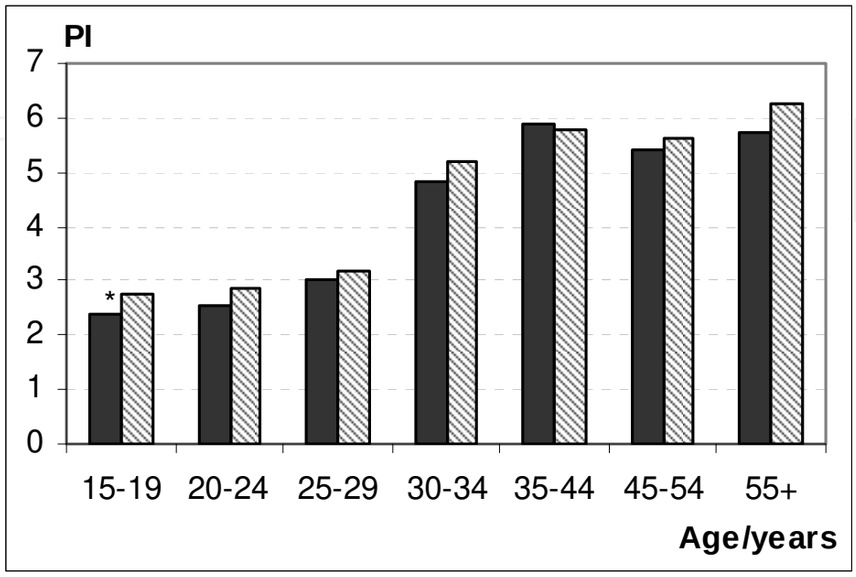
A number of studies have demonstrated a relationship between DM and periodontal diseases, which are among the most prevalent complications of DM.[38-57] Individuals with DM tend to have a higher prevalence of periodontal diseases and more severe and rapidly progressing forms than those who do not have DM.[41,48] DM is a known risk factor for periodontitis in adults. Seppälä et al.[49] demonstrated that patients with type 1 DM exhibit a higher degree of attachment loss and bone loss than control subjects under similar dental plaque conditions. This finding was confirmed in a follow-up site-by-site study by the same authors.[50]

The changes in the periodontal conditions are mostly expressed in the first year of the disease, and the damage to the periodontium which develops at this time is not greatly influeced in the further course of the disease (Fig 4).

It is an interesting result that younger DM subjects display more periodontal destruction than do non-DM subjects at a later age. In the all-age groups, the periodontal status varied according to the age of the patient at the onset of DM. This suggests that the early onset of DM (before 14) is a much greater risk factor for periodontal diseases than mere disease duration (Fig 5).

Earlier investigators[51,52] noted that the duration of DM was greater in groups with severe periodontal disease. Our results[53] indicated that DM is associated with an increased risk of the development of periodontal disease in the event of an increased duration of the DM, and the level of oral hygiene is considered to be a contributory factor rather than the primary etiologic factor in the initiation of gingivitis and periodontitis in those with DM. In agreement with Gusberti et al.[57] the findings of our study[53] demonstrate that poorly controlled type 1 DM patients with elevated blood glucose and HbA_{1c} levels have a greater

