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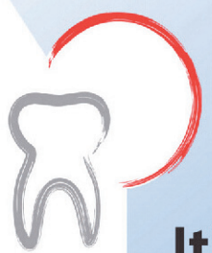

PERIODONTITIS – PERI-IMPLANTITIS

aMMP-8
Study 2011

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Adjuvant treatment of refractory chronic periodontitis with orthomolecular substances – a prospective pilot study in practice

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Indices: refractory chronic periodontitis, orthomolecular therapy, matrix metalloproteinase-8

Periodontitis is the most common chronic inflammation worldwide. According to epidemiological studies (Micheelis and Schiffner, 2006), at least 25 million adults suffer from this disease in Germany, alone. The usual treatment is the so-called "scaling & root planing" (SRP). In most cases, this mechanical measure is successful and leads to the remission of inflammatory symptoms and also decreases progression of the disease.

In this context, the terms "resistant to therapy" and "refractory periodontitis" are disputed. While the existence of the latter is sometimes negated, there are also studies which specifically focus on this group of patients (Lee et. Al 1995b, Colombo et al. 1998). The question remains whether patients with refractory periodontal inflammation require further treatment that should not be based on mechanical measures. Although the prescription of antibiotics for short-term effects may seem appropriate, the long-term focus lies in the diet. The goal of this prospective study was to test whether a standardized adjuvant treatment with complex orthomolecular substances on a collective of patients suffering from refractory periodontitis, who did not see improvement after at least four attempts of standard therapy, could lead to an improvement of the periodontological situation. The activated matrix metalloproteinase-8 (aMMP-8, collagenase 2) was the parameter to be tested.

The correlation between diet and the development or progression of periodontitis has been examined since the mid-seventies (Alvares et al. 1984, Pack 1988, Olbertz 2005). Meanwhile, there are several experimental studies evaluating specific nutrients such as vitamins and trace elements and their possible effects on the disease process. These studies focus on oxidative stress (Chapple et al. 2007), the action of vitamins (Staidte et al. 2005) or the impact of a general change in diet (Jenzsch et al. 2009). In the following study, a comprehensive, balanced, standardized orthomolecular therapeutic regimen with especially pure dietary supplements without additives was applied as a so-called hypoallergenic orthomolecular therapy. Methodologically, there was the question about how the process of periodontal tissue degradation could be determined objectively. The measurement of the pocket depth or the attachment level as well as x-rays show all decay processes in the patient's history, possibly dating back for several years – completely independent of the current status. Bleeding on Probing (BOP) can only give a retroactive assessment about non-existing loss of tissue after several measurements with a negative result (Lang et al. 1986, Lang et al. 1990). A test for the quantitative measurement of the activated form of the matrix metalloproteinase-8 (MMP-8; synonymous, collagenase 2) has recently become available. This collagenase, which destroys the collagen network of the periodontium, is detected in increased concentration during periodontitis and peri-implantitis in the gingival crevicular fluid or peri-implant sulcus fluid (PISF) (Sorsa et al. 2004, Prescher et al. 2007, Xu et al. 2008). Consequently, the concentration of aMMP-8 in the GCF is reduced after successful treatment (Kinane et al. 2003). The activity of collagenase or the concentration of aMMP-8 in the GCF is of prospective significance (Lee et al. 1995a, Reinhardt et al. 2010). The following prospective pilot study aimed to provide patients suffering from refractory periodontitis over a longer period of time with an adjuvant therapy with especially pure, hypoallergenic encapsulated orthomolecular substances in the form of a dietary supplement. Quantitative measurement of the aMMP-8 in the sulcus fluid was used during patient selection and testing.

