

ABSTRACT

Patients diagnosed with diabetes mellitus require a coordinated team of experienced health care professionals to support and guide them through the often complex and stressful day-to-day management of their illness. Diabetes in itself is a major life-changing event that challenges patients and their caregivers. Establishing clear directions, such that patients' coping, cooperation, and collaboration with their health care providers, are facilitated from the very beginning and this form the initial framework for effective management of their diabetes. These steps include helping them to make adjustments in their lifestyles and adhere to medications in order to optimise their eventual outcomes as much as possible. The following is an outline of the fundamental "stepping stones" that aims to assist physicians managing these patients achieve their treatment targets effectively.

SFP 2008; 34(2): 10-14

INTRODUCTION

Diabetes mellitus, regardless of its form, takes a profound toll with major impact on patients, their families, and society. Despite the challenges in controlling the disease, significantly improved outcomes have been achieved with better understanding of diabetic complications through basic science research, translational research, and clinical trials and applications of various evidence-based management guidelines. How this costly burden can be reduced obviously depends on the colossal efforts fostered out of close collaboration of a multitude of physicians, nurses, diabetes educators, dietitians, exercise physiologists, and other related health care providers.

From the viewpoints of most diabetic patients, there is a need for substantial adjustment across many facets of their lives upon diagnosis. That itself poses considerable psychosocial stress which all clinicians should appreciate, recognise and empathise. It is a crucial point that determines how successful the doctor-patient relationship will be, and hence, would be an important initial step in effective management of diabetes mellitus. Following the establishment of an excellent therapeutic liaison, the subsequent likelihood of success for attaining goals and treatment objectives for each diabetic patient depends a lot on formulating a realistic and manageable plan that should be versatile and easily fine-tuned according to changes during the lifetime of the patient. Unlike

certain disorders, such as cancer and infections whereby physicians probably exert the most influence while there is only a limited degree to which the patient can participate in his management, diabetes is a condition that is quite the opposite. This implies that all diabetics should be strongly encouraged to assume more responsibility in handling their disease and be motivated in much self-management.

In terms of an effective plan, this article will mainly focus on three key components that represent essentially the initial steps, namely:

- Lifestyle
- Diet
- Medications

For the purpose of this discussion, type 2 diabetes, which is the most prevalent form of diabetes, will be alluded to. Although the principles also apply to type 1 diabetes, there exist salient differences and this group of patients is best referred to the endocrinologists and diabetologists to manage.

LIFESTYLE

Lifestyle and behavioural modification form a critical cornerstone of effective diabetes management because an overwhelming proportion of patients with diabetes are obese and sedentary. A sedentary lifestyle is well established as a risk factor for obesity and diabetes, and conversely, the beneficial preventive effect of exercise on development of diabetes has also been proven¹. It is not surprising as such that exercise remains a cornerstone in the management of diabetes. While dietary patterns is very much integral to lifestyle per se, this is best discussed separately as diet is so central to diabetes management it merits a section in its own right.

A. Exercise

Patients with type 2 diabetes have heightened insulin resistance (often in association with the metabolic syndrome) that can be ameliorated by regular exercise. Physical activity, unless absolutely contraindicated in any given person, is definitely beneficial and should be recommended at the outset in the treatment algorithm as one of the most important lifestyle intervention to control diabetes². The potential benefits include:

- Enhanced insulin sensitivity and hence, improved glucose tolerance
- Weight loss or maintenance of healthy body weight
- Optimising cardiovascular risk profile and improving HDL-C
- Improved response to pharmacologic therapy
- Better energy level, muscle strength and well-being

Aerobic activities, strength training, or stretching can all be beneficial. In any case, a balanced exercise routine should include a brief warm-up of about 5-10 mins, 20-30 mins of exercise at the target heart rate (~ 70% of maximum heart rate) and a cool-down until the heart rate has returned to baseline; it should be performed at least 3 times weekly with no more than 2 consecutive days of physical inactivity. One of the most common pitfalls of failed diabetes management is the inability of patients to factor in exercise into their daily regimen for various reasons, such as busy occupations, frequent overseas travelling, intractable pain from arthritis limiting exercises, etc. The physician in-charge should always explore the possibilities of overcoming some of these barriers before concluding that exercise cannot be feasible as part of the strategy for diabetes management. Exercise goals should also be realistic in order for patients to remain motivated to continue on with it as part of a daily routine. It could be useful to engage in several different activities to hinder failure to adhere to exercise from boredom. Sports or activities that the patients enjoy doing fare better in becoming part of daily routine. Overall, as glycaemic control, physical endurance, and energy level improve, the patients experiencing such benefits can in turn feel a better sense of their level of fitness and will more likely continue exercising in the long-term. Research has shown over and over again that fitness through regular exercise has dramatic health benefits. For instance, a large study of over 25,000 volunteers found that men who were overweight or obese but physically active had lower risks of death compared to men with healthy body weight but physically sedentary³.

However, as a precaution, exercise should always be started at a low level and then gradually escalated to avoid injury, hypoglycaemia, and cardiac morbidities because many diabetics have not been active and are fairly deconditioned. Exercising with an exercise physiologist or professional trainer in some instances can help reduce such untoward events especially in those initiating it after a long spell of physical inactivity. As for medications, an exercise regimen may be prescribed by an exercise physiologist or sports physician, and individualised based on physical status, patients' interests, and motivation in certain instances. Yet, for many diabetic patients without professional specialised assistance, just coaxing them to start exercise by initiating any simple activity such as brisk walking, cycling, or swimming is probably a very important and worthwhile first step to overcome their inertia. An exercise stress test is recommended for previously sedentary diabetic patients whose 10-year cardiovascular risk is³ 10% before embarking on any exercise regimen to exclude significant cardiovascular disease and silent myocardial ischaemia, given that diabetes is an ischaemic heart disease equivalent. Also, strenuous physical exertion is to be avoided in those with poor metabolic control and significant complications as a safety precaution. Other exercise guidelines include monitoring blood glucose pre-exercise and post-exercise, being alert to symptoms of hypoglycaemia during or after exercise, drinking sufficient fluids before, during or

after exercising for maintenance of adequate hydration, and carrying personal identifications and ready carbohydrates to reverse hypoglycaemia.

B. Behavioural Modification

In addition to changing lifestyles such that regular exercise can be incorporated into the management paradigm of diabetes, several other important behavioural modifications deserve to be addressed as well. This includes eliminating any other unhealthy habits that might aggravate the underlying diabetes and reinforcing any good habits the patient might already have to increase the chances of better outcomes.

Among various behaviors that need to be tackled, smoking cessation is one of the most challenging and yet important to be modified. To be effective, this anti-smoking message should be delivered repetitively, consistently, and emphatically by different members of the diabetes team of health care providers. Any diabetic patients known to be smoking should be actively encouraged to quit smoking through counselling and referral to smoking cessation programmes that manage smoking cessation through a combination of techniques that may include specific pharmacotherapy.

Diabetic patients who were taught behavioural modification techniques, such as coping strategies, target setting, positive reinforcement, stress reduction skills, and making contractual agreements for continuing support and return appointments for medical reviews, have higher rates of improved metabolic control and greater readiness for lifestyle changes, including overcoming phobia of needles with greater acceptance of self-blood glucose monitoring and insulin injections. As with any form of medical intervention, the extents to which the patients' knowledge, beliefs, and attitude that is translated into practice ('KAP' model) often predict the final outcome⁴. Behavioural modification is therefore a necessary prerequisite to ensure that the education the patient receive will eventually be applied and integrated into their lifestyles.

C. Self-Management Processes

Diabetes self-management education is the foundation of disease management and should be provided to all diabetic patients by their health care providers. Doctors, registered nurses accredited as diabetes nurse clinicians, and dietitians can all contribute positively toward such self-management education of diabetic patients. It involves equipping patients with the technical know-how of whatever that is needed to perform self-care (e.g. self-monitoring of blood glucoses) and improve glycaemic control on a daily basis. However, it is often the case that doctors lack the time to provide adequate self-management education when diabetes is initially diagnosed. Hence, ancillary health care professionals, such as certified diabetes educators, become key in the continued support and education of these patients. Education on self-management processes should shift from being purely didactic to a skill-based approach that when imparted to patients will allow them to be empowered with the ability to make informed decisions that translate into better metabolic control, reduced

diabetic complications, and maximised quality of life. There is much evidence to support the significant benefits and positive outcomes of patients provided with diabetes self-management education that were tailored to individual needs and preferences, and those that addressed psychosocial issues and included follow-up support^{5,6}. Indeed, diabetes education should always be designed with special consideration of the patient in mind, such as the learning ability, occupational constraints, presence of any physical handicaps, and even cultural and religious influences.

DIET

This is possibly the single most challenging aspect of diabetes self-management. There is no longer one diabetic diet for all diabetic patients. Instead, patients with diabetes are now often recommended a diet that is based on individual assessment of nutritional requirements, treatment goals, and desired outcomes⁷. A registered dietitian is almost always depended upon to provide the patients with the most practical aspects relating to dietary discretions and adherence to recommended nutrition prescription and meal plans. Needless to say, a proper nutritional assessment takes into account of such factors as the HbA1c, finger-sticks glucose records, blood pressure, renal status, body weight, blood lipids, patient lifestyle, occupation, cultural, ethnic, and financial backgrounds.

A. Dietitian Referral

It is highly recommended for any patient newly diagnosed with diabetes to be referred to a dietitian. This is to ensure that patients are provided with advice and counselling from relevant health care professionals with the necessary expertise and updated knowledge of the current principles and recommendations regarding diet suitable for those with diabetes.

The same is true even for known cases of diabetes as it is potentially helpful for diabetic patients to be evaluated once a year by the dietitian, so that their meal plans can be reviewed or even revised depending on changes in jobs and levels of physical activities.

Among some of the tasks that a dietitian can do include:

- Evaluate nutritional status and requirements based on diet history, eating habits, and lifestyle
- Draw individualised meal plans to suit the patient such that compliance may be less difficult to achieve
- Do follow-up assessment of effectiveness of meal plans that were instituted, such as improvements in glucose, lipid, and weight; introduce further changes to meal plans depending on the responses of such parameters and any new medications added
- Provide continued education and support to facilitate change in eating habits and behaviours, and assist patients to cope with adjustments with meal changes

B. Body Weight and Calorie Intake

As many type 2 diabetes patients are obese, dietary control to

result in weight reduction is one of the primary targets of effective diabetes management. Even modest decrease in body weight of up to 5-10% of baseline weight can be expected to lead to significant improvements in insulin sensitivity, glycaemic control, lipid profile, and blood pressures, which in turn may be correspondingly associated with the ability to reduce the doses of various medications used⁸. Thus, calorie intake should be coordinated with exercise and medications (including insulin) to achieve near normal blood glucose levels. Standardised calorie-level meals based on exchange lists have traditionally been used to plan meals for hospitalised patients until today. A typical meal would provide about 1,500-2,000 Calories with about 50% from carbohydrates, 30% from fat and 20% from proteins. Estimation of calorie requirement is based on the Harris-Benedict formula that takes into account of the basal metabolic rate that varies with body weight, height, gender and age, as well as on the level of physical activity⁹. Dietitians who recommend various food combinations satisfying the required calorie restriction usually perform such calorie calculations.

C. Nutrition Composition

Generally, carbohydrates should provide 55-60% of total daily calories, fats should provide 20-30% of total daily calories, while protein should provide 15-20% of total daily calories¹⁰. The Recommended Dietary Allowance (RDA) for protein intake for type 2 diabetes is 0.8g/kg body weight/day. For those with diabetic patients with renal insufficiency, more severe restriction of protein to 0.6g/kg body weight/day has been shown to retard the progression of diabetic nephropathy. Saturated fat should be limited to < 10% of total calories, and < 7% in those with elevated LDL-C. Polyunsaturated fats should not exceed 10% of total calories, and daily cholesterol consumption should be limited to 300 mg. The carbohydrate allowance is then determined after protein and fat intake have been calculated, and should be individualised.

There are several dietary approaches to control and limit calories intake. Carbohydrate counting to track the number of grams of carbohydrates ingested each day is one of the commonest ways. Emphasis is placed on starches, whole grains, and vegetables. Previous notions that complex carbohydrates result in less glycaemic excursions than simple sugars have been disproved by clinical research. Hence, methods that rely on the glycaemic indices of various foods to control sharp escalations of blood sugars have evolved in its place¹¹. Diabetic exchange lists represent one common method to maintain a proper balance of carbohydrates, fats, and proteins throughout the day. The American Diabetes Association (ADA) and the American Dietetic Association have exchange lists that divide foods into categories.

MEDICATIONS

There are at present at least 6 distinct pharmacological classes of antidiabetic agents available in the armamentarium to treat type 2 diabetes. These can broadly be divided into:

A. Insulin Secretagogues

1. Sulfonylureas
 - tolbutamide (1st generation; chlorpropamide rarely used nowadays)
 - glibenclamide, glipizide, gliclazide, glimepiride (2nd generation)
2. Meglitinides
 - repaglinide
 - nateglinide

B. Insulin Sensitisers

1. Biguanides
 - metformin (the only biguanide widely used, unlike phenformin and buformin)
2. PPAR γ receptor agonists
 - thiazolidinediones (rosiglitazone - main TZD promoted here as pioglitazone not actively marketed locally)

C. Alpha-Glucosidase (Disaccharidase) Inhibitors

- acarbose (the only aGI available locally, while miglitol available abroad)

D. Incretin-Based

1. Incretin analogues (as subcutaneous injectables only)
 - exenatide, liraglutide
2. Dipeptidylpeptidase inhibitors (DPP4 inhibitors)
 - sitagliptin, vildagliptin

E. Insulin Therapy

- up to 8 different types of insulins (including rapid-acting and basal insulin analogues are currently available) which will be discussed in a separate section

Apart from these established agents, others such as amylin analogues (e.g. pramlintide, a subcutaneous injectable for both type 1 and 2 diabetes) are available overseas and not widely used locally. New experimental therapies are currently still being investigated for potentials in being developed for future clinical use. Dual PPAR α -PPAR γ receptor agonists ('glitazars') demonstrate favourable lipid effects from its 'fibrate-like' PPAR α effect, in addition to PPAR γ insulin sensitising effects, and may therefore hold promise for type 2 diabetes as this disease is clearly a disorder of both insulin resistance and lipid metabolism.

Glitazars development suffered a setback from its oncogenic potentials in mouse models, though cancers have not been observed in human studies as yet. While it is uncertain if any glitazars would eventually reach the bedside, it is an interesting target that is still being pursued. Still other agents in the pipeline include glucagon receptor antagonists, which could become very useful in blocking the glucagon excess seen in type 2 diabetes. For details

regarding dosing, pharmacokinetics and pharmacodynamics of the antidiabetic agents listed above, physicians should consult established pharmacopoeias and drug guides.

One of the most updated strategies in the area of pharmacotherapy for type 2 diabetes is the consensus guidelines and treatment algorithm jointly issued by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) in 2006¹². This differs somewhat from the practice norm for the United Kingdom where the National Institute for Clinical Excellence (NICE) guidelines are more often used¹³. For instance, according to the NICE guidelines, metformin or sulfonylurea is started only after a trial of failed lifestyle intervention, and TZD is only considered if hypoglycaemia from sulfonylurea is a limiting factor or if metabolic syndrome is an issue; insulin is only introduced after failed combination sulfonylurea and metformin. However, the principles behind the joint ADA-EASD guidelines provide a much greater flexibility in drug selection and emphasise the possible early start of agents and drug combinations that would otherwise be delayed till a later stage. These guidelines are very useful and easily adapted by any clinician managing diabetes. The major goal of this algorithm is based on achieving and maintaining glycaemic targets within, or as close as possible to, the non-diabetic range.

Essentially, the Step 1 (**lifestyle intervention and metformin**) in this algorithm consists of initiating healthy lifestyle interventions plus metformin simultaneously at the time of diagnosis. The rationale behind this recommendation lies in the fact that lifestyle intervention, while being effective, has a high failure rate if depended upon alone. When combined with metformin, it is expected to lower HbA1c by between 1-2%.

Step 2 (**additional medication**) states that a second agent should be added if the above fails to achieve glycaemic targets. A HbA1c level of $\geq 7\%$ (after approximately 3 months) is an indication to proceed with this second step. As to selection of the second agent, this is based primarily on their glucose-lowering efficacy. Basal insulin could be chosen, as it is most effective, while sulfonylurea could be chosen alternatively as it is least expensive, and a TZD ('glitazone') could be considered instead, if hypoglycaemia from insulin or sulfonylurea is a major concern for the particular patient in question.

With regards to glitazones, fluid retention with its attending risks of congestive cardiac failure and aggravation of macular edema as well as the more recent – though controversial – findings of increased association of rosiglitazone with myocardial infarction and fractures in the distal skeleton, especially in postmenopausal women with both rosiglitazone and pioglitazone, have led to greater precautions in its usage for type 2 diabetes^{14,15}. Although DPP4 inhibitors and incretin mimetics are not emphasised in the present algorithm in view

of their costs and uncertain long-term side effect profile, they can still be considered in suitable patients as a second step add-on agent too according to the updated joint ADA-EASD guidelines.

Following the addition of one of the above agents as a second step, should the glycaemic targets not be met, Step 3 (further adjustments) will then be instituted. Those on basal insulin will require intensification of their insulin while those on sulfonylurea can either be augmented with basal insulin or a glitazone, and those on glitazone can have either basal insulin or a sulfonylurea added. Failing this third step, patients will generally have to be on intensive insulin and metformin. As there is increased risk of fluid retention when glitazone is combined with insulin therapy, this is not advised without consultation with the endocrinologists. Notably, TZD in combination with insulin is not currently approved in the European Union.

REFERENCES

1. Knowler WC, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; 346(6): 303-403.
2. Kirk A, et al. Increasing physical activity in people with type 2 diabetes. *Diabetes Care* 2003; 26(4): 1186-92.
3. Barlow CE et al. Physical fitness, mortality and obesity. *International Journal of Obesity and Related Metabolic disorders*. 1995; 19 (Suppl 4): S41-S44.
4. Searle A, et al. A prospective examination of illness beliefs and coping in patients with type 2 diabetes. *Br J Health Psychol* 2007; 12(Pt 4): 621-38.
5. Steed L, et al. A systematic review of psychosocial outcomes following education, self-management and psychological interventions in diabetes mellitus. *Patient Educ Couns* 2003; 51(1): 5-15.
6. Gage H, et al. Educational and psychosocial programmes for adolescents with diabetes: approaches, outcomes and cost-effectiveness. *Patient Educ Couns* 2004; 53(3): 333-46.
7. ADA Task Force. American Diabetes Association position statement: evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. *J Am Diet Assoc* 2002; 102(1): 109-18.
8. Zanella MT, et al. Treatment of obesity, hypertension and diabetes syndrome. *Hypertension* 2001; 38(3 pt 2): 705-8.
9. McCarron DA, et al. Nutritional management of cardiovascular risk factors: A randomized clinical trial. *Arch Intern Med* 2007; 157(2): 169-77.
10. Dietary recommendations for people with diabetes: an update for the 1990's. Nutrition Subcommittee of the British Diabetic Association's Professional Advisory Committee. *Diabet Med* 1992; 9(2): 189-202.
11. Riccardi G, et al. Role of glycemic index and glycemic load in the healthy state, in pre-diabetes, and in diabetes. *Am J Clin Nutr* 2008; 87(1): 269S-274S.
12. Nathan DM, et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2006; 29: 1963-72.
13. National Institute for Health and Clinical Excellence (NICE) Guidelines for Management of Blood Glucose in Diabetes Website: <http://www.nice.org.uk/>.
14. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007; 356(24): 2457-71.
15. Grey A. Skeletal consequences of thiazolidinedione therapy. *Osteoporos Int* 2008; 19(2): 129-37.

LEARNING POINTS

- o As diabetes is a complex and chronic disease of lifestyle, educating and guiding patients with regards to healthy lifestyle intervention and their synergism with pharmacotherapy will facilitate patients' coping, cooperation, and collaboration with their health care providers from the very beginning and this form the initial framework for effective management of their diabetes.
- o Physical activity, unless absolutely contraindicated in any given person, is definitely beneficial, and should be recommended at the outset in the treatment algorithm as one of the most important lifestyle intervention to control diabetes.
- o Even modest decrease in body weight of up to 5-10% of baseline weight can be expected to lead to significant improvements in insulin sensitivity, glycaemic control, lipid profile, and blood pressures.
- o All newly diagnosed patients with diabetes (including their caregivers) are highly recommended to be referred to a registered dietitian for proper counselling on the most current principles and advice regarding dietary control; subsequent re-evaluations by the dietitian could be helpful once a year or so depending on changes in jobs and levels of physical activities.
- o One of the most updated strategies in the area of pharmacotherapy for type 2 diabetes is the consensus guidelines and treatment algorithm jointly issued by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).