

Oral biomarker diagnostics for early detection of periodontal disease and for interdisciplinary risk analysis

Pathological enzyme reaction of the active matrix-metalloproteinase-8 (aMMP-8) and its influence on premature births, diabetes, rheumatism, arthritis, heart attacks, strokes, cancer and tumor growth

TOPIC:

Modern biomarker analysis to determine the risk of periodontal disease

METHOD:

Rapid chair-side test

aMMP-8 screening for dentists, internists and naturopaths

Laboratory test

Highly sensitive quantitative oral in-vitro diagnostic instrument for dentists with various specializations

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INTERDISCIPLINARY DIAGNOSTIC INITIATIVE

FOR PERIODONTAL AND SYSTEMIC DISEASE

“The new BioMarker test method numbers among the first commercially available tests that is also able to produce objective figures for the assessment of a core aspect of the host response to periodontal and periimplant inflammation.” March 2010

Prof. Dr. Ulrich Schlegelhauf

Director of the Department of Periodontology at the University of Würzburg,
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“Regarding cardiovascular diseases pathologically excessive MMP-8 has been implicated to atherosclerotic plaque destabilization and rupture through it’s capacity to thin the protecting collagenous fibrous cap.”

March 2010

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“From a cardiological standpoint, careful observation of the status of teeth is gaining more and more significance. Today, we no longer replace heart valves without checking whether the patient has periodontitis.” May 2010

OA PD Dr. med. Heinrich Körtke

Head of the Institute for Applied Telemedicine, Clinic for Thoracic and Cardiovascular Surgery,
Heart and Diabetes Center North Rhine-Westphalia, Bad Oeynhausen, Germany

“Active-aMMP-8 is an ideal test which is quantitative, highly sensitive and specific, reproducible, and easy to perform” August 2010

Maria Emanuel Ryan, D.D.S., Ph.D.

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“Evidence shows the lack of knowledge about the aMMP-8 related interactions between periodontal disease and general diseases. This must change.” March 2010

Laurenz Meyer

Economist, Politician of the Christian Democratic Union, former Member of Parliament,
former General Secretary, former spokesman for economic affairs, Berlin, Germany

“The chosen treatment can only be as good as the diagnosis that led to it. Today’s diagnostics must be interdisciplinary. The aMMP-8 analysis facilitates communication between various areas of medical specialisation.” April 2010

Prof. Dr. rer. nat. Siegmund Bornemann

Biochemist, Consultant in Health Communication, Expert for quality assurance in medicine,
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Table of Content

Chapter 1:

Modern biology mark investigation, diagnostics and science

| | |
|--|----|
| Modern biology mark investigation | 6 |
| Timo Sorsa: MMP-8 as a point-of-care biomarker of periodontitis, peri-implantitis, cardiovascular systemic diseases | |
| Diagnostics and science | 7 |
| OA PD Dr. med. Heinrich Körtke: aMMP-8, the instrument for precision diagnostics and improved follow-up therapy in all specialized areas of medicine | |
| aMMP-8: Life-threatening “agent provocateur” in every mouth | 8 |
| The threat: Pathogenic enzyme activity destroys tissue, bone and organs and increases the risk of disease | |
| Matrix-metalloproteinase-8: a periodontitis indicator | 9 |
| This is the enzyme which, in its activated form, is responsible for the destruction of collagen in the case of periodontitis and peri-implantitis, and can therefore be used to analyze risk | |
| A new testing procedure developed in Finland and the USA | 10 |
| The University of Helsinki and Stony Brook University of New York did research into the aMMP-8 method to measure pathogenic enzyme activity | |
| aMMP-8: one enzyme, two testing methods | 11 |
| A novelty on the world market. For the first time, two scientifically developed tests can detect periodontitis early one by measuring enzyme levels | |
| aMMP-8 diagnostics using a chairside rapid test | 12 |
| Screening method for rapid diagnosis of elevated aMMP-8 levels | |
| aMMP-8 using quantitative laboratory diagnostics | 13 |
| In-vitro method to control the periodontitis treatment | |
| Bacteria tests are not an indicator for tissue degradation | 14 |
| Based on the abstracted germ spectrum, no conclusion can be drawn about what is occurring at the extraction point | |
| aMMP-8 tests are used to diagnose progressive tissue destruction | 15 |
| The person treating the patient will immediately see if the site has to be under medical observation | |

Chapter 2:

Innovative dentistry, Parodontology and diagnostics

| | |
|--|----|
| Biomarker diagnostics: from dentistry to medicine | 16 |
| Maria Emanuel Ryan, D.D.S., Ph.D.: Technology transfer makes the identification of oral inflammation possible for dentists, physicians and other health care professionals | |
| Parodontology and diagnostics | 17 |
| Prof. Dr. Ulrich Schlegelhauf: The aMMP-8 test optimizes treatment and prevention of periodontal disease | |
| Diagnostics 2011: The interdisciplinary medical approach | 18 |
| For cardiology, rheumatology, gynecology, general medicine and oral medicine courtesy of modern biomarker diagnostics | |
| Prevention trumps healing | 19 |
| The aMMP-8 early detection system helps make diagnoses across medical disciplines | |
| Periodontitis: From an interdisciplinary and scientific perspective | 20 |
| Periodontitis and general health have a multifaceted relationship | |

| | |
|--|----|
| aMMP-8 a threat to the fetus | 21 |
| aMMP-8 levels should be controlled regularly if a patient is trying to get pregnant or is pregnant already | |
| Diabetes: increased periodontal bone loss | 22 |
| Diabetes patients can minimize the “periodontitis risk factor” via periodontal therapy | |
| Periodontitis: significantly increased mortality rate in diabetics | 23 |
| Studies show that periodontitis patients are six times more at risk for diabetes | |
| aMMP-8 attacks arterial plaque | 24 |
| Patients with cardiovascular problems should have their enzyme levels tested | |
| aMMP-8: dangerous thrombi develop in blood vessels | 25 |
| Patients with high blood pressure should have their aMMP-8 levels checked regularly | |
| Periodontitis is associated with greater occurrence of carcinomas | 26 |
| Patients at risk should pay attention to their oral hygiene | |
| aMMP-8 damages the joints | 27 |
| Rheumatologists and dentists should also treat periodontitis in their rheumatism and arthritis patients | |

Chapter 3: Politics and the economics of health, Quality control and patient information

| | |
|---|----|
| Politics and the economics of health | 28 |
| Laurenz Meyer: Educating the public about the interaction between periodontal disease and other common diseases must be optimized | |
| Quality control and patient information | 29 |
| Prof. Dr. rer. nat. Siegmur Bornemann: Nowadays, modern, interdisciplinary diagnostics are necessary to guarantee quality control in medicine | |
| Interdisciplinary Diagnostic Initiative | 30 |
| Early detection of periodontal disease, interdisciplinary risk diagnostics and an optimal education of patients are the cornerstones of the multidisciplinary net | |
| Health communication means education | 31 |
| Diagnostics and information are the cornerstones of solid interdisciplinary medical care | |

Forms and Test for Patients

| | |
|--|----|
| Your web page entry on www.parofrueherkennung.de | 33 |
| Fax response | 35 |
| Test for patients | 37 |
| Imprint | 39 |

Modern biology mark investigation

MMP-8 as a point-of-care biomarker of periodontitis, peri-implantitis, cardiovascular systemic diseases

Neutrophil collagenase or collagenase-2 (matrix metalloproteinase [MMP] -8) belongs to collagenase subgroup of MMP super family. MMP-8 is catalytically most competent enzyme to initiate type I collagen and extracellular matrix degradation associated to periodontal and peri-implant tissue destruction leading to tooth and dental implant loss.

Regarding cardiovascular diseases pathologically excessive MMP-8 has been implicated to atherosclerotic plaque destabilization and rupture through its capacity to thin the protecting collagenous fibrous cap. During the initiation and course of inflammatory responses in periodontal, peri-implant and cardiovascular diseases proinflammatory mediators including especially MMP-8 are up-regulated not only in affected tissues but also in secreted disease-affected oral fluids (gingival crevicular fluid [GCF], peri-implant sulcular fluid [PSF], mouth-rinse and saliva) as well as in serum (Sorsa et al. Oral Dis 2004, Sorsa et al. Ann Med 2006, Tuomainen et al. ATVB 2007).

Regarding periodontitis, peri-implantitis and cardiovascular diseases oral fluid and serum MMP-8 analysis has proved to an objective biomarker that has been evaluated and confirmed as an indicator of health, pathologic processes and pharmacologic response to therapeutic intervention (Sorsa et al. Oral Dis 2004, Sorsa et al. Ann Med 2006, Tuomainen et al. ATVB 2007, Reinhardt et al. J Periodontol 2010). Oral fluids i.e. GCF, PISE, mouth-rinse and saliva, are easily and non-invasively collected for the site and patient-specific diagnostic analysis in periodontitis and peri-implantitis (Sorsa et al. 2004, 2006).

For diagnosis and monitoring of cardiovascular diseases plasma and or serum sample collection is required (Tuomainen et al. ATVB 2007, 2008). Research has consequently been conformed with a need for development for innovative point-of-care diagnostic tests for MMP-8 (Sorsa et al. Oral Dis 2010, Gursoy et al. J Clin Periodontol 2010, Leppilahti et al. Oral Dis 2010).

Prof. Timo Sorsa, PhD
Helsinki, Finland, March 2010



Prof. Timo Sorsa, PhD

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Diagnostics and science

aMMP-8, the instrument for precision diagnostics and improved follow-up therapy in all specialized areas of medicine

Each year, over 1,600 patients are diagnosed tele-medical at the Institute for Applied Telehealth (IFAT) at the Heart and Diabetes Center in North Rhine-Westphalia in order to guarantee the best possible surgical and therapeutic treatment. Our motto, “the more precise the diagnosis, the better the following treatment,” is a fundamental medical postulate. As the North Rhine-Westphalian hub for tele-medical cardiolog-ical diagnostics, we have a leading role to play; we depend on the best possible interdisciplinary and differential thera-peutic treatment.

The Institute for Applied Telehealth is actively involved in the development of integrated patient care and is instru-mental in the further development and introduction through-out Germany of telemedical supervision for patients with cardiological findings. In my opinion the periodontal portrait of patients with cardiovascular disease gets more useful than ever before.

From a cardiological standpoint, careful observation of the status of teeth is gaining more and more significance. Today, we no longer replace heart valves without checking whether the patient has periodontitis. Thanks to the new aMMP-8 rapid test, we can get a picture of the oral situation within minutes, and if necessary communicate with colle-agues from the periodontology and dentistry departments, so they can ensure that the oral cavity is free of inflammation.

International studies have clearly shown that strokes and heart attacks are heavily influenced by periodontitis. An early diagnosis can significantly reduce the risks the patient faces. Furthermore, the study by the Aetna company shows that the cost for treating cardiological therapy can be consi-derably reduced in the case of patients whose periodontitis has been treated. In other words, in addition to the medical necessity of early diagnosis and therapy, we now have the crucial economic proof for the connection between peri-odontal and cardiological diagnostics. The aMMP-8 rapid test is an important connection for our interdisciplinary communication.

