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TEETH EXTRACTION DURING DIABETES: A SYSTEMIC REVIEW

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ABSTRACT

Diabetes mellitus (DM) is recognized as an enormous menace to the general population globally, which affects 463 million adults. It is a systematic metabolic disorder characterized by defective insulin secretion and impaired insulin, resulting in microvascular complications and hyperglycemia. Diabetes is divided into diabetes mellitus type 1 (T1DM) and diabetes mellitus type 2 (T2DM), withT2DM making up 90% of cases worldwide and thus more relevant research. Patients with DM are associated with a high risk of hyperlipidemia, obesity, and healing disorders. Considering that diabetes ranks 3th in the most prevalent chronic disease in the oral field, number of diabetic patients experiencing oral manifestations exceeded 90 %. Diabetic patients have a prevalence of missing teeth, prolonged wound healing, xerostomia, caries, burning mouth disorder, lichen planus, and even bacterial osteomyelitis of the jaw, which could increase the treatment difficulty and compromise the treatment outcome of various oral diseases. They have a higher risk of tooth extraction due to periodontal disease than non-diabetic patients. The origin of the medication- related osteonecrosis of the jaws tends to be tooth extraction in elderly patients with uncontrolled diabetes. Besides bacteraemia and fungal infection caused by diabetes- related tooth extraction seem to be a triggering factor for osteomyelitis and mucormycosis. Therefore, elucidating the mechanism and investigating the approaches to promoting the healing of tooth extraction sockets is of great clinical importance, especially for the patients with DM. In this review, we systematically searched and appraised the current literature to summarize and discuss the mechanisms and managements of delayed extraction sockets in patients with diabetes.

KEY WORDS: Diabetes mellitus (DM)**,** Insulin resistance, Diabetes-related ketoacidosis (DKA)**,** Insulin, bone morphogenetic protein (BMP), microRNA's

INTRODUCTION:

Diabetes is one of the most common life style diseases prevalent across all ages and classes that happens when your blood sugar (glucose) is too high. It is characterized, by the body's inability to use the blood sugar for energy. Pancreas is the organ in our body which produces insulin and releases it in the body, Insulin is the key which allows the cells in our body to uses it to process the blood sugar and convert it to energy. When pancreas

does not release the insulin, the sugar level increases in the body and affect our internal organs adversely, sometimes resulting in death. Most forms of diabetes are chronic (lifelong), and all forms are manageable with medications and/or lifestyle changes. Glucose (sugar) mainly comes from carbohydrates in your food and drinks. It's your body's go-to source of energy. Your blood carries glucose to all your body's cells to use for energy. When glucose is in your bloodstream, it needs help — a "key" — to reach its final destination. This key is insulin (a hormone). If your pancreas isn't making enough insulin or your body isn't using it properly, glucose builds up in your bloodstream, causing high blood sugar (hyperglycemia). Over time, having consistently high blood glucose can cause health problems, such as heart disease, nerve damage and eye issues. The technical name for diabetes is diabetes mellitus. Another condition shares the term "diabetes" — diabetes insipidus — but they're distinct. They share the name "diabetes" because they both cause increased thirst and frequent urination. Diabetes insipidus is much rarer than diabetes mellitus.

TYPES OF DIABETES

There are several types of diabetes. The most common forms include:

- **Type 2 diabetes**: With this type, your body doesn't make enough insulin and/or your body's cells don't respond normally to the insulin (insulin resistance). This is the most common type of diabetes. It mainly affects adults, but children can have it as well.
- **Prediabetes**: This type is the stage before Type 2 diabetes. Your blood glucose levels are higher than normal but not high enough to be officially diagnosed with Type 2 diabetes.
- **Type 1 diabetes**: This type is an autoimmune disease in which your immune system attacks and destroys insulin-producing cells in your pancreas for unknown reasons. Up to 10% of people who have diabetes have Type 1. It's usually diagnosed in children and young adults, but it can develop at any age.
- **Gestational diabetes**: This type develops in some people during pregnancy. Gestational diabetes usually goes away after pregnancy. However, if you have gestational diabetes, you're at a higher risk of developing Type 2 diabetes later in life.

