Diabetes Mellitus and Related Oral Manifestations

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Summary: Diabetes mellitus is a common chronic metabolic disease associated with substantial risk for morbidity and premature mortality. Type 1 diabetes results from a T-cell-mediated autoimmune destruction of the insulin-producing pancreatic β-cells leading to an inability to secrete insulin. Type 2 diabetes is characterized by hyperglycaemia due to both reduced insulin sensitivity and impaired insulin secretion. The incidence of type 2 diabetes, which is the most prevalent form of diabetes, is increasing to near-epidemic levels in industrialized countries. About 50% of patients are thought to be undiagnosed. Early detection and intervention are important in order to reduce the risk for systemic complications. Diabetes mellitus is also associated with oral health complications such as periodontitis and candidiasis. Uncontrolled and poorly metabolic controlled diabetic patients are in particular at risk of developing oral diseases, and may need individual intensive dental treatment. Furthermore, mounting evidence in the last decade indicates that treatment of chronic periodontal infection has a beneficial effect on the metabolic status of diabetics. Dentists can play an important role not only in the detection and management of diabetic patients, but also in patient education aimed at promoting healthier lifestyle in general through counselling in diet and smoking cessation. This paper presents current knowledge on diabetes mellitus and outlines the implications of diabetes mellitus on oral tissues and dental treatment.

Key words: diabetes mellitus, xerostomia, salivary glands, oral candidiasis, periodontitis, dental caries

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INTRODUCTION

Worldwide around 150 million people suffer from diabetes mellitus. Without preventive measures, the number of diabetics is expected to reach 300 million by the year 2025 (King et al, 1998). This has caused the World Health Organization (WHO) to characterize this development as an epidemic (Report of a WHO Consultation on Obesity, 1997). In particular the prevalence of type 2 diabetes, previously known as "adult-onset diabetes", is increasing dramatically, and is affecting more young people. Type 2 diabetes counts for about 90% of the global incidence of diabetes (Report of a WHO study group, 1994). Overweight with abdominal fat distribution, obesity (Body Mass Index, BMI, >30 kg/m^2) and physical inactivity apparently account for 80-90% of all cases of type 2 diabetes (Astrup and Finer, 2000). As for diabetes mellitus, the prevalence of overweight and obesity is rapidly increasing, including among children and adolescents (Deckelbaum and Williams, 2001; Wiegand et al, 2004). Diabetes mellitus and diabetic complications in the eyes, kidneys, nerves, heart and blood vessels do not only affect the patient's quality of life, but also lead to substantial morbidity and premature mortality (Harris et al, 1998; Alberti and Zimmet, 1998). In addition, the disease is a major socio-economic burden (Sandø et al, 1993; Rubin et al, 1998).

Several studies have shown that both type 1 and type 2 diabetes mellitus is associated with an increased risk of developing oral diseases including periodontal disease, oral candidiasis, dental caries, salivary gland hypofunction, sialosis, and taste impairment (Lamey et al, 1992; Sreebny et al, 1992; Karjalainen et al, 1994; Oliver and Tervonen, 1994; Karjalainen et al, 1997; Guggenheimer et al, 2000a, b). Conversely, control of periodontal infections seems to have beneficial effects on the metabolic control in diabetics (Miller et al, 1992; Stewart et al, 2001). This article outlines some of the medical aspects of diabetes mellitus including classifi-

cation, aetiology, clinical features and treatment. Special attention is paid to the association between diabetes mellitus and oral manifestations and the impact of diabetes on dental treatment.

DEFINITION AND CLASSIFICATION

Diabetes mellitus designates a group of metabolic diseases characterized by hyperglycaemia due to insufficient insulin secretion and/or reduced insulin sensitivity, and associated with abnormal glucose, lipid and protein metabolism. The chronic hyperglycaemia leads to an increased risk of developing microangiopathy, accelerated atherosclerosis, neuropathy and impaired wound healing (Santiago, 1986; Alberti and Zimmet, 1998; WHO, 1999). Type 1 and type 2 diabetes are the two major forms of diabetes mellitus, but as shown in Table 1 there are other specific forms of diabetes, which have different aetiology, pathogenesis and clinical expression.

Table 1 Characteristics of different types of diabetes mellitus (Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997 and 2003)

Type 1 diabetes. Destruction of insulin-producing pancreatic β-cells due to a T-cell mediated autoimmune process. The cause may also be idiopathic. Usually normal bodyweight or thin, mainly adolescents aged under 30 years. Often abrupt onset with symptoms of insulin deficiency (polyuria, polydipsia, weight loss, and fatigue), may present with ketoacidosis. Exogenous supply of insulin is vital.

Type 2 diabetes. Develops due to a combination of insulin resistance and impaired insulin secretion. Mostly individuals aged over 40 years, often overweight/obese, few classical symptoms of hyperglycaemia, not prone to ketoacidosis except during stressful periods. Exogenous insulin supply is not vital, but as the disease progresses and endogenous insulin secretion decreases, most patients will require insulin therapy, either alone or in combination with oral hypoglycaemic agents.

Other specific types. Genetic β-cell functional defects, exocrine pancreatic disorders with secondary diabetes, autoimmune endocrinopathies with secondary diabetes, drug-induced diabetes, infection-induced diabetes, etc.

Gestational diabetes. Impaired glucose tolerance occurring during pregnancy. Usually disappears after delivery. Mostly affects women with familial predisposition to diabetes and/or who are overweight. Women who have had gestational diabetes are at increased risk for later developing type 2 diabetes. Produces few symptoms and is usually discovered by routine screening.

Type 1 Diabetes

Type 1 diabetes, previously known as juvenile-onset diabetes or insulin-dependent diabetes (IDDM), is characterized by a gradual cell-mediated autoimmune destruction of the insulin-producing β-cells in the pancreas (Nerup et al, 1971; Alberti and Zimmet, 1998; Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003). The rate of β-cell destruction is usually rapid in children and adolescents, i.e., 1-2 years after the time of diagnosis, but slow in adults (Atkinson and Maclaren, 1994; Zimmet et al, 1994). Exogenous supply of insulin is vitally necessary, and left untreated, type 1 diabetes will always lead to diabetic coma and ultimately to death. Type 1 diabetes mainly affects children and adolescents (<30 years), but it may occur at any age. A minority of patients with type 1 diabetes, and mostly those of African or Asian origin, have an idiopathic variant of this type of diabetes. These patients exhibit varying degrees of insulin deficiency and are prone to ketoacidosis, but their form of diabetes lacks evidence of β-cell autoimmunity and is not HLA associated (Banerji and Lebovitz, 1989; Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003).

Type 2 Diabetes

Type 2 diabetes, formerly known as adult-onset diabetes, or non-insulin-dependent diabetes mellitus (NIDDM), is caused by a combination of insufficient insulin secretion in the pancreatic β-cells and insulin resistance in tissues, primarily in skeletal muscles and hepatic cells (Alberti and Zimmet, 1998; WHO, 1999). Initially, type 2 diabetes is characterized by hyperinsulinemia due to an increased insulin synthesis and secretion by pancreatic β-cells in order to overcome the insulin resistance of the muscles and the liver, but eventually the pancreatic β-cells fail to produce sufficient amounts of insulin leading to fasting hyperglycaemia. Type 2 diabetes is considered part of the 'metabolic syndrome', which is characterized by a clustering of risk factors including insulin resistance, hypertension and abdominal obesity that predispose to the development of cardiovascular disease (Bloomgarden, 1998; Harris et al, 1998).

