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TLALELETSO

Managing Complicated Diabetes

Diabetes is increasingly common

Managing diabetes and working as part of a multi-disciplinary team is essential for the effective management of diabetes mellitus.

INTRODUCTION

Diabetes is an important emerging problem in Botswana. Current estimates indicate that at least 4.3% of adults aged 20-79 years have diabetes. The true number of patients with DM is likely to be much higher than this, especially in urban centers. The World Health Organization predicts that the number with Type 2 Diabetes Mellitus (T2DM) will increase by 160% of the next 20 years.

The impact of urbanization cannot be overstated. In 2009, the STEPS survey demonstrated that 23% of adults are overweight and over half of all women aged 25-64 years are obese or overweight. The link between urbanization, sedentary lifestyles, unhealthy eating and rising levels of obesity and T2DM have been demonstrated universally. Effective prevention of obesity and T2DM requires a paradigm shift across the health care system in Botswana. However, DM is also an increasing phenomenon among people living with HIV. The interrelation of DM and HIV has been discussed at length in a previous issue of

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Notes from the Editor….

Tlaleletso is a monthly publication produced by the Botswana UPenn Partnership, in response to your expressed need for accessible, digestible clinical information.

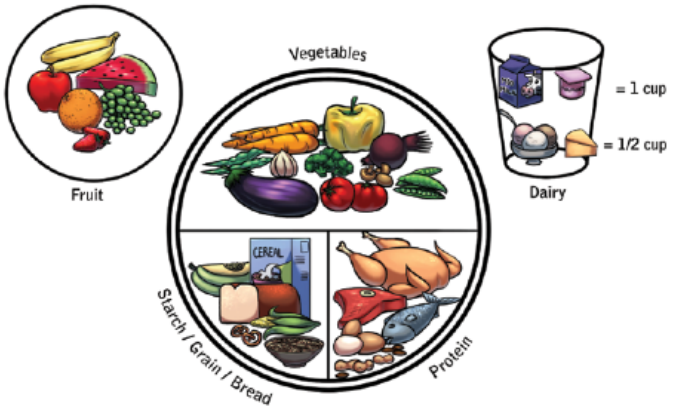
In this issue, we focus on managing diabetes and how to ensure that patients maintain healthy lifestyles and do not develop complications of persistent hyperglycemia

DID YOU KNOW?

Eating too much sugar is a key determinant of whether individuals develop diabetes. Encouraging patients to increase the amount of fiber that they eat is protective against developing diabetes!

TREATMENT OPTIONS

In this issue of Tlaleletso we review the best-practice evidence for managing diabetes in Botswana. This edition complements the March 2013 outreach lecture, 'Managing complicated diabetes.' We will discuss the medications available in Botswana and address questions about when to start insulin and what insulin dosing schedules to use and when. We will also review the new outpatient guidelines will soon be made available across the country.



There are several interventions that can be employed to treat diabetes: lifestyle changes, diet and medicine all play important roles. This edition of Tlaleletso will primarily focus on *medications* that doctors can prescribe. Nevertheless it is important that all health care providers understand the importance of diet and exercise as components of any diabetes treatment program.

Medical Nutritional Therapy (MNT) is essential for the prevention, treatment and self-management of diabetes and prevention or delay of diabetes related complications. MNT can reduce HBA1c by 1-2% depending on the duration of diabetes. Weight loss is an important therapeutic intervention in obese and overweight individuals with type 2 diabetes. Individuals with type 2 diabetes should be encouraged to implement the health lifestyle changes, including reducing calorie intake, consuming less saturated fats, cholesterol and sodium and increasing physical activity. These are all part of an effort to improve blood glucose control, dyslipidemia and blood pressure.

Medical Nutritional Therapy

- A patient centered-approach
- Assessing the patient's nutritional status and diabetes self-management knowledge and skills
- Identifying and negotiating nutritional goals
- Consistent carbohydrate intake and regular distribution of meals may help to control weight and control blood sugar levels

DIETARY ADVICE FOR PATIENTS

- Eat a variety of fresh fruit and vegetables every day, but avoid fruit juices.
- At least half of the grain intake should be wholegrain.
- Consume low-fat dairy products and soya beverages, fortified with calcium.
- Use a variety of meat alternatives, including pulses, soya and (if you can get it!) tofu.
- Consume fish (ideally twice a week).
- Limit the intake of processed and convenience foods.