OA PD Dr. med. Heinrich Körtke
Bad Oeynhausen, May 2010



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aMMP-8: Life-threatening “agent provocateur” in every mouth

The threat: Pathogenic enzyme activity destroys tissue, bone and organs and increases the risk of disease

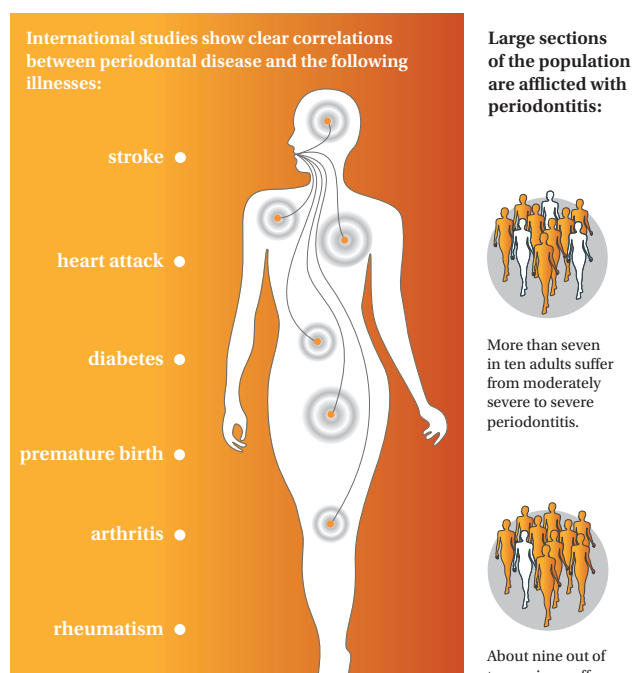
In Germany, 4 million people suffer from diabetes – 70 percent of them will probably die prematurely from complications related to the disease. Each year in Germany, 70,000 people succumb to a heart attack. Worldwide, one million premature babies die per year. And, as recent studies show, that’s just the tip of the iceberg: What most people fail to realize is that their risk of developing an illness is often determined within their own bodies. Every human body contains enzymes that, when active, can be life threatening. The so-called MMP-8 (matrix-metalloproteinase-8) enzyme sets in motion pathogenic enzyme activity, a reaction of the immune system to periodontitis or peri-implantitis bacteria.

A minuscule enzyme destroys mouth and organ tissues

Until now the fact that an enzyme existing within the human body could have such grave effects when in an activated state was not really taken into consideration. During the onset of an illness or during its particular treatment, identifying the enzyme as a culprit was not possible usually, owing to a lack of available diagnostic methods. The enzyme aMMP-8 (active matrix-metalloproteinase, also known as collagenase 2) is part of the immune system. In the event of an inflammation, it begins destroying gum tissue to defend against periodontal bacteria. The mouth then serves as the gateway to the “agent provocateur” that is aMMP-8, the tissue-destroying enzyme that can also attack other organs and, thereby, wreak life-threatening havoc.

Almost anyone can become a victim:

Eight in ten Germans become ill from germs on their teeth or on implants. It’s not surprising that periodontitis was the most widespread disease according to the Guinness Book of Records 2001. This is just the beginning, because the disease has a whole set of complications with wide-ranging impact.



Quelle: Deutsche Mundgesundheitsstudie IV, 2006

Damage throughout the whole body

Intensive studies over the past two decades have uncovered the fact that the activated aMMP-8 enzyme arising from an inflammation in the oral cavity, doesn’t just damage gums. It also operates as a kind of „free-fire“ command in the entire body. The enzyme activation that takes place at the affected tooth can also activate the MMP-8 enzyme in other parts of the body.

Increased enzyme counts in cases of diabetes, pregnancy and arthritis

Reciprocal interactions are synchronized in the bloodstream. In pre-existing conditions, such as diabetes mellitus, or the often casually-labeled “high blood pressure,” rheumatoid arthritis, and even in pregnancy, the increase in the enzyme counts can have drastic consequences:

- heart attack
- stroke
- premature birth and subsequent death
- deterioration of blood sugar levels and difficulty in adjusting medications
- rheumatism and arthritis

Up to a sevenfold increase in the risk of disease

Periodontitis increases the risk of heart attack threefold, the risk of cancer fourfold, the risk of arthritis and diabetes sixfold and the risk of stroke and premature births sevenfold.

2011 outlook – aMMP-8 is manageable

The good news: The dramatic effects of the enzyme can be prevented. A new early detection test has been developed to measure pathogenic enzyme activity once it has begun. Until now, such tests were very complex and quite expensive – and so they were reserved for just a few select clinics and specialized labs, because the sulcus fluid samples had to be processed immediately. Now, an optimized collecting system – with optimized features for the stable transport of aMMP-8 samples – allows any doctor or dentist to perform the test right in his or her office.

Matrix-metalloproteinase-8: a periodontitis indicator

This is the enzyme which, in its activated form, is responsible for the destruction of collagen in the case of periodontitis and peri-implantitis, and can therefore be used to analyze risk

When a patient is suffering from periodontitis or peri-implantitis, the activated form of matrix-metalloproteinase-8 (aMMP-8) comes at the end of the inflammatory cascade and is responsible for the destruction of tissue. The aMMP-8 destroys the collagen fibers that hold the teeth in place.

The aMMP-8 test permits accurate identification of healthy individuals and sick patients

The University of Helsinki and Medix Biochemica Oy, Helsinki, Finland, developed monoclonal antibodies (MAB) that are mainly able to ascertain and diagnose the aMMP-8. International publications have demonstrated, using these two highly specific MABs to diagnose sulcus fluid samples does produce basic and clear information. Thanks to the identification of aMMP-8 in sulcus fluid, healthy individuals can be differentiated from patients with gingivitis or even periodontitis.

Diagnosis through aMMP-8 produces quantitative findings that make the success of the treatment being performed by the dental team absolutely clear to the patient. In the case of recall patients, aMMP-8 will identify any endangered sites where periodontal tissue destruction is recurring again. Early detection is even more important at the beginning of peri-implantitis, at which point aMMP-8 is found in exorbitantly high concentrations. This can, in part, have a dramatic impact on subsequent treatment. Identifying tissue destruction from peri-implantitis by means of aMMP-8 while it is still at the easily treated mucositis stage is an extremely significant step in order to prevent a far more acute peri-implantitis, which is difficult or impossible to treat.

⊖ Risks:

Sharp increase of aMMP-8 in peri-implant sulcus fluid in the case of peri-implantitis

aMMP-8 is a relevant biomarker for the early ascertainment of peri-implant bone loss.

In the case of periodontitis, the level of aMMP-8 is 80 times higher than with healthy control teeth and intact implants, and 970 times higher in the case of peri-implantitis.

Ma et al.: Collagenases in different categories of peri-implant vertical bone loss. *J Dent Res* 2000; 79: 1870

Xu et al.: Characteristics of collagenase-2 from gingival crevicular fluid and peri-implant sulcular fluid in periodontitis and peri-implantitis patients. *Acta Odont Scand* 2008; 66: 219

aMMP-8 in sulcus fluid provides a great deal of prospective information

Wherever the pocket depths continued to remain stable („stable sites“) for 12 months following periodontal therapy, the level of aMMP-8 also remained steady at a low level.

No demonstrable and significant success in treatment („unstable sites“), on the other hand, correlated with a pathological increase in aMMP-8 concentrations. If an increase in the aMMP-8 values in a patient was measured during recall in the first year of „periodontal maintenance,“ it resulted in a significant increase in attachment loss in the two years following.

Sorsa et al.: Detection of GCF MMP-8 levels with different laboratory and chair-side methods. *Oral Diseases* 2010; 16: 39

Reinhardt et al.: Association of gingival crevicular fluid biomarkers during periodontal maintenance with subsequent progressive periodontitis. *J Periodontol* 2010; 81: 251

With periodontitis, the presence of the enzyme MMP-8 is significantly higher in the serum

Marcaccini et al.: Circulated matrix metalloproteinase-8 (MMP-8) and MMP-9 are increased in chronic periodontal disease and decrease after non-surgical periodontal therapy. *Elsevier, Clinica Chimica Acta* 2009.

+ Recommendation:

Determination of aMMP-8 levels in the sulcus fluid is significant evidence of the therapeutic status

A number of independent international studies show that the high aMMP-8 values measured during periodontitis decline with the onset of periodontal therapy, like scaling and root planning (SRP). This is statistically significant after a period of 14 days already.

Chen et al.: Matrix metalloproteinase-8 levels and elastase activities in gingival crevicular fluid from chronic adult periodontitis patients. *J Clin Periodontol* 2000; 27: 366

Kinane et al.: Changes in gingival crevicular fluid matrix metalloproteinase-8 levels during periodontal treatment and maintenance. *J Periodont Res* 2003; 38: 400

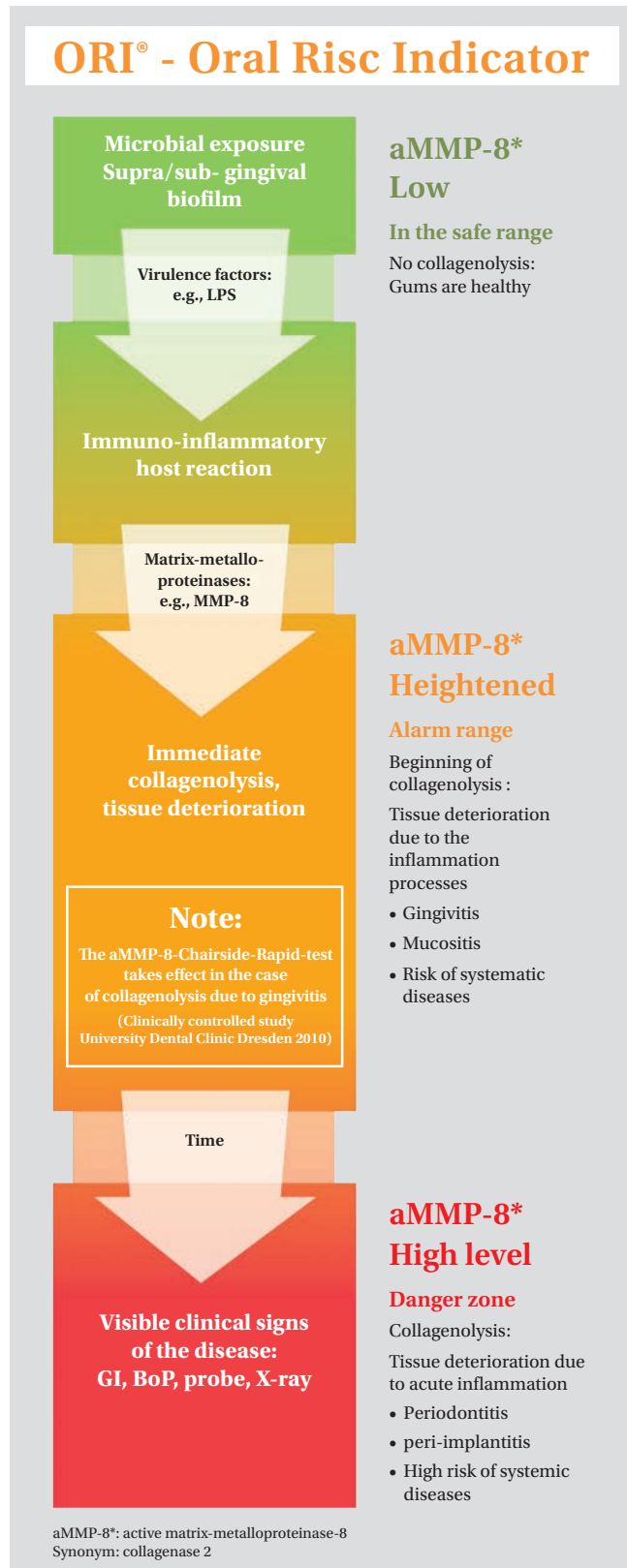
Recommendation for physicians:

Continuous measurement of aMMP-8 values is a good way of detecting a risk of periodontitis early on and taking appropriate measures.

