GP Handbook

Diabetes Mellitus

(last update 20080822)

AN OVERVIEW

In Hong Kong, 10% of people have diabetes mellitus; the prevalence ranges from 2% in people < 35 years of age to 20% in those > 65. Over 30% of patients hospitalized with stroke, heart failure, acute myocardial infarction or requiring renal dialysis have diabetes as a major contributing factor.

Consider screening patients for glucose intolerance and other cardiovascular risk factors when one or more of the following are present:

- Family history of diabetes melitus
- Overweight (BMI > 23)
- Hyperlipidaemia
- Hypertension
- History of gestational diabetes
- Age > 45 years

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MANAGEMENT OF DM PATIENTS IN PRIMARY CARE SETTINGS

- The Mnemonic D I A B E T I C -

10 August 2008, Certificate Course of Diabetes Mellitus Management 2008
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Diagnosis (WHO 2006)

Diabetes mellitus (DM)

FBS >= 7.0	**OR**	2-hour >= 11.1

Impaired glucose tolerance (IGT)

FBS < 7.0	**AND**	2-hour >= 7.8 - < 11.1

Impaired fasting glucose (IFG)

FBS 6.1 – 6.9	**AND**	2-hour < 7.8

NB: specimen: plasma glucose; unit: mmol/L
FBS = fasting blood sugar, which is actually fasting plasma glucose
2-hour = venous plasma glucose 2 hours after ingestion of a 75g oral glucose load

Consideration should be given to replacing IGT and IFG (both representing a status of intermediate hyperglycaemia) by an overall risk assessment for diabetes and cardiovascular disease.

Oral glucose tolerance tests (OGTT)

- A diagnostic test when fasting plasma glucose alone fails to diagnose approximately 30% of cases of previously undiagnosed DM.
- The only means of identifying people with IGT
- Frequently needed to confirm or exclude an abnormality of glucose tolerance in asymptomatic people
- Indicated in individuals with FBS 6.1–6.9mmol/l to determine glucose tolerance status.

Insulin

Once-daily regime
Insulin glargine (Lantus) is the only 24-hour insulin approved exclusively for use once a day subcutaneously for long-term glycaemic control.

Initiating Lantus:
- Insulin-naïve patients: add 10 IU/d to oral anti-diabetic drugs
- Switching from once-daily medium-acting insulin: use 1 IU for 1 IU
- Switching from twice-daily medium-acting insulin: use 80% of total daily dose
- Switching from premix insulin: use 80% of the medium-acting portion of premix +/- oral anti-diabetic drugs +/- short-acting insulin

Titrating Lantus:
- Increase by 1 IU daily until FBS < 5.6 mmol/l

A reusable insulin delivery device (aka insulin pen) called OptiClik (to be used with a special Lantus cartridge) is highly recommended for its ease of use.

Twice-daily regimes
Injections 2 times a day (30 min before meal) using medium-acting insulin with or without short-acting insulin combinations are preferred.

- Recommended starting dose: 0.5 IU/kg/d
- Give 2/3 of total insulin in the morning and 2/3 as medium-acting

To improve control
- before breakfast: adjust evening medium-acting insulin
- before lunch: adjust morning short-acting insulin
- before dinner: adjust morning medium-acting insulin
- before sleep: adjust evening short-acting insulin

Mixtard carries different combinations (20:80 or 30:70) of short- and medium- acting insulin, and can simplify treatment. Insulin pens like NovoPen and Innovo are highly recommended.

Aspirin

A diabetic without any cardiovascular disease have the same cardiovascular risk as a non-diabetic with a prior cardiovascular event. Outcomes after cardiovascular events are significantly worse in DM patients and about 70% of DM patients will die from a cardiovascular event or its complications. The majority of diabetics have coexisting cardiovascular risk factors, including hypertension, dyslipidaemia, central obesity and microalbuminuria (30-150mg/24-hr), all of which need to be aggressively controlled with life-style modification PLUS medications.

Low-dose aspirin (eg Cartia 100mg qd) is a recommended yet grossly under-prescribed primary preventative therapy in DM patients who are at increased risk of cardiovascular diseases (age > 40,

dyslipidaemia, HT, albuminuria, smoking, family history of cardiovascular diseases).

Plavix (Clopidogrel) is used if aspirin is contraindicated (eg allergy, peptic ulceration).

CONCLUSION: Virtually every DM patient should receive an anti-platelet agent in addition to their anti-diabetic medications.

