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CONSENSUS REPORT

Consensus report of the joint workshop of the Italian Society of Diabetology, Italian Society of Periodontology and Implantology, Italian Association of Clinical Diabetologists (SID-SIdP-AMD)

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Abstract Periodontitis has been defined as the Sixth complication of Diabetes Mellitus. Since both diabetes mellitus and periodontitis have a high prevalence in the general population, the Italian Society of Diabetology, the Italian Society of Periodontology and Implantology and the Italian Association of Clinical Diabetologists revised the present scientific literature in the present consensus report.

A bi-directional interaction was demonstrated: Patients affected by type 1 and type 2 diabetes have a higher prevalence of periodontitis than the general population, due to several metabolic factors (e.g. chronic hyperglycemia, autoimmunity, dietary and life-style factors); similarly, periodontitis predisposes to type 2 diabetes mellitus mainly via the increase of systemic cytokines release. Conversely, improvement of metabolic control of diabetic patients delay the progression of periodontitis as well as periodontitis treatment reduces glycosylated hemoglobin levels in blood.

Due to the bi-directional causal interaction between periodontitis and diabetes mellitus, a strict collaboration among dentists and diabetologists is required and strongly recommended. The inter-societies consensus proposes specific flow-diagrams to improve the treatment of patients and management of the general population regarding the issue of periodontitis and diabetes.
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Introduction

In the Unites States, 34.2 million people of all ages—or 10.5% of the US population—had diabetes mellitus which is the 8th cause of death in the general population with more than 5.0 million people deceased per year [1]. Obesity recently reached pandemic proportion in U.S., reaching a 36% prevalence and causing an increased risk of severe comorbidities, mainly diabetes mellitus, and also cardiovascular diseases and cancer [2]. Medical specialists in Endocrinology and Metabolic Diseases are therefore essential in the prevention, management and treatment of diabetes and obesity.

Periodontitis is a ubiquitous chronic inflammatory non-communicable disease with a prevalence of 50% in adults at the stage I and II and of 10% for severe stages III and IV [3,4]. Dental practitioners, other than treating periodontal diseases have an important chance of implementing preventive activities as they are the most frequently consulted specialists in the medical field and they can easily convey to their patients their best advice on the major risk factors concerning periodontal and mouth mucosal diseases. Dental plaque biofilm, diet, tobacco, and alcohol, represent major risk factors for mouth diseases whereas the same etiologic factors are again between the principal public health problems in industrialized countries. Therefore, Dentists, while fighting mouth risks factors, support the battle of Endocrinologists against the common enemies. In fact, their preventive initiatives for oral diseases are counteracting the same risk factors feared by Internists and Endocrinologists, activating a common virtuous path for early diagnosis and management of systemic diseases. The association between severe periodontitis and altered glycemic homeostasis, which affects 7–8 million Italian peoples, went recently into the spotlight since diabetic patients have a two to three-fold risk of periodontal disease [5].

The evaluation by Dentists of age, morphometric measurements and periodontal assessment, may become a cornerstone in prevention of diabetes. In fact, it can help people unaware of their diabetic condition, to receive an early diagnosis of Diabetes and prevent appearance of diabetic complications [6]. Similarly, since periodontitis is s a concomitant initial factor in the onset of type 2 diabetes, Diabetologists can refer to Dentists newly diagnosed diabetic patient for periodontal assessment since the release into the bloodstream of pro-inflammatory systemic cytokines inducing insulin-resistance may worsen diabetic prognosis [7].

The present consensus report is based on the strong rationale of interactive pathogenesis between diabetes mellitus and periodontal disease and stems from the collaboration among Italian Society of Diabetology, Italian Society of Periodontology and Implantology and Italian Association of Clinical Diabetologists, enabling synergies for health maintenance.

Periodontitis

Etiology and pathogenesis

Periodontitis is a chronic non-communicable disease characterized by loss of tooth-supporting tissues, namely gingiva, alveolar bone, root cement and periodontal ligament [8]. It has a progressive nature and it may determine tooth loss if left untreated. Periodontitis is an inflammatory disease caused by specific bacteria contained in the dental plaque: these bacteria are periopathogens. Dental plaque is a biofilm that has physiologically formed in the oral cavity and, if not removed mechanically through adequate home oral hygiene procedures, tends to increase in dimension and complexity. As the biofilm grows, it selects a group of Gram-negative, mainly anaerobic bacteria with high proportions of periopathogens. Plaque accumulation invariably determines an inflammation of the gingival tissues, called gingivitis [9,10]. Gingivitis is a reversible condition characterized by swelling, redness and bleeding of the gingival tissues. Gingival bleeding may follow probing during dental examination, but it may also be spontaneous. In a subset of individuals, gingivitis may progress toward periodontitis, due to a dysbiosis of the bacterial biofilm that leads to chronic inflammation and periodontal tissues destruction [11].