OTHER TYPES OF DIABETES INCLUDE:

- **Type 3c diabetes**: This form of diabetes happens when your pancreas experiences damage (other than autoimmune damage), which affects its ability to produce insulin. Pancreatitis, pancreatic cancer, cystic fibrosis and hemochromatosis can all lead to pancreas damage that causes diabetes. Having your pancreas removed (pancreatectomy) also results in Type 3c.
- **Latent autoimmune diabetes in adults (LADA)**: Like Type 1 diabetes, LADA also results from an autoimmune reaction, but it develops much more slowly than Type 1. People diagnosed with LADA are usually over the age of 30.

- **Maturity-onset diabetes of the young (MODY)**: MODY, also called monogenic diabetes, happens due to an inherited genetic mutation that affects how your body makes and uses insulin. There are currently over 10 different types of MODY. It affects up to 5% of people with diabetes and commonly runs in families.
- **Neonatal diabetes**: This is a rare form of diabetes that occurs within the first six months of life. It's also a form of monogenic diabetes. About 50% of babies with neonatal diabetes have the lifelong form called permanent neonatal diabetes mellitus. For the other half, the condition disappears within a few months from onset, but it can come back later in life. This is called transient neonatal diabetes mellitus.
- **Brittle diabetes**: Brittle diabetes is a form of Type 1 diabetes that's marked by frequent and severe episodes of high and low blood sugar levels. This instability often leads to hospitalization. In rare cases, a pancreas transplant may be necessary to permanently treat brittle diabetes.

HOW COMMON IS DIABETES?

Diabetes is common. Approximately 37.3 million people in the United States have diabetes, which is about 11% of the population. Type 2 diabetes is the most common form, representing 90% to 95% of all diabetes cases.

About 537 million adults across the world have diabetes. Experts predict this number will rise to 643 million by 2030 and 783 million by 2045.

SYMPTOMS OF DIABETES?

Symptoms of diabetes include:

- Increased thirst (polydipsia) and dry mouth.
- Frequent urination.
- Fatigue.
- Blurred vision.
- Unexplained weight loss.
- Numbness or tingling in your hands or feet.
- Slow-healing sores or cuts.
- Frequent skin and/or vaginal yeast infections.

Additional details about symptoms per type of diabetes include:

- **Type 1 diabetes**: Symptoms of T1D can develop quickly — over a few weeks or months. You may develop additional symptoms that are signs of a severe complication called diabetes-related keto acidosis

(DKA). **DKA is life-threatening and requires immediate medical treatment.** DKA symptoms include vomiting, stomach pains, fruity-smelling breath and labored breathing.

- **Type 2 diabetes and prediabetes**: You may not have any symptoms at all, or you may not notice them since they develop slowly. Routine blood work may show a high blood sugar level before you recognize symptoms. Another possible sign of prediabetes is darkened skin on certain parts of your body (acanthosis nigricans).
- **Gestational diabetes**: You typically won't notice symptoms of gestational diabetes. Your healthcare provider will test you for gestational diabetes between 24 and 28 weeks of pregnancy.

WHAT CAUSES DIABETES?

Too much glucose circulating in your bloodstream causes diabetes, regardless of the type. However, the reason why your blood glucose levels are high differs depending on the type of diabetes.

Causes of diabetes include:

- **Insulin resistance**: Type 2 diabetes mainly results from insulin resistance. Insulin resistance happens when cells in your muscles, fat and liver don't respond as they should to insulin. Several factors and conditions contribute to varying degrees of insulin resistance, including obesity, lack of physical activity, diet, hormonal imbalances, genetics and certain medications.
- **Autoimmune disease**: Type 1 diabetes and LADA happen when your immune system attacks the insulin-producing cells in your pancreas.
- **Hormonal imbalances**: During pregnancy, the placenta releases hormones that cause insulin resistance. You may develop gestational diabetes if your pancreas can't produce enough insulin to overcome the insulin resistance. Other hormone-related conditions like acromegaly and Cushing syndrome can also cause Type 2 diabetes.
- **Pancreatic damage**: Physical damage to your pancreas — from a condition, surgery or injury — can impact its ability to make insulin, resulting in Type 3c diabetes.
- **Genetic mutations**: Certain genetic mutations can cause MODY and neonatal diabetes.

