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## REVIEW ARTICLE

# Update on diabetes mellitus and related oral diseases

**M Manfredi[1,2], MJ McCullough[1,3], P Vescovi[2], ZM Al-Kaarawi[1], SR Porter[1]**

[1]*Oral Medicine Department, Eastman Dental Institute, UCL, London, UK;* [2]*Sezione di Odontostomatologia, Università degli Studi di Parma, Parma, Italy;* [3]*Dental School, University of Melbourne, Melbourne, Vic., Australia*

**Diabetes mellitus (DM) is a group of complex multisystem metabolic disorders characterized by a relative or absolute insufficiency of insulin secretion and/or concomitant resistance to the metabolic action of insulin on target tissues. The chronic hyperglycaemia of diabetes is associated with long-term systemic dysfunction. The present article summarizes current knowledge of DM and details the oral and dental implications of this common endocrine disorder.**
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## Introduction

Diabetes mellitus (DM) is a complex multisystemic disorder characterized by a relative or absolute insufficiency of insulin secretion and/or concomitant resistance to the metabolic action of insulin on target tissues (Garber, 1998).

Hyperglycaemia is the immediate metabolic consequence of DM but, ultimately, there is widespread multisystem damage. In particular microvascular disease (microangiopathy) with capillary basement membrane thickening, macrovascular disease (macroangiopathy) with accelerated arteriosclerosis, neuropathy involving both the somatic and autonomic nervous system, neuromuscular dysfunction, embryopathy, and decreased resistance to infection (Garber, 1998).

Diabetes mellitus can have variable, and sometimes, profound effects upon the oral tissues, patients with poor glycaemic control being particularly prone to severe and/or recurrent bacterial or fungal infections.

Correspondence: Maddalena Manfredi, Sezione di Odontostomatologia, Università di Parma, Viale Gramsci 14, 43100 Parma, Italy. Tel.: +39 0521 991034, Fax: +39 0521 292955, E-mail: maddalenamanfredi@hotmail.com
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## Classification and pathogenesis of diabetes mellitus

A number of different classification systems for DM have been proposed (National Diabetes Data Group, 1979; World Health Organization, 1985). The American Diabetes Association has recently (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1998; The American Academy of Periodontology, 1999) developed a classification system based upon disease aetiology. The classification scheme includes two major forms of DM: type 1 (previously insulin-dependent diabetes mellitus or IDDM) and type 2 (previously non-insulin-dependent diabetes mellitus or NIDDM). Type 1 disease includes a type A immune-mediated, and a type B idiopathic DM. Type 2 includes the most common form of diabetes, which combines insulin resistance with an insulin secretory defect (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1998).

In addition to these types of DM there are other specific forms of disease such as diabetes secondary to autoimmune endocrinopathies, infection (e.g. congenital rubella, cytomegalovirus, coxsackie virus), genetic disease or DM induced by drugs or pregnancy.

All types of DM are biochemically characterized by hyperglycaemia tested during an oral glucose tolerance test (OGTT) (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1998). Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are used to indicate a metabolic stage intermediate between normal glucose homeostasis and DM.

## General signs and symptoms of diabetes mellitus

The initial clinical features of type 1 DM include the typical triad of polyuria, polydypsia and polyphagia. Irritability, malaise, apathy and pruritus can also be early features of type 1 DM (Teuscher *et al*, 1989; Rees and Otomo-Corgel, 1992; Nathan, 1993; Rees, 1994; Bell and Hockaday, 1996; Garber, 1998; The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1998). Patients with undiagnosed

type 1 DM are prone to ketoacidosis (Bell and Hockaday, 1996; The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1998). The features of type 1 DM are reversible with effective insulin therapy. The features of type 2 DM are of slower onset and less specific than those in type 1, sometimes only being detected when patients are being investigated for disease unrelated to DM. Patients with type 2 disease are often obese and although the relevant biochemical defect is not profound, complications of long-standing DM still arise. Both type 1 and 2 of DM have equal risk of developing vascular complications.

## Complications of diabetes mellitus

While good glycaemic control can prevent or reduce the likelihood of the possible complications of DM, approximately 50% of patients with DM develop vascular chronic complications following years of DM (Rees, 1994).

The chronic complications of DM are summarized in Table 1 (Teuscher *et al*, 1989; The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1998). The eyes (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1998) (Teuscher *et al*, 1989; Rees, 1994) and kidneys are particularly liable to disease (Bennet and Seltzer, 1970; Burrows, 1979; Warram *et al*, 1991; Partanen *et al*, 1995; Little *et al*, 1997). Diabetic retinopathy is one of the most common causes of loss of vision in the USA (Rees, 1994; Little *et al*, 1997). Proliferative retinopathy is particularly problematic and is more common in type 1 than type 2 DM. Cataract occurs at an earlier age and with a higher frequency in patients with DM than those without DM (Kannel and McGee, 1979). Progressive renal disease can arise in 30–40% of patients with DM, especially those with type 1 disease. The majority of these patients will develop end-stage renal disease and require haemodialysis or combined renal-pancreas transplantation.

Accelerated arteriosclerosis, with resultant cerebrovascular, cardiovascular and other vascular disease occurs in long-standing DM (Table 1). Myopathy can produce progressive weakness and exercise intolerance. Peripheral neuropathies cause paraesthesia and anaesthesia, reduced motor function, while autonomic neuropathy can cause orthostatic hypotension (Bell and Hockaday, 1996) and may reduce salivary flow rate (Marchetti *et al*, 1989; Newrick *et al*, 1991). Recently, it has been reported that peripheral diabetic neuropathy may be a risk factor for severe temporomandibular joint dysfunction (Collin *et al*, 2000).

