PEER-REVIEWED

Diabetes mellitus and its relevance to the practice of dentistry

Diabetes mellitus is a syndrome of abnormal carbohydrate, fat and protein metabolism that results in acute and chronic complications due to the absolute or relative lack of insulin. Globally, it is expected that the number of people with diabetes will increase, and as a result dental practitioners will encounter an increasing number of patients affected by this chronic condition, which may have implications for the provision of safe and appropriate dental treatment. This article aims to provide an overview of diabetes and to discuss aspects of the condition relevant to dentistry. The article also discusses the management of diabetic emergencies in a dental practice setting.

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Introduction

Diabetes mellitus is a syndrome of abnormal carbohydrate, fat and protein metabolism that results in acute and chronic complications, and is due to the absolute or relative lack of insulin. The disease is a significant global public health problem and is a major source of morbidity and mortality in the world today.

Globally, it is expected that the number of people with diabetes will increase from the current estimate of 150 million to 220 million by the year 2010 and to 300 million by the year 2025.[1] Consequently, dental practitioners will encounter an increasing number of patients with diabetes presenting for dental treatment in years to come.

This article aims to provide an overview of diabetes and to discuss aspects of the condition relevant to dentistry.

Prevalence

In 2005 the estimated population prevalence of type 1 and type 2 diabetes in adults was 4.7% in the Republic of Ireland. This equated to just over 141,000 adults. Taking into account population change and assuming the most realistic scenario that obesity rates will continue to rise in a linear fashion, the population prevalence of diabetes in adults in 2015 will be in the order of 5.6% (193,944 adults) in the Republic of Ireland.[2]

Classification of diabetes mellitus

There are three main categories of diabetes:

1. Type 1 (insulin-dependent diabetes mellitus), which results from an absolute insulin deficiency.
2. Type 2 (non-insulin-dependent diabetes mellitus), which is the result of insulin resistance and an insulin secretory defect.
3. Gestational diabetes presenting for the first time during pregnancy, which occurs in 2-5% of all pregnancies.

Impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG) (**Table 1**) are intermediate conditions in the transition between normality and diabetes. Patients with these conditions are now referred to as having 'pre-diabetes' and are at high risk of progressing to type 2 diabetes mellitus, although this is not inevitable. IGT and IFG are associated with metabolic syndrome, which includes obesity (especially abdominal or visceral obesity), dyslipidaemia of the high triglyceride and/or low high-density lipoprotein (HDL) type, and hypertension.

Diagnosis

The criteria for diagnosis of diabetes include symptoms of hyperglycaemia (polyuria, polydipsia, unexplained weight loss, visual blurring, genital thrush, lethargy) associated with a raised random venous plasma glucose (≥11.1mmol/l) level, or a raised fasting plasma glucose level (≥7.0mmol/l) in the presence or absence of symptoms, with the test being performed on two separate occasions.

TABLE 1: Impaired glucose tolerance and impaired fasting glycaemia.[4]

Fasting plasma glucose level	Diagnosis
<5.6mmol/l	Normal fasting glucose
5.6-6.9mmol/l	Impaired fasting glycaemia
≥7mmol/l	Provisional diagnosis of diabetes
Two-hour postload glucose level	**Diagnosis**
<7.8mmol/l	Normal glucose tolerance
7.8-11.1mmol/l	Impaired glucose tolerance
≥11.1mmol/l	Provisional diagnosis of diabetes

TABLE 2: Type 1 and type 2 diabetes mellitus at a glance.

	Type 1 diabetes	Type 2 diabetes
Epidemiology	Younger patient	Older patient
Genetics	HLA D3 and D4 linked	No HLA association
Aetiology	Autoimmune ß cell destruction	Insulin resistance, ß cell dysfunction
Presentation	Polydipsia, polyuria, weight loss, ketoacidosis	Polydipsia, polyuria, fatigue and weight loss, though often asymptomatic; can present with micro- or macrovascular complications.

