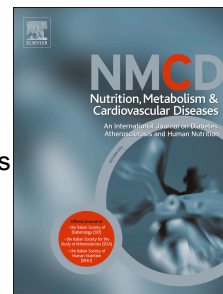


Journal Pre-proof

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PII: S0939-4753(21)00215-5

DOI: <https://doi.org/10.1016/j.numecd.2021.04.022>

Reference: NUMECD 2673

To appear in: *Nutrition, Metabolism and Cardiovascular Diseases*

Received Date: 4 February 2021

Revised Date: 19 April 2021

Accepted Date: 24 April 2021

Please cite this article as: Codella R, Della Guardia L, Terruzzi I, Solini A, Folli F, Varoni E, Carrassi A, Luzi L, Physical activity as a proxy to ameliorate inflammation in patients with type 2 diabetes and periodontal disease at high cardiovascular risk, *Nutrition, Metabolism and Cardiovascular Diseases*, <https://doi.org/10.1016/j.numecd.2021.04.022>.

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- Viewpoint -

Physical activity as a proxy to ameliorate inflammation in patients with type 2 diabetes and periodontal disease at high cardiovascular risk

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Manuscript counts:

Abstract	144 (words)
Body text	4 347 (words)
References	97
Tables	1
Figures	4

Running head: *Diabetes, periodontitis and physical activity*

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Abstract

While the beneficial impact of physical activity has been ascertained in a variety of pathological scenarios, including diabetes and low-grade systemic inflammation, its potential remains still putative for periodontal health. Periodontal disease has been associated with inflammatory systemic alterations, which share a common denominator with type 2 diabetes mellitus and cardiovascular disease. Physical exercise, along with nutritional counseling, is a cornerstone in the treatment and prevention of type 2 diabetes, also able to reduce the prevalence of periodontal disease and cardiovascular risk. In addition, considering the higher incidence of periodontitis in patients with type 2 diabetes compared to healthy controls, the fascinating research question would be whether physical activity could relieve the inflammatory pressure exerted by the combination of these two diseases. This multi-disciplinary viewpoint discusses available literature in order to argue the hypothesis of a “three-way relationship” linking diabetes, periodontitis, and physical activity.

Keywords:

Exercise, glycemic control, oral health, cytokines, insulin resistance, metabolism, skeletal muscle.

Abbreviations:

AGEs, advanced glycation end-products; BDNF, brain-derived neurotrophic factors; BOP, bleeding on probing; CRP, C-reactive protein; CV, cardiovascular; FFAs, Free fatty acids; HbA_{1c}, glycosylated hemoglobin; HFD: high fat diet; IL, interleukin; MIP macrophage inflammatory protein-1 α ; PA: Physical Activity; PD: Periodontitis; RAGE, Receptor of advanced glycation end-products; RANKL: Receptor Activator of Nuclear Factor κ B; RCT, Randomized controlled trial; T2D, type 2 diabetes; TNF α , tumor necrosis factor; TLR, toll-like receptor.

1. Introduction

Since 1990s, periodontitis (PD) has been described as the sixth complication of diabetes [1]. Meaningfully, type 2 diabetes mellitus (T2D) has been recognized as the chronic systemic disease with the most frequently observed correlations with PD [1]. The risk of developing PD is increased by 2-3 times in T2D subjects with respect to healthy individuals [2]. In addition, an unhealthy nutritional behavior favors both PD and T2D, which is often associated with obesity.

T2D is well known for inducing multiple damages to several organs and tissues through chronic hyperglycemia, thus representing the *primum movens* leading to the development of long-term complications. All T2D patients have a moderate to high cardiovascular (CV) risk. Emerging evidence suggests that T2D and PD may have a reciprocal detrimental impact on the other, constituting a significant public health challenge [3, 4]. Especially in the presence of impaired metabolic control, T2D yields a biochemical and microbiological *milieu* predisposing to PD development. A large number of studies have highlighted the occurrence of a shared pathogenic process linking T2D and PD [1]. T2D is characterized by an overproduction of pro-inflammatory molecules such as advanced glycation end-products (AGEs) interleukin-1 β (IL-1 β), tumor necrosis factor- α (TNF α), and interleukin-6 (IL-6), which constitute the background inflammatory setting, potentially linking the two conditions [1-3].

Periodontal disease (PD) encompasses one or more damages in periodontal supporting tissues: gingiva, periodontal ligament, and alveolar bone. It is characterized by a periodontal tissue breakdown mainly determined by the immune-inflammatory host response (subgingival microbiota) to the attack of the pathogens contained in the subgingival biofilm [5]. In poorly controlled T2D, when glucose accumulates in the gingival crevicular fluid, an imbalance in oral bacteria and cito/chemokines is documented [6]. Subjects with scarcely

controlled T2D and chronic PD showed higher concentrations of cyto/chemokines such as macrophage inflammatory protein-1a (MIP-1 α), IL-1 β , IL-6, IL-12, TNF α , with respect to non-diabetic controls with PD, at both diseased and healthy periodontal sites [7, 8].