**Table 1** Cronich systemic complications of DM (Bell and Hockaday, 1996)

1. Macroangiopathies
   - Atherosclerosis
   - Myocardial disease
   - Ischaemic heart disease
   - Cerebrovascular disease
   - Intermittent claudication
   - Gangrene of feet
2. Microangiopathies
   - Retinopathy
   - Nephropathy
   - Capillary basement membrane thickening
3. Neuropathy
   - Peripheral sensory neuropathy
   - Femoral neuropathy
   - Mononeuropathy
   - Autonomic neuropathy
     - Postural hypotension
     - Impotence
     - Diabetic diarrhoea
     - Urinary retention
     - Gustatory sweating
     - Abnormal pupillary reflexes
   - Cardiac autonomic disturbance

## Type 1 diabetes mellitus

Type 1 DM immune-mediated (A) (previously termed juvenile-type onset diabetes or insulin dependent) constitutes 5–15% of all cases of diabetes. Although having a worldwide distribution, this condition affects North Americans and Europeans more frequently than other ethnic groups (Atkinson and Maclaren, 1994; Winter, 1996). This type of DM is due to cell-mediated autoimmune destruction of the $\beta$-cells of the islet of Langerhans of the pancreas (Atkinson and Maclaren, 1994) leading to a complete inability of the cells to secrete insulin.

Type 1 DM usually develops before 30 years of age, although can occur at any age. It is suggested that pancreatic destruction occurs when genetically predisposed individuals are subjected to a triggering event, such as viral infection, that induces the destructive autoimmune response (Smith, 1987; Rees, 1994).

The rate of $\beta$-cell destruction is variable, being rapid in some individuals (usually infants and children) and slow in others (typically adults) (Zimmet *et al*, 1994). There are two age-associated peaks of incidence most commonly in the middle of the first decade, and in adolescence.

Recently, the $\beta$-cell damage has been suggested to be due to islet cell autoantibodies (ICAs), autoantibodies to insulin (IAAs), autoantibodies to glutamic acid decarboxylase (GADA65) and autoantibodies to the tyrosine phosphatases IA-2 and IA-2$\beta$. Individuals (85–90%) with initial hyperglycaemia have one or more of these autoantibodies, which can be considered as markers of this type of DM. It has been reported that genes for type 1 DM can provide both susceptibility and protection in relation to the disease, as summarized in Table 2 (Cantor *et al*, 1995; Atkinson and Eisenbarth, 2001; Bingley *et al*, 2001).

The idiopathic form of type 1 DM (B) is of unknown aetiology. Most affected patients have a permanent insulinopenia and are prone to ketoacidosis. A minority of patients with type B disease, most of whom are Asian or African, suffer episodic ketoacidosis and have varying degrees of insulin deficiency between these episodes. This form of diabetes is strongly inherited, but lacks immunological evidence for $\beta$-cell autoimmunity and it is not human leucocyte antigen associated (Banerji and Lebovitz, 1989; The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1998).

**Table 2** Type 1 DM risk associated with HLA-DR and HLA-DQ haplotypes (Atkinson and Eisenbarth, 2001)

| | *HLA* | | |
|---|---|---|---|
| *Risk* | *DRB1* | *DQA1* | *DQB1* |
| High risk | 0401, 0402, 0405 | 0301 | 0302 |
| | 0301 | 0501 | 0201 |
| Moderate risk | 0801 | 0401 | 0402 |
| | 0101 | 0101 | 0501 |
| | 0901 | 0301 | 0303 |
| Weak or moderate protection | 0401 | 0301 | 0301 |
| | 0403 | 0301 | 0302 |
| | 0701 | 0201 | 0201 |
| | 1101 | 0501 | 0301 |
| Strong protection | 1501 | 0102 | 0602 |
| | 1401 | 0101 | 0503 |
| | 0701 | 0201 | 0303 |

## Type 2 diabetes mellitus

Type 2 DM, previously termed NIDDM, often arises in middle to late life and is the more common form of DM, representing between 80 and 93% of all affected patients (National Diabetes Data Group, 1985; The American Academy of Periodontology, 1999). Type 2 DM is characterized by a $\beta$-cells dysfunction to secrete adequate amounts of insulin, particularly after meals, and/or peripheral insulin resistance. Patients with type 2 DM have some endogenous insulin secretory capability, but have overt abnormalities of glucose homeostasis, including fasting hyperglycaemia (Reaven *et al*, 1976; Turner *et al*, 1979; Bell and Hockaday, 1996; Garber, 1998). Depending upon the degree of accompanying hyperglycaemia, patients with type 2 DM are managed by dietary control of sugars and/or with oral hypoglycaemic agents, although sometime insulin therapy becomes necessary if their disease can not be managed adequately with oral agents and diet.

Type 2 DM frequently remains undiagnosed for many years as in the early stages of disease the hyperglycaemia develops gradually and is often not severe enough to give rise to polyuria, polydypsia nor weight loss (Fujimoto *et al*, 1987; Harris, 1989).

Unlike patients with type 1 disease, those with type 2 DM are relatively resistant to the development of ketoacidosis, as a consequence of the retention of endogenous insulin secretion. Type 2 DM often has a familial basis, although does not clinically manifest until middle to late life. As a consequence of an accompanying insulin resistance, obesity is a major risk factor for the development of this type of DM, indeed up to 80% of patients with type 2 DM have mild to marked overweight (Zimmet, 1992; Harris *et al*, 1995). Women with prior gestational diabetes mellitus (GDM) may also be liable to type 2 DM as can individuals with hypertension or hyperlipidaemia (Barnett *et al*, 1981; Newman *et al*, 1987).

## Diagnostic criteria for diabetes mellitus

The diagnostic criteria for DM as recommended by National Diabetes Data Group (National Diabetes Data Group, 1979) or World Health Organization (World Health Organization, 1985) have been recently modified by an Expert Committee (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1998). The primary methods to diagnose DM and monitor blood glucose levels have traditionally been fasting blood glucose, a combination of fasting blood glucose plus a 2 h test after glucose loading (2 h postprandial), and OGTTs. The revised criteria suggest the diagnosis of DM by one of three methods, each requiring confirmation by repeat testing (Table 3) (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1998).

## Assessment of glycaemic control in patients affected by diabetes mellitus

Different methodologies are available to assess glycaemic control, these depending exact upon the severity of the disease and the clinical setting.