Long-term use of certain medications can also lead to Type 2 diabetes, including HIV/AIDS medications and corticosteroids.

WHAT ARE THE COMPLICATIONS OF DIABETES?

Diabetes can lead to acute (sudden and severe) and long-term complications — mainly due to extreme or prolonged high blood sugar levels.

Acute diabetes complications

Acute diabetes complications that can be life-threatening include:

- **Hyperosmolar hyperglycemic state (HHS)**: This complication mainly affects people with Type 2 diabetes. It happens when your blood sugar levels are very high (over 600 milligrams per deciliter or mg/dL) for a long period, leading to severe dehydration and confusion. It requires immediate medical treatment.
- **Diabetes-related ketoacidosis (DKA)**: This complication mainly affects people with Type 1 diabetes or undiagnosed T1D. It happens when your body doesn't have enough insulin. If your body doesn't have insulin, it can't use glucose for energy, so it breaks down fat instead. This process eventually releases substances called ketones, which turn your blood acidic. This causes labored breathing, vomiting and loss of consciousness. DKA requires immediate medical treatment.
- **Severe low blood sugar (hypoglycemia)**: Hypoglycemia happens when your blood sugar level drops below the range that's healthy for you. Severe hypoglycemia is very low blood sugar. It mainly affects people with diabetes who use insulin. Signs include blurred or double vision, clumsiness, disorientation and seizures. It requires treatment with emergency glucagon and/or medical intervention.

LONG-TERM DIABETES COMPLICATIONS

Blood glucose levels that remain high for too long can damage your body's tissues and organs. This is mainly due to damage to your blood vessels and nerves, which support your body's tissues.

Cardiovascular (heart and blood vessel) issues are the most common type of long-term diabetes complication. They include:

- Coronary artery disease.
- Heart attack.
- Stroke.
- Atherosclerosis.

Other diabetes complications include:

- Nerve damage (neuropathy), which can cause numbness, tingling and/or pain.
- Nephropathy, which can lead to kidney failure or the need for dialysis or transplant.
- Retinopathy, which can lead to blindness.
- Diabetes-related foot conditions.
- Skin infections.

- Amputations.
- Sexual dysfunction due to nerve and blood vessel damage, such as erectile dysfunction or vaginal dryness.
- Gastroparesis.
- Hearing loss.
- Oral health issues, such as gum (periodontal) disease.

Living with diabetes can also affect your mental health. People with diabetes are two to three times more likely to have depression than people without diabetes.

HOW IS DIABETES DIAGNOSED?

Healthcare providers diagnose diabetes by checking your glucose level in a blood test. Three tests can measure your blood glucose level:

- **Fasting blood glucose test**: For this test, you don't eat or drink anything except water (fast) for at least eight hours before the test. As food can greatly affect blood sugar, this test allows your provider to see your baseline blood sugar.
- **Random blood glucose test**: "Random" means that you can get this test at any time, regardless of if you've fasted.
- **A1c**: This test, also called HbA1C or glycated hemoglobin test, provides your average blood glucose level over the past two to three months.

To screen for and diagnose gestational diabetes, providers order an oral glucose tolerance test.

The following test results typically indicate if you don't have diabetes, have prediabetes or have diabetes. These values may vary slightly. In addition, healthcare providers rely on more than one test to diagnose diabetes.

TYPE OF TEST	IN-RANGE (MG/DL)	PREDIABETES (MG/DL)	DIABETES (MG/L)
Fasting blood glucose test	Less than 100.	100 to 125.	126 or higher.
Random blood glucose test	N/A.	N/A.	200 or higher (with classic symptoms of hyperglycemia or hyperglycemic crisis).
A1c	Less than 5.7%.	5.7% to 6.4%.	6.5% or higher.

MANAGEMENT AND TREATMENT

How is diabetes managed?

Diabetes is a complex condition, so its management involves several strategies. In addition, diabetes affects everyone differently, so management plans are highly individualized.