A certain degree of susceptibility for periodontitis is required to allow the progression from gingivitis to periodontitis. Susceptibility is generally related to a hyper-inflammatory reaction in the periodontal tissues, which may be innate or acquired [12]. Innate susceptibility is usually expressed through a hyper-inflammatory phenotype characterized by an exaggerated cytokine secretion (i.e. IL-1β, PGE2, TNF-α, ecc.) [13,14] and by alterations in the host's immune response [15]. Acquired susceptibility is generally due to alterations caused by concomitant pathologies and conditions such as diabetes mellitus, obesity, high cholesterol, and metabolic syndrome or by bad habits such as tobacco smoking and high levels of stress.

When periodontal inflammation remains untreated, it progresses until the periodontal ligament-alveolar bone complex is destroyed, causing tooth loss to an extent that may lead to unpaired masticatory function and edentulism. Unlike caries, periodontitis causes a damage, which is not limited to the tooth structure but has extended to the surrounding soft and hard tissues. As a consequence, periodontitis does not only cause aesthetic and masticatory impairment, but also anatomical deformities due to severe alveolar bone resorption that increase the complexity for the subsequent dental rehabilitation that the patients may be in need of [16,17].

Clinical features of periodontitis

Periodontitis is the most common inflammatory, non-communicable disease in the world. Among western populations over 35 years old its prevalence is 47% and it exceeds 60% among elderly (≥65 years old) [3,4,18]. Severe

cases account for 11% of the population. The incidence peak of the disease is between the third and fourth decade [19]. The clinical course of the disease is subtle until the disease progresses to severe forms. In fact, in early phases, halitosis, gingival redness, swelling and bleeding may be the only signs patients may notice. However, these symptoms are often underestimated, and when tooth displacement and mobility occur, the disease is already at an advanced stage. At this point, a diagnosis is achieved by probing the gingival sulci, to establish the level of alveolar-dental attachment loss. To complete the clinical evaluation a targeted radiographic examination (systematic intra-oral radiographic examination) is also necessary.

Pathology occurs in various forms, recently classified according to their stage and grade. The stage, from I to IV, reflects the severity and complexity of the pathology at the time of diagnosis. In stage I the involvement of the periodontium is limited to the coronal portion, while in stage IV it involves the apical third of the teeth and causes tooth loss, displacement and mobility of residual teeth, as well as reduction/loss of the masticatory function. Grade, from A to C, reflects biological characteristics of the disease related to its risk of progression and its ability to respond to therapy. Stage III and IV periodontitis (i.e. severe periodontitis) is considered the sixth most common disease in the world, affecting on average 11% of the population, equal to about 800 million people in the world. It is the main cause of tooth loss in adults, impairing nutrition, language, self-esteem and quality of life [8]. Severe periodontitis is independently associated with mortality in different populations [20–23]. Comorbidity in patients suffering from chronic kidney disease (CKD) increases the risk of all-cause mortality and cardiovascular mortality up to 41% and 22%, respectively, after 10 years (compared with an increase of 36% and 16%, respectively, in patients with CKD without periodontitis) [24]. It is known that the comorbidity of periodontitis and diabetes in patients with chronic renal failure increases the 10-year risk of mortality for all causes of 23%, and the risk for cardiovascular mortality of 16%.

Periodontitis is treatable in a very effective and predictable way especially if an early-diagnosis is made or in any case before the destruction of a large part of the alveolar-dental ligament [25]. The therapy consists of several phases [26]. During the first fundamental phase called causal therapy, it is necessary to:

- Teach the patient how to achieve an adequate level of oral hygiene,
- Promote the adoption of healthy lifestyles,
- Perform a thorough removal of bacterial plaque and calculus above and below the gingival margin by means of professional debridement procedures,
- Add a systemic antibiotic therapy, but only in cases of severe disease, and mostly in cases of juvenile onset.

This phase, performed by the dentist and the dental hygienist, usually does not involve surgical therapies and ends with the clinical re-evaluation of the patient. In Stage I and II periodontitis this phase of treatment is sufficient to achieve the treatment goals and restore periodontal health. The patient is placed in a supportive care program with periodic recall visits.

- In most severe cases, (stage III and IV) a subsequent surgical phase of therapy is suggested and specialized knowledge and skills in periodontics are required.
- Stage IV periodontitis requires a multidisciplinary treatment approach including orthodontic and prosthodontic therapies.

Once the disease and its possible sequelae are under control, it is necessary to enroll the patient into a phase of monitoring and supportive therapy, which is the cornerstone of the necessary secondary prevention, together with home oral hygiene. Lack of follow-up and patients compliance are always associated with a high risk of relapse in susceptible patients.

What is the scientific evidence linking periodontal diseases and diabetes mellitus?

Periodontitis has been associated to various chronic non-transmissible diseases, especially in older people [27,28]. Periodontitis has also linked to adverse events during pregnancy [29]. Diabetes and periodontitis are two diseases related to the point that a two-way relationship has been theorized [30].

In the direction diabetes-periodontitis, hyperglycemia and poor metabolic control are associated with an increased risk of onset and periodontitis severity [31–34] and to worse clinical outcomes after periodontal therapy [35].

In the direction periodontitis-diabetes, periodontitis increases the risk of diabetes and it is associated with significantly higher serum levels of glycated hemoglobin (HbA1c) in people without diabetes (blood sugar to the upper normal limits) and in those with diabetes (hyperglycemia) [27].

