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IFEG

Scientific Monograph
Dossier 3

Personalized Oral Medicine with Biomarker Diagnostics in 2020

Sponsor

dentognostics GmbH
Tatzendpromenade 2
D-07745 Jena
Germany

Expert

Prof. Dr. Dr. med. Reinhard Rychlik
Am Ziegelfeld 28
D-51399 Burscheid
Germany

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Signature

Prof. Dr. Dr. med.
Reinhard P. T. Rychlik

Dr. med. dent.
Cornelia Fietz

The Institute of Empirical Health Economics is an extra-universitary research unit for the areas of medical and pharmaceutical research. The assignments involved aspects of medicine, clinical research, marketing and controlling.

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The clientele includes the areas of the pharmaceutical industry, medical technology and pharmaceutical manufacturers, hospitals, health insurance companies, ministries and health policy institutions, as well as the professional organization of the medical and pharmacy community and organizations in the medical assistance and nursing professions.

CONTENT

Abbreviations

ACPA	anti-citrullinated peptide antibodies
aMMP	activated matrix-metalloproteinase
APD	active periodontal / peri-implant soft and hard tissue degeneration
BOP	bleeding on probing
CAGR	compound annual growth rate
DPSI	Dutch Periodontal Screening Index
GCF	gingival crevicular fluid
GDM	gestational diabetes mellitus
LBW	low birth weight
MMP	matrix-metalloproteinase
PISF	Peri-implant sulcus fluid
PoC	point-of-care
RA	rheumatoid arthritis

1 EXECUTIVE SUMMARY

Periodontal and peri-implant diseases are among the most common chronic inflammatory diseases in the world. In the age group of 35–44 years, nearly every second patient suffers from mild periodontitis, in the elderly (75–100 years), nine out of ten suffer from mild or severe periodontitis, and one in three patients or one in five implants are affected by peri-implantitis.
Following a progressive course, periodontal and peri-implant diseases lead to inflammation and degradation of the soft- and hard-tissue stabilizing the tooth or implant. Worst consequences are tooth or implant loss. This has a huge socio-economic impact as tooth loss requires expensive prosthodontic treatment and will affect masticatory function and quality of life.
As an inflammatory disease, periodontal and peri-implant diseases may increase systemic inflammatory load and affect or impair general diseases like diabetes mellitus, cardiovascular and rheumatic diseases or cause adverse pregnancy outcomes.

Activated matrix-metalloproteinase-8 (aMMP-8) is the leading enzyme for cleavage of collagen type I in the periodontium. Increased levels of aMMP-8 are associated with active periodontal / peri-implant soft- and hard-tissue degeneration (APD). aMMP-8 levels precede, predict, are associated with and reflect current or future / progressive often hidden and subclinical periodontal and peri-implant disease activity. They show a positive correlation with clinical parameters (BOP, probing depths) and radiological measurements.

Point-of-care (PoC) aMMP-8 immunoassays (PerioSafe®, ImplantSafe®) were designed to qualitatively and quantitatively determine aMMP-8 levels in oral fluids quickly and easily. They reveal ongoing APD and are able to predict future APD progression with a high diagnostic sensitivity and specificity. Thus, subclinical, developing periodontitis and peri-implantitis and related collagen degradation can be detected even before clinical and radiological symptoms appear. After successful periodontal or peri-implant therapy and elimination of inflammation, aMMP-8 levels decrease.
aMMP-8 PoC tests are used as a predictive tool for diagnosis, screening, monitoring, and indicating / timing / targeting preventive measures in periodontal and peri-implant diseases.

The market potential for the products is enormous. Dentists all over the world can use the test for their periodontitis and dental implant patients to screen, check-up and personalize preventive and treatment measures, thus enhancing customer visit frequency and satisfaction. Clinicians in general medicine can use the test to screen their patients for concomitant periodontal diseases and thus improve treatment outcome in diabetes or cardiovascular disease.

2 INTRODUCTION

2.1 Periodontitis

Periodontal diseases comprise a wide range of inflammatory conditions that affect supporting structures of the teeth (gingiva, bone, periodontal ligament, collagen fibers), can lead to tooth loss, and contribute to systemic inflammation.[52]

Periodontitis is one of the most common non-communicable chronic diseases of mankind. The 2016 Global Burden of Disease Study ranks periodontal diseases as the 11th most prevalent disease globally.[26]

Periodontitis is defined by pathologic loss of periodontal ligament and alveolar bone caused by complex dynamic interaction of destructive immune response, specific bacterial pathogens and others.[99] Risk factors include smoking, obesity, poor nutrition, physical inactivity and co-morbidities like diabetes or rheumatoid arthritis.[15]

2.2 Peri-implantitis

Introduction of dental implants has opened up new possibilities in dentistry. Single tooth crown implants or implant-supported fixed partial dentures are available. Implant stability originates from osseointegration of the implant, i.e. the osteoblasts directly integrate the implant surface into the bone.[39]

Peri-implantitis is a common complication of dental implant therapy. It is defined as a plaque-associated destructive inflammatory process and subsequent progressive loss of supporting tissue and bone.[9,58] Progression of peri-implantitis is gradual and often clinical signs and symptoms need years to occur. Predisposing conditions include diabetes, osteoporosis, smoking, long-term steroid treatment, radiation, and chemotherapy.[39]

A reversible inflammation of the soft tissues around a functioning implant without bone loss is referred to as peri-implant mucositis.[29]

2.3 Staging and Grading of Periodontal Diseases

Recently, the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions proposed a new classification system for periodontitis.[111] Until then, four different forms of periodontitis were recognized: Necrotizing periodontitis, chronic periodontitis, aggressive periodontitis, and periodontitis as a manifestation of systemic diseases. This classification was based on identification of specific bacteria, etiologic agents, risk factors or genetic susceptibility.

In the light of new evidence, concept of precision medicine, and biomarker-aided diagnosis and prognosis, the new classification relies on a staging and grading system, comparable to the well established system in oncology. Stages I-IV classify the severity, complexity, and extent of periodontitis (initial, moderate, severe, advanced) and grades A-C estimate the future risk of progression (slow, moderate, rapid) of the disease and responsiveness to standard therapeutic principles to help guide intensity of therapy and monitoring.[45,111]

3 RELEVANCE

3.1 Relevance in Dentistry

Teeth are vital for daily activities like mastication, speech, and smiling and play an important role in esthetics and self-esteem.[16] Studies confirmed reduction of quality of life with progressive tooth loss.[106]
Periodontitis is the major cause of tooth loss in adults worldwide.[112] Affected patients are thus at risk of multiple tooth loss, edentulism, and masticatory dysfunction which will affect nutrition, quality of life, and self-esteem. Periodontitis requires complex therapy and close monitoring, resulting in huge healthcare costs and socio-economic impact.[112]
In addition to treatment costs, indirect costs - mainly in terms of productivity losses due to absenteeism from work - result from periodontal diseases. Indirect costs for severe periodontitis amount to USD 54 billion per year.[70] Total direct and indirect costs of dental diseases worldwide are estimated at USD 544 billion. Severe tooth loss and severe periodontitis account for 67% and 21% of global productivity losses, respectively.[90]

Globally, severe chronic periodontitis accounted for a total 3.5 million DALYs (disability/disease-adjusted life years) or 49 DALYs (age-standardized) per 100,000 person-years in 2015.[48]
The 2018 annual report of the BARMER statutory health insurance in Germany shows that 23.2% of all patients received a diagnosis of periodontal disease but only 1.5% underwent specific treatment.[84] The annual costs of periodontal treatment in 2017 amounted to EUR 476 million for the German statutory health insurance which is the smallest fraction (3.4%) of the total amount spent on dentistrydentistry (EUR 14.1 billion). 1.07 million periodontal treatments were billed in Germany in 2017.[49]

3.2 Relevance in Dental Implantology

Teeth lost due to periodontitis often leave deficiencies of the hard- and soft-tissue behind. Lack of buccal bone, recession of peri-implant mucosa and lack of keratinized tissue can complicate or impede placement of a dental implant. If an implant is successfully placed, peri-implantitis can lead to loss of alveolar bone and soft-tissue and impacts implant stability. In the worst case, the implant is lost and cannot be replaced. With it, the (costly) prosthetic construction is lost and has to be rescheduled.[9]
Costs for non-surgical treatment alternatives of peri-implantitis are reported from EUR 33–131 per implant and session.[69] Surgical treatment options will be even more costly.