Once periodontal treatment has begun, routine control of aMMP-8 values can be used to control and enhance the stability of the treatment results.

A new testing procedure developed in Finland and the USA

The University of Helsinki and Stony Brook University of New York did research into the aMMP-8 method to measure pathogenic enzyme activity



The good news: aMMP-8 is now controllable and the pathogenic enzyme reactions can be detected early on. So one can guard against any deleterious effects by measuring aMMP-8 during – and at times even before – an inflammation of the gums that might not appear to serious. Prof. Timo Sorsa (University of Helsinki) and Prof. Maria Ryan (Stony Brook University of New York) developed the test to measure pathogenic enzyme activity.

What used to be limited to just a few specialized universities, can now be tested in any dental office or clinic.

Until recently, testing for aMMP-8 was rather unwieldy and, owing to the technological conditions required, could only be done on location at a few universities. The samples of sulcus fluid were not stable and had to be processed immediately or frozen. A unique and affordable collection method has now been developed for use in clinics and practices to ensure stable transportation of the aMMP-8 sulcus fluid samples. The aMMP-8 biomarker test for risk diagnostics is available to all physicians and dentists for use in preventative medicine.

The new test measures aMMP-8 enzyme activity quickly, efficiently and accurately

The new early detection test measures the strength of any initiated enzyme activity. This enables a practice with the right equipment to detect risks of illness rapidly as well as the deterioration of the tooth socket before the aMMP-8 creates irreversible damage. Countermeasures can be adopted in both cases.

Probes and X-ray images do not measure pathogenic enzyme activity

Conventional testing methods, like probes or X-rays, are not enough for early detection, because they cannot identify any enzyme activity. What they do show, is the negative aftermath and tissue destruction following advanced enzyme activity. The renowned Universities of Helsinki (Prof. Timo Sorsa) and Stony Brook (Prof. Maria Ryan) developed the early detection test in collaboration with the biotechnology experts from dentognostics and MatrixLab. The test demonstrates the level of threat from aMMP-8 using a numerical value.

aMMP-8: one enzyme, two testing methods

A novelty on the world market. For the first time, two scientifically developed tests can detect periodontitis early one by measuring enzyme levels

For years already, scientists have been facing the technological challenge of developing a point-of-care method to detect periodontitis early on. The idea is to give medical practitioners from all areas of specialization a molecular biological procedure that can be used in their practices. The researchers have now achieved a breakthrough. The aMMP-8-Chairside-Rapid-test represents the first point-of-care periodontitis test that is based on a test of enzyme levels.

An unique proposition: combining of screening test and quantitative laboratory diagnostics

The chair-side rapid test has the advantage of producing findings that are relevant for treatment while the patient is actually in the office. What is genuinely unique is the combination with the quantitative aMMP-8 enzyme test (aMMP-8-laboratory-test) This allows periodontitis to be detected early on by the respective specialist. The course of the treatment can then be monitored very precisely and the outcome controlled by the dentist.

Dental implant need special attention

Starting 2012 a slightly modified rapid test will be available for the screening of dental implants.

More than 20 Mio. patients worldwide have received dental implants. The modified aMMP-8 Implant-Marker test allows a professional maintenance and care monitoring to prevent peri-implant-disease.

1. Testing method:

Screening with the aMMP-8-Chairside-Rapid-test

The aMMP-8-Chairside-Rapid-test measures whether the MMP-8 enzymes are already active in the sulcus fluid. In other words, this is the first point-of-care periodontitis test ever worldwide that is not based on testing for bacteria.

Specialists from all medical disciplines can now generate interrelationships between a case of periodontitis and the patient's general health status.



2. Testing method:

Quantitative measurement with a lab diagnosis

If the result of the screening test is positive – that is if MMP-8 enzymes are already active in the sulcus fluid – the dental practitioner can then use the aMMP-8-laboratory-test to measure precisely in what concentration the matrix-metalloproteinase is present.

Quantitative laboratory diagnostics allow for a precise monitoring of the course of the periodontal treatment and control of its outcome.



aMMP-8 diagnostics using a chairside rapid test

Screening method for rapid diagnosis of elevated aMMP-8 levels

The aMMP-8-Chairside-Rapid-test is ideal for rapid testing for elevated aMMP-8 levels. It offers medical practitioners from all fields the possibility of assessing whether the patient is suffering from a pathogenic periodontitis.

How does screening with a rapid chairside test function?

Simple and safe application

The screening test generates fast, qualitative data on the increase of aMMP-8 levels in the oral cavity. The simple system uses a mouth rinse and is based on a lateral flow sandwich immunoassay.

Who can use the test?

- Dentists
- Dental hygienists
- Gynecologists
- Rheumatologists
- Cardiologists
- Diabetologists
- Oncologists
- General practitioners

Application instructions

1. The patient must pre-rinse his or her mouth
2. The patient must then rinse his or her mouth with 3 ml of the rinse solution
3. Thanks to the vigorous swishing around the teeth, the fluid absorbs aMMP-8 from the sulcus
4. The patient then spits the fluid into a beaker, from which it is pipetted out, filtered and placed on the test cassette
5. Within 5-10 minutes, the results can be read out from the cassette



In what situations can the test be used meaningfully?

1. **In the case of existing systemic illnesses, with patients suffering from cardiovascular illnesses, women wanting to get pregnant, or during prenatal diagnostics**
 - For periodontitis and peri-implantitis to prevent chronic or systemic illnesses
 - To analyze risks during pregnancies and prevent preterm births
 - To minimize risk if suspecting an undiagnosed diabetes mellitus, on suspicion of cardiovascular diseases and to determine the course of treatment in the case of rheumatoid arthritis (RA)
2. **Dentistry/periodontology: For quick control of the treatment outcome**
 - Documentation of the status of treatment
 - Proof of treatment success after 2 to 3 weeks already
 - For early detection of recurring tissue destruction
 - Once a year during the regular recall, or twice a year for high-risk patients
 - To ensure that an inflammation is no longer present
 - For use of regenerative measures in the periodontium, e.g., membranes, enamel-matrix proteins, bone replacement materials

aMMP-8 using quantitative laboratory diagnostics

In-vitro method to control the periodontitis treatment

The aMMP-8-laboratory-test is a highly sensitive and quantitative testing procedure for controlling the periodontitis treatment and monitoring the therapy. The laboratory diagnostic tool is a complement to the rapid test and lets the practitioner determine the exact aMMP-8 levels during the course of a treatment.

How does a quantitative laboratory test function?

Simple and safe application

The new quantitative aMMP-8 test measures the strength of enzyme activity. The dentist can therefore recognize pending deterioration of the tooth socket before the aMMP-8 creates irreversible damage.

Who can use the test?

- Dentists
- Periodontologists
- Oral and maxillofacial surgeons
- Implantologists
- Oral surgeons
- Dental hygienists

Application instructions

1. 10 - 30 (seconds):
The user collects some fluid from the gum seam (CSS) with the filter paper strip
2. The sample is sent to the laboratory and analyzed
3. The user then receives a comprehensive report and can discuss the findings with the patient



In what situations can the test be used?

1. **In the case of existing systemic illnesses, with patients suffering from cardiovascular illnesses, women wanting to get pregnant, or during prenatal diagnostics**
 - For periodontitis and peri-implantitis, to prevent chronic or systemic illnesses
 - To analyze risks during pregnancies and prevent preterm births
 - To minimize risk if suspecting an undiagnosed diabetes mellitus, on suspicion of cardiovascular diseases and to determine course of treatment in the case of rheumatoid arthritis (RA)
2. **Dentistry/periodontology**
For quick control of therapeutic success
 - Documentation of the status of treatment
 - Proof of treatment success after 2 to 3 weeks already
 - For early detection of recurring tissue destruction
 - Once a year during the regular recall, or twice a year for high-risk patients
 - On suspicion of a refractory course
 - To ensure that an inflammation is no longer present
 - For use of regenerative measures in the periodontium, e.g., membranes, enamel-matrix proteins, bone replacement materials
3. **Implantology: To control whether an inflammation is still present**
 - Prior to setting an implant
(see DGP annual conference, Bonn 2007)
 - Before setting the abutment
 - Before setting the prosthetic supraconstruction
 - For the routine check-up of the implant (early detection, peri-implantitis)
 - 3-6 months before setting the prosthetic supraconstruction, during the first recall
 - During the annual recall
 - Suspicion of peri-implantitis
 - For the forensic safeguard of therapeutic interventions

Bacteria tests are not an indicator for tissue degradation

Based on the abstracted germ spectrum, no conclusion can be drawn about what is occurring at the extraction point

What information does the bacteria test provide?

The bacteria test makes a semi-quantitative statement about the presence of bacteria. It cannot, by definition, give data about a patient's immune response. It says nothing about the reaction status, nothing about the degree of inflammation of the periodontal pocket/the implant and nothing about the potential for destructive tissue breakdown at the extraction point.

Does the bacteria test make a prognosis?

No. No meaningful statement about the future development of the extraction point can be won from either the bacterial germ spectrum abstracted from the test, or from the quantity or the proportion of bacteria in that amount. The bacteria test has absolutely no prognostic significance.

Kinane DF: Causation and pathogenesis of periodontal disease. *Periodontology* 2000 2001; 25: 8-20

When is the bacteria test applied?

Too late. The extraction methods alone make it clear that in the bacteria test, the microflora of the subgingival pocket – the bacterial contents of the pocket – are examined. From a diagnostic perspective, the damage has already long been done, the tissue has already been heavily damaged. The only reasonable use of the bacteria test is:

- in existing cases of periodontitis / peri-implantitis

Are there therapeutic consequences from the bacteria test?