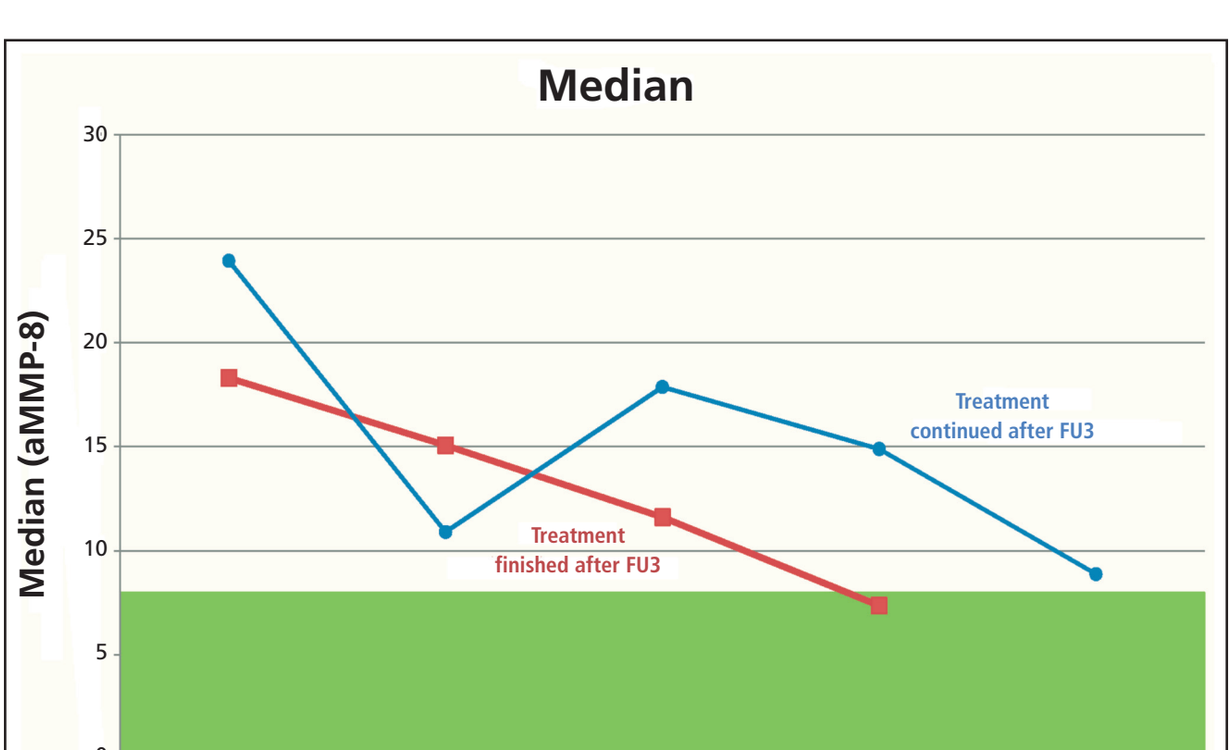

Fig. 1: medians of aMMP-8 values from GCF of the collective (n=20) of patients suffering from refractory periodontitis under adjuvant therapy. Red: subgroup A to FU3; blue: subgroup B to FU4; green: area described as healthy based on aMMP-8 values.

Material and Methods

Patients and clinical parameters:

Participants in the study were recruited from the patient collective of a group practice. They were successively selected by an independent person who did not participate in the study. All subjects have been in the controlled recall for at least two years. In the course of a supplemental periodontal therapy, biofilm management (initial therapy) had been performed at least four times without achieving expected improvements with regard to the visually and via BOP estimated inflammatory condition. Inclusion criteria: despite local therapy still an aMMP-8 concentration in GCF sample > 20ng aMMP-8/ml eluate (based on Preschner et al. 2007), positive BOP > 30%, plaque index according to the Plaque Assessment Scoring System, PASS (Butler et al. 1996) < 20% and previously in the practice via BOP "documented case of refractory periodontitis."

Clinical Parameters:

Plaque according to Butler et al. (1996); Bleeding on Probing (BOP; Ainamo and Bay 1975); determination of depth of probing standardized with WHO-probe.

Fig. 2: compound 3-SymBiose plus

Quantification of the activated matrix metalloproteinase-8 in the sulcus fluid:

During each examination, GCF samples were extracted with special strips from four periodontitis pockets with the largest depth (Prescher et al. 2007). The strips were inserted 2 to 3 mm into the sulcular recess of the pocket and remained there for 30 seconds to absorb sulcus fluid. The strips were immediately prepared for shipping, and the concentration of activated MMP-8 was tested with well-established methods at the laboratory of the dentognostics GmbH (Jena) (quantitative results in ng aMMP-8 per ml eluate). The cut-off value between healthy and beginning collagenolytic tissue degradation was set at 8 ng aMMP-8/ml eluate based on the literature (Prescher et al. 2007).

General procedure and therapy to be tested:

After selection of the subjects, another local therapy was performed. Seven to fourteen days later, the aMMP-8 level was determined (base examination) in order to test the inclusion criterion of > 20 ng aMMP-8/ml in at least one point of withdrawal once again. Afterwards, the adjuvant therapy (see table 1 for the procedure) was administered as specified by the manufacturer. At the end of each treatment interval (follow-up examinations FU1, FU2, FU3 and FU4), the above mentioned clinical parameters as well as quantification of aMMP-8 was performed once again.

