Abstract

This paper presents the basic characteristics of diabetes mellitus, a disease that affects about 10% of the population, with a tendency to further increase in frequency. There is a special focus on the oral manifestations of diabetes and the specifics of diabetic patients undergoing various dental procedures and interventions. In this context, hyper and hypoglycemic crises, which can quickly progress to coma, if not recognized and treated promptly, are especially apostrophized. With the goal of timely diagnosis, clinical manifestations and laboratory parameters of acute diabetic complications are presented, as well as risk factors that contribute to the occurrence of these complications. The recommendations of the American and European Diabetes Associations, as well as the Serbian National Guide for the Diagnosis and Treatment of Diabetes mellitus, are given regarding the necessary pre-procedural evaluation of these patients and the equipment of dental offices, to successfully prevent and treat acute complications of diabetes.

Keywords: diabetes mellitus, oral manifestations of diabetes, dental interventions, acute complications of diabetes, therapy of acute complications of diabetes

Introduction

Diabetes mellitus (DM) is a metabolic disorder caused by insufficient insulin production in the pancreas (Type 1 DM), inadequate insulin utilization in the periphery (Type 2 DM), or a combination of both mechanisms. Many substances have different effects on insulin secretion, which can lead to significant imbalances in blood glucose levels, even to hypo- or hyperglycemic crises. The main stimulators of insulin secretion are glucose and fructose, while other stimulators include amino acids, gastrointestinal hormones (gastrin, cholecystokinin, secretin, incretins), acetylcholine, and certain medications (β-adrenergic receptor agonists). The most important inhibitors of secretion are stress hormones (known as counterregulatory hormones), including catecholamines (epinephrine and norepinephrine), cortisol, growth hormone, and glucagon. Cytokines, as well as some medications (such as α-adrenergic receptor agonists, glucocorticoids, etc.), also inhibit insulin secretion.

The normal range for fasting blood glucose levels is 3.5-6.0 mmol/L, and for glycosylated hemoglobin (HbA1c) it is 3.5-6%. The diagnosis of diabetes mellitus (DM) is established based on elevated blood glucose levels, specifically ≥ 7.0 mmol/L or ≥ 11.1 mmol/L, 120 minutes after an Oral Glucose Tolerance Test (OGTT). Since 2009, the criteria for diagnosing DM have also included an elevated level of glycosylated hemoglobin (HbA1c ≥ 6.5%) as an indicator of long-term metabolic control (around three months, or 6-8 weeks in pregnant women).

The prevalence of diabetes mellitus is high in all developed countries worldwide, with a tendency for further growth. While in 2000 there were 6.4% of affected individuals, by 2014 the number increased to 8.3% of the world’s population, with a forecast for further growth. According to the World Health Organization (WHO), this could exceed 12% by 2040. Diabetes mellitus occurs in all age groups, with the highest prevalence observed after the age of forty, especially in underdeveloped and developing countries where there is a higher number of undiagnosed cases of DM, reaching over 40%. In the geriatric population, the prevalence of DM is highest (>20%), with diabetes being more commonly associated with chronic complications and other comorbidities in older age, whether related to diabetes or independent of it. According to WHO data, there are currently around 400 million registered diabetics worldwide, and in Serbia, according to the Institute of Public Health of Serbia, there are approximately 700,000 cases.

Diabetes also has oral manifestations that are significant in dental practice. However, even without oral manifestations, patients with diabetes deserve special attention.
from dentists and require careful pre-procedural evaluation because they are a particularly sensitive group of patients in terms of the possibility of developing acute complications. Dentists must be familiar with the basic characteristics of diabetes to be able to react promptly and adequately if hyperglycemic or hypoglycemic crises occur in the dental office. In such cases, it is necessary to act following the recommendations of the National Guideline for the Diagnosis and Treatment of Diabetes Mellitus issued by the Ministry of Health of the Republic of Serbia.