3.3 Relevance in Internal Medicine / Interdisciplinary Relevance

Apart from loss of integrity and function of the local periodontium, systemic inflammatory load will be increased by periodontitis. Pathogenic bacteria and inflammatory mediators invade the vascular system and interact with the endothelium. Epidemiologically proven relationships between periodontitis and earlier onset or increase in incidence of diabetes, cardiovascular diseases (coronary artery disease, stroke), chronic respiratory diseases, adverse pregnancy outcomes, osteoporosis and rheumatoid arthritis exist.[24,44,81]
In the last few years, the connection between periodontitis and general diseases has increasingly become the focus of research. Even an inflammatory disease limited to the oral cavity, such as periodontitis, can have an influence on the general health or the course of systemic diseases in different ways.
The relevance of periodontitis for internal medicine will be discussed in the following section with a focus on diabetes, cardiovascular diseases, rheumatoid arthritis and adverse pregnancy outcomes.

3.3.1 Periodontitis and Diabetes mellitus

To begin with, the relationship between periodontitis and diabetes mellitus will be discussed in the following section. We were able to identify various systematic reviews and meta-analyses in which the relationship between the two diseases was analyzed.

Based on the results of different observational studies on the effect of periodontitis on diabetes, *Graziani et al.* came to the conclusion that periodontitis has a significant impact on diabetes control, incidence and complications. The authors explain these causal relationships with the fact that individuals with periodontitis exhibit a poor glycemic control and therefore have an increased risk of developing diabetes and a higher prevalence of diabetes-related complications.[36] The authors also clarify that the evidence for gestational diabetes and type I diabetes is considerably more limited.[36]

Nascimento et al. evaluated the data from a total of 13 studies in their systematic review with meta-analysis. The data set contained data on 49,262 patients, including 3,197 patients with diabetes.[80] The authors found that the relationship between diabetes and periodontitis was very well established. The central question of their systematic review was to determine whether poorly controlled diabetes was associated with periodontitis onset or progression.[80] The results of the performed meta-analyses of adjusted estimates showed that diabetes increased the risk of incidence or progression of periodontitis by 86% (RR 1.86 [95% CI 1.3-2.8]). Therefore the study provides additional evidence that diabetes is associated with an increased risk of periodontitis onset and progression.[80]

The authors *Abariga et al.* provide a comprehensive analysis of the relationship between periodontitis and gestational diabetes mellitus (GDM) in their meta-analysis.[1] A total of 10 studies met the inclusion criteria and were taken into account for the meta-analysis. The analysis of a total of 5,724 participants, showed that periodontitis is associated with an increased risk of GDM by 66 %, (OR = 1.66, 95 % CI: 1.17 to 2.36; $p < 0.05$).

Comparable results were observed in sub-analyses restricted to high quality case-control studies with a total of 1,176 participants (OR = 1.85, 95 % CI: 1.03 to 3.32); $p < 0.05$).[1] The results suggest that periodontitis is associated with an increased risk for GDM compared to patients without periodontitis.[1]

Further meta-analyses have repeatedly demonstrated that periodontitis therapy in patients with diabetes mellitus led to an average reduction of HbA1c by 0.27% to 0.65%.[28,74,98]

A relevant topic concerning the relationship between periodontitis and diabetes is the causal direction of this relationship. *Agarwal et al.* present the current knowledge on the interplay and interaction processes between both diseases.[2] According to the authors, the association between diabetes and inflammatory periodontal disease is not only bidirectional but cyclical as diabetes not only predisposes the individual to oral disease but also periodontitis, once established, exacerbates diabetes and worsens the metabolic control outcomes.[2]

Based on the extensive evidence and a consensus paper of diabetologists and periodontists,[23] German Society of Parodontologists (DG PARO), German Society of Dentistry and Oral Medicine (DGZMK) and the German Diabetes Society (DDG) are currently preparing a guideline “Diabetes and Periodontitis” in order to improve the interdisciplinary cooperation between general practitioners/internists and diabetologists and periodontologists in the care of patients with diabetes and/or periodontitis.[25,27]

De Morais et al.[19] reviewed the relationship between glycemic state and MMP-8 levels in patients with periodontal disease and diabetes. They discovered that glycemic state modulate aMMP-8 concentrations in diabetes patients, but the influence of (pre)diabetes as aMMP-8 rising factor were controversial.[19]

3.3.2 Periodontitis and Cardiovascular Diseases

In addition to the relationship with diabetes, there is evidence that periodontitis is also correlated to the risk of developing cardiovascular diseases. In this context, some systematic reviews and meta-analyses were identified.

Overall the relationship between cardiovascular disease and periodontitis was demonstrated in epidemiological, in vitro and in vivo studies.[110] In addition, there is some evidence that both diseases share central genetic risk factors including cigarette smoking, age, and diabetes mellitus.[11,71,93,94]

Stewart et al. shows that evidence for a causal relationship between periodontitis and cardiovascular diseases, including stroke, myocardial infarction, peripheral vascular disease, abdominal aortic aneurysm, coronary heart disease, and cardiovascular death comes from a large number of cohort and case control studies.[107]
A systematic review by *Berlin-Broner et al.*[10] analyzed the association between apical periodontitis and cardiovascular diseases based on a total of 19 relevant studies (including 10 case-control studies, five cross-sectional studies and four cohort studies). Thirteen of these studies identified a significant positive association between periodontitis and cardiovascular disease.[10]
In the context of a very extensive meta-analysis, *Leng et al.* analyzed patient data of 230,406 participants from a total of 15 prospective cohort studies to quantify the association between periodontal disease and risk of coronary heart disease.[63] The results showed that patients with periodontal disease were at a significantly increased risk of developing coronary heart disease (RR: 1.19, 95% CI: 1.13-1.26; p <0.001) compared to patients without periodontitis.[63]
An older systematic review by *Humphrey et al.* shows comparable results based on seven prospective cohort studies.[43] Relative risk estimates for periodontal disease (including periodontitis, tooth loss, gingivitis, and bone loss) ranged from 1.24 (95% CI 1.01-1.51) to 1.34 (95% CI 1.10-1.63) compared to patients without periodontal disease.[43]
In a more recent analysis, *Yu et al.* compared effects of incident versus prevalent periodontal disease in developing cardiovascular diseases based on a prospective cohort of 29,863 women.[116] The incidence rates of all cardiovascular disease outcomes were higher in women with periodontal disease. For patients with periodontal disease, risk factor adjusted hazard ratios (HRs) were 1.42 (95% CI, 1.14-1.77) for major cardiovascular disease, 1.72 (1.25-2.38) for myocardial infarction, 1.41 (1.02-1.95) for ischemic stroke and 1.27 (1.06-1.52) for total cardiovascular disease.[116]
Vedin et al. analyzed the associations between self-reported tooth loss and cardiovascular outcomes in a global stable coronary heart disease cohort and the results showed that there is a significant association between tooth loss and stroke, cardiovascular death, and all-cause mortality in patients with coronary artery disease.[115]