Results

42 patients were selected for the initial examination. Unfortunately, several patients had to be excluded from the evaluation of the study due to various reasons. Nine of the 42 (21%) did not show an initial aMMP-8 value of over 20 ng/ml eluate and were not included in the study, because they did not fulfill the inclusion criteria. For 11 patients (26%), only the data for the base examination and for FU1 were available at the end of the trial or they did not take advantage of all follow-up appointments. 2 (5%) patients were excluded subsequently due to non-compliance with the medication.

At the point in time for FU2 and FU3, 10 out of the 20 available patients had experienced significant improvements. They did not continue on to Stage IV (Itis Protect IV) and were statistically regarded as one group (A). The 10 remaining patients did not show the same success of the adjuvant therapy during FU3. They continued, and were statistically regarded as another group (B) (Table 2).

The mean values of probe depths showed only a very small, non-significant change due to the therapy to be tested. The aMMP-8 concentration in the sulcus fluid improved for all patients in the course of the study. For subgroup A, which could discontinue the adjuvant therapy after FU3, this occurred continuously; the aMMP-8 base value (determined in base examination) had decreased by a statistically significant value of 60% ($p = 0.0002$). In subgroup B, the decrease of the median value of the pool-aMMP-8 between base examination and FU4 was also statistically significant ($p = 0.0005$) at 63%. A graphic depiction of the changes in median values of both subgroups is shown in Figure 1.

Combination of compounds[1]	Duration of therapy	Brief description of ingredients[2]	Corresponding follow-up examination[3]
Itis-Protect I	4 weeks	Vitamins ADEK in omega-3 fatty acids AZN (natural vitamin C, zinc) Mineral plus (Ca, Mg, Se, vit. B5, folic acid)	FU 1
Itis-Protect II	4 weeks	Black cumin seed oil 3-SymBiose (probiotics and vitamins) Potassium (K, molybdenum, iodine) ADEK, AZN, Mineral plus	FU 2
Itis-Protect III	4 weeks	Salmon oil, black cumin seed oil 3-SymBiose plus (probiotics and vitamins) Magnesium-calcium ADEK, AZN, Mineral plus	FU 3
Itis-Protect IV	4 weeks	3-SymBiose plus Q10 plus vit. C, Magnesium-calcium ADEK, AZN, Mineral plus	FU 4

[1] hypo-A GmbH, Luebeck / [2] Compounds by hypo-A GmbH, only main ingredients listed / [3] each follow-up examination after 4 weeks

Table 1: Course of the adjuvant periodontitis therapy

The cut-off value which is defined as healthy in the literature (Prescher at al. 2007) is shown in green in the chart. At the time of the base examination (7 to 14 days after mechanical therapy), all aMMP-8 values are still very high (inclusion criterion). At the end of the study (FU3 or FU4, depending on subgroup), about 50% of the aMMP-8 values lie in the normal range, marked in green. In addition, the aMMP-8 values of all other patients were reduced.

Discussion

In a periodontological and implantological group practice, there were several patients who did not seem to respond to the standard treatment (e.g. SRP) and who were classified as refractory. They were to receive adjuvant therapy (Itis-Protect) which had only recently become available.

In order to develop a more objective definition of the disputed term "refractory periodontitis", the matrix metalloproteinase-8 (MMP-8, synonymous, collagenase 2) in samples of the sulcus fluid was chosen as the parameter to be measured. There are several, unambiguous international publications available with regard to MMP-8 (Prescher et al. 2007; Reinhardt et al. 2010; Sorsa et al. 2004, Xu et al. 2008). This parameter can be used to specifically quantify the collagenolytic tissue degradation. As several studies confirm, successful therapy results in significant reduction of the amount of aMMP-8 in the sulcus fluid (for example, Kinane et al. 2003). In the following study, the diagnostic of aMMP-8 was used to

- form an objective definition of refractory periodontitis as an inclusion criterion for the study, i.e. to detect areas with high collagenolytic tissue degradation which have remained despite prior mechanical therapeutic measures. Based on Prescher et al. (2007), a value of > 20 ng aMMP-8 per ml eluate was considered to be negative (refractory) and therefore deserving of treatment.
- serve as the main parameter used in the determination of the success (or lack of success) of the adjuvant therapy with orthomolecular substances to be tested. Also based on Prescher et al. (2007), values of < 8 ng aMMP-8 were defined as healthy and without collagenolytic tissue degradation.

There was no control group. Since the inclusion criterion of "high aMMP-8 value in the sulcus fluid" implies a high risk due to acute tissue degradation, no patient group could be refused additional therapy. In the following practice study, adjuvant therapy should not involve the use of antibiotics. Although this can result in short-term success, the general problem of the possibility of the development of drug resistance exists. Support of the organism's immunological defence was expected under the therapy to be tested (Olbertz 2005, El-Sharkawy et al. 2010).