Specific forms of hyperglycemia

Stress hyperglycemia (SHG) is defined as hyperglycemia in previously euglycemic patients, with blood glucose levels \( \geq 7.0 \) mmol/L in two successive measurements or blood glucose levels \( \geq 11.1 \) mmol/L in random measurements in previously normoglycemic patients. SHG most commonly occurs concerning an acute process, such as trauma or another acute illness, including situations in the dental office. According to various reports, the frequency of SHG ranges from 3% to 80% of cases among hospitalized patients. This wide variability is explained by the imprecise definition of stress hyperglycemia and the fact that in a large number of cases, diabetes mellitus already existed but was unrecognized and untreated.

Insulin resistance represents the inability to effectively utilize insulin, despite sufficient levels present in the body, which can result in hyperglycemia. This resistance may be influenced by genetic factors or caused by certain medications (such as corticosteroids). However, it most commonly occurs within the context of stressful conditions, such as infection, sepsis, critical illness, and others. It also occurs during pregnancy, in obese individuals, and in those with high blood pressure, as part of hyperlipidemia (elevated cholesterol and/or triglycerides), etc. The release of stress hormones and cytokines plays an important role in reducing the insulin/glucose ratio. Insulin stimulates glucose uptake in insulin-sensitive tissues (liver, skeletal muscles, and adipose tissue), thereby reducing glucose release from the liver.

Oral manifestations of diabetes mellitus

Numerous studies have demonstrated an association between diabetes mellitus (DM) and periodontal diseases. Patients with diabetes often experience a burning sensation and discomfort in the oral cavity, as well as bad breath (fetor ex ore). The oral mucosa may appear swollen, and darker in color, and ulcerations in the oral cavity are possible. The tongue may also appear swollen, red, with atrophic papillae (lingua geografica). The gingiva tends to bleed easily and is prone to infections (especially candidiasis), while the salivary glands are prone to calculus formation. Periodontal disease and periodontal abscesses are common findings in individuals with diabetes, and they are more frequent and severe in younger age groups. Due to a deficiency in vitamin B, stomatodinia and stomatopyrosis may be present, which can be further aggravated by candidiasis.

The pathophysiology of oral manifestations of diabetes is not fully elucidated, but there is a known association with the occurrence of dental caries. In individuals with diabetes, there is an elevated glucose level in saliva (glycosylatation), and saliva pH is decreased (acidosis). Additionally, there is reduced saliva secretion (xerostomia), which complicates chewing and swallowing food and prevents adequate self-cleaning of the oral cavity, creating favorable conditions for the development of microorganisms and infections. It has been demonstrated that periodontal disease and oral disorders are more common in individuals with diabetes compared to healthy individuals.

In individuals with diabetes, oral blood vessels exhibit increased permeability due to microangiopathy, leading to the deposition of mucopolysaccharides and glycoproteins in oral tissues. Gingival blood vessels are affected by atherosclerosis and atheromatous changes, resulting in narrowed lumens. Microthromboses and microangiopathies are present, leading to stasis, disturbances in the nourishment and oxygenation of oral tissues, as well as impaired elimination of harmful metabolic byproducts. Alveolar bone undergoes significant resorption and the formation of pockets that suppurate, thus predisposing to the development of abscesses. In the periodontium, there is progressive destruction of all components, increased collagenolysis, and reduced synthesis of new collagen.

Periodontitis is a chronic inflammation of the gums caused by an inflammatory disease, which can not only lead to tooth loss but also is considered a modifying factor that affects overall systemic health. Recent studies have shown an association between periodontitis and chronic diseases such as Alzheimer’s disease, cancer, rheumatoid arthritis, and others. In addition to the known impact of DM on the occurrence and outcome of treatment in patients with the coronavirus, studies by Santana and other authors have shown that the combination of diabetes and periodontal diseases increases the risk of COVID-19 infection. Numerous studies indicate a connection between diabetes and the outcome of dental implants. Also, many studies have examined the impact of local anesthesia on glycemic levels in individuals with diabetes during dental procedures. However, there is no evidence that a local anesthetic with the addition of adrenaline significantly alters glycemic levels.