EPIDEMIOLOGY

Type 1 Diabetes

Type 1 diabetes, which accounts for 5-10% of all cases of diabetes, has a worldwide distribution (Harris,

1995). The global incidence and prevalence, however, vary considerably. Northern Europe and the United States have the highest incidence of type 1 diabetes (Karvonen et al, 2000). In Scandinavia, the prevalence of type 1 diabetes is about 0.4-0.6% being lowest in Denmark and highest in Finland. Sardinia and Finland have the highest incidence of type 1 diabetes among children ≤14 years (Karvonen et al, 2000). In about 50% of cases, onset occurs after the age of 30. A recent Danish study indicates that the incidence of type 1 diabetes in children under the age of 15 years, especially those aged 0-4 years, is increasing. Thus children born after 1985 have a higher risk of developing diabetes before they turn 15 than those born before 1985 (Svensson et al, 2000). The strongest predictor of developing type 1 diabetes before the age of 15 is first-order relatives with diabetes. A correlation has also been found between diabetes and environmental factors such as smoking during pregnancy, early introduction of cow's milk and neonatal infections (Svensson et al, 2000). The incidence of type 1 diabetes appears to be increasing worldwide and especially in populations with a low incidence, but it is still unclear whether this increase reflects changing environmental or lifestyle factors, or simply a global improvement in case ascertainment (Karvonen et al, 2000). The rate of new-onset diabetes shows seasonal variations, with more cases being diagnosed during the winter months and fewer during the summer months (Christau et al, 1977; Atkinson and Maclaren, 1994). The cause of this phenomenon is not known.

Type 2 Diabetes

The frequency of type 2 diabetes varies markedly around the world, and it is relatively rare in populations with low standards of living. The overall global prevalence of diabetes is rapidly increasing and projected to rise from 135 million in 1995 to 300 million by the year 2025 (King et al, 1998). Type 2 diabetes counts for 90-95% of diabetes (Report of a WHO study group, 1994; Harris, 1995). Type 2 diabetes is predominantly a disease of middle-aged and older people with an estimated prevalence at about 10% at age 60-74 years and 20% at age 75 years and older (Harris et al, 1998; Poulsen et al, 1999). However, in recent decades the age of onset had decreased and type 2 diabetes has been diagnosed in children and adolescents (Wiegand at al, 2004). With obesity also constituting an increasing problem among children and adolescents, the onset age of type 2 diabetes is expected to drop even further. The number of pregnant women with type 2 diabetes has doubled during the last decade (Helmuth et al, 1997; Hieronimus and Fenichel, 2004). This can presumably partly be ascribed to changes in the ethnic make-up of the population, with a higher proportion of women of childbearing age coming from countries where the incidence of type 2 diabetes and overweight/obesity in young adults is higher than in Northern European countries like Denmark (Heitmann, 2000).

AETIOLOGY AND PATHOGENESIS

Type 1 Diabetes

Type 1 diabetes is caused by a selective autoimmune destruction of the insulin-producing β-cells of the islet of Langerhans of the pancreas. The classification of type 1 as an autoimmune disorder is based on the infiltration of lymphocytes into the islets of Langerhans and the detection of humoral and cellular autoimmunity to the endocrine pancreas (Pociot et al, 2001). Autoantibodies targeted against glutamic acid decarboxylase (GAD65), insulin (IAAs) and tyrosine phosphatases (IA-2 and IA2β) can be detected several years before the type 1 diabetes becomes clinically manifest (Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003). Environmental factors are assumed to be capable of triggering an inflammatory process in the islets of Langerhans in genetically predisposed individuals. This genetic predisposition is related to human leukocyte antigen (HLA) class II alleles (DQA1, DQB1 and DRB1) on chromosome 6 (Atkinson and Eisenbarth, 2001). Genetic predisposition is only part of the explanation, as the concordance for monozygotic twins is low (30-40%) and incidence differs between genetically comparable populations. The significance of environmental factors is emphasized by the fact that immigrants from countries with a low risk of type 1 diabetes, e.g., Japan, settling in countries where there is a high risk of diabetes such as the United States, are more prone to develop type 1 diabetes and vice versa. Bacteria and viruses are also thought to be involved in the pathogenesis (Pociot et al, 2001). Both intrauterine rubella infection and exposure to enteroviral infections in the uterus or during infancy are associated with an increased risk of developing type 1 diabetes later in life (Ginsberg-Fellner et al, 1985; Dahlquist et al, 1995). The pathogenetic role of infections in the initiation of autoimmune destruction of pancreatic β-cells has not yet been clarified.

Type 2 Diabetes

Type 2 diabetes develops in individuals with insulin resistance in the muscles and liver and an inadequate compensatory insulin secretory response, either due to

reduced β-cell mass or reduced β-cell reactivity. The aetiology is still unknown, but interaction between genetic risk factors and the impact of lifestyle and environmental factors are thought to be part of the pathogenesis (Yki-Jarinen, 1994). Studies of monozygotic twins suggest that inheritance plays some role (Newman et al, 1987). Similarly, the children of parents with type 2 diabetes have a 40% risk of developing the disease. Lifestyle factors include overweight/obesity, physical inactivity and dietary content of saturated fatty acids. A history of gestational diabetes and low birth weight in full-term children (Barker, 1998) also predisposes to the later onset of type 2 diabetes. Before developing hyperglycaemia, the classical type 2 diabetic appears to be characterized by abdominal obesity, hyperinsulinemia and to be prone to arterial hypertension. This phase of the disease is thought to set in around the age of 20 or possibly during childhood (Beck-Nielsen and Groop, 1994). About 10-15% of type 2 diabetics are of normal weight and characterized by impaired insulin secretion. In some middle-aged and elderly individuals, diabetes may present with symptoms and organic complications that are consistent with type 2. Based on the presence of antibodies to β-cell antigens and HLA class II alleles, however, this group has a slowly progressing type 1 diabetes known as latent autoimmune diabetes of adults (Tuomi et al, 1999).

SYMPTOMS, CLINICAL FINDINGS AND COMPLICATIONS

The initial classical symptoms of diabetes mellitus include polydipsia, polyphagia, polyuria, fatigue, weakness, irritability, weight loss and pruritus (Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003).

Type 1 Diabetes

The onset of type 1 diabetes is usually abrupt (from days to a few months). Impairment of growth is often observed in children. Laboratory findings include elevated concentrations of glucose and triglycerides in the blood, glucosuria and ketonuria. Type 1 diabetics are more prone to develop ketoacidosis than type 2 diabetics. Usually ketoacidosis develops in combination with absolute insulin deficiency, and is the most common cause of diabetes-related mortality in childhood (Edge and Dunger, 1996; Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003).

Type 2 Diabetes

In type 2 diabetes, the classical diabetes symptoms are often mild and occur slower than in type 1 diabetes, which often result in a substantial delay in clinical diagnosis (Harris and Eastman, 2000). In USA, one-third of all cases of type 2 diabetes are undiagnosed. Several studies indicate that in type 2 diabetes, there is an asymptomatic preclinical period during which hyperglycaemia and other risk factors are present and widespread micro- and macrovascular complications are developing. The risk factors include abdominal obesity, dyslipidaemia (elevated fasting plasma triglyceride and reduced plasma HDL-cholesterol), essential hypertension (>140/90 mmHg) and cigarette smoking (Harris and Eastman, 2000; Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003). About 80% of all type 2 diabetics are overweight. At the time of clinical diagnosis, approximately 50% of the patients exhibit signs of micro- and/or macroangiopathy. In Finland, for example, 59% of newly diagnosed patients had coronary heart disease (Uusitupa et al, 1985). Type 2 diabetics, including newly diagnosed patients, have two- to three-fold higher mortality rate compared to non-diabetic adults, and cardiovascular diseases accounts for up to 80% of deaths in diabetics (Morrish et al, 1991; de Grauw et al, 1995; Gu et al, 1998). Ketoacidosis is unusual, since these patients often produce sufficient amounts of insulin to prevent lipolysis. Finally it should be mentioned that women with pregestational type 2 diabetes are at increased risk of giving birth to children with congenital malformations and of perinatal mortality (Hieronimus and Fenichel, 2004). The risk is even higher than in women with type 1 diabetes (Dunne et al, 2003).