*Blood glucose monitoring*

Levels of blood glucose can be self-monitored by patients, using blood glucose test strips. The advantage of this

**Table 3** Diagnostic criteria for diabetes (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1998)

Diabetes mellitus may be diagnosed by any one of three methods. Whatever method is used it must be repeated on a subsequent day.

1. Symptoms of diabetes plus random (non-fasting) plasma glucose $\geq$200 mg $dl^{-1}$. The blood foe examination of glucose may be drawn at any time of day and without regard to time since the last meal. The relevant symptoms of diabetes include polyuria, polydypsia and unexplained weight loss (or)
2. Fasting plasma glucose $\geq$126 mg $dl^{-1}$. Fasting is defined as no caloric intake for at least 8 h (or)
3. Two-hour postprandial glucose $\geq$200 mg $dl^{-1}$ during an oral glucose tolerance test (OGTT). The test should be performed using a glucose load containing the equivalent of 75 g of anhydrous glucose dissolved in water (this method is not recommended for routine clinical use)

Categories of 2-h postprandial glucose (2hPG) include:

1. 2hPG $<$ 140 mg $dl^{-1}$ = normal glucose tolerance
2. 2hPG $\geq$ 140 mg $dl^{-1}$ and $<$200 mg $dl^{-1}$ = impaired glucose tolerance
3. 2hPG $\geq$ 200 mg $dl^{-1}$ = provisional diagnosis of diabetes (this must be confirmed on subsequent day)

Categories of fasting plasma glucose (FPG) include:

1. FPG $<$ 110 mg $dl^{-1}$ = normal fasting glucose
2. FPG $\geq$ 110 mg $dl^{-1}$ and $<$126 mg $dl^{-1}$ = Impaired fasting glucose
3. FPG $\geq$ 126 mg $dl^{-1}$ = provisional diagnosis of diabetes (this must be confirmed on subsequent day)

self-monitoring of capillary blood glucose concentration is that the information is available immediately hence permitting the motivated patient to appropriately adjust their insulin dose on a day-to-day basis. This approach allows ketoacidosis to be avoided and encourages good compliance with dietary sugar intake.

*Glycosylated haemoglobin*
The estimation of blood level of glycosylated haemoglobin ($HbA1_c$) provides an accurate and objective measure of glycaemic control over past weeks to months. Several minor components of adult haemoglobin (HbA1) can be separated from unmodified haemoglobin (HbA0) by ion-exchange chromatography, and these haemoglobin moieties are increased in DM by the slow non-enzymatic covalent attachment of glucose and other sugars (glycation). The rate of formation of this glycosylated haemoglobin is directly proportional to these ambient blood glucose concentrations.

Glycosylated haemoglobin is expressed as a percentage of the normal haemoglobin. Non-diabetic subjects have HbA1c values of less than 6%, while levels in poorly controlled patients may reach 10–12%, and can be as great as 20%.

Glycosylated haemoglobin estimates may be incorrectly reduced with anaemia or during pregnancy, and some assay methods are complicated by uraemia or haemoglobinopathy. In clinical practice glycosylated haemoglobin is usually measured periodically (at least twice yearly) to assess glycaemic control, permit appropriate changes to treatment and to determine the degree of inconsistency with a patient's records of home blood glucose monitoring.

*Plasma fructosamine*
In situations where the HbA1c cannot be measured (e.g. haemolytic anaemias), glycated serum protein (GSP) may also be measured by means of the fructosamine assay as an index of glucose control. A single measurement of GSP provides an index of glycaemic status over the preceding 1–2 weeks, while a single HbA1c test provides an index of glycaemic status over a considerably longer period of time, 2–3 months. Other than in diabetic pregnancy, this is generally too short a time period to allow appropriate clinical decisions of therapy to be made (Goldstein *et al*, 2003).

*Urine testing*
Testing of urine for glucose has been used as a method of diabetic monitoring for over 50 years. However, the introduction of new and more efficient methods of blood glucose has permitted much closer good glycaemic control. Negative urine tests fail to distinguish between normal and low blood glucose levels, which is a particular disadvantage since the aim of treatment is to obtain normal blood glucose level avoiding hypoglycaemia. Urine tests are routinely performed to monitor the levels of urinary proteins and ketones to confirm prior diagnosis of renal-insufficiency in patients with DM (Bell and Hockaday, 1996). However, long-term follow-up studies suggested that raised urinary albumin secretion is a predictive parameter for overt diabetic nephropathy in DM patients, particularly in type 1 DM. It has been reported that achievement of a satisfactory metabolic control, in the early stage of renal dysfunction, reduces or normalizes the increased glomerular capillary permeability to albumin, which is the cause of the so-called microalbuminuria (Viberti *et al*, 1979, 1982; Parving *et al*, 1982; Pickup *et al*, 1984; Lugari *et al*, 1988).

## Management of diabetes mellitus

The aims of management of DM are to maintain a normal blood glucose levels without episodes of hypoglycaemia, and to prevent or lessen, the complications of long-standing disease. These aims cannot be achieved without good patient compliance.

Type 2 DM can usually be managed with control of dietary carbohydrates, control of body weight and increased physical activity (Lomasky *et al*, 1990; Watts *et al*, 1990; Little *et al*, 1997). If this fails to adequately reduce blood glucose levels, oral hypoglycaemic agents are required in addition to diet control.

*Oral hypoglycaemic agents and insulin*
The drugs commonly used to manage DM are sulphonylureas and biguanides. In particular, sulphonylureas stimulate the secretion of insulin, increase the number of insulin receptors if there is some endogenous insulin production. Examples of currently employed sulphonylureas are indicated in Table 4.

Metformin is the only available biguanide. This drug acts mainly by decreasing hepatic gluconeogenesis and increasing peripheral utilization of glucose. Metformin is the drug of first choice in grossly obese patients in whom diet has failed to control the DM. The use of metformin is contraindicated in patients with renal-insufficiency (i.e. a serum creatinine concentration exceeds 1.4 mg $dl^{-1}$ in women or 1.5 mg $dl^{-1}$ in men, or abnormal creatinine clearance), acute or chronic metabolic acidosis or in patients with severe hepatic dysfunction. In these patients, metformin use may contribute to the development of lactic acidosis (Scheen, 1997).