3.3.3 Periodontitis and Rheumatic Diseases

Periodontitis and rheumatic diseases are characterized by chronic inflammation of the bone, which is manifested locally in periodontitis and systematically in inflammatory rheumatic diseases. Many case control studies have shown that there is a bidirectional correlation between periodontal disease and rheumatoid arthritis with regards to both incidence and severity.[8]
Fuggle et al. tried to interrogate the relationship between rheumatoid arthritis (RA) and periodontitis in their meta-analysis.[30] A total of 21 papers met the eligibility criteria and were evaluated during meta-analysis; 17 of these studies (including a total of 153,492 participants) compared patients with RA to healthy controls while 4 publications (including a total of 1,378 participants) included patients with RA and osteoarthritis. The results showed a significantly increased risk of periodontitis in people with RA compared to healthy controls (RR: 1.13; 95% CI: 1.04, 1.23; p=0.006; N: 153,277).[30]
The systematic review by *Kaur et al.*[50] demonstrated strong evidence supporting a causal relationship between both diseases. The authors additionally conclude that common risk factors or common pathologic processes may be responsible for this relationship. Regarding study quality, it has to be mentioned that most of the included studies were limited by small sample sizes of 100 RA patients or less[50].
Another more recent study investigated the relationship between periodontal disease and RA in 287 RA cases and 330 osteoarthritis controls.[78] The results show that RA patients with anti-citrullinated peptide antibodies (ACPA) were much more likely to develop a periodontal disease and that, on the other hand, patients with periodontal disease had a increased risk to suffer from RA and also had higher ACPA and rheumatoid factor titers.[78]

3.3.4 Periodontitis and Adverse Pregnancy Outcomes

The last relevant indication in the context of the relevance of periodontitis for internal medicine is the effect of periodontitis during pregnancy, which can result in severe consequences for mothers and unborn children. This relationship can be primarily explained by the assumption that periodontitis is often referred to as a potential risk factor for negative pregnancy outcomes such as low birth weight (LBW), premature birth, and preeclampsia.[12]

The most extensive and relevant work in this context is a meta-analysis by *Daalderop et al.*,[18] which summarizes the results of 23 systematic reviews, comparing pregnancy outcomes among women with and without periodontal disease. The pooled results of systematic reviews with the lowest risk of bias consistently demonstrated positive associations between periodontal diseases and preterm birth (relative risk, 1.6; 95% confidence interval, 1.3 to 2.0; 17 studies, 6,741 participants), LBW (relative risk, 1.7; 95% CI, 1.3 to 2.1; 10 studies, 5,693 participants), preeclampsia (odds ratio, 2.2; 95% CI, 1.4 to 3.4; 15 studies, 5,111 participants), and preterm LBW (relative risk 3.4; 95% CI, 1.3 to 8.8; 4 studies, 2,263 participants).[18]

These findings can be interpreted as a clear indication that untreated periodontitis represents a key risk factor for several adverse pregnancy outcomes and should therefore be treated at an early stage or preferably already preventively.

4 INCIDENCE AND PREVALENCE

In general, oral health in Germany significantly improved over the last decades. Still, one in every two Germans is affected by periodontal diseases. The fifth German Oral Health Study (DMS V),[47] which was conducted in 2014, shows that 43.4% of Germans aged 35 to 44 years suffer from mild periodontitis, whereas 8.2% present with severe periodontitis. This chronic, inflammatory disease advances with increasing age: one in five people aged 65 to 74 years demonstrate with severe periodontitis and among the elderly (75 to 100 years) nine out of ten suffer from moderate or severe periodontitis.[47] In 2015, 6 million incident cases of severe periodontitis were found worldwide.[48] The age-standardized, worldwide prevalence rate of severe chronic periodontitis was found to be 7.4% (538 million).[48]

As a precursor for peri-implantitis, peri-implant mucositis is found frequently with prevalence rates reported to be up to 80% of the patients and up to 60% of the implants after a minimum of five years.[29]

A recent retrospective cohort study found prevalence rates for peri-implantitis of 34% on patient- and 21% on implant-level over an average follow-up of 2 years. Corresponding incidence rates for peri-implantitis were 0.16 per patient-year and 0.10 per implant-year.[58] If follow-up times in studies were extended, prevalence of peri-implantitis would be even higher, as shown by Derks.[22] He followed-up 427 individuals with 1578 implants over 9 years and found that only 23.0% of patients and 39.3% of implants were healthy after this period. Prevalence of (pre-)peri-implantitis was thus 77.0% on patient- and 60.7% on implant-level.[22]

5 ACTIVATED MATRIX-METALLOPROTEINASE-8

5.1 aMMP-8 Overview

Matrix-metalloproteinases (MMPs) form a family of zinc-dependent proteolytic enzymes that play a pivotal role in the catabolic turnover and degradation of extracellular matrix.[3,73] The MMPs are divided into six protease groups of which the collagenases are particularly relevant for collagen cleavage in periodontal diseases. MMP-8, also known as collagenase-2, is mainly responsible for active periodontal / peri-implant soft- and hard-tissue degeneration (APD).[3] MMP-8, in elevated concentrations, preferably and efficiently cleaves collagen type I, interstitial collagen fibers of the soft and hard periodontal tissue. Physiological levels of MMP-8 exert protective and anti-inflammatory characteristics.[4,102]

In the last decade, increased levels of activated, not latent or total, MMP-8 (aMMP-8) were shown to be associated with or predict periodontal and peri-implant inflammation in active or progressive phases.[31,101,103-105] Inflammation in the periodontal pockets leads to increased exudation of gingival crevicular fluid (GCF) and migration of neutrophilic granulocytes. Neutrophils are triggered by pathogenic bacteria and inflammatory mediators to release aMMP-8.[101,105] Gingival fibroblasts also produce aMMP-8 when stimulated by proinflammatory mediators.[17]

5.2 aMMP-8 in periodontal progression

aMMP-8 levels precede, predict, are associated with and reflect current or future / progressive often hidden and subclinical periodontal and peri-implant disease activity.[3,51,62,100,101,103,105] Independent immune and catalytic assays confirmed that patients with stable periodontitis exhibit different aMMP-8 levels than subjects with progressing periodontitis.[75,103,104]

Elevated aMMP-8 levels in oral fluids correlate with clinical periodontal parameters, i.e. probing depth, bleeding on probing (BOP) and clinical / radiological attachment loss.[77]

Nwhator et al. showed that aMMP-8 levels, measured with PerioSafe®, are directly proportional to the oral hygiene status (96% sensitivity).[83] Furthermore, in presence of two or more sites with probing depths >5mm (sensitivity 95%) or BOP (82.6% sensitivity), aMMP-8 levels show a positive correlation with chronic periodontitis and BOP. In single sites affected by APD, correlation was less.[83]

Several authors could demonstrate a correlation of aMMP-8 in oral fluids and probing depths or BOP.[3,38,59,77,91] aMMP-8 levels are also associated with radiological parameters, as studies showed that aMMP-8 could differentiate subjects with severe bone loss from those with slight bone loss.[38,64,91] Likewise, for peri-implant sulcus fluid, positive correlations between aMMP-8 levels and plaque index and BOP were reported.[4,87] Elevated levels of aMMP-8 were also significantly associated with osteolysis / bone loss in peri-implantitis.[54,55] Low (<20 ng/ml) aMMP-8 levels were shown to reflect healthy implants or successfully treatment of peri-implant diseases.[4]

After successful periodontal or peri-implant treatment aMMP-8 levels in oral fluids are significantly reduced (<20 ng/ml).[3,4,57,66,100,101,105] *Konopka et al.* demonstrated that scaling and root planing significantly decreased the amount of aMMP-8 in oral fluids, especially four weeks after treatment.[57] This could be confirmed by *Gonçalves et al.* who demonstrated that nonsurgical periodontal therapy effectively reduced aMMP-8 levels, especially in the first 3-6 months after treatment.[33] If active sites remain after therapy, aMMP-8 levels at these sites do not decrease significantly and still mark the collagenolytic progression.[42]

As most studies evaluating the effect of aMMP-8 testing on the progression of periodontitis and outcome parameter are observational or retrospective cohort studies, randomized controlled trials would be desirable to further certify benefits of aMMP-8 testing.