The four main aspects of managing diabetes include:

- **Blood sugar monitoring**: Monitoring your blood sugar (glucose) is key to determining how well your current treatment plan is working. It gives you information on how to manage your diabetes on a daily — and sometimes even hourly — basis. You can monitor your levels with frequent checks with a glucose meter and finger stick and/or with a continuous glucose monitor (CGM).
- **Oral diabetes medications**: Oral diabetes medications (taken by mouth) help manage blood sugar levels in people who have diabetes but still produce some insulin — mainly people with Type 2 diabetes and prediabetes. People with gestational diabetes may also need oral medication. There are several different types. Metformin is the most common.
- **Insulin**: People with Type 1 diabetes need to inject synthetic insulin to live and manage diabetes. Some people with Type 2 diabetes also require insulin. There are several different types of synthetic insulin. They each start to work at different speeds and last in your body for different lengths of time. The four main ways you can take insulin include injectable insulin with a syringe (shot), insulin pens, insulin pumps and rapid-acting inhaled insulin.
- **Diet:** Meal planning and choosing a healthy diet for you are key aspects of diabetes management, as food greatly impacts blood sugar. If you take insulin, counting carbs in the food and drinks you consume is a large part of management. The amount of carbs you eat determines how much insulin you need at meals. Healthy eating habits can also help you manage your weight and reduce your heart disease risk.
- **Exercise:** Physical activity increases insulin sensitivity (and helps reduce insulin resistance), so regular exercise is an important part of management for all people with diabetes.

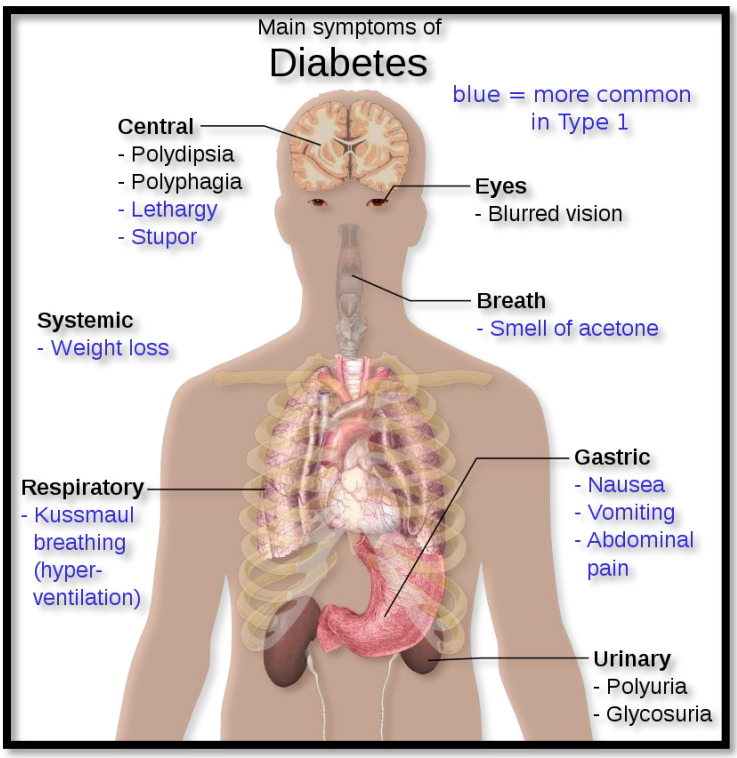

FIGURE 1: SYMPTOMS OF DIABETES

Mechanistic insight into delayed tooth extraction socket healing among diabetic patients

The histological healing process in extraction-sockets is a four-stage process involving the blood clot phase, the inflammation phase of granulation tissue formation, the proliferation phase with woven bone formation and the modeling and remodeling phase, as shown below (Figure 2) [1,2]. Osteogenic tissue proliferates and bone maturity following trabecular bone formation occurs between 4 and 8 weeks after extraction [3,4].