The risk of developing PD was shown to be higher for increased levels of glycosylated hemoglobin (HbA1c) and fasting glucose, in individuals with or without T2D. In non-diabetic subjects, severe PD is associated with a greater risk of developing T2D with respect to periodontally healthy controls [9]. In subjects with T2D, PD is associated with severity of diabetic complications [10]. Generally, when treatment is provided to either of the two diseases, the benefits are reciprocally gained. A number of controlled trials demonstrated that periodontal therapy (even simple hygienic measures like a mouthwash) can reduce HbA1c in patients with T2D, therefore improving metabolic control [11-13].

The improvement of nutritional habits of T2D patients (e.g. hypocaloric and low-fat diet or dietary regimens rich in anti-oxidant foods or nutraceuticals with anti-oxidant/anti-inflammatory properties) determines a clinical improvement of periodontitis [14]. Interestingly, the inflammatory picture common to T2D and PD can be outweighed also by physical exercise. Physical activity (PA) is claimed as cornerstone strategy in the prevention and treatment of T2D, as well as other clinical conditions linked to the metabolic syndrome like hypertension and dyslipidemia. The anti-inflammatory effects of exercise can be effective even in PD, for which a protective health behavior ensured by regular PA might reflect better general health as well as a better periodontal health [15]. Although a clear relationship between physical activity and PD has not been clearly ascertained, several lines of evidence suggest a potential protective role, mainly anti-inflammatory, exerted by physical exercise. In fact, PA might positively interact with systemic inflammatory diseases by modulating immune markers. These immunomodulatory mechanisms of exercise have been extensively described [16]. Amongst others, practicing regular PA has been associated with

favorable changes in inflammatory markers; for instance, the reduction of Protein C reactive levels [17,18]. The increased expression of this protein has been documented in a variety of diseases, including PD [19].

Oral hygiene, periodontal- and nutritional/metabolic treatments ameliorate T2D and PD, and exercise could be an important additional driver capable to positively act on both conditions. The present viewpoint challenges a “three-way hypothesis” in which exercise promotes an anti-inflammatory activity able to potentially ameliorate clinical outcomes of PD and T2D, in co-existence.

2. Periodontal disease: definition and epidemiology.

Periodontal health is characterized by the absence of inflammatory changes of the periodontal tissues [20]. Absence of inflammation characterizes the periodontal tissues before the disease commences or once the periodontal disease has been treated and the inflammation is under control. In periodontal health conditions, the gingival tissues adhere to the tooth at the level of the enamel-cementum junction with an epithelial and a connective attachment, and the root of the tooth is completely surrounded by the alveolar bone (Figure 1).

The term periodontal disease includes a group of inflammatory, chronic conditions affecting the tissues surrounding the teeth and is caused by gram-negative bacteria and the effects of host-parasite interaction products [21]. PD is characterized by inflammation, loss of the alveolar bone and migration of the attachment of the soft tissues in the apical direction leading to the formation of the so-called "Periodontal Pocket". The disease is chronic, affecting 45-50% of adults in its mildest form and approximately 10% of the global population in its severe form [10,22]. If left untreated, it leads to tooth loss (Figure

2). PD is considered a major health problem worldwide, being the sixth most common, non-communicable disease [23]. A recent study, conducted in the USA on a sample of 10,683 adults aged between 30 and 79, indicates that periodontal disease affects 42.2% of the population and 34% of cases are severe [24]. Severe PD, therefore, represents a significant healthcare, social, and economic problem.

3. T2D and PD are mutually reinforcing conditions

A growing body of evidence suggests the existence of a two-way relationship: chronic PD appears to negatively affect glycemic control, while T2D increases the risk for development and progression of PD [25].

3.1 PD affects glycemic control

Periodontal inflammation may adversely impact on glucose homeostasis, thus fueling the onset/progression of T2D-affected subjects [2,26]. PD was shown to increase the mortality rate in T2D subjects [27]. Incidence of PD has been associated with poorer glycemic control in people with T2D and increased risk of complications [27]; yet, PD rises in parallel to HbA1c levels [28]. The presence of early-glomerular dysfunction and end-stage renal failure is doubled in T2D individuals carrying severe PD [20]. Reduction in periodontal inflammation has been associated with decreased inflammation and improved vascular function and metabolic markers [11-13]. A number of studies [11,12,29] have investigated the effect elicited by PD treatment on glycemic control in T2D-subjects and HbA1c decreased by 0.3–0.4 percentage points. D’Aiuto et al. showed that, following a 12-month periodontal treatment, metabolic control improved in T2D patients compared to controls [11]. Reductions in HbA1c and fasting plasma glucose concentrations were accompanied by

improved vascular and kidney function and reduced systemic inflammation. Similarly, Sun and colleagues [12], in a RCT on 157 patients affected by T2D and PD, reported a small yet significant reduction in in the HbA1c concentration (0.4%), fasting plasma glucose (9.83 vs 8.66 mmol/L) and HOMA-IR (5.06 vs 3.92), after 3 months of PD treatment. A systematic review of Simpson et al. showed that patients treated for PD gained an overall reduction in HbA1c of ~ 0.4% [9]. Consistently, other meta-analyses [30,31] exhibited the positive effects of periodontal treatment on glycemic control in T2D patients with at least 3-months follow-up.