A number of other agents are available to manage DM. $\alpha$-Glucosidase inhibitors, such as acarobose and miglitol delay the digestion and absorption of complex carbohydrates, and although these agents do not increase the response to insulin in any tissues, their ability to limit postprandial glucose increases can reduce plasma insulin levels and the need for insulin supplements. The drugs are generally safe, but they often cause flatulence, especially when the dosage is increased rapidly.

Repaglinide is a benzoic acid derivative and the first of the non-sulphonylurea meglitinides introduced in 1998. The mechanism of action of this drug is similar to those of the sulphonylureas. Repaglinide is the most rapid and short-acting agent and reduces fasting hyperglycaemia. It is a suitable option for patients with a recent diagnosis of type 2 DM who have high postprandial glucose levels. All types of oral hypoglycaemic agents should be used carefully in elderly patients

**Table 4** Major hypoglycaemic agents used to control DM type 2

| *Drug class* | *Daily dose range (mg)* | *No. of daily doses* | *Site of metabolism* | *Mechanism of action* |
|---|---|---|---|---|
| Sulphonylureas | | | | Stimulate insulin secretion |
| Glibenclamide | 5–15 | 1–3 | Oxidized in liver-excreted in urines; 50% excreted unchanged in faeces | |
| Gliclazide | 40–320 | 1–3 | 95% liver | |
| Glimepiride | 1–4/6 | 1 | | |
| Glipizide | 2.5–20 | 2–3 | 90–95% liver-excreted unchanged in urine; 12% excreted in faeces | |
| Gliquidone | 15–180 | 2–3 | 90–95% liver-metabolites excreted in bile | |
| Biguanides | | | | Increase hepatic glucose output |
| Metformin | 500–1700 | 1–3 | Liver, not metabolized-excreted unchanged in the urine | |
| α-Glucosidase inhibitors | | | | Decrease gastrointestinal absorption of carbohydrates |
| Acarbose | 25–100 | 1–3 | Liver | |
| Miglitol | | | Liver | |
| Meglitinides | | | | Stimulate insulin release |
| Repaglinide | 0.5–1/16 | 1–3 | Most excreted in urine | |
| Thiazolidinediones | | | | Reduce peripheral insulin resistance |
| Pioglitazone | 15–30 | 1 | Liver | |
| Rosiglitazone | 4–8 | 1–2 | Liver | |
| Troglitazone | 400–600 | 1 | Liver (liver toxicity) | Withdrawn |

and in those with renal or hepatic dysfunction (Riddle, 1999).

Pioglitazone, rosiglitazone and troglitazone belong to a new class of oral glucose-lowering drugs (thiazolidinediones) that enhance the response of muscle and adipose tissue to insulin in patients who are otherwise relatively unresponsive, for example the extremely obese. However, troglitazone was withdrawn from the USA in March 2000, following 61 deaths from hepatic failure and seven liver transplants associated with the drug. This drug has also been withdrawn in Europe (Riddle, 1999; Bailey, 2000; Krentz *et al*, 2000).

The newer antidiabetic drugs are usually prescribed in combination with sulphonylureas and biguanides, when the older agents prove inadequate in reducing the high blood glucose levels.

Insulin therapy is required for type 1 DM, and for patients with long-standing type 2 DM when there is a failure of other therapies. Insulin is administered by subcutaneous injection and is available as short-action for 2 to 6–8 h, intermediate-action (1–20 h) and long-acting (over 40 h) forms (Mealey, 1998). Recently, a rapid-acting insulin analogue has became available for maintaining blood glucose levels below 180 mg $dl^{-1}$ for 2 h after a meal (Hirsch, 1999). Mixed insulin preparations are also available. Management typically involves a combination of short-acting and intermediate-acting insulin (Table 5). Continuous subcutaneous insulin infusions or 'insulin pumps' are now available. These deliver a basal dosage of insulin to maintain glucose control without hypoglycaemia (Varon and Mack-Shipman, 2000).

Insulin is available in three different types: human (produced synthetically or by DNA recombinant technology using *Escherichia coli*), porcine and bovine. Human insulin has a more rapid onset and shorter duration of action than porcine insulin, while bovine insulin has the longest duration of activity (Mealey, 1998), although the non-human forms are now rarely employed.

The absorption of insulin from subcutaneous sites is variable both within and between individuals. Most patients with type 1 DM require three to four injections of insulin daily, but it is clearly necessary to individualize therapy and even then the same dose of insulin may have quite different effects on different days in the same patients (Bell and Hockaday, 1996). The main aim of insulin therapy is to reproduce the natural peak levels of insulin during and after meals with basal concentration postprandially. Detailed descriptions of insulin therapy can be found elsewhere (Garber, 1998). The pharmacokinetics of insulin make this difficult and hypoglycaemia is the most common complication of inadequate management (Bell and Hockaday, 1996).

Hypoglycaemia may give rise to a variety of clinical features that include reactions: irritability, tachycardia, palpitations, confusion and possibly coma. Hypoglycaemia (blood sugar $< 60$ mg $dl^{-1}$) could develop during dental treatment, but can be corrected by administration of quickly absorbed sources of glucose (tablets, juice, candy), or in case of unconsciousness, intravenous glucose. Furthermore, to reduce the risk of hypoglycaemia on the day of dental procedure, patients with diabetes should be scheduled for a morning appointment, with possible insulin dosage modifications for delayed and/or reduced food intake (Burrows, 1979; Smith, 1987; Lomasky *et al*, 1990; Nathan, 1993; Bell and Hockaday, 1996; Scully *et al*, 1998; Varon and Mack-Shipman, 2000).

## Oral manifestations of diabetes mellitus

A wide spectrum of oral manifestations of DM have been reported.