LONG-TERM COMPLICATIONS OF DIABETES

The diabetic complications are related to chronic hyperglycaemia, which results in alterations in blood vessels, nerves and connective tissue. Formation of advanced glycation end products (AGEs) and the consequent accumulation of AGEs in the plasma and tissues of diabetics are among the mechanisms thought to induce tissue damage from chronic hyperglycaemia (Offenbacher and Salvi, 1999). Vascular changes comprise microangiopathy (arterioles, venules and capillaries) and macroangiopathy (accelerated atherosclerosis). Diabetic microangiopathy, which is characterized by a thickening of the basal membrane of the small blood vessels, can lead to nephropathy and retinopathy. Diabetic macroangiopathy, characterized by atheroscler-

osis with thickening of the intima, can lead to cardiovascular disease with myocardial infarction and stroke (Santiago, 1986; Coutinho et al, 1999). Long-term diabetic complications are seen with both type 1 and type 2 diabetes, but microangiopathy is more common in type 1 diabetics, while macroangiopathy is more common in type 2 diabetics. The duration of diabetes and the quality of metabolic control are decisive for the risk of developing renal failure later on, and there is evidence that good glycaemic control can prevent or delay the onset of microvascular complications (Diabetes Control and Complication Trial Research Group, 1993). Diabetic neuropathy is characterized by axon degeneration and demyelinization and occurs frequently in both type 1 and type 2 diabetes. Peripheral neuropathy increases the risk of foot ulcers and amputation, and autonomic neuropathy may be associated with sexual dysfunction, and gastrointestinal as well as cardiovascular symptoms (Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003).

DIABETIC KETOACIDOSIS VERSUS INSULIN REACTION

In the dental clinic, diabetics may be encountered who either have hyperglycaemia with the early stages of ketoacidosis or insulin reaction (hypoglycaemia). Both conditions require the dentist's intervention. The symptoms of hyperglycaemia, which include fatigue, apathy, irritability and dizziness, may be mistaken for symptoms of hypoglycaemia. Information concerning the level of blood glucose can usually be obtained by the patients themselves using blood glucose test strips, monitoring the capillary blood glucose concentration, or the dental clinic may have a blood glucose meter. In case of doubt, i.e., when it is not possible to obtain a current blood glucose value, the condition should always be regarded as hypoglycaemia and treated accordingly, with administration of glucose (sweet juices, syrups, dextrose). If, on the other hand, it is a case of hyperglycaemia, the patient will not respond to the treatment, but neither will the intake of glucose harm the patient. On suspicion of diabetic ketoacidosis, the patient should be admitted to hospital, where treatment should be aimed at gradually re-establishing normal clinical and metabolic conditions. The most marked differences in symptoms and clinical findings between diabetic ketoacidosis and insulin reaction are summarized in Table 2. Cases of hypoglycaemia are usually the result of an imbalance between antidiabetic treatment, energy expenditure and food ingestion. Alcohol intake increases the risk of hypoglycaemia. Hypoglycaemia may occur in relation to fever and infections, but may also be a sign of prolonged poor diabetes control.

Table 2 Differences in symptoms and clinical findings between diabetic ketoacidosis and insulin reaction

Diabetic ketoacidosis	Insulin reaction (hypoglycaemia)
Develops within hours to days	Develops within minutes
Symptoms:	Symptoms:
Abdominal pain, nausea, vomiting, thirst	Sensation of hunger, no thirst
Dry oral mucosa and skin	Cold sweat
Clinical findings:	Clinical findings:
Fast respiration	Normal respiration
Acetone breath	No acetone smell
Low blood pressure	Normal blood pressure
Rapid and weak pulse	Normal pulse
Rarely palpitations	Palpitations
Rosy cheeks	Pallor
Frequent urination	Normal urination
Laboratory findings: Hyperglycaemia (blood glucose >240 mg/dl, or 20-40 mmol/l), glucosuria, ketonuria, and slight proteinuria, reduced plasma bicarbonate concentrations, and reduced blood pH.	Laboratory findings: Hypoglycaemia (blood glucose <60 mg/dl, or 3.0 mmol/l), no glucosuria or ketonuria, normal plasma bicarbonate concentrations, and normal blood pH.
Intake of glucose has no effect. Requires medical treatment with replacement of fluids, insulin, and potassium	Treatment with glucose (sweet juices, candy or milk) has an immediate effect

Table 3 Diagnostic criteria for diabetes mellitus (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997 and 2003)

The diagnosis of diabetes mellitus is made by any one of three methods. Each method used must be confirmed by repeating testing on a different day.

1) Symptoms of diabetes mellitus (polyuria, polydipsia and unexplained weight loss) and random plasma glucose of ≥200 mg/dl (11.1 mmol/l). 'Random' is defined as any time of the day without any relation to the previous meal.

Or

2) Fasting plasma glucose ≥ 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.

Or

3) Two-hour postprandial plasma glucose concentration of ≥ 200 mg/dl (11.1 mmol/l) after a 75 g oral glucose challenge (OGTT). This test is not recommended for routine use in clinical practice.

Categories of fasting plasma glucose:
Normal fasting plasma glucose: <110 mg/dl (<6.1 mmol/l).
Impaired fasting plasma glucose: ≥110 mg/dl (≥6.1 mmol/l) and <126 mg/dl (>7.0 mmol/l).

Categories of 2-h postprandial glucose:
Normal 2-h postprandial plasma glucose: <140 mg/dl (<7.8 mmol/l).
Impaired 2-h postprandial plasma glucose: ≥140 mg/dl (≥7.8 mmol/l) and <200 mg/dl (11.1 mmol/l)

DIAGNOSTIC CRITERIA FOR DIABETES MELLITUS

Table 3 summarizes the current diagnostic criteria for diabetes mellitus, which have been modified by an expert committee in 1997 (Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997) and recently adopted by the American Diabetes Association (Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2000).

The methods used for diagnosing diabetes include a random blood glucose in the presence of symptoms of diabetes, a fasting blood glucose, or a two-hour postprandial plasma glucose during an oral glucose tolerance test (OGTT) using 75 g of anhydrous glucose dissolved in water. Any one of these three methods may be used for diagnosing diabetes mellitus, but requires confirmation by repeat testing on a separate day (Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003). However, although included in the current diagnostic criteria, the OGTT is not recommended for routine diagnostic use in clinical practice (Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003). The test is difficult to perform, time-consuming and therefore used infrequently in ordinary clinical practice. Furthermore, more cases of undiagnosed diabetes are being detected by means of fasting plasma glucose than by the OGTT (Harris and Eastman, 2000).

Table 4 Individuals at risk for type 2 diabetes or with undiagnosed type 2 diabetes, and for whom screening for type 2 diabetes is recommended (Harris and Eastman, 2000)

- siblings or children of type 2 diabetics
- severely overweight individuals (BMI >30 kg/m2)
- patients with ischemic cardiovascular disease
- patients with arterial hypertension
- patients with dyslipidaemia
- patients with known impaired glucose tolerance (characterized by postprandial hyperglycaemia)
- women with a history of gestational diabetes

It may be difficult to distinguish between the two types of diabetes, although the patient's medical history, age, weight, symptoms and signs and the severity of the disease at the time of diagnosis often provide a guide as to whether the diagnosis should be type 1 or type 2 (WHO, 1999). A glucagon test with determination of C-peptide can be applied in difficult differential diagnostic cases. A low level indicates type 1 diabetes and a high level type 2 diabetes. Diabetes mellitus should be considered not just in patients with the classical symptoms of marked hyperglycaemia, but also in those with recurrent furuncles, recurrent oral candidiasis, idiopathic facial paresis, a history of cardiovascular disease, and cataract (Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003). At present it is not possible to identify individuals at risk with certainty by using genetic markers. Table 4 shows persons at high risk of developing or having undiagnosed type 2 diabetes for whom screening is recommended (Rubin et al, 1998; Harris and Eastman, 2000).