3.2 T2D enhances PD onset and severity

The prevalence of PD in T2D subjects is estimated to be even triple than in normal population, and the risk for PD increases as glycemic control worsens [2,25]. Increasing evidence suggests that systemic metabolic alteration due to T2D may foster gingival inflammatory response in case of ongoing PD, which would partly account for the greater susceptibility of T2D subjects to PD breakdown [2,26]. In this respect, increased concentration of IL-1 β (i.e. a bone-resorptive cytokine, which mediates soft-tissue destruction) was detected in gingival fluid [8]. Moreover, both IL-1 β and IL-6 resulted higher in gingival biopsies of subjects affected by both PD and T2D with respect to subjects with PD only [32]. Poor glycemic control in T2D subjects has been associated with higher concentration in periodontal area of oral pathogens: this condition is likely susceptible to the onset or worsening of chronic PD [22]. On the other hand, the tighter glucose control in T2D patients with PD was able to improve gingival status by mitigating chronic inflammation at the gingival sites [33].

4. Inflammation links T2D and PD

Although the underlying mechanisms linking T2D and PD are undetermined, they are prone to implicate an expected immune response, microbiota deregulation and cytokine signaling [25]. Indeed, similarly to PD, T2D is currently regarded as a chronic dysmetabolic disease highly influenced by the low-grade systemic inflammatory status [34], hence inflammation pertains both conditions as a common, key pathogenetic element (Figure 3).

4.1 T2D-related pro-inflammatory status boosts PD

A significant increase in circulating and local pro-inflammatory mediators (i.e., IL-6, TNF α and IL-12) [35] is often seen in T2D subjects, compared to healthy controls. Experiments in animal models and clinical studies suggest that IL-1 β , TNF α , IL-6, are implicated in PD development/progression in T2D-subjects [11,25]. Low-grade inflammation, which is frequently observed in T2D-overweight patients, is thought to be instrumental for the development of insulin resistance and glycemic impairment [36,37]. Obesity itself has been associated with the development and worsening of local inflammatory response in PD [25], suggesting that the low-grade inflammation and the systemic metabolic adaptations imposed by obesity possibly act as independent variables enhancing PD inflammation. Zimmermann et al.[38] showed that chronic PD lowers adiponectin (an adipocyte-derived insulin sensitizer, anti-inflammatory adipokine) levels, and that obese subjects presented higher levels of TNF α at periodontal sites, irrespectively of the local inflammatory condition. Moreover, circulating IL-6 was found to be elevated in obese individuals with PD compared to non-obese controls [38]. Circulating pro-inflammatory mediators, secreted by dysfunctional adipose tissue, impair insulin signaling by inflaming tissues critical for glucose regulation [39]. Lifestyle interventions and/or drug therapy (i.e.,

interleukin-1 antagonists) blunt inflammation, improve insulin secretion and insulin sensitivity and decrease glycemia in T2D subjects [40,41]. Individuals with T2D with coexisting chronic PD showed higher systemic inflammation at periodontal sites compared to non-diabetic controls [6]. TNF α plays a critical role in the genesis of systemic insulin resistance [42] and the severity of PD was shown to correlate with systemic levels of TNF α in patients with T2D [43]. In the study of D'Aiuto et al. [11], a similar correlational pattern regarded reductions in: i) markers of systemic inflammation (namely, CRP and TNF α); ii) periodontal inflammatory parameters (probing pocket depths, number of deeper periodontal pockets, and gingival bleeding); iii) systemic cardio-metabolic responses; iv) kidney function. Altogether, these data would pinpoint at inflammation as a key mediator of the binomial T2D-PD relationship.

Free fatty acids (FFAs) are typically higher in obesity as well as in T2D due to altered response of adipose tissue to insulin stimulation [39]. The continuous spillage of FFAs is currently seen as a possible factor influencing periodontal inflammation [44]. Further, the interaction of AGEs with their receptor (RAGEs) is another factor likely involved in the common pathophysiological framework of PD in T2D [2]. Persistent hyperglycemia is responsible for an increased rate of AGEs formation. AGEs fuel the ignition of cellular oxidative stress and pro-inflammatory pathways, through the bond of RAGEs on different cell types like endothelial-, immune- and bone-forming cells. The AGE-RAGEs axis sets the stage for the alveolar bone reabsorption and on-site chronic inflammation [45]. Interestingly, AGE proteins were found in saliva of T2D-patients and follow dental plaque levels [46]. Also, serum AGEs levels demonstrated to be proportional to the severity of PD in individuals with T2D [47].