5.3 Predictive Capability of aMMP-8

Diagnosis of periodontitis and peri-implantitis is clinically based on probing depths, attachment loss, BOP, and radiographic bone loss.[4,9,99] Periodontal diseases need to be far progressed till clinical measurements can detect them and episodic progression of the disease complicates accurate measurement. Furthermore, clinical diagnosis can only detect previous soft- and hard-tissue destruction and does not provide information about the current activity of the disease or its future progression, since the clinical and radiological measurements have a low sensitivity and low predictive value.[4,52,100]

As aMMP-8 levels in oral fluids are already elevated subclinical phases of periodontal diseases, the predictive value of the aMMP-8 test lies in its ability to detect APD before clinical or radiological manifestations can be determined.[62,66,67,75,100,105] *Izadi Boroujeni et al.* demonstrated a high sensitivity and specificity of aMMP-8 in a PoC detection of generalized chronic periodontitis.[44] Highest sensitivity was shown in salivary / oral fluid, whereas high specificity could be demonstrated in GCF.[53,65,67,82]

6 THE PRODUCTS

PerioSafe® and ImplantSafe® are commercially available chair-side and PoC lateral flow immunoassays for the detection of aMMP-8 in oral fluids with a quantitative detection limit of 10 ng/ml for PerioSafe® and 20 ng/ml for ImplantSafe®.[4,100] They were discovered in Finland and further developed in Germany and are based on monoclonal antibodies against aMMP-8.[4,83,100]
For qualitative testing, the products are used like at-home pregnancy tests. The antibody for aMMP-8 is attached to blue latex particles. If the enzyme is present, the antibody (along with blue latex particles) will attach to it and collect along the test line. A control line always collects the blue particles even if there is no enzyme. Appearance of only one line indicates negative results, i.e. aMMP-8 levels <20 ng/ml and thus a healthy oral status. Appearance of two lines indicates an increased risk for periodontal / peri-implant diseases, either already existing or developing with aMMP-8 levels >20 ng/ml.[3,100]
In combination with a quantitative lateral flow test reader equipped ORALyzer® they are designed to quantify aMMP-8 levels (ng/ml) in oral fluids like saliva, mouth rinse, GCF or peri-implant sulcus fluid (PISF).[3,100,101] They reveal ongoing APD and are able to predict future APD with a diagnostic sensitivity and specificity of 76–83% and 96%, respectively.[76,88,100-103] Thus, subclinical, developing periodontitis and peri-implantitis and related collagen degradation can be detected even before clinical and radiological symptoms and signs appear.[100,109] Detection occurs by real-time measurement with turnaround times of 5–7 minutes.[100]

The tests have been validated repeatedly and independently in Finland, Germany, Nigeria, Turkey, the Netherlands and the USA.[40,41,44,46,72,83,100] Patents have been granted in the US and Finland and are pending in the EU, China, Japan, Korea, Brazil, and Canada.
Thus, the tests are suited for quantitative evaluation of periodontal progression (i.e. periodontal grading A-C). To assess progression, two analyses are needed, to calculate the difference in aMMP-8 levels. To evaluate the episodically collagenolytic degradation, analysis of aMMP-8 can be part of prophylaxis and recall visits.[96]
As aMMP-8 in oral fluids decreases after successful periodontal treatment, aMMP-8 analysis can be used to document and control therapy outcomes.[100,101]
According to the manufacturer, aMMP-8 testing on a yearly basis is recommended for all patients aged <25 years and predisposed adolescents >17 years. High risk patients (smokers, diabetics) should be tested at least twice a year. After successful periodontal treatment, aMMP-8 testing should take place 6–8 weeks after treatment and in the course of periodic three monthly recalls. aMMP-8 testing is also recommended prior to orthopedic or cardiac interventions and twice during pregnancy (15^{th}-18^{th} and 25^{th}-30^{th} week).

6.1 PerioSafe®

PerioSafe® PRO DRS is a qualitative and quantitative aMMP-8 immunoassay designed as a lateral flow test. It is a whole mouth saliva test whereby aMMP-8 is rinsed from the crevicular sulcus fluid from all teeth in a 30 second mouth rinse with distilled water. Sampling takes about 2 to 3 minutes and automated quantitative analysis another 5 minutes. The result is the aMMP-8 level from 10 ng/ml up, pooled from all teeth. The PerioSafe® PRO DRS is used for screening and early diagnosis of collagenolytic degradation in periodontal diseases. In general / internal medicine, the test can be used in patients with diabetes, cardiovascular diseases, rheumatoid arthritis, or osteoporosis to screen for concomitant periodontal diseases. The PerioSafe® DRS is not suited for dental implant diagnostic or obvious periodontitis and selective site testing.[100,102]
Owing to the quick and easy mouth-rinse sampling, the test is also suitable for at-home application for which, so far, only a qualitative analysis is possible.

6.2 ImplantSafe®

ImplantSafe® DR is a qualitative and quantitative aMMP-8 immunoassay designed as a dip-stick test. PISF or GCF from one site is absorbed by a stick. Sampling takes about 2 min then the stick is eluted for 5 min and can be quantitatively analyzed in 5 minutes. The result is the aMMP-8 level from 20ng/ml up from one implant or tooth.
The ImplantSafe® DR is used for screening and early diagnosis of collagenolytic degradation in peri-implantitis and periodontitis and for monitoring of periodontitis and implant patients to control treatment progress or identify non-responder.[100,102]

6.3 PerioSafe® ImplantSafe® POOL DR

PerioSafe® ImplantSafe® POOL DR is a qualitative and quantitative aMMP-8 immunoassay designed as a dip-stick test. PISF or GCF from up to four sites is absorbed by a stick. Sampling takes about 2 min then the stick is eluted for 5 min and can be quantitatively analyzed in 5 minutes. The result is the pooled aMMP-8 level from 20ng/ml up from four sites in the mouth.
The PerioSafe® ImplantSafe® POOL DR is used for screening and monitoring of periodontitis and implant patients.

7 UNMET NEED, BENEFIT, AND COST-EFFECTIVENESS

7.1 Unmet Need

Like in general medicine, the era of predictive, preventive, and personalized medicine is rapidly incoming in dentistry. The present actual "reactive" therapeutic point of view has to change into a futuristic "predictive" point of view.[13] *Cafiero & Matarasso* describe this as the "5Ps: predictive, preventive, personalized and participatory periodontology".[13] The patients play an important role in that concept as a responsible driver of their health by active participation in the treatment and prophylactic measures.[13]
Clinical and radiological diagnostic measures for periodontal / peri-implant diseases have a low sensitivity and a low predictive value. This means that periodontal / peri-implant diseases are often detected as late as the disease has already progressed and soft- and hard-tissue of the periodontium are lost. Accurate clinical measurement is further complicated by the episodic progression of the disease with active and stagnant phases. Clinical measurement can only describe the current state of the disease and does not provide information about disease activity or future progression.[4,52,100] Probing of clinical attachment has additional shortcomings as size of probe tips, probing force, tooth angulations, and examiner's experience influence the measurement.[68] Thus, diagnostic tests are needed to identify early, subclinical stages of periodontal / peri-implant diseases to prevent progression and APD. This tests need to be rapid, sensitive, specific and inexpensive.
Dentistry is by far not the only discipline which would benefit from such a test. There is growing knowledge on interactions between periodontal and general disease like cardiovascular disease, diabetes mellitus, chronic obstructive pulmonary diseases, rheumatoid arthritis or adverse pregnancy outcomes (see also Chapter 3.3).[44,81] With a quick and easy-to-use test, clinicians (with no expertise in periodontal diagnostics) could screen their patients for developing periodontal diseases and thus improve clinical outcome, morbidity, and mortality or exclude the oral cavity as a source of inflammation prior to major surgery.