PHYSICAL ACTVITIY

Large cohort studies have demonstrated that in patients with type 2 diabetes mellitus (T2DM), regular physical activity and moderate to high levels of cardiorespiratory fitness are associated with reductions in cardiovascular and overall mortality of 39-70% over a 15 to 20 year period (Hu, Diabetes Care 2005, Hu, Ann Intern Med, 2001).

People with T2DM will derive the following benefits from regular physical activity:

- Increased cardiorespiratory fitness
- Improved glycemic control
- Decreased insulin resistance
- Improved blood lipid profile
- Improved blood pressure

TREATMENT TARGETS

There is a strong epidemiological evidence base for selecting a target glycated haemoglobin A1c (HbA1c) level of < 7%. Patients with type 2 diabetes with HbA1c levels> 7.5% have a 2.5 to 5-fold greater risk of developing microvascular complications (neuropathy, nephropathy, retinopathy) and a five-fold greater risk of developing peripheral artery disease (Duckworth, NEJM, 2009).

However, in Botswana it is often very difficult to get HbA1c readings and when they are ordered it can be some time before the results are available. In such settings it is reasonable to monitor treatment outcomes using fasting plasma glucose (FPG). The normal FPG is accepted as 6.1mmol/l. However, a meta-analysis of 38 prospective studies has found an association of increased risk of cardiovascular events with FPG>5.5mmol/l (Levitan, Arch Intern Med, 2004). Overall, a fasting or pre-prandial target of 4.0-7.0 mmol/l is recommended.

DID YOU KNOW?
Diabetes increases the risk of tuberculosis by three times. Furthermore, patients with diabetes are 2 times more likely to die compared to non-DM patients if they get TB. Make sure you screen!

ORAL MEDICATIONS

Patient and clinician acceptance make non-insulin based therapies the backbone of type 2 diabetes management . The most widely used oral therapy is metformin.

Metformin: Metformin was isolated from Galega Officinalis, (goats rue, an herbaceous plant) which was used to treat symptoms characteristic of diabetes mellitus in medieval times. The plant extract however, was found to be toxic in studies carried out in the 1920s. Metformin, as we know it, was developed in the 1950s.

Mechanism of action: Metformin causes a reduction in hepatic glucose production via multiple intracellular pathways. It also causes an improved uptake of glucose in the peripheral tissues and reduction in gastrointestinal glucose absorption.

Efficacy: Metformin is well establishing to be the anchor anti-diabetic drug in the management of T2DM. It is the only drug with proven efficacy for reducing cardiovascular outcomes and mortality (UKPDS). However, metformin has not been proven to have any impact on microvascular end-points. When used as monotherapy, metformin can reduce HbA1c by 1-2%.

Dosing/Adverse effect: The minimum effective dose of metformin is 500mg once daily, and the optimal dose is about 2000mg per day in two to three divided doses. About 30% of users will report gastrointestinal side-effects (eg diarrhoea, cramping, bloating, flatulence). These can be minimized by titrating the dose gradually over 1 to 2 months, or by temporarily discontinuing the drug before reintroducing it. Fewer than 10% of patients will need to discontinue the drug permanently because of gastrointestinal intolerance. Metformin should be used cautiously in patients with advanced.

Metformin (cont.d)

Lactic acidosis with metformin is now known to be rare (0.05/1000 patient years) and most of these cases occur in the context of inappropriate usage. While there are concerns that lactic acidosis may occur more commonly in patients with liver disease, metformin has been used successfully in patients with non-alcoholic fatty liver disease, and may actually improve liver function. Metformin has also shown to have been beneficial compared to insulin and sulphonylureas in the aftermath of acute myocardial infarction (DIGAMI-2 study).

Guideline recommendations for Botswana: New guidelines for the management of T2DM are being rolled out across the country imminently. Metformin is the initial therapy choice and should be started at the time of diagnosis in all patients (overweight and normal weight) unless specifically contraindicated. It is recommended that metformin therapy continue even when other classes (including insulin) are subsequently added.