Low grade-inflammation is likely to deregulate the ecosystem of microbial gingival biofilm, possibly promoting pathogen adhesion [48]. Th17-released IL-17 plays a

pivotal role in sustaining low-grade inflammation and insulin resistance [49]. In T2D-rodents, treatment with IL-17 antibody decreased the pathogenicity of the oral microbiota. Specifically, the oral microbiota transplant from IL-17-treated donors to germ-free animals, reduced IL-6 in gingival tissue, RANKL (key-factor for osteoclast activation) and bone resorption in the recipients [50]. Finally, the higher lipopolysaccharide (LPS) translocation from the intestinal lumen into circulation, as observed in case of obesity and metabolic syndrome [51], can be further implicated in the rise of periodontal inflammation, as demonstrated in animal models [52].

4.2 PD enhances sub-inflammation and hyperglycemia

In patients with PD, increased levels of CRP and IL-6 are associated with T2D and other cardiovascular conditions [19]. Circulating CRP, TNF α , IL-6 were shown to significantly decrease after 3 months of periodontal treatment [12]. Recent findings suggest that oral microbiome may help maintain systemic health and blood glucose levels, while certain bacterial *taxa* are associated with a higher risk of developing T2D [53]. PD is characterized by the alteration of the polymicrobial biofilm [48] and periodontal infection with gram-negative microorganisms probably affects systemic glyceemic balance [2,26]. In patients with both PD and T2D, glyceemic control is potentially influenced by the adherence to oral mucosa of *Porphyromonas gingivalis*, [54], which has been demonstrated to be a potent inducer of cytokine production (namely IL-1 β , IL-8, IL-12 and TNF α) [55]. LPS of oral pathogens can represent a trigger for initiating mouth inflammation in subjects with PD. LPS leakage, facilitated by high permeability of oral mucosa during PD, may be modulating the inflammatory status via TLR4/nf-KB pathway [56]. As such, also proinflammatory cytokines (IL-6, TNF α , IL-12) originated from the interaction of oral mucosa with PD-pathogens (*P. gingivalis*, *Bacteroides forsythus*, *Streptococcus mutans*) can translocate into

the bloodstream along with endotoxins and oxidized lipids. In fact, this cytokine cascade is possibly implicated in the systemic low-grade inflammation and peripheral insulin-resistance [57].

4.3 PD and cardiovascular disease

The systemic subclinical inflammation triggered and/or perpetuated by PD is regarded as common soil for the increased CV risk profile shown by these individuals, irrespective of the presence of other comorbidities like T2D or hypertension [58,59]. The presence of PD and tooth loss has been strongly associated with peripheral artery disease, stroke and myocardial infarction, with a predictive value on such severe conditions [60, 61], and oral pathogens have been repeatedly identified in target tissues and organs, including atherosclerotic plaques [62]. Intriguingly, after years of elusive evidence of a beneficial effect of PD treatment on CVD risk or progression, recent strong results, also coming from randomized clinical trials, support such concept: for example, treatment of PD is able to lower blood pressure values [63], and a better oral hygiene has reduced occurrence of stroke [64]. Such evidence reinforces the indication for an accurate screening and an early treatment of PD aimed at reducing CV morbidity and mortality.

5. The impact of exercise on the common inflammatory *milieu*

Exercise is an effective countermeasure against aging-associated muscle wasting. It can relieve systemic markers of oxidative stress and immune-mediated inflammation [65,66,67]. Daily PA was shown to decrease molecules critical for controlling inflammatory pathways in peripheral tissues, such as nuclear factor- κ B. Moderate-intensity exercise also diminishes systemic oxidative stress, as testified by: a) the decrease in plasma

malondialdehyde of *Advanced Oxidation Protein* [68,69]; b) the activation of leukocyte-induced oxidative burst owing to reduced NADPH-oxidase activity and p47phox expression (NADPH functional site) in animals [68], and healthy and diabetic humans [70].

5.1 Exercise modulates metabolic status and inflammation

The beneficial effect of PA has been established in a variety of pathological scenarios, including T2D [35]. Exercise improves adipose tissue function [35], glycemic control and insulin sensitivity via boosting mitochondrial efficiency, glucose uptake, intramyocellular fatty acid oxidation [35] and by exerting an overall anti-inflammatory activity [71] (Figure 4). A single bout of exercise was sufficient to increase skeletal muscle glucose uptake for several hours, and regular training improved whole-body glucose metabolism and insulin levels in diabetics [72]. In T2D subjects, metabolic improvements can occur independently of changes in body composition, suggesting that adaptation of myocytes to exercise accounts for the greatest part of the metabolic gain obtained [73]. PA was associated with significant reduction in low-grade systemic inflammation [74], circulating leukocytes [61], and it is currently seen as a viable strategy to improve metabolic status in chronic inflammatory diseases and cardio-vascular inflammation [75,76]. Muscles of untrained T2D individuals show lower insulin sensitivity, lipotoxicity-related features and release an array of diabetogenic mediators (TNF α , IL-1), therefore feeding insulin resistance [35]. Conversely, well-conditioned muscles are responsible for the majority of insulin-stimulated glucose disposal and secrete an array of mediators and myokines (IL-10) with anti-diabetic and anti-inflammatory function [77]. Exercise training was found to effectively reduce IL-6, CRP, and IL-18 in a group of T2D subjects [78]. Physical exercise activates anti-inflammatory molecules like IL-1receptor antagonist, IL-10, and soluble TNF-Receptor [35, 76, 77]. An acute bout of exercise produces a strong anti-inflammatory effect,