7.2 Benefit

PerioSafe® and ImplantSafe® with the ORALyzer® digital reader are quick and easy-to-use modern in vitro immunological diagnostic tests or preventional technologies for examination of the periodontal / peri-implant status of teeth and dental implants to detect acute or the risk of periodontal tissue degeneration and loss of soft- and hard-tissue before they can be clinically or radiologically detected.[3,100,102] They are described as a reliable, noninvasive, safe and inexpensive tool for diagnosis, screening, monitoring and prevention of periodontal and peri-implant diseases.[4]

Their predictive value is tremendously high as they reveal ongoing APD and are able to predict future APD with a diagnostic sensitivity and specificity of 76–83% and 96%, respectively.[76,88,100-103] In contrast, BOP only showed sensitivity and specificity of 88% and 29%, respectively.[61]

aMMP-8 levels in oral fluids can serve as a predictive tool to indicate, time, and target preventive interventions (secondary prevention or supportive periodontal / peri-implant therapy) and to stop subclinical pre-periodontitis or pre-peri-implantitis from progression. Thus, periodontal risk assessment would be enhanced and patients with high risk of APD and treatment need reliably identified.[4,20,62,85,100,102] The tests can also help to assure tissue stability prior to implant placement or preparation of dental restorations.

Active participation of the patient and effective preventive measures can prevent tooth loss and costly prosthetic reconstructions. *Axelsson et al.*[6] evaluated the long-term effects of a carefully managed plaque control program on tooth mortality, caries and periodontal diseases in adults over 30 years. They could show that with efficient plaque control only 0.4–1.8 teeth per individual were lost during 30 years of maintenance. Only 21 teeth in 375 subjects were lost due to periodontitis or caries over the course. They could also demonstrate that most tooth sites did show no sign of attachment loss and approximal surfaces even gained some attachment over the course of treatment.[6] R*äisänen et al.* demonstrated that patient outcomes were improved and overtreatment avoided.[85] All in all, this would result in enormous gain in quality of life and considerable costs savings for the patient and the health care system.

The tests are further suitable for monitoring the disease's development and progression and the outcome of therapeutic measures.[3,4,33,42,57,66,97,100,101,105] *Sexton et al.* successfully discriminated responder and non-responder of periodontal treatment with aMMP-8.[97] A Dutch study with 219 patients showed, that 58% of aMMP-8 tested patients (positive and negative test) decided to comply with treatment intensification recommendations.[113] Thus, patient adherence and visit frequencies can be enhanced and lead to better outcomes.

A great advantage, especially in the field of general medicine, is that the test is noninvasive and does not cause bacetaeremia like BOP.[4] *Räisänen et al.* could recently show, that the aMMP-8 PoC test had 2.8-5.3 times stronger association with initial or subclinical periodontitis compared to BOP.[86]

7.3 Cost-effectiveness

We could not identify any cost-effectiveness / cost-utility / cost-benefit studies related to aMMP-8 PoC testing in periodontal / peri-implant diseases. As cost-effectiveness analyses are a powerful tool for marketing and reimbursement, cost-effectiveness needs to be adapted to / assessed in the respective countries in which the products are sold.

Studies by *Räisanen et al.* report a strong association between aMMP-8 test results and the patient's periodontal treatment needs.[85,86] In both studies, aMMP-8 testing did not cause any overtreatment of patients. Thus, the authors assume that the aMMP-8 PoC test could be a cost-efficient method used in pre-periodontitis diagnostics. Still, further research is needed to confirm this assumption.[85,86]

8 MARKETING

In the following section the central key markets for aMMP-8 patented biosensor technology for check-up and prevention of periodontal and peri-implant disease will be defined and described. This enables a comprehensive assessment of the international market potential of the entire product range. We focus on the implant-health market and briefly touch the general dentistry and medical market.

8.1 Numbers of Dentists in Europe and Worldwide

To estimate the total market potential for the products, knowledge of numbers of dentists, specialized dentists, practices, frequency of attendance etc. is required. We focus on key countries / markets and examine figures of the European Union, the USA, Canada, Brazil, China and Japan.

The Council of European Dentists regularly releases the EU Manual of Dental Practice which provides comprehensive and detailed information for dental practice and regulation throughout the EU.[60] At the time of data collection, the population covered by the manual was about 519 million. The percentage of GDP spent on oral health varied between 0.06% and 3.0% in the different countries (Fig.1). The dental associations reported about 361,000 active dentists (which excludes retired dentists or those on maternity leave). The average dentist to population ratio was 1:1,433.[60] Numbers of registered and active dentists and dentists to population ratios for each country are shown in Fig. 2&3.