Beta-Cell Dysfunction

The pathophysiology of type 2 diabetes mellitus (T2DM) involves both genetic and acquired factors, PLUS the dual defects of **insulin resistance** (decreased peripheral uptake and increased hepatic production of glucose) and **beta-cell dysfunction** (reduced insulin secretion).

In the absence of a defect in beta-cell function, individuals can compensate indefinitely for insulin resistance with appropriate hyperinsulinaemia, as observed even in obese populations such as the Pima Indians of Arizona. However, loss of beta-cell function leads eventually to the postprandial and fasting hyperglycaemia that characterizes T2DM. This progression occurs despite initially effective anti-diabetic therapies, a situation clearly demonstrated by the United Kingdom Prospective Diabetes Study (UKPDS). Acquired factors (access to high-calorie foods, lack of exercise, weight gain), the increased insulin requirements imposed by insulin resistance, and toxicities from hyperglycaemia and elevated free fatty acids may all contribute to beta-cell deterioration. Free fatty acids, resistin, and tumour necrosis factor (TNF)-alpha potentially worsen insulin resistance. Beta-cell dysfunction resulting from glucose toxicity and lipotoxicity is potentially reversible with restoration of metabolic control. Therefore, attention to these toxicities may delay the deterioration of beta-cell function and suggest new approaches to the management of T2DM.

Early Combination Treatment

The UKPDS demonstrated that:

- chronic complications of T2DM are reduced with improved glycaemic control
- there is a progressive requirement for multiple therapies to maintain HbA1c < 7.0%
- every 1% increase in HbA1c would result in ~ 20% increase in any diabetic-related endpoints, ~ 15% increase macrovascular complications (eg MI, CVA) and ~ 40% increase in microvascular complications (eg ophthalmopathy).

However, it has been shown that glycaemic control alone is unlikely to significantly reduce the alarming morbidity and mortality from these complications. **Aggressive glycaemic control** PLUS **global cardiovascular risk reduction** is the new paradigm for DM management.

In TY Medical Practice, we advise an aggressive **combination treatment at an early stage**:

1) As soon as a diagnosis of DM is made, initiate lifestyle modification and treatment with metformin, unless contraindicated (eg renal failure).
2) If HbA1c > 6.5% by the end of the 3rd month of treatment, either insulin, a secretagogue or a thiazolidinedione are added.
3) If HbA1c is still > 6.5% in another 3 months, insulin therapy is initiated or intensified; other oral hypoglycaemic agents may be used instead of insulin if HbA1c < 8.0%. Sulphonylureas, if used, are stopped at this stage as they are not synergistic with insulin. Coadministration of rosiglitazone and insulin is not recommended.

Targeting A to E

The Hong Kong Diabetes Advisory Panel (HKDAP) promotes the message "Targeting A – E in Diabetes Mellitus" which recommends careful monitoring and management of:-

- A – Hb**A**1c (=< 6.5%)
- B – **B**P (< 130/80 mmHg)
- C – **C**holesterol (LDL < 2.6 mmol/l*; HDL > 1.0 mmol/l; triglycerides < 1.7 mmol/l)
- D – **D**iet and weight control**
- E – **E**xercise (walking > 150 min/wk)

** According to ATP-III (2004), LDL-C is the lower the better in DM patients, with a recommended treatment target of < 2.6 mmol/L. For those with both DM and coronary heart disease, lowering LDL-C to < 1.8 mmol/L is now a therapeutic option.*

CONCLUSION: Virtually every DM patient should receive a lipid-lowering drug in addition to their anti-diabetic medications.

*** For weight control, we recommend a target body mass index (BMI) of 23 kg/m^2.*

Eye: Diabetic Retinopathy

Among adult patients with T2DM, 20-40% have signs of diabetic retinopathy and ~ 8% have a more severe form associated with visual impairment at first presentation. American Diabetic Association (ADA) recommends that patients receive a comprehensive dilated retinal eye examination and assessment of visual acuity by an ophthalmologist soon after diagnosis of T2DM, and an annual examination afterwards.

Capillary vs Plasma

ADA recommends that self-monitoring of blood glucose (both fasting and postprandial) should be an integral component of diabetic management. As home blood glucose meters (with blood sampled by finger-pricks) measure capillary*, rather than plasma, glucose, knowledge of the difference between these 2 kinds of specimen becomes vital to clinicians.

