

EVIDENCE-BASED CARE OF TYPE 2 DIABETES MELLITUS: NON-PHARMACOLOGICAL AND PHARMACOLOGICAL MANAGEMENT

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ABSTRACT

This three-part article provides an overview of the evidence-based care of patients with type 2 diabetes mellitus, in the view of recent literature and research. Type 2 diabetes is the focus of this review, since, it is much more common and accounts for 90-95% of all diabetic cases worldwide.

Part-I discussed the epidemiological overview of the disease at the global and national levels; followed by the rationale and criteria for screening and diagnosis of type 2 diabetes including the important components that should be assessed at an initial evaluation of the patient. Part-II provides key information about the non-pharmacological and pharmacological management of type 2 diabetes. Meanwhile, part-III will review the prevention, screening and management of long-term complications among persons with type 2 diabetes.

KEY WORDS: *Type 2 Diabetes. Management. Evidence Based Care.*

INTRODUCTION

Type 2 Diabetes Mellitus is well recognized as a chronic and progressive metabolic disorder. Its management requires continuous pains-taking efforts to achieve meticulous metabolic control and treatment objectives. Management goals and importance of continuous patient education for type 2 diabetes have been discussed previously in details.¹ Control of glycemic level is a mainstay in the management of diabetes. A number of epidemiological studies revealed the significance of glycemic control for the better achievement of short-term and long-term desirable goals for the management of this disease. In the United Kingdom Prospective Study (UKPDS),² a total of 3,867 patients with newly diagnosed type 2 diabetes have been observed for at least 10 years. A 0.9% reduction in HbA_{1c} was associated with a reduction in risk of 12% diabetes-related end points (i.e., sudden death, death from hyperglycemia or hypoglycemia, myocardial infarction, angina, heart failure, stroke, renal failure, amputation, and eye complications) and reduction of myocardial infarction by 14%. Similarly, in a randomized prospective 6-years study in Japan,³ persons with type 2 diabetes with an average HbA_{1c} level of 7% were compared with those having HbA_{1c} level of 9% and translated into less retinopathy (7.7% versus 32%), less nephropathy (7.7% versus 28%), and improvement in nerve conduction.

The traditional approach to the treatment of type 2 diabetes has been a stepwise introduction of non-

medication intervention followed by oral agents. Insulin therapy, despite the most versatile and potent agent available for establishing normoglycemia, has generally been used as a last resort. It is usually suggestive that at the diagnosis of diabetes, if Fasting Blood Sugar (FBS) is < 200 mg/dl, nutritional and exercise prescription is required and then reviewed after 2-3 months period. In case, if FBS is 200-300 mg/dl, along with nutritional and exercise, an oral hypoglycemic drug should be advised and reviewed after 2-3 weeks period. However, if FBS at diagnosis is > 300 mg/dl, in addition to nutritional and exercise regime, insulin therapy is better option to initiate.⁴

NON-PHARMACOLOGICAL MANAGEMENT

Non-pharmacological treatment usually implies to make nutritional and exercise/physical activity recommendations, and to obtain and maintain overall goals for the management of diabetes. There is a large number of evidence to suggest the significance of this approach for the better outcomes of this particular metabolic syndrome.^{5,6} The goals of this approach that apply to persons with diabetes, should be to attain and maintain optimal body weight, to reduce insulin resistance and improve metabolic outcomes including glycemic levels. However, to facilitate adherence, the plan should be individualized and realistic by taking into account the social, cultural, lifestyle, and financial considerations.

Nutritional management in diabetes: Nutritional management is an essential and elementary

component for the total diabetes care and management. A balanced, hypocaloric nutritional therapy is usually recommended for persons with diabetes. However, before prescribing nutritional therapy, nutritional assessment to evaluate the patient's food intake; body weight; metabolic status; lifestyle and readiness to make changes and goal settings is mandatory. To achieve nutrition-related goals, continuous and coordinated team effort is mandatory including the person with diabetes and his/her family. Nevertheless, if goals are not met, changes must be made in the overall diabetes care and management plan.

Most recent evidence-based recommendation⁷ for nutritional therapy for persons with diabetes is that carbohydrate and monosaturated fat together, should provide 60–70% of energy intake. Further, protein intake should account for 15–20% and less than 10% of energy intake should be derived from saturated fats. Some individuals (i.e., persons with LDL cholesterol \geq 100 mg/dl) may benefit from lowering saturated fat intake to $<$ 7% of energy intake. Dietary cholesterol intake should be $<$ 300 mg/day. Some individuals (i.e., persons with LDL cholesterol \geq 100 mg/dl) may benefit from dietary cholesterol to $<$ 200 mg/dl. People with diabetes are encouraged to choose a variety of fiber-containing foods, such as whole grains, fruits, and vegetables, because they provide fiber, vitamins, minerals, and other substances important for good health. Non-nutritive sweeteners (saccharine, aspartame, acesulfame potassium, and sucralose) are safe when consumed within acceptable daily intake levels.

Exercise/Physical activity in diabetes: Regular physical activity serves as a cornerstone in the management of diabetes and in the prevention and delaying of its complications. Extensive evidences are available to demonstrate a consistent beneficial effect of regular physical activity for patients with diabetes.^{4,6} Regular physical activity/exercise has been proved to have substantial benefit on glycemic control, prevention of cardiovascular disease, hyperlipidemia, hypertension and obesity. It is also evident that the benefit of physical activity in improving metabolic abnormalities of type 2 diabetes is probably greatest when it is used early in its progression.⁸

It is recommended that individuals accumulate 30 to 60 minutes sessions of moderate physical activity, three to four times a week, which can reduce HbA1c levels by 10–20%.⁸ According to most recent evidence,⁸ physical activity includes a proper warm-up and cool-down period. A warm-up should consist of 5–10 minutes of aerobic activity (walking, cycling, etc.) at a low intensity level. After that, muscles should be

gently stretched for another 5–10 minutes. Primarily, the muscles used during the active physical activity session should be stretched, but warming up all muscles is optimal. After the activity session, a cool-down should be structured similar to the warm-up. The cool-down should last about 5–10 minutes which gradually brings the heart rate down to its pre-exercise level.

There are some specific exercises that are particularly harmful or not advisable for patients with specific diabetic complications. Prolonged walking, jogging and step exercise in patients with loss of sensation of feet should not be allowed. Patients with proliferative diabetic retinopathy should avoid anaerobic exercise and physical activity that involves straining and jarring which may precipitate vitreous hemorrhage and retinal detachment. Thus, preparing the individual with diabetes for a safe and enjoyable physical activity program is as important as physical activity itself. Before beginning a physical activity program, the person with diabetes should have a detailed medical evaluation with appropriate diagnostic studies. A careful medical history should focus on risk factors, symptoms and signs of disease affecting the cardiovascular system, kidneys, eyes, nervous system and feet. Physical examination should screen for the presence of macrovascular and microvascular complications that may be worsened by the physical activity program. For example, patients with known coronary artery disease should undergo a supervised evaluation of the ischemic response to exercise, ischemic threshold, and the propensity of arrhythmia during exercise.

PHARMACOLOGICAL MANAGEMENT

It is recommended that if desirable goals for management are not achieved with three months trial of non-pharmacological intervention as first-line therapy in the patients with type 2 diabetes, pharmacological intervention is required.⁹ This decision should be made jointly by the physician and patient to achieve the best results. It is quite evident that whatever the drug used, the ultimate objective should be to control glycemic level and other metabolic outcomes. A large number of oral hypoglycemic drugs (i.e., sulfonylureas, biguanides, thiazolidinediones, meglitinides, etc.) and insulin preparations (ultra-short acting, short acting, intermediate acting, long acting, etc., and their different combinations) are available for the use of persons with diabetes with their specific mode and duration of action, advantages, side effects, cost and contra-indications. It is prudent, therefore, to consider patient specific characteristics (age, weight, level of glycemic control, co-morbidities) and agent-specific

characteristics (relative potency, duration of action, possible side-effects, cost, availability) to make agent choice more appropriate and ensuring better compliance, once the decision is made to initiate with oral hypoglycemic agent. It is a general principle that for newly administered oral hypoglycemic drug to reach equilibrium concentration, the response to the drug should be measured 1 to 2 weeks later by measuring plasma glucose levels.¹⁰

Oral hypoglycemic preparations: It is beyond the scope of this review to discuss each group of oral agents individually in detail. However, most commonly used agents (sulfonylureas, biguanides, alpha-glucosidase inhibitors) are discussed here with their particular indications, unwanted effects and contraindications in the light of recent research. It is generally acceptable that oral hypoglycemic drugs are contraindicated during pregnancy. **Table no. 1** is demonstrating the indicators to use different types of oral agents.

Sulfonylureas have remained the mainstay of anti-diabetic therapy since early 1950s. Following the release of the University Group Diabetes Program (UGDP) study,¹¹ which implicated tolbutamide in increased cardiovascular mortality, the use of the first generation sulfonylureas quickly fell out of favor.¹² Recent evidence² suggest no difference in cardiovascular mortality rates between patients treated with sulfonylureas and those receiving insulin. Also, availability of newer generation sulfonylureas with more favorable side-effect profiles and once daily dose has contributed to their renewed popularity.¹³ Sulfonylureas work mainly by stimulating insulin release from the beta cells of the pancreas. On average, this class reduces HbA_{1c} levels by 0.8-2.0% and FPG concentrations by 60-70 mg/dl.^{13,14} Hypoglycemia is the most worrisome side effect of the sulfonylureas and is also associated with weight gain, thus, may not be the optimal first choice for obese and elderly patients. These agents should be taken about 20 minutes before meal. When initiating sulfonylurea therapy, the lowest effective dose should be used and titrated to the desired effect thereafter. The commonly used drugs are glibenclamide (2.5-20 mg/dl) and glimepiride (1-8 mg/dl). Most of the hypoglycemic effects of the sulfonylureas will be observed at one half of the maximum dose recommended for a specific agent. Unfortunately, not all patients treated with a sulfonylurea have an adequate response and treatment failure with sulfonylurea therapy may occur as primary or secondary.¹⁵ Primary failure results when a patient exhibits an initial poor response to sulfonylurea therapy (a decrease in FPG levels of < 20 mg/dl). Secondary failure results when the patient responds

well to treatment initially but then no significant beneficial effect (a decrease in FPG of > 30 mg/dl) with continued therapy. Approximately, 20-25% of patients with diabetes demonstrate primary failure and approximately 5-10% of patients report secondary failure per year.

Biguanides mainly works by reducing hepatic glucose output and to a lesser extent, enhancing insulin sensitivity in hepatic and peripheral tissues. Metformin, the widely available drug in this group has been shown to reduce HbA_{1c} levels by approximately 1.5-2.0% and FPG levels by 50-70 mg/dl.^{13,14} Other effects include a reduction in plasma triglyceride levels and low-density lipoprotein cholesterol levels. Metformin therapy should be initiated at 500 mg twice daily with meals and can be increased by 500 mg (maximum dosage of 2,000 mg/day). This drug is usually associated with a lack of weight gain and even weight loss, which makes it an ideal first-line agent in overweight/obese patients. Metformin is also a better option for patients with diabetes along with some specific concurrent endocrine and metabolic syndromes like Poly cystic ovaries and Cushing's syndrome. This agent is also advisable to prescribe along with insulin to counter-effect the weight gain by insulin. Most of the side effects (including metallic taste, gastrointestinal discomfort) are transient and commonly reported only during initiation of therapy. Patients should be instructed to take this medication with food to lessen the severity of the side effects. Because, metformin does not affect insulin secretion, it is not associated with hypoglycemia when used as monotherapy, but can potentiate hypoglycemia when used in combination with other hypoglycemic agents. A rare, but more worrisome side effect is lactic acidosis (3 cases/100,000 patient-years).¹⁶ Metformin should not be used in patients with elevated serum creatinine levels (> 1.4 mg/dl). Other situations, in which metformin therapy should be avoided include cardiogenic or septic shock, congestive heart failure, severe liver disease, pulmonary insufficiency with hypoxemia or severe tissue hypoperfusion.^{17,18}

Alpha-glucosidase inhibitors act by inhibiting the enzyme alpha-glucosidase, which cleaves more complex carbohydrates into sugars. The largest impact of these drugs is on postprandial hyperglycemia. Their effect of this agent is modest with a reduction in HbA_{1c} by 0.7-1.0% and FPG levels by 35-40 mg/dl.¹⁴ Thus, these agents are most useful in patients who have mild FPG elevations or in

patients with predominant postprandial hyperglycemia. The most bothersome side effects observed with these agents are gastrointestinal but are reversible with discontinuation of the drug. Patients should be instructed to take this medication with food to diminish the severity of the side effects. Therapy with acarbose has been linked to elevations in serum transaminase levels and the use of this agent is contraindicated in patients with liver cirrhosis. Alpha-glucosidase inhibitors are not indicated in patients with a serum creatinine level more than 2.0 mg/dl. Therapy should be initiated with the lowest effective dose and titrated slowly over intervals.

Combination therapy: Evidence shows the disappointing results with monotherapy, especially the worsening metabolic control often seen within five years after the initiation of an oral hypoglycemic agent,¹⁹ have led to the use of combination therapy. The principle behind combination therapy should be to use drugs with different mechanisms of action that may have additive therapeutic effects and results in better glycemic control,²⁰ along with counter acting

TABLE I
SHOWING INDICATORS FOR USE OF ORAL HYPOGLYCEMIC DRUGS

Oral hypoglycemic agent	Indicators for use of oral agents	
	Positive	Negative
Sulfonylurea	CPG > 300 mg/dl, CPG > 300 mg/dl	Hypoglycemia, weight gain sulfa allergy
Metformins	Obesity, dyslipidemia	Lactic acidosis, liver failure, hypoxia, CCF
α-glucosidase inhibitors	Post-meal hyperglycemia	Post-meal hyperglycemia

each-others unwanted effects. Usually, combinations of two agents from different mode of actions are recommended and reasonable combinations include sulfonylurea plus metformin, sulfonylurea plus alpha-glucosidase inhibitor and biguanide plus alpha-glucosidase inhibitor. Some physicians, however, advocate therapy combining three oral agents, (sulfonylurea, metformin, and alpha-glucosidase

TABLE II
SHOWING POSSIBLE OPTIONS OF COMBINATION THERAPY FOR USE

Current therapy	Add one of these pharmacological agents			
	Sulfonylurea	Metformin	α-Glucosidase Inhibitors	Bedtime NPH insulin
Sulfonylurea		Positive: obesity, dyslipidemia, FPG>200 mg/dl Negative: CHF, renal disease, lactic acidosis	Positive: Elevated postprandial glucose Negative: Limited glucose Lowering	Positive: Transition therapy to multi-dose insulin, FPG>300 mg/dl
Metformin	Positive: FPG> 250mg/dl, CPG > 300mg/dl, consider in lean patients Negative: Weight gain, Hypoglycemia, Sulfa allergy		Positive: Elevated post-prandial glucose Negative: Limited glucose lowering	Positive: Best with bedtime NPH, limited weight gain Negative: May not lower postmeal glucose
α-Glucosidase Inhibitors	Positive: FPG > 250mg/dl, CPG > 300 mg/dl, consider in lean patients Negative: Weight gain, Hypoglycemia, Sulfa allergy	Positive: Obesity, dyslipidemia Negative: CHF, renal disease, lactic acidosis		Positive: FPG> 300 mg/dl

inhibitor), although this approach has not been extensively studied.²¹ Significant data support the combination of bedtime insulin with daytime sulfonylurea therapy.^{10,22} This combination can be quite effective in reducing FPG. Along with better glycemic control, further advantage of combination therapy is counter-effect of two groups of drugs used such as; combination therapy with metformin results in the reduction of weight gain that occurs with sulfonylurea and insulin. **Table no. II** is showing the different options of combination therapy for use.

Insulin therapy: Insulin, despite being the most potent and durable hypoglycemic intervention available, has generally been saved for last, presumably because of the need to administer it by injection. It is best option for patients with type 2 diabetes having persistent hyperglycemia and on maximum, tolerated dose of hypoglycemic agents should be considered for insulin. Other indications for insulin use in patients with type 2 diabetes are: allergy and other serious reactions to oral hypoglycemic agents, renal disease, liver disease, acute myocardial infarction, upcoming surgery, pregnancy, uncontrolled weight loss and severe hyperglycemia with ketonemia and ketonuria.

Insulin is only hypoglycemic agent that occurs naturally in humans and has no upper dose limits. There is insufficient data to determine the best insulin regimes. It is, however, usually recommended^{4,10} to calculate the total dose at 0.3 u/kg body weight of the patient/day and then adjust according to the glycemic control. Two-third and 1/3rd regime is commonly used for morning and evening times. However, different regimes and dose-adjusted recommendations are available.¹⁰ With the development of highly purified human insulin preparations, immunogenicity has been markedly reduced, thereby decreasing the incidence of therapeutic complications such as insulin allergy, immune insulin resistance, and localized lipoatrophy at the injection site.²³ However, the problems of hypoglycemia and weight gains should be considered before prescribing insulin. It is suggested to educate and well inform the patient and his/her family about the signs and symptoms of hypoglycemia, its prevention and emergency measure to take in case of hypoglycemia. It is very important that patient does not feel of failure when insulin is considered, even if non-compliance with diet and exercise has contributed.²⁴ This can be prevented by discussing the progressive nature of diabetes early on as well as the concept of insulin and how conversion can be avoided or delayed.

CONCLUSION

Type 2 diabetes is a progressive metabolic disease associated with large number of acute and chronic complications. Control of glycemic level is fundamental principle for the management of diabetes. Life-style modifications including hypocaloric nutritional diet and regular physical activity are the mainstay for the control of glycemic level and to achieve both short-term and long-term management goals. These interventions should be formulated on individual basis keeping in the mind the patients' socio-cultural factors and the cost along with concurrent diseases and complications. If patient does not obtain specified management objective after three months of trial, management plan should be revised and oral hypoglycemic drugs is a better option to prescribe. Approach should be step-wise with optimal acceptable dose of oral drug, which should be agent specific and patient specific. Sulfonylureas are customary used as first choice for younger and non-obese patients while biguanides are better choice for elderly and obese patients. If patient, on optimally recommended oral hypoglycemic agent does not attain the target levels of glycemic control in four weeks, should be considered for alternative oral agent or for combination of oral agents or switch over to insulin.

ACKNOWLEDGEMENT

I am very much indebted to Dr. Naushaba Mobeen (Department of Community Health Sciences, The Aga Khan University, Karachi) and Dr. Nadya Khan (Aga Khan Diagnostic Center, Garden, Karachi) for their help in review of the manuscript.

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