Correlations between diabetes and diseases of the oral cavity
edited by Carmen Mortellaro, Professor of Odontostomatological Diseases

On November 14th it is celebrated the World Diabetes Day, established in 1991 by the International Diabetes Federation (IDF) and the WHO, to inform public opinion on diabetes, prevention, disease management and complications.

Numerous scientific evidences confirm that diabetes can have important repercussions on the condition of the teeth and mouth, but only 42% of patients are aware of it and 49% of them have never received information about it. This despite the fact that 76% lost one or more natural teeth and many found themselves living with bleeding (43%) or gum recession (24.7%), dry mouth (35.6%), halitosis (25.6%), mucosal ulcers (20.4%).

This is the picture that emerges from a survey conducted by the Italian Diabetics Association (FAND) on a large sample of Italians over the age of 30, suffering from Type 1 and 2 diabetes, at the end of 2017.

The survey clearly revealed a substantial lack of the essential cognitive tools for a person affected by diabetes to preserve the integrity of his mouth over time, ignoring, on the other hand, that through the examination of the oral cavity, an attentive specialist could also intercept signs of pre-diabetes and help diagnose the disease early.

The survey also focused on patients' information needs. Almost one in two persons affected by diabetes has never talked about the complications that the disease can cause to the oral cavity and the precautions needed to prevent them. Those who have received explanations indicate the dentist (51.4%) and the diabetologist (49.3%) as main sources, followed by the patient associations (32.6%) and the general practitioner (19.6%). However, there are some who rely on the press and the web (13%) or on relatives and friends (5.8%), with the risk of running into fake news and uncertified information.

Diabetes is one of the most common chronic diseases that show a rapid and progressive spread throughout the world, on the point that it appears unstoppable and predictive of a global catastrophic health event.
In Europe, there are about 60 million patients, in 2040 it is estimated that there will be 71 million patients (prevalence 10.7%). And at the world level there are over 425 million people suffering from diabetes (prevalence 8.3%).

As for Italy, over 3,200,000 diagnosed cases are estimated, equal to 5.3% of the population, Sardinians are the second population in the world for incidence of Type 1 diabetes and, from the data provided by the Italian Society of Pediatric Diabetology, approximately 120 new cases are diagnosed in the island every year in the age group 0-14 years. Sardinia has always had the sad Italian record and today, with over 12,000 adults, more than 1,500 under the age of 18 and about 120 new cases diagnosed every year, it also ranks at the top of the world rankings, second only to Finland.

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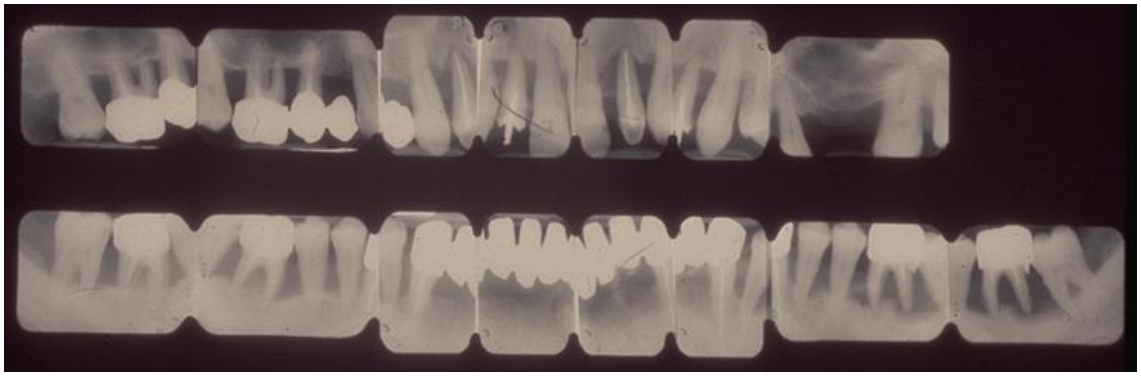
Diabetes mellitus groups a series of metabolic diseases which, albeit with different etiologies, evolve into a state of chronic hyperglycemia. During the course of the disease, hyperglycemia is associated with microvascular damage to the kidneys, eyes, nervous system, and macrovascular damage to the heart and large vessels, gradually worsening the clinical picture of those affected and bringing with it a high economic and social cost.

Regarding the oral cavity, a large amount of data published over the last 50 years suggests that diabetes is associated with increased prevalence and severity of gingivitis and periodontitis. Other important oral manifestations found in diabetic patients are: xerostomia, glossopyrosis, acetonemic halitosis, dental caries, polymicrobial stomatitis and particular predisposition to Candida infections.