The hypoallergenic compounds were used in several stages, and their composition is very complex and varies from stage to stage which is why only the most important components could be listed in table 1. In the first preparatory stage, the main components are vitamins, omega-3 fatty acids, trace elements and minerals. The further stages include adjuvant therapy and intestinal regeneration with probiotic bifido bacteria, lactobacillus sp., streptococcus faecalis as well as B-vitamins, folic acid and vitamin D3, supported with black cumin and salmon oil as well as a base therapy with magnesium-calcium as carbonates.

There is a significant reduction of the aMMP-8 values during the first four weeks of initial therapy. In the following months, the adjuvant orthomolecular substances caused a significant reduction of the tissue degradation caused by aMMP-8 (table 2). In the further course of the study, two reaction patterns among the participants emerged. This is to be understood as a sign for differences in reactive patterns among individual patients.

It must be assumed that the adjuvant therapy has activated a healing phase (Olbertz 2005) which is revealed in the change in aMMP-8 levels in the patients. The FU3 or FU4 revealed that the adjuvant therapy leads to a statistically certain and significant improvement of the collagenolytic degradation. At the end of the therapy about half of the patients were in the "green range" with < 8 ng aMMP-8 per ml eluate. In the remaining patients, the aMMP-8 values, which were elevated in the base examination, were now significantly lower which could be interpreted as a sign for reduced tissue degradation in the periodontium.

	Group A		Group B	
Point in time	**n**	**Median**	**n**	**Median**
BU	10	18.3	10	23.9
FU1	10	15.1	10	10.9
FU2	10	11.6	10	17.9
FU3	10	7.4*	10	14.9**
FU4	–	–	10	8.9**

aMMP-8: activated matrix metalloproteinase-8, listed in ng/ml eluate (median values)
BU: base examination / FU: follow-up examination
*statistically significant difference (*p<0.0008, **p<0.0005) compared to the base examination (BU)

Table 2: Progress of the aMMP-8 values in the GCF in the collective of patients suffering from refractory periodontitis under adjuvant therapy.

Final remarks:

A long-term therapy with complex orthomolecular substances resulted in a statistically significant improvement of the periodontal situation in a collective of patients suffering from therapy-resistant periodontitis which had not been improved during multiple attempts of standard therapy. The parameter tested was aMMP-8 (activated collagenase 2). The enzyme, which destroys the collagen network of the periodontium, was initially present in dangerously high concentrations in 100% of the patients, and the concentration was significantly reduced in the course of the treatment until it was within healthy limits in 50% of the patients at the end of the therapy.

The remaining patients who were still refractory at the end of the study, showed aMMP-8 values that were significantly lower which can be seen as a sign for decreased periodontal tissue degradation. Due to the reduction in aMMP-8 values of these patients, a continuation of the substitution for two to three months and after a thorough assessment of their diet would be desirable.

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Examined Recommendation for Intake

Itis-Protect I *

Product	Week 1 to 4
ADEK	3 x 1 capsule before a meal
Acerola Zinc	3 x 1 capsule with a meal
Mineral plus	3 x 1 capsule after a meal

*Maintenance dosage: For 3 months, 1 capsule per day along with intake of following treatments

Itis-Protect II

Product	Week 5 to 8
Black cumin seed oil	3 x 2 capsules before a meal
3-SymBiose	3 x 1 capsule with a meal
Potassium	3 x 1 capsule with a meal

Itis-Protect III

Product	Week 9 to 12
Salmon oil **	3 x 2 capsules before a meal
Black cumin seed oil **	3 x 2 capsules before a meal
3-SymBiose plus	3 x 1 capsule with a meal
Magnesium-calcium	3 x 1 capsule after a meal

** Alternating daily

Itis-Protect IV

Product	Week 12 to 16
Vitamin AE + lycopene	3 x 1 capsule before a meal
3-SymBiose plus	3 x 1 capsule with a meal
Q10 plus vitamin C	3 x 2 capsules with a meal
Magnesium-calcium	3 x 1 capsule after a meal

Periodontitis – peri-implantitis

Causes and Dietary Recommendations

Periodontitis is a disease typical of civilization, and it surpasses caries as the main cause for tooth loss in adults over 43 years of age in the European Union. Along with environmental stresses, the modern diet with fast food, additives and stress is the central cause. One can prevent chronic inflammation with a diet of fresh organic foods without additives, sufficient hydration with at least 2 litres of clear water a day and an adequate supply with vitamins and minerals. Sufficient amount of sleep, stress management, outdoor activity and relaxation techniques such as autogenic training are supporting factors.

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Special information for therapists.
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