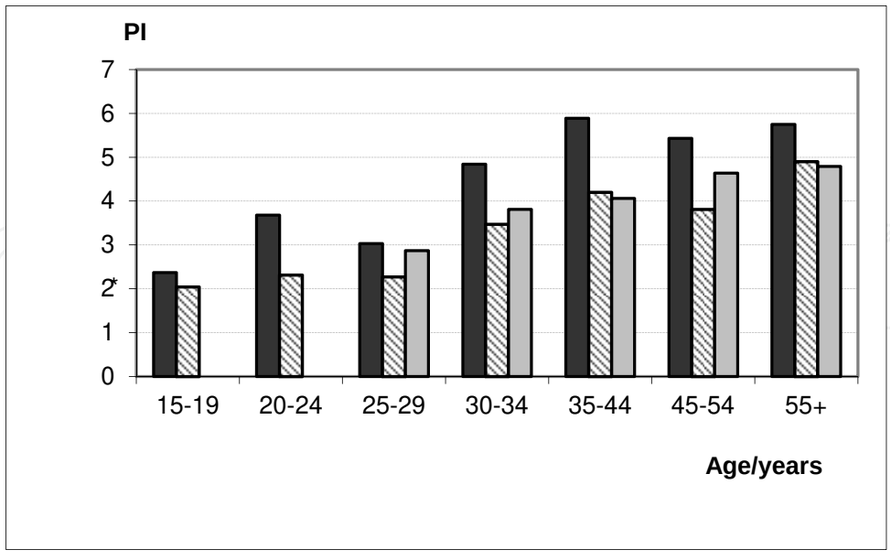
prevalence to more severe periodontal diseases. The severity of periodontal disease was observed to decrease as the control of the DM improved, in agreement with Tervonen and Knuuttila[55], Rylander et al.[58]



Duration of DM: < 1year / > 1year: *P<0.001

Duration of DM: ■ <1 year, ▢ >1 year

Fig. 4. Periodontal conditions (PI) in patients with short and long histories of DM.

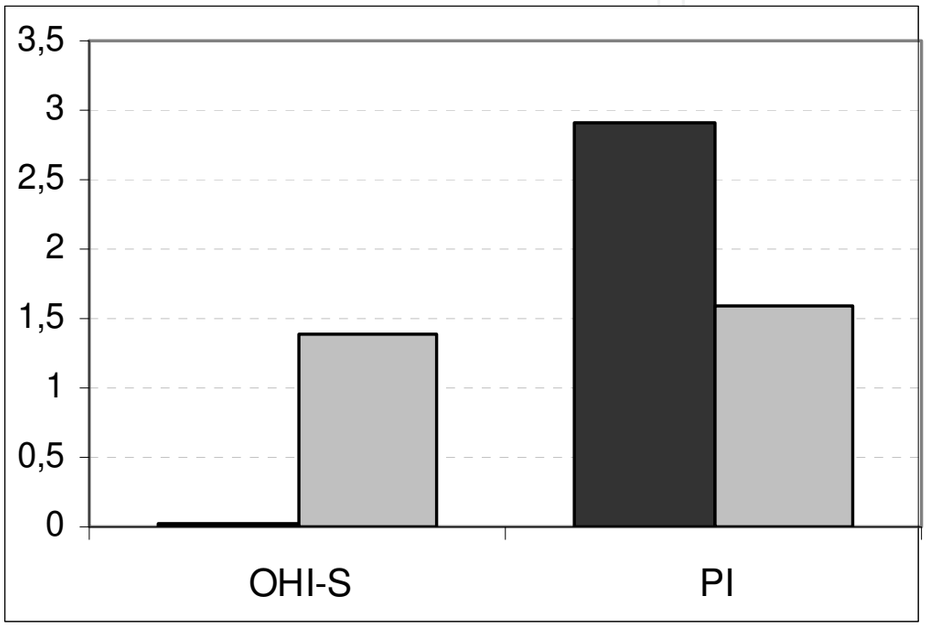


< 14 year / > 14 year: P<0.0001

■ < 14 year, ▨ 15-25 year, ▢ > 25 year

Fig. 5. Age of the patient at the onset of DM

Type 1 DM to increase the prevalence and severity of periodontitis independent of the effects of oral hygiene, and duration time of DM.[42] However the severity of periodontal disease increased with the duration of DM only among those with an adequate level of oral hygiene (OHI-S = 0) The association between periodontal disease and the duration of diabetes mellitus is consistent with trends seen in other complications of DM whereas the longer duration of diabetes mellitus is in direct proportion of the prevalence and severity of periodontal disease. The development of systemic complications of diabetes such as retinopathy, nephropathy, is also is relationship with the duration of diabetes mellitus agreement with Rylander[58], Galea et al.[59], Rosenthal et al.[60] and Lopez.[52]



PI = The intensity of gingivitis and periodontitis
OHI-S = oral hygiene
OHI-S= 0 / PI: p<0.0001
Duration time: ■ < 1 year ▫ > 5 year