METABOLIC CONTROL OF DIABETES MELLITUS

Blood Glucose Measurement

The diabetic is instructed in measuring the blood glucose level repeatedly and regularly using a blood glucose meter. This method provides immediate information concerning the capillary blood glucose concen-

tration and permits rapid adjustment of the insulin dose and thereby the blood glucose level in order to avoid episodes of hypoglycaemia or ketoacidosis.

Test for Glycosylated Haemoglobin

Persistent hyperglycaemia leads to non-enzymatic glycosylation of polypeptides and proteins, including haemoglobin. Measurement of blood level of glycosylated haemoglobin (HbA1c) reflects the average blood glucose level over the past two to three months (mean life of red blood cells is 120 days), thereby providing a valuable tool for monitoring the treatment of diabetes (American Diabetes Association. Test of glycemia in diabetes, 1998). Estimation of the blood concentration of HbA1c has also proved to be a valuable parameter for predicting the risk of later onset of diabetic complications (Diabetes Control and Complications Trial Research Group, 1995). However, HbA1c is not currently recommended for the diagnosis of diabetes. Glycosylated haemoglobin is expressed as a percentage of the normal haemoglobin. Normal levels are below 6% and HbA1c levels of 8.6-10% indicate poor metabolic control. In clinical practice the blood level of HbA1c are usually determined at least twice annually in order to make adjustments to treatment. In cases of anaemia and during pregnancy, the levels of HbA1c may be erroneously low and the test therefore inappropriate. In such cases, measurement of glycosylated plasma fructosamine may be useful (American Diabetes Association. Test of glycemia in diabetes, 1998).

TREATMENT OF DIABETES MELLITUS

The aims of treatment of diabetes mellitus are to achieve near-normal and stable metabolic control without triggering an unacceptable number of episodes of hypoglycaemia, and to prevent or delay progression of diabetic complications (American Diabetes Association. Clinical practice recommendations, 2003). Self-management training, diet, regular exercise, medication and options for the detection and treatment of complications are the key elements of all diabetes management.

Insulin and Oral Hypoglycaemic Agents

Various types of insulin preparations are marketed, including rapid-onset short-acting insulin, rapid-onset intermediate-acting insulin, and insulin with intermediate onset and duration of action. Also new insulin analogues with very rapid onset and a short duration of action are available (Hirsch, 1999). A recent Cochrane analysis indicates, however, that the advantage of using the new fast-acting insulin analogues is minimal compared with the conventional insulin preparations. In addition to this there are the uncertain long-term effects of using insulin analogues (Siebenhofer et al, 2004). Insulin treatment can be planned in different ways depending on the patient's level of physical activity and food intake (Hirsch, 1999). Type 1 diabetes usually requires subcutaneous injection of insulin two to three times daily. A combination of short-acting and intermediate-acting insulin is often used in order to reduce the number of injections that are required during the day. Insulin requirement increases with stress, fever and infections and during pregnancy, but decreases with muscular activity.

Type 2 diabetes is initially treated with diet and exercise. However, this treatment is often inadequate to maintain metabolic control due to poor long-term adherence and/or to the progressive nature of the disease requiring the addition of pharmacotherapy to sustain metabolic control (Buse, 2000). Monotherapy is usually initiated with a biguanide or a sulphonurea, but increasing evidence suggests that combination therapy with oral hypoglycaemic agents and/or insulin more effectively controls glucose levels, thereby reduces diabetic complications, than monotherapy (Goudswaard et al, 2004; Tanenberg, 2004).

Biguanides such as metformin are often used preferentially in overweight or obese type 2 diabetics and widely used in combination with sulphonurea, a thiazolidinedione or insulin (Cusi et al, 1998; Goudswaard et al, 2004). Metformin, which is contraindicated in patients with significant cardiac, hepatic and renal insufficiency, acts by decreasing hepatic gluconeogenesis and increasing peripheral utilization of glucose. Sulphonylureas stimulates the secretion of insulin by pancreatic β-cells and is mostly used for normal-weight or moderately overweight type 2 diabetics (Lebovitz, 1997). Several other oral agents are used in the management of diabetes mellitus including α-glucosidase inhibitors, which can reduce the plasma insulin levels and the need for insulin supplements by a delay in the digestion and absorption of complex carbohydrates. Benzoic acid derivatives like repaglinide act similar to sulphonylureas by stimulating insulin secretion and are useful in newly diagnosed type 2 diabetics with high postprandial glucose levels. Thiazolidinediones are a new class of oral hypoglycaemic agents that decrease insulin resistance and enhance the response of muscle and adipose tissue to insulin. Heart failure and hepatic disease are considered contraindications for using these agents. Insulin used in combination with oral

agents usually includes a single injection of either long-acting human insulin (NPH) or insulin glargine, which is a long-acting insulin analog (Tanenberg, 2004). Recent clinical studies suggest that early addition of insulin to oral agents can significantly improve glycaemic control in type 2 diabetics without promoting increased hypoglycaemia or weight gain (Wright et al, 2002; Tanenberg, 2004).

Prevention and Treatment of complications of Diabetes Mellitus

The main feature in preventing diabetic complications is early diagnosis and intensive glycaemic control by means of oral hypoglycaemic agents and/or insulin (Diabetes Control and Complications Trial Research Group, 1993, 1995). Treatment of diabetes not only requires intensive metabolic control, but should also aim at eliminating or reducing risk factors such as obesity, dyslipidaemia, hypertension, smoking and physical inactivity. Thus, pharmacological treatment of dyslipidaemia (usually with statins) and hypertension (ACE inhibitors, beta-blockers, diuretics or calcium antagonists) may also contribute considerably to reducing the risk of cardiovascular disease (for review see Khan et al, 2004; Sandeep and Hayward, 2004). The goals of diabetic treatment are listed in Table 5.

ORAL MANIFESTATIONS RELATED TO DIABETES MELLITUS

In addition to diseases in the eye, kidneys, heart, nerves and blood vessels, oral diseases may also represent a significant complication of diabetes. The oral conditions associated with diabetes mellitus are listed in Table 6.

Periodontal Disease

Substantial epidemiological and clinical evidence demonstrates that periodontal disease is more prevalent and more extensive in both type 1 and type 2 diabetics as compared to non-diabetics (Hugoson et al, 1989; Schlossman et al, 1990; Thorstensson and Hugoson, 1993; Löe, 1993; Solskolne, 1998; Tsai et al, 2002), although other studies have failed to show any association (Beneviste and Conneally, 1967; Hove and Stallard, 1970; Barnett et al, 1984; Sandholm et al, 1989). Periodontal disease has been referred to as the sixth complication of diabetes mellitus (Löe, 1993). In addition, a large number of studies have reported an association between poor metabolic control and poor periodontal status in both type 1 and 2 diabetics (Tervonen and Knuttilia, 1986; Harrison and Bowen, 1987; Seppala et al, 1993; Tervonen and Oliver 1993; Karjalainen and Knuuttila, 1996; Tervonen and Karjalainen, 1997; Firatli 1997; Novaes et al, 1996; Taylor et al, 1998; Tsai et al, 2002), but this association has not been supported by the results of several other studies (Hove and Stallard, 1970; Barnett et al, 1984; Ervasti et al, 1985; Rylander et al, 1987; Sandholm et al, 1989; Bridges et al, 1996).