Capillary blood glucose vs plasma glucose

Glucose measured in plasma** is ~ 11% higher than that measured in whole blood, because glucose passes freely in and out of the RBCs, which have a lower content of water than plasma. However this difference is dependent on haematocrit, increasing to 15% at a haematocrit of 0.55 and decreasing to 8% at a haematocrit of 0.30.

Capillary blood usually has ~ 5% more glucose than venous whole blood because of glucose utilization by peripheral tissues even after overnight fasting. With a carbohydrate load (as during a glucose tolerance test), this difference may become grossly exaggerated.

In conclusion, laboratory readings (plasma glucose) are generally 10% higher than those of home blood glucose meters (capillary glucose). The difference is smaller or even negligible for fasting samples, but could be enormous in post-prandial measurements.

** Some manufacturers claim that their home blood glucose meters can give plasma readings. In reality these "plasma" values are derived, rather than measured.*

*** As glycolysis in the RBCs reduces glucose in the blood sample, plasma should theoretically be separated from the blood sample within minutes after collection. In daily clinical practice this seldom occurs. Collection into*

a container with a glycolytic inhibitor (eg NaF) is only partially effective because it takes time to penetrate into the RBCs. Rapid cooling can reduce this loss. It is therefore recommended that the sample should be placed immediately in ice-water after collection and before separating but even so separation should be done as soon as possible. Otherwise the glucose level in the specimen will be under-estimated (ie a falsely low level).

METABOLIC SYNDROME

Definition

Metabolic syndrome is a collection of metabolic risks predisposing to artherosclerosis and T2DM. The dominant underlying factors are **abdominal obesity** and **insulin resistance**. In some studies, the prevalence of metabolic syndrome in the USA has been estimated to be 25% of the population.

The definition of metabolic syndrome given by International Diabetes Foundation (IDF):-

(1) CENTRAL OBESITY
- Waist circumference of > 90 cm in men or > 80 cm in women in Chinese,

(2) PLUS 2 OF THE FOLLOWING:
- Low HDL: HDL < 1.0 mmol/L in men or < 1.3 mmol/L in women
- Hypertriglyceridaemia: TG > 1.7 mmol/L
- Hypertension: BP > 130/85 mmHg or known hypertension
- Dysglycaemia: FBS > 5.6 mmol/L or known diabetes

Although metabolic syndrome is associated with an increased risk of cardiovascular diseases, its presence alone is insufficient for assessing global cardiometabolic risk, the building blocks of which consist of the classic cardiovascular risk factors. In this context, metabolic syndrome is simply another block that has an effect on global cardiometabolic risk.

Aetiology

The causes of metabolic syndrome are complex and have only been partially elucidated. The most important factors in order are:
- Aging
- Genetics, and
- Lifestyle (ie low physical activity and high caloric intake)

Management

The goal of management is to reduce the risk for cardiovascular disease and T2DM:

- **Lifestyle:** caloric restriction and exercise
- **Drug treatment:** eg ARBs for hypertension, lipid-lowering drugs for dyslipidaemia. Using metformin and/or thiazolidinediones to prevent worsening of insulin resistance is promising.
- **Bariatric surgery:** for morbid obesity.

Rimonabant (Acomplia)

Rimonabant (brand name: Acomplia) is an oral selective cannabinoid CB1 receptor antagonist. It is licensed for use as a weight loss aid in obese patients with T2DM or dyslipidaemia.

Rimonabant is particularly useful in obese patients with T2DM, as improvement in glycaemic control

with most of the current anti-diabetic agents, except for metformin and incretin-derivatives, is often associated with weight gain, which may have a negative effect on global cardiometabolic risk. The RIO (Rimonabant In Obesity) studies are a series of randomized, double-blinded, placebo-controlled trials on > 6,000 obese or overweight patient. The RIO-Diabetes study showed rimonabant 20mg qd can not only reduce body weight but also improve HbA1c, and a number of cardiovascular and metabolic risk factors in overweight or obese patients with type 2 diabetes.

The main reasons that patients stop taking rimonabant are gastrointestinal side effects (2.3% vs placebo 0.4%), mood disorders (6.7% vs placebo 3.2%), and nervous system symptoms (2.1% vs placebo 1.1%).

The current recommendation is that rimonabant should not be used for more than a year, which is in line with that for orlistat (Xenical) and sibutramine (Reductil). Patients will need to be motivated to stick to a calorie controlled diet and exercise plan to see the best results.

