Periodontal Health Status Is Pivotal for an Effective Disease Prediction, Targeted Prevention and Personalised Treatments of Associated Pathologies

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1 Why Predictive, Preventive and Personalised Medicine Is Considered an Optimal Approach in Oral Cavity Healthcare?

Oral cavity health plays a key role in predicting and preventing periodontal and dental diseases which frequently cascade systemic effects such as chronic inflammation and associated pathologies [1–6]. Individualised patient profiling is instrumental for implementing 3PM strategies in periodontology and dentistry [7–9]. To this end, suboptimal health conditions demonstrating a reversible damage to health are in focus of primary healthcare promoting targeted prevention against health-to-disease transition that is pivotal for the cost-effective healthcare meeting needs of the society at large [5, 7, 10, 11].

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2 Periodontal Diseases Affect Majority of Adult Populations

Periodontal diseases (PDs) affects up to over 50% of populations in developed and developing countries worldwide. The entire age spectrum from adolescence to elderly is affected that makes PDs to a global challenge [12]. An extensive destruction of connective tissues of the periodontium and alveolar bone is characteristic for PDs and has been associated in a reciprocal manner with cascading systemic diseases including cardiovascular diseases, diabetes mellitus type 2 with complications, liver and chronic obstructive pulmonary diseases as well as several types of malignancies [13–15].

3 Risk Factors, Pathomechanisms and Systemic Effects of the Chronic Periodontitis

Chronic periodontitis (CP) is a bacterial inflammatory disease damaging oral cavity health and teeth structures [16, 17]. CP creates tremendous socio-economic burden to populations and requires in-depth understanding of risk factors and treatments tailored to the person [18]. Most prominent risk factors comprise both non-modifiable such as ageing and medication, and modifiable, i.e., preventable ones such diabetes mellitus type 2, inadequate oral hygiene and dental care, smoking, and stress overload [8]. Individually and synergistically the risks promote CP development [12]. Proposed pathmechanisms are based on bacteraemia and systemic inflammation indicated by elevated C-reactive protein patterns and highly increased oxidative stress [3, 15]. Despite local symptoms of the CP, inflammatory mediators produced as well as subgingival species and shifted microbiome become spread systemically leading to cascading extra-oral pathological changes at molecular, cellular, and organ levels [19]. To this end, CP associated carcinogenesis is relevant for both – the oral cavity and extra-oral sites typical for the orodigestive cancers extended to the oral, oesophageal, gastric, colorectal, and pancreatic malignancies [19]. There is an evident reciprocal relationship between CP development and severe systemic diseases which an altered microbiome and chronic inflammation are relevant for [3, 8, 15, 20]. For example, CP significantly increases risks of cardiovascular complications and concomitant mortality in the diabetic patient cohort, while diabetic history is in turn a well-acknowledged risk factor of CP [19]. Clinically established CP has been, further, associated with maternal infections, foetal growth restriction, preterm birth, and strong predisposition to preeclampsia—all demonstrated as life-long health risks of mother and offspring [11].

4 Patient Stratification Is a Multi-Factorial Approach in Periodontology

Our recent study performed at the Periodontology Department, Pavlov First Saint Petersburg State Medical University, has analysed prevalence of chronic disorders in the age-stratified patient groups such as diabetes mellitus type 2, cardiovascular

and gastrointestinal diseases, chronic kidney and liver diseases, amongst others. High prevalence of collateral pathologies has been demonstrated for patients diagnosed with periodontitis: 87.5% in the age group between 61 and 75 years old followed by 75.8% in the age group between 45 and 60 years old.

Age is a multi-faceted determinant for the patient stratification and tailored 3 PM strategies.

An important aspect is the age-specific behavioural patterns towards healthcare measures, offered services, their duration, quality, and costs. From this point of view, elderly is associated with challenging care and strong socio-economical limitations. Contextually, highly specific medical, mental, social, and financial aspects should be carefully considered for this sub-population optimally meeting its needs [21–26]. Essential expertise carries a multi-professional character including geriatrics and gerontology preventing oral dryness / dry mouth syndrome, tongue-lip motor, masticatory and swallowing dysfunction – all together leading to the oral hypofunction which is characteristic for elderly and other vulnerable groups in the population [27–29].