Fig. 6. The intensity of gingivitis and periodontitis(PI) according to the level of oral hygiene (OHI-S) and the duration of DM

On the other hand, the presence of severe periodontal infection may also increase the risk for microvascular and macrovascular complications. DM patients with severe periodontal disease demonstrate a significantly higher prevalence of proteinuria and a greater number of cardiovascular complications.[31,54,55] Karjalainen et al.[56], Genco,[31] Lopez et al.[52], Albrecht[59] examined the association between the severity of periodontal disease and organ complications (retinopathy) and found that advanced periodontal disease was associated with severe ophthalmic complications in type 1 DM.

A more pronounced incidence of poor glycemic control in subjects with a shorter duration of DM would be consistent with the hypothesis that hyperglycemia increases linearly with time, but at different rates in different people. This hypothesis suggests that patients with

rapidly increasing hyperglycemia would have more severe periodontal disease at the onset of DM, resulting in damage to the periodontium.

A positive correlation between the level of control of the disease and the intensity of gingivitis and periodontitis. In the well-controlled type 1 DM patients the intensity of gingivitis and periodontitis was lower than in those with poor glycemic control agreement with Gusberti et al.[57], Albrecht et al.[41] Good metabolic control of DM reduces the susceptibility to infection and is therefore also important for the prevention of periodontal disease in people with type 1 DM. In patients with poorly controlled DM, an improvement of the metabolic control may improve the periodontal condition.[61-64] Conversely, periodontal disease can interfere with the control of DM and can increase the insulin requirements in previously stable patients.[65-67,56,68,2,69]

Smoking is associated with an increased intensity of periodontitis. Very light or occasional smokers did not show statistically significant differences compared to non-smokers respect to the prevalence and intensity of gingivitis or periodontitis. No periodontally healthy subjects who has been, or who use to be heavy smokers. Tobacco contains cytotoxic substances such as nicotine which may also have a negative effect on the cellular turnover and repair of the periodontium.[68,70,53]

9. Genetic predisposition and periodontal disease in type 1 DM

Recently several study demonstrates that specific genetic markers, that have been associated with increased IL-1 production, are a strong indicator of susceptibility to severe periodontitis in healthy adults. [22,29,31] The study presented here was to explore a possible association between IL-1A and IL-1-B genotypes in patient with type 1 DM and controls with periodontitis. The frequency -in type 1 DM and controls- of the composite genotype that comprises allele 2 of the IL-1A plus IL-1B is shown in Fig.7. All subject were non-smokers.