Contraindications include mood disorder, impaired liver or renal function, age over 75 or under 18. Pregnant or lactating women, epilepsy, and lactose intolerance. It should be used with caution in combination with CYP3A4 inhibitors, such as ketoconazole, ritonavir, clarithromycin…etc.

ANTI-DIABETIC DRUGS (NON-INSULIN)

Oral Medications

Biguanides

- Metformin (Glucophage)

Thiazolidinediones (TZDs)

- Rosiglitazone (Avandia)
- Avandamet is a combination of rosiglitazone and metformin.

Insulin secretagogues (Insulin secretion stimulators)

- Sulphonylureas: eg chlorpropamide, tolbutamide, glibenclamide, gliclazide, glipizide, glimepiride
- Metiglinides: eg repaglinide (Novo-norm)

Alpha-glucosidase inhibitors

- Acarbose (Glucobay)

DPP-4 Inhibitors

- Sitagliptin (Januvia)

Injectable Agents

Synthetic amylin

- Pramlintide (Symlin)

Incretin Mimetics

- Exenatide (Byetta)

Metformin

Metformin is the only biguanide available in Hong Kong. It is the first-line therapy for adults with T2DM. The results of UKPDS showed that metformin was significantly better than sulphonylurea/insulin therapy in the overweight group for any diabetes related endpoint and all cause mortality. Metformin acts as an insulin sensitizer. It decreases hepatic glucose production, decreases intestinal absorption of glucose and to a lesser extent enhances glucose uptake by peripheral tissues. It also lowers triglycerides, LDL-C, and total cholesterol (-16%, -8% and -5% respectively). When used as a monotherapy, metformin is associated with less weight gain than that seen in sulphonylureas and insulin, and may even promote weight loss. As metformin does not increase insulin secretion, it confers nearly no risk of hypoglycaemia.

Adverse effects

The most serious complication of metformin is lactic acidosis (<1%), which can be fatal. As metformin is excreted through kidneys, the risk of acidosis is increased in renal insufficiency. Metformin is contraindicated in patients with creatinine > 130mmol/L or low creatinine clearance. It should be withheld when renal function may potentially be impaired such as in radiographic contrast procedure (not restarted for 48 hours), concomittant use of nephrotoxic antibiotics or procedures that can cause significant blood loss.

Gastrointestinal disturbances such as nausea/vomiting, dyspepsia and diarrhoea are common (reported in up to 50% of patients). Patients usually become more tolerant to metformin with time.

Thiazolidinediones (TZD)

Like metformin, thiazolidinediones (TZD) are also insulin sensitizers. They are slow in onset of action and the hypoglycaemic effect is usually apparent only after 4 weeks treatment. The full impact may not be seen until 3 to 4 months of therapy. TZD are effective as monotherapy but due to their slow onset, they are generally not preferred as first-line therapy in poorly controlled type 2 diabetes. They are very effective in combination with other antidiabetic agents such as sulphonylureas, metformin or insulin.

TZD have several biological actions, namely fat redistribution and improvement in insulin sensitivity by altering hormone production by adipocytes. They exert their effect by activating nuclear receptor called peroxisome proliferator-activated receptor-g (PPARg) in metabolically active tissues such as adipose tissue.

As TZD act by increasing insulin sensitivity instead of increasing insulin secretion, they do not induce hypoglycaemia.

Adverse effects of TZD

All TZD cause dose-related weight gain. However, visceral fat, which is more harmful metabolically than peripheral fat, is not increased and may in fact, decreased with TZD therapy.

Another contributing factor for the weight gain is fluid retention which may exacerbate congestive heart failure. Hence, TZD should be used with caution in patients with suboptimal cardiac reserve (eg patients experiencing an acute coronary event) or when other drugs that may cause fluid retention are used in conjunction with TZD, eg calcium channel blockers. Diuretics may sometimes be required to reduce peripheral oedema.

Hepatotoxicity can be monitored by pre-treatment and interval LFT. It is contraindicated in patients with liver enzymes > 2.5 times the upper limit of normal.

Another concern is the potential complication of macula oedema associated with the use of Avandia (rosiglitazone). Patients on rosiglitazone treatment are advised to seek medical advice if any changes in vision are experienced.

In 2006, a meta-analysis of 42 clinical trials on Avandia (rosiglitazone) revealed an increased risk of myocardial ischaemic events (incidence rate 2% vs 1.5%). The co-administration of rosiglitazone with insulin or nitrates is not recommended because of a higher risk of myocardial ischaemia observed thereof. However, the above findings were seen predominantly in short-term studies, and in patients with heart failure. Pioglitazone has shown similar problems in heart failure patients. As TZD can cause fluid retention, cardiac failure may occur in susceptible individuals. It is therefore advisable to avoid TZD in patients with heart failure or unstable heart disease.