If there is any doubt, an oral glucose tolerance test is used. This involves giving the patient 75g of glucose in 300ml of water to drink the morning after an overnight fast. Venous plasma glucose levels are taken just before and two hours after the glucose. The test is positive if the two-hour plasma glucose ≥11.1mmol/l.[3]

Pathophysiology

Type 1 diabetes mellitus was formally known as insulin-dependent diabetes mellitus and is an autoimmune disease. It is most commonly diagnosed in young patients but can manifest at any age. Pathologically it is characterised by lymphocytic infiltration and destruction of insulin-secreting cells of the islets of Langerhans in the pancreas, causing insulin deficiency. These patients require lifelong exogenous insulin and without it, diabetic ketoacidosis (DKA) can develop, which may result in coma or death.

Type 2 diabetes mellitus was formally known as non-insulin-dependent diabetes mellitus and is a group of disorders characterised by hyperglycaemia. However, unlike type 1 diabetes mellitus, patients are not absolutely dependent upon insulin for life, even though many of these patients are ultimately treated with insulin. It is associated with obesity and lack of exercise, and has a higher prevalence in Asian men. It typically affects the over 40s but more and more cases are now being diagnosed in the teenage population. Type 2 diabetes mellitus may go unnoticed for years because symptoms are typically mild, non-existent or sporadic, and usually there are no ketoacidotic episodes. Because it may go unnoticed for long periods, type 2 diabetes may already be associated with microvascular (i.e., retinal, renal), macrovascular (i.e., coronary, peripheral vascular), and neuropathic (i.e., autonomic, peripheral) complications at the time of diagnosis (**Table 2**).

Long-term complications

The long-term complications associated with diabetes mellitus can be broadly characterised as either macrovascular or microvascular in nature. Macrovascular complications arise as a result of accelerated atherosclerosis. The atherosclerotic processes are made worse by the presence of other conventional risk factors, such as smoking, hypertension and dyslipidaemia.

1. Macrovascular complications

Heart disease and stroke

People with diabetes are two to four times more likely to die from heart disease than people of similar age without diabetes.[5] People with diabetes are also two to four times more likely to suffer a stroke than a person without diabetes.[6] Together, heart disease and stroke account for about 65% of deaths in people with diabetes.[5]

Amputations

More than 60% of non-traumatic lower limb amputations occur in people with diabetes and the rate of amputation for people with diabetes is 10 times higher than for people without diabetes.[5]

2. Microvascular complications

Diabetic retinopathy

Diabetes is the leading cause of new cases of blindness in adults between the ages of 20 and 74 years.[6] Approximately 20% of patients with type 2 diabetes mellitus have evidence of diabetic retinopathy at the time of diagnosis.[6] Cataracts and glaucoma are also commonly seen in people with diabetes.

Diabetic nephropathy

Nephropathy can result in elevated urinary protein excretion in a person with diabetes in the absence of other renal disease. Patients may ultimately develop end stage renal disease (ESRD) with renal failure. Diabetes accounts for approximately 35% of all new cases of ESRD in the United States and is the leading cause of newly diagnosed ESRD. People with diabetes comprise the fastest growing group of renal dialysis and transplant recipients.[6]

Peripheral neuropathy

About 60-70% of people with diabetes have mild to severe forms of nervous system damage. The results of such damage include impaired sensation or pain in the feet or hands, slowed digestion of food in the stomach, carpal tunnel syndrome, and other neurological problems.[5]

Sexual dysfunction

Diabetes significantly increases the risk for sexual dysfunction.