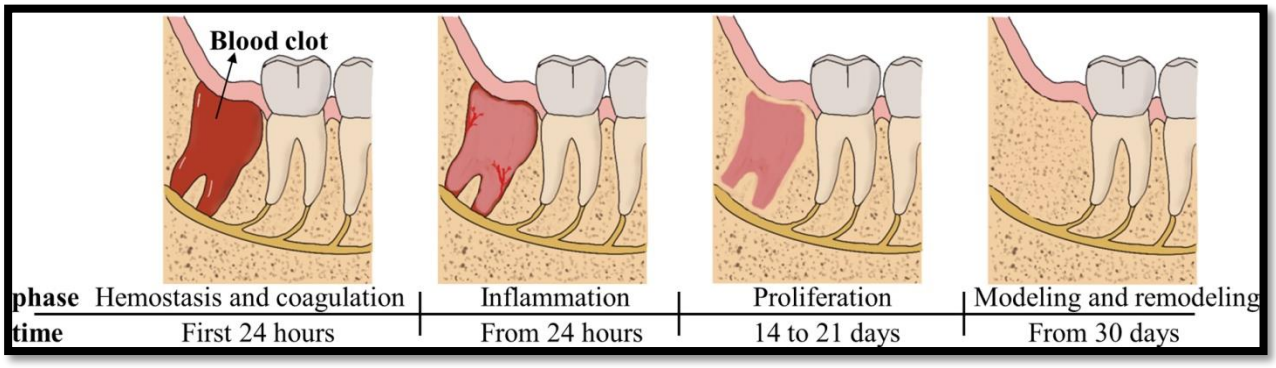

FIGURE 2: Main processes of wound healing occurring in the socket after tooth extraction depicted as four time-related phases.

Delayed tooth extraction socket (TES) healing were often found in patients with poorly controlled or untreated DM [5]. Tooth extraction healing is slower for diabetic than the group without diabetes, particularly on day 7 post-operatively [6]. However, not all studies have reached the conclusion that diabetics have increased delayed healing [7]. In the study by Goss et al. there was no statistically significant difference in healing rate after tooth extraction in either T1DM or T2DM compared to non-diabetic patients, a result that supports the tendency for diabetic patients to recover well after tooth extraction when they are well controlled [8,9]. For instance, it has been shown that the duration of bone healing is similar in diabetic and normal individuals [8]. Still, due to the specificity of diabetes and the possibility of delayed-wound-healing risk after tooth extraction, it is of great value to understand the mechanisms involved and the potential treatments. In recent years, the field of wound research has been broadened by an in-depth understanding of diabetes and its various aspects of physiological, inflammatory, immunological, endocrine, neurological mechanisms and microRNAs (miRNAs) associated with the healing of extracted tooth sockets [10]. Long-standing wound healing in patients with diabetes is generally attributed to the abnormal expression of all the cells involved as well as the dysregulation of the expression of growth factors, cytokines required to coordinate the normal healing process as suggested by these research. Factors accounting for the healing process of diabetic extraction sockets is presented in Figure 3.