**Table 5** Principal insulin preparations used to control DM

| *Insulin preparation types* | *Onset of duration (hours–minutes)* | *Peak of action (h)* | *Maximal duration of action (h)* | *Commonly used regimens* |
|---|---|---|---|---|
| Short-acting insulin | 0.5–1 h | 1–3 | 6–8 | Given 20–30 min before meals |
| Insulin soluble | 30 min | 1–3 | 8 | |
| Rapid-acting insulin analogue | 10–30 min | 1–3 | 3–5 | Given immediately before meals |
| Insulin Lispro | 30 min | 1–2 | 8 | |
| Insulin Aspart | 30 min | 1–2 | 8 | |
| Intermediate acting insulin | 1.5–2 h | 4–12 | 18–24 | 1. Given before bed<br>2. Given before bed, in combination with tablets in overweight patients<br>3. Given once daily before breakfast, in elderly<br>4. Given twice a day, in type 2 DM |
| Long-acting insulin | 1–2 h | 4–12 | 20–40 | Once daily, or twice daily with a short-acting (soluble) insulin |
| Biphasic action (combination of rapid or short and intermediate action) | 0.5–1 h | 1–10 | 18–24 | |
| 10/90 (10% solubile-90% isophane insulin) | 30 min | 2–8 | 24 | Given 20–30 min before breakfast and evening meal, as a twice day regimen |
| 20/80 (20% soluble–80% isophane insulin) | 30 min | 2–8 | 24 | Given 20–30 min before breakfast and evening meal, as a twice day regimen |
| 30/70 (30% soluble–70% isophane insulin) | 30 min | 2–8 | 24 | Given 20–30 min before breakfast and evening meal, as a twice day regimen |
| 40/60 (40% soluble–60% isophane insulin) | 30 min | 2–8 | 24 | Given 20–30 min before breakfast and evening meal, as a twice day regimen |
| 50/50 (50% soluble–50% isophane insulin) | 30 min | 2–8 | 24 | Given 20–30 min before breakfast and evening meal, as a twice day regimen |
| 25% insulin Lispro–75% insulin Lispro protamide | 30 min | 2 | 24 | Given immediately before breakfast and evening meal, as a twice day regimen |

*Xerostomia*

Dryness of the mouth as a feature of uncontrolled diabetes was first described in 1942 (Sheppard, 1942; Lamey *et al*, 1992). The xerostomia may be a consequence of dehydration, although long-standing oral dryness may be due to microvascular disease and neuropathy affecting the major salivary glands (Newrick *et al*, 1991). In addition the xerostomia may be due to concomitant drug therapy (antihypertensives, diuretics, anxiolytics or antidepressants) (Sharon *et al*, 1985; Albrecht *et al*, 1987; Harrison and Bowen, 1987; Finney *et al*, 1997).

Prolonged xerostomia predisposes to local accumulation of plaque and debris and may contribute to the development of opportunistic oral infections (liability to dental caries, periodontal disease), altered taste (Rees, 1994; Finney *et al*, 1997), oral malodour and oral mucosal soreness.

Xerostomia in type 1 DM seems to be dependent upon glucose control (Conner *et al*, 1970; Tenovuo *et al*, 1986; Sreebny *et al*, 1992; Swanljung *et al*, 1992) whereas in type 2 DM, salivary secretion seems to be particularly influenced by xerogenic drugs and autonomic neuropathy (Meurman *et al*, 1998).

*Taste impairment*

Diabetes mellitus can cause a loss of the sweet taste sensation (Lawson *et al*, 1979; Le Floch *et al*, 1989) indeed this may be present at time of diagnosis. Although the taste impairment is usually not severe, and is generally tolerated without complaint, the undiagnosed diabetic patient may favour sweet, sugary food hence exacerbating any hyperglycaemia. Many patients with polydypsia with hyperglycaemia have a predilection for sweet drinks, which have a high content of refined carbohydrate (Lamey *et al*, 1992). Altered taste sensation of DM may reflect taste receptor anomalies (Hardy *et al*, 1981). In addition, sulphonylureas may cause an alteration of the taste sensation (Rollin, 1978).

*Sialosis*

It has been previously reported that almost 10–25% of patients with long-standing type 1 and 2 DM can develop asymptomatic, non-inflammatory, non-neoplastic enlargement of the salivary glands (Russotto, 1981; Murrah, 1985; Lamey *et al*, 1992; Greenspan, 1996), however recently, a low correlation between DM and parotid enlargement was reported, only 3% of 405 patients with DM type 1 being found to have such salivary gland enlargement (Guggenheimer *et al*, 2000a).

Both parotid glands are usually affected, although the submandibulary glands may be also involved (Russotto, 1981; Greenspan, 1996). Histologically the enlargement, sometimes termed sialosis, comprises fatty infiltration of the interstitium (Davidson *et al*, 1969) and enlargement of acinar cells (Donath and Seifert, 1975). It is suggested that patients may be predisposed to calculus formation and obstruction, however in general salivary function is preserved and the sialosis does not influence the duration nor the severity of DM.

*Dental caries*

It remains unclear if patients with DM are at increased risk of dental caries (Karjalainen *et al*, 1997; Ponte *et al*,

2001). Cross-sectional and controlled studies (Kirk and Kinirons, 1991; Jones *et al*, 1992; Swanljung *et al*, 1992) have reported conflicting results (Reuterving *et al*, 1986; Harrison and Bowen, 1987). Several studies suggested that poor glycaemic control could be a risk factor for caries in children and adolescents with type 1 DM (Karjalainen *et al*, 1997), while type 2 DM seemed have no effect on the prevalence of caries (Collin *et al*, 1998). Although dietary intake of carbohydrates by diabetics is lower than that of non-diabetics, a higher number of meals per day could promote caries development (Lamey *et al*, 1992; Karjalainen *et al*, 1997).

Any increased liability to caries in DM may of course reflect elevated concentrations of glucose in saliva and gingival crevicular fluid of diabetic patients (Kjellman, 1970) but more likely individuals with DM develop caries as a consequence of poor oral hygiene (Karjalainen *et al*, 1997).