Reassuringly, the larger long-term studies with rosiglitasone, including one specifically designed to examine cardiovascular end-points, RECORD, have not demonstrated any increase in ischaemic events. In 2008, new data from 2 long-term, large scale, independent studies were reported at the 68th Scientific Sessions of ADA:-

(1) VADT (Veterans Affairs Diabetes Trial): there were no increased deaths associated with the use of rosiglitazone.
(2) ACCORD (Action to Control Cradiovascular Risk in Diabetes): patients in the standard-group and those in the intensive-control group had similar risks and rates of death, whether or not

they were prescribed rosiglitazone.

Insulin Secretagogues

Sulphonylureas

Sulphonylureas are indicated as an adjunctive therapy for patients with T2DM uncontrolled by lifestyle modification and metformin. They are only effective in patients with some residual pancreatic beta-cells activity and are not indicated for patients with type 1 DM.

Sulphonylureas reduce blood glucose by directly stimulating pancreatic b-cells to produce insulin. They increase circulating insulin and reduce both fasting and postprandial glucose. However, their efficacy declines over time, with about 5-10% of patients per year failing to maintain the initial glycaemic control. First generation sulphonylureas are now less frequently prescribed because the newer second generation sulphonylureas have less side effects and less drug interactions.

Newer preparations of sulphonylureas

Gliclazide (Diamicron) is a commonly used sulphonylureas. It has an immediate release and a modified release formulations. The modified release formulation is to be taken once daily. It provides gradual release of the drug which parallels the 24-hour glycaemic profile in untreated patients with type 2 diabetes mellitus. Significant HbA1C reductions of 0.9% and 0.95% were seen at 10 and 24 months in patients on gliclazide modified release 30 to 120mg once daily.

Glimepiride (Amaryl) is the newest compound of this group. It has quick onset and lower incidence of hypoglycaemia in comparing to the first generation sulphonylureas. It demonstrates extrapancreatic (liver, adipose tissue, muscle) effect and has insulin-sparing effect when administered with insulin in patients with secondary sulphonylurea failure. It lowers blood glucose even in absence of insulin either by reduction of glucagons release or by activation of glucose transport and non-oxidative glucose metabolism. This results in equal or better glycaemic control with less insulin secretion than other agents of this group.

Adverse effects

Significant adverse effects include hypoglycaemia, increase in cardiovascular events, weight gain, water retention with hyponatremia (resulted from increased ADH release), gastrointestinal disturbances (nausea, vomiting and diarrhoea) and haematological disorders (aplastic anaemia, thrombocytopenia, leukopenia, agranulocytosis).

The long-acting sulphonylureas, chlorpropamide and glibenclamide (Daonil), are associated with a greater risk of hypoglycaemia and should be avoided in elderly and patients with renal impairment. For these patients short-acting sulphonylureas such as gliclazide should be considered.

Non-sulphonylurea insulin secretagogues (Meglitinides)

The currently available meglitinides are repaglinide (Novonorm) and nateglinide. They are indicated as an adjunct to diet and exercise to improve glycaemic control in type 2 diabetes, or in combination with metformin or thiazolidinediones to lower blood glucose in patients whose hyperglycaemia cannot be controlled by diet, exercise and either agent alone.

Meglitinides act directly on the pancreatic b-cells to stimulate insulin release. They are differentiated from the sulphonylureas by their receptor binding site, fast onset and short duration of action. As a result meglitinides are suited for prandial regulation of glucose when taken in association with meals, but with minimal risk of hypoglycemia between meals. On average, the HbA1c reduction seems to be equivalent to the sulphonylureas (0.5-2.0%).

The adverse effects of hypoglycaemia and weight gain are probably less pronounced than those caused by sulphonylureas. In contrast to sulphonylureas, patients on repaglinide or nateglinide can

simply avoid the dose accompanying a skipped meal without suffering hypoglycaemia. The main drawback of these agents is the need for frequent dosing before meals.

Alpha-glucosidase Inhibitors

Acarbose (Gluobay) is the commonly used agent in this group. It is indicated as a monotherapy, and as an adjunct to diet in type 2 diabetics. It is also indicated as a combination therapy with a sulphonylurea, metformin, or insulin.