Yes. It is useful to conduct the bacteria test for the clarification of potential antibiotics in already therapeutically difficult cases.

In such cases, the bacteria test provides information useful in the treatment of bacteria, i.e., choosing the right antibiotic (according to the dental association DGZMK).

aMMP-8 tests are used to diagnose progressive tissue destruction

The person treating the patient will immediately see if the site has to be under medical observation

What does the aMMP-8 test reveal?

The aMMP-8 test produces quantitative data about the patient. It diagnoses the reaction status of the patient, i.e., his or her immunological response to bacteria. It also differentiates the level of risk to the pocket or implant. Is the collection site free of risk, is there no evidence of tissue destruction, or is there evidence of collagenolytic tissue deterioration? In some cases (like pregnancy, diabetes, rheumatoid arthritis), patients do have an exaggerated immunological reaction to even a slight bacterial infection, but the aMMP-8 test does produce more meaningful diagnostic data.

Does the aMMP-8 test permit prognoses?

Yes. The evidence of greater MMP-8 activity (Lee et al., 1995), as well as that of higher concentrations of aMMP-8 in the sulcus fluid (GCF, gingival crevicular fluid) allows the carer to forecast progressive tissue destruction.

Lee W, Aitken S, Kulkarni G, Birek P, Overall CM, Sodek J, McCulloch CA: Collagenase activity in recurrent periodontitis: relationship to disease progression and doxycycline therapy. *J Periodontol Res* 1995; 26: 479-485

Reinhard RA, Stoner JA, Golub LM, Lee H-M, Nummikoski PV, Sorsa T, Payne JB: Association of gingival crevicular fluid biomarkers during periodontal maintenance with subsequent progressive periodontitis. *J Periodontol* 2010; 81: 251-259

Sorsa T, Hernandez M, Leppilahti J, Munjal S, Netuschil L, Mäntylä P: Detection of GCF MMP-8 levels with different laboratory and chair-side methods. *Oral Diseases* 2010; 16: 39-45

When is the aMMP-8 test used?

In time. The aMMP-8 test involves collecting sulcus fluid, either from healthy sulci, or from sites or periodontal / peri-implant pockets afflicted by gingivitis / peri-implant mucositis. So the aMMP-8 test can be applied to various situations:

- prophylactically for healthy teeth (if requested)
- in the case of gingivitis / peri-implant mucositis!
- after professional tooth cleaning or implant cleaning, as proof of no inflammation
- as evidence of successful therapy
- to educate refractory patients
- during a periodontal or implantological recall, to ascertain a flare-up of tissue destruction early on

Can the aMMP-8 test have therapeutic consequences?

Yes. However, since it would be a treatment for the specific patient, proper recommendations cannot be formalized (like the recommendations for certain antibiotics).

The carer will be given clear information

- if there is no tissue destruction, then no treatment is needed
- if an acute limited tissue deterioration is observed, the collection point will have to remain under observation
- if acute, severe tissue destruction is observed, then the collection site will need treatment urgently

The carer is responsible for devising the appropriate treatment plan and weaponry to meet the patient's specific needs.

Biomarker diagnostics: from dentistry to medicine

Technology transfer makes the identification of oral inflammation possible for dentists, physicians and other health care professionals

Research conducted over the past decade has led to an increased awareness of the systemic consequences of chronic inflammation by dentists, physicians and other health care professionals. The public has been alerted to the impact of chronic inflammation on their overall health. The fact is that the most common chronic inflammatory condition known to mankind is periodontal disease. The research has supported a link between periodontitis and many other disease states such as diabetes, stroke, rheumatoid arthritis and heart disease, as well as adverse pregnancy outcomes.

The problem has been that periodontal disease is often a silent condition that can progress over the years if left unchecked by a healthcare provider. Recent studies have also indicated that dental implants often used to replace natural teeth, can become diseased as well, generating a significant inflammatory response that may exceed the inflammation that has been associated with natural teeth experiencing the same clinical level of disease. Current methods of diagnosis for both teeth and implants are based on clinical observations by the dental professional of pocketing, attachment loss around teeth, radiographic evidence of bone loss, redness, swelling, bleeding and suppuration. In addition, once identified, periodontitis is known to have periods of exacerbation and remission. The development of biochemical diagnostic tests to aid in the identification of disease and to determine levels of disease activity can help in establishing a more accurate diagnosis and prognosis. A biochemical marker allows for optimal treatment planning and follow-up for both natural teeth and dental implants. Based on numerous studies it appears that the matrix metalloproteinases are ideal biochemical markers, particularly active-MMP-8.

Due to the known impact of untreated periodontitis on overall health and well-being, there has been a transition toward the interdisciplinary management of patients so as to provide the most comprehensive treatment possible. Screening for oral inflammation can now easily be conducted using the a-MMP-8 marker, prompting a physician referral to the dental care professional for a thorough oral examination. Once a referral is made, the source of the a-MMP-8 can be identified and the appropriate treatment can be provided. The source of a-MMP-8 can then be monitored until the levels of a-MMP-8 are reduced and the inflammatory process is resolved.

Evidenced-based practice would say that reducing the inflammatory burden to our patients, whatever the source



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of inflammation, is a winning strategy. Active-MMP-8 is an ideal test which is quantitative, highly sensitive and specific, reproducible, and easy to perform. The adoption of this test into the medical and dental communities will help to facilitate a new interdisciplinary approach to the management of diseases.

Maria Emanuel Ryan, D.D.S., Ph.D.
New York, August 2010

Parodontology and diagnostics

The aMMP-8 test optimizes treatment and prevention of periodontal diseases

The appearance of periodontal inflammation is closely tied to the presence of specific microorganisms in the area of the gingival sulcus or, more specifically, the periodontal pockets. It is, therefore, no surprise that past periodontal research efforts focused mostly on detailed analysis of presumed bacterial virulence mechanisms. Such mechanisms were ultimately made responsible for initiating the disease.

In the meantime, a multitude of clinically experimental data has shown unequivocally that periodontal diseases do not correspond to the communicable bacterial infections in the manner enunciated in the Koch Postulates. Rather, they are seen more as opportunistic infections whose development is largely centered on dysregulation of the oral immune system. From a clinically practical point of view, a strict regime of plaque control is still the method of choice for reducing the intensity of periodontal inflammatory processes.

But according to the current understanding of etiology, even documenting an optimally plaque-free set of teeth is not enough to exclude the occurrence or reoccurrence of the disease. For the accurate assessment of disease risk, it is imperative to also assess the state of the oral immune system. To date, however, no generally accepted concepts have been developed that are supported beyond the shadow of a doubt by clinical studies.

The new BioMarker test method serves to detect the activity of tissue-destroying metallo-matrixproteinases in sulcus fluid or saliva. It numbers among the first commercially available tests that is also able to produce objective figures for the assessment of a core aspect of the host response to periodontal and peri-implant inflammation. This creates more opportunities to optimize treatment and prevent periodontal diseases.

Prof. Dr. Ulrich Schlegelhauf
Würzburg, March 2010



Prof. Dr. Ulrich Schlegelhauf

Director of the Department of Periodontology at the University of Würzburg

President of the German Society for Periodontology (DGP)

Diagnosics 2011: The interdisciplinary medical approach

For cardiology, rheumatology, gynecology, general medicine and oral medicine courtesy of modern biomarker diagnostics

Until now, periodontitis or its cause, pathogenic bacteria, could only be diagnosed after the first damage appeared. Such diagnoses are made by probing the gingival pocket or performing a radiological examination. These, however, don't provide information on the activity of the enzymes already mobilized.

And so, there has been no way so far to address the systematic effects of acute pathogenic enzyme activity. Many diseases progress in spurts, however, and this information is of incalculable value to physicians of every specialty. As doctors search for the causes of disease – before pregnancies and before cardiological procedures, for instance – ruling out pathogenic enzyme activity as a risk factor is of paramount importance.

Interdisciplinary diagnostics – at a glance:

- Monitoring of pathogenic enzyme activity remains the focus of treatment
- aMMP-8: makes possible and optimizes interdisciplinary diagnostics
- Periodontitis has a considerable influence on the progression of systemic diseases

Science has proven that periodontitis

- Increases the risk of premature birth
- Increases the risk of heart attack
- Increases the risk of stroke
- Increases the risk of rheumatoid arthritis
- Worsens diabetes mellitus

It is recommended that doctors of all disciplines continue cooperating with regard to aMMP-8 diagnostics and to build an interdisciplinary network.

Interdisciplinary: the sensible approach to treatment

At the center of interdisciplinary diagnostics is the monitoring of enzyme activity, with which the organism reacts to the bacterial infection in the oral cavity.

In the past 20 years, intensive research uncovered a multitude of interactions between periodontal disease and a variety of other illnesses. The interactions between dental health and the rest of the body are more complex than is widely assumed.

After many years of research and development, it is now possible to broaden the scope of oral medicine to include the diagnostics of pathogenic enzyme processes and to bring correlations to light.

aMMP-8 diagnostics: indicator of systemic disease risk and treatments

aMMP-8 diagnostics can provide important insights in the event of resistance to treatment, sluggish progress of the treatment or even unforeseen deterioration. Such diagnostics are especially important prior to planned, extensive cardiovascular procedures and transplantations, before implant surgeries or during pregnancies.

A set of crucial recommendations can be extrapolated for the various systemic conditions and therapeutic procedures. Specialists from the areas of dentistry, diabetology, cardiology, gynecology, rheumatology and oncology now have a robust diagnostic instrument, one that enables regular check-ups during a course of treatment and systematic monitoring of results.

Prevention trumps healing

The aMMP-8 early detection system helps make diagnoses across medical disciplines and it serves as a preventative as well

aMMP-8 analysis facilitates communication across areas of specialization. Thanks to the biomarker, interdisciplinary networks can communicate using objective, quantitative values that were ascertained using a validated and scientifically recognized method.

This offers a major advantage in for the early detection and treatment of systemic illnesses. A new path has been carved into the scientific discourse, it's goal can be summed up as „prevention is better than healing.“

Desiring children and pregnancy

Just as they do in the sulcus, the aMMP-8 enzymes destroy the collagen fibers in the amniotic sac. Hence, control of aMMP-8 values is recommended for pregnant women or patients aiming to have a children. The interdisciplinary approach here is in the collaboration between gynecologists and dentists.