A recent systematic review supports the two-way relationship between diabetes and periodontitis pooling data from 53 observational studies. Among patients with periodontitis, the prevalence of T2DM is greater than that observed among healthy patients after adjustment for other risk factors (OR = 4.04, p = 0.0001) [36]. The bi-directional relationship between periodontitis and diabetes has been confirmed evaluating the association of both diseases with polycystic ovary syndrome. In fact, women affected by this syndrome have a four times higher chance of suffering from T2DM [37] and were 28% more likely to suffer from periodontitis [38].

Diabetes mellitus as a risk factor for periodontitis

Increased susceptibility to periodontitis in diabetics is due to an altered response to the perio-pathogens, following the dysbiosis of the sub-gingival biofilm. This alteration is possible through three main mechanisms:

A. Cytokines/adipokins production,
B. Alteration of Cell-mediated Immunity,

C. Hyperglycemia.

Diabetes affects qualitatively and quantitatively the cytokine profile of patients with periodontitis. In fact, subjects with T2DM and periodontitis show, compared to diabetics without periodontitis, a higher level of cytokines both locally, at the level of the gingival crevicular fluid and systemically in the blood stream [39]. A similar picture is present also in T1DM patients, with the adjunct of the coexistence of autoimmune factors [40]. Poorly controlled diabetes is characterize by high levels of pro-inflammatory mediators (IL-1β, TNF-α, IL-6, receptor activator of nuclear factor kappa-B ligand (RANKL)/ osteoprotegerin (OPG) ratio and oxidative stress) inside the periodontium that enhance the damage to the periodontal structures [41,42]. Further, this finding is confirmed by in vitro or ex-vivo cellular models exposed to high levels of glucose [43]. An increased production of IL-1β, TNF-α, PGE2 has been described in the monocytes of subjects with T1DM and periodontitis after stimulation with lipopolysaccharide compared to subjects without T1DM. In addition, the immune response, mediated by neutrophils in the gingiva, was found insufficient in diabetic patients [44].

High blood glucose has an impact on periodontal health based on four key mechanisms related to 1) cell stress, 2) advanced end-products glycation (AGEs) and their receptors (RAGE), 3) homeostasis of the alveolar bone, and 4) bacterial biofilm dysbiosis [45].

There is a direct relationship between the severity and extent of periodontitis and the worsening of glycemic control [46]. Poor glycemic control is responsible for reduced collagen production and increase of collagenolytic activity of gingival and periodontal fibroblasts. In fact, glycated proteins (i.e. AGEs) are present in the gingival tissues and in the saliva of diabetic patients with periodontitis and the AGEs blood levels are significantly associated with periodontitis extension in T2DM patients [47].

If diabetes is poorly controlled, high levels of RANKL (a member of TNF family) can be found in the periodontal tissues. This contributes to the alteration of the bone metabolism that enhances the alveolar bone resorption in subjects with periodontitis. Finally, the presence of a higher quantity of periopathogens in the bacterial flora of the dental biofilm of diabetic patients compared to that of non-diabetic subjects has recently been confirmed [48].

It was estimated that T2DM increases up to 34% the risk of developing periodontitis. In fact, T2DM patients have on average deeper periodontal pockets (0.61 mm), a greater loss of attachment (0.89 mm), and lose on average two teeth more than subjects without diabetes [19].

Periodontitis as diabetes risk factor

Substantial evidence demonstrates that periodontitis worsens the glycemic control even in non-diabetic subjects with periodontal patients that display higher HbA1c values compared to healthy controls without periodontal disease [41,49,52].

Experimental data suggest that periodontitis enhances the risk to develop diabetes [42]. Euglycemic subjects affected by periodontitis display an increased risk to develop HbA1c $\geq$ 6.5% after a 5-year follow-up, irrespective of confounding factors as BMI, alcohol consumption, smoking status, sex, and age [46]. Furthermore, C-reactive protein (C-RP) levels correlated with the increase of HbA1c [50,51]. Six studies comprising USA, Japan and Taiwan populations for a total of 77,716 participants have been summarized in a meta-analysis and showed that patients with periodontitis are more likely to develop pre-diabetes and diabetes (range adjusted HR: 1,19-1,33) [52]. In T2DM subjects, periodontitis is significantly associated to a worse glycemic control in terms of HbA1c. Moreover, higher insulin resistance (Homa-IR levels) was observed in studies on patients with periodontitis [52]. On the other hand, there is not enough data to confirm that periodontitis is associated with worse glycemic control in T1DM patients, even though an association is biologically plausible.