From the aforementioned, it unequivocally emerges that dentists often encounter patients with diabetes because they constitute a vulnerable population concerning oral and dental diseases. Although the association between diabetes and increased prevalence of oral and dental diseases is well-known, unfortunately, there are no specific protocols...
and recommendations to ensure a safe environment for these patients in dental practices. The focus of dentists when performing interventions in these patients still lies on the potential occurrence of hypo- and hyperglycemia, their prevention, and appropriate management.

**Evaluation and preparation of patients with diabetes before dental interventions**

From a dental perspective, the most important elements of pre-procedural evaluation of patients with diabetes mellitus (DM) include: assessing the duration of the disease and treatment regimen, the presence of DM complications and/or other comorbidities, and reviewing laboratory tests (blood glucose levels, glycosylated hemoglobin, and other necessary analyses) (Table 1). The extent of pre-procedural evaluation depends on the complexity and urgency of the dental intervention, estimated duration of the procedure, the time elapsed since the last meal (and last dose of antidiabetic therapy), as well as the expected level of stress, which is largely a subjective category and depends on the patient’s personality structure. However, the most important question is whether diabetes is well controlled. For major dental interventions, especially surgical procedures, consultation with an endocrinologist or anesthesiologist is mandatory.

**Table 1. Elements of pre-procedural evaluation of patients with DM**

<table>
<thead>
<tr>
<th>Elements of preoperative evaluation</th>
<th>Pay attention to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. DM characteristics</td>
<td>Type of DM; Duration of illness</td>
</tr>
<tr>
<td>2. Presence of DM complications</td>
<td>Treatment regimen-therapy (oral hypoglycemic agents, insulin, combined)</td>
</tr>
<tr>
<td>3. Presence of other comorbidities that may (but not necessarily) be associated with DM</td>
<td>Acute (DKA, HHS, hyperglycemia)</td>
</tr>
<tr>
<td>4. Laboratory analyses</td>
<td>Chronic (micro and macroangiopathies, especially DAN)</td>
</tr>
<tr>
<td>5. Assessment of the airway</td>
<td>Hypertension and other diseases</td>
</tr>
<tr>
<td></td>
<td>CV, NAFLD</td>
</tr>
<tr>
<td></td>
<td>Glycemia and HbA1c are mandatory, and as needed: urea, creatinine, electrolytes, urine analysis (albumin, ketones)</td>
</tr>
<tr>
<td></td>
<td>Possibility of the need for emergency tracheal intubation, which is often difficult in diabetics</td>
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</tbody>
</table>


The primary goals of pre-procedural assessment and preparation of patients with DM are to avoid hyperglycemia (> 10 mmol/L), and hypoglycemia (< 3.8 mmol/L), as well as large fluctuations in blood glucose levels and electrolyte loss. The American Diabetes Association (ADA) issued recommendations in 2014, which are still in effect today, stating that the target glucose values for patients scheduled for invasive diagnostic and therapeutic procedures or surgical interventions should be as close to the physiological range as possible, but definitely < 10 mmol/L. This is also supported by the Canadian and Australian Diabetes Associations, as well as the majority of authors. HbA1C, as an indicator of long-term metabolic control, is a more important laboratory parameter than blood glucose levels because blood glucose levels fluctuate throughout the day (depending on the time of day, meals, stress...).

Preprocedural preparation of patients with diabetes mellitus for dental procedures certainly includes evaluation of diabetes complications (acute and chronic) and other comorbidities that may not necessarily be related to diabetes mellitus. However, it is important to keep in mind that among other comorbidities, hypertension is present in 40-50% of diabetics and may be associated with atherosclerosis, while approximately 17% of patients with diabetes have occult infections. Coronary artery disease is often present, especially in young individuals (which is atypical), as well as congestive heart failure, hepatic steatosis, and others.

Furthermore, it is important to consider that patients with diabetes mellitus have an increased susceptibility to infection, particularly concerning dental surgeries. Additionally, they experience delayed wound healing. They are also prone to dehydration due to osmotic diuresis in hyperglycemia, leading to the development of hyperosmolality. Serious complications such as diabetic ketoacidosis (due to ketogenesis), thromboembolism (due to increased blood viscosity and thrombogenesis), or cerebral edema are not uncommon.