Rheumatism, arthritis, diabetes

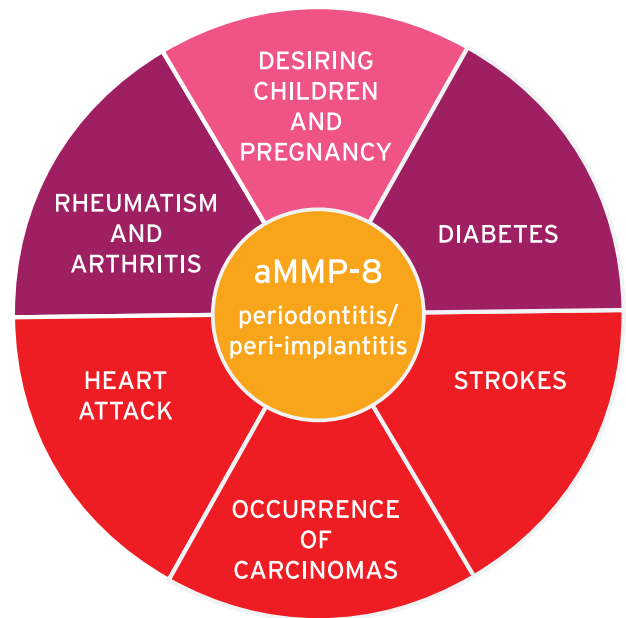
Rheumatism patients have been diagnosed with higher aMMP-8 values in the tooth attachment system and the synovial fluids. Diabetics have significantly increased levels of activated aMMP-8 enzymes in the sulcus. The interaction between both rheumatism and periodontitis and diabetes and periodontitis can lead to complications in the patient. Rheumatologists, diabetologists and dentists are advised to engage in interdisciplinary collaborations.

Cardiovascular conditions and strokes

The activation of the MMP-8 at the tooth affected by periodontitis can also bring about activation of the enzymes in another part of the body. Reciprocal interactions are synchronized over the bloodstream.

As with the aMMP-8-related collagen deterioration in the tooth attachment, the activated matrix-metalloproteinase-8 also attacks arterial plaque, which can cause infarctions in the brain or heart.

Patients with high blood pressure in particular are advised to control their aMMP-8 values on a regular basis. This is where the interdisciplinary collaboration between the cardiologist and dentists will be effective.



Recommendations for physicians:

Collaborative work between gynecologists, Rheumatologists, diabetologists, cardiologists and dentists is important as a preventative for systemic illnesses.

Periodontitis: From an interdisciplinary and scientific perspective

Periodontitis and general health have a multifaceted relationship

Medicine and dentistry – for much of the past century, the two were separate worlds. For a long time, the influence that periodontal inflammatory events had on general health was not seen as a problem and, therefore, it was not a subject of research. It wasn't until the 1980s and 1990s that more and more high-level international studies began to emerge. These proved that there existed a clear connection between periodontitis and other illnesses, including diabetes mellitus and heart disease. The results of these studies quickly made their way into review articles and specialized publications. At first, the pathogenically relevant questions about cause and effect were heavily debated. But today it is clear that, in the case of illnesses such as diabetes, heart disease and stroke, periodontitis has a significant influence on how the diseases progress. This is especially true the earlier the onset of periodontitis.

Periodontitis influences us from birth on

It is, therefore, in no way an exaggeration to maintain that, beginning with gingivitis and periodontitis in pregnancy, periodontal inflammations negatively influence us from birth forward, and continue to follow us into old age. They can even add to our risk of death.

Risikokompodium Parodontitis (Hrsg.: Deutsche Gesellschaft für Parodontologie / KZV Hessen / LZK Hessen). Quintessenz Verlag 2002

Risk of premature birth

Periodontitis increases the risk of premature birth. Not only has this been proven in studies but, here, the pathogenic path can also be traced. In both cases, the periodontitis and the premature birth, the triggering enzyme is known – matrix-metalloproteinase-8 (MMP-8) – which becomes activated equally in both in the periodontium and the amniotic sac. In this active form, MMP-8 attacks and destroys the respective collagen fiber networks. Thus, the body triggers periodontitis and premature birth with the same biochemical mechanism. For this reason, pregnant women need special care and monitoring of their oral aMMP-8 status.

Diabetes mellitus

Diabetes is hard to regulate when the patient is suffering from some additional chronic inflammation. With an open wound surface of 20 to 40 cm², periodontitis is such an inflammation. For this reason alone, it is imperative that diabetics have excellent periodontal care and treatment. In cases of periodontitis and diabetes mellitus this influence is not unidirectional: Both diseases negatively influence one another.

Periodontitis influences diabetes

A chronic inflammatory process, periodontitis hinders glycemic control, so it becomes a strong risk factor for late complications of diabetes – nephropathies, for example.

Diabetes influences periodontitis

Changes in the periodontium are the very first signs of clinical complications caused by diabetes. Periodontitis in young diabetics is much more pronounced than in their non-diabetic peers. Furthermore, poor metabolic control is a risk factor for periodontitis.

Heart disease/heart attack and stroke

Both life-threatening diseases, heart attack (myocardial infarction) and stroke (apoplexy) stem from arteriosclerotic changes in blood vessels. Periodontal bacteria have been found in the atheromatous plaque of blood vessel walls. This clearly shows that there is a direct path – periodontitis, blood stream, arteriosclerosis. But the actual threat is posed by matrix-metalloproteinases. These have significant ties to the alteration and deterioration of arteriosclerotic plaques. They can “blast off” pieces of the plaque. An increased concentration of aMMP-8 in serum is associated with the risk of death from heart attack.

Rheumatoid arthritis

Both rheumatic diseases and periodontitis form the body's immunological response to a stimulus. While, for instance, rheumatoid arthritis is seen as an autoimmune disease, periodontitis represents the reaction to dental plaque bacteria. As is the case with diabetes mellitus, here, too, there are inter-relationships between the two diseases: Periodontitis patients suffer from rheumatoid arthritis more often than those in periodontal good health. Periodontal therapy reduces the symptoms of rheumatoid arthritis. Because of other strong similarities, it is recommended that the physician and the dentist collaborate on devising a way to treat both diseases.

aMMP-8 a threat to the fetus

aMMP-8 levels should be controlled regularly if a patient is trying to get pregnant or is pregnant already

In Germany alone, around 50,000 babies are born prematurely each year. The definition of a preterm birth is when the infant is born before completion of the 37th week of pregnancy. Measured as of the last menstruation, a pregnancy should last 280 days. In the case of preterm babies, that period is less than 260 days. Premature babies weigh less than 2,500 grams as a rule. Nowadays, the baby can survive with medical assistance as of the 23rd week.

Seven-and-a-half times the risk of a premature birth

Today, premature births are considered the main reason for newborns falling ill, as well as for 50 percent of all later complications. The weight of the newborn at birth by and large determines his or her chances of survival and healthy development. Research has shown that periodontal disease increases the risk of premature birth by a factor of 7.5. Pregnant women suffering from periodontal disease showed a significantly high level of aMMP-8. Just as they do in the periodontium, the aMMP-8 enzymes destroy the collagen fibers in the amniotic sac. Hence, one can say that the dentist can become a major carer during a pregnancy.

⊖ Risks:

Periodontitis during a pregnancy is considered the principal factor in premature births and for the most part determines weight at birth

Periodontitis multiplies the risk of premature birth by a factor of 7.5. In contrast, alcohol, which is a well-known factor, only increases the risk threefold.

Offenbacher et al: Periodontal infection as a Possible Risk Factor for Preterm Low Birth Weight. *J Periodontol* 1996; 67: 1103

Offenbacher et al: Potential Pathogenic Mechanisms of Periodontitis-Associated Pregnancy Complications. *Ann Periodontol* 1998; 3: 233

Lopez et al: Higher risk of preterm birth and low birth weight in women with periodontal disease. *J Dent Res* 2002; 81: 58

Radnai et al: Possible association between mother's periodontal status and preterm delivery. *J Clin Periodontol* 2006; 33: 791

Causal connection between periodontitis and premature births

Periodontitis germs were found in greater quantities in the group of mothers with low-weight newborns. The germs, in fact, have a direct influence on inducing the birthing process. Periodontal germs were also found in the placenta and in non-survivable fetuses.

Offenbacher et al: Potential Pathogenic Mechanisms of Periodontitis-Associated Pregnancy Complications. *Ann Periodontol* 1998; 3: 233

Ratka-Krüger et al: Parodontitis als möglicher Risikofaktor für untergewichtige Frühgeburten (Periodontitis as a possible risk factor for low-weight preterm infants). *Risikokompendium Parodontitis* 2002, S. 85

Han et al: Term still birth caused by Oral Fusobacterium nucleatum. *Obstetrics & Gynecology* 2010; 115: 443

Inducing childbirth with aMMP-8

What aMMP-8 does with the periodontium, it also does with the amniotic sac, namely dissolve collagen fibers, which induces the birthing process. The risk of preterm birth is therefore connected to the activity of the aMMP-8.

Biggio et al: Midtrimester amniotic fluid matrix metalloproteinase-8 (MMP-8) levels above the 90th percentile are a marker for subsequent preterm premature rupture of membranes. *Am J Obstet Gynecol* 2005; 192: 109

Yoon et al: An elevated amniotic fluid matrix metalloproteinase-8 level at the time of mid-trimester genetic amniocentesis is a risk factor for spontaneous preterm delivery. *Am J Obstet Gynecol* 2001; 185: 1162

+ Recommendation:

Periodontal treatment reduces the risk of preterm births

Intervention studies show that the risk of complications described above – like preterm births – is considerably reduced if mothers undergo periodontal treatment.

Jeffcoat et al: Periodontal disease and preterm birth: results of a pilot intervention study. *J Periodontol* 2003; 74: 1214

Lopez et al: Periodontal therapy reduces the rate of preterm low birth weight in women with pregnancy-associated gingivitis. *J Periodontol* 2005; 76: 2144

Cruz et al: Periodontal therapy for pregnant women and cases of low birth weight: an intervention study. *Pediatr Int* 2009 (EPub ahead of print)

Optimal solution: Early detection before pregnancy

Since periodontitis represents the greatest risk of preterm birth, it is imperative that pregnant women be checked for this parameter. The best scenario would be detection even prior to the pregnancy, i.e., when trying to get pregnant.

Important:

The risk is different for each pregnant woman. The RQ (risk quotient) values are spread from normal to very high.

Recommendation in the case of women wanting a child or already pregnant:

1. Testing in the case of wanting a child
2. Testing in weeks 15-18 of the pregnancy
3. Testing in weeks 25-30 of the pregnancy

Periodontitis: significantly increased mortality rate in diabetics

Studies show that periodontitis patients are six times more at risk for diabetes

In Germany, 6-8 million people suffer from diabetes. The World Health Organization (WHO) estimates that, in the next 25 years, the number of diabetics will rise by 40 percent. The number of new cases of diabetes mellitus in Germany now stands at 12 per 100,000.

aMMP significantly higher

Studies show that diabetes and periodontitis negatively influence one another. Periodontitis patients proved to have a six times greater risk for deteriorating blood glucose levels. The aMMP-8 in the sulcus of diabetics is of an extraordinarily higher form. Therefore, diabetic patients with periodontitis should seek treatment from a dentist with diabetological knowledge.