Diabetic periodontal disease with extensive bone loss

Ref. Oliver & Tervonen - J Am Dent Assoc 1993 Karjalainen et al.–
J Periodontol 1994 Patino-Marin et al.–Acta Odontol Latinoam 2008
Tanwir et al. – Acta Odontol Scand 2009

Methodological problems have often accompanied the scientific literature in this specific sector creating, at times, interpretative uncertainties. In addition to the biases related to the numerical representativeness of the sample under examination, the difficulties concerned the classification criteria adopted by the various researchers for the different types of diabetes, the radiographic criteria and the clinical indices used to assess the prevalence and severity of periodontitis and the blood chemistry tests for assessing the level of glycemic control.

An important clarification must be made regarding the periodontal picture in diabetic subjects with a different degree of glycemic control, that is, of their disease. From the numerous studies, many of which carried out within the Italian Society of Periodontology (SIdP) engaged for years in a vast prevention campaign at national level and which we are reporting, it is clear that there is an inversely proportional correlation between the effectiveness of glycemic control and severity of the periodontal picture.

It is generally established that the prevalence of periodontitis in subjects suffering from Type I, Type II and Type IV diabetes, is major than in healthy subjects. Studies both of the cross-over and longitudinal type have shown an important risk factor for periodontitis in diabetes and an important complication of diabetes in periodontitis. The risk for a diabetic subject of getting periodontitis is estimated to be three times greater than that of a non-diabetic subject in the adult age and up to six times greater in adolescents and young teenagers. Pregnant women with diabetes, lastly, have a risk of suffering from periodontitis that is over nine times higher than non-diabetic subjects.

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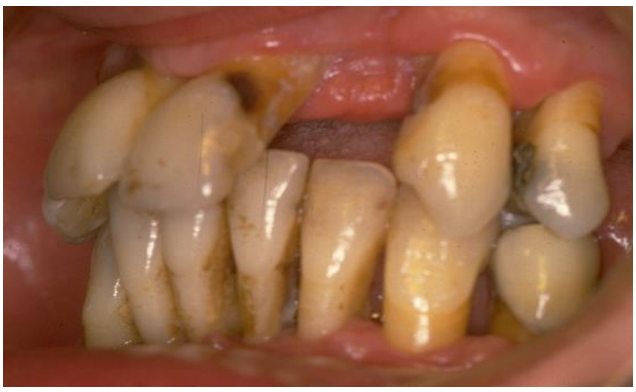
The important message to stress is that people with diabetes have a tendency to develop periodontitis just as people with periodontitis have a tendency to develop diabetes.

The increased susceptibility to periodontitis in diabetics is due to the altered response following bacterial insult of periodontal pathogenic bacteria associated with a dysbiosis of the subgingival biofilm. This alteration can happen through three mechanisms: cytokines / adipokines, altered cellular immunity and hyperglycemia.

Diabetes qualitatively and quantitatively influences the cytokine profile of patients with periodontitis. In fact, subjects affected by both Type 2 diabetes mellitus and periodontitis show, compared to diabetic subjects without periodontitis, a higher level of blood cytokines and in the crevicular gingival fluid; the same picture can be observed in Type 1 diabetes.

In the monocytes of subjects with both T1D and periodontitis, a higher production of Interleukin-1β, TNF-α, PGE2 has been described after stimulation with Lipopolysaccharide compared to subjects without T1D. Furthermore, in subjects with diabetes there is a deficient neutrophil-mediated immune response at the gingival level.

Hyperglycemia has an impact on periodontal health thanks to four fundamental mechanisms related to: cellular stress, advanced glycation end-products (AGEs) and their RAGE receptors, alveolar bone homeostasis and bacterial biofilm dysbiosis. There is a direct relationship between the severity and extent of periodontitis and worsening of glycemic control. This condition is responsible for a reduced production of collagen and an increase in collagenolytic activity of gingival and periodontal fibroblasts. Glycosylated proteins (advanced glycation end-products, AGEs) are present in the gum tissues and saliva of diabetic patients affected by periodontitis. The levels of blood AGEs are significantly associated with the extent of periodontitis in patients with T2D. If diabetes is poorly controlled, there is in periodontal tissues a high level of membrane protein receptor activator of nuclear factor kappa-B ligand (RANKL), a member of the TNF family. This contributes to an alteration of bone metabolism with resorption of the alveolar bone in the subject with periodontitis.