In type 2 diabetes, the risk for periodontal disease is estimated to be two to three-fold that of non-diabetics (Schlossman et al, 1990; Emrich et al, 1991; Thorstensson and Hugoson, 1993; Löe, 1993). It has been reported that the risk for periodontal disease and its progression increases with the patient's age (Hugoson et al, 1989; Thorstensson and Hugoson, 1993), duration

Table 5 Goals for optimum diabetes management (Olivarius et al, 2001)

1) To achieve stable blood concentrations of glucose and lipids within or near normal ranges
2) To achieve and maintain acceptable body weight
3) To prevent or delay the development of long-term diabetic complications, which implies:
Fasting blood glucose 4-7 mmol/l
Postprandial blood glucose <200 mg/dl (<11 mmol/l)
Glucosuria 0-5 g/24 hours
Proteinuria 0-30 mg/24 hours
Absence of ketonuria
HbA1c <7.5%
BMI normal for age and gender
Blood pressure normal for age
Smoking cessation
Physical exercise (particularly relevant for type 2 diabetes)

Table 6 Oral symptoms and conditions associated with both type 1 and type 2 diabetes

Gingivitis
Periodontitis
Dental caries
Tooth loss
Oral candidiasis
Oral mucosal lesions such as traumatic ulcers and irritation fibroma
Impaired wound healing
Xerostomia
Salivary gland hypofunction
Sialosis
Burning mouth sensations
Impairment of taste

of diabetes (Thorstensson and Hugoson, 1993; Firatli et al, 1996; Moore et al, 1999), the presence and severity of diabetic complications and the degree of metabolic dysregulation (Löe, 1993; Karjalainen and Knuuttila, 1996; Tervonen and Karjalainen, 1997; Tervonen et al, 2000; Tsai et al, 2002). Hugoson et al (1989) found significantly more periodontal disease in terms of probing depths (>5 mm) and/or attachment loss in diabetics than in non-diabetic controls in the age of 40-49 years, and consequently concluded that age at time of diagnosis has an impact on the extent of periodontal disease. However, it has also been shown that the prevalence and extent of periodontal disease in diabetics is not associated with age (Schlossman et al, 1990; Emrich et al, 1991) or oral hygiene (Emrich et al, 1991; Dahms, 1991).

Children and adolescents with poorly controlled type 1 diabetes appear to have more advanced gingivitis as compared to non-diabetics, despite comparable plaque indices and level of oral hygiene (Karjalainen and Knuuttila, 1996). The extent of gingival bleeding is most prominent in patients with newly diagnosed type 1 diabetes, and improvement of the metabolic control by intensified insulin treatment reduces the extent of gingival bleeding (Karjalainen and Knuuttila, 1996). Furthermore, some studies have found that children and adolescents with type 1 diabetes have significantly deeper periodontal pockets and more extensive attachment loss than age-matched controls (Leeper et al, 1985; Firatli et al, 1996), while others have not found any differences (Sbordone et al, 1998; Tervonen and Karjalainen, 1997). However, substantial evidence indicate that adult type 1 diabetics with poor metabolic control have more extensive attachment loss (Seppala et al, 1993; Bridges et al, 1996), alveolar bone loss (Seppala et al, 1993; Taylor et al, 1998; Tervonen et al, 2000) and deeper periodontal pockets than well-controlled type 1 diabetics (Karjalainen et al, 1994; Collin et al, 1998a; Aren et al, 2003). Moreover, the severity of periodontal disease seems not only related to poor long-term metabolic control, but also to the presence of diabetic complications (Karjalainen et al, 1994, 1997; Tervonen et al, 2000).

Poor oral hygiene, current cigarette smoking and irregular dental care seem to be more common among patients with poor metabolic control and/or severe long-term diabetic complications, which further increases the risk for developing periodontal disease (Taylor et al, 1996; Moore et al, 1999; Syrjala et al, 2003). Health behaviour, which is closely related to psychological characteristics such as self-efficacy, is an important factor that should be considered, when the risk for periodontal disease is evaluated. Thus, poor adherence to both diabetes regimens and dental treatment is associated with poor metabolic control and oral diseases (Kneckt et al, 2000; Syrjala et al, 2004).

The response to non-surgical periodontal treatment has been shown to be equal among diabetics and non-diabetics, provided regular plaque control is ensured by frequent dental follow-ups (Tervonen et al, 1991; Westfelt et al, 1996). Consequently, the principles of periodontal treatment in diabetics are the same as those for non-diabetic patients and are consistent with the therapeutic approach to all high-risk patients with manifest periodontal disease. Furthermore, evidence suggests that elimination of periodontal infection improve tissue sensitivity to insulin and thereby the metabolic control. Indeed, studies have shown that non-surgical periodontal treatment can have a positive effect on HbA1c levels in diabetics, reducing the need for insulin (Miller et al, 1992; Grossi and Genco, 1998; Stewart et al, 2001; Rodrigues et al, 2003). In the study by Grossi and Genco (1998), the metabolic status improved most significantly in patients who received systemic antibiotic therapy with doxycycline in addition to conventional periodontal treatment. The reduced HbA1c levels were ascribed to the beneficial effect of antibiotics on the periodontal pathogens (Grossi and Genco, 1998). On the other hand, in a recent study type 2 diabetics receiving scaling and root planing alone achieved more significant reduction in HBA1c values than those patients who received scaling and root planing in combination with amoxillin/clavulanic (Rodrigues et al, 2003).

The underlying pathogenic mechanisms behind the increased risk for developing periodontal disease in diabetes are still not clear. The advanced periodontal disease has been ascribed to a number of structural and functional hyperglycaemia-related alterations, such as thickening of the basement membranes of blood vessels (microangiopathy), which leads to deterioration of the microcirculation in the periodontal tissue and consequently to decreased supply of oxygen and nutrients to the tissues and accumulation of harmful metabolites; impaired functions of polymorphonuclear leukocytes leading to abnormalities of adherence, phagocytosis and chemotaxis; impaired gingival fibroblast proliferation and collagen synthesis; enhanced collagenase activity; and formation of AGEs, which bind to monocyte receptors, thereby inducing production of inflammatory mediators such as tumour necrosis factor, prostaglandin E-2 and interleukin-1, and genetic predisposition for Gram-negative infections (Leeper et al, 1985; Oliver and Tervonen, 1994; Salvi et

al, 1997; Lalla et al, 2000). All these mechanisms may lead to impaired host resistance to infection and accelerated inflammatory host response and result in loss of periodontal fibres, loss of the alveolar supporting bone, and eventually loss of teeth (Taylor et al, 1998; Tervonen et al, 2000).

Early microbiological reports indicate that the oral microbial flora is changed due to increased levels of glucose in saliva and crevicular fluid. It has been shown that type 1 diabetics have more *Capnocytophaga* in their periodontal pockets (Mashimo et al, 1983), and a higher proportion of gram-negative bacteria in their dental plaque than non-diabetics (Sandholm et al, 1989), but other studies have not supported these findings, since they found no significant changes in the microbial flora in type 1 diabetics (Zambon et al, 1988; Sastrowijoto et al, 1989; Sbordone et al, 1998). In addition, a recent study, revealed no difference in the occurrence of periodontal pathogens between type 2 diabetics and healthy controls (Yuan et al, 2001). It has also been reported that the duration of diabetes, type of diabetes and metabolic control of the disease have no significant influence on the prevalence of periodontal pathogens such as *Actinobacillus actinomycetemcomitans*, *Fusobacterium nucleatum*, *Eiknella corrodens*, *Porphyromonas gingivalis* and *Prevotella intermedia* (Tervonen et al, 1994).

In summary, strong evidence suggest that diabetes is associated with an increased risk for developing periodontal disease, especially in diabetics with inadequate metabolic control. Conversely, periodontal treatment seems to improve the metabolic control of diabetes suggesting a bidirectional relationship between the two diseases. The increased susceptibility to periodontal disease may be explained by hyperglycaemia-related alterations in the inflammatory host response.

Dental Caries

Results are conflicting as to whether diabetics have an increased risk of developing dental caries. Thus, some cross-sectional and controlled studies have found no difference in the prevalence of caries between diabetics and non-diabetics (Kjellman et al, 1970; Tenovuo et al, 1986; Swanljung et al, 1992; Moore et al, 2001a), and other studies have found even less caries in diabetics than in non-diabetics (Sterky et al, 1971; Leeper et al, 1985; Kirk and Kinirons, 1991). A higher caries experience and incidence has, however, also been demonstrated among diabetics as compared to non-diabetics (Pohjoma et al, 1991; Jones et al, 1992, Karjalainen et al, 1997; Twetman et al, 2002). An association between metabolic control and dental caries has been reported in type 1 diabetics (Twetman et al, 1992; Karjalainen et al, 1997), but other studies have failed to show any association in type 1 diabetics (Bacic et al, 1989; Pohjamo et al, 1991; Moore et al, 2001; Syrjala et al, 2003) and in type 2 diabetics (Collin et al, 1998b). Increased caries activity and experience have been found in children and adolescents with type 1 diabetes of short duration and poor metabolic control, i.e., HbA1c values >10%, but once metabolic control has been stabilized, caries activity often decreases (Karjalainen et al, 1997). Moore et al (2001a) showed an association between dental caries and diabetic nephropathy, whereas Bacic et al (1989) were unable find any association between dental caries and diabetic complications of retinopathy and neuropathy.