Acarbose produces reduction in postprandial hyperglycaemia by inhibiting the a-glucosidase enzyme, which is responsible for the breakdown of disaccharides to form single sugars, in the brush border of the small intestines. Taken right before a meal, it can reduce postprandial glucose level by delaying both the absorption of carbohydrates and entry of glucose into liver and muscle tissues.

When using acarbose as monotherapy, it is associated with low risk of hypoglycaemia both in fasting and postprandial states.

Gastrointestinal side effects (> 10%) include abdominal pain, diarrhoea and flatulence. Starting with a low dose with slow titration up to the effective doses can help to make them more tolerable.

Deranged liver function is reported in patients on high dose of acarbose (eg 200mg tds).

DDP-4 Inhibitors

Sitagliptin (Januvia from Merck) and vildagliptin (Galvus from Novartis) belong to an oral anti-diabetic drug of the dipeptidyl peptidase-4 (DPP-4) inhibitor class. They are to be used either alone or in combination with metformin or a thiazolidinedione for control of T2DM. It is not useful in treating type 1 DM, and its safety and effectiveness has not been established in pregnant and lactating women.

The incretin system is a natural body system which helps to regulate glucose by affecting the alpha and beta cells in the pancreas. Its main members, glucagons-like peptide 1 (GLP-1) and glucose dependent insulinotropic peptide (GIP), account for the majority of incretin action. GLP-1 stimulates insulin secretion from pancreas in a glucose-dependent manner. By inhibiting its degradation by DDP-4, sitagliptin increases GLP-1, resulting in enhanced incretin action and improved plasma level glucose.

As sitagliptin is excreted by kidneys, its dosages are to be reduced in patients with renal impairment.

Adverse effects

Since the mechanism of DDP-4 is glucose-dependent, there is no significant difference in the occurrence of hypoglycemia between placebo and. Another advantage of is that DDP-4 was not associated with weight gain in clinical trials. Adverse effects of this class of medications are usually mild and self-limiting:

- Common cold-like symptoms (6%)
- Headache (5%)
- Sore throat (5%)
- Diarrhea (3%)
- Nausea and stomach discomfort (2%)

Sitagliptin may increase the blood level of digoxin.

Synthetic Amylin

Pramlintide (Symlin) is a synthetic form of the hormone amylin, which is produced along with insulin by the beta cells in the pancreas. Amylin, insulin, and another hormone, glucagon, work in an interrelated fashion to maintain normal blood glucose levels.

Pramlintide injections taken with meals have been shown to modestly improve HbA1c levels without causing increased hypoglycemia or weight gain and even promoting modest weight loss. The primary side effect is nausea, which tends to improve over time and as an individual patient determines their optimal dose.

Because of differences in chemistry, pramlintide cannot be combined in the same vial or syringe with insulin and must be injected separately. Pramlintide has been approved for treating both type 1 and type 2 diabetes who are using insulin and are not achieving their HbA1c goals.

Incretin Mimetics

Exenatide (Byetta) is the first in a new class of drugs for the treatment of type 2 diabetes called incretin mimetics. Exenatide is a synthetic version of exendin-4, a naturally-occurring hormone that was first isolated from the saliva of the lizard known as a Gila monster. Exenatide works to lower blood glucose levels primarily by increasing insulin secretion. Because it only has this effect in the presence of elevated blood glucose levels, it does not tend to increase the risk of hypoglycemia on its own, although hypoglycemia can occur if taken in conjunction with a sulfonylurea. The primary side effect is nausea, which tends to improve over time.

Like pramlintide, exenatide is injected with meals and, as with pramlintide, patients using exenatide have generally experienced modest weight loss as well as improved glycemic control. Exenatide has been approved for use by people with type 2 diabetes who have not achieved their target HbA1c levels using metformin, a sulfonylurea, either alone or in combination.