Clinical picture - Role of inflammation

The cytokines produced in the course of periodontal disease can produce an insulin resistance syndrome similar to that seen in diabetes and can initiate the destruction of pancreatic beta cells which leads to the development of diabetes.
Ref. (Iacopino – Ann Periodontol 2001)

Taking into consideration the literature data used by us and widely dispensed in the prevention campaigns of SIdP, the pathophysiological alterations that contribute to the development of degenerative processes and typical oral lesions of diabetes are essentially:

Microangiopathy
The persistent increase in blood glucose causes a thickening of the basement membrane of the capillaries by non-enzymatic glycosylation of membrane proteins, such as to affect the basal

permeability. This process, consequently, also changes the nutrition of the tissues, the oxygen diffusion and the elimination of metabolites.
This is associated with a deficit of blood perfusion and leukocyte migration (diapedesis), making the tissues more susceptible to microbial attacks.

Defects of the immune response
In diabetes, there is a reduction in the chemotactic activity of neutrophils and the phagocytic activity of macrophages, which could be responsible for the altered response of periodontal tissues to bacterial plaque. The origin of this deficit would seem to depend on ketoacidosis and hyperglycemia which act negatively against the phagocytic activity of macrophages, while the reduced or absent production of insulin may reduce the chemotactic activity of neutrophil granulocytes. In addition to these factors, it has been hypothesized an acquired functional deficit which involves the formation of free radicals in the dental plaque, capable of reducing and inhibiting the activity of macrophages and neutrophils.

Hemorheological alterations
Diabetic disease is often accompanied by structural and functional changes in red blood cells, such as less deformability and hyperaggregability. Equally relevant are the platelet alterations such as hyperadhesiveness, hyperaggregability that lead to blood hypercoagulability.
At the periodontal level, these haemorological changes would contribute to causing ischemic and / or thrombotic episodes, which associated with the decrease in the gingival rate of oxygen utilization, could facilitate the onset of periodontal disease or aggravate its course.

Alterations in the periodontal connective tissue
The reduced synthesis of collagen, its decreased solubility and the degradation of newly synthesized collagen, associated with a low production of platelet and epidermal growth factors by monocytes and a reduction in bone matrix production by osteoblasts, are responsible for the increased difficulty in wound healing in patients with diabetes mellitus.

Alterations of the salivary composition
An alteration of the biochemical composition was found in the saliva of diabetic subject. This alteration is responsible for affecting the pH values and the component of the bacterial flora present in the oral cavity. The salivary pH is lower due to blood acidosis and the presence of fermentable glucose, due to more frequent meals not always followed by thorough oral hygiene. Saliva is more sticky and as such less cleansing, with a reduction in salivary flow that varies approximately from one third to one half compared to non-diabetic patients.
The biochemical changes in the saliva of diabetic subjects are: the decrease in the number of enzymes such as "peroxidase" (direct action on the functionality of the glandular acinus); the decrease in protein synthesis and enzymatic activity (these factors can be corrected within 3 hours by administering insulin); the alterations of some antibacterial factors such as: lactoferrin, lysozyme and lactoperoxidase; the increase in IgA and IgG due to an increase in the permeability of the basement membranes.

Finally, the increased concentration of calcium and glucose in saliva would favor the development of a pathogenic periodontium flora, as well as the deposition of significant amounts of tartar. Among the other affections found in diabetic patients, the first specific lesion is *benign migratory glossitis* (geographic tongue): it is noted in particular in the elderly, associated with a rather prolonged duration of the disease.
Other lesions are *irritative fibroid* and *traumatic ulcer* often found in association with lichen planus, hyperplastic gingivitis and enlargement of the parotid gland. The relationship between lichen planus and diabetes is thought to be linked to an immunological defect that accompanies the two diseases.

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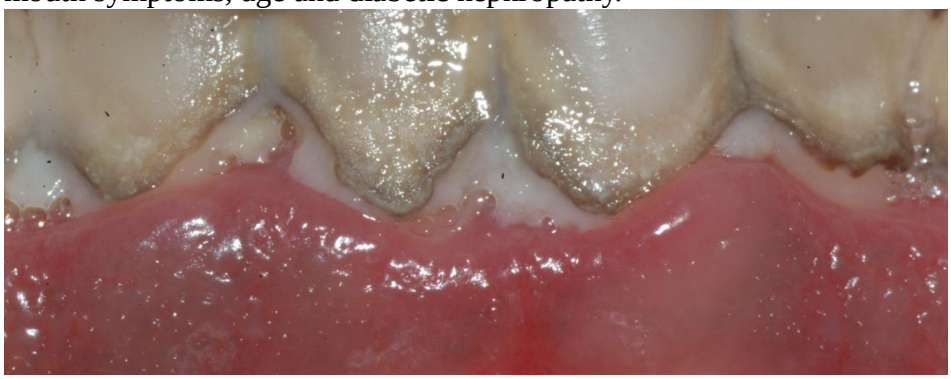
The presence of these manifestations is directly proportional to the use of alcohol, smoking, dry mouth symptoms, age and diabetic nephropathy.