The subject affected by periodontitis is more prone to hyperglycemia, mediated by a sustained systemic inflammation and a series of complex mechanisms including: 1) a high cytokine production that could contribute to insulin-resistance by modifying the insulin receptor substrate-1; 2) an alteration of the adipocyte function with increased free fatty acids; and 3) a decreased endothelial nitric oxide production. Thus, diabetic subjects with periodontitis have a worse glycemic control and an increased risk of the development of diabetes complications. For instance, in T1DM patients affected from periodontitis the risk of renal and cardiovascular complication is increased [40,52]. Parallel, in T2DM affected from moderate-to-severe periodontitis, microalbuminuria and renal failure are more frequent, and the risk of cardio-renal mortality is three to five-fold higher in T2DM patients with severe periodontitis compared to T2DM subjects without periodontitis [53,54]. Diabetic retinopathy is significantly associated with periodontitis irrespective of other confounders (OR 1.2−2.8), and there is an assumed dose−effect relationship between periodontitis severity and retinopathy [55]. Finally, neuropathic foot ulcers in diabetic patients have been associated with severe periodontitis when compared to periodontally healthy controls (OR 6.6) [56].

Etiological periodontal therapy has proven effective in improving glycemic control in terms of HbA1c. The meta-analytical value of the reduction of HbA1c to three months from the end of periodontal therapy is 0.36% [57]. This figure was confirmed by a systematic review of previous meta-analysis [58]. However, the impact of periodontal therapy on the value of HbA1c depends on the operating protocol adopted.

A recent publication has shown that periodontal treatment (referred to as “intensive periodontal treatment”), which included removal of sub-gingival calculus, surgical access to residual pockets and enrollment of patients in a

strict periodontal maintenance program resulted in a reduction of HbA1c of 0.6% compared to the control treatment which provided for only supra-gingival oral hygiene [59].

A network meta-analysis reported that the different therapeutic protocols of periodontitis had an impact on the reduction of HbA1c from 0.4 to 1.1% compared to patients who had not received any treatment [60]. Periodontal therapy has also shown potential significant effectiveness in controlling the lipid profile of T2DM patients and a significant effect in reducing serum levels of C-RP. A recent systematic review reported that three months after the end of the non-surgical treatment of periodontitis a statistically significant reduction of cholesterol levels, (0.47 mmol/L, $p = 0.001$) and triglycerides (0.20 mmol/L, p 0.00001) was observed in patients who received treatment, compared to those who underwent only supra-gingival oral hygiene or no periodontal treatment. In the latter a significant reduction in high-density HDL lipoprotein levels has also been reported (- 0.06 mmol/L, p 0.00001) [61]. The local co-administration of statins and metformin in gel has shown favorable effects for the treatment of periodontitis, both in patients with T2DM (2 studies) and in patients with good systemic health [62]. Both the use of statins and metformin (1% gel) have produced significantly better results in terms of radiographic fill of intraosseous defects (data present only for statins), reduction of periodontal pocket depth and gain of clinical attachment [63].

What is required to do in the suspect of diabetes?

T2DM may remain asymptomatic for a long time. Therefore, the diagnosis requires a proactive attitude (disease search through screening procedures). The estimate percentage of undiagnosed T2DM cases is very high [1], and belonging to the pre-clinical cohort is not harmless. Frequently, at the time of diagnosis, patients have already chronic complications, with a serious impact on the quality of life, and a high cost to the community.

The advantage of implementing effective screening programs with non-invasive simple and relatively inexpensive tests such as fasting blood sugar, Oral Glucose Tolerance Test (OGTT) or, HbA1c is crystal−clear. We can confirm the diagnosis of diabetes also in a single random occasion with a blood glucose level $\geq$200 mg/dl and in presence of typical symptoms and signs of the disease (polyuria, polydipsia and weight loss).

In the absence of typical symptoms and signs of diabetes, diagnosis must be made with:

a. Fasting glycemia $\geq$126 mg/dl confirmed on at least two different occasions
b. Glycemia $\geq$200 mg/dl 2 h after OGTT (75 g)
c. HbA1c $\geq$ 48 mmol/mol (6.5%)

Conversely measurements of post-prandial blood sugar, hourly glycemic profile, insulin blood level (basal or during OGTT), C-peptide, and autoantibodies against β-cell are considered useless for T2DM screening.

During diabetes screening, individuals with dysglycemia may be identified having impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) and borderline HbA1c (prediabetes) with 39 < HbA1c < 47 mmol/mol or 5.7 < HbA1c <6.4%. In those patients, lifestyle interventions can prevent/delay disease development. If the screening test is normal, it needs a repeat at least every 3 years.

The presence of IFG is the main risk factor for the development of diabetes. Furthermore, among the known risk factors a BMI >25 kg/m2 and older age are of particular relevance. The effectiveness of population screening tests in asymptomatic subjects was not confirmed. The most advantageous strategy appears to be the identification of high-risk categories to develop diabetes. Screening should be recommended for adults with BMI $\geq$25 kg/m^2 and one or more the following known risk factors for diabetes:

- having first-degree familiarity with T2DM (parents, siblings)
- being physical inactive
- belonging to a high-risk ethnic group
- having arterial hypertension ($\geq$140/90 mm/hg) or being on anti-hypertensive therapy
- having low HDL-cholesterol levels (<35 mg/dl) and/or high triglyceride values (>250 mg/dl)
- for women: delivery of an infant weighing >4 kg or previous gestational diabetes
- having polycystic ovary syndrome or other extreme insulin resistance conditions such as acanthosis nigricans
- clinical evidence of cardiovascular disease
- HbA1c $\geq$ 39 mmol/mol (5.7%), IGT or IFG in a previous screening test