Medical management

Diet therapy and lifestyle modification are key factors in the management of diabetes mellitus. The goal of diet therapy is to prevent complications that result from hyperglycaemia. Tight blood glucose control prevents microvascular complications in both type 1 and type 2 diabetes mellitus.[7] Although glycaemic control may not be as effective in reducing macrovascular complications, aggressive therapies targeting blood pressure, lipid levels and smoking cessation are effective in preventing macrovascular complications.[8]

Type 1 diabetes mellitus

Insulin replacement therapy forms the mainstay of treatment in patients with type 1 diabetes mellitus. Approaches to insulin replacement include:

1. Subcutaneous insulin administration either by basal/bolus regime with multiple daily injections, or by continuous subcutaneous insulin infusion.
2. Implantable insulin pumps.
3. Whole pancreas and pancreatic islet transplantation.

Subcutaneous insulin therapy

Insulin therapy should ideally mimic the physiological release of insulin, which is characterised by a continuous basal secretion, to prevent fasting hyperglycaemia, as well as mealtime insulin release to prevent post-prandial hyperglycaemia.

The basal/bolus insulin regime is currently the most commonly employed treatment and involves subcutaneous administration of a long-acting basal insulin (e.g., Glargine/Detemir), which suppresses glucose production between meals and overnight, and a bolus injection of fast-acting insulin (e.g., Aspart/Lispro/Glulisine) at mealtimes to produce a peak coinciding with absorption of ingested carbohydrates and thus prevent post-prandial hyperglycaemia.

Continuous insulin infusions can be achieved by using an insulin pump. The external pump can provide an excellent method of administering exogenous insulin, which more closely mimics the actions of a normal functioning pancreas than multiple daily injections. Insulin pumps also make it possible to deliver more precise amounts of insulin than can be injected using a syringe. This supports tighter control over blood sugar, reducing the chance of long-term complications associated with diabetes. However, the pumps are expensive, and carry a risk of infection because of the need for an indwelling cannula, and a risk of ketoacidosis, as only rapid-acting insulin is used and it has a short duration of action so that the sugar level can rise rapidly in the event of a pump malfunction.

In the past, insulin was derived from animal sources; however, recombinant human insulin has now become the preferred source.

Implantable pumps and the artificial pancreas

Implantable pump technology involves surgical placement of an insulin pump in the body, which can remain in situ for many years. The pump is designed to deliver short, frequent pulses of insulin into the peritoneal cavity, where it can be more rapidly and predictably absorbed than in the subcutaneous tissue. If this technology can some day be successfully linked in with a continuous blood glucose monitoring system to form a closed loop system and allow real-time control of the blood sugar levels, then the system would effectively work like a mechanical artificial pancreas. In 2006, the US Food and Drug Administration (FDA) said that a mechanical artificial pancreas system has enormous potential benefit for a substantial proportion of patients with diabetes and flagged the concept as priority within its Critical Path Initiative.[9] As a result, much research has been targeted at developing an artificial mechanical pancreas and it would now appear that the technology is certainly on the horizon and only requires more sophisticated applied engineering, not basic science breakthroughs.[10]

TABLE 3: Oral hypoglycaemic agents and their mechanism of action.

Oral hypoglycaemic agent	Mechanism of action
Biguanides, e.g., metformin	Increase insulin sensitivity, reduce gluconeogenesis and, importantly, help maintain weight loss
Sulfonylureas, e.g, gliclazide, glimepiride, glipizide, glibenclimide	Increase insulin secretion. Can result in unwanted hypoglycaemia
Thiazolidinediones, e.g., rosiglitazone, pioglitazone	Increase insulin sensitivity
Alpha-glucosidase inhibitors, e.g., acarbose	Decrease the breakdown of starch to sugar in the gastrointestinal tract
Incretin mimetics, e.g., exenatide, liraglutide	Stimulate insulin release and inhibit glucagon release. Reduce appetite and may cause weight loss
DPP IV inhibitors, e.g., vildagliptin, sitagliptin	Prolong the action of endogenous incretin hormones, thereby stimulating insulin release and reducing glucagon

Transplantation

Whole pancreas transplantation can be undertaken in isolation, in combination with kidney transplantation, or after kidney transplantation. Its success can be limited by the availability of organs, graft failure and morbidity associated with long-term immunosuppressive therapy and complications arising from the surgery.[11]