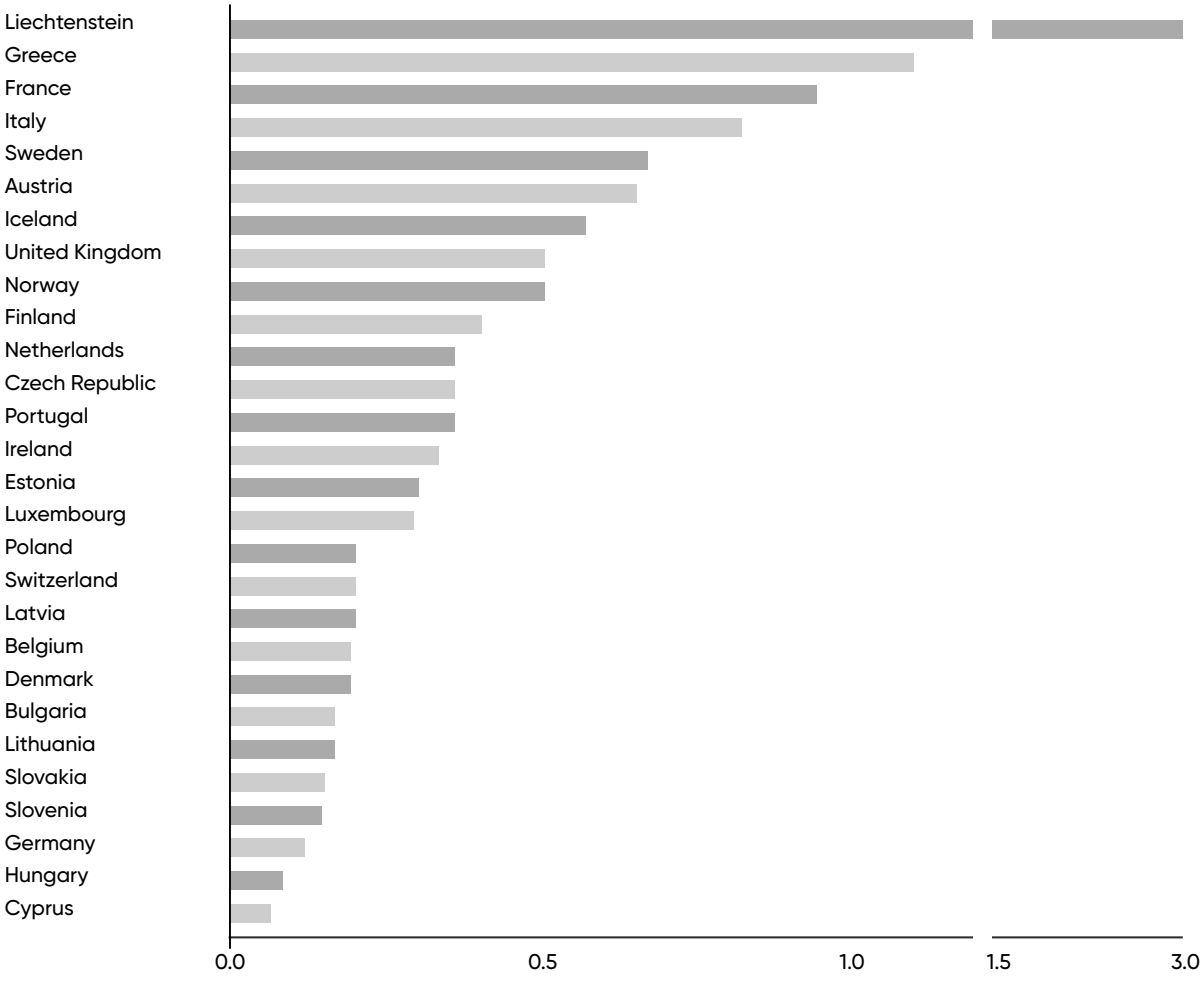


Fig. 1 Percentage of GDP spent on oral health in the EU[60]

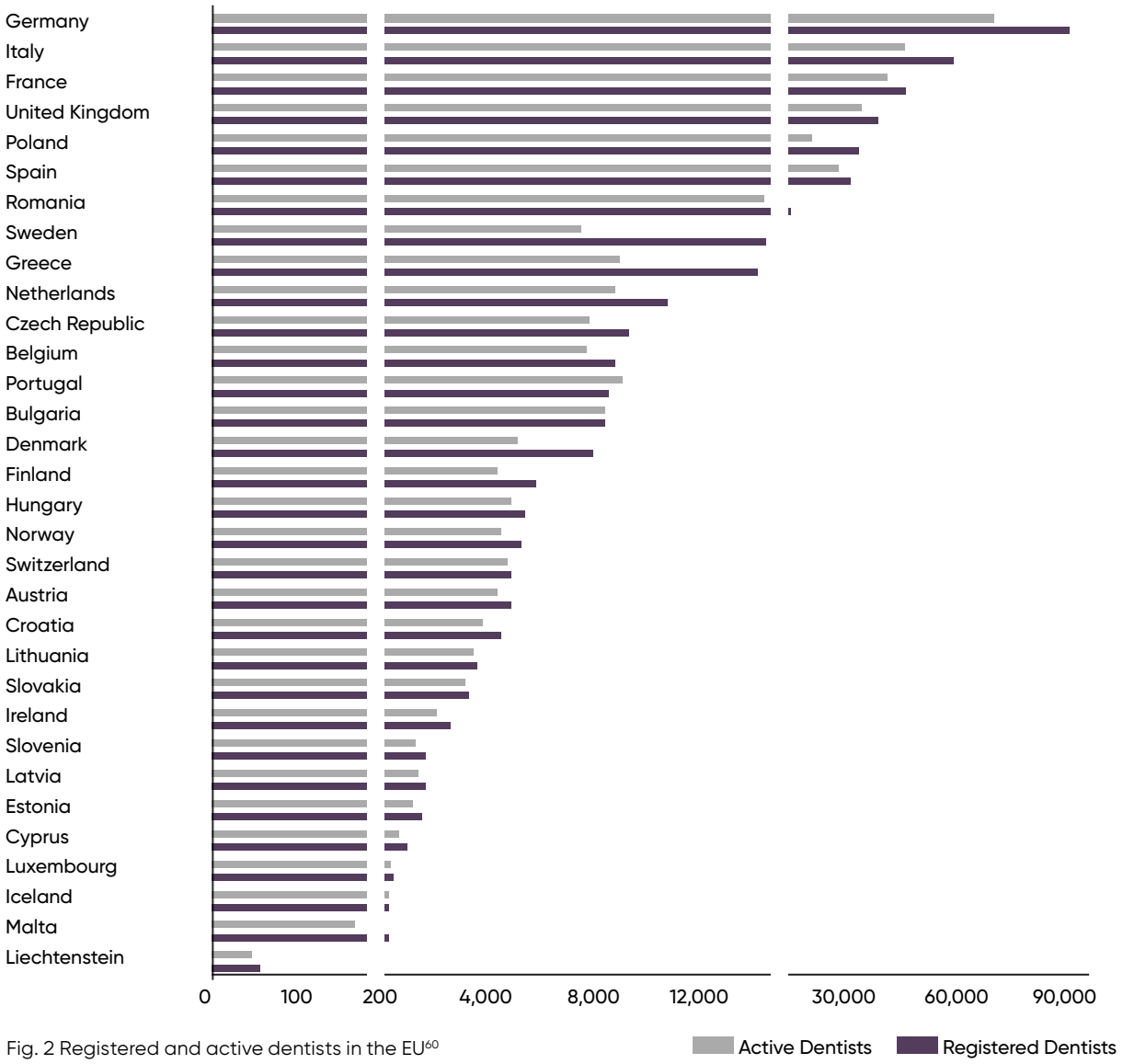


Fig. 2 Registered and active dentists in the EU[60]

As far as dental specialties were recognized and numbers available, the Council of European Dentists could identify >8,600 dentists specialized in oral surgery or oral maxillo-facial surgery. If dental auxiliaries, e.g. the about 44,600 dental hygienists, were taken into account, the total dental workforce exceeded 1.12 million workers. The percentage of dentists who work in a general practice (owned or employed) varied between 44% in Finland and 100% in Iceland and the Netherlands. The remaining worked in public clinics, hospitals, universities or the armed forces. List sizes of practices, i.e. numbers of regularly attending patients, were not available in all countries and varied between 650 and 4,000 per practice.[60]

The **American** Dental Association reports 199,486 dentists working in dentistry in the USA in 2018. This corresponds to a dentist to population ratio of 1:1,640 and 60.97 dentists per 100,000 people. 79.0% are working in a general practice and 3.8% and 2.9% are specialized in oral and maxillo-facial surgery and periodontics, respectively.[5]