In all individual over 45 years of age, even in the absence of risk factors, the execution, on a three-year basis, of fasting blood glucose is, however indicated. Diabetes screening in the dental practice has been effective in detecting both prediabetes and diabetes. This early diagnosis has led to the introduction of cost-effective lifestyle change that has encouraged a significant portion of patients to back off from prediabetes to normoglycemia during the trial period. Those results were confirmed by another study with 10,472 adult subjects whose 7.73% had been followed by dentists but not by a GP in the previous 12 months: 15.83% of these subjects had HbA1c levels in prediabetes or diabetes range. In UK, the National Institute of Clinical Excellence suggested that health professionals other than doctors, including dentists, should perform screening for diabetes. Among people over 45 years, the screening in the dental office is the best setting to identify patients at risk of diabetes and prediabetes.

What is required to do in the suspect of periodontitis?

Periodontitis may remain asymptomatic for long-lasting period. Gingival bleeding is usually the first sign of disease. However, this sign is common to gingivitis and thus, differential diagnosis is necessary though screening procedures. The percentage of undiagnosed cases of periodontitis is high, and usually when the diagnosis has made, the patients already suffered the complications of periodontitis such as, dental mobility, impairment of masticatory function, gingival recessions, dentinal hypersensitivity and dental migration. These in turn have a serious impact on the patients' quality of life and are responsible for an increase in the costs of dental treatments.

The diabetologist and oral pathology (Fig. 1)

Diabetologists must inform patients with diabetes that they have a higher risk to suffer from periodontal diseases and that a bi-directional relationship exists between the two pathologies. In particular, they should enlighten the increased risk for cardiovascular and renal complications when a diabetic patient suffers from periodontitis.

The signs and symptoms of periodontitis are many. A legit suspect of periodontitis may exist whenever the patient reports for events such as gingival bleeding, gingival recession, halitosis or breath alterations, gingival swelling and discomfort, dentinal hypersensitivity, dental mobility or migration. The assessment of those signs and symptoms should be integrated into the routine of the diabetologist's visit. The clinical inspection of the oral cavity should be performed as part of the initial evaluation of the diabetic patients. If periodontitis is not present, the inspection should be repeated during the yearly follow-up visits with specific attention to the gingival conditions of the patients. At the same time, patients should be instructed to perform adequate home oral hygiene as a form of primary or secondary prevention of periodontitis. Diabetics children of 7 years of age or older should be referred to the dentist at least once every year in order to assess their oral conditions.

If the diabetologist suspects that the patient has periodontitis, she/he should refer him to the dentist for a visit with the specific request for periodontal diagnosis. If the patients have already lost some teeth, the importance of an adequate masticatory function, should be reinforced during structured education programs. It is important to remind to patients to seek for dental treatment whenever they experience dryness or burning sensations in the mouth. They should act the same as they observe the occurrence of whitish patches (mycosis).

The diagnosis of periodontitis is clinical. It is performed via a clinical dental examination including a procedure named periodontal probing that measure the depth of the gingival sulci. In case of periodontitis, the probing pocket depth (i.e. the depth of the gingival sulcus) is increased.

