

## Review Article

# Management of Diabetes Mellitus: Principles and Practice\*

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### INTRODUCTION

Diabetes Mellitus is a chronic metabolic disorder, which usually manifests as hyperglycaemia and glycosuria. It is due either to an absolute lack of insulin, or to its biological ineffectiveness, resulting in a wide range of abnormalities of carbohydrate, fat and protein metabolism.

Diabetes Mellitus affects more than 140 million people worldwide<sup>[1]</sup>. By the year 2025, the number of persons with diabetes may reach nearly 300 million<sup>[2]</sup>. Diabetes is one of the leading causes of morbidity and mortality due to the specific microangiopathy and the associated macroangiopathy. It is the leading cause of blindness and visual impairment in adults in the western hemisphere, and the risk of cardiovascular disease is two to five times more in persons with diabetes, as compared to normal adults<sup>[3]</sup>. For the purpose of rational management, it is appropriate to classify diabetes as Type 1 (also called insulin-dependent diabetes mellitus or IDDM) and Type 2 (also called noninsulin-dependent diabetes mellitus or NIDDM), and to understand the pathophysiological basis of metabolic derangement.

### Pathophysiology of Diabetes Mellitus<sup>[4,5]</sup>

In type 1 diabetes mellitus (type 1 DM), the onset is generally before the age of 30 years, most often in childhood or adolescence, although it may occur at any age. The disease usually has an abrupt onset with increased thirst, increased appetite, and excessive urination and weight loss. Occasionally, it may be diagnosed when the patient presents for the first time in ketoacidosis or coma, especially during an intercurrent illness or surgery. Diabetic ketoacidosis is a serious complication, and if left untreated, often a fatal one. The patients usually are not obese and may even be wasted and underweight. These are the patients in whom the

secretion of insulin is extremely low or nil, generally due to an immune-mediated destruction of  $\beta$  cells in the islets of Langerhans, and where life can be sustained only with supplementation of insulin from external sources.

Hyperglycaemia and ketonaemia constitute the most important sequelae of insulin deficiency in type 1 DM. While hyperglycaemia is essentially due to varying combination of lack of glucose utilization and overproduction of glucose through accelerated gluconeogenesis, ketonaemia is a resultant of impaired lipogenesis and enhanced lipolysis leading to a release of free fatty acids (FFA) into the circulation. The synthesis of triglycerides from FFA is regulated by the molar ratio of insulin and glucagon in the liver. There is secondary hyperglucagonaemia in diabetes mellitus, leading to a reduced activity of malonyl CoA, thereby affecting triglyceride synthesis. In addition, enhanced activity of carnitine acyltransferase facilitates FFA entry into mitochondria, where through beta-oxidation, excessive amounts of acetyl CoA are generated, leading to formation of large amounts of ketone bodies, which are utilized only in part by muscle and other peripheral tissues.

### Type 2 DM

In contrast to type 1, type 2 diabetes mellitus (type 2 DM) usually begins in middle life or beyond 40 years of age, although it is now being increasingly recognized in the younger, adolescent and paediatric age groups<sup>[6]</sup> where it is generally associated with childhood obesity<sup>[7]</sup>. Classically, the patients are obese (80-85%), but may occasionally be normal (10-15%) or at times even underweight (< 5%). This provides the basis for a sub classification into obese type 2, and non-obese type 2 DM. The onset is usually insidious, and not infrequently, a diagnosis is made in an otherwise completely asymptomatic person on laboratory

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investigations. The patients with type 2 DM may have varying amounts of circulating insulin, depending upon the secretory capacity of pancreatic  $\beta$  cell. They are, therefore, not dependent on insulin for prevention of ketonuria, and are generally not prone to ketosis. Nevertheless, they may require insulin for correction of hyperglycaemia, if such a therapeutic approach is otherwise indicated. However, it needs emphasis that these patients may develop ketosis under stressful situations e.g. fulminant infections, burns, trauma, or surgery; treatment with insulin is essential under such circumstances.

Although type 2 DM is by far the commoner type, much less is known about its pathogenesis. The major risk factors include genetic susceptibility, obesity, physical inactivity, and western lifestyle including change in dietary pattern involving both the total quantity and altered quality of food intake, as well as life stress. Intervention strategies aimed at some of these risk factors are being recommended for the prevention of type 2 DM, as also in its therapeutic management. However, at the time of clinical onset, type 2 DM reflects the culmination of a chronic and progressive process caused by a combination of insulin resistance and decreased pancreatic  $\beta$  cell function<sup>[8]</sup>. While the secretory defect in the  $\beta$  cell results in impaired basal and stimulated insulin secretion, insulin resistance at the level of muscle, liver and adipose tissue leads to both inefficient peripheral glucose utilization as well as enhanced endogenous hepatic glucose production and release.

Most longitudinal studies indicate that insulin resistance precedes the development of type 2 DM, in some cases even by a decade or more. In the years preceding the clinical onset of diabetes, insulin resistance may be present with totally normal glucose tolerance. Alternatively, it may be associated with central or truncal obesity, impaired glucose tolerance, hypertriglyceridaemia, hypertension and accelerated atherosclerosis; the terms plurimetabolic syndrome, or syndrome X, or insulin resistance syndrome have been assigned to such a clinical and metabolic phenotype<sup>[9]</sup>. The intra-abdominal fat content is significantly related to the degree of insulin resistance, as reflected in a high waist/hip ratio. In central (visceral) adiposity with increased waist-hip ratio, there is an increased level of free fatty acids (FFA) in the portal circulation, possibly as a result of high lipid turnover due to increased metabolic activity of visceral fat, coupled with an increase in blood flow to these metabolically active adipose depots.

Increased FFA at the hepatocyte membrane lead to (i) decreased insulin binding, (ii) reduced insulin degradation and (iii) decreased insulin action. These effects contribute to both hepatic insulin resistance and increased hepatic gluconeogenesis.

Insulin resistance may thus play a significant role at the level of hepatic tissue, or at the peripheral tissue sites such as muscle and adipose tissues, or both. Hepatic glucose production in type 2 DM is generally increased and such high rates are inappropriate in relation to the levels of circulating glucose. Thus, there is a close correlation between the increased glucose production by the liver and the degree of fasting hyperglycaemia. Increased hepatic glucose output results from lack of sensitivity to the effect of insulin in the liver, which in turn is possibly due to a reduction in the number of insulin receptors on the hepatocytes. Although the level of glucose itself regulates hepatic glucose output, such a mechanism is impaired in type 2 DM. Increased hepatic glucose output is possibly due to both a reduced hepatic sensitivity to the action of insulin, and a defect in the ability of glucose to inhibit its own release from the liver; hyperglucagonaemia may contribute partly to this dual defect<sup>[10]</sup>. In the peripheral tissues, notably muscle, insulin resistance leads to a decrease in glucose uptake. This decrease results in more marked and longer-lasting hyperglycaemia following meals (postprandial hyperglycaemia). Although obesity is a well-recognized cause of defective insulin binding to its receptors, the non-obese type 2 DM also exhibit insulin resistance, which can only be due to one or more post-receptor events. Post-binding abnormalities are primarily responsible for the insulin resistance in a majority of such subjects.

### Therapeutic Rationale

A clear insight into the differential characteristics of the pathophysiology of type 1 and type 2 DM provides the base and basis for a rational therapeutic approach to management. Obviously, in type 1 DM with absolute lack of insulin, insulin is an essential component of treatment. Not only is it necessary as a replacement therapy for the treatment of hyperglycaemia and prevention of ketonaemia, but it is also of considerable importance in the prevention of the chronic complications, notably microangiopathy, provided a tight metabolic control is achieved (as discussed under therapeutic goals). In contrast, the therapeutic approaches in the management of type 2 DM essentially include life style intervention strategies (diet, exercise, normalization of body weight), and pharmacological interventions aimed at (i)

enhancing the secretion of insulin from the  $\beta$  cells, and/or (ii) reducing the degree of insulin resistance at muscle, liver and adipose tissue, thereby enhancing the biological effectiveness of available insulin. Nevertheless, if both life style and pharmacological interventions at an optimized level are unable to provide requisite glycaemic control, or having achieved such a control are unable to maintain it subsequently, insulin therapy in type 2 DM is indicated. Irrespective of the type of diabetes, education of the patient and the family enhances their ability to comprehend, plan and organize a meaningful and appropriate program of self-care and home-care<sup>[11]</sup>, the key to the participatory management of diabetes as a life-long commitment.

### Therapeutic Goals

Having spent more than four decades in the management of patients with diabetes mellitus, the recognition of enlightenment and empowerment of the patient emerges as the foremost goal<sup>[11]</sup>. Information is power and a well-informed patient capable of self-care, is a valuable member of the diabetes care team. This must be recognized by all members of the team including the physician, nurse, dietician, pharmacist, social worker, and all those who may interact with the patient to provide information and support. No person with diabetes can lead life as normally as a non-diabetic person, without a proper understanding and acceptance of diabetes as a real life-long situation. Patient education thus is not just an adjunct, but constitutes an essential and vital component of the total therapeutic plan. Every encounter of the patient (and the family in some cases) with any member of the diabetes care team must provide an opportunity to exchange information and to facilitate transformation of such information into knowledge. This knowledge then becomes a key motivating factor in ensuring compliance with the prescribed daily regimen. The main objectives of a diabetes education program include<sup>[12]</sup>:

- (i) Enhancing quality of life of the patient and to gain quality - adjusted life years;
- (ii) Enabling the patient to prevent, and recognize, symptoms of hypoglycaemia, to initiate timely and appropriate management, as well as to prevent situations that may result in ketoacidosis,
- (iii) Reducing the number of days of hospitalization by taking adequate measures to prevent infections (i.e. foot care, personal hygiene) and other acute complications,
- (iv) Preventing or minimizing long-term microvascular complications through a meticulous control of hyperglycaemia, and

delay their progression, in case already present at the time of diagnosis,

- (v) Improving the outcome of gestational diabetes, both for the mother and the child,
- (vi) Facilitating normal growth, physical development and sexual maturation in case of childhood diabetes; and
- (vii) Ensuring a well-informed, active, participatory management by the patient as a member of the health care team.

Within the broad framework of defined objectives, which are shared commonly by all persons with diabetes, specific goals can be defined for type 1 and type 2 DM, in addition to goals which are shared commonly.

### Type 1 DM

The immediate therapeutic goal is to control polyuria, nocturia and polydypsia as soon as possible. Intermediate goal includes avoiding hypoglycaemia and ketonaemia. The long-term goals include normal growth and development including sexual maturation in case of onset in childhood or early adolescence, and the prevention of chronic microvascular complications specially retinopathy and nephropathy<sup>[13]</sup>. Although insulin has been in use for nearly 80 years, it is only during the last decade that evidence has become available confirming that a tight control of blood glucose in type 1 DM prevents the onset, and if already present, delays the progression of microvascular complications including retinopathy, nephropathy and neuropathy (Diabetes Control and Complications Trial, 1993)<sup>[14]</sup>. This landmark study, DCCT, was planned and organized by the National Institutes of Health, Washington D.C. It was a long-term, prospective, randomized, international multicenter clinical trial wherein 1441 subjects with type 1 DM were followed over a period of nine years. The patients were randomized at the onset into either, (i) an intensive treatment (IT) group (multiple insulin injections or subcutaneous insulin pumps; frequent home glucose monitoring with assured medical or paramedical support for any emergency situation; the treatment goal set at normalization of glycosylated haemoglobin), or (ii) a conventional treatment (CT) group receiving one or two insulin injections a day, with the aim to avoid symptoms of hypoglycaemia or hyperglycaemia. Data analysis overtime showed that the mean HbA1C achieved by the IT group was approximately <7.0% or as close to normal as possible. In contrast, the CT group achieved a mean HbA1C of approximately 9.0%.

Intensive glycaemic control reduced the adjusted mean risk of developing new retinopathy by 76% and delayed its significant progression by 54% in subjects who already had retinal involvement at the time of randomization. The intensively and conventionally treated groups started to diverge at approximately three years following