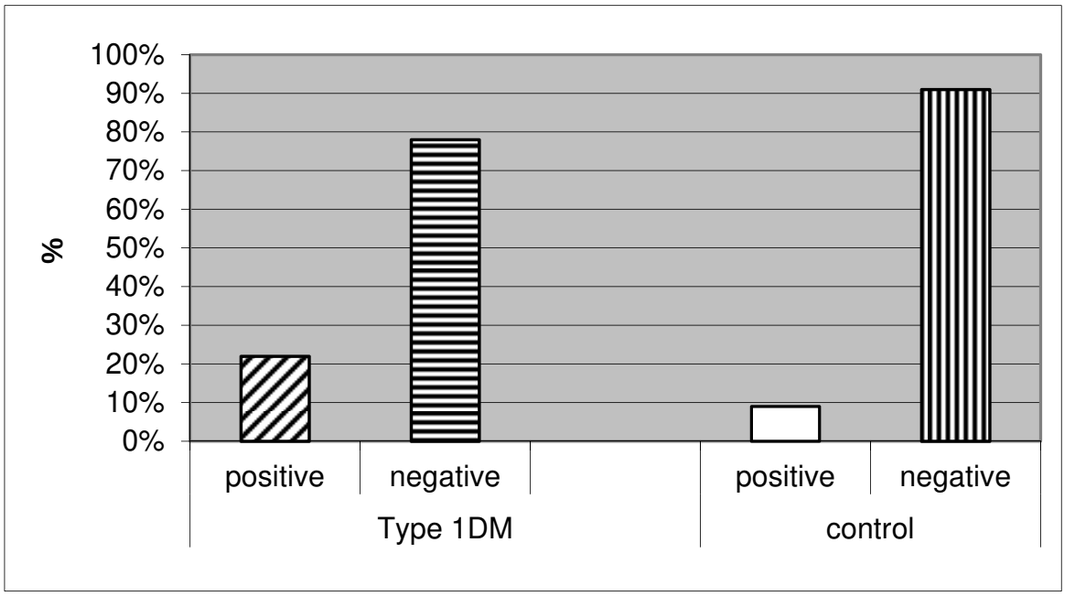


Fig. 7. Frequency of the Genotype[R] PRT positive and negative type 1 DM adult patients and control with periodontitis.

To control the effect of age on disease severity, data were analyzed separately for type 1 DM adolescents aged 14-19 years. In this age range, the composite genotype was present in 22,7 % of DM adolescents and 8,57% of healthy individuals were estimated to carry the IL-1 risk genotype. Distribution of the PAG (Periodontitis Associated Genotype)[21] positive and negative subjects in type 1 DM adolescents shows the Fig. 8.

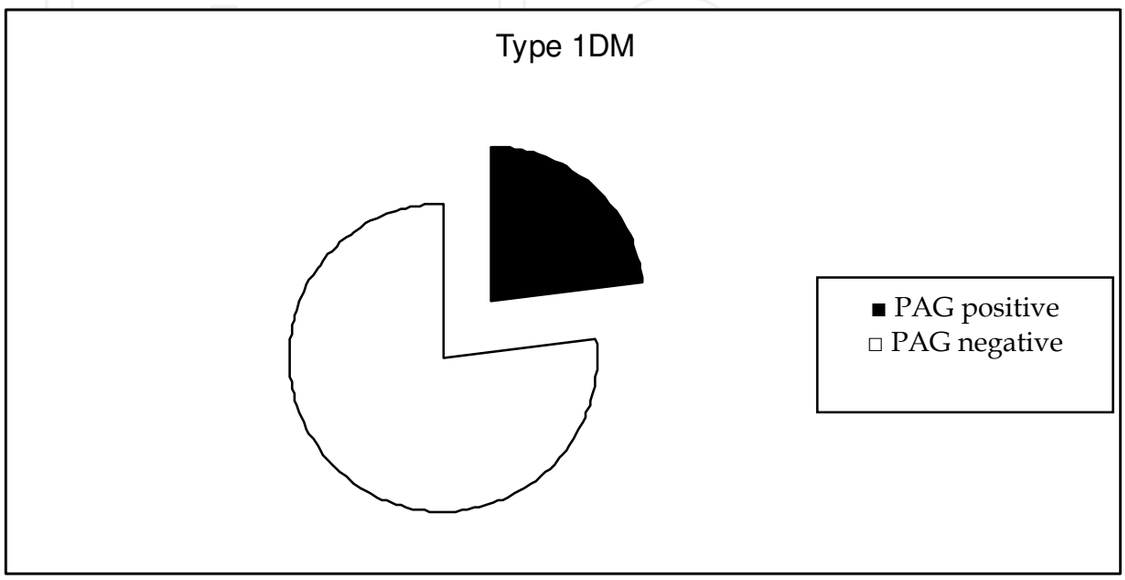
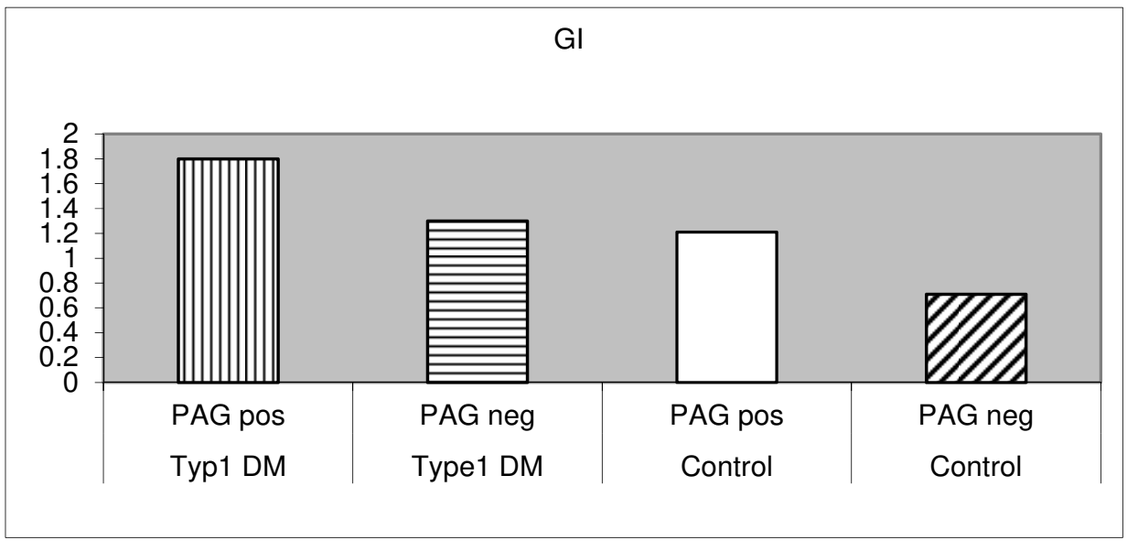