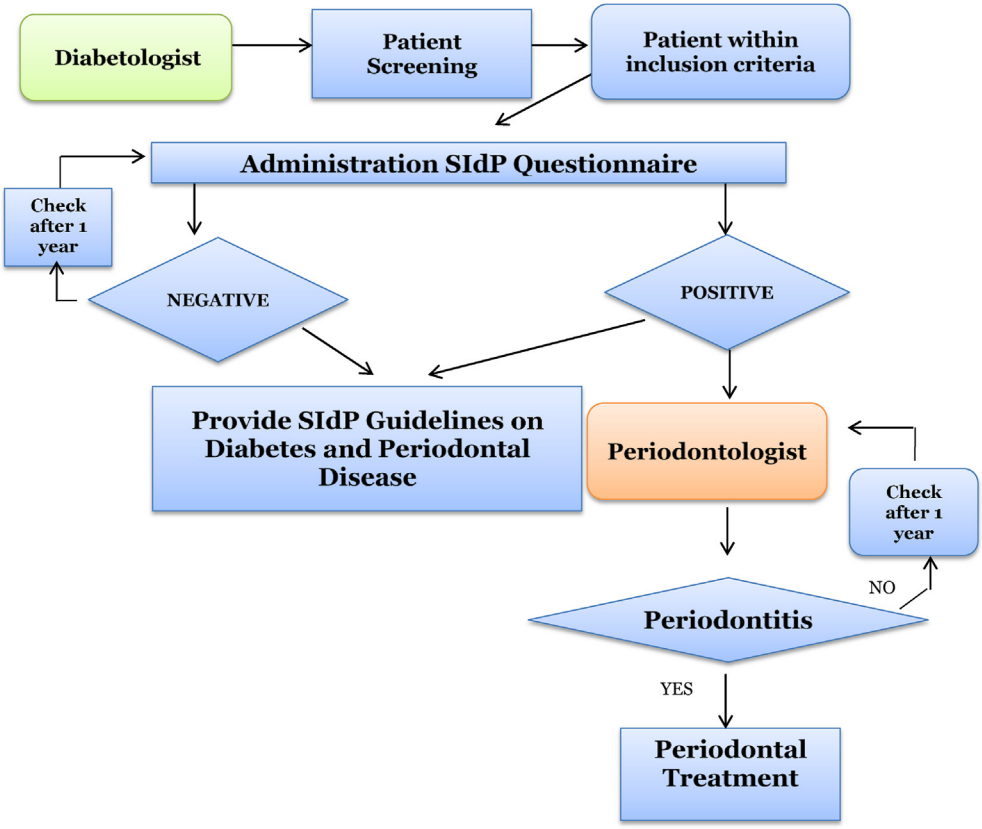

Figure 1 From diabetologist to dentist.

Parallel, a radiographic evaluation is important to assess the severity and the pattern of bone resorption around the affected teeth.

The diabetologist is also entitled to co-operate with the dentist in order to manage the medications of the diabetic subjects (i.e. oral therapy or insulin therapy) in the 24 h following a dental procedure. In fact, during the post-operative period, the alimentation could be difficult and patients are at risk of hypoglycemia.

The dentist and the diabetic patient (Figs. 2 and 3)

The dentist must inform the diabetic patient of the increased risk of periodontal diseases, and of the bi-univocal relationship that links diabetes and periodontitis. In particular, the patient needs to know of the increased risk of cardio-vascular and renal complications, therefore calling attention to the value of healthy periodontal conditions. Patients need to know that periodontal health is beneficial for the control of diabetes itself. During the first visit, clinical records of the periodontal situation should contain the appropriate Periodontal Screening Record (PSR). Whenever periodontitis has diagnosed, an adequate therapeutic program needs to be started and the patient placed in a program of regular monitoring and secondary prevention visits. If the patient presents already a partial loss of dental elements, the importance of a correct masticatory function for good nutrition should be highlighted, especially as a fundamental cornerstone of diabetes' therapy. The Dentist must prepare for the treatment of the diabetic patient by respecting the simple rule "diabetes is not a contraindication to dental therapy nor to surgical dental therapy". In cases of insulin-treated

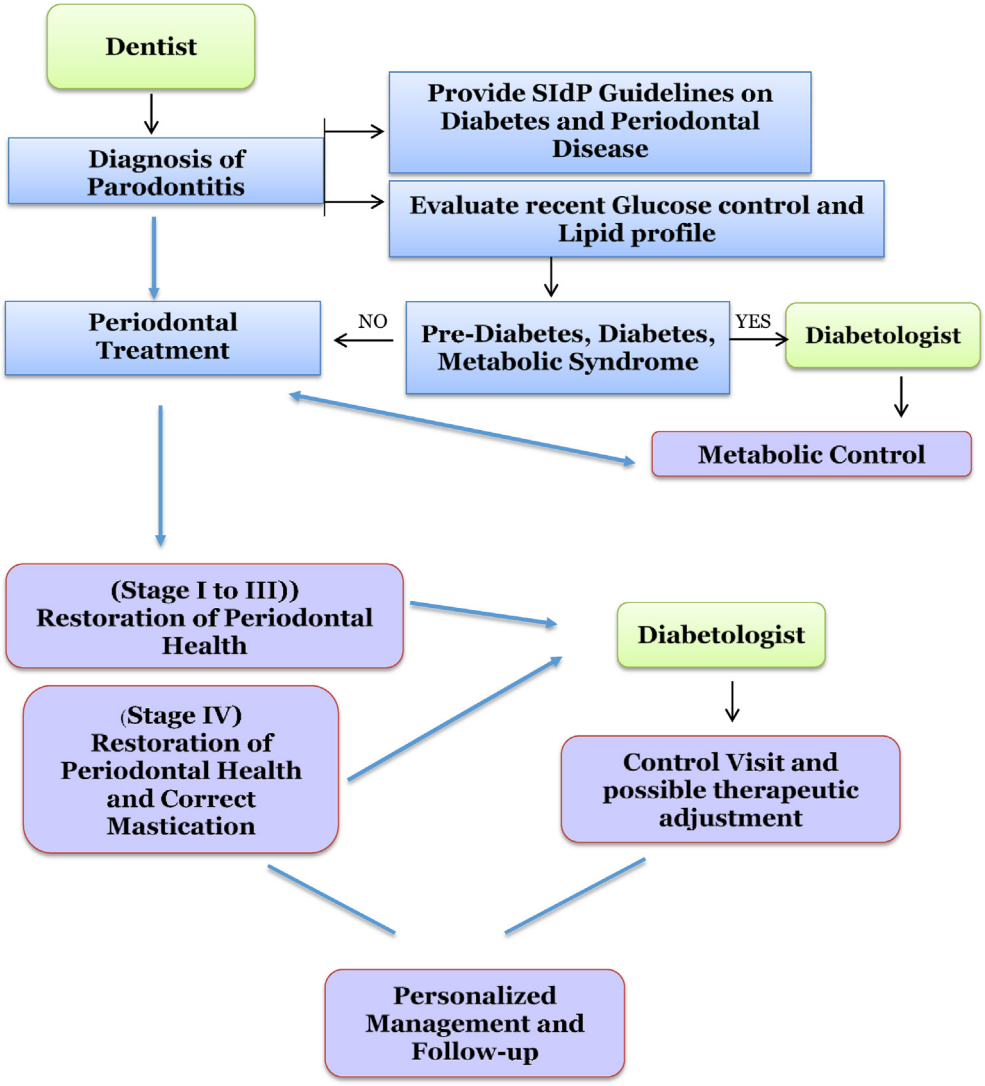

Figure 2 From dentist to diabetologist.

