Abstract. – Relationship between diabetes mellitus (DM) and periodontal disease has been the subject of many studies that underline that diabetic patients are two/three times more susceptible to have an increased risk of periodontal disease, especially when metabolic control is inadequate. In this review the Authors analyze, in diabetic patient, biochemical, histological and microbiological aspects of periodontal disease. Recent studies reported the results obtained in not diabetic patients, both periodontopatic and not: in periodontopatic subjects, the value of glycated hemoglobin was higher. As regards type 2 DM has a positive relationship between periodontal inflammation and glycemia, with good probabilities of disease development. Some Authors showed how the hygiene and the professional/domiciliary control could support a reduction of the glycate hemoglobin and, therefore, of the periodontal disease. The glucose accumulation in the crevicular fluid, noticed in pockets with a depth >4 mm, causes an increase of spirochetes and bacteria. Some research reported that scarcely controlled patients show high levels of interleukin-1beta (IL-1β). This alteration together with the prolonged expression of Tumor Necrosis Factor (TNF) could represent a mechanism used by bacteria to cause a major damage during the inflammation process, sometimes favoured by immunological defects, due to the mobilization of lymphocytes sub-populations. By measuring the values of TNF-α, fibrinogen, high sensitive Capsule Reactive Protein (hs-CRP), IL-4, IL-6, IL-8, IL-10, at the beginning of non-surgical periodontal therapy and it has been after 3 months of treatment, noticed a relevant reduction only of TNF-α and fibrinogen. Concerning vascular alteration, vascular endothelium growing factor (VEGF) could play a major role in the tissues ischemia. The VEGF should determine the tissue ischemia, the angiogenesis and the alteration of glucose haematic level, in patients affected by micro-vascularopathies due to diabetes and to periodontal diseases. Particularly, the angiogenesis should favor the chronic inflammation, caused by increasing concentration of cytokines and other pro-inflammatory factors.

Introduction

Diabetes mellitus (DM) is characterized by an impaired metabolism of glucose. In type 1 DM a viral infection, in genetically susceptible individuals, has been hypothesized as “triggering” of the disease. Type 2 DM is the most common one, particularly in obese individuals and should be associated to a genetic defects of insulin secretion or an acquired glucose intolerance. In 2002 Matthews has reported that, statistically, only for 50% of the diabetic population a diagnosis has been performed.

The Glycosylated Hemoglobin

Haemoglobin (Hb) is an iron-containing quaternary protein derived from a non-covalent bound of four subunit (tetramer form – two α e two β protein chains). The valinic NH2 terminal of the β chain can bind glucose molecules diffused from plasma into the erythrocyte through a non enzymatic binding, thus forming glycosylated hemoglobin (HbA1c). Hb doesn’t undergo a regular turnover during the erythrocyte live (approximately 120 days). Thus, HbA1c quantity is proportional to glucose concentration and to the exposure time. For these reasons, HbA1c can be considered a more reliable marker of glucose concentration when compared with home daily glucose monitoring.

In 2009 the International Expert Committee revaluated the importance of the HbA1c in the diagnosis of DM using the standard Diabetes Control and Complications Trial/UK Prospective Diabetes Study (DCCT/UKPDS). This method

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achieved promising results in individuals, not showing the following pathologies: type 1 DM in rapid growth, pregnancy, hemoglobinopathies, chronic anemia, hemolytic anemia, uremia. The advantages of the DCCT/UKPDS method consist of a better dosage standardization, a lower biological variability, a longer pause (>8 hours) among blood drawings test. Actually, if the classical symptoms of polyuria, polydipsia and loss of weight are not recorded, the diagnosis is performed if the following values are repeated almost twice:

- HbA1c > or equal to 6.5%
- FPG (Fasting Plasma Glucose Concentration) > or equal to 126 mg/dl (glycemic control before meals for almost 8 hrs)
- OGTT (Oral Glucose Tolerance Test) > or equal to 200 mg/dl (glycemic test must be performed according to the WHO protocol: after 2 hrs from the assumption of a quantity of glucose equal to 75 g of anidro glucose solved in H2O).

Viceversa, as reported in 2007 in the “WHO Consultation” if the DM typical symptoms are noticeable, the diagnosis must be performed, also referring to the only glycemic value, when > or equal to 200 mg/dl.

In many papers it has been noticed that, in case of inflammations or cellular adhesion in non-medically controlled type 1 DM, the defense mechanisms can result altered. Particularly, if the oral cavity is involved, a diminution in the salivary flux (caused by hyperglycemia) can induce the production of a selected microbial and mycotic flora. In case of a relevant decrease in the salivary flux, it has been noticed an increase in the mucine and glucose concentration and a reduction of antimicrobial elements, often followed by candidiasis and exfoliation of the epithelium. Furthermore, caries, lichen planus and ulcers of the oral mucosa can be consequences of a chronic reduction of salivary flux.

The relationship between DM and periodontal disorders has been also discussed and demonstrated: in fact, diabetic subjects are two/three times more susceptible to this pathology. Other Authors reported a calculation method to verify the consumption of alveolar bone in type 1 diabetic patients or screening examinations regarding plaque, gingivitis, probing depth and probing attachment level, 12, 24 and 60 months after the baseline examination. Teeuw et al, analyzing a sample of 639 papers, have observed a statistically relevant correlation between periodontopathy and type 2 diabetes. Recently, Covani et al have studied, by genomic approach, using the “Leader Gene Approach” method, the relationships between type 2 diabetes and periodontal disease. The “Leader Gene Approach” method, as described in that report, allows to identify and characterize, according to the number of interconnections, the genes bound to a specific biological process. The genes, showing the highest number of interconnections, are defined “leader”, since they are the most involved in the disease. The aim of that research is to identify the interconnections between the genes of periodontal disease and diabetes, using the genes of sinusitis as control. The results obtained showed that 4 out of 5 genes leader, identified for the periodontal disease, were in common with diabetes genes leader; viceversa, as expected, no interconnection has been discovered with the sinusitis genes, used as control. Among the shared genes, the Reticulo Endotheliosis Viral Oncogene Homolog A (RELA) and the Nuclear Factor of Kappa Light Polypeptide Gene Enhancer in B-Cells 1 (NFKB1) are more significant, since both appear in the inflammation chemical mediators. Moreover, the Authors have suggested an improved analysis method, the Real Time Polymerase Chain Reaction (RT-PCR), that should simplify the results interpretation.

Other genomic researches have been performed to verify the existence of a correlation between the periodontal disease and diabetes among individuals, expressing for IL-1. Periodontitis was significantly associated with some IL-1 gene polymorphisms. Anyway, the relationship between diabetes and IL-1A and -1B gene polymorphisms has not been observed.

Eventually, it has been noticed that in the progression of periodontal disease, the insufficient metabolic control and the duration of pathologic status are really relevant, especially in presence of vascular complications, inflammations, alteration of microbial flora. These researches prove that the diagnosis is fundamental in the disease prevention and medical treatment.

Diabetes, Periodontium and Glycemic Control

The relationship between DM and periodontal disease has been widely studied, obtaining het-
Dietary mellitus: biochemical, histological and microbiological aspects in periodontal disease

The bacterial plaque, as result of a selected bacterial flora, is supported by a salivary flux reduction, by high glucose concentrations in the saliva and in the gingival crevicular fluid. The selected bacterial flora could lead to an increasing of non-enzymatic glycosylation of proteins (i.e. immunoglobulins). High quantities of glucose can lead to the development of periodontogenic flora as a consequence of the reduced oxygen production and of the following defense cells reduction. The glucose accumulation in the crevicular fluid, noticed in pockets with a depth >4 mm, causes an increase of spirochetes and bacteria. The subgingival plaque, associated to bacteria, damages both periodontal tissues that the patients response ability, particularly at the beginning of the disease. Different studies have shown the relationship between some micro-organisms and periodontopathy: generally in periodontal patients is noticed the presence of Porphyromonas gingivalis (associated to low levels of "supra-gingival" plaque), Tannerella forsythenis (together with the previous, associated to high levels of plaque with risk of loss of attack), Actinobacillus actinomyctetcomitans (in association with the first, causes serious periodontal destructions). Sometime, other bacteria, such as Treponema denticola and Treponema sorcansii are associated to serious damages. Bacteriological researches demonstrated that 70/80% of type 2 DM patients showed as most frequent bacteria species: Prevotella intermedia, Campylobacter rectus, Porphyromonas gingivalis. Moreover, the interaction among Porphyromonas gingivalis, Treponema denticola, Eikenella corrodens and Candida albicans is particularly damaging both in type 2 DM that in healthy patients showing a probably common etiology.

The relationship between Porphyromonas gingivalis and Tannerella forsythenis could play a major role in the virulence and in the periodontal disease progression, promoting adhesion and invasion of tissues (i.e. the OMV’s – outer membrane vesicles) with the beginning of infections and chronic periodontitis.

In 2001 Yaun et al. studied the correlation among different bacterial strains. The results reported that the relationship among periodontitis and bacteria Streptococcus oralis, Eikenella corrodens, Staphylococcus intermedius, Fusobacterium nucleatum subsp. ventincetti, Eubacterium nodatum and Treponema denticola, both if associated or not with Porphyromonas gingivalis and Tannerella forsythenis, is particularly active at the beginning of the disease. Anyway, the bacterial strain can play a very important role; i.e. Porphyromonas gingivalis type II film A is associated to periodontitis progression. Instead, the strains I and IV don’t seem to be bound to the...
disease development. Besides this, in diabetic individuals, the disease development is also promoted by bacterial strains, normally not very virulent.

From a proteomic and a physiological approach, it has been reported that Porphyromonas gingivalis and Treponema denticola can activate the metal and serine matrix of protease of neutrophil bacteria during the phagocytosis. Moreover, the pro-inflammatory mediators (IL-1β, IL-6, IL-8, TNF-α PGE2), the metal protease (MMP-9) and the presence of seric antibodies for the “Heat Shock Proteins” (HSP90, HSP70, GAD65 and LPS) can promote or give information on the therapy in case of periodontium lesions.

In type 1 DM patients, Porphyromonas gingivalis and P. intermedia play a major role in the invasion of oral epithelium; the role of Capnocytophaga sp is, on the contrary, still under discussion.

Some reports analyzed the bound among periodontal disease, species of bacteria (spirochetes and motiles) and their distribution in healthy and DM individuals.

An other Author described the relationship, in type 1 DM individuals, between the hyperglycemia and the selection of pathogenic microorganisms, such as spirochetes and rod-shaped, especially in the apical section of periodontal pockets.

Safkan-Seppala et al (2001) showed that in diabetic patients, both scarcely (PIDD) that well compensated (CIDD), the amount of cocci and other bacteria (filiform and fusiform) in pockets with a depth <4 mm were the same. Instead, in pockets >4 mm, the quantity of bacteria and spirochetes was major in PIDD subjects.

Finally, the predisposition of DM patients to the infections caused by Candida albicans is now well known. These candidiasis are often associated to immunity deficits, xerostomia, low glycemic control, use of prosthesis.

Biochemistry and Host Response

In diabetic subjects, the periodontium is highly susceptible to the pathogenic activity of the collagenases, of the metallo-proteases (MMP), of the collagen reduction and of the glycosaminoglycans synthesis. Furthermore, the metabolic anomalies of the fibroblasts of periodontal ligament (PDL) play a major role. Moreover, the oxidant agents, supported by other bacterial proteases, potentially periodontogenic, can activate destructive neutrophils, epithelial, endothelial, bone cells and derivatives of metallo-proteases (MMP-8 and MMP-13).

As regards to the diagnostic, it has been observed that the MMP-2, in adolescents with type 1 DM, could be markers of microangiopathy; besides, the collag enases in the GCF of type 1 patients are activated, as in case of patients with chronic periodontitis.

As results, nowadays, the identification of individuals with high risk of periodontal disorders is significatively easier and the relationship between periodontal disease and scarcely controlled diabetes is really clear.

The main focus of many reports was to study the response of the host. It has been observed that not controlled DM subjects have an altered cellular response to the inflammation, probably due to a deficit of inflammatory cells and to the altered functions of neutrophils and macrophage monocytes.

It has been also demonstrated that the advanced glycation endproducts (AGE) can lead the macrophages to produce high levels of IL-1, IL-6 and TNF-α, which could indicate altered immune functions. Moreover, the AGE alters the endothelium permeability, favouring the inflammatory processes due to the increasing of adhesion molecules expression. Bulut et al reported that scarcely controlled patients show high levels of IL-1β. This alteration together with the prolonged expression of Tumor Necrosis Factor (TNF) could represent a mechanism used by bacteria to cause a major damage during the inflammation process, sometimes favored by immunological defects, due to the mobilization of lymphocytes sub-populations.

Other Authors observed an interaction between non-enzymatic glycosylation and the function of proteins and defense cells. It has been reported that high levels of circulating immunocomplexes (CIC) could show a reduction of host defenses, particularly in case of diabetic patients.

Recently, Kshirsagar et al hypothesized that a minor humoral immunity, verified in type 2 DM patients and compared to those affected by type 1 DM, were caused by hyperinsulinaemia associated to insulin-resistance.

Beside this, Salvi et al have noticed that, inducing an experimental gingivitis for 35 days in type 1 diabetic patients and in healthy patients, in the former the MMP-8 and the IL-1β levels were
significantly higher. Many researchers, anyway, don’t agree to compare the experimental gingivitis with gingivitis induced by real pathologies, since many values are often contrasting.

Other studies have examined the non-surgical periodontal therapy. Kardesler et al. obtained a reduction of the elements bound to the inflammation (IL-6, TNF-α, reactive Protein C) and as a consequence, an increase of adiponectin (hormone with anti-inflammatory properties). Correa et al. measuring the values of TNF-α, fibrinogen, high sensitive capsule reactive protein (hs-CRP), IL-4, IL-6, IL-8, IL-10, at the beginning of non-surgical periodontal therapy and after 3 months of treatment, have noticed a relevant reduction only of TNF-α and fibrinogen.

Periodontal Disease and Diabetic Complications

The periodontal disorders frequently lead to other complications: i.e. an increasing of diabetic nephropathy (micro-albuminemia included) and cardiovascular disturbs in type 1DM, affected by heavy periodontal disorders.

Sadzeviciene et al. analyzed the effect of periodontal disease on other organs: the periodontal tissues have been evaluated according to the Community Periodontal Index of Treatment Needs (CPITN) index of OMS. The results obtained showed that the periodontal inflammation is closely associated to a vascular complications increasing and diabetic retinopathy, nephropathy and neuropathy development are frequently related to periodontal tissues, with CPITN index around 3 and lack in tissues with CPITN around 2, as a consequence of a major loss of attack.

Several studies reported interactions between periodontal disease and the development of other pathologies. In general, the most significant results showed a positive correlation among neuropathy, dental loss and ATD disorders, especially type 2 DM. Further studies, associating the periodontal disease, high levels of IgG or high quantity of bacterial periodontogenic flora to renal disorders or artherosclerosis, myocardial infarction and cardiovascular disorders seem to be necessary.

In fact the periodontitis could play a major role in the atherogenesis (with thickness increase of the intima and medium lamella of the carotid artery) in the risk of coronary heart disease (CHD) and in the myocardial infarction particularly in male individuals and, above all, in case of infections due to Porphyromonas gingivalis and/or A. actinomycetencomitans.

Furthermore, have been noticed infections, caused by mycotic systemic inflammations, in patients affected by non-controlled DM: these pathologies, usually, start in the maxillary sinus (antrum of Highmore) and show themselves with ulcerations or palate necrosis, sometimes with bone exposure.

Histological Aspects of Tissues

A metabolic study of tissues, especially of sub-epithelial inflamed connected tissues (ICT), in both PIDD that well CIDD diabetic patients, appears to be necessary. Several papers report that an altered inflammatory response leads to a depletion of neutrophils and/or monocytes/macrophages functions. Moreover, Saftkan-Sep-pala et al. observed that in PIDD patients, the histological analysis showed a high concentration of plasma cells and a lower quantity of lymphocytes, associated to a reduction of fibroblasts, collagen fibers and pericytes. The endothelial cells appeared also re-inflated and proliferated and in the ICT of the gingiva of type 1 DM was found the presence of Russell bodies.

Other studies reported dysfunctions of vascular tissues, that interfere with the nutrients transport and lymphocytes migration from gingival tissue: these dysfunctions lead to a reduced oxygen diffusion process and to a scarce destruc-tive capability of metabolic excretes. The scarce glycemic control and the long disease duration worse the tissues condition: the gingiva small blood vessels in long-term diabetic patients, often show microangiopathic alterations and obstruction or vascular thickening.

Aspriello et al. suggested that vascular endothelium growing factor (VEGF) could play a major role in the tissues ischemia. The authors have studied the function of VEGF and of microvessels in gingival tissues in both diabetic and non diabetic patients. The VEGF should determine the tissue ischemia, the angiogenesis and the alteration of glucose haematic level, in patients affected by micro-vasculopathies due to diabetes and to periodontal diseases. Particularly, the angiogenesis should favor the chronic inflammation, caused by increasing concentration of cytokines and other pro-inflammatory factors. Besides this, the researchers have proposed a survey method of the angiogenesis level, based on the antibodies calculation versus a transmembrane protein (CD 34), present in pre-endothelial
cells. A study carried out on periodontopathic diabetic or non-diabetic patients showed higher VEGF concentrations and a major micro-vascular density in type 1 compared to healthy and type 2 diabetic individuals.

Many researches performed with electron microscopy showed a statistically significant increase of widthness of epithelial basal cells in type 1 diabetes subjects, respect to control subjects. Vascular complications, due to prolonged type 1 diabetes, can occur. In fact modified proteins, the advanced glycation end-products (AGEs), can induce oxidative stress to the gingival tissues, that, anyway, could be used as biological reference markers.

References

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