Regardless of the type of dental intervention being performed on individuals with DM, dentists should be familiar with the basic characteristics of diabetes before starting treatment. Although many authors recommend screening patients at risk of diabetic complications, clear protocols for managing high-risk patients in dental offices have not been provided. It is considered that all patients with blood glucose levels > 16 mmol/L are at risk of complications, regardless of whether alarming clinical manifestations of hyperglycemia, such as headache, sweating, dizziness, tremors, blurred vision, etc., are present. To avoid acute complications of diabetes, it is recommended that dental procedures for patients with DM be performed in the morning, after breakfast and administration of insulin or the morning dose of oral hypoglycemic agents. Additionally, it is necessary to measure blood glucose levels before and after the intervention.

**Complications of diabetes mellitus**

Complications of diabetes can be acute or chronic, with acute complications being more significant from a dental perspective. Acute complications of diabetes include those associated with severe hyperglycemia: diabetic ketoacidosis (DKA), hyperglycemic hyperosmolar state (HHS), combined disorders (DKA/HHS), as well as those associated with hypoglycemia, which can vary in severity. Both hyperglycemic and hypoglycemic complications can quickly progress to coma if not promptly diagnosed and urgently prevented. If acute complications of diabetes are present, all elective procedures and interventions, including elective surgeries,
are contraindicated. Only emergency interventions, for vital indications, should be performed\textsuperscript{29}.

Hyperglycemia occurs as a result of the combined action of three processes: increased gluconeogenesis, accelerated glycolysis, and reduced utilization of glucose by peripheral tissues. In DKA is also lipolysis (increased release of fatty acids from adipose tissue into circulation), leading to uncontrolled oxidation of fats in the liver, resulting in the formation of ketone bodies (ketonemia and metabolic acidosis)\textsuperscript{29, 36}. Hyperglycemia occurs in the presence of risk factors (among which infection is the most significant, responsible for > 20% of hyperglycemic events) or as a result of stress (stress hyperglycemia) (Table 2).

Diabetic ketoacidosis is the most common hyperglycemic complication, with an annual incidence of approximately 4.6-8.0 per 1,000 (adult) diabetic patients and a mortality rate of about 1-5%. In pediatric populations, the incidence of DKA is much higher, with around 40% (ranging from 26% to 67%) of newly diagnosed cases of diabetes in children presenting as DKA, especially among younger children. The mortality rate in pediatric patients is approximately 0.15-0.30%. The frequency of HLS is much lower (around 1 per 1,000 patients), but the mortality rate is significantly higher than that of DKA (5-20%), especially among young obese patients and those with comorbidities\textsuperscript{29, 30}.

Hypoglycemia is the most common and therefore the most significant acute complication of diabetes mellitus from the perspective of dentists. It is more common in type 1 diabetes mellitus, with estimates suggesting that one-quarter to one-third of insulin-treated patients experience severe hypoglycemia at least once a year. Generally, hypoglycemia is a more severe disorder than hyperglycemia because some cells/tissues can exclusively use glucose as an energy substrate (e.g., the brain)\textsuperscript{32}. Hypoglycemia occurs in the presence of risk factors such as missed meals or prolonged fasting, malnutrition, circulatory disorders, septic shock, liver and/or kidney and/or adrenal insufficiency, more frequently in geriatric patients, unconscious patients, and hypoglycemia can also be contributed by hypopituitarism, immobilization, and others. Sometimes, just missing one meal, changing anti-diabetic therapy, or the site of insulin injection is enough to cause hypoglycemia. The clinical presentation and treatment of hypoglycemia depend on its severity, ranging from mild to very severe\textsuperscript{29} (Table 3).

Chronic complications of DM are often present, especially in patients with long-standing disease and those with poorly controlled diabetes\textsuperscript{2, 34}. These include macrovascular and microvascular complications (diabetic nephropathy, retinopathy, polyneuropathy). Of particular importance in the perioperative period is the presence of DAN (diabetic autonomic neuropathy).