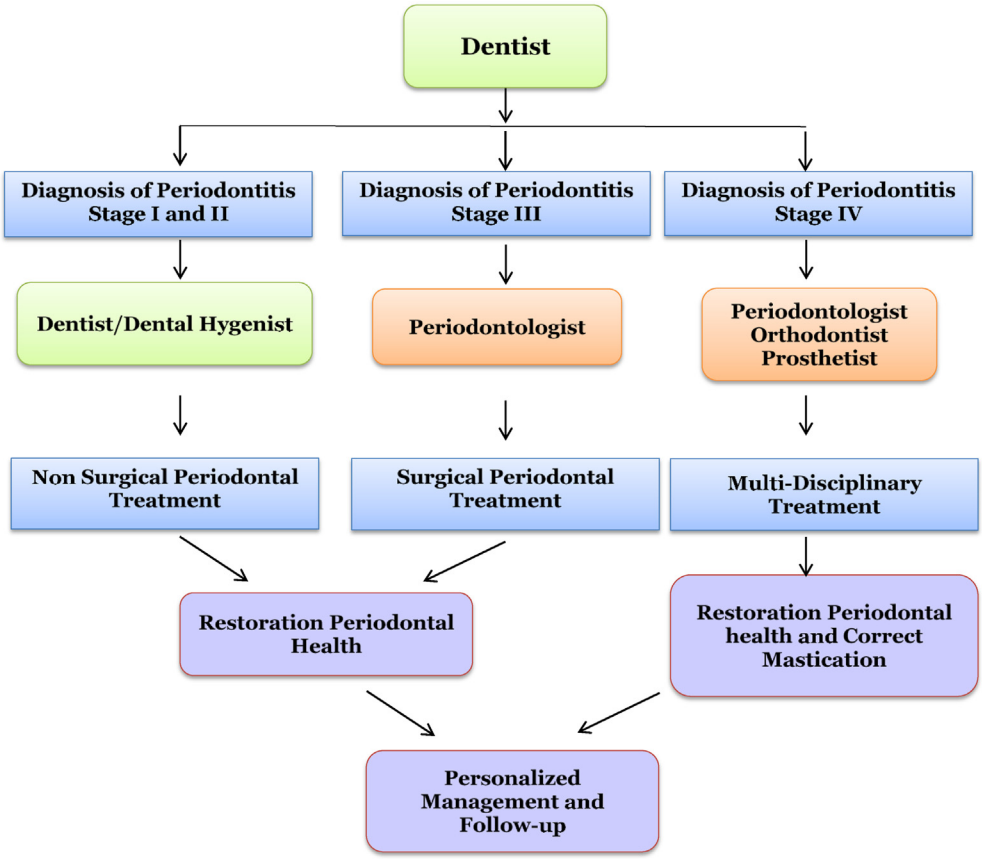

Figure 3 Stepwise approach of periodontal treatment.

diabetes, a possible therapeutic change must be evaluated by the diabetologist to reduce the risk of intra-operative hypoglycemia. It is recommended to collect a careful medical history to highlight the type of diabetes, the duration of the disease, the presence of any complications, the diabetic therapy and concomitant therapy in place; this should be done remembering that most diabetic patients are also being treated with anticoagulants/anti-aggregants, antihypertensive and lipid-lowering drugs.

The practitioner should evaluate glycemic compensation through the value of HbA1c and self-monitoring of the patient, checking scrupulous compliance with medical therapy. It is also suggested to plan and choose the most appropriate time to carry out the surgical intervention: the best time to intervene on the diabetic patient for an extraction or oral surgery procedures is in the middle of the morning, from 1 to 3 h after breakfast and the possible administration of insulin dose. It is recommended to implement rigorous asepsis and to institute systemic antibiotic prophylaxis in order to prevent infectious complications, quite frequent in the post-operative period. Preference should be given to broad spectrum semi-synthetic penicillins, cephalosporins and macrolides. Given the possible interference with antibiotics, patients should be asked as a precaution to check with their doctor the appropriateness of a possible (but frequent) therapy with cholesterol-lowering drugs (statins). There are no clear indications on the use of a vasoconstrictor under local anesthesia. It is advisable not to use preparations containing adrenaline or derivatives, as catecholamines determine arterial hypertension, hepatic neoglucogenesis and glucagon secretion increase, as well as reducing glucose clearance, with the consequence of worsening hyperglycemia. However, the anesthetic effect needs to be guaranteed during the therapeutic act so to avoid the release of endogenous catecholamines. A careful assessment of the presumed duration of the therapeutic act will be therefore be necessary.