⊖ Risks:

The influence of periodontitis on diabetes

Periodontitis and diabetes mellitus influence one another

Copious information suggests that not only is periodontitis a complication of diabetes mellitus, but it also strengthens the severity of diabetes mellitus and makes it hard to control.

Sculean & Jepsen: Diabetes mellitus als Risikofaktor für Parodontitis (Diabetes mellitus as a risk factor for periodontitis). *Risikokompodium Parodontitis 2002*, S. 7.

Mealey & Rethman: Periodontal Disease and Diabetes mellitus – Bidirectional Relationship. *Dent today April 2003*: 107.

Lamster et al: The relationship between oral health and diabetes mellitus. *JADA 2008*; 139: 19S.

Periodontitis leads to an extremely high death rate among diabetics

The annual death rate per 1,000 people: those with no or “mild” periodontitis, 3.7; patients with moderate periodontitis, 19.6 (increased by factor 5.3); those with severe periodontitis, 28.4 (increased by factor 7.7).

Saremi et al: Periodontal disease and mortality in type 2 diabetes. *Diabetes Care 2005*; 28: 27

Periodontitis hinders control of glycemia

Patients with severe periodontitis have around a sixfold increased risk of worsened glycemic control.

Taylor et al: Severe periodontitis and risk for poor glycemic control in patients with non-insulin-dependent diabetes mellitus. *J Periodontol 1996*; 67: 1085.

Periodontitis is a greater risk factor for late complications of the diabetes

Nephropathies in diabetics with periodontitis have 2- 2.6 times greater incidence than in diabetics without periodontitis. For final-stage kidney diseases, the risk increase is factors 2.3 - 4.9.

Shultis et al: Effect of periodontitis on overt nephropathy and endstage renal disease in type 2 diabetes. *Diabetes Care 2007*; 30: 306.

Thorstensson et al: Medical status and complications in relation to periodontal disease experience in insulin-dependent diabetics. *J Clin Periodontol 1996*; 23: 194.

Increased MMP-8 activity in the sulcus fluid of diabetics

The matrix-metalloproteinase-8 (or neutrophil collagenase or collagenase 2) in the sulcus fluid of diabetics with poor metabolisms is an extraordinarily high percentage of 50–60% in its active form, compared with the normal, 10-percent-active form MMP-8 usually takes.

Safkan-Seppälä et al: Collagenases in gingival crevicular fluid in type 1 diabetes mellitus. *J Periodontol 2006*; 77: 189.

Sorsa et al: Cellular source and tetracycline-inhibition of gingival crevicular fluid collagenase of patients with labile diabetes mellitus. *J Clin Periodontol 1992*; 19: 146.

The severity of periodontitis influences illnesses in diabetics

In insulin-dependent diabetics, the severity of periodontitis (minor to severe) has an impact on additional complications. Incidences of proteinuria, stroke, angina and myocardial infarction are significantly increased. A close cooperation between the diabetologist and the dentist makes good sense for such patients.

Thorstensson et al.: Medical states and complications in relation to periodontal disease experience in insulin-dependent diabetics. *J Clin Periodontol 1996*; 23: 194

Diabetes: increased periodontal bone loss

Diabetes patients can minimize the “periodontitis risk factor” via periodontal therapy

Most studies are not gender-specific when looking at the number of those affected by the disease. Type 1 diabetes mellitus appears in all ages groups. More than 90 percent of all diabetics also suffer from type 2 diabetes mellitus. The prevalence of the disease increases with age.

Poor metabolic control

Changes in the gingiva and periodontium number among the first complications of diabetes. Here, the largest risk factor is the insufficient regulation of blood glucose levels. In fact, studies show no difference in the periodontia of well-adjusted diabetics and those who do not suffer from the disease.

The influence of diabetes mellitus on the periodontium

Periodontal bone loss takes place more rapidly in diabetics

After two years, 67 percent of periodontitis patients with type 2 diabetes showed significant “radiographic bone loss” compared to the 44 percent of periodontitis patients not suffering from diabetes. The patients with diabetes lost more bone substance.

Taylor et al: Non-insulin dependent diabetes mellitus and alveolar bone loss progression over 2 years. J Periodontol 1998; 69: 76.

Changes in the gingiva and periodontium are the very first clinical complications caused by diabetes

For children and youths (ages 6 and 18), diabetes leads to more strongly pronounced gingivitis and periodontitis (increase by a factor of 3). The signs of inflammation do not trace back to an increase in plaque accumulation.

Lalla et al: Diabetes mellitus promotes periodontal destruction in children. J Clin Periodontol 2007; 34: 294.

Lamster et al: The relationship between oral health and diabetes mellitus. JADA 2008; 139: 19S.

Ryan et al: The influence of diabetes on the periodontal tissues. JADA 2003; 134: 34S.

Poor metabolic control is a significant risk factor for periodontitis

The time period since the onset of diabetes, as well as the insufficient regulation of blood glucose levels, are both significant risk factors for the increase in periodontal tissue breakdown.

By contrast, diabetics whose blood-sugar levels are well regulated experience periodontal disease no differently than non-diabetics.

Lamster et al: The relationship between oral health and diabetes mellitus. JADA 2008; 139: 19S.

Ryan et al: The influence of diabetes on the periodontal tissues. JADA 2003; 134: 34S.

Sculean & Jepsen: Diabetes mellitus als Risikofaktor für Parodontitis (Diabetes mellitus as a risk factor for periodontitis). Risikokompodium Parodontitis 2002, S. 7.

+ Recommendation:

Diabetics who undergo periodontal therapy experience a 0.4 to 0.8 percent reduction of the HbA1c level

Lamster et al: The relationship between oral health and diabetes mellitus. JADA 2008; 139: 19S.

Teeuw et al: Effect of periodontal treatment on glycemic control of diabetic patients: a systematic review and meta-analysis. Diabetes Care 2010; 33: 421.

Cooperation between diabetologists, internists and dentists

Diabetologists and internists are advised to monitor the periodontal status of their patients and refer them to a periodontologist for treatment to reduce the periodontitis risk factor.

Measuring the aMMP-8 concentration is an easy-to-manage diagnostic tool

Analysis of the concentration of tissue-destroying aMMP-8 found in the gingival crevicular fluid (GCF) is an easy-to-handle diagnostic tool, that can quantify the status of inflamed tissue in cases of existing periodontitis and in patients with diabetes mellitus.

Recommendation for diabetics:

1. In case of diabetes: the acute risk from an elevated level of aMMP-8 should be excluded immediately
2. In the case of hard-to-regulate blood glucose levels, the patient should promptly make a dental appointment to have enzyme activity tested
3. Testing every 6 months

aMMP-8 attacks arterial plaques

Patients with cardiovascular problems should have their enzyme levels tested

Heart attacks are considered the most frequent cause of death. Each year, about 300,000 people die of a heart attack. Over 170,000 die of the complications. The therapeutic focus, therefore, should be in identification, assessment and treatment of the causes and risk factors for heart attack. Even the invasive methods of modern cardiology can only be really successful if the fundamental risk factors are identified and treated resolutely.

Risk of heart attack multiplied by a factor of two to three

Studies prove the connection between heart attack and periodontitis. Sixty to eighty percent of all adults have periodontitis. What most do not realize is that the higher aMMP-8 levels increase the risk of heart attack two- and threefold. Activation of the MMP-8 at the affected tooth frequently means activation at another part of the body: reciprocal interactions are synchronized over the bloodstream. This can have a drastic effect on the coronary arteries in the case of a preexisting condition, such as what is often described somewhat casually as high blood pressure.

⊖ Risks:

Periodontitis increases in particular the risk of fatal heart attacks

Periodontitis increases the risk of coronary heart diseases by a factor of 1.5. The number of fatal heart attacks is influenced even more strongly. The risk here increases by a factor of 1.9.

Beck et al: Periodontal disease and cardiovascular disease. J Periodontol 1996; 67: 1123

An increase in the concentration of MMP-8 multiplies the risk of dying from a heart attack by three

Tuomainen et al: Serum Matrix Metalloproteinase-8 Concentrations Are Associated With Cardiovascular Outcome in Men. Arterioscler Thromb Vasc Biol. December 2007

Periodontitis represents a separate risk factor for heart diseases

The medical community used to think that periodontitis and cardiovascular diseases derived from common risk factors, like smoking or diabetes mellitus. Today, it's known that periodontal disease represents a separate risk factor for heart disease.

Lösche W & Kocher Th: Parodontitis als Risikoindikator für Herz-Kreislauf-Erkrankungen (Periodontitis as a risk indicator for cardiovascular diseases). Risikokompodium Parodontitis (publisher: Deutsche Gesellschaft für Parodontologie / KZV Hessen / LZK Hessen). Quintessenz Verlag 2002, p. 67

Periodontal germ infection on the arterial walls

Proof of an infection from periodontal germs was demonstrated in arteriosclerotically changed arteries (e.g., *P. gingivalis*, *A. actinomycetemcomitans*), but not in healthy ones. Researchers assume that these germs spread from the periodontium through the blood stream.

Chiu B: Multiple infections in carotid atherosclerotic plaques. Am Heart J 1999; 138: 534

Haraszthy et al: Identification of periodontal pathogens in atheromatous plaques. J Periodontol 2000; 71: 1554

+ Recommendation:

General aMMP-8 testing prior to operations on the cardiovascular system

In the case of existing cardiovascular disease, the acute risk from an elevated level of MMP-8 should be excluded

The risk of heart attack in patients with high blood pressure can be distinctly reduced patients by excluding any threat from MMP-8

Recommendation for patients with cardiovascular problems:

1. In the case of an existing condition, the acute risk from an elevated levels of aMMP-8 should be excluded immediately
2. Control testing every two months
3. In the case of elevated aMMP-8 levels, the dentist should start the appropriate treatment and check levels on a regular basis

aMMP-8: dangerous thrombi develop in blood vessels

Patients with high blood pressure should have their aMMP-8 levels checked regularly

Each year, around 200,000 Germans suffer from stroke. Twenty percent of stroke patients die within four weeks of the incident, more than 37% die within one year. Stroke is the third most common cause of death in Germany and it is the largest cause of physical and mental disabilities. Optimal treatment can be administered if early symptoms of stroke are diagnosed. For this reason, the recognition and treatment of risk factors are of great importance.

A sevenfold increase in the risk of stroke

The international numbers regarding the increased risk of stroke caused by periodontitis show a doubling of stroke risk and depending on reference information, that increase can even be as high as sevenfold. High blood pressure is caused by thickening of the blood vessel walls. The thickening acts as an inner cuff within the blood vessels, a condition the body continually tries to repair. During this repair process, courtesy of active aMMP-8, dangerous thrombi develop within the vessels. These clots can disperse within the blood stream and cause cerebral or heart infarctions.