suppressing TNF α and stimulating the upregulating IL-1 receptor antagonist and IL-10 [79]. IL-10 exerts an anti-inflammatory activity by inhibiting the secretion of pro-inflammatory cytokines and the expression of MHC-II in immune cells [79]. Muscle-derived IL-15 and Brain-derived neurotrophic factors (BDNF) are involved in the regulation of lipid metabolism, visceral fat deposition and fatty acid oxidation [35,79]. Further, exercise indirectly ameliorates immuno-metabolic setting by reducing adipose tissue mass and the adipose-tissue-related pro-inflammatory secretome [28, 72]. The increased uptake and oxidation of circulating FFAs during exercise also contribute to reduce muscle and liver inflammation, and insulin resistance [35]. Lastly, regular exercise was shown to efficiently decrease AGEs in obese-diabetic animal models [68,79] and in humans [80]. AGEs production is mainly triggered by hyperglycemia and oxidative stress, and contributes to increase organ-specific and systemic inflammation [81]. Exercise-induced higher energy demands may lessen reactive intermediates of glycolytic (i.e. glucose-6-phosphate; fructose-6-phosphate) and polyol (eg, fructose-3-phosphate, 3- deoxyglucosone) pathways, which constitute powerful glycating species [69, 80]. The decrease in inflammation and a greater oxidation rate of these intermediates during physical activity can account for the exercise-associated reduction in plasma- and tissue AGEs.

5.2 Exercise improves PD outcomes

Available findings indicate that PA is associated with reduced prevalence of PD [82]. Subjects with higher maximal oxygen consumption (VO₂max) were found to have less chance of developing PD [83]. In a prospective study, the number of teeth with a probing pocket depth \geq 4 mm and teeth with bleeding on probing (BOP), significantly decreased following exercise (respectively from 14.4% to 5.6%, and from 39.8% to 14.4%). Merchant et al. [84] reported that individuals with higher levels of routine PA have a lower relative risk

of developing PD. Similar results were obtained in other studies [15,84,85] reporting consistent reductions in PD prevalence. Individuals engaging in weekly sessions of PA (3-5 times/week) presented lower prevalence of PD in comparison to controls [15,84]. In the study of Sander et al.[86], PA was capable to significantly reduce IL-1 β and CPR concentrations in gingival fluid in a large cohort of PD-affected individuals. The reduction of AGEs [69] and the mitigation of local and systemic inflammatory status achieved through the practice of regular moderate-intensity exercise is likely to account, to a large extent, for the exercise-associated improvements observed in PD subjects [18,86]. Part of the mechanisms by which exercise would provide benefits to PD can be possibly ascribed to the favorable modulation of oral bacteria through promoting changes in the acid/base balance of the oral *milieu* [87]. The copy counts of *Tannerella forsythia* and *Treponema denticola* (pathogens implicated in PD onset) decreased significantly after exercise intervention in a group of obese individuals [88]. Exercise may also reduce the risk of infections by increasing salivary cystatins levels, which seem to inhibit bacterial growth and bacterial adhesion to oral mucosa [89]. Alternatively, via increasing circulating lactate, exercise is likely to stimulate changes in the composition and activity of the oral microbiome, as demonstrated in the gut [90].

6. A possibility for a three-way relationship linking T2D, PD and physical activity

PD can be either seen as a T2D complication as well as a concurring factor to T2D progression, since PD can fuel systemic inflammation (Figure 4). An epidemiological analysis on 60 adults showed that individuals with the higher PA level and lower adiposity presented a better oral health status [83]. The cross-sectional study of Merchants et al. showed that, for higher degrees of PA (estimated in METs), the prevalence of PD and T2D lowers as well as BMI does, suggesting that the improvement of PD, following PA, comes

along with the improvement of systemic dysmetabolic setting [84]. According to our literature analysis, evidence concerning exercise trials on the positive modulation of the PD progression in T2D subjects, remains limited. In a 3-month trial on T2D- subjects, recommendations on healthy lifestyle, oral hygiene and PA performed 3 times/ week improved markers of oral health (pocket depth, clinical attachment level, and percentage of site with BOP) and metabolic control (HbA_{1c}, fasting glycemia) as compared to controls [91]. Similarly, in obese subjects with borderline fasting glycemia, regular exercise led to an improvement in oral markers of PD (probing pocket depth and BOP), coupled with a slight decrease in fasting glucose and serum insulin level [88]. When subjected to exercise training (60 min/day for 8 weeks), HFD-fed rats with streptozotocin-induced diabetes and surgically-induced PD, showed decreased alveolar bone loss, lower plasma glucose, HbA_{1c} with respect to non-trained controls [92]. In that study, PA was shown to lower both TNF α and IL-6, while increasing IL-10 concentration [92]. This study confirms the efficacious anti-inflammatory activity elicited by exercise on the binomial PD-T2D relationship.