*Periodontal disease*

Although not universally agreed, an increased in the risk of periodontal disease association with both type 1 and type 2 DM with has been reported (Albrecht *et al*, 1987; Bacic *et al*, 1989; Emrich *et al*, 1991; Moore *et al*, 1999; American Academy of Periodontology, 2000).

Uncontrolled or poorly controlled DM may give rise to an increased susceptibility to oral infections, including periodontitis (Bartolucci and Parkes, 1981; Ureles, 1983) and diabetic patients with severe periodontal disease are much more at risk of microvascular and macrovascular diabetic complications (Thorstensson *et al*, 1995; The American Academy of Periodontology, 1999; Lalla and D'Ambrosio, 2001). The incidence of periodontitis increases among diabetic subjects after puberty and as the adult population ages (Cohen *et al*, 1970; Cianciola *et al*, 1982; Galea *et al*, 1986; Albrecht *et al*, 1987; de Pommereau *et al*, 1992; Seppala *et al*, 1993). It has been suggested also that the disease is associated with poor glycaemic control and hyperglycaemia (American Academy of Periodontology, 2000). It has also been reported that patients with type 1 DM have an increased risk for developing periodontal disease with age, past and current cigarette smoking, infrequent dental attendance (Moore *et al*, 1999).

Epidemiological studies of Pima Indians, a group with an extremely high prevalence of type 2 DM (Shlossman *et al*, 1990), have found that, irrespective of age, affected patients have a higher prevalence of periodontal disease than other ethnic groups. Other studies (Emrich *et al*, 1991) have also found that patients with type 2 DM were more likely to have periodontal disease from non-diabetic control subjects, this risk not being influenced by age, gender or oral hygiene. Some studies however, have found that periodontal attachment loss, probing depth and gingivitis occur more frequently and more extensively in moderately and poorly controlled diabetic patients of either type than in those with good glucose control (Shlossman *et al*, 1990; Katz *et al*, 1991; Tervonen and Oliver, 1993).

However, while the above-mentioned would seem to be the most consistent trends, there is considerable conflicting data on any possible increased liability of periodontal disease in DM (Porter and Scully, 1994). Potentially a number of factors could contribute to any enhanced of periodontal disease in diabetes (American Academy of Periodontology, 2000) notably the oral microflora, phagocytic and connective-tissue defects of affected individuals.

Several reports have suggested that the oral flora in patients with DM is different to that of healthy subjects. Experimentally induced DM in rats causes a shift in the subgingival bacteria to a more periodontopathic flora, predominantly composed of Gram-negative bacteria (McNamara *et al*, 1982). An increase of *Capnocytophaga* in patients with type 1 DM has been reported (Mashimo *et al*, 1983), although other studies have failed to show any statistical association between these bacterial species and periodontal disease in type 1 DM (Zambon *et al*, 1988; Sastrowijoto *et al*, 1989; Sbordone *et al*, 1998).

More recent studies, however, suggest that the composition of the subgingival microorganisms, detected by immmunofluorescence and cultural methods in type 2 DM patients is similar to that found in chronic adult periodontitis (Zambon *et al*, 1988). A study of five periodontal pathogens (*Actinobacillus actinomycetmcomitans*, *Fusobacteria nucleatum*, *Eikenella corrodens*, *Porphyromonas gingivalis* and *Prevotella intermedia*) in individuals with type 1 and type 2 DM revealed that the duration, type, and metabolic control of diabetes had no statistically significant effect upon the prevalence of these microorganisms (Tervonen *et al*, 1994). Another recent study (Yuan *et al*, 2001) using PCR techniques, found that there was no difference in the frequency of detection of putative periodontal pathogens between type 2 DM and healthy subjects.

Polymorphonuclear (PMN) leucocyte function (chemotaxis, adherence, phagocytosis and killing) can be reduced in DM leading to impaired host resistance to infection (Hill *et al*, 1974; Molenaar *et al*, 1976; Bagdade *et al*, 1978; Repine *et al*, 1980; Manouchehr-Pour *et al*, 1981; Iacono *et al*, 1985; Leeper *et al*, 1985; Wilson and Reeves, 1986; Kjersem *et al*, 1988; Marhofer *et al*, 1992). However, most of these PMN anomalies can usually be corrected by good glucose control.

Any increased risk of periodontal diseases in DM may be influenced by hyperglycaemia-associated reduction in cell proliferation and growth and synthesis of collagen and glycosaminoglycans (Golub *et al*, 1978; Weringer and Arquilla, 1981; Lien *et al*, 1984; Seibold *et al*, 1985).

## Fungal infections

*Oral Candida and candidosis*

Poor control of DM may predispose to superficial and systemic fungal infections (Fisher *et al*, 1987; Hill *et al*, 1989; Lamey *et al*, 1992; Finney *et al*, 1997; Guggenheimer *et al*, 2000b; Lalla and D'Ambrosio, 2001), and the clinical course of oral candidosis can be more severe than that of patients without DM. However, although the majority of reports show a correlation between *Candida* and DM (Ueta *et al*, 1993; Guggenheimer *et al*,

2000b), the notion that candidal infection is more severe and common in DM than healthy individuals, remains unresolved (Samaranayake, 1990; Vazquez and Sobel, 1995). It also remains unclear if the candidal load [e.g. in terms of colony forming units (cfu)] is a true reflection of likely clinical manifestation of fungal disease and if the oral load of *Candida* increases liability to systemic infection.