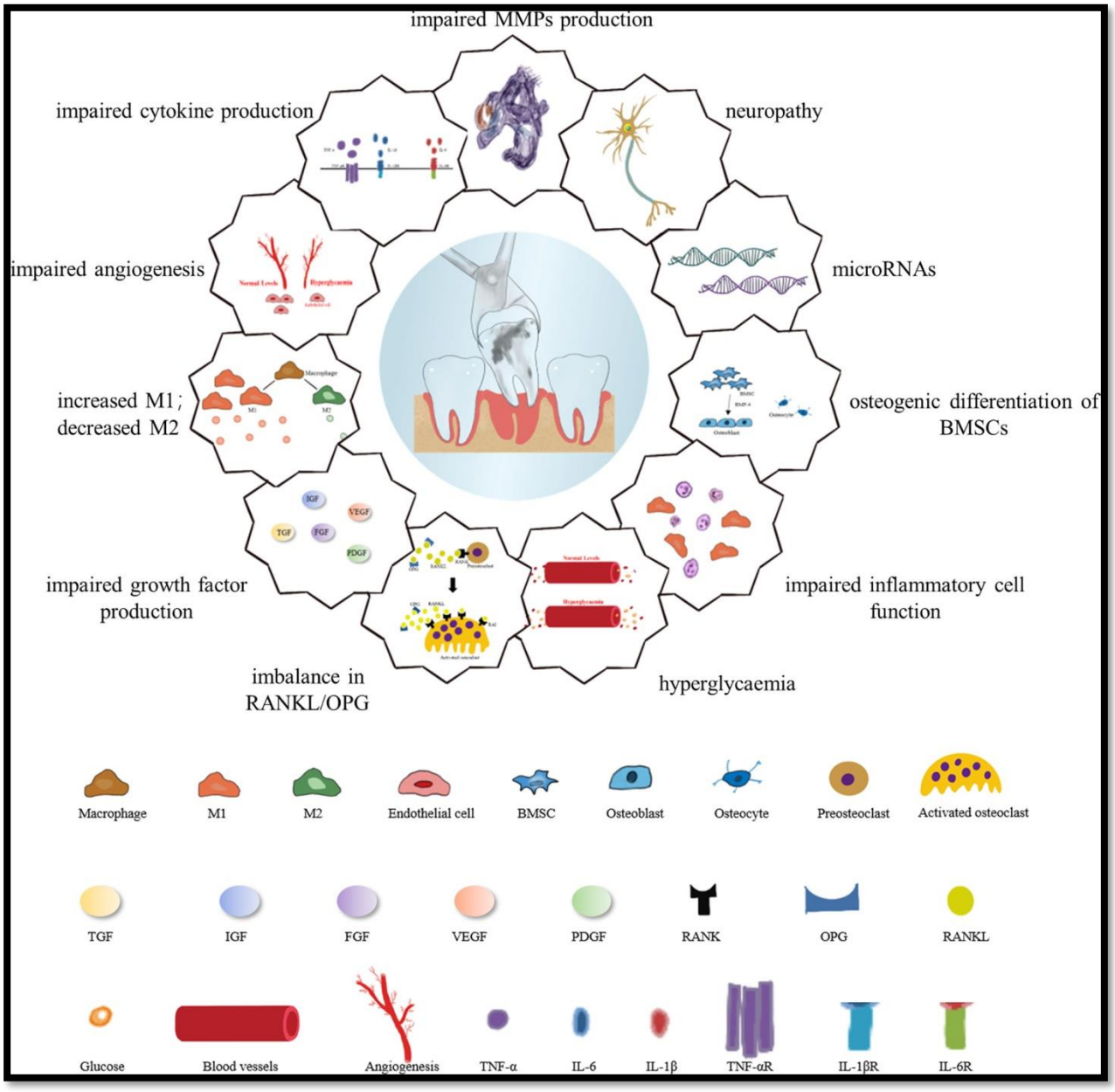

FIGURE 3: Factors responsible for the healing process of diabetic extraction sockets. Diabetes inhibits mitotic growth factor expression through epigenetic mechanisms; difficulty in wound healing after tooth extraction is associated with diminished osteogenic differentiation of mesenchymal stem cells, activation of matrix metalloproteinase-9, persistent imbalance of RANKL/OPG ratio, and reduced expression of neuropeptides. Hyperglycemia affects hormone receptor conversion as well as the formation of new blood vessels, and impaired angiogenesis not only hinders bone formation but also affects the rate of wound healing. Diabetic wounds are characterized by chronic inflammation due to high levels of reactive oxygen species, dysregulated M1/M2 macrophage polarization, and pro-inflammatory chemokines. High glucose levels have a negative impact on macrophage function, mainly in the form of dysregulated levels of cytokine secretion such as TNF-α, IL-6 and IL-1β, in addition to the inability of neutrophils to function in the inflammatory response phases of wound healing, migration, chemotaxis and adhesion. MicroRNAs also influence the different phases of diabetic wound healing.

TOOTH EXTRACTION

Teeth are made to last a lifetime, provided we take good care of them. But due to various reasons, there arises a need to extract the tooth. The reasons for tooth extractions vary a great deal, the most common being tooth decay, and infection. Other common reasons are crooked teeth, poor alignment, gingivitis, and trauma. Tooth decay is caused by many factors one of which is a faulty life style, where starchy and sugary foods predominate among pre teens, and young adults. Lack of good oral hygiene is also responsible for tooth decay among other things.