Correlation between diabetes and periodontal disease
Ref. (O'Connell et al. - J Periodontol 2008.)

Indications for the management of periodontal risk in diabetic patients

If the diagnosis is made early and in any case before the destruction of a large part of the alveolar-dental ligament, periodontitis can be treated effectively and efficiently in most patients.
Untreated periodontal disease, moreover, can lead to increased glycemic instability and increased insulin requirements, thus creating a vicious circle of worsening of the diabetic disease. In general, inflammatory periodontal symptoms prevail in Type 1 juvenile diabetes with a more acute course than the picture found in the adult suffering from Type 2 diabetes, in which the gingival pathology has a slow evolution, mostly without painful symptoms and with late compromise of dental stability.
Diabetic patients should be monitored for the following clinical symptoms / signs of periodontitis: gingival bleeding, recession of the gingival margin, tooth mobility, migration or loss of some teeth, presence of halitosis.
The diabetic patient who does not show signs of periodontitis must maintain a high level of oral hygiene and undergo regular dental checks and prevention.
If chronic periodontitis is diagnosed, this must be quickly treated and the patient must re-enter a secondary dental prevention program with the aim of preserving periodontal health and chewing function.

The educational programs of diabetic patients in the dental field must include health education interventions for the prevention of oral pathology, educating the patient to the daily use, in addition to the toothbrush, of dental floss, interdental brushes and all the interventions deemed most appropriate to safeguard the health of the periodontium.
The therapeutic protocols to be adopted for each type of conservative, endodontic, periodontal or prosthetic intervention do not differ substantially from those used in the healthy subject, except for the assiduity and incisiveness that must characterize the operation, by virtue of the subject's predisposition to get sick.
After a careful examination, both clinical and instrumental, a scrupulous anamnesis evaluating the diabetes and medical therapy in progress (with judgment on the treatment also with anticoagulant antiplatelet, antihypertensive, hypolipidemic drugs), besides the glycemic compensation, arranging a rigorous asepsis, establishing where a systemic antibiotic prophylaxis is necessary to prevent complications and an accurate assessment of the periodontal situation to reach a precise diagnosis, it is possible to move on to the patient's therapeutic planning.
Particular attention is needed for difficult oral surgery and implantology interventions.
In cases of extensive and hard operations it is preferable to operate in structures in which both the stomatologist and the diabetologist are present, so that the patient can be fully controlled.
The patient should be educated on the dietary and therapeutic changes to be made during these phases.

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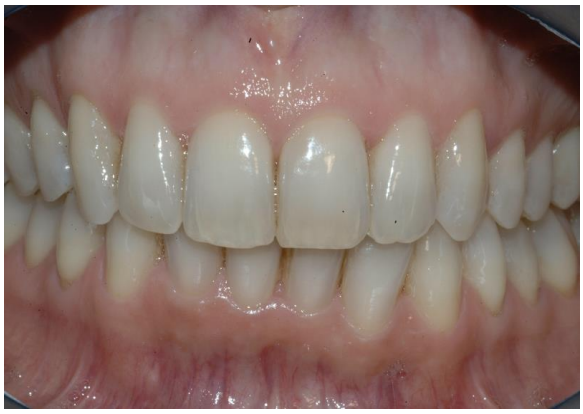
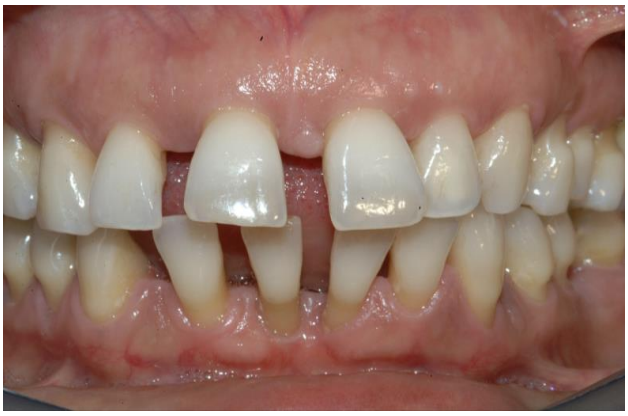
In fact, stress and an incorrect diet after surgery could develop keto-acidosic decompensation or hypoglycemic crises due to a reduction in caloric intake.
The possible hypoglycemic crisis, in fact, can be an emergency of no small importance and must be promptly identified and treated. Lastly, recent publications indicate that using age, weight, morphometric values and possible presence of periodontitis as evaluation criteria, allows, in a dental setting, to start a successful diagnostic path. This path, improved and managed by the diabetic doctor, is able to lead, in subjects who are unaware of their condition, to an early diagnosis of diabetes and the implementation of a timely therapy able to prevent and counter the frequent complications associated with this disease.



Healthy periodontium



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