Characteristics of DAN, such as silent cardiac ischemia, orthostatic hypotension, gastroparesis, bladder dysfunction, lack of sweating (thermoregulation disorder), and others, can result in numerous complications, especially during major dental surgeries under general anesthesia, such as acute myocardial infarction, hypotension, aspiration of gastric contents into the lungs (due to delayed gastric emptying), urinary retention, ileus, and others\textsuperscript{2}.

### Table 2. Precipitating factors for the onset of hyperglycemic crises

<table>
<thead>
<tr>
<th>Precipitating factors</th>
<th>Explanations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>Pneumonia, urinary tract infection, sepsis</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>Insulin, oral hypoglycemics</td>
</tr>
<tr>
<td>Other diseases</td>
<td>Cushing’s syndrome, thyrotoxicosis, acromegaly</td>
</tr>
<tr>
<td>Medications</td>
<td>Acute pancreatitis, acute intestinal obstruction, AMI, CVI, heat stroke</td>
</tr>
<tr>
<td>Medications</td>
<td>Corticosteroids, thiazide diuretics, β-blockers, chlorpromazine, phenytoin</td>
</tr>
</tbody>
</table>

Legend: AMI - Acute Myocardial Infarction; CVI - Cerebrovascular Insult; Th - Therapy.

### Table 3. Severity of hypoglycemia

<table>
<thead>
<tr>
<th>Level (severity) of glycemias</th>
<th>Value of glycemias</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1 Mild hypoglycemia</td>
<td>&lt; 3.9</td>
<td>Sufficiently low value for treatment with rapidly acting carbohydrates</td>
</tr>
<tr>
<td>Level 2 Clinically significant hypoglycemia</td>
<td>&lt; 3.0</td>
<td>Sufficiently low value indicative of the development of severe, clinically significant complications of hypoglycemia</td>
</tr>
<tr>
<td>Level 3 Severe hypoglycemia</td>
<td>there is no specific threshold; usually &lt; 2.3</td>
<td>Severe accident accompanied by a change in mental and/or somatic status and requiring treatment for recovery</td>
</tr>
</tbody>
</table>

**Diagnosis and treatment of acute complications DM in the dental office**

The clinical picture of acute complications of DM is not specific\textsuperscript{29}. Symptoms and signs of hyperglycemic crises have many similarities among themselves, as well as with hypoglycemia, but also with some other diseases and conditions, so laboratory confirmation is crucial for diagnosis. Therefore, it is important to adhere to the recommendations of various associations (American, European, and others) in dental offices and, most importantly, to the National Guide for the Diagnosis and Treatment of DM issued by the Ministry of Health of the Republic of Serbia\textsuperscript{8, 30, 35}. These guidelines, among other recommendations, suggest that equipment for measuring capillary blood glucose should always be available at sites where any procedures and/or interventions are performed\textsuperscript{8, 36}.

The treatment of hypoglycemia should be tailored to the severity of symptoms and signs. Mild hypoglycemia is characterized by symptoms such as hunger, drowsiness, nausea, weakness, mild dizziness, and headache. Moderate
hypoglycemia presents with tachycardia, restlessness, confusion, and irritability, accompanied by sweating, pallor, and tremors. Severe hypoglycemia is marked by hypotension and loss of consciousness. According to our National Guidelines for the Diagnosis and Treatment of Diabetes Mellitus, for grades 1-2 (mild/moderate hypoglycemia), the recommended treatment is to administer 2-4 glucose tablets or two teaspoons (10 g) of sugar, honey, or jam, or a small bottle of juice containing sugar. For grades 3-4 (severe hypoglycemia), the recommended therapy is parenteral: slow intravenous bolus or infusion of glucose (25 mL of 50% or 100 mL of 20% solution). This therapy raises the blood sugar level by 12.5 mmol/L within five minutes, making it the best way to manage severe hypoglycemia. However, caution is needed as extravascular administration can cause necrosis. An alternative to glucose is glucagon (1 mg = 1 unit), which can be administered intravenously, intramuscularly, or subcutaneously. However, this therapy may be ineffective if the patient has been fasting or consuming alcohol for an extended period (as glycogen stores for glucose mobilization may be depleted). Therefore, it is necessary for dental offices to be equipped following the recommendations of the National Guide and to always have available (in addition to the equipment for measuring blood glucose levels in capillary blood): a sugar cube or chocolate, fruit juice, or another sweetened beverage, and a glucagon injection kit. It is recommended that during dental procedures in patients with diabetes, verbal contact should be maintained continuously, and if hypoglycemia has occurred (which has been successfully managed), such patients should be monitored in the dental office for at least another hour.