*Candida albicans* is the most prevalent *Candida* species isolated either from the oral cavity of diabetic patients and healthy individuals (Dorocka-Bobkowska *et al*, 1996; Willis *et al*, 1999). Recently, *C. dubliniensis*, a newly described species of *Candida*, mostly isolated from the oral cavity of HIV-infected patients, was isolated from the oral cavity of 58 of 318 insulin-treated DM patients (Willis *et al*, 2000a). *Candida dubliniensis* has also been isolated from the oral cavity of patients with both type 1 and type 2 diabetes (Manfredi *et al*, 2002) and seems to have a predilection for dentate patients. The pathogenic significance of this new species in the oral cavity of patients with DM remains unknown. The frequency and density of *Candida* colonization and the development of oral candidosis in DM patients seem more the result of a combination of host and fungal risk factors (e.g. degree of glycaemic control, presence of dentures, smoking habits, age, medications, adherence of *Candida* spp.), rather than any other single factor (Darwazeh *et al*, 1990, 1991a) (Table 6). As with healthy individuals, there could be great variation in the isolation rates of oral *Candida* in patients affected by DM. A recent study (Manfredi *et al*, 2002) found that patients with DM are no more likely to harbour yeast in their oral cavity than healthy individuals, thus diabetes itself may not place a person at increased risk of fungal carriage or clinical infection although poor diabetic control, with a high level of glycosylated haemoglobin ($>12\%$) (Hill *et al*, 1989; Vazquez and Sobel, 1995) may increase the susceptibility to fungal infection (Gibson *et al*, 1990; Ueta *et al*, 1993; Willis *et al*, 2000b).

The hyperglycaemia of poorly controlled DM may influence the pathogenic colonization of *Candida* (Samaranayake and MacFarlane, 1982). Yeast growth and adhesion may be enhanced by high glucose concentration (Samaranayake *et al*, 1984) in blood (Odds *et al*, 1978) and in saliva (Knight and Fletcher, 1971), which can serve as nutrients for *Candida* organisms. The reduced *Candida* killing capacity by neutrophils in the presence of high glucose concentrations may also account for any increased colonization by *Candida* (Hostetter, 1990; Ueta *et al*, 1993; Vazquez and Sobel, 1995) . *In vitro* studies have demonstrated that in type 1 DM, the adhesion of *Candida* seems to be greater with palatal cells than buccal mucosal epithelial cells. The adhesion of *Candida* strains to oral mucosa seems to be influenced by the availability of sugars in the growth medium and by the host *Candida* strain, that could modify its surface composition in response to high salivary glucose concentration (Willis *et al*, 2000a). It has been also reported that the adhesion of *Candida* to buccal epithelial cells collected from patients affected by DM is significantly greater than adhesion obtained from

**Table 6** Oral *Candida* carriage in patients with diabetes mellitus investigated by different authors

| *Authors*[a] | *Oral Candida* carriage in diabetics (%) | *Methods of sampling* | *Total number of diabetic patients investigated* | *Number of patients with DM type 1* | *Number of patients with DM type 2* | *Oral Candida* carriage in controls (%) | *Increased oral Candida* carriage in DM patients denture wearers | *Oral Candida* carriage related to type of DM | *Increased oral Candida* carriage with poor metabolic control |
|---|---|---|---|---|---|---|---|---|---|
| Barlow *et al* (1969) | 62.5 | Swab | 24 | _[a] | _[a] | 35 | Not investigated | Not investigated | No |
| Tapper-Jones *et al* (1981) | 60 | Imprint culture | 50 | _[a] | _[a] | 42 | Yes | Not investigated | Not investigated |
| Fisher *et al* (1987) | 51 | Oral rinse | 412 | 232 | 180 | – | Yes | Not investigated | No |
| Lamey *et al* (1988) | 57 | Oral rinse | 106 | 57 | 52 | 27 | Yes | No difference | No |
| Hill *et al* (1989) | 49 | Swab | 51 | _[a] | _[a] | – | Yes | Not investigated | Yes |
| Darwazeh *et al* (1990) | 54 | Swab and smear | 50 | 19 | 31 | 40 | No | No difference | No |
| Aly *et al* (1992) | 66 | Swab and oral rinse | 436 | 231 | 205 | – | No | Yes: more *Candida* carriers in DM type 1 | No (oral rinse), yes (palatal carriage in dentures) |
| Dorocka-Bobkowska *et al* (1996) | 54 | Swab and imprint culture | 70 | 0 | 70 | 41 | Yes | Not investigated | No |
| Willis *et al* (2000a,b) | 77 | Oral rinse | 414 | 414 | 0 | – | Not investigated | Not investigated | No |
| Guggenheimer *et al* (2000a,b) | 23 | Cytologic smear | 405 | 405 | 0 | 5.7 | Yes | Not investigated | Yes |
| Manfredi *et al* (2002) | 60 | Oral rinse | 137 | 56 | 83 | 57 | Yes | No difference | No |

[a]In these studies the researchers did not differentiate between type 1 DM and type 2 DM.

buccal cells from non-diabetic controls (Darwazeh *et al*, 1990). Thus in diabetic patients intrinsic qualitative changes on the cell surface receptors may modulate yeast adhesion (Samaranayake, 1990).

It has been suggested that oral carriage of *Candida* species (in terms of cfu $ml^{-1}$) may be influenced by the type of DM. However, there is no confirmed association between oral candidal carriage and type (or severity) of DM. The different reported rates of oral carriage of *Candida* obtained (Aly *et al*, 1992; Bai *et al*, 1995; Manfredi *et al*, 2002) may reflect the different sample sizes or differences in the sample populations (e.g. age, diabetic therapies, dentures status) rather than any influence by diabetes.

Indeed, denture wearing may influence yeast colonization in patients with DM (Tapper-Jones *et al*, 1981; Fisher *et al*, 1987; Lamey *et al*, 1988; Hill *et al*, 1989; Aly *et al*, 1992; Dorocka-Bobkowska *et al*, 1996; Willis *et al*, 1999) more than any systemic aspect of DM.

It has been suggested that there is a correlation between *Candida*-associated denture stomatitis and type 2 DM (Odds, 1988; Budtz-Jorgensen, 1990), particularly in patients with DM-associated peripheral neuropathy. Hyperglycaemia and high salivary glucose levels can lead to some nutritionally derived enhancement of candidal growth, but probably they are not the only factors that enhance the growth of *Candida* species in the oral cavity of patients with DM (Darwazeh *et al*, 1991b; Vitkov *et al*, 1999). It is probable that the association of type 2 DM with denture stomatitis reflects some reduced immunosurveillance to *Candida*.