EXERCISE PRESCRIPTION

Primary Function

Type 1 Diabetes	Type 2 Diabetes
(1) Adjunct therapy for dietary and drug treatment (2) Long-term metabolic control (3) Prevention of microvascular complications	(1) Improving glycemic control (2) Maintaining weight (3) Reducing risks of cerebrovascular diseases

General Exercise Prescription

	Type 1 Diabetes	Type 2 Diabetes	
Mode	Aerobic	Aerobic	Strengthening
Intensity	Low/Moderate	Moderate	Moderate
Duration	20-60 min/d	150 min/wk	3 sets of 8-10 reps involving all major muscle groups at a weight that cannot be lifted > 8-10 times
Frequency	4-6 d/wk	3 d/wk	3 d/wk

Special Considerations

- Postpone exercise if blood glucose > 16.7 mmol/L or > 13.3 mmol/L with positive urinary ketones.
- Monitor blood glucose before, during and after exercise if taking insulin or oral agents.
- Exercising late in the evening increases risk of nocturnal hypoglycemia.
- Proper hydration is essential.
- A diabetes identification card should be worn when exercising.
- Autonomic neuropathy may be associated with silent ischemia, postural hypotension and/or blunted heart rate response. Exercise in excessive heat may exacerbate the risk of heat injury in patients with autonomic neuropathy.

Energy Consumption of Common Household Activities

Activities	METS
Lying quietly	1.0
Sitting: light activity	1.5
Walking from home to car/bus	2.5
Taking out trash	3.0
Walking the dog	3.0
Vacuuming	3.5

Energy Consumption of Common Sports Activities

Activities	METS
Golf (with cart)	2.5
Walking (2 mph)	2.5
Ballroom dancing	2.9
Walking (3 mph)	3.3
Cycling (leisurely)	3.5
Golf (without cart)	4.4
Swimming (slow)	4.5
Walking (4 mph)	4.5
Tennis (doubles)	5.0
Ballroom dancing (fast)	5.5
Cycling (moderate)	5.7
Hiking (no load)	6.9
Swimming (fast)	7.0
Walking (5 mph)	8.0
Jogging (10 min/mile)	10.2
Rope skipping	12.0
Squash	12.1

MET (Metabolic Equivalent) = resting metabolic rate = 3.5ml of O_2/kg/min

Activity Limitation in Diabetic Retinopathy

Level of Diabetic Retinopathy (DR)	Acceptable Activities	Discouraged Activities	Ocular Review
Nil	Dictated by medical status	Dictated by medical status	12 months
Mild non-proliferative diabetic retinopathy (NPDR)	Dictated by medical status	Dictated by medical status	6-12 months
Moderate NPDR	Dictated by medical status	Activities that dramatically elevate BP, eg power lifting, Valsalva manoeuvres	4-6 months
Severe NPDR	Dictated by medical status	Activities that increase SBP, Valsalva manoeuvres, boxing, competitive sports	2-4 months
Proliferative DR	Low-impact, cardiovascular conditioning, eg swimming, walking, low-impact aerobics, stationary cycling, endurance exercise	Strenuous activities, Valsalva manoeuvres, weight lifting, jogging, high-impact aerobics, racquet sports	1-2 months

Prescription for Patients with Peripheral Neuropathy

Recommended Exercises	Contraindicated Exercises
Swimming Cycling Rowing Other non-weight-bearing exercise	Treadmill Prolonged walking Jogging Step exercise

Diabetes and Oral
Health Problems

The more severe form of gum disease is called periodontitis. When you reach this stage, your gums begin to pull away from your teeth. Pockets form between your teeth and gums. These fill with germs and pus, and deepen. When this happens, you may need gum surgery to save your teeth. If nothing is done, the infection goes on to destroy the bone around your teeth. The teeth may start to move or get loose. Your teeth may fall out or need to be pulled.

Is There an Association Between Gum Disease and Diabetes?

For the nearly 21 million Americans that have diabetes, many may be surprised to learn about an unexpected complication associated with this condition. Research shows that there is an increased prevalence of gum disease among those with diabetes, adding serious gum disease to the list of other complications associated with diabetes, such as heart disease, stroke and kidney disease.

Is There a Two-Way Street?

Emerging research also suggests that the relationship between serious gum disease and diabetes is two-way. Not only are people with diabetes more susceptible to serious gum disease, but serious gum disease may have the potential to affect blood glucose control and contribute to the progression of diabetes. Research suggests that people with diabetes are at higher risk for oral health problems, such as gingivitis (an early stage of gum disease) and periodontitis (serious gum disease). People with diabetes are at an increased risk for serious gum disease because they are generally more susceptible to bacterial infection, and have a decreased ability to fight bacteria that invade the gums.

The Surgeon General's Report on Oral Health states that good oral health is integral to general health. So be sure to brush and floss properly and see your dentist for regular checkups.

If I Have Diabetes, am I at Risk for Dental Problems?

If your blood glucose levels are poorly controlled, you are more likely to develop serious gum disease and lose more teeth than non-diabetics. Like all infections, serious gum disease may be a factor in causing blood sugar to rise and may make diabetes harder to control.