Sulphonylureas

Sulphonylureas have been used in the treatment of T2DM since the 1950s. These drugs induce insulin release by binding to specific receptors on the pancreatic beta cell wall. This subsequently induces release of stored insulin. Sulphonylureas have several additional effects including decreasing growth-hormone secretion, increased lipogenesis and glycogen synthesis.

At present the only sulphonylurea available in the public health system in Botswana is the glibenclamide. Others available at private clinics include glicazide, glipizide, and glimepiride.

Efficacy: The clinical efficacy of sulphonylurea drugs has been demonstrated in many studies, including the large UKPDS trial.

The reduction in HbA1c levels ranges from 1.5-2.0%. The UKPDS trial showed significant reductions in microvascular complications with sulphonylurea therapy. More recently the ADVANCE study showed that glicazide significantly reduced microvascular complications in a large cohort of patients with risk factors for vascular disease. By contrast there was no reduction in risk of coronary heart disease in the ADVANCE study.

Dosing/Adverse effects: Glibenclamide starting dose is 2.5mg once daily. Maximal daily dose is 15mg daily. Doses exceeding 10mg per day should be given in two divided doses. The major adverse effects of sulphonylureas include weight gain and hypoglycemia. The UKPDS reported a mean weight gain of 5.3kg over the first six years of the study, with most of the weight gain occurring in the first year of treatment. Hypoglycemia is the most serious adverse effect of therapy with sulphonylurea therapy. The incidence of sulphonylurea drug-induced hypoglycemia is unknown. In the first 10 years of the UKPDS hypoglycemia occurred in 17.7% of patients receiving glibenclamide, compared with 36% receiving insulin. Glibenclamide is associated with far higher rates of hypoglycemia than other sulphonylureas.

Guideline recommendations for Botswana: Glibenclamide is recommended as the second stage of diabetes care for all patients that continue to have uncontrolled diabetes in spite of maximal dosing of metformin. The starting dose is 2.5mg. Clinicians are advised to increase the dose by increments of 2.5mg every 2 weeks if random blood sugars are greater than 8.

DID YOU KNOW?
Losing weight is incredibly important! A 5% drop in body weight is associated with 0.5-1.0% reduction in HbA1c. It will also improve life expectancy by up to 4 years!

INSULIN

Patients with type 2 DM often require insulin to achieve glycemic control. In such instances it is important to transition patients from oral medications onto an appropriate insulin regime. Unfortunately, it is often challenging to persuade patients that insulin therapy is indicated. Furthermore, there is frequently confusion about what insulin regimen should be prescribed and whether it should be co-prescribed with oral medications. In this section, we will review some of the important evidence supporting best practice for insulin therapy and review the Botswana guidelines.

4-T study (Holman, NEJM, 2008): The 4-T study showed that in patients with T2DM randomly assigned to receive either a once a day long acting insulin (protophane) or biphasic insulin with meals (actrophane), reductions in HbA1C were better in the biphasic group compared to the basal insulin group. However, this slightly superior reduction in HbA1c was accompanied by a higher number of hypoglycemic events per patient year and higher mean weight gain. The three year follow up to this study showed that HbAIc levels were similar across all groups. But the median rates of hypoglycemia were lowest in the group receiving a basal dose of insulin (Holman, NEJM, 2009). Based on this and other data, new guidelines in Botswana suggest the following approach to initiation of insulin therapy:

Starting Insulin at the time of initial diagnosis

Consider insulin therapy as first line in the setting of uncontrolled diabetes with any of the following features:

- Marked weight loss
- Fasting plasma glucose >14mmol/l
- Random glucose levels consistently >16.7mmol/l
- DKA or ketonuria

In this situation, start with either actrophane twice daily or protophane basal-bolus intensive insulin therapy.