Elevated salivary glucose concentrations reduced salivary flow rates and low salivary pH are well-known risk factors for dental caries, and salivary flow rates and salivary glucose levels have been found to be inversely correlated in type 1 diabetics (Karjalainen et al, 1996). High salivary glucose concentrations have also been shown to correlate with high blood glucose concentrations (Tenovuo, 1986; Karjalainen et al, 1996). In addition, increased salivary glucose concentrations have been related to an increased number of lactobacilli and yeasts in the saliva (Twetman et al, 1989; Swanljung et al, 1992; Karjalainen et al, 1996; Syrjala et al, 2003). Poor oral health and poor adherence to dietary recommendations are other important factors associated with an increased risk for dental caries (Kneckt et al, 2000).

In conclusion, despite conflicting results, evidence suggests that an increased risk for dental caries in diabetes is related to poor metabolic control, salivary gland hypofunction, and high salivary glucose concentrations, which promotes growth of *Streptococcus mutans* and *Lactobacillus*.

Tooth Loss

A significant correlation between tooth loss and type 1 diabetes has been reported (Moore et al, 1998; Guggenheimer et al, 2000a), and diabetics are about 5 times more likely to be partially edentulous than non-diabetics (Moore et al, 1998). Both advanced periodontal disease and dental caries may lead to the loss of teeth. An association between diabetic peripheral neuropathy and autonomic parasympathetic neuropathy and tooth loss has been found (Collin et al, 2000). A possible explanation for this association may be that autonomic neuropathy can reduce salivary flow rate (Newrick et al, 1991), which can lead to tooth decay and hence tooth loss. The consequences of being

partially or completely edentulous not only include changes in personal appearance, but also impairment of masticatory function and avoidance of certain foods, and ultimately poor diet quality and poor nutritional status (Sheiham and Steele, 2000). Thus, replacement of missing teeth, particularly the posterior tooth pairs, is important in order to avoid persistent oral health problems (Sheiham and Steele, 2000). Placement of endosseous dental implants may be a preferable alternative to conventional dentures in partially or complete edentulous diabetics, who are susceptibility to oral candidiasis, traumatic ulcers and who suffer from hyposalivation (Beikler and Flemmig, 2003). Placement of dental implants has been reported to be just as successful as in the general population, provided that the patients exhibit adequate metabolic control and adherence to oral hygiene regimens (Olson et al, 2000; Fiorellini et al, 2000). On the other hand, the failure rate appears to increase after about one year (Fiorellini et al, 2000), which could indicate that implant failure is related to uncovering of implants and to the early phase of implant loading. Diabetes-related microangiopathy leading to impaired immune response and reduced bone turnover has been suggested as an important risk factor to implant failure (Olson et al, 2000). There are still no definitive guidelines that can aid in the predictability of dental implants in patients with diabetes mellitus (Beikler and Flemmig, 2003).

Xerostomia, Salivary Gland hypofunction, and Sialosis

Xerostomia, the term for the subjective sensation of a dry mouth, is a common symptom in diabetics. The prevalence of xerostomia is 16% among type 1 diabetics with a disease duration of 10 years (Moore et al, 2001b), and 54% among type 2 diabetics with similar duration (Sandberg et al, 2000). The marked variation in prevalence may be due to the fact that type 2 diabetics often are older, have more long-term diabetic complications and concomitant medical disorders, and take more medications that may cause xerostomia and/or hyposalivation than type 1 diabetics (Meurman et al, 1998). Several studies of both type 1 and type 2 diabetics have shown that the sensation of oral dryness is related to a reduced flow rate of both unstimulated and stimulated whole saliva (Kjellman, 1970; Ben-Aryeh et al, 1988; Thorstensson et al, 1989; Newrick et al, 1991; Sreebny et al, 1992; Lamey et al, 1992; Moore et al, 2001b). However, other studies have not revealed lower salivary flow rates in diabetics as compared to non-diabetics (Sharon et al, 1985; Tenovuo et al, 1986; Belazi et al, 1998; Swanljung et al, 1992; Meurman et al, 1998). Poorly controlled (defined as HbA1c >9%) type 2 diabetics appear to have lower stimulated parotid flow rates than those who are well-controlled (Chavez et al, 2000). In children and adolescents with type 1 diabetes, high blood glucose values, but not high HbA1c values, are associated with low stimulated whole saliva flow rates and high salivary glucose concentrations (Karjalainen et al, 1996). The glucose concentration in the saliva is assumed to increase at blood glucose values of 10-15 mmol/l, (Reuterving et al, 1987).

Salivary composition including antimicrobial substances, total protein, electrolytes, salivary pH and buffer capacity has also been investigated, but the results are contradictory, regarding both whole saliva, and saliva collected separately from the parotid glands and the submandibular/sublingual glands (Sharon et al, 1985; Tenovuo et al, 1986; Ben-Aryeh et al, 1993; Dodds and Dodds, 1997). The contradictory results may reflect differences in the selection of patients (age, duration of disease, metabolic control and medication) and methodology. Salivary flow rate, salivary pH, buffer capacity or microbial counts have not been found correlated to the duration of diabetes (Tenovuo et al, 1986; Thorstensson et al, 1989; Swanljung et al, 1992). A recent study found lower salivary pH, buffer capacity and salivary peroxidase activity in children with type 1 diabetes than in healthy controls (Aren et al, 2003). Total salivary protein concentrations have been found to be similar (Harrison and Bowen, 1987; Tenovuo et al, 1986; Ben-Aryeh et al, 1993; Dodds and Dodds, 1997), higher (Ben-Aryeh et al, 1988) or lower (Streckfus et al, 1994) in diabetics as compared to non-diabetics. Increased concentrations of salivary potassium and amylase have also been reported (Sharon et al, 1985; Ben-Aryeh et al, 1993; Dodds and Dodds, 1997). A recent study revealed increased levels of salivary calcium, but reduced levels of salivary magnesium, zinc and potassium in both type 1 and type 2 diabetics as compared to healthy, age-matched controls (Mata et al, 2004).

The pathogenetic mechanisms behind diabetes-related changes in salivary gland function remain unclear. Dehydration, as the result of prolonged hyperglycaemia and consequently polyuria, is considered a major cause of xerostomia and salivary gland hypofunction in diabetics (Sreebny et al, 1992). However, dehydration alone cannot explain the functional changes of the salivary glands. Lymphocytic infiltrates have been observed in labial salivary gland tissues of children with type 1 diabetes, indicating that the salivary gland tissue may be a target for the same autoim-

mune process as the pancreatic β-cells (Markopoulos and Belazi, 1998). Gradual degeneration of salivary gland tissue can lead to salivary hypofunction and altered salivary composition. In addition, 10-25% of type 1 or type 2 diabetics may develop a bilateral asymptomatic enlargement of the parotid glands and, more rarely, of the submandibular glands, known as diabetic sialosis (Russotto, 1981; Murrah, 1985; Lindeberg and Andersen, 1987; Greenspan, 1996). Histologically the salivary gland tissue from the enlarged parotid glands and the submandibular glands is characterized by fatty infiltration, fibrous tissue, enlargement of acinar cell and reduction in acinar tissue, but without signs of inflammation (Donath and Seifert, 1975; Lindeberg and Andersen, 1987). The two frequently occurring degenerative complications of diabetes mellitus, autonomic neuropathy and microangiopathy, are thought to contribute to the development of structural alterations in the salivary gland tissue and thus the hypofunction of this gland by affecting the autonomic innervation and the microcirculation of the glandular tissue (Lamey et al, 1986; Newrick et al, 1991; Moore et al, 2001b). However, patients with diabetic neuropathy have been reported to have both increased and decreased salivary flow rates (Lamey et al, 1986; Newrick et al, 1991; Moore et al, 2001b). Other studies have shown no association between salivary dysfunction and diabetic neuropathy (Meurman et al, 1988; Ben-Aryeh et al, 1996).