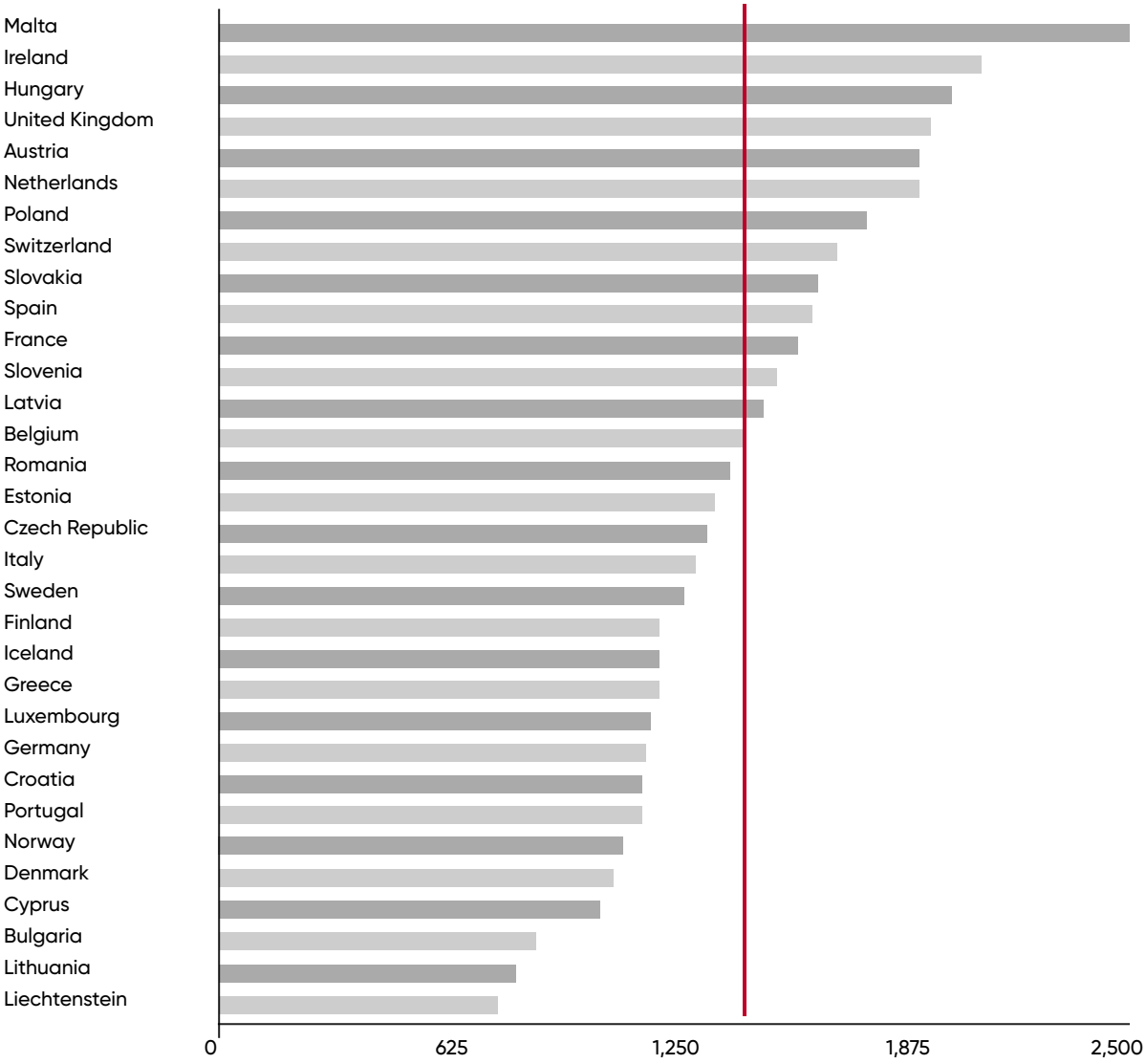


Fig. 3 Dentist : Population Ratio and EU average (red line)[60]

In 2016 there were about 21,600 licensed dentists in **Canada** which corresponds to a dentist to population ratio of 1:1,622 or 61.6 dentists per 100,000 people. However, the distribution of dentists varies widely by province.[14] 92% of the Canadian dentists work in general dentistry, 8% are specialists. Canadian dentists treat 11.3 patients in an average day.[21]

In **Brazil** there are about 274,000 registered dentists, with highest density in the capital region. This corresponds to a dentist to population ratio of 1:735 or 136 dentists per 100,000 people.[95]

Research in **China** reports 15 dentists per 100,000 Chinese in 2018 which corresponds to 209,300 dentists in the country and a dentist to population ratio of 1:6,666. About 20,000 dentists work in 750 stomatological hospitals.[89]

In **Japan**, the total number of dentists was 104,533 in 2016. The dentist ratio per 100,000 people was 82.4 practitioners. The average dentist to population ratio was 1:1,210, however in Tokio it amounted to 1:118. 85.3% of Japanese dentists work in private dental practices (as employer or employee) and there were 68,730 dental facilities (mainly private dental clinics) in total throughout Japan in 2016. About 90% of the 123,831 dental hygienists work in private dental clinics.[117]

8.2 Implant Health – The Dental Implant Market

The main concept for the dental implant market resolves around implant health, implant follow-up and dental implant check-up and services. The main customers in the dental implant market are implantologists, maxillofacial surgeons, oral surgeons, periodontists, and prosthodontists. The flagship product for this market is ImplantSafe® DR with the ORALyzer® automated lateral flow reader.

As Straumann AG describes it, the dental implant market offers considerable potential with main growth drivers like:[108]

- Demographics (growing need for tooth replacement in ageing population)
- Affordability (growing middle class in most countries)
- Treatment provision (more dentists are trained and confident to place implants)
- Awareness (patients are aware of negative effects of poor oral health)
- Esthetics (more people chose cosmetic treatments and esthetic tooth replacement).

Globally, an estimated number of 12-18 million implants are sold annually. The global market volume of placed implants is around 100 million implants that need regular prevention checkups and treatments to achieve sustainable implant health.[37]

The annual European dental implant market alone has been estimated at 5.5-6 million implants. Exact figures are not publicly available but *Klinge et al.* provide a possible trend for the dental implant market (Fig. 4).[56]

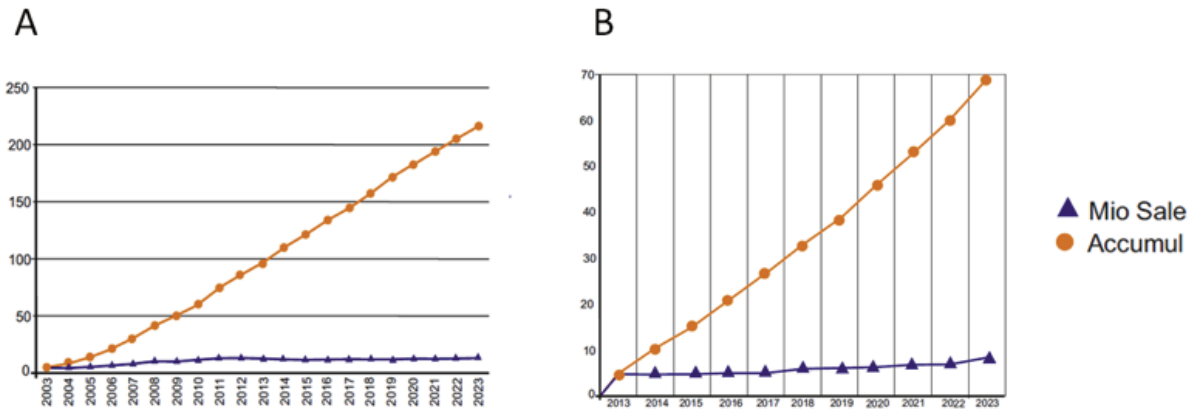


Fig. 4 Estimated figures for the annual sales (blue triangles) of dental implants at the Global (A) and European (B) market and accumulated (orange dots) total numbers of implants sold globally according to *Klinge et al.*[56]

Large market and business research firms periodically rate the size of the dental implant market. According to Grand View Research, the **global** dental implant market size was valued at USD 3.77 billion in 2016 with a forecasted compound annual growth rate (CAGR) of 7.7%. The largest market share was found in Europe followed by North America and the Asian Pacific.[34]

Three quarters of the dental implant market are controlled by only six leading companies. Straumann is number one with 25% market share. Their annual report estimates the global dental implant market at CHF 4 billion.[108]

The **European** dental implant market size was valued at USD 1,576.3 million in 2017 and is expected to increase with a compound annual growth rate of 4.1% from 2018 to 2024, according to Graphical Research.[35] The **German** dental implant market accounted for the largest market size of USD 289.6 million.35 Straumann AG estimates the dental implant penetration in Germany to 30%.[108]

Over three million people in the **USA** have dental implants and each year about 5 million implants are placed in the US.[7,34] The American Academy of Implant Dentistry estimated the dental implant and prosthetic market to reach USD 6.4 billion in 2018 and the dental implant market alone to reach USD 4.2 billion by the year 2022.[7] According to Straumann AG, more than 120 million Americans are missing at least one tooth but only 0.5 million are treated annually and only one in four medical eligible residents who seek treatment for tooth loss receive an implant (corresponding to 2.7 million dental implants).[108]