INSULIN – A PRACTICAL APPROACH

In almost all instances the patient should continue to take their oral diabetes medications. The treatment steps are outlined below:

1. Start with 10 units of protophane insulin at bedtime (9-10pm)
2. The patient should monitor fasting fingerprick glucose each morning and titrate the insulin dose according to the average fasting glucose recorded at home. If the patient does not have access to a home glucometer, they should be advised to return to the clinic 7 days after initiating protophane. If the fasting glucose is greater than 7 mmol/l then the evening dose of protophane should be increased by 2 units.
3. Thereafter the doctor/nurse should titrate the insulin dose by 2 units every 7 days, until the morning fasting glucose is within the target range (i.e. less than 7 mmol/l).
4. If unexplained nocturnal hypoglycemia occurs, the patient should be instructed to reduce the insulin dose by 10% and to stop titration until seen in a weeks time. Ideally in this situation , the patient should be switched from medium acting insulin (protophane) to a long acting insulin (such as glargine or determir). Unfortunately, long acting insulins are not currently available in Botswana.

If the patient continues to have uncontrolled sugars and fasting glucose are consistently above 7 mmol/l despite titrating up the dose of protophane, then it may be necessary to switch to pre-mixed insulin (actrophane). Switching to actrophane is appropriate when patients are receiving 20units of protophane and still the fasting sugars are higher than 7mmol/l. In such situations, the new guidelines recommend the following:

5. Stop all oral medications except metformin. Because of the risk of hypoglycemia, glibenclamide should not be co-prescribed with actrophane.
6. Calculate the starting total daily insulin dose using the following formula: Total number of units of insulin per day = 0.3 x body weight (kg) An alternative is to start with 10 units twice a day before meals.
7. Start by giving two thirds of the dose before breakfast and one third of the dose before supper.
8. The patient should then be instructed to return to the hospital so that the dose can be titrated as necessary. While there are several different ways to determine the best dose for each person (some doctors use a modified sliding scale to calculate how much to adjust doses), a simple approach is to increase both morning and evening doses by 2 units if the morning fasting glucose is greater than 7 mmol/l. To this end, each week the patient should be advised to come in to get their glucose checked until the fasting glucose is consistently under 7.
9. If the patient experiences unexplained hypoglycemia, they should be instructed to reduce the last injected insulin dose (the dose preceding the hypoglycemic event) by 10% and to stop titration for the time being.
10. If glycemic targets are still not met with this twice daily biphasic approach, then intensive insulin therapy (with multiple daily injections) should be considered. Patients should be referred to the medical clinic at PMH, where one of the specialists can help determine the best approach.

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During periods of illness and stress patients with DM may require additional insulin or escalation of therapy. Only short-acting insulin should be used and it should be added to the usual insulin doses and injected before each meal. The usual insulin doses should not be stopped and oral agents should also still be taken. However, if the patient is vomiting or dehydrated, metformin should be discontinued until a full medical evaluation can occur. Plenty of fluids should be ingested. If the patient is feeling nauseous and not tolerating solids, she or he should drink unsweetened drinks. Small quantities of sweetened drinks may also be included to prevent hypoglycemia. If the patient is vomiting or if consciousness is impaired, urgent admission may be required. The urine of patients who require additional insulin should be checked for ketones. This also applies to patients with Type 1 DM. If the ketones are strongly positive and if the blood glucose is >22mmol/l then the patient needs urgent inpatient management.

HIV and DM

Patients with HIV who are on HAART have a longer life expectancy than those not yet on HAART. However, there is a definite increase in chronic metabolic complications related to HIV itself, but also related to HAART. Some of these metabolic complications include dysglycemia, insulin resistance, dyslipidemia, lipodystrophy and accelerated atherosclerosis. This subject ahs been covered in more detail previously in Tlaleletso. For more in depth discussion on this topic consider reviewing the article, 'HIV and diabetes in Africa' in last month's edition of the Africa Journal of Diabetes Medicine.

Summary

Type 2 DM is an emerging problem in Botswana. Early and good control of glycemia is key to prevent and reduce morbidity and mortality. It is also vital that nurses and doctors understand that managing patients with diabetes requires a holistic approach – managing blood pressure, dyslipidemia, together with regular examinations for microvascular and macrovascular complications. Well organized clinics with adequate staff suitably trained in diabetes care will facilitate improved quality of diabetes care.

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