Islet cell transplantation involves injecting islet cell grafts from a donor pancreas into the liver of the recipient. Early studies into the efficacy of intensive immunosuppression combined with multiple infusions of islet cells from multiple donors showed huge promise.[11,12] However, long-term follow-up studies disappointingly showed that essentially all individuals lose islet graft function over time and thus insulin therapy is again required in most patients within five years.[13]

Type 2 diabetes mellitus

Patients with type 1 diabetes mellitus invariably require insulin replacement therapy, whereas patients with type 2 diabetes may be managed initially by diet modification and increased exercise alone,

but may progress to medical therapies such as oral hypoglycaemic agents (OHA) and then insulin depending on the level of blood glucose control. Examples of some of the agents and their mode of action can be seen in **Table 3**.

Oral manifestations of diabetes mellitus

1. Gingivitis and periodontitis

Prolonged poor glycaemic control has been associated with an increased incidence and progression of gingivitis, periodontitis and alveolar bone loss.[14,15]

Recently, a prospective longitudinal study of 628 Pima Indians with diabetes, aged 35 years and over, showed that periodontal disease is a strong predictor of mortality from ischaemic heart disease and diabetic nephropathy, adding further evidence to the link between oral health and diabetes.[16] The exact mechanisms of action are not fully understood; however, current areas of research examine alterations in host response, subgingival microflora, collagen metabolism, vascularity, gingival crevicular fluid and heredity patterns.

2. Dental caries

The relationship between diabetes and dental caries has been investigated, but no clear association has been clarified. However, studies have reported a greater history of dental caries in people with diabetes.[17]

3. Salivary gland dysfunction

People with diabetes have been reported to complain of dry mouth, or xerostomia, and experience salivary gland dysfunction.[18] Xerostomia in diabetes mellitus occurs because glycosuria induces an osmotic diuresis and is not due to an effect on salivary glands per se. Diabetes can also be associated with sialosis.

4. Oral mucosa disease

There are reports of a greater prevalence of lichen planus;[19] however, it appears likely that this may represent a lichenoid drug reaction to medications used in treating diabetes or its associated complications.[20]

5. Oral infections

Opportunistic infections such as oral candidiasis are encountered in poorly controlled diabetic patients. This may be due to a combination of immunosuppression and salivary hypofunction.[21] It has also been shown that patients with elevated salivary glucose levels carry candida intra-orally more often than those with lower glucose levels.[22]

6. Oro-facial sensory disturbances

Burning mouth or tongue has been reported in patients with diabetes, possibly as a result of xerostomia and/or secondary candidiasis. It has also been suggested, but not clearly established, that burning tongue may occur in patients with severe diabetes mellitus as a result of diabetic neuropathy.[23] It has also been reported that people with diabetes have a blunted taste response, which displays a degree of specificity to glucose.[24]

Dental treatment considerations for patients with diabetes

Patients with well-controlled diabetes can often be treated in a similar way to non-diabetic patients.

The measurement of glycosylated haemoglobin, or HbA1c, is an excellent measure of long-term (six to 12 weeks) glucose regulation. For people with diabetes, the goal is to maintain HbA1c levels below 7% (normal range in health is 4-6%). HbA1c levels above 9% strongly indicate poorly controlled diabetes. The most recent value may be recalled by the patient or may be available to the patient's general medical practitioner and can be requested in an effort to assess glycaemic control.