In summary, there is no consensus on the association between diabetes mellitus and salivary gland dysfunction. However, xerostomia and salivary gland hypofunction are commonly reported among diabetics, and may be indicative of poor metabolic control. In addition, hyposalivation and changes in salivary composition may contribute to the increased susceptibility to oral infections, impaired wound healing and increased rate of dental caries in diabetics.

Oral Candidiasis

Fungal infections are more common in type 1 and type 2 diabetics than in non-diabetics (Lamey et al, 1992; Vazquez and Sobel, 1995; Bai et al, 1995; Guggenheimer et al, 2000b; Kadir et al, 2002), and the oral infections appear to be more severe in diabetics than in non-diabetics (Guggenheimer et al, 2000b). *Candida albicans* is the most common species isolated from the oral cavity of diabetics, and of non-diabetics (Samaranyake, 1990; Dorocka-Bobkowska et al, 1996; Willis et al, 1999; Kadir et al, 2000). Recently, a new *Candida* species, i.e., *Candida dubliniensis*, has been isolated from the oral cavity of both type 1 and type 2 diabetics (Manfredi et al, 2002), but the significance of this species in relation to pathogenesis of fungal infections in diabetics remains to be elucidated.

Substantial evidence suggests that the carriage frequency and the density of candidal colonization are increased in diabetics as compared to non-diabetics (Bartholomew et al, 1987; Bai et al, 1995; Dorocko-Bobkowska et al, 1996; Guggenheimer et al, 2000b), although some studies have failed to show a significant difference between diabetics and non-diabetics (Lamey et al, 1988; Manfredi et al, 2002; Kadir et al, 2002). It remains controversial whether the diabetes itself increases the risk of candidal carriage and whether the increased candidal carriage actually reflects clinical manifest infection (Vazquez and Sobel, 1995; Manfredi et al, 2002; Kadir et al, 2002). Several studies have shown that poor metabolic control, high concentrations of glucose in blood and saliva, long disease duration and presence of diabetic complications (retinopathy) are associated with increased candidal carriage and clinical manifestations of candidiasis (Aly et al, 1992; Ueta et al, 1993; Vazquez and Sobel, 1995; Guggenheimer et al, 2000b; Kardir et al, 2002), but others have not found such relationships (Bartholomew et al, 1987; Fisher et al, 1987). High concentrations of glucose in the blood and saliva may promote growth and enhance adherence of yeasts to epithelial cells surfaces (Samaranayake, 1990). Also the impaired functions of polymorphonuclear leukocytes leading to reduced phagocytosis, intracellular killing and chemotaxis may contribute to the increased colonization of *Candida* and increased susceptibility to oral candidiasis (Ueta et al, 1993; Vazquez and Sobel, 1995). However, a substantial number of local and systemic factors that are not related to diabetes may also influence candidal carriage status and the susceptibility to oral candidiasis (Aly et al, 1992; Vazquez and Sovel, 1995; Guggenheimer et al, 2000b). These factors include gender, oral hygiene habits, smoking habits, intake of medications, denture wearing, salivary flow rate, and salivary composition (Samaranayake, 1990; Budtz-Jorgensen, 1990; Willis et al, 1999; Guggenheimer et al, 2000b; Kadir et al, 2002). Inadequately controlled diabetics who wear dentures have a higher oral candidal load and higher prevalence of denture stomatitis than non-diabetic denture wearers (Vitkov et al, 1999; Guggenheimer et al, 2000b). Furthermore, low salivary flow rates and low salivary pH have been found associated with high incidence of *Candida* (Banoczy et al, 1987; Karjalainen et al, 1996; Kadir et al, 2002).

Oral infection with *Candida* may clinically present as median rhomboid glossitis, atrophic glossitis, denture stomatitis, pseudomembranous candidiasis and angular

cheilitis (Farman, 1976; Guggenheimer et al, 2000b). Oral candidiasis may be accompanied by burning mouth sensations, taste disturbances (usually metallic taste) and sensation of dry mouth. The presence of median rhomboid glossitis and denture stomatitis has been found to be related to long disease duration, long-term diabetic complications (nephropathy and retinopathy), poor metabolic control and smoking (Vitkov et al, 1999; Guggenheimer et al, 2000b).

In conclusion, diabetics have a high rate of oral candidal carriage and an increased risk for oral candidiasis, which is related to poor metabolic control, high concentrations of glucose in the blood and saliva, reduced salivary flow rates, low salivary pH and a reduction in antimicrobial substances in the saliva. However, other risk factors such as oral hygiene, smoking and dentures also have a substantial influence on oral candidal status in diabetics and their susceptibility to oral candidiasis.

Other Oral Mucosal Lesions

An increased occurrence of oral lichen planus has been observed in both type 1 and type 2 diabetics as compared to healthy controls (Lundström, 1983; Albrecht et al, 1992). It has therefore been suggested that diabetes is a pathogenic factor in relation to oral lichen planus (Lundström, 1983). However, several other studies have reported a low prevalence of oral lichen planus in diabetics (Van Dis and Parks, 1995; Petrou-Amerikanou et al, 1998; Scully et al, 1998) and not being significantly different to that of healthy non-diabetic controls (Guggenheimer et al, 2000a). The occurrence of diabetes mellitus in patients with oral lichen planus has also been examined and varies from 1.6-37% (Grinspan, 1966; Lundström, 1983; Bagan-Sebastian et al, 1992; Bagan et al, 1993; Petrou-Amerikanou et al, 1998). The contradictory results may reflect differences in criteria used for diagnosing both diabetes mellitus and oral lichen planus.

An increased occurrence of oral leukoplakia has also been observed in both type 1 and type 2 diabetics as compared to healthy controls. Oral leukoplakia, as well as oral lichen planus lesions, was most prevalent in insulin-treated diabetics, who were smokers and approximately 2 years disease duration (Albrecht et al, 1992).

Geographic tongue, also known as benign migratory glossitis, has been observed in 8% of patients with diabetes mellitus indicating an association between the two diseases (Wysocki and Daley, 1987). On the other hand, Guggenheimer et al (2000a) examined 405 type 1 diabetics and found no significant correlation between geographic tongue and type 1 diabetes.

An increased prevalence of fissured tongue has been observed in diabetics as compared to non-diabetics (Farman et al, 1976; Guggenheimer et al, 2000a) and especially in older type 1 diabetics with long disease duration and complaints of dry mouth (Guggenheimer et al, 2000a).

In general, type 1 diabetics have an increased risk for oral mucosal lesions, in particular fissured tongue, irritation fibromas and traumatic ulcers as compared to healthy controls and the risk is related to age, duration of diabetes and presence of diabetic complications.