As in the individuals without DM, tobacco smoking may favour the carriage of *Candida* in diabetics: indeed it has been shown that the association of smoking habits and wearing dentures increase both the frequency and the density of *Candida* colonization (Tapper-Jones *et al*, 1981).

*Rhinocerebral zygomycosis (mucormycosis)*

Diabetic ketoacidosis is a major predisposing factor of the rare infection caused by fungi of the family *Mucoraceae* of the class of Zygomycetes (Sugar, 1992; Nussbaum and Hall, 1994; Eliopulos, 1995): indeed approximately 50% of patients with rhinocerebral murcomycosis have DM (Joshi *et al*, 1999). This infection usually initially arises in the nose or palate and manifests as bloody ulceration of the nose or as a pseudomembrane with ulceration of the palate. The infection spreads to the paranasal sinuses, orbits or brain; soft and hard tissue necrosis is prominent because of blood vessel invasion. Fever, lethargy, headache and facial swelling are often present. Orbital invasion causes proptosis, decreased ocular motion and loss of vision. Thrombosis of the venous sinuses or carotid system may occur (Eliopulos, 1995). Treatment requires prompt control of DM, correction of any acidosis, aggressive surgical debridement of infected tissue and systemic antifungal therapy.

*Aspergillosis*

*Aspergillus* species are filamentous saprophytes that live in soil and decadying vegetation. Aspergillosis particularly affects patients with prolonged and profound neutropenia and less frequently, invasive aspergillosis may occur in patients with DM (Rinaldi, 1983). Infections can arise in any part of the respiratory tract, including the paranasal sinuses, larynx and lungs. Primary lesions can also be localized to the eyes, ears and oral cavity (Benson-Mitchell *et al*, 1994; Myoken *et al*, 1995) and underlying structures, as well the skin of the face. Oral lesions can be predominant in immunocompromised patients and are described as grey necrotic ulcers affecting the gingiva, alveolar bone, palate or occasionally the posterior tongue (Dreizen *et al*, 1985; Napoli and Donegan, 1991; Chambers *et al*, 1995; Myoken *et al*, 1996). Infections may be spread to brain, bone or endocardium via bloodstream (Scully and de Almeida, 1992). Therapy for invasive aspergillosis often requires systemic amphotericin, and systemic azoles (Vazquez and Sobel, 1995). Surgical therapy, either alone or in combination with antifungal therapy, may be required in selected patients with localized disease (Scully and de Almeida, 1992; Vazquez and Sobel, 1995).

*Oral lichen planus*

An increased incidence of oral lichen planus (OLP) in DM, particularly the erosive form, has been reported in some groups of patients with DM (Lundstrom, 1983; Bagan-Sebastian *et al*, 1992). However, these studies suggest that there is no association between OLP and DM. Several studies have reported only a low prevalence of OLP in DM patients (Borghelli *et al*, 1993; Van Dis and Parks, 1995; Petrou-Amerikanou *et al*, 1998; Scully *et al*, 1998) (Table 7). The reverse association, incidence of DM in patients with OLP, has also been studied and has been reported to range from 1.6 to 37% (Grinspan *et al*, 1966; Lundstrom, 1983; Bagan *et al*, 1993; Petrou-Amerikanou *et al*, 1998; Romero *et al*, 2002). These variations may be explained by the different methods and criteria used to classify both OLP and DM diseases (Petrou-Amerikanou *et al*, 1998).

An association between OLP, DM and hypertension has been suggested (Grinspan syndrome, Grinspan *et al*, 1966), although this probably reflects lichenoid reactions associated with sulphonylureas and/or antihypertensive (e.g. $\beta$-blockers) drug therapy reported by several studies (Scully and el Kom, 1985; Rees and Otomo-Corgel, 1992;

**Table 7** Prevalence of oral lichen planus (OLP) (%) in patients affected by DM

| *Authors* | *Number of patients with DM* | *Prevalence of OLP (%)* |
|---|---|---|
| Grinspan *et al* (1966) | 20 | 40 |
| Grinspan *et al* (1966) | 70 | 5.71 |
| Borghelli *et al* (1986) | 240 | 0.42 |
| Borghelli *et al* (1987) | 584 | 0.17 |
| Albrectht *et al* (1992) | 1600 | 1 |
| Borghelli *et al* (1993) | 729 | 0.55 |
| Van Dis and Parks (1995) | 273 | 4 |
| Petrou-Amerikanou *et al* (1998) | 492 | 3.65 |

Robertson and Wray, 1992; McCartan and McCreary, 1997; Savage, 1997; Scully *et al*, 1998). Treatment of OLP associated with DM is not specific and a wide range of therapies are commonly used for symptomatic lesions. Topical treatments are usually preferred to avoid any interferences with the medications used to control DM.

*Geographical and fissured tongue*

Geographical tongue (benign migratory glossitis; erythema migrans), is a common inflammatory disorder that typically affects the dorsum of the tongue. An association between geographical tongue and DM (Wysocki and Daley, 1987) has been suggested, as the former has been reported to be present in up to 8.0% of patients with DM (Wysocki and Daley, 1987). However, a recent study, which had investigated oral soft tissue pathologies in 405 type 1 DM patients (Guggenheimer *et al*, 2000a), did not report a statistically significant correlation between geographic tongue and DM.

Fissuring in the tongue, can affect about 5% of the general population (Neville *et al*, 1995). The fissuring is probably genetically determined (Kullaa-Mikkonen *et al*, 1985) although a higher prevalence (8% in comparison with 2% of no-diabetic population) has been reported in type 1 DM patients (Farman, 1976; Guggenheimer *et al*, 2000a), particularly patients who have type 1 DM of long duration. There is, however, little other supporting data for this suggested association.

## Conclusion

Several oral diseases are frequently related to DM. The degree of metabolic control seems to influence the susceptibility of patients affected by DM to periodontal diseases, presence of fungal infections and taste alterations. Less clear is whether diabetes is correlated to OLP and to dental caries, as the various studies in the literature have reported widely diverging results.

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