Therefore, although evidence is still embryonic, literature guarantees a number of clues that are suggestive for a potential therapeutic PA role to blunt PD in subjects with T2D, through modulating the common sub-inflammatory background (Table 1).

As a concluding remark, intensity, volume and frequency of exercise are important determinants to maximize the beneficial effects of PA [16]. Merchants et al. observed an inverse association with PD in the highest quintiles of PA, suggesting that the greater benefit of PA may correlate with exercise intensity [84]. In T2D subjects, both endurance and resistance exercise are equally effective in controlling metabolic status. Similarly, engaging in high-intensity interval training (short) or low-intensity continuous (long-duration) training [79] may lead to favorable metabolic outcomes. Since in special subclasses of individuals with T2D (e.g. obese, subjects with complications) high intensity

exercise is not always advisable, engaging into a moderate-intensity, regular exercise (at least 3 times/week) [82] could be a reasonable strategy for mitigating inflammatory status and improving PD outcomes in T2D subjects.

7. Conclusions

We attempted to draw a plausible framework in order to legitimate physical exercise as adjunctive therapeutical mean to ameliorate periodontal inflammation in T2D. According to available data, T2D and PD are likely mutually reinforcing diseases, sharing common pathogenetic mechanisms. A complex interplay of pro-inflammatory intermediates exacerbates both diseases, affecting their clinical outcomes. Exercise has been shown to lower glycemia and the incidence of T2D complication, as well as to control systemic inflammation, efficaciously. On the other side, exercise was shown to potentially curb local inflammation in PD, and embryonic interventional evidence pinpointed at alleviating effects on both pathological conditions. Although the paucity of evidence makes this topic still an open question, to the best of our knowledge, sufficient elements emphasize the potential protective and the adjuvant therapeutic role of PA in the management of PD in T2D individuals. *Ad hoc* clinical trials are warranted to investigate the “three-way” relationship in order to directly test the model proposed. Attention should be drawn to further evaluate the modulation of oral microbiota, biochemical markers, circulating and periodontal pro-inflammatory mediators (IL-1 β , IL-6, TNF α , FFAs), in individuals with co-existing morbidities. Future investigations are encouraged to address the optimal amount of PA bearing tailored benefits with clear-cut clinical relevance in T2D patients with moderate-to-high CV risk. In theory, any kind of PA routine eliciting an anti-inflammatory pattern is capable to reduce the prevalence of PD. Thus, regularity of PA may be necessary to improve

periodontal condition and to reduce signs and symptoms brought by pro-inflammatory cytokines [82]. We therefore encourage to fulfill the WHO guidelines for recommended doses of physical activity in the general population in order to benefit from exercise-induced protective health behaviors, even on a periodontal health standpoint. One-hundred and fifty minutes of moderate-vigorous intensity (aerobic or mixed) PA should be weekly pursued. Individuals maintaining body weight, consuming high-quality diet, and practicing regular PA, might have better general health as well as a better periodontal health.

8. Take Home message: more interactions between medicine and dentistry are needed!

The study of the relationship between periodontitis and extra-oral diseases has brought increasing attention to the need for greater integration between the field of medicine in a broad sense and that of dentistry. The Report of the Surgeon General in 2000 stated that *"Oral Health and general health should not be interpreted as separate entities oral health is a critical component of health and must be included in the provision of health care and the design of community program "* [93]. It is particularly appropriate to integrate oral health within the wider area of public health and to promote greater collaboration between doctors, dentists, dental hygienists, nurses and other health professionals. Concerning T2D, this disease can be an example of the usefulness of greater collaboration between doctor and dentist. Numerous studies have shown how the dental setting can be congenial to a preliminary diagnosis of prediabetes or diabetes, not only in subjects with PD [94], but more generally in subjects with risk factors for this condition [95,96]. Dental chair-side screening of HbA1c level in patients unaware of their glycaemic status is a cost-effectiveness means of identifying unrecognized dysglycemic individuals [97]. Dentists should be aware that they can contribute to the general well-being of their patients by chair-side targeted screening for

medical conditions such as hypertension, dysglycemia or obesity. The training of the dentists should, therefore, prepare them to be patient-centred or healthy-centred rather than disease-centred.