The dentist and the patient with unknown diabetes

In the case, the Dentist, as part of a normal visit to a patient, does detect or is reported signs and/or symptoms of suspected diabetes (polydipsia, polyuria, weight loss and asthenia, urinary genital infections) should refer the patient to her/his family Doctor.

The Dentist should identify suspects for diabetes screening among her/his patients and refer them to the family doctor with specific indications. Candidates suitable for the screening are: i) subjects over the age of 45 who are asymptomatic for diabetes and did not check their blood sugar in the previous three years; ii) subjects with body mass index $\geq$25 kg/m^2 presenting at least one of the following characteristics:

- first degree family history of T2DM (parents, siblings)
- physical inactivity
- belonging to a high-risk ethnic group (Afro-American, Hispanic)
- arterial hypertension (≥140/90 mmHg) or antihypertensive therapy in progress
- low HDL cholesterol levels (HDL< 35 mg/dl) and/or high triglyceride values (TG > 250 mg/dl)
- in women: birth of a newborn weighing> 4 kg or previous gestational diabetes
- polycystic ovary syndrome or other conditions of extreme insulin resistance such as acanthosis nigricans
- clinical evidence of cardiovascular diseases
- HbA1c ≥ 39 mmol/ml or ≥ 5.7%, IGT or IFG in a previous screening test.

For the diabetologist

Recommendations

- To inform the diabetic patient about the high risk of periodontitis (referred as the sixth complication of diabetes) besides other systemic diseases (cardiovascular, renal, and ocular complications);
- To ask the patient and check for the presence of signs and symptoms of periodontitis such as gingival bleeding, taste alterations, gingival swelling and discomfort, dental mobility. In case of a positive feedback, refer the patient to the dentist for a thorough examination of the oral conditions;
- To inform the patient that good oral health may be beneficial for glycemic control;
- To hand to the patient the SIdP handbook during the first visit;
- To advise the patient to carry out dental check-ups at least once per year even in the absence of pain or other symptoms.

For the dentist

Recommendations

- To inform the patient about the association between periodontitis and systemic diseases (cardiovascular diseases, dysmetabolic and rheumatic disorders);
- To collect a detailed individual and familiar medical history and notice patient's BMI and to advise the patients to perform blood tests whenever recent blood analysis results are not available (>1 year);
- To advise for a diabetes check up in patients with severe periodontitis and first degree familiarity for diabetes;
- To pay attention to the medications of the diabetic patients such as cardio-aspirin, statins, and beta-blockers for their possible implications in dental treatments;
- For the diabetic patients to program the time of the appointments, the type of anesthesia and if necessary administer an antibiotic prophylaxis. Furthermore to avoid, as much as possible, stress, trauma and pain;
- To pay attention to the anti-diabetic therapy especially if it includes insulin and sulfonylureas in order to avoid hypoglycemic shock.
- To keep in the dental office an "Emergency Kit" including:
- Refractometer to measure blood glucose
- Ultra-rapid insulin
- Glucagen Hypokit
- Sugar packets
- Capoten, Lasix
- Carvasin for sublingual administration

Feasibility and future

The therapeutic cost of diabetes diagnosed in U.S. has increased progressively starting from 2007 up to 2017 (from 174 to 327 billion dollars) and it continue to increase due to the number of new diagnosed cases [64]. Noteworthy, approximately a third of the entire expense (107 billion dollars) is due to the indirect costs of this disease: working absenteeism, reduced productivity, unemployment produced by disabilities associated with diabetes and loss of productivity due to early mortality.

In Italy diabetes expense amount to 9% of medical resources which is over 9.22 billion euro per year (1,05 million euro per hour). In general, the health care expenses for an Italian citizen with diabetes is close to 3500 € per year (Source: Quotidiano Sanità, Italy 28/2/2020), more than double the cost for non-diabetic population of the same age and sex. High costs for diabetes management appear to be related to three fundamental events:

1. T2DM onset in "at-risk" individuals (obesity, hypertension, metabolic syndrome, familiarity) which lead *per se* to an increase *per capita* direct costs per year of approximately 100% compared to the population not affected by diabetes mellitus [65];
2. Incidence of clinical burden of chronic diabetes complications (e.g. E.R. admissions and hospitalizations) [65];
3. Drugs expenditure in the diabetic patient population is certainly higher than that of general population, and predominantly related to the presence of complications [65].

Italian diabetes-related health expenditure represents about 10% of European expenditure, with a *per capita*

figure appreciably lower than that recorded in France, Germany and United Kingdom (Source: Ministry of Health-DG Health Planning-National Diabetes Commission 2013).

In light of the elevated costs related to diabetes the development of *ANY* social and health strategies aimed at early screening of the disease and to reduce the onset of clinical complications is essential. The multidisciplinary approach (Periodontologist-Diabetologist) based on different clinical expertise can meet the health needs of counteracting both new cases of diabetes in the population at risk, and the development and/or the progression of micro and macro-vascular chronic complications.

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