Taste Impairment

Several reports indicate that the ability to detect and recognize sweet, salty and bitter taste is impaired in both type 1 and type 2 diabetics (Lawson et al, 1979; Hardy et al, 1981; Le Floch et al, 1989; Perros et al, 1996; Stolbova et al, 1999). Electrogustometric studies have revealed that hypogeusia and ageusia are significantly more prevalent in type 1 and type 2 diabetics than in non-diabetics (Le Floch et al, 1989; Stolbova et al, 1999). Accordingly, 33-73% of type 1 diabetics and 40% of type 2 diabetics fulfil the criteria for hypogeusia (Perros et al, 1996; Stolbova et al, 1999). Ageusia has been found in 3% of type 1 diabetics and 5% of type 2 diabetics (Stolbova et al, 1999). It has been suggested that the impaired taste acuity, especially for sweet, can lead to hyperphagia and increased intake of sugar, and hence obesity and impairment of the metabolic status (Perros et al, 1996; Stolbova et al, 1999). In newly diagnosed type 2 diabetics, taste impairment for glucose and salt partially reversed after correction of hyperglycaemia with diet and oral hypoglycaemic agents suggesting an association between blood glucose concentrations and taste acuity (Perros et al, 1996). Taste impairment has also been found associated with long disease duration and long-term diabetic complications, particularly peripheral neuropathy (Le Floch et al, 1989, 1992). However, taste impairment has also been observed in diabetic patients without peripheral and/or autonomic neuropathy (Lawson et al, 1979; Perros et al, 1996). Several other factors such as salivary gland hypofunction, intake of medications and smoking may be responsible for impaired taste acuity and should be considered when evaluating the relationship between taste impairment and diabetes.

Burning Mouth Sensation

Many diabetics complain of burning sensations in the oral cavity. The burning mouth sensations have been found related to increased candidal density (Vitkov et

al, 2003) and *Candida*-associated stomatitis (Dorocka-Bobkowska et al, 1996; Vitkov et al, 1999). It has therefore recently been suggested that the sensation of burning mouth in diabetics occurs via stimulation of the capsaicin receptor by *Candida* metabolites, since capsaicin receptors are responsible for the detection of pain-producing chemical and thermal stimuli (Vitkov et al, 2003). An association between poor metabolic control and burning mouth sensations has also been suggested (Brody et al, 1971; Gibson et al, 1990; Carrington et al, 2000). Reports further indicate that burning mouth sensation is an early sign of undiagnosed diabetes (Gibson et al, 1990; Vitkov et al, 2003). On the other hand, burning mouth sensations have been associated with long disease duration. Thus, glossodynia has been reported in 18% of type 2 diabetics with disease duration of 13 years (Collin et al, 2000). It has been suggested that glossodynia is an oral manifestation of peripheral neuropathy, a common long-term diabetic complication (Collin et al, 2000). However, several local and systemic conditions may be accompanied by burning mouth sensations including such as hyposalivation and oral habits like tongue thrusting and haematinic deficiencies. Persistent burning mouth sensations are also the cardinal symptom of burning mouth syndrome, a condition of remaining unknown aetiology, although numerous potential aetiological factors have been proposed including diabetes mellitus (Pedersen et al, 2004).

Impaired Wound Healing

Impaired wound healing is a prevalent complication of diabetes mellitus. The underlying pathophysiological mechanisms of impaired wound healing in diabetics are, however, poorly understood. Wound healing is a multi-step process that includes an inflammatory response, granulation tissue formation, wound closure and angiogenesis, and tissue remodelling (Hunt et al, 2000). An adequate blood and nerve supply is required for efficient wound healing. In diabetics, several structural and functional hyperglycaemia-related abnormalities are thought to contribute to impaired wound healing (Silhl, 1998). First of all, the host response to inflammation is reduced in diabetics due to impairment of polymorphonuclear leukocyte functions leading to abnormalities of adherence, phagocytosis, chemotaxis, and intracellular killing (Rosenberg, 1990; Terranova, 1991). Secondly, human and animal studies have shown that the synthesis of collagen, which is the main component of extracellular matrix, is decreased, the degradation of newly synthesised collagen is accelerated and collagenase activity is increased (Goodson and Hunt, 1979; Rosenberg, 1990). Thirdly, accelerated formation of AGEs may lead to increased thickness of basement membranes of blood vessels, which impairs the supply of oxygen and nutrients to tissues (Rosenberg, 1990; Reiser, 1991). In addition, interaction of AGEs with the receptor for AGEs (RAGE) results in an exaggerated inflammatory response and compromised collagen production, which can lead to impaired wound healing (Wear-Maggitti et al, 2004). Finally, also growth factors have received particular attention due to their importance in stimulating and directing cellular activity in the wound environment. Thus, experimental studies using diabetes animal models suggest that impaired tissue repair may be a result of a deficient production of insulin-like growth factor (Brown et al, 1997), saliva-derived epidermal growth factor (Nagy et al, 2001) and/or platelet-derived growth factor (Doxey et al, 1995). Recent clinical studies indicate that the use of growth factors offer promising future therapeutic possibilities for enhancing wound healing (Bennett et al, 2003).

Considerations for Dental Treatment of Patients with Diabetes Mellitus

As health care providers, dentists will encounter an increasing number of patients with known or undiagnosed diabetes. Dentists can play an important role in identifying children and adults at risk of developing diabetes mellitus. Regular dental visits provide an obvious opportunity for prevention of the disease among healthy individuals and for screening children and adults with early signs and symptoms suggestive of diabetes. Early intervention in patients at particular risk, e.g., overweight children, may include dietary counselling to reduce sugar intake and thus contribute to reducing the risk for developing both obesity and dental caries.

Diabetics with poor metabolic control are at higher risk for oral diseases, and will more often develop complications in relation to dental procedures. This makes it important for the dentist to check the patient's blood glucose prior to an invasive procedure. Dental appointments should preferably be scheduled in the morning, i.e., a few hours after the usual insulin dose and breakfast. The dentist should instruct the patient always to measure blood glucose before a dental follow-up visit and to continue normal dietary intake before dental procedures. Dental treatment can be performed at blood glucose levels of 5-6 mmol/l, although this entails a higher risk of hypoglycaemia that would require rapid intake of glucose in the form of sweet juices, syrups or dextrose. Special precautions are not required

during the dental procedures of a well-controlled diabetic patient. In the case of poorly controlled diabetics and/or diabetics with long-term diabetic complications, however, antibiotic prophylaxis may be indicated in relation to even simple surgical procedures due to impaired wound healing and lowered resistance to infections. Acute oral infections and stress in relation to dental procedures increase blood glucose levels and thus insulin requirements. The need for adjustment of insulin dose in individual cases as well as the need for antibiotic therapy should always be established in consultation with the patient's physician. Furthermore, the dentist should be aware of potential interaction between oral hypoglycaemic agents and other medications when prescribing medication. Thus miconazole and fluconazole (a topical and a systemic antifungal agent, respectively) prolong the plasma half-life of coadministered tolbutamide (sulphonylurea).

Intensive prevention and control of periodontal disease is of significant importance, not only in children and adolescents with poorly controlled type 1 diabetes but also in adults with type 1 or type 2 diabetes, to prevent further disease progression and to improve metabolic control of diabetes. Frequent and regular dental visits (about every three months) are recommended for diabetics with reduced salivary gland hypofunction in order to reduce the risk of developing dental caries. The function of partial and complete dentures should be checked regularly due to increased risk for oral candidiasis and traumatic ulcers and in order to maintain adequate masticatory function and thereby sufficient nutrition intake. In the future, an increasing number of partially or completely edentulous diabetic patients will have dental implants. At present, dental implant surgery should only be performed by dentists who are experienced in the management of the complications that may occur peri- and postoperatively (Beikler and Flemmig, 2003). The patient must be under adequate metabolic control in order to enhance successful osseointegration and wound healing.

CONCLUSION

Epidemiological studies indicate that the incidence of diabetes mellitus, in particular type 2 diabetes, will increase significantly over the next few years. As primary health care providers, dentists play an important role, not only in identifying children and adults at risk for developing diabetes mellitus, but also in prevention of disease progression by improvement of oral as well as general health behaviour. Early detection and intervention may help to reduce the incidence and progression of diabetic complications. Diabetics with poor metabolic control have a significant increased risk for oral diseases, especially periodontal disease, and these patients should be offered an individual intensive dental care. A combination of conventional periodontal treatment and antibiotics (doxycycline) appears to have beneficial effects on the metabolic control in diabetics, and some evidence suggests a bi-directional relationship between periodontitis and diabetes.

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