Fig. 8. Frequency of PAG positive and negative adolescents with type 1 DM

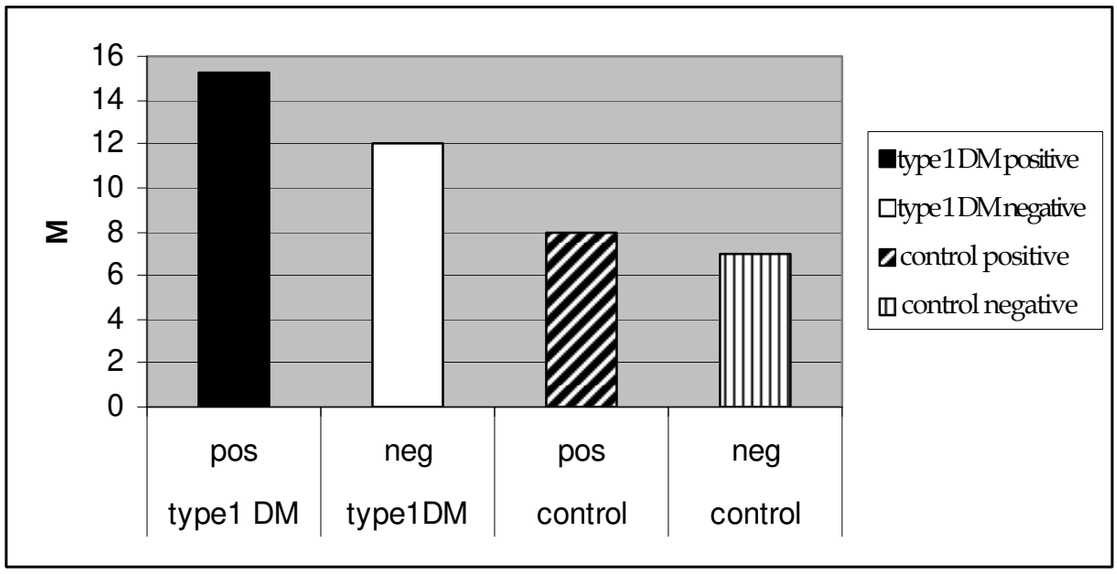
Gingivitis was more severe in those adolescents with positive GenoType^{R}PRT test (Fig.9).



PAG positive/PAG negative: $p<0.001$

Fig. 9. The intensity of gingivitis (GI) of PAG positiv and in negative adolescents with type 1 DM.

In type 1 DM there was significant more extracted teeth in Genotype^{R} PRT positive subjects than in negative group or non-diabetic people ($p< 0.001$) (Fig.10).