5 Challenges of Participatory Medicine

Inadequate periodontal health services provided to the population may be caused by several deficits such as insufficient awareness of corresponding impacts in affected subpopulations and subpopulations in suboptimal health conditions, low educational level with consequent ignorance towards the periodontal health, low socio-economic status of affected individuals, lack of the relevant insurance, insufficient density of specialised medical units, amongst others [8, 30, 31]. Contextually, to raise awareness towards periodontal health and corresponding services is pivotal to advance health quality in the population [8, 32, 33]. This is the task for participatory medicine focused on the active participation of populations in maintaining satisfactory health status. Promoting participatory medicine in the population, generally it should be kept in mind that healthcare remains unsatisfactory as long as the patient does not feel responsible for their health condition [34]. This conclusion can be well exemplified by chronically diseased patients observed in periodontology [8].

6 Virome–Microbiome Axis: A Vicious Circle in Disease Promotion

An association between periodontal diseases, viral and bacterial overload with poor outcomes is clearly demonstrated in several studies [27, 35]. The human body hosts vast microbial and viral communities collectively termed "**microbiome"** and "**virome,**" respectively. The human virome is complex consisting of about 10^{13} particles per individual [36]. Both human virome and microbiome are highly heterogeneous. Depending on individual profiles of microbial and viral communities, they can be associated with adverse outcomes for the human host, whereas other states are characteristic of health. Furthermore, there are evident synergies in the host–virome–microbiome interactions in health and disease. To this end, during the past influenza outbreaks, such as influenza in 1918, H1N1 influenza in 2009 these

interactions have been demonstrated for the respiratory viruses, in turn associated with bacterial superinfections as the main risk of a severe disease course and death [37]. Periodontopathic microfora is implicated in systemic microbiome composition alterations promoting chronic inflammation, systemic health-to-disease transition leading to sepsis, pneumonia development, and death. The dual antiviral and antibiotic medication is considered optimal to protect human body against pathologic shift in the virome–microbiome axis leading to the vicious circle in disease promotion.

7 Periodontal Disease as the Clue to the COVID-19-Associated Poor Outcomes

Clear association has been demonstrated between clinically manifested periodontitis in COVID-19 infected patients and high risk of their admission to intensive care units and related death [28]. The absolute majority of the affected patients exhibited bacterial superinfections and severe disease course as demonstrated in the UK study of COVID-19-infected individuals [27]. Patients with poor COVID-19 outcomes demonstrated high levels of periodontopathic bacteria communities comprising Prevotella, Staphylococcus, and Fusobacterium. For 80% of patients treated at intensive care units, a particularly high periodontal bacterial was characteristic. Noteworthy, advanced age, diabetes mellitus, and cardiovascular diseases are frequently associated with both poor periodontal health and poor outcomes of the COVID-19 infection. In common are significantly shifted virome–microbiome profiles and systemic inflammation [29]. Suggested pathomechanisms include virome–microbiome–host interactions in the respiratory and gastrointestinal tracts [37]. On the molecular level, the overexpression of angiotensin-converting enzyme 2—the receptor for SARS-CoV-2—and production of inflammatory cytokines in the lower respiratory tract are characteristic for poor outcomes in COVID-19 infected individuals. To this end, an aspiration of periodontopathic bacteria induces the angiotensin-converting enzyme 2 actively contributing therefore to the cytokine storm typical for the COVID-19 aggravation and associated severe disease course [38]. Contextually, periodontal health is crucial for the cost-effective primary prevention, improved individual outcomes, and reduced morbidity under pandemic conditions [27, 39]. Application of oral probiotics is strongly recommended to stabilise the gut–lung axis and health microflora [40].

8 Individualised Patient Profiling: Risk Factors and Big Data Analyses Exemplified by "Dry Mouth" Syndrome Phenotype

Implementation of individualised patient profiles (IPP) is strongly recommended for protective periodontal care. Phenotyping and genotyping are instrumental for IPP and demand big data analysis comprising non-modifiable (e.g., genetic

predisposition) and modifiable risk factors such as behavioural and dietary habits. Relevant surveys have been developed, for example, to identify individuals with the dry mouth syndrome phenotype. To this end, dry mouth syndrome is highly relevant for xerostomia-associated disorders such as periodontitis and systemic inflammation predisposition to which can be detected early in life [4]. Predisposition to xerostomia in otherwise healthy young individuals can be further associated with the stress overload that is well detectable using non-sophisticated health risk assessment tools [5] followed by the targeted primary prevention [5, 41–44]. Health risk assessment under stress condition is further discussed by Golubnitschaja O. in the book chapter dedicated to the mitochondrial health.

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