Presently, **Brazil** is the second largest market for dental implants in the world. According to the Brazilian Association of the Medical and Dental Equipment and Supplies Industry (ABIMO), 2.5 million implants are placed per year and the figure is expected to increase to 5 million by 2020.[32]

2.4 million **Japanese** had dental implants in 2011.92 In 2002, the Japanese market for dental implants was valued at almost USD 50 million with a CAGR of 10%. More than 20% of Japanese dentists were involved in at least one implant placement or restoration in 2002.[79]

The annual survey of the Dental Industry Association of **Canada** reveals implant-supported crowns, bridges, and dentures among the five most likely products to increase in frequency in the next years. Canadian dentists further indicate that 44% place implants themselves or plan to do so in the future and 56% have a specialist place their implants.[21]

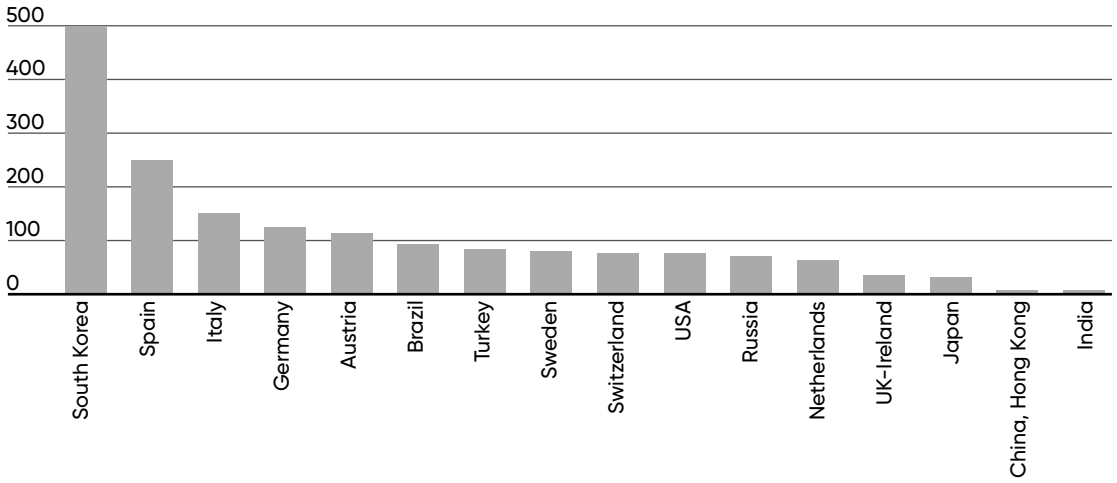


Fig. 5 Implant penetration: Patients treated annually (per 10,000 adult population) according to Annual Report 2018 by Straumann AG[108]

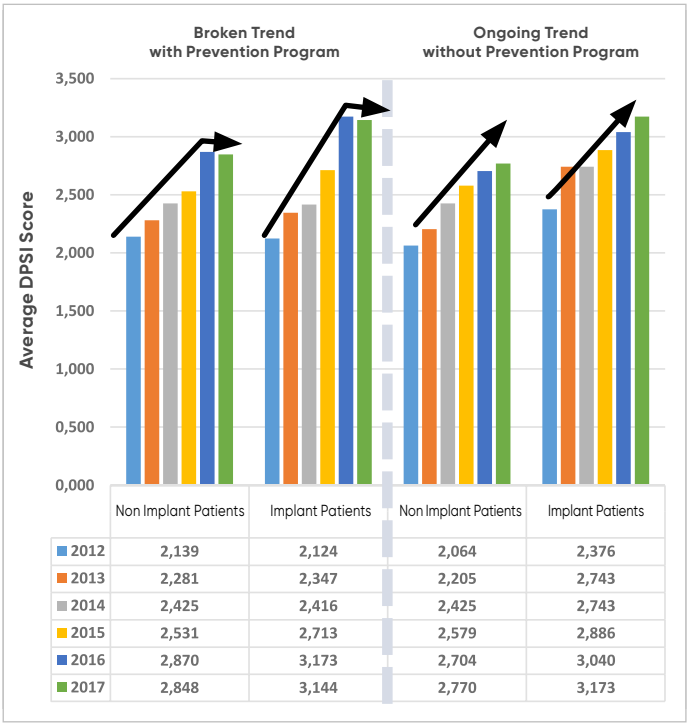
Straumann's chart shows that Spain and Italy are the largest markets in Europe. Dental implant penetration in highly populated countries like USA, UK, China, Japan, and India is below European average and shows a considerable growth potential for these countries in the coming years. Penetration in South Korea is exceptionally high, as reimbursement for tooth replacement was introduced for senior citizens in 2014. In most of the other countries tooth replacement is an out-of pocket expense.[108]

As shown in Figure 4, several hundred million patients worldwide have been provided with dental implants over the last decades (accumulated numbers). All these implants need check-ups on a regular basis to prevent peri-implantitis.

9 CLINICAL EFFECTIVENESS & RELEVANCE

9.1 Precision Medicine and Targeted Prevention

A recent study by van der *Schoor et al.* evaluates the clinical effectiveness of classic periodontal diagnostic assessment tools (Dutch Periodontal Screening Index, DPSI) and chairside aMMP-8 oral fluid biomarker analysis. Patients identified to have APD were guided to a secondary prevention program.[114]
Patients in the prevention program had a higher visit frequency and longer hygiene visits than control patients. Thus, practice hygiene revenues increased by up to 250%.



	Non Implant Patients	Implant Patients	Non Implant Patients	Implant Patients
2012	2,139	2,124	2,064	2,376
2013	2,281	2,347	2,205	2,743
2014	2,425	2,416	2,425	2,743
2015	2,531	2,713	2,579	2,886
2016	2,870	3,173	2,704	3,040
2017	2,848	3,144	2,770	3,173

Fig. 6 Development of DPSI scores in study patients with and without dental implants enrolled or not enrolled in the secondary prevention program over six years.[114]

In the study period the researchers compared DPSI periodontal screening scores, which were assessed once a year based on the common Dutch treatment standards, from 2012-2015, during which conventional dental hygiene was done, with scores from 2016-2017, during which aMMP-8 screening was done in combination with a targeted prevention program.

The goal of this study was to evaluated if clinical decision making can be based on aMMP-8 assessment and if periodontal and peri-implant disease development can be stopped or reduced by integrating aMMP-8 screening into the daily check-up routine.
Patients who tested positive for aMMP-8 were therefore grouped as “deterioration patients“ and were recommended to participate in a perio-prevention program (2-4 dental hygiene treatments plus individualized home care instructions).
The study investigated over 600 patients over a period of 6 years and was able to prove that the ongoing periodontal progression trend, which occurred despite the fact of regular DPSI inspections, could be broken with the new approach of early aMMP-8 activity detection in combination with targeted prevention treatments taking place over 24 months after the initial diagnosis.

This documents a highly significant improvement in the effectiveness of periodontal an peri-implant disease prevention by implementing aMMP-8 screening into the daily checkup routines of periodontal and peri-implant inspections. Due to the high prevalence of both disease types and the poor treatment outcome of late-stage treatment concepts, aMMP-8 is a recommendable biomarker for future integration into the new EFP/AAP classification for the early detection and prevention of periodontal and peri-implant disease (*van der Schoor, et al.*).

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dentognostics GmbH
Ober der Mühle 39 | 42699 Solingen | Germany
Tel +49 (0)212 645 747 9-31 | Fax +49 (0)212 645 747 9-10
info@dento.de | www.dentognostics.de

responsible for the content (p.3 to 22):
Institut für Empirische Gesundheitsökonomie
Prof. Dr. Dr. Reinhard P. T. Rychlik
Am Ziegelfeld 28 | 51399 Burscheid
Tel: +49(0)2174 7151-12 | Fax: +49(0)2174 7151-98