Oral health is much more than healthy teeth and gums, and oral tissues are fundamental for several key physiological and psychosocial functions. A greater doctors' attention to their patients' oral health and a greater collaboration with the dentist can prove extremely useful in the control of diseases of the mouth. Consequently, this tight teamwork may reduce all local and systemic problems related to periodontal diseases and to edentulism.

Conflict of interest

The authors declare no conflict of interest

Contribution statement

All authors were responsible for drafting the manuscript and revising it critically for valuable intellectual content. All authors approved the version to be published.

Financial support

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Ricerca Corrente of IRCCS MultiMedica partially funded the present article.

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Table 1. Systemic and local effects induced by the practice of regular exercise relevant for T2D and PD.

PD*	T2D*	Effects of exercise
↑ Periodontal inflammation	↑ Oral inflammatory response	↓ Gingival IL-1 β and CRP
↑ Oral mucosa dysbiosis	↑ Oral pathogen colonization	↑ Oral microbiota composition ↓ Oral pathogens
↓ Glycemic control	↑ Glycemia	↑ Glucose uptake and re-balance of glycemia
↑ Release of pro-inflammatory mediators	↑ Systemic pro-inflammatory mediators	↑ Anti-inflammatory activity through the release of anti-inflammatory mediators
Oral Pro-inflammatory activity of AGEs and FFAs	↑ AGEs and FFAs	↓ AGEs formation and FFAs clearance
Oral Pro-inflammatory effect of Adipose tissue-released mediators	↑ Adipose tissue expansion and inflammation	↑ Weight loss and adipose tissue proper functionality

* Columns list the pathological conditions associated or secondary to either PD or T2D.

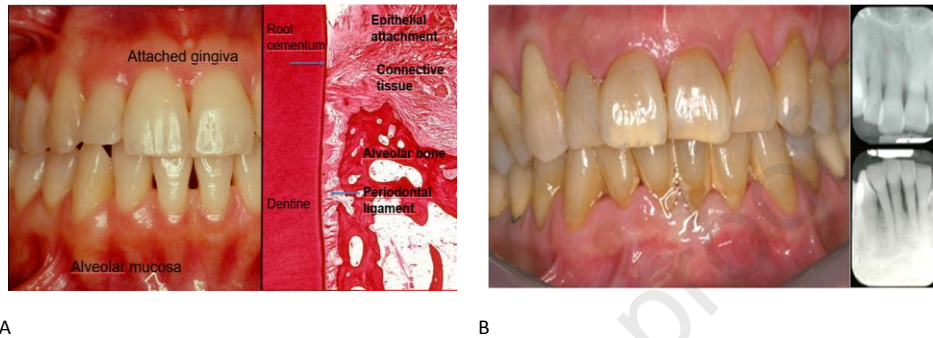


Figure 1. **A.** Healthy status of periodontal tissues. No signs of soft tissues and periodontal pocket are present. The root of the tooth is connected to the alveolar bone by the periodontal ligament. **B.** Pathological status of periodontal tissues. This picture shows *edema* of the gingival tissues, minimal gingival recessions and abundant deposits of calculus. Only a periodontal probe can give us an indication of how much periodontal support tissue has been lost in this patient, as evidenced by the radiographic images.

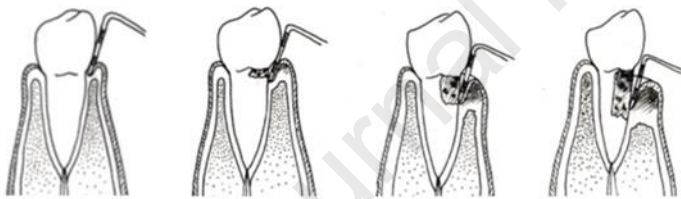


Figure 2. Periodontal disease has a chronic and progressive course. It is possible to pass from a state of health to a state of mild, moderate and finally severe periodontitis