P< 0.001

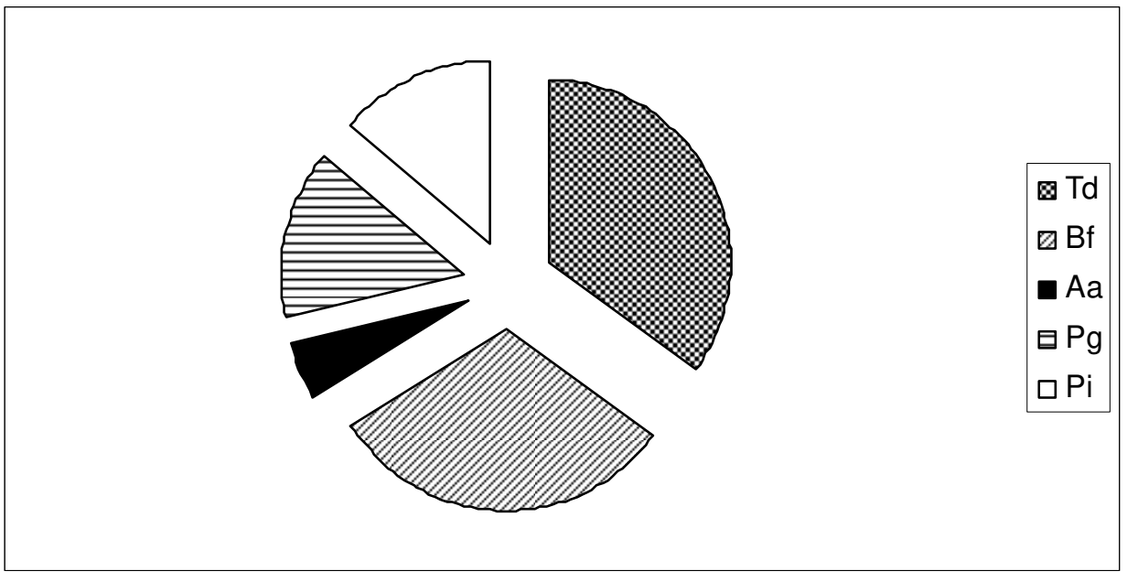
Fig. 10. The mean value of extracted teeth (M) in DM patients and metabolically healthy individuals with positive Genotype.

Periodontitis involves multiple clinical patterns including various severities of periodontitis, uncommon early onset forms that affect children and young adults with type 1 DM, and patients who do not respond predictably to conventional therapy refractory periodontitis.
Guzman et al.[71] have shown a possible interactions between genetic an enviromental factors that there is interplay between genetic an environmental factors that results in periodontal disease.
The finding that a specific genotype in the IL-1 gene cluster correlates with severe periodontitis suggest a genetic mechanism by which some individuals, if challenged by bacterial accumulations, may have a more vigorous immuno-inflammatory response leading to more severe periodontitis in type 1 DM. The lack of reliable markers for type 1 DM patient susceptibility to severe periodontitis has prevented the early identification of those at most risk and has prevented delivery of therapy appropriate for the degree of the risk.

10. The modification of the subgingival microflora in patients with type 1 DM

Periodontopathogenic bacteria activate inflammatory mechanisms within the local periodontal tissue throught the production of toxins and other metabolites. The degree of this response depends on the general health and immunologic state of the patients. Besides that, exogenic risk factors such as heavy smoking, stress, and medication can negatively influence the progression of periodontal disease. Of all of the various microorganism that colonize the mouth in healthy subjects, there are three, Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans, and Bacteroides forsythus have been implicated as etiologic agents in periodontitis. The presence of periodontal pathogen, though necessary to

cause disease, is not sufficient. According our findings there were a significant difference between the severity of the gingivitis, parodontitis and the bacteria identified from the gingival pocket of patients with type 1 DM (Fig.11, Table 2). In case of gingivitis alone, the most prevalent bacterium was *Bacteroides forsythus* (11.11%), whereas in parodontitis it was *Treponema denticola* (75.92%). In type 1 DM the presence of *Treponema denticola* no additional risk of developing agressive periodontitis, despite the fact its presence is necessary for the disease to develop. The *Bacteriodes forsythus, Prevotella intermedia, Porphyromonas gingivalis, Actinobacillus actinomicetemcomitans* may be risk indicators for periodontal disease in population with type 1DM though they are not risk factors.
Patients who in addition are PRT positive suffer from an overproduction of IL-1 leading to a significantly increased immunologic response to the presence of periodontopathogenic bacteria. These individuals therefore are at an even higher risk for developing severe disease and losing teeth.