The therapy for DKA is complex. In cases of milder DKA (conscious patient, good general condition), attempts can be made with oral rehydration and subcutaneous injections of regular or rapid-acting insulin. However, for severe forms of DKA, therapy is exclusively parenteral (intravenous) and requires laboratory and other monitoring, making it unsuitable for administration in a dental office. Hospitalization is necessary in such cases. Therefore, it is important to promptly suspect DKA in a dental to arrange for the patient’s transport to the hospital. Unfortunately, the symptoms and signs of DKA are not particularly specific, necessitating laboratory confirmation. DKA presents with a sensation of dryness in the mouth, thirst, general weakness, fatigue, exhaustion, anorexia, decreased sweating, and possible nausea and vomiting. Various levels of consciousness disturbances may also occur, depending on the severity of DKA. However, assessing the severity of DKA without laboratory analysis, particularly gas analysis (blood pH and serum bicarbonate), is difficult. Therefore, the primary guide in the clinical assessment of DKA severity is the patient’s level of consciousness.

The treatment for DKA, as per the National Guidelines, involves rehydration, electrolyte replacement (primarily potassium), insulin administration, and other measures. Fluid and electrolyte replacement must be done slowly over an extended period because the goal is not to achieve normoglycemia instantly (which is not possible anyway, as the number and sensitivity of insulin receptors are limited). During DKA therapy, it’s essential to frequently repeat laboratory tests, and monitoring of electrocardiogram (EKG) is necessary if potassium levels are too low or too high (<3 mmol/L or >6 mmol/L). Fractionated bolus doses of short-acting insulin can be used in DKA therapy, but continuous intravenous infusion of this insulin is recommended. Bicarbonate replacement in DKA treatment should be very cautious and limited to cases where metabolic acidosis is severe (bicarbonate level <8 mmol/L or pH <7.0). The fundamental requirement for successful DKA treatment is continuous monitoring and care of the patient during the first 24 hours of therapy.

Certainly, the most important aspect is the prevention of these complications, and in this context, as part of the pre-procedural preparation for dental interventions, patients should receive advice on the importance of regular check-ups with an endocrinologist, maintaining a proper dietary regimen, especially for particularly vulnerable categories of diabetic patients such as children, pregnant women, and elderly patients.
Conclusion

Diabetes mellitus is the most common endocrine/metabolic disorder affecting approximately 10% of the population with a tendency for further growth. Such a high prevalence implies that dentists frequently encounter individuals with diabetes in their practice. Diabetes has various oral manifestations that may be the reason for a visit to the dental office. Every dentist needs to be familiar with the basic characteristics of diabetes, especially its acute complications, to recognize them promptly and apply appropriate therapeutic measures. Before any dental procedure or intervention, an evaluation of patients with diabetes of varying extent is necessary, depending on the type, urgency, and planned duration of the dental intervention. The most important aspect is that diabetes is well-controlled, best confirmed by normal (or acceptable) levels of glycosylated hemoglobin. All diagnostic and therapeutic measures aimed at preventing and treating acute complications of diabetes must be in line with the recommendations of the National Guidelines for the Diagnosis and Treatment of Diabetes. Every dental office must-have equipment for measuring blood glucose from capillary blood, as well as the recommended means for treating hypoglycemia, while patients with diabetic ketoacidosis or other hyperglycemic complications must be hospitalized.

Literature

4. ADA. Diabetes Care 2023; Summary of Revisions: Standards of Care in Diabetes—2023.


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