DIABETES AND TOOTH EXTRACTION

We all have bacteria all around us, in hundreds and thousands. Our mouth is no exception. Bacteria grow in good growth conditions which can be provided by high blood sugar. If your blood has higher sugar levels than required, these bacteria will thrive in your mouth and multiply which will affect your gums adversely. They will slowly destroy all the tissues, and also the fibres connecting teeth to gums. Eating away on soft tissue make them inflamed, and results loosened teeth and periodontal disease. Diabetic people are more prone to develop decayed teeth and periodontal disease than other people, because high blood sugar level affects immune system, making it ineffective. 22% of people who have been diagnosed with gum diseases have diabetes. Increasing age with uncontrolled blood sugar levels pose more risk developing gum problems in older people. Serious gum problems in turn will cause blood sugar to rise and the circle repeats. The gum disease makes diabetes more difficult to control because the person is unable to fight the bacteria in the gums, making it difficult to bring down sugar levels in blood.

LET'S COME TO THE POINT OF EXTRACTING A TOOTH WHEN THE PATIENT IS DIABETIC.

Whenever an extraction has to be done, the doctor always asks for report whether the blood sugar level is within limit. The blood sugar level should be 13mmmol/L. If you have higher blood sugar level, the wound may take longer to heal. If the blood sugar is not controlled than there is a possibility of having cytokines, a harmful protein in the gingivitis tissue, blocking the growth proteins to heal the wound. High blood sugar also interferes with clotting of blood and making dental work difficult to heal faster. It is vital that before extraction you take proper medication to bring blood sugar to optimum level. After the extraction it is essential to keep blood glucose in control so that healing takes place. In diabetic patients if blood glucose is under control, gingival tissues will react normally after tooth extraction. Oral hygiene is critically important when tooth extraction is planned and executed because the mouth has to be prepared for tooth extraction. The healing process should take place immediately after the extraction so that no infection sets in. People with diabetes need to be careful because extractions open the gum to infection. This infection may cause hyperglycaemia and mobilize fatty acids leading to acidosis. All these conditions make control of blood sugar level extremely difficult. The major threat posed to diabetic patients

with raised glucose levels for tooth extraction is not during actual extraction. The worry is how the healing will take place. The healing can be delayed, the socket may get dried and also a possibility of osteomyellitis. And if the diabetes is accompanied by hypertension, the result would be affected severely. Complications can arise after the extraction. The patient who is on oral tablets to control diabetes will need to be observed for two weeks on extended medications like antibiotics, analgesics, etc. and assessment has to be done again to make sure he is maintaining the ideal blood glucose level. If a tooth decayed and infected, immediate extraction has to be carried out, but in such a situation the presence of a physician during the operation is required. But all said and done, the diabetic people who are conscious of their blood glucose level and take proper care to keep it under control can safely go for tooth extraction after two weeks of medication. Then it may be like any other people having no diabetes.

POSSIBLE EMERGENCY ISSUES WITH TOOTH EXTRACTIONS IN DIABETIC PATIENTS

BLOOD GLUCOSE LEVELS

Infection raises blood sugar levels, putting the body under stress to eliminate the infectious cells. Glucagon and cortisol are released under stress, which causes your liver to release more glucose into the bloodstream. As a result, the blood sugar levels rise.

Dehydration is prevalent in diabetics, and it causes a drop in saliva production which normally helps fight candidiasis in the mouth. The decrease in saliva disturbs the mouth's pH balance and raises the risk of candidiasis. Infections in these persons can be more severe, necessitating medical care for consequences and even hospitalization if the infection spreads.

RELATIONSHIP BETWEEN INFECTION AND HYPERGLYCAEMIA

People with diabetes are seen to experience far more significant difficulties than non-immunocompromised individuals. Also, with root canal treatment, they have a higher risk of dental cavities, different fungal and bacterial infections, and overall tooth loss due to a shorter tooth lifespan.

These individuals are seen to have a lot of periodontal diseases. In addition, there is an increase in osteonecrosis of the jaw in diabetic patients who are elderly.

The injection of PRGF, or plasma-rich growth factor, to extraction sites in diabetes patients speeds up the healing process by promoting socket closure and tissue growth.