Td: *Treponema denticola*
Bf: *Bacteroides forsythus*
Aa: *Actinobacillus actinomycetemcomitans*
Pg: *Porphyromonas gingivalis*

Fig. 11. The distribution of the subgingival microflora in adult patient with type 1 DM.

Subgingival bacterial flora in type 1 DM

Actinobacillus actinomycetemcomitans(Aa)	Porphyromonas gingivalis (Pg)	Prevotella inermedia(Pi)	Bacteroides forsythus (Bf)	Treponema denticola (Td)
5%	15%	14%	31%	35%

Table 2. Distribution of the Subgingival Microflora in Type 1 DM with Periodontal Disease

11. Diagnosis and therapy of periodontal disease in type 1 DM

A considerable fraction of periodontal diseases can be stabilized for years using classical mechanical treatments as root planing or deep scaling. However, this treatment often is not sufficient for elimination of the tissue invading periodontal pathogens. Subsequently, progressive loss of attachment and bone tissue might occur in spite of diligent treatment. In these cases a specific concomitant therapy with antibiotics promises to be more efficient -of course only after careful microbiological testing-.

The choice of medication and mode of application depends on the composition of the subgingival flora and the clinical manifestation of the periodontitis. Where tissue-invasive, periopathogenic bacteria such as *Treponema denticola* are present, mechanical methods like root-planing or deep-scaling are often ineffective in eliminating the pathogen. Despite careful treatment, the result is progressive attachment loss and bone resorption. In such cases, a one-of antimicrobial concomittal therapy – only undertaken after microbiological diagnostics, of course – is much more effective while causing less side effects.

In the main, both local and systemic antibiotic applications are available. In the case of a generalized periodontal disease, an adjuvant systemic therapy is indicated. If the infection focus is limited to individual sites, a local treatment is a sensible alternative.

Antibiotic therapies should in any case only be implemented after microbiological diagnostics (e.g.microDent^{R} test) have been completed, in order to avoid both excessive and under treatment.

In most cases a negative bacterium test result can be equated with periodontal stability. However, the presence of periodontal marker organisms indicates an increased risk for progressive destruction of the periodontium. It is obvious that a therapy with antibiotics should be initiated only after thorough microbiological test.

A sustained success of the therapy depends on an optimal compliance of the patients and regular recall sessions. Regular control examinations of the subgingival flora are rather helpful in early diagnosis of potential rezidives.

Genetics factors should also be determined because they play a key role in providing information to make better treatment decisions. A genotype result is always important to consider when making treatment decisions, even if the patient is genotype-negative. A negative result does not mean that a patient will be periodontal-disease-free. Genotype negative individuals must still be cautious about other risk factors, such as stress, smoking, bad oral hygiene-, and diabetes control.

The genetic predictive test for periodontitis complements the dentist's full scope of services by providing additional wanted and useful information. Indications for the genetic predictive test may be of value to the following patients groups:

- DM patients exhibiting refractory, therapy-resistent periodontitis. A positive test result might explain previous treatment failures and is an indicator for planing an alternative therapy.
- DM patients exhibiting progressive periodontitis. A positive test result might indicate the necessity for a more agressive therapy and shortes recall intervals.
- Type 1 DM adolescens -under 14 years- exhibiting early clinical sign of periodontitis. Before starting treatment, the test helps to plan an individual therapy maching the patient's t.i. a therapy stopping progress of the disease without risking over-treatment.
- Haewy smokers patients with type 1 DM.