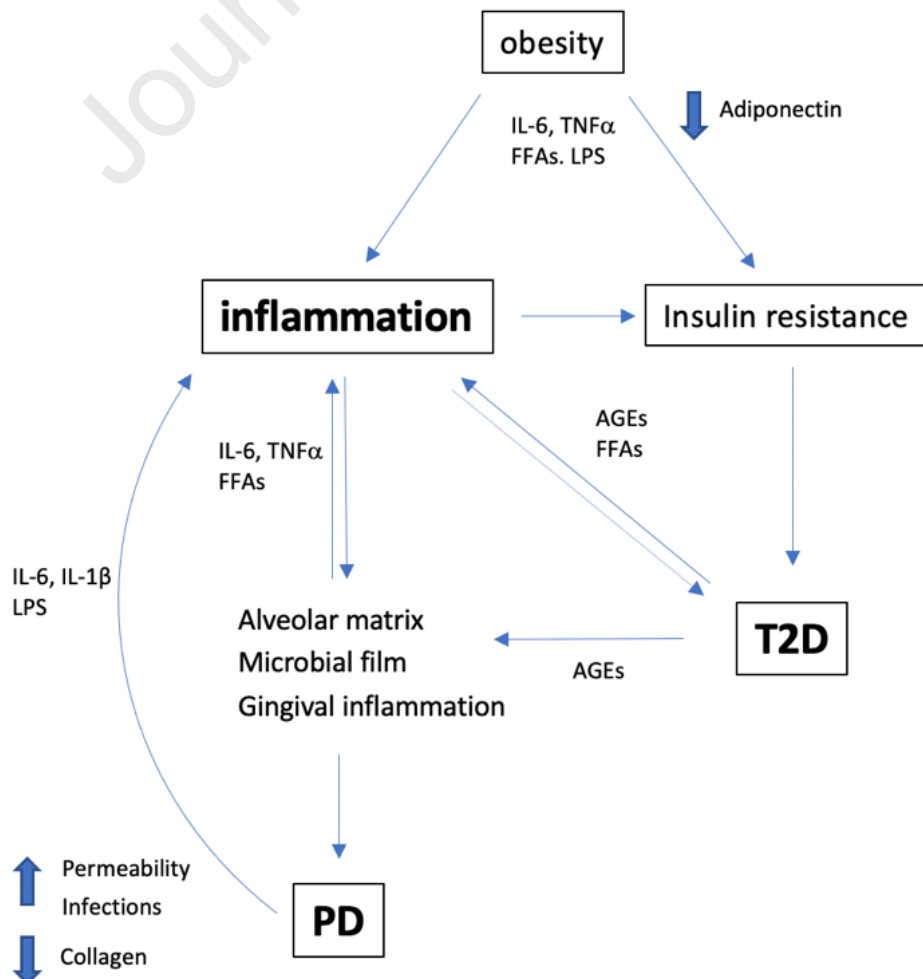


Figure 3. Model showing the pathogenetic mechanisms linking T2D with PD.
AGEs = advanced glycation end-products; FFAs = Free Fatty Acids; IL = interleukin; PD = Periodontitis; T2D = Type 2 diabetes; TNF = tumor necrosis factor.

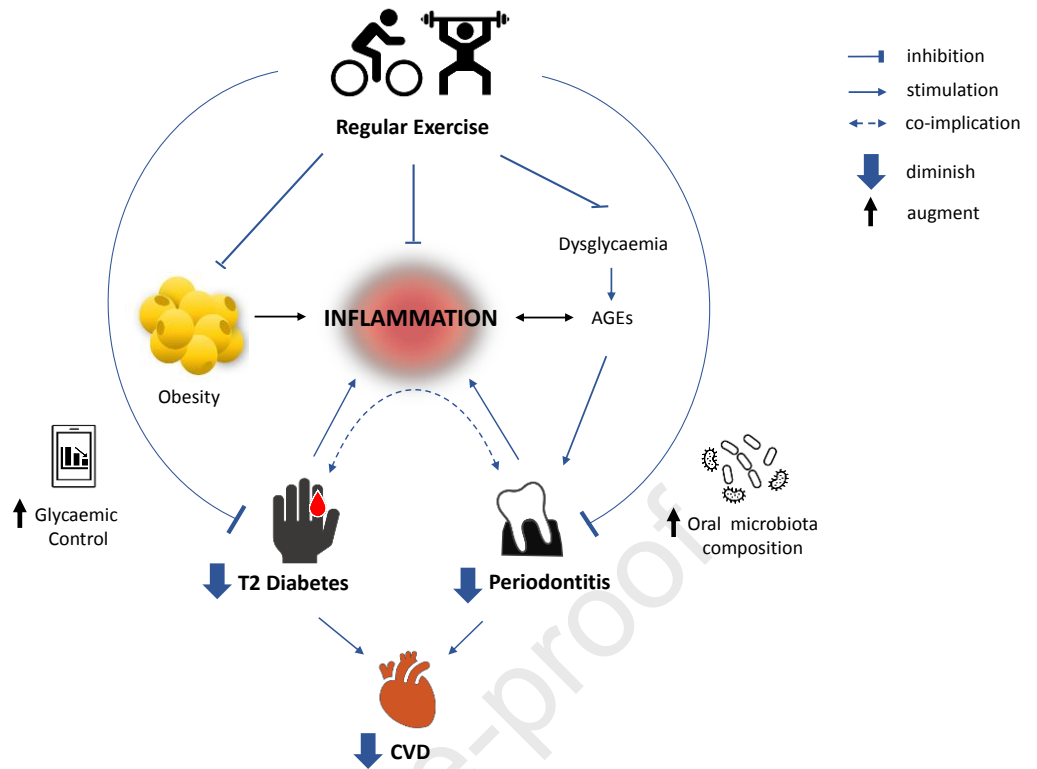


Figure 4. Synoptical model showing the possible role of physical exercise in the modulation of PD and T2D. AGEs = advanced glycation end-products.