1. Patients with diabetes, especially those with poor glycaemic control, require more frequent oral examinations to monitor and aggressively treat gingival and periodontal disease.
2. Emphasis should be placed on preventive measures.
3. Morning appointments should be offered where possible, as patients with diabetes are often more stable and better able to tolerate dental procedures in the morning. Furthermore, short multiple appointments are more suitable than a single prolonged appointment.
4. The use of antibiotics for the prevention of post-operative infection in patients with diabetes who undergo dentoalveolar surgery has become a controversial talking point in recent years. Traditionally, the provision of prophylaxis to this group of patients has been commonplace. However, it has been largely based on anecdotal evidence due to a lack of good quality research in this area. Barasch *et al* [25] recently conducted a review of the literature and highlighted the fact that there are few good quality studies available that attempt to investigate the infection rates in patients with diabetes who undergo surgery within the mouth. It was also noted that there is overwhelming evidence demonstrating the greater incidence of post-operative infection and poorer outcomes in patients with diabetes undergoing general and cardiothoracic surgery. The mouth can be regarded as a unique environment due to the fact that the oral mucosa has an extensive vascular supply and that saliva has antimicrobial properties that are protective for wound healing. Therefore, it is difficult to directly extrapolate from the studies conducted in general surgical patients. Nevertheless, it would seem prudent to provide prophylactic cover to patients who are known to have poor glycaemic control and who present for dentoalveolar surgery as a precautionary measure until more evidence becomes available. In the absence of guidelines, this decision will ultimately rest with the individual practitioner as he or she must weigh up the risks and benefits of providing cover.
5. Oral-facial infections require close monitoring as systemic involvement can proceed rapidly and may require hospital admission for observation and administration of an intravenous antibiotic regime. Dentoalveolar infections have been reported to precipitate DKA in patients with type 1 diabetes mellitus.[26]
6. Many drugs such as non-steroidal anti-inflammatory drugs, mono-amine oxidase inhibitors, and some antifungal and antibiotic agents can interact with oral hypoglycaemics and may potentiate their hypoglycaemic actions. Dentists should be encouraged to check the interaction section of the British National Formulary when prescribing for patients on these drugs.

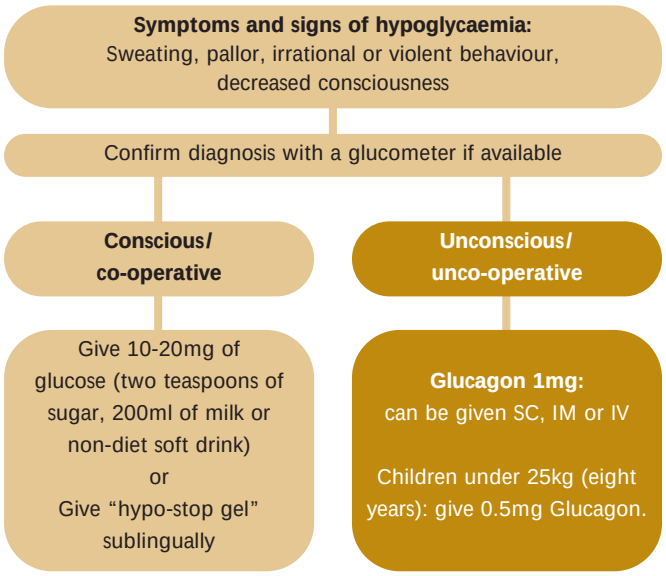

FIGURE 1: Algorithm for the management of hypoglycaemic episodes.[28]

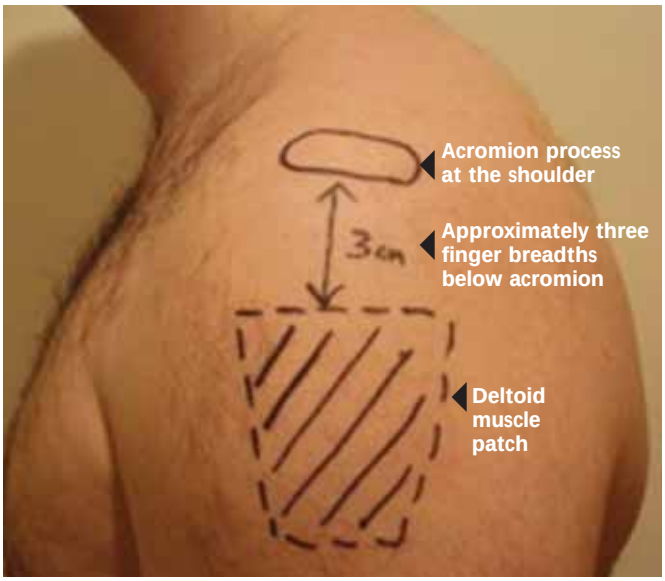

FIGURE 3: Deltoid intra-muscular injection location.

