DIABETES MELLITUS AND PERIODONTAL DISEASE – A TWO-WAY ROAD: CURRENT CONCEPTS AND FUTURE CONSIDERATIONS (LITERATURE REVIEW)

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Abstract

Introduction: Scientists have developed an emerging interest regarding the interrelationship between periodontal disease (PD) and systemic conditions. The best documented condition related to PD is diabetes mellitus (DM). PD is considered to be the sixth complication of DM, both having inflammation process and increased oxidative stress as primary etiologic features.

Aim: This paper is aimed at reviewing and evaluating the DM's role as the main risk factor in PD and the immunological correlations between these two pathologies in search of future and new considerations, beginning with current meanings.

Materials and methods: Epidemiological, immunological, clinical and experimental studies assessing the relationship between PD and DM were selected and studied from medical and dental journals and books.

Results: Periodontal inflammation leads to increased circulating cytokines, inflammatory mediators and autoimmune response to infection. The severity of periodontal destruction is demonstrated to be linked to glycemic control effects, other factors also being involved. In diabetic patients with PD, IL-1β, IL-6, and TNF rise gradually with the evolution of DM, consecutive to microangiopatic complications and to the installation of periodontal bone lesions. A significant correlation between metabolic control and the severity and extend of periodontal lesions has also been reported.

Conclusions: Although literature is full of articles and studies that demonstrate the close relationship between diabetes and periodontal disease, larger intervention studies are needed to assess if periodontal health improvement can lead to improved metabolic control. It is also considered that the management of oral health should play an important role in diabetes management and vice-versa.

Keywords: Periodontal disease, inflammatory mediators, autoimmune response, cytokines, gene polymorphism

Introduction
Current Concepts and Future Considerations

Society evolution is commonly associated with the increased spread of diseases such as diabetes mellitus (DM) and periodontal disease (PD). DM and PD are known to be among the most prevalent human disorders and they are frequently and concurrently present in many people.

World Health Organization states in 2000, that there are nearly 177 million diabetic people worldwide and approximately 1 million in Romania. The same organization estimates an increase in the diabetic population of over 370 million worldwide and of 1.8 million in Romania, until 2030.

It has been known for a long period of time, that periodontitis is a common chronic gram-negative anaerobic infectious disease.

Other authors consider periodontitis as a chronic inflammatory disease characterized by connective tissue attachment loss and alveolar bone resorption which leads to tooth loss, by periodontal pocket formation. (Katz et al.1991).

In all the studies linked to these two pathologies, periodontitis is regarded as having a bidirectional relationship with diabetes mellitus. (Katz et al.1991).

In 1997, the American Diabetes Association stated PD as the sixth complication of DM after retinopathy, nephropathy, neuropathy, macroangiopathy and delayed wound healing (Furukawa et al. 2007).

Although there are several risk factors for PD, DM has been until now, the only systemic disease connected through biochemical mechanisms with PD (Gheric et al. 2008).

The most common effect of type 1 and type 2 DM is noticed on the physiological immune system and inflammatory defense (Tesseromatis et al. 2009), affecting its severity (Enrich et al. 1991, Sandler et al. 1960).

Defined in different ways during the years, DM identifies a group of disorders characterized by elevated blood glucose levels (Lamster et al. 2008). Its complications can cause high morbidity and premature mortality. This chronic metabolic disorder has a large impact on society by affecting over 100 million people worldwide (Harris et al. 1995).

During the years, DM proved to have the responsibility of tooth deprivation by decay and PD. (Tesseromatis and all. 2009). This is acknowledged by the known fact that DM patients present: gingival inflammation, levels of plaque and calculus that are higher than in other cases and also, when present, deeper periodontal pockets (Christgan et al. 1998).

Clinical studies relate and connect severe periodontitis with periodontal destruction with the lack of metabolic control, pathologies not seen in individuals with well-controlled blood glucose levels.

In a study published in “Clinical Science”, in 2010, Martin G. Lazenby and Martin A. Crook considers aggressive periodontitis as having a non-contributory medical history and family aggregation of cases (Lang et al. 1999). In the same study, they state, after some observations by Nishimura and co-workers (Nishimura et al. 1998), that glycemic status is important for the well being of periodontal cells, taking in consideration their susceptibility to variation and rapid fluctuation of glucose levels. They also conclude that hyperglycemia can exacerbate inflammatory tissue destruction indirectly and also that both hyper- and hypo-glycaemia can perturb, this time directly, the “biological functions of periodontal connective tissue via cell-matrix interactions”. (Jacopino 2001).

Bradford Hill (Hill 1965), considers that periodontitis precedes the development of DM, but this is still difficult to establish. However, Demmer et al. show, in a cohort study that non-diabetic periodontal patients have an increased risk of developing diabetes. This can be explained throughout the known fact that acute focal dental inflammation can determine a

sudden increase in insulin requirements. It has also been shown that endodontic treatment "is associated with attenuation of insulin resistance and reduced insulin requirements" (Schulze et al. 2007).

Type 1 and type 2 DM have different etiologies but despite this, they share common symptoms like glucose intolerance, hyperglycemia and also many of the same complications, as Kahn and Flier report (Naguib et al. 2004).

Another fact related to the relationship between PD and DM, that may help demonstrate it, is that diabetics are more susceptible to gingivitis and periodontitis than non-diabetic persons. But it is not known for sure if diabetics are more prone to infections in general. In some studies, there appeared a correlation between the degree of gingival inflammation and the level of HbA1C in children and adolescents with type 1 DM (Reutervig 2010).

A very important fact that must be taken into consideration is that only approximately 5% of diabetics are classified as being insulin dependent, so having type 1 DM (Hee-Kyung 2009).

This paper is aimed at reviewing evidences that support the connections between periodontal disease and diabetes mellitus. It also addresses future concepts and even research directions needed to elucidate this two-way relationship

Main Text

The Incidence And Prevalence Of Pd In Diabetic Patients

It has been suggested that PD acts, in diabetics, as a crucial aggravating factor in maintaining a chronic systemic inflammatory process (Mealey et al. 2006).

Although global prevalence of periodontitis is hard to estimate, a recent extensive review showed the variability of the worldwide prevalence of periodontitis. This prevalence is assumed to be under 10-15% (Löe 1993). Despite the fact that PD has a big impact in type 1 and type 2 DM, individuals with type 1 DM are exposed to a greater risk of gingivitis and periodontitis (Rylander H. et al 1987).

Researchers concluded that children and adolescents with DM have a prevalence of developing gingivitis, twice the one observed in children and adolescents without diabetes (De Pommerean et al. 1982).

The association: type 1 DM with gingivitis is widely accepted. In the most recent classification of PD, DM- associated gingivitis is considered to be a specific entity (Armitage 1999, Mariotti 1999).

Periodontitis is fairly uncommon in children younger than 12 years, even among those with diabetes. Even so, the prevalence of PD in children with type 1 DM has been reported at 9.8 percent, compared to 1.7 in those without diabetes (Cianciola et al. 1982).

After extended research, it has been concluded that 64 percent of diabetics may have gingival inflammation compared to 50 percent of healthy individuals, but the existence of gingivitis is not mandatory (Albandar et al.2002).

Patients who have developed type 1 DM for over 10 years, appear to have lost more periodontal attachment than patients who have diabetes for less than 10 years. Related to the severity and extent of the metabolic condition, patients aged 40 to 50 years, with type 1 DM for a long period of time exhibited more sites with advanced periodontitis and bone loss (Hugoson et al. 1989).

The prevalence of periodontitis has been reported up to 9.8 % in patients between the age of 13-18 years and is increasing to 39% in those older than 19 years.

Type 2 diabetes is the most widespread type of diabetes all over the world.

Researchers suspect that the prevalence of periodontitis in diabetic subjects, may be the result of impaired immune response against the infectious processes. This appears to be higher in individuals with poorly controlled diabetes (Mealey et al. 2006).

In type 2 DM, the prevalence of gingival inflammation occurs at higher rates than in adults without diabetes (Ryan et al. 2003). In a study developed during a two-year period, Taylor and colleagues, reported that 67 percent of patients with type 2 DM presented significant bone loss compared to individuals without DM, which presented a percentage of 44. They concluded that PD progresses faster in patients with diabetes (Taylor et al. 1998).

Furthermore, evidence show that the prevalence, extent, severity and progression of PD are higher in patients with DM (Mealey et al 2006). It is also believed that PD in diabetic patients is associated with the existence of chronic diabetic complications. (Taylor G.W. et al 2008).

Several authors show that metabolic disturbances in PD decrease diabetic patients' resistance to infections and along with this, comes the initiation, development and progression of PD.

Epidemiologic Data

Epidemiologic studies indicate that 5-20 % of the population suffer from severe forms of periodontal disease (Brown I.J., H. Löe, 1993).

According to Löe (1993), aggressive periodontitis is recognized as the sixth complication of diabetes mellitus. He also agreed with the conclusions of multiple

epidemiologic studies which demonstrated that type 1 and type 2 diabetes are predictors of PD, when there is a lack in the metabolic control.

According to all studies, more than one quarter of subjects with type 1 DM who had poor metabolic control, presented sites with attachment loss of 5 millimeters or more in comparison to 10 percent of the subjects that have a good metabolic control (Tervonen et al. 1993).

Investigations suggest that patients with well-controlled diabetes do not have an increased risk of developing PD (Tsai et al. 2002).

Pathologic Mechanisms

Periodontal disease is a chronic gram-negative infection thought to increase insulin resistance.

Through this mechanism, it contributes as known, to the development of metabolic imbalance (Genco et al 2005).

As multiple studies, recognize, the pathogenesis of periodontal disease is complex. It shows a combination of 2 processes: the initiation and maintenance of a chronic inflammatory process, developed with the help of a diverse microbial flora with its diversity of bacterial products.

The host response to this infectious mechanism mediates a “cascade” of tissue destructive pathways (Page R 1991).

Some time ago, researchers linked the role of microorganisms as being the main etiologic factor in PD. Nowadays this is not sufficient. The major component of periodontal tissue destruction is believed to be the result of the host immune-inflammatory response to bacterial challenge.

Plaque biofilm and the associated host response are involved in PD pathogenesis (Card et al. 2006).

The stimulation of the host response results in affecting strictly the gums developing gingivitis or in the initiation of periodontitis. *(fig. no. 1, fig. no.2, fig. no. 3)*

After PD is being initiated in every form, researchers believe and have shown that perpetuation of the host response disrupts homeostatic mechanisms and finally results in neutrophil and macrophage recruitment. Along with this recruitment, in PD process, mediators as: pro-inflammatory cytokines, matrix metalloproteinase, arachidonic acid metabolites, reactive oxygen species and also mediators for osteoclastic bone resorption, are being released. The host response is protected by the recruitment of neutrophils, protective antibodies production and as some authors acknowledge possibly by the release of anti-

inflammatory cytokines the most representative being: growth factor-β, IL-1, IL-4, IL-8, IL-10 and IL-11 (Card et al. 2006).

Other pathological mechanisms involved, are related to the elevated levels of blood glucose. These mechanisms also include the activation of the sorbitol pathway, the formation of advanced glycation end-products (AGEs), the alteration of lipid metabolism, and last but not least, the presence of the damaging effect of oxidative stress.

AGEs "have been implicated in susceptibility of oral infections, exaggerated inflammatory response and destruction of alveolar bone" (Llambes et al. 2005).

All mechanisms involved in periodontal tissue destruction and metabolic imbalance, have been associated with the classical complications of DM: retinopathy, nephropathy, neuropathy, macrovascular disease and also poor wound healing.

Among the increased production of circulating cytokines and inflammatory mediators, several authors have found mechanisms as an autoimmune response to the chronic periodontal infection leading to endothelial dysfunction (Silvestre et al. 2009). Several other factors beyond microbial plaque and hyperglycemia are believed to influence the initiation and progression of periodontal lesions in diabetic patients.

Recent investigations found that the irregular production of cytokine by immune cells and increased inflammatory destruction of periodontal tissue is a response to hyperglycemia combined with dyslipidemia. (Buhlin K. et al 2003) Dyslipidemia represents a disorder of lipoprotein metabolism, including lipoprotein overproduction or deficiency. Lately, there has been a growing evidence in literature that implicates reactive oxygen species (ROS) in the pathogenesis of various diseases, including PD. (Waddington et al.2000).

It has been concluded with no doubt, that local infection in the periodontal pockets initiates a systemic inflammatory response. Associated with this process, there are elevated levels of antibodies especially linked to Porphyromonas gingivalis.

From the other point of view, several mechanisms that could explain the increased susceptibility to infection in diabetic patients have been suggested .Some of these mechanisms are "impaired chemotactic, phagocytic and bacterial killing by cells of the innate immune response" (Naguip et al. 2004).

What came as a surprise for researchers and clinicians, is the fact that diabetics are not more susceptible to all infections. They mainly seem to be more vulnerable to gram-negative infections as specified by Joshi et al in a study developed in 1999. These infections include among others, soft-tissue infections and periodontal disease (Loe 1993; Nishimura el al 1998, Naguip et al. 2004).

Immunologic Data

Throughout several studies conducted over the years, it had been at first suggested and then proved that the innate immune system modulates the effects of genes, ethnicity, nutrition, aging and even fetal programming upon metabolic complications. These complications are often associated with insulin resistance.

A great amount of studies revealed that systemic markers of inflammation increase in PD and also in DM.

PD appears as known, due to the plaque biofilm, consisting of hundred species of bacteria. This biofilm initiates an immune response in the periodontal tissues, the main action of the *innate* immune system. The *adaptive* immune system plays an important role too (Berglundg 2005).

Periodontal bacterial byproducts interacting with mononuclear phagocytic cells and fibroblasts induce the chronic release of cytokines (IL-1β, IL-6, TNF-α) (D'Ainto et al. 2004). Local infection in the periodontal pockets initiates a systemic inflammatory response that releases inflammatory mediators.

Literature suggests that there exists a genetic component to the development and propagation of periodontitis caused by gene polymorphism that affects some cytokine expression, especially IL-1 (Nikolopoulos et al. 2008).

Phylogenetically older than the acquired immunity, the innate immune system represents a first-line defensive mechanism based on macrophages and neutrophils non-lymphoid tissue components. Researchers propose periodontitis to be an acute phase response that activates the innate immune system (Lazenby et al. 2010).

This acute phase response changes the concentration of plasma proteins in response to infection, tissue trauma and inflammation.

CRP, haptoglobyn, fibrinogen and amyloid A are acute-phase proteins synthesized in the liver and stimulated by IL-1, IL-6 and TNF cytokines.

In periodontal disease, the innate immune response is active, and it proves to be an important mediator in insulin resistance and type 2 DM etiology.

It has been demonstrated that between DM and PD a strong link is represented by the actions of the immune system. If the metabolic control is disturbed, the periodontal lesions evolve faster and with a worse prognostic. On the other hand, if the PD is not firmly maintained under control, there will always be a metabolic imbalance. In both situations, the inflammatory cytokine levels rise during each lack of balance.

As Desfaits et al. prove in 1998, higher levels of inflammatory cytokines especially TNF (tumor necrosis factor) are seen in type 2 DM.

An explanation for this process could be the production of TNF in the adipose tissue as Hotamisligl et al show in a study conducted in 1995. Enhanced cytokine production caused by the effects of hyperinsulinemia or hyperglycemia, as Soop and colleagues affirm in 2002 could also represent a reason.

Because a great amount of research has been developed, but there is still a lot to find out about how type 2 DM alters the inflammatory response to bacteria, Zubery and collaborators developed in 1998, an innovative experiment. This helped them assess the response of normal and diabetic mice. They used a suited scalp model to study the host – bacteria interactions in a connective tissue setting. The study proved that there exists a certain mechanism through which diabetes alters the response to bacteria (Lang et al. 1999).

Three pro-inflammatory cytokines are assumed to play a central role in periodontal tissue destruction. These cytokines are IL-1, IL-6 and TNF-α. (Nisengard et al.2007).

IL-1 and TNF are two of the most important pro-inflammatory cytokines.

The pro-inflammatory cytokine TNF-α represents an important trigger in TNF-α/ NF-kB signaling pathway.

Three cytokine – induced nuclear import and export of these signaling proteins are believed to be essential in different biological systems (Brivanlon A.H. et al. 2002).).

There have been identified two distinct TNF receptors, in men and mice: TNF-R1 and TNF-R2 .TNF-R1 is responsible through its higher affinity and dissociation rate for TNF, for the most inflammatory activities of TNF. On the other hand, TNF-R2 is believed to enhance TNF's activity by binding TNF and then passing it on the TNF-R1.

A cause-effect relationship between inflammatory cytokines and several diseases has been established by using IL-1 antagonists.

IL-1 has three ligands: IL-β, IL-α and IL-1ra- receptor antagonist. IL-1α and IL-β present similar biological activities. Il-1ra binds to IL-1 receptors acting as a competitive inhibitor. (Shannon P. et al. 2003) IL-1 ligands bind to the IL-1 receptor type I and type II. Most of the studies developed have focused on the type I receptor.

Researchers utilized for the investigation of the role of IL-1 and TNF, Macaca fascicularis monkey experimental model, in which the periodontal bone loss was induced by tying silk ligatures around the posterior teeth of these monkeys (Assuma et al. 1997). Along with this experiment, it has been revealed that the application of IL-1 and TNF blockers

caused an ~80% reduction of inflammatory cell recruitment deep in the gingival connective tissue.

Another conclusion is that IL-1 and TNF present little direct chemotactic activity for leucocytes.

In order to examine the effects of IL-1 and TNF blockers on bone resorption, a histomorphometric analysis was conducted. This exam measures the number of osteoclasts formed and also the quantity of bone loss occurred. Kimball provided throughout his studies evidence that the activity of IL-1 contributes to the appearance of osteoporosis due to endocrine changes (Kimble et al. 1995). This study observed that the inadequate production of IL-1 and TNF may provide a mechanism that can explain bone resorption in a great amount of diseases having diverse causes from bacterial stimulation to endocrine- associated bone loss.

Researchers and clinicians also speculate that enhanced bacterial challenge as that occurred in experimental periodontitis raises the levels of pro-inflammatory cytokines (IL-1/TNF), a situation that results in exacerbated recruitment of inflammatory cells.

Il-6 is an acute phase response mediator with many diabetogenic actions including the stimulation of the adrenocorticotropic hormone (ACTH) (Hagopian et al. 2006).

Although few studies regarding the influence of IL-6 and TNF-α over metabolic control have been conducted, controversial results have been reported. One of the most eloquent study was the in-vitro evaluation of IL-6 and TNF-α production by adherent peripheral blood mononuclear cells obtained from patients with type 1 and type 2 DM. These patients were evaluated before and after adequate metabolic control (Foss-Freitas et al. 2006).

Therapeutic Implications

Researchers have conducted studies that investigated the association between periodontal therapy and improvement of glycemic control (Foss-Freitas et al. 2006).

It is known that a considerable amount of medical resources is utilized for managing the several complications that can occur in DM.

As PD has been cited as the sixth complication of DM, it has also been demonstrated that the metabolic control and periodontal disease share a similar platform and need a high degree of patient compliance. Patients with poor glycemic control have been found to have more severe forms of periodontitis. On the other hand, researchers find it not so clear if effective control of PD is always and entirely associated with a concomitant improvement of glycemic control (Tan et al. 2006, Taylor G.W et al. 2008). Other studies conducted recently have shown that the increasing duration of diabetes and the presence of complications,

namely retinopathy, as presented in this study, impaired a significantly greater risk of developing PD (Schlossman et al. 1994).

Because of the large amount of studies regarding the relationship between PD and DM, a meta-analysis has been developed (Janket et al. 2005).

This meta-analysis and the Consensus Report of the Sixth European Workshop on Periodontology found that it is inconclusive that periodontal therapy results in an improved metabolic control (Kinane et al. 2008).

Researchers concluded that a more intensive therapy may be needed and also longer follow-up times, for more evident therapeutic benefits. Beside scaling and root planing, several adjuvant therapies have been proposed and developed for the elimination of periodontal infection. *(fig. no 4, fig. no. 5).*

Some researchers and clinicians used systemic antibiotics as doxycycline topical antiseptics as Clorhexidine or Povidoneiodine. All these substances combined with a thorough scaling and root planing improved the metabolic control of diabetic patients, reducing the levels of HbA1c and the insulin requirements (Grossi et al. 1997).

An innovation could be considered the local administration of minocycline microspheres inserted into the periodontal pockets; a therapy also improving HbA1c (Skaleric et al. 2004). A main conclusion is observed from this meta-analysis. Glycemic control can improve with the help of scaling and root planing combined with short-term antimicrobial therapy. This result is more accurate if patients present an advanced PD and if they present a poor metabolic control before treatment.

A comparison study stated that in type 2 DM control group there was observed a 6.7% improvement in glycemic control, which was less compared to the 17.1% improvement seen in the group that underwent periodontal treatment (Stewart et al. 2001).

Another meta-analysis conducted in 2007 demonstrated a moderate, but statistically significant result in favor of the therapeutic group that proved a slight improvement in metabolic control.

An association between PD and DM therapies exists. One of the best information available suggests that periodontal treatment improves glycemic control, but Taylor (1999), Janket and colleagues (2005)**,** concluded that more evidences are needed to assure clinicians that periodontal treatment improves metabolic control in diabetic patients. Authors that developed this study also found a correlation between glycemic control, represented by HbA1c levels and the severity of PD. They suggested that enhanced oxidative stress and inflammation exacerbate both diseases.

Another study investigated the therapeutic implications of scaling and root planing therapy combined with doxycycline therapy for 2 weeks in type 1 diabetic patients. These patients presented improved periodontal health and a significant improvement in metabolic control during and after this therapy.

Also, patients who demonstrated a small amount of clinical effect from the periodontal therapy, had no change in their glycemic values.

Sometimes patients with moderately controlled and well controlled diabetes and PD who overcome only a mechanical therapy, may present no significant changes in their metabolic control, but they can present an improvement in their periodontal status.

Discussions

Many studies found in scientific literature offer inconsistent or vague evidences regarding the implications involved in these two pathologies. A cause of these inconsistencies could be the methodology that has been followed for the studies, different criteria used to diagnose and assess the levels of glycemic control.

Some of the studies concentrated on both type 1 and type 2 DM, while some of them only on one of these two pathologies.

Correlations between metabolic control and PD also suggest that oxidative stress and inflammation exacerbate both pathologies. Speculations talk about the bacterial challenge that stimulates pro-inflammatory cytokine levels involved in DM and in its complications development.

It is well accepted, regardless of the style of the study or of its methodology, that pro-inflammatory cytokine levels are elevated when DM is poorly controlled. If complications appear, or if the period of DM evolution is longer than 10 years, proinflammatory cytokine levels rise as well. More debated subjects are linked to the way periodontal treatment improves metabolic control by reducing HbA1c levels. These levels rise during PD development too, this disease being connected at several different levels.

Long-term studies are needed to examine the role of PD therapy on metabolic control in both types of DM and also, to examine the role of well controlled DM in PD patients.

Researchers should assess the degree of healing needed to affect glycemic control, and the effect for metabolic monitoring before, during and after periodontal therapy.

Conclusion

- A considerable amount of medical resources is being used for managing DM, PD and their several complications that can occur.

- PD is initiated by bacteria that colonize the root surface and this develops an inflammatory cascade
- Diabetes is associated with periodontal breakdown in every kind of research listed.
- The extent of periodontal destruction in diabetic patients is influenced by glycemic control and the individual immune-regulatory capacity.
- Cytokine titre and inflammatory mediators levels rise with the extend of PD and DM, and after several complications are installed.
- Periodontal therapy may or may not have a direct impact on glycemic control.
- It is not very clear whether a good periodontal therapy contributes to the management of metabolic control in both type 1 and type 2 DM.
- Defective phagocytosis of Porphyromonas gingivalis by neutrophils was observed in diabetic patients.
- The super oxide release in diabetes is drastically increased.
- Glycemic control can be improved with the help of scaling and root planing combined with short-term antimicrobial therapy, especially in patients with advanced PD and poor metabolic control.

Acknowledgements: The researcher was financed by the project POSDRU/107/S/1.5/78702

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Illustrations

Fig. no. 1 – Diabetic Gingivitis (case from personal archive)

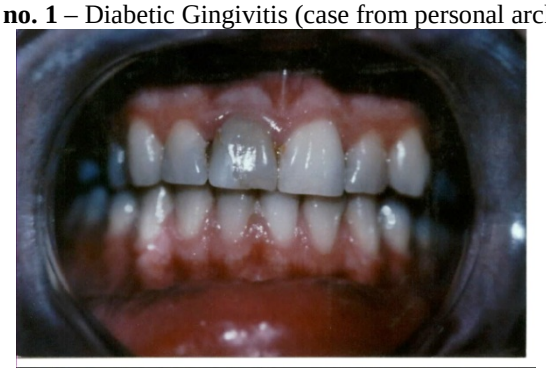

Fig. no. 2 – Diabetic Periodontitis (case from personal archive)

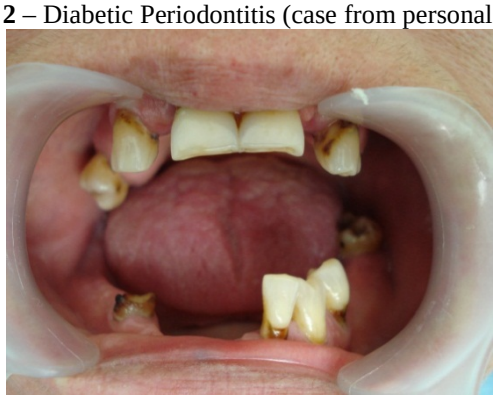

Fig. no. 3 – Diabetic Periodontitis (case from personal archive)

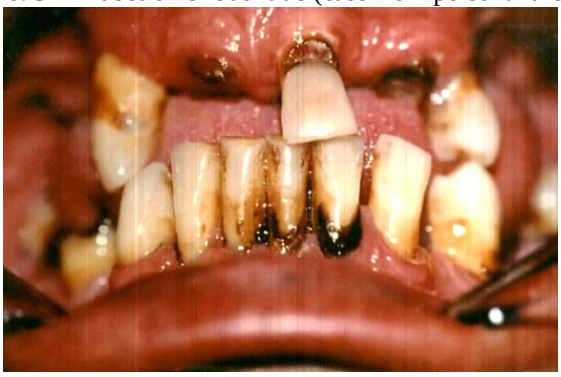

Fig. no. 4 – Gracey currettes kit for scaling and rootplaning

Fig. no. 5 – Scaling and rootplaning in a patient with generalized chronic periodontitis