Treatment decisions will be affected if a patient has risk factors, for example, haevy smokers. Haevy smokers are counseled that the treatment outcome from regenerative therapy will not be as good as outcomes for those who do not smoke.
In all cases where patient motivation and compliance are major obstacles to efficient prophylactic measures the situation can be dramatically improved when high risk patients are informed about their condition.
Knowledge of the IL-1 genotype, the bacterial load, and possible additional risk factors allow for the prediction of the patient's future periodontal status including the risk of further tooth loss. For the first time, these data enable the dentist to plan an individual therapy matching the patient's needs. Knowledge of the IL-1 genotype also allows a more efficient therapy from an economic point of view because over- and under-treatment can be minimized.

12. Conclusion

Periodontitis is a complex multifactorial disease. Similarly, Type 1 DM is a complex metabolic syndrome. Periodontal disease can be especially problematic for individuals with type 1 DM, in whom the disease may have an early onset or may progress more rapidly. Many characteristics and local factors such as dental calculus, the smoking habits and general factors (the duration of DM, the age, the degree of metabolic control, and the complications of DM) have been identified as factors that put people et an enhanced risk.
The initial dental therapy for patients with type 1 DM, as for all patients, must be directed toward the control of acute oral infections at the onset of DM. It is important to advise the phisician of the periodontal status, since the presence of infections including advanced periodontal disease may increase the insulin resistance and cotribute to a worsening of the DM state. Regular dental care may help maintain good oral health and it is especially important at the onset of the disease. Patients should also be checked regularly for bleeding gums or inflammation. Educating the patient in proper home oral care is a standard routine of periodontal treatment and prevention. Plaque control and scaling procedures frequently resolve gingivitis. However, where more tissue destruction has occurred, it may still be difficult or impossible for the patient to remove plaque deposits from the periodontal pockets.
Periodontitis is a disease leading to destruction of connective tissue and bone that support the teeth. Due to the multifunctional etiology of the disease its clinical appearence and progression greatly vary resulting in difficulties in planing an effective therapy. Smoking should be avoided because it is associated with an increased intensity of periodontitis.
Patients who are genotype positive do not lose all of their teeth to periodontitis because, for the most part, it is a treatable and preventable disease. If patients are identified as having the genetic susceptibility factor and begin a treatment or prevention plan, there are high expectations for favorable outcomes and there is no known risk from being tested. Determining the patient's genetic susceptibility in the future helps to plan a comprehensiv therapy and regular dental control to improve patients care prevent to developing severe, generalized periodontitis and toothlos. This IL-1 genotype does not cause periodontal disease directly, this marker is not a causative factor, instead it is a severity risk factor for susceptibility or predisposition to periodontitis. Optimal prophylaxis and efficient therapy of the polymorphisms defining the periodontitis risk genotype (PRT-positive) patients a careful microbiological testing of the subgingival bacterial flora for allows for the timely

application of appropriate therapeutic measures. In case of positive test results proving the presence of specific periodontopathogenic bacterial species antibiotics should be applied. Choice of medication and mode of application depend on the composition of the subgingival flora and the clinical manifestation of the periodontal disease.

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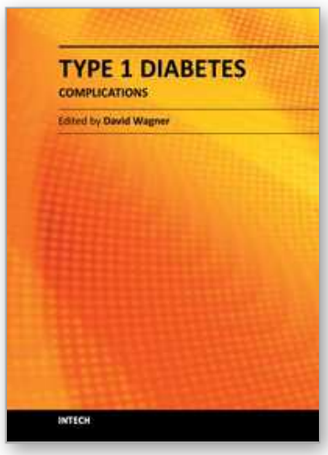

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This book is a compilation of reviews about the complication of Type 1 Diabetes. T1D is a classic autoimmune disease. Genetic factors are clearly determinant but cannot explain the rapid, even overwhelming expanse of this disease. Understanding etiology and pathogenesis of this disease is essential. The complications associated with T1D cover a range of clinical obstacles. A number of experts in the field have covered a range of topics for consideration that are applicable to researcher and clinician alike. This book provides apt descriptions of cutting edge technologies and applications in the ever going search for treatments and cure for diabetes.

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