Other oral problems associated to diabetes include: thrush, an infection caused by fungus that grows in the mouth, and dry mouth which can cause soreness, ulcers, infections and cavities.

How Can I Help Prevent Dental Problems Associated with Diabetes?

First and foremost, control your blood glucose level. Then, take good care of your teeth and gums, along with regular checkups every six months. To control thrush, a fungal infection, maintain good diabetic control, avoid smoking and, if you wear them, remove and clean dentures daily. Good blood glucose control can also help prevent or relieve dry mouth caused by diabetes.

What Can I Expect at My Checkup? Should I Tell My Dental Professional About My Diabetes?

People with diabetes have special needs and your dentist and hygienist are equipped to meet those needs - with your help. Keep your dentist and hygienist informed of any changes in your condition and any medication you might be taking. Postpone any non-emergency dental procedures if your blood sugar is not in good control.

DIABETES & THE MOUTH

A number of oral conditions have been associated with DM, particularly in patients with poor control. Unfortunately most diabetic patients, and a significant number of physicians, are unaware of the oral health complications of DM. Therefore, it is important for us to educate patients about the oral implications of DM and the need for proper preventive care.

Periodontal Disease

In 1999, the American Academy of Periodontology issued a position paper about diabetes and periodontal diseases. This report indicates that **DM, especially when poorly controlled, increases the risk of periodontitis**. Several contributing factors have been proposed, including reduced leukocyte function, abnormalities in collagen metabolism and impaired vascular integrity. **Conversely, severe periodontal infection may increase the risk of diabetic complications via the mechanism of increased insulin resistance**. Control of periodontal infection has been shown to have a positive effect on glycaemic control.

It is worth noting that patients whose diabetes is well controlled have no more periodontal disease than persons without diabetes. When diabetes is poorly controlled, high salivary glucose levels may encourage bacterial growth and set the stage for gum disease.

Since prevention plays a primary role in periodontal disease control in diabetic patients, they may need more frequent plaque control and scaling than nondiabetic patients.

Studies have indicated that smoking increases the risk of periodontal disease several fold in diabetic patients. A smoker with diabetes, age 45 or older, is 20 times more likely than a person without these risk factors to get severe gum disease, bone loss and tooth loose!

It has been established that a well-controlled diabetic experiences the same short-term responses to periodontal therapy as non-diabetic individuals. While procedures rendered to diabetic individuals should be of shorter duration and less traumatic so as not to stress their systems, well-controlled diabetics can expect to receive "normal" care for all their dental needs, including periodontal surgeries and dental implants

Salivary Gland Dysfunction

Studies have reported xerostomia in 40-80% of diabetic patients. Diabetic patients with poorly controlled disease have been found to have lower stimulated parotid flow rates than people with well-controlled DM and non-diabetic control subjects. Frequent sipping of water or use of sugarless gum may alleviate the dryness.

Asymptomatic, bilateral enlargement of the parotid glands has been reported in 24-48% of patients with DM, and patients with uncontrolled DM have exhibited a greater propensity for enlargement.

Fungal Infections

Patients with DM are more susceptible to oral fungal infections, including median rhomboid glossitis, denture stomatitis and angular cheilitis. Candidiasis has been found to be associated with poor

glycaemic control and use of dentures. This predisposition may be due to xerostomia, increased salivary glucose levels or impaired immunity.

Oral Burning & Taste Disturbances

In one study of patients with undiagnosed T2DM, 37% of subjects reported experiencing burning mouth or tongue. Therefore, clinicians should consider DM in the diagnosis of such complaints. The burning may be due to peripheral neuropathy, xerostomia or candidiasis. Good glycaemic control may alleviate the burning sensation. Recent reports have indicated that clonazepam may be beneficial in some patients with complaints of oral burning sensation.

Some studies showed that diabetic patients may have a mild impairment of the sweet taste sensation. This may be related to xerostomia or disordered glucose receptors. Taste alterations may be more common in people with uncontrolled DM.

Lichen Planus & Lichenoid Reactions

It has been reported that the prevalence of oral lichen planus is slightly higher in patients with T2DM. However, this may be a side effect of oral hypoglycemic agents or antihypertensive medications.

Dental Caries

Some studies have demonstrated that diabetic patients have more active dental caries than control subjects. Elevated salivary glucose levels and xerostomia may predispose this population to caries.