FIGURE 2: Glucagon intra-muscular injection kit.

Diabetic emergencies

Hypoglycaemic crisis

Hypoglycaemia is potentially fatal, and accounts for approximately 2-4% of deaths in patients with diabetes on insulin replacement therapy.[27] Normal blood glucose is maintained at 3.6-5.8mmol/l. Cognitive impairment develops at levels <3mmol/l; however, the threshold for symptoms can be highly variable. The most common precipitant is a relative imbalance of therapeutically administered insulin or oral hypoglycaemic medications versus actual required insulin. This may result from unplanned exertion, insufficient carbohydrate intake or excessive insulin administration. Alcohol is also a common hypoglycaemic precipitant.

Hypoglycaemia may present as sweating, tachycardia, hunger, trembling, irritability, irrational or violent behaviour, altered or loss of consciousness, and seizure. A glucometer, if available in the surgery, can be used to confirm the suspicion of hypoglycaemia. Treatment will depend on the level of consciousness. Appropriate treatment will result in 90% of patients making a full recovery within 20 minutes (**Figure 1**). Medical follow-up is wise to identify the precipitating event.

Glucagon administration

It may take five to 10 minutes for Glucagon to work and it requires the patient to have adequate glucose stores. Re-check blood glucose with a glucometer if available after 10 minutes to ensure that it has risen to a level of 5mmol/l or more, in conjunction with an improvement in the patient's mental status.

It is important, especially in patients who have been given Glucagon, that once they are alert and able to swallow, they are given a drink containing glucose and if possible some food high in carbohydrate. The patient may go home if fully recovered and if they are accompanied. Their general medical practitioner should be informed and they should not drive (**Figures 2** and **3**).

Hyperglycaemic crises

DKA and hyperosmolar non-ketotic hyperglycaemia (HONK) are caused by absolute or relative decreased insulin levels. High levels of plasma glucose cause an osmotic diuresis, with sodium and water loss, which can lead to hypotension and shock. In DKA, the normal compensatory hormonal mechanisms are overwhelmed and lead to increased lipolysis. This results in the production of non-esterified fatty acids, which are oxidised in the liver to ketones.

DKA most commonly occurs in the young patient with type 1 diabetes. It usually develops gradually over one to three days, and may be the initial mode of presentation.

Symptoms include polydipsia, polyuria, anorexia, vomiting and abdominal pain. Deep rapid breathing (Kussmaul breathing) and

acetone smell on the breath is suggestive of DKA in a patient with type 1 diabetes mellitus.

These conditions develop relatively slowly and abrupt onset in the dental surgery is unlikely. However, if suspected, then prompt transfer to the emergency department is required. If a decrease in the level of consciousness or coma develops then alert the emergency medical services, commence basic life support and give supplemental oxygen.

Conclusions

Diabetes mellitus is a significant global public health problem and is a major source of morbidity and mortality in the world today. The number of people affected by the disease is predicted to increase as population obesity rates are rising. As a result, dental practitioners will encounter an increasing number of patients with diabetes presenting for dental treatment in years to come. A patient with well-controlled diabetes can often be treated in a similar way to a patient who does not have diabetes. However, if the condition is poorly controlled, more aggressive preventive measures and treatment are required, as this group is more susceptible to dental disease.

Diabetic emergencies, especially hypoglycaemic events, can present in the dental practice setting, and dental practitioners should be aware of its presentation and emergency management.

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