BONE LOSS AND TOOTH MOBILITY

The complex and soft tissues that connect the tooth to the jaw deteriorate due to decreased blood flow caused by increased glucose levels. In periodontal issues, inadequate blood circulation produces stasis due to the lack of oxygen. As a result, the teeth will weaken and fall out.

EXTRACTION OF TOOTH WHEN THE PATIENT IS DIABETIC

Whenever an extraction is necessary, the doctor always requests a report on the patient's blood sugar level. If your blood sugar level is elevated, the wound may take longer to heal. If blood sugar is not regulated, there is a danger that cytokines, a potentially damaging protein, will accumulate in the gingival tissue, inhibiting the growth proteins necessary to cure the wound. Additionally, high blood sugar impairs blood coagulation, making dental procedures more difficult to heal.

You must take the right medicine before extraction to get your blood sugar to an optimal level. Following the extraction, it is critical to maintain a healthy blood glucose level to allow for recovery. If blood glucose levels are controlled in diabetic people, gingival tissues will respond appropriately following tooth extraction.

Oral hygiene is vital while planning and performing tooth extractions, as the mouth must be prepped for tooth extraction. In addition, the healing process should begin soon following the extraction to avoid infection.

Individuals with diabetes must exercise caution, as extractions expose the gum to infection. This infection can result in hyperglycaemia and the mobilization of fatty acids, resulting in acidosis. In addition, these diseases make it extremely difficult to maintain a healthy blood sugar level.

The primary danger to diabetic patients with elevated glucose levels after tooth extraction does not occur during the extraction itself. Instead, the concern is how the mending will occur. Healing may be slowed, the socket may become dry, and there is a risk of osteomyelitis. And if the diabetes is combined with hypertension, the outcome is far worse. In addition, complications can occur following the extraction.

The patient on oral pills for diabetes control will need to be followed for two weeks while on extended drugs such as antibiotics, analgesics, and so on. Assessment will need to be repeated to ensure he maintains an optimal blood glucose level.

If a tooth becomes decaying and infected, quick extraction is essential; however, in this case, the presence of a physician is required during the procedure.

After two weeks of medication, diabetic patients who know their blood glucose level and take sufficient care to keep things under control can safely undergo tooth extraction. Then it may be just like any other person who does not have diabetes.

DELAYED SOCKET HEALING AFTER TOOTH EXTRACTION

Insufficient insulin slows the healing process, giving fungus and germs more time to lurk within the socket where it's warm and moist. In addition, these people have a weakened immune system. Increased insulin levels reduce nitric oxide, which narrows blood vessels directly.

Diabetic individuals are seen to have clogged blood vessels and lengthy healing times. In addition, the blood becomes acidic during ketoacidosis, which is typical in these patients and is not favourable to healing or battling intruders.

PRINCIPLES OF TREATMENT FOR PATIENTS WITH DIABETES

If a patient states they have diabetes orally or on paper, the safest approach is to treat them as immunocompromised. Treatment with antibiotics should begin well before any surgeries, and hypoglycaemia must be avoided if possible. Ascertain that your patient is at ease enough with you to express their feelings and request what they require.

MANAGEMENT OF DENTAL EXTRACTION UNDER LOCAL ANAESTHESIA

Local anaesthetic and early morning consultations may reduce an individual's stress levels, lowering the chance of a higher blood sugar range, even if just a little. Before any procedure, a patient can carry in their glucose meter, and the readings can be noted for safety.

The blood glucose level at which tooth extraction is safe is 180 mg/dl. Any higher puts the hygienists and practitioners at risk and may necessitate emergency procedures. It's better to be safe than sorry.

CONCLUSION:

The healing period is directly related to tooth extraction and diabetes. High blood sugar levels (PP greater than 200 mg/dl) must be optimally taken in controlled before extraction can begin. Fasting blood glucose level of 180 mg/dl is a cut-off point for any selective dental extraction. However, Random blood glucose level of 234 mg/dl (13 mmol/l) is a cut-off point for an emergency tooth extraction. Tightly controlled diabetic patients (blood glucose level below 70 mg/dl) are susceptible to hypoglycemia. Various factors such as tooth movement, infection, and emergency extraction due to trauma also influence extraction in such patients.

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