⊖ Risks:

Periodontitis increases the risk of stroke in general by factor 2. For fatal strokes in particular, the risk factor is 3

Wu et al: Periodontal disease and risk of cerebrovascular disease: the first national health and nutrition examination survey and its follow-up study. Arch Intern Med 2000; 160: 2749

Periodontitis is the significantly highest risk factor for stroke

A pocket deeper than 4.5 mm has been proven to be the greatest influential factor for strokes. It increases the risk by a factor of 8.5. This makes periodontitis more dangerous than high blood pressure and smoking.

Pradeep et al: Periodontitis as a risk factor for cerebrovascular accident: a case-control study in the Indian population. J Periodontol Res 2009 [Epub ahead of print]

Periodontitis has a significantly greater influence on stroke than on heart attack

For those with periodontitis, the risk of a stroke increases to the factor 2.8, in comparison to 1.5 for heart attacks and 1.9 for deadly heart attacks.

Beck et al: Periodontal disease and cardiovascular disease. J Periodontol 1996; 67: 1123

Meurman et al: Oral health, atherosclerosis, and cardiovascular disease. Crit Rev Oral Biol Med 2004; 15: 403

Stroke risk dependent on the severity of periodontal bone loss

In the case of radiologically visible bone loss, the risk increases by a factor of 3.6. In the case of a clinically confirmed attachment loss of more than 6 mm, it increases by a factor of 7.4.

Dörfer et al: The association of gingivitis and periodontitis with ischemic stroke. J Clin Periodontol 2004; 31: 396

+ Recommendation:

By eliminating the danger presented by aMMP-8, the risk of stroke in patients with high blood pressure can be greatly reduced

aMMP-8 testing for those with chronic vascular disease is obligatory

aMMP-8 testing prevents blood vessel operations – inserting stents, for instance

Recommendation for high blood pressure patients:

1. For those with existing conditions, the acute risk posed by raised aMMP-8 levels must be immediately eliminated
2. Testing before every cardiological operation
3. Testing every six months
4. In general: Regular aMMP-8 testing for those at risk of stroke and heart attack

Periodontitis is associated with greater occurrence of carcinomas

Patients at risk should pay attention to their oral hygiene

In Germany, about 400,000 malignant tumors are diagnosed each year. At the beginning of the 19th century, 10% of all deaths could be traced to cancer. In the meantime, that number has risen to 29% and there is no sign of decline. Cancer is the second most frequent cause of death after cardiovascular illnesses. In other words, there is a definite need to detect early development of carcinoma.

Risk of tumor development multiplied fourfold

Scientific investigations have proven the connection between periodontitis and the development of malignant tumors. Untreated gingivitis increases the risk of developing a carcinoma fourfold, in particular pancreatic carcinomas, as well as renal cell carcinomas and hematologic neoplasia. Tumors do not grow in the human body in an isolated and separate way from the extrinsic and intrinsic signal transfer sensor systems of the basic metabolic supply. Many tumor traits are triggered or enabled by some metabolic lapse. Many of the known risk factors of periodontitis also stem from an altered primary metabolic supplying of the cells and cannot merely be explained by a dysbalance of the biofilm. Regular dental check-ups are therefore crucial aspects of cancer prevention.

⊖ Risks:

Every millimeter of alveolar bone loss increases the risk of a squamous cell carcinoma in the head and neck by a factor of 4.4.

Overall, the risk of this type of cancer developing due to periodontitis rose just under threefold. Every millimeter of alveolar bone loss increased the risk by a factor of 4.4.

Tezal et al: Chronic periodontitis and the incidence of head and neck squamous cell carcinoma. *Cancer Epidemiol Biomarkers Prev* 2009; 18: 2406.

Increase in the “relative risk” for various types of cancer is evidenced by a variety of studies

A case of periodontitis exposes non-smokers to a higher risk of cancer than smokers.

Of the 100,000 or so cancer fatalities per year, tens of thousands of cases can be traced back to the elevated risk indicators from periodontitis.

Hujoel et al: An exploration of the periodontitis-cancer association. *Ann Epidemiol* 2003; 13: 312.

Michaud et al: Periodontal disease, tooth loss, and cancer risk in male health professionals: a prospective cohort study. *Lancet Oncol* 2008; 9: 550.

Michaud et al: A prospective study of periodontal disease and pancreatic cancer in US male health professionals. *J Natl Cancer Inst* 2007; 99: 171.

Every millimeter of alveolar bone loss increases the risk of tongue cancer by a factor of 5.2

Tezal et al: Chronic periodontitis and the risk of tongue cancer. *Arch Otolaryngol Head Neck Surg* 2007; 133: 450.

The dramatic influence of periodontitis on the risk of cancer and the consequent mortality rate calls for a general and careful handling of periodontitis in the general population

Rosenquist et al: Oral status, oral infections and some lifestyle factors as risk factors for oral and oropharyngeal squamous cell carcinoma. A population-based case-control study in southern Sweden. *Acta Otolaryngol* 2005; 125: 1327.

+ Recommendation:

The risk of oral and oropharyngeal squamous cell carcinoma is reduced by a factor of 0.4 with regular dental check-ups

Rosenquist et al: Oral status, oral infections and some lifestyle factors as risk factors for oral and oropharyngeal squamous cell carcinoma. A population-based case-control study in southern Sweden. *Acta Otolaryngol* 2005; 125: 1327.

Recommendation for risk patients:

1. Control testing every 6 months
2. Regular control of aMMP-8 levels in risk patients

aMMP-8 damages the joints

Rheumatologists and dentists should also treat periodontitis in their rheumatism and arthritis patients

In Germany, 1.3 million people suffer from rheumatic illnesses. Next to activated arthritis, rheumatoid arthritis is the most frequent inflammatory joint disease. It affects between 0.5% and 1% of the world population. In Germany, about 800,000 people suffer from rheumatoid arthritis (RA), whereby women are three times more likely to have it than men. People of all ages can be afflicted with rheumatoid arthritis.

Risk of arthritis increased ninefold

A moderately severe case of periodontitis already increases the risk of rheumatism and arthritis by a factor of 6 and will influence the severity of the illness. The risk of contracting arthritis increases by a factor of 2.6 for patients with periodontitis and by a factor of 9 for non-smokers with periodontitis. So for RA patients, it is well worth seeking treatment from a dentist from a rheumatological standpoint. The pathophysiological connections between RA and periodontitis are well-known in the meantime. Citrullinated proteins and an RA-specific glycoprotein complex were shown in vivo in periodontal tissue. In the case of RA, cytokines like IL-1, IL-6 and TNF α and the connective tissues of the synovial membrane release substances such as prostaglandin E2 (PGE2) and matrix-metalloproteinase (MMP), which destroy structures. The levels of these substances are also higher in patients with periodontitis.

⊖ Risks:

Matrix-metalloproteinase-8 (MMP-8) is a major pathological factor in the case of rheumatoid arthritis and periodontitis

In contrast to healthy controls, patients with rheumatoid arthritis have a 1000-times higher MMP-8 level in their synovial fluid. Both periodontitis patients and rheumatism patients have MMP-8 in the gum pockets. The two illnesses do a great deal to feed each other.

Tchetverikov et al: MMP profile in paired serum and synovial fluid samples of patients with rheumatoid arthritis. *Ann Rheum Dis* 2004; 63: 881

Biyikoğlu et al: Gingival crevicular fluid MMP-8 and -13 and TIMP-1 levels in patients with rheumatoid arthritis and inflammatory periodontal disease. *J Periodontol* 2009; 80: 1307

Strong similarities between periodontitis and rheumatoid arthritis

Theoretical considerations and clinical studies prove the strong similarities in the development of the two illnesses. One can assume that the biochemical inflammatory reaction pattern is similar in all affected patients.

Bartold et al: Periodontitis and rheumatoid arthritis: a review. *J Periodontol* 2005; 76: 2066

Modi et al: Rheumatoid arthritis and periodontitis: Biological links and the emergence of dual purpose therapies. *Indian J Dent Res* 2009; 20: 86

Clinical interrelations: patients with periodontal disease have rheumatoid arthritis six times more frequently than healthy patients

If, conversely, rheumatism patients are tested for periodontitis, one usually finds deeper pockets as well as more missing teeth. Indicators of rheumatic illnesses, like swollen joints, are associated with periodontal bone loss.

Mercado et al: Is there a relationship between rheumatoid arthritis and periodontal disease? *J Clin Periodontol* 2000; 27: 267

Mercado et al: Relationship between rheumatoid arthritis and periodontitis. *J Periodontol* 2001; 72: 779

⊕ Recommendation:

Therapeutic approach: Periodontal treatment significantly reduces the symptoms of rheumatoid arthritis

Ortiz et al: Periodontal therapy reduces the severity of active rheumatoid arthritis in patients treated with or without tumor necrosis factor inhibitors. *J Periodontol* 2009; 80: 5

Taking all above-mentioned aspects into account – analogous etiology, MMP-8 effect, reciprocal increase of prevalence – general practitioners suggest treating both diseases together with the dentist

Ortiz et al: Periodontal therapy reduces the severity of active rheumatoid arthritis in patients treated with or without tumor necrosis factor inhibitors. *J Periodontol* 2009; 80: 535

It has been shown that oral bacteria from the periodontal pockets settle on the endoprostheses. This can have a considerable impact, including the need to surgically remove the prosthesis and re-implanting one

Dyck, Huggett: Der klinische Fall: odontogene Infektion einer Knieendoprothese Knieendoprothese (Odontogenous infection of a knee endoprosthesis). Vortrag Jahrestagung Deutsche Gesellschaft für Krankenhaushygiene (Lecture at the Annual Meeting of the German Society for Hospital Hygiene)

Recommendations for rheumatism and arthritis patients:

1. In the case of an existing condition, the acute risks from an elevated levels of aMMP-8 should be excluded immediately
2. Control testing prior to each joint-replacement operation
3. Control testing every 6 months
4. Regular professional tooth cleaning every 6 months

Politics and the economics of health

Educating the public about the interaction between periodontal disease and other common diseases must be optimized

Seventy percent of Germans suffer from some health condition affecting the oral cavity and do not know it. The condition is connected to illnesses in other parts of the body in multifarious ways. Increasingly, scientists are finding interactions between general illnesses and periodontitis. The negative consequences have a massive personal impact on those affected and considerable economic impact for society as a whole.

Physicians and dentists are facing a challenge that their training has not prepared them for.

This forward-looking interdisciplinary diagnostic approach is concerned with the subject of pathogenic „enzyme activity“ and reveals the complex links between dental health and general health. The interaction between periodontal disease and diabetes and heart disease, for example, has been scientifically proven.

This has really boosted the significance of interdisciplinary collaboration: Illnesses can be detected earlier and combated, and the risks of complications limited.

The US-American Aetna study expels to a possible cost reduction with the cardiological treatment of Parodontitis treated patient. In my opinion the Aetna study delivers an important economic proof of the relevance of an interdisciplinary cooperation. On this occasion, the principle is always valid „precaution trumps healing“.

Laurenz Meyer
Berlin, April 2010



Laurenz Meyer

Economist
Politician of the Christian Democratic Union
Former Member of Parliament
Former General Secretary
Former spokesman for economic affairs

Quality control and patient information

Nowadays, modern, interdisciplinary diagnostics are necessary to guarantee quality control in medicine

Mouth-to-mouth recommendation has long proven its worth in medicine. Patients ask other patients for their opinion about doctors and treatments. Quality and sustainability in medicine are also becoming more important from the patients' standpoint as well. That's why it is important to inform patients properly about prevention, possible risks and effects.

In medicine, quality assurance means that the chosen treatment can only be as good as the diagnosis that led to it.

Modern, viable diagnostics require a glimpse beyond the horizon. Diagnostics should inform a patient about all the different medical areas, list the possibilities, offer a series of solutions and support comprehensive care. Today's diagnostics must be interdisciplinary.

The aMMP-8 analysis bridges a very important gap between the largest „most hidden infection worldwide,“ periodontitis, and common diseases. Early diagnosis of the aMMP-8 values can prevent illnesses like rheumatism, diabetes, heart attacks, strokes, and even premature births.

The two new testing methods to determine pathogenic enzyme activity facilitate communication between various areas of medical specialization. Doctors from all disciplines are advised to make use of this possibility to create a broad-based interdisciplinary network and to continue promoting collaboration. It's in the interest of the patients.

That's why maximum education plus maximum interdisciplinary cooperation and communication produces maximum health.

Prof. Dr. rer. nat. Siegmur Bornemann
Leverkusen, April 2010



Prof. Dr. rer. nat. Siegmur Bornemann

Biochemist

Consultant in Health Communication

Expert for quality assurance in medicine

Interdisciplinary Diagnostic Initiative

Early detection of periodontal disease, interdisciplinary risk diagnostics and an optimal education of patients are the cornerstones of the multidisciplinary net

The exchange of data among areas of medical specialization is gaining significance in order to better understand the proven scientific connections between healthy teeth and general health. Medical practitioners from many disciplines must cooperate if they wish to keep their patients fully informed, which, in turn, is necessary for optimal treatment.

This concept is very well explained at www.parofrueherkennung.de. The medical practitioners involved in this initiative are identified by name, so the network is actually visible to patients.



Education

Among a physician's obligations is that of informing patients about diagnosis and treatment. The Interdisciplinary Diagnostic Initiative (IDI) aims to expand this particular area. The IDI provides comprehensive information for the patients about the interrelationship between dental health and general health. Hence, it has opened an important door and paved the way to productive cooperations among dentists, cardiologists, gynecologists, rheumatologists, diabetologists, oncologists and general practitioners.

Early detection

The aMMP-8-tests are crucial to this idea of the informed patient and also offers a solution to closing the gap between periodontitis and general health. „Prevention trumps healing“ is the idea guiding the use of modern aMMP-diagnostics to develop an early-warning system that protects the patient from the “periodontal“ risk factor.

Treatment

The aMMP-8-laboratory-test allows medical personnel from all areas of specialization to monitor treatment on a regular basis. So it really rounds off the concept of the IDI.

Health communication means education

Diagnostics and information are the cornerstones of solid interdisciplinary medical care

The medical education of the general population covers communication of health risks. This involves, on the one hand, scientifically verified information about factors that endanger health or make people sick, and, on the other hand, showing the options of how to avoid or minimize these risks. Successful education requires the interdisciplinary cooperation of all medical areas of specialization. The Interdisciplinary Diagnostic Initiative has adopted this holistic medical concept and offers solutions as well. Most patients don't know that their wellbeing is closely connected to the health of their teeth. However, studies do show that an untreated case of periodontitis does have a considerable effect on general health. The Interdisciplinary Diagnostic Initiative is aware of the connections between systemic illnesses and periodontitis and educates the public.

Modern communications works online

Polls confirm that people use the Internet as a source of health information even before they go see the doctor. So the Initiative's Website also informs patients of the potentially negative impact of periodontitis on an individual's health and how to minimize risks by using the novel aMMP-8 testing system.

A password-protected area informs medical practitioners from all areas of specialization about novelties from the worlds of research, business and industry and also enables interdisciplinary exchanges.

Strong partners from practise and science

With the companies Matrix Lab GmbH and dentognostics GmbH the Interdisciplinary Diagnostic Initiative for the early detection of periodontal disease has two strong cooperation-partners from the research and development of the aMMP-8-Biomarker-Tests.

The Matrix Lab GmbH has sat down to the aim to optimise the early detection of periodontal disease. Therefore, the MatrixLab GmbH investigates with partners from practise and science the effects of a periodontitis/peri-implantitis on the health of the body.

Since the foundation the dentognostics GmbH is specified on the proof by aMMP-8 inflammation markers. With the advancement of the aMMP-8 test to the use in practice the breakthrough succeeded dentognostics in the early detection of periodontal disease. In the research labs and production rooms in Jena dentognostics develops new parameters and platforms for an improving diagnostics in cooperation with the Matrix Lab GmbH.

Promoting interdisciplinary cooperation:

More and more doctors use a holistic approach when examining their patients. They are aware that excluding other causes (from other areas of specialization as well) of illness could contribute significantly to the success of treatment in their own special field. Professional periodontal diagnostics are especially important in this regard. Acute periodontitis has an enormous effect on the bulk of systemic illnesses

and can do a great deal to hamper treatment. The new testing procedure enables medical practitioners from many specialized fields to detect periodontitis early on and monitor treatment results.

The aim of the Interdisciplinary Diagnostic Initiative is to facilitate interdisciplinary communication through aMMP-8 analysis and hence to optimize the ability of specialists to look beyond their horizons.



Your web page entry on www.parofrueherkennung.de

The Interdisciplinary Diagnostic Initiative has adopted an holistic medical concept and keeps the patients fully informed as well.



- Yes, I would like to take part in the health initiative for early detection of periodontal disease, interdisciplinary risk diagnostics and education and agree to the registration of my doctor's office as a participant.

My website

My Faculty

Name

Address

Phone

E-Mail

Stamper

Queries or suggestions?



Fax response Please send to: 0049 2054 – 938 596-9

- I'm interested in the aMMP-8-Chairside-Rapid-test.
Please contact me.

- I'm interested in the aMMP-8-laboratory-test.
Please contact me.

- Please send me more information about the settlement
of the aMMP-8-test:
 - For dentists
 - For specialists
 - For operators
 - For natural health professionals

My website

My Faculty

Name

Address

Phone

E-Mail

Stamper

Queries or suggestions?



Patient test Please check the appropriate box:

Moderate risk factors

| GENERAL | YES | NO |
|---|--------------------------|--------------------------|
| Are you noticing shifting teeth and/or moving teeth | <input type="checkbox"/> | <input type="checkbox"/> |
| Are your teeth loose? | <input type="checkbox"/> | <input type="checkbox"/> |
| Do you have implants? | <input type="checkbox"/> | <input type="checkbox"/> |

| PERIODONTAL TREATMENT | YES | NO |
|---|--------------------------|--------------------------|
| Have you ever been, or are you being treated for periodontal disease? | <input type="checkbox"/> | <input type="checkbox"/> |
| Were you treated more than a year ago? | <input type="checkbox"/> | <input type="checkbox"/> |
| Do you go to the dentist less than once a year? | <input type="checkbox"/> | <input type="checkbox"/> |
| Was the last professional teeth cleaning over 6 months ago? | <input type="checkbox"/> | <input type="checkbox"/> |

| GENERAL HEALTH | YES | NO |
|---|--------------------------|--------------------------|
| DIABETES | | |
| Do you have diabetes? | <input type="checkbox"/> | <input type="checkbox"/> |
| Are your blood sugar levels difficult to adjust | <input type="checkbox"/> | <input type="checkbox"/> |
| Do you suffer from heavy fluctuations in your blood sugar levels? | <input type="checkbox"/> | <input type="checkbox"/> |
| Has your medication been changed in the past 6 months? | <input type="checkbox"/> | <input type="checkbox"/> |
| ARTHRITIS | | |
| Do you suffer from rheumatoid arthritis? | <input type="checkbox"/> | <input type="checkbox"/> |
| Are the flare-ups regular? | <input type="checkbox"/> | <input type="checkbox"/> |
| CARDIOVASCULAR DISEASES | | |
| Do you have high blood pressure? | <input type="checkbox"/> | <input type="checkbox"/> |
| Do you wear a pacemaker or other endoprotheses (hip joint/heart valve)? | <input type="checkbox"/> | <input type="checkbox"/> |
| Do you take blood-thinning medication? | <input type="checkbox"/> | <input type="checkbox"/> |

Severe risk factors

| GENERAL | YES | NO |
|--|--------------------------|--------------------------|
| Do you have bleeding gums? | <input type="checkbox"/> | <input type="checkbox"/> |
| Do you suffer from halitosis? | <input type="checkbox"/> | <input type="checkbox"/> |
| Have you noticed receding gums? | <input type="checkbox"/> | <input type="checkbox"/> |
| Do you smoke? | <input type="checkbox"/> | <input type="checkbox"/> |
| Has someone in your family had cancer? | <input type="checkbox"/> | <input type="checkbox"/> |
| Do you have a hip or knee prosthesis? | <input type="checkbox"/> | <input type="checkbox"/> |

| PERIODONTAL TREATMENT | YES | NO |
|---|--------------------------|--------------------------|
| Have you ever had or do you have periodontitis? | <input type="checkbox"/> | <input type="checkbox"/> |
| Have you been diagnosed with gum pockets? | <input type="checkbox"/> | <input type="checkbox"/> |
| Do you have a tooth implant? | <input type="checkbox"/> | <input type="checkbox"/> |

| CARDIOVASCULAR DISEASES | YES | NO |
|---|--------------------------|--------------------------|
| Have you already had a heart attack/bypass operation? | <input type="checkbox"/> | <input type="checkbox"/> |
| Are you scheduled for a bypass operation scheduled? | <input type="checkbox"/> | <input type="checkbox"/> |

| PREGNANCY | YES | NO |
|---|--------------------------|--------------------------|
| Are you planning a pregnancy? | <input type="checkbox"/> | <input type="checkbox"/> |
| Have you notice gums bleeding more frequently (pregnancy gingivitis)? | <input type="checkbox"/> | <input type="checkbox"/> |
| Have you already had a preterm birth? | <input type="checkbox"/> | <input type="checkbox"/> |

YES:

YES:

Evaluation:

ORANGE: „YES“ less than 6x / RED: no „YES“

You are not at risk. Nevertheless, keep an eye on the factors in order to recognize warning signals in good time and begin treatment.

ORANGE: „YES“ 6x or more

You are showing risk factors that need to be explored. You should have your aMMP-8 levels tested in the near future.

ROT: „YES“ 1x or more

You are at risk! You should see a dentist as soon as possible to have your aMMP-8 levels tested.



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