### University for Business and Technology in Kosovo

## **UBT Knowledge Center**

**UBT International Conference** 

2021 UBT International Conference

Oct 30th, 12:00 AM - 12:00 AM

## Dental management considerations for the patients with Diabetes Mellitus in Oral Surgery and Pediatric Dentistry

Vullnet Fazliu

University for Business and Technology - UBT, vullnet.fazliu@ubt-uni.net

Aferdita Rizai

University for Business and Technology - UBT, aferdita.rizaj@ubt-uni.net

Follow this and additional works at: https://knowledgecenter.ubt-uni.net/conference



Part of the Medicine and Health Sciences Commons

#### **Recommended Citation**

Fazliu, Vullnet and Rizaj, Aferdita, "Dental management considerations for the patients with Diabetes Mellitus in Oral Surgery and Pediatric Dentistry" (2021). UBT International Conference. 423. https://knowledgecenter.ubt-uni.net/conference/2021UBTIC/all-events/423

This Event is brought to you for free and open access by the Publication and Journals at UBT Knowledge Center. It has been accepted for inclusion in UBT International Conference by an authorized administrator of UBT Knowledge Center. For more information, please contact knowledge.center@ubt-uni.net.

#### Dental management considerations for the patiens with diabtes mellitus

#### In oral surgery and pediatric dentistry

#### A review

#### Vullnet Fazliu 1, Aferdita Gashi-Rizaj2

#### **Abstract**

The incidence of patients suffering from diabetes is increasing. Due to the increase in population, the pediatric dentist as well as the oral surgeon must effectively treat the patients based on the protocol as efficiently as possible.

Based on the review of various literature, the authors present relevant information about diabetes mellitus, its type, manner of occurrence, complications, medical and dental management of these patients.

There is a lot of medical and dental data which the pediatric dentist and the oral surgeon should take into consideration when treating patients with diabetes mellitus.

Keywords: diabetes mellitus, oral surgery, pediatric dentistry

#### Introduction

Diabetes mellitus is a metabolic disease of glucose, fat, and protein that results from either impaired insulin secretion, high insulin resistance, or both. This chronic disease is characterized by hyperglycemia and complications including microvascular changes of the kidneys, eyes, and nervous system (neuropathy). These complications are responsible for the high rate of mobility and mortality in the diabetic population. (1)

In addition to these changes, oral manifestations are also evident, which also affects oral care.

Diabetes mellitus is classified as:

- Type 1 diabetes insulin dependent: absolute lack of insulin due to autoimmune destruction or accelerated destruction of pancreatic B cells, this is in fact inherited with a disorder of the genes on chromosome 6.
- Type 2 diabetes not insulin dependent: absolute lack of insulin or insulin resistance (inability to produce insulin by the pancreas resulting in lack of circulating insulin and consequently the appearance of Diabetes Mellitus Subsequent hyperglycemia).

**Gestational**: which occur in 5-7% of all pregnancies and result in loss of fetus. In case of surviving fetuses, the usually overwiught . When pregnancy over, mother glycemic control return to normal but this women are at developing diabetes in the next 5-10 years,

#### **Epidemiology**

According to data from 2006, 23.6 million people (about 7.8% of the population) in the USA have been diagnosed with diabetes, while now after this period of time, 34.2 million people have been diagnosed with diabetes mellitus, meaning 1 in 10 people have diabetes mellitus, whereas 1 in 3 are prediabetic. The increase in the number of young people 10-19 years diagnosed with diabetes mellitus is worrying. (2)

Nearly 6 million people are not aware they have diabetes, and they only realize this after a complication arises. The prevalence increases with age and about 245 million people are over the age of 60 years. An epidemic of type 2 diabetes is almost on the rise knowing that globally the number of patients with type 2 diabetes is increasing year by year. Based on 150 - 220 million cases in 2010, this number is expected to reach 300 million in 2025, which shows us that will cost a lot to treat DM, as well as this disease being a clinical problem.

In addition, DM is considered to be the leading cause of blindness and kidney damage (in adults between the ages of 20-74), gingivitis and periodontitis.

Also 1/3 of people with DM have severe periodontal disease, with loss of gingival connections to the teeth on average 5mm-or more.

High morbidity with this disease, puts this disease among the 7 leading causes of death certified in the USA in 2006. The risk of death in patients with DM is 2 times higher than in people without DM, of the same ages.

#### **Pathophysiology**

Understanding the pathophysiology of diabetes still remains based on basic knowledge about carbohydrate metabolism and insulin action. After consuming food, carbohydrates are broken down into glucose molecules in the gut. Glucose is absorbed into the bloodstream, raising its level in the blood. This increase in blood glucose stimulates the secretion of insulin by pancreatic  $\beta$ -cells. The insulin produced binds to specific cellular receptors and enables the introduction of glucose into the cells, which enables its use for energy as needed.

If the production and secretion of insulin changes, this is accompanied by a change in the dynamics of glucose in the blood. If insulin production decreases, glucose uptake into cells is inhibited, resulting in hyperglycemia. The same effect can be encountered if insulin is produced by the pancreas but not used properly by the target cells. If the secretion of insulin increases, more glucose is stored in the cells, as a result we have a small amount of glucose in the blood, which leads to hypoglycemia (3).

Cells store sufficient amounts of glucose. But if there is still a large amount of glucose in the blood, the excess amount is stored in the liver, in the form of glycogen, which serves as a constant reservoir in the future. When energy is needed, the glycogen stored in the liver by glycogenolysis is converted to glucose as an energy source. But if the amount of glucose in the blood remains small even after glycogenolysis, then the liver produces glucose from lipids (fatty acids) and proteins (amino acids), through the process of glycogenesis. Thus, glycogenolysis and glycogenesis are processes that regulate the amount of glucose

in the blood. In this case the body must find an alternative way as an energy source, and in this case utilizes triglycerides in fatty acids, this process is also known as gluconeogenesis, where in addition to glucose production it also produces ketonic bodies that in a long period leads in diabetic ketoacidosis.

In addition, as a result of hyperglycemia, glucose is excreted through the kidneys and Polyuria (frequent urination) occurs as a result of osmotic diuresis. Excessive fluid loss in this case leads the patient to dehydration where the patient needs to drink as much fluid as possible (polydipsia). Also the lack of glucose in the cells results in the patient starving (polyphagia), and all these consequences in the inability to utilize glucose in the cells lead the patient to weight loss (depletion of fatty acid and protein reservoirs).

In addition to the hormone insulin which plays a key role in the regulation of carbohydrates in the blood, other hormones such as: glucagon, catecholamines, growth hormones, thyroid hormones and glucocorticoids. (4)

#### **Etiology:**

Diabetes mellitus can result in any of the following causes:

- genetic disorders which attack both types of Diabetes, but mostly Type 2, because as a cause of Type 1 is mostly attributed to the role of viral infections and autoimmune reactions.
- primary disorders of pancreatic cells during inflammation, cancer, or surgery
- endocrine disorders such as hyperpituitarism or hyperthyroidism
- during other disorders in the body where the administration of high doses of steroids is required.

#### **Complications of diabetes mellitus**

Chronic increase in plasma glucose levels results in accumulation of glucose and extracellular metabolic products, and as a result then we also have complications which are:

Acute complications

- Ketoacidosis
- Non-ketotic hyperosmolar hyperglycemic syndrome
- Hypoglycemia

**Chronic Complications** 

- microvascular changes in the eye (retinopathy- microaneurysm of the retina)
- kidney (nephropathy), and
- neuropathy.

Macrovascular changes

Ulcers on foot.

In the group of patients with poor diabetic controls, it is more important that in these cases the prolongation of wound healing after surgical-oral and pediatric interventions may appear and as a result it may increase the chances for postoperative infections.

Also special attention should be paid to the non-enzymatic process Glycation - (binding of glucose to proteins and fats) which results in the release of Piole products - Sorbitol or Mannitol which are metabolic products of glucose that also cause tissue damage. (6)

#### Diabetes and manifestations in the oral cavity

The manifestation of diabetes is also encountered in the oral cavity. Xerostomia as a symptom of diabetes in the mouth, leads to dry surfaces of the mouth and as a result burns off the oral mucosa, as well as creating a suitable environment for the development of candidiasis or bacterial infections.

In addition to the above, according to numerous studies, the reason that leads to a high incidence of infections either before or after certain surgical interventions is attributed to the fact that the defense mechanisms are severely impaired starting from deficient vascularization, reduction of production of growth factors, reduced immunity as well as psychological stress. All these then affect the prolongation of processes such as those of regenerative oral soft tissue or bone healing processes (7).

The effect of diabetes on the appearance of caries is still unclear, although some studies suggest that xerostomia and increased glucose in the gingival fluid, creates the possibility of the appearance of caries. But, knowing that patients with diabetes have limited intake of fermented carbohydrates, the studies between patients with type II diabetes and the control group, show that there are no significant differences regarding the increased incidence of caries with 2 groups. Data in Sweden also shows that the percentage of the population affected by gingivitis and moderate periodontitis has decreased and the percentage of the population with healthy peridoncium has increased, all as a result of diabetes and oral health management. For example, this percentage of healthy periodontium was for 1983-23%, in 1993-22% and in 2003-44%.

#### **Diabetes and periodontium**

Diabetes and periodontal disease are the two most common chronic diseases in some parts of the world. Research shows that there is a two-way relationship between diabetes and periodontal disease, so that diabetes endangers periodontal health due to poor glucose control, which leads to periodontal disease, which also worsens diabetes. This shows how important it is not only for oral health professionals, but for all health professionals, to understand the role and importance of oral health management in patients with diabetes. We will focus on some key objectives, based on research done on diabetes and periodontal disease, such as:

- 1-The negative effect that diabetes has on periodontal health,
- 2-Negative effect of periodontal infection on glucose control in diabetes and
- 3-Periodontal infection and the development of complications in diabetes, but also the impact on the pathogenesis of diabetes itself (8).

#### The negative effect of diabetes on periodontal health

It is known that diabetes affects periodontal diseases, but that it also depends on the controls against diabetes. Patients who have good control over diabetes show the same degree of gingivitis compared to healthy people. Although numerous epidemiological studies suggest impairment of ligaments in the periodontium and bone resorption, almost 3 times more than in people without diabetes. Also patients with diabetes easily develop periodontal disease as a complication of diabetes, if they do not take care of oral hygiene, always knowing that dental plaque is the main cause of periodontal diseases. But in patients with well-managed diabetes and careful oral health care there are no significant differences with incidence of periodontal disease in healthy individuals.

Hyperglycemia encountered in the blood will be found increased in the gingival fluid and this leads to vascular changes in the gingiva, as well as other complications in the retina, kidneys, etc. Atherosclerotic changes lead to narrowing of blood vessels, resulting in increased periodontal tissue destruction and poor reparative potential. (10)

Diabetes also damages immune cells, such as polymorphonuclear leukocytes, monocytes, and macrophages, impairing polymorphonuclear adhesion, chemotaxis, and phagocytosis. This leads to increased inflammation in the periodontal epithelium and connective tissue, increasing the degradation of tissue connections and bone loss because bacterial agents act freely.

Collagen, as the primary structural protein in the periodontium, is also damaged. This is because it increases the production of collagenase, a collagen-destroying enzyme that continuously destroys the collagen produced. Thus, diabetes affects the normal synthesis of collagen, and consequently the difficult healing of wounds.

Tetracycline agents reduce collagen production and collagen degradation by antimicrobial action, therefore indicated for the treatment of periodontitis, arthritis, diabetes, osteoporosis, etc. (11)

#### The negative effect of periodontal infection on glucose control in diabetes

The data show that periodontal infection can affect glycemic control of diabetes, because periodontal infection increases the risk for minimal control against glycemia, especially in cases with complications of diabetes, such as nephropathy and macrovascular disease. In one study, 82% of patients with advanced diabetes and periodontitis had a cardiovascular, cerebrovascular, or peripheral vascular attack during the 1-11 years of the study, compared with only 21% of individuals with milder-grade diabetes. low or no periodontal disease. (12).

In patients with diabetes, periodontal treatment has an effect on glycemic control. Studies have confirmed this in patients with diabetes and periodontal tissue treatment with combination therapy with tetracycline (doxycycline), but not in patients treated with periodontitis but without antibiotics.

The mechanism by which antibiotics, together with periodontal treatment, have a positive effect on glycemic control is not yet known. Perhaps this is because subgingival pathogens are eliminated and collagen production is suppressed, which destroys collagen.

Oral manifestations that occur in diabetic patients are

Gingival and periodontal pathologies

Prevalence / assessment in the progression of oral changes, accurate instructions for oral hygiene, dietary instructions, frequent periodic examinations, and prophylaxis.

Salivary gland dysfunctions and xerostomia / caries, mucosa, absence of papillae.

Prevalence / mouthwash Rich in fluoride as well as saliva substitutes (xylitol-carboxymethylcellulose - or hydroxyl cellulose, stimulating muscle receptors. (13)

# Medical treatment and dental treatment of patients who undergo surgeries in oral surgery and pedodontics.

The main purpose of treating patients with DM is to keep blood glucose levels as normal as possible, and this is achieved by controlling glucose which also prevents concomitant complications.

Normal blood glucose values;

Beetwen 4.0 -5.4 mmol / I (72-99mh.DI),

Up to 7.8 mmol / L (140 mg / Dl) 2 hours after meals

For diabetic patients, the target values should be:

Before meals: 4-7 mmol / type 1 and 2 After feeding: below 9 mmol / L for Type 1 and 8.5 mmol / L for Type 2.

According to the American Diabetes Association, it is recommended that people over the age of 45 have a diabetes test every 3 years.

As glucose circulates in the blood, it attaches to a portion of the hemoglobin molecule in the erythrocytes, and as blood glucose rises, so does the percentage of hemoglobin that binds to glucose. There are 2 tests that measure glucose hemoglobin:

- 1. Hemoglobin A1 (HbA1), normal value is less than 8% and
- 2. Hemoglobin A1c (HbA1c), normal value is 6.0-6.5%.

The other method for measuring blood glucose levels is the fructosamine test, where normal values range from 2.0-2.8mmol / L and measures glucose in the next 2-4 weeks.

Glucose monitoring is also performed by the patient himself, with the help of glucometers. Patients with type I diabetes measure their blood glucose level several times a day, compared to patients with type II diabetes. (14)

The target values to be achieved in diabetic patients are:

Target values HbAIC Pre-meal value of blood glucose mod/L 2 hafter meal mod/L  $\leq 7.0\%$  4.0-7.0 5.0-10.0

#### **Drug management**

The main goal of medical management in all diabetic patients is to keep blood glucose levels as normal as possible.

As a medication for the treatment of Diabetes is Insulin which is administered either subcutaneously or per os .

Insulin - which is used to treat patients with diabetes is found in several forms, based on the time of action:

Rapid - reacts within 15 min. with the highest point of activity in 45-90min

Short action - reacts within 30 min. With the highest point of activity in 2-5 h

Intermediate action (lens) - reacts within 1-2 h, with the highest point of activity 6-12h

Long action (Ultralente) - reacts within 4-6 h, with the highest point of activity 8-20 h. (15)

In cases of type 1 diabetes, due to the correlation between suboptimal glucose control and vascular complications, intensive management is the main way recommended to all patients. This is actually achieved even through more frequent insulin administration (up to 4 times a day) or the use of different types of insulin as well as the monitoring of blood glucose.

Insulin administration should be done individually, adapting to each patient separately, age and lifestyle.

For example, adults and adolescents are given intermediate-acting insulin at bedtime, school-age children are given short-acting insulin, and give a glass of tea in the afternoon instead of lunch to prevent hyperglycemia, while preschool children may be given manage a dose of intermediate-acting insulin in the morning and small doses of fast-acting insulin analogues to prevent hyperglycemia later.

In order to minimize the risk of any intraoperative emergency, clinicians need to correctly apply management protocols based on a few points:

#### Medical history

Have a clear glucose value before each treatment, as well as previous glucose values or any previous hypoglycemic condition.

We should also be informed about antidiabetic medications, the dose and time at which they are administered. In addition, we should be informed about medications that may interfere with blood glucose levels either in the role of insulin or in carbohydrate metabolism.

Drugs that have hypoglycemic action - salicylates, dicumerol, b-adrenergic blockers, sulfanamides or even angiotensin inhibitory converting enzymes. (16)

While drugs with hyperglycemic action are: corticosteroids, epinephrine, oral contraceptives or calcium channel blocker drugs.

#### Scheduling an appointment for a medical visit

Generally, morning visits are recommended because the level of endogenous cortisol in this daily period is high (the role of cortisol - increases the level of glucose in the blood), also patients should definitely take the daily dose of insulin since in the morning its peak of action is low and thus prevents the occurrence of any eventual state of Hypoglycemia. (17)

#### Diet:

It is much more important for clinicians to make sure that the patient has eaten breakfast and has received the necessary therapy (insulin). On the contrary if the patient has not eaten breakfast but has taken a certain dose of insulin then he is at risk for a hypoglycemic crisis.

In cases when it is necessary to make major interventions under sedation or anesthesia, food should be avoided before this procedure, the insulin dose should be modified in consultation with the specialist doctor who is checking the patient (18).

#### **Blood glucose monitoring:**

Depending on the medical history, therapy or even the procedures that need to be performed, dentists need to measure the level of glucose in the blood.

If the blood glucose level is less than 70 mg / Dl, then we should prescribe sugars before the intervention in order to minimize the hypoglycemic crisis. While in patients when the blood glucose level is too high, then in we refer the patient to make a consultation with the specialist doctor before treatment. (19)

#### **Management during treatment**

The critical condition that may occur during the treatment of patients with Diabetes Mellitus is the hypoglycemic crisis. This is when insulin levels exceed physiological needs, and usually occur when the effect of insulin is maximal.

The initial clinical signs during a hypoglycemic episode are:

Mood swings, weakness, and then accompanied by sweating, tachycardia, and if we do not react immediately the patient may experience consciousness, hypotension, hypothermia, fever, coma and eventually death. (20)

How to manage: To stop the intervention, then to administer 15 g of glucose or any glucose tablet, chocolate, but in cases when the patient has already lost consciousness then administer intravenously25 -30 mL of 50% dextrose solution or 1mg of glucagon ( it can also be administered subcutaneously or intravenously) ( 21 )

If the long period of hyperglycemia persists, then ketoacidosis appears when the patient clinically results in theft, loss of concentration, abdominal pain and bad acetone odor. In these cases, insulin administration is required.(22)

Intraoperative management of hypoglycemic emergency

**Signs and Symptoms Managing emergencies** 

Mild	
<ul><li>hunger</li></ul>	
<ul> <li>fatigue</li> </ul>	
<ul><li>sweating</li></ul>	Terminate dental treatment immediately
<ul><li>nausea</li></ul>	Awake/alert patient
<ul><li>abdominal pain</li></ul>	<ul> <li>Administer 15 g oral carbohydrate (i.e., glucose tablet, 180 mL orange juice, 15–25 mL sugar)</li> </ul>
• headache	<ul> <li>Monitor blood glucose and repeat carbohydrate dosing as necessary</li> </ul>
<ul> <li>tachycardia</li> </ul>	Uncooperative patient
<ul> <li>irritability</li> </ul>	Seek emergency medical assistance
Moderate	Administer glucagon 1 mg via subcutaneous or intramuscular
<ul> <li>incoherence</li> </ul>	injection followed by oral glucose supplement or
<ul> <li>uncooperative</li> </ul>	Administer 20–50 mL of 50% dextrose solution intravenously
<ul> <li>belligerence</li> </ul>	Unconscious patient
<ul><li>resistive</li></ul>	Seek emergency medical assistance
behaviour	Administer 20–50 mL of 50% dextrose solution
Severe	
<ul> <li>unconscious</li> </ul>	

## After treatment

seizure

Clinicians should also consider possible postoperative changes in this group of patients.

In the case of the group of patients with poor control of Diabetes Mellitus are more at risk of developing infection and wound healing, therefore if we are dealing with major surgical interventions then we must take certain doses of antibiotics for preventive.

Also patients who use drugs such as salicylates increase insulin secretion and as a result may lead to hypoglycemia. Therefore, aspirin should be avoided in the postoperative period.

As a conclusion in the context of dental management we need to take the following steps:

- Consultation with a specialist doctor regarding diabetes
- To receive an accurate medical history including medications which are under the prescription of the patient
- To be confirmed by the patient who has eaten food and taken medication before treatment
- The pedodontist or oral surgeon should be aware of the emergency symptoms of diabetes and how to manage that emergency condition
- Prevention, treatment and elimination of infections in advance
- Do not use aspirin
- Achieve deep local anesthesia (to reduce stress)
- Ensure good oral hygiene
- Provide a regular diet and medication
- Provide a glucometer when we have conservative treatment or oral surgery. (23)

#### **Conclusion**

Based on the fact that now with about 318 million people worldwide suffer from Diabetes, it is clear that Oral Surgeons or Pediatric Dentist during their professional careers with treat such patients suffering from this chronic disease, add here the number of oral manifestations and the risk of intraoperative emergencies, it is necessary for us to have the knowledge about the underlying disease, the consequences that appear from this disease which result in the oral cavity and to have accurate knowledge about how to treat these manifestations, and as a professional doctor to cooperate together so as to effectively inform the patient about exemplary oral health care.

#### References

- 1. American Diabetes Association (2010) Diagnosis and classification of diabetes mellitus. Diabetes Care 33(Suppl 1): s62-s69.
- 2. Wild S, Roglic G, Green A, Sicree R, King H (2004) Global prevalence of diabetes: American Estimates for the year 2000 and projections for 2030. Diabetes Care 27): 1047-1053.
- 3. Karvonen M, Viik-Kajander M, Moltchanova E, Libman I, LaPorte R, et al. (2000) Incidence of childhood type 1 diabetes world-wide. Diabetes Mondiale (DiaMond) Project Group. Diabetes Care 23(10): 1516-1526.
- 4. (2000) Variation and trends in incidence of childhood diabetes in Europe. EURODIAB ACE Study Group. Lancet 355(9207): 873-876.
- 5. Diabetes diagnosis National Diabetes information clearinghouse (2001) National institute of Diabetes and digestive and kidney diseases. National Institute of Health 41: 31-35. 9. American Diabetes Association (2003)
- 6. Goldmann DR: Surgery in patients with endocrine dysfunction. Med Clin North Am 71:499–509, 1987
- 7. Hempel A, Maasch C, Heintze U, Lindschau C, Dietz R, Luft FC, Haller H: High glucose concentrations increase endothelial cell permeability via activation of protein kinase C alpha. Circ Res 81:363–369, 1997
- 8. Rayfield EJ, Ault MJ, Keusch GT, Brothers MJ, Nechomias C, Smith H: Infection and diabetes: the case for glucose control. Am J Med 72:439–450, 1982
- 9. Marhoffer W, Stein M, Maeser E, Federlin K: Impairment of polymorphonuclear leukocyte function and metabolic control of diabetes. Diabetes Care 15:256–260, 1992
- 10. Hugoson A,Sjodin B,Norderyd O,Trends over 30 years 1973-2003,in the prevalence and severity of periodontal disease. J Clin Periodont2008;35:405-414
- 11. Kolterman O,Scarlett JA,Olefsky JM,Insulin Resistance in non-insulin-dependent, type II diabetes mellitus Clin Endocrinol M,tab 1982;11:363-388
- 12. Lamster b,DePaola DP, Oppermann RV,Papanou PN.Wilder RS,The relationship disease to disease and disorders at distant sites: communication to health care professionals and patient.J.Am Dent Ass.c 2008;139:1389-1397
- 13. Pipeleers D. Ling Z.Pancreatic beta cells in insulin-dependent diabetes. Diabetes M tab R v 1992;8:209-227 andgepts W.Lecompte Pm.The pancreatic islets in diabetes.Am J M d 1981;70:105-115
- 14. Robert J. Genco, Ray G. Williams Periodontal disease and overall health:a Clinician's guideCare diabetesjournal.org
- 15. Working together to manage diabetes, Departments of health and human services, National center for chronic disease prevention and health promotion, Atlanta, 2007)
- 16. American Academy of Peridontology, Diabetes and Periodontal disease. J Periodontal 1999;70:935-49Care diabetesjournal.org

- 17. American Diabetes Association. Diagnosis and Classification of diabetes mellitus. Diabetes Care 2008; 31:S55-60
- 18. Buse JB Polonski KS Burant CF. Tipe 2 diabetes mellitus. In: KronenbergHM Melmed S. Polonski KS,Larsen RP,eds,Kronenberg:Williams textbook of Endokrinology,11th edition. St.Louis:W.B.Saunders
- 19. "Burket's Oral Medicine Diagnosis and Treatment" tenth edition, Greenberg, Glick
- 20. Company; 2008:1329-1330 National Institute of Diabetes, and Digestive and Kidney Diseases-NIDDK, National diabetes statistic2007, vol 2008: national diabetes information clearinghouse. Available at;http://diabetes.niddk.nih.gov/dm/pubs/statistic/index.htm.Accesed Dec 28, 2008
- 21. Elwood J. "Critical Appraisal of epidemiological Studies and Clinical Trial. New York. Oxford University press;1988
- 22. Genco RJGrossi SG,Ho A,Nishimura FMurayama Y, A proposed model linking inflammation to obesity,diabetes and periodontal infection. J periodont/2005;76:2075-2084
- 23. Golub LM, Lee H-M, Ryan ME, Tracyclines inhibitors connective tissue breakdown by multiple non-antimicrobial mechanism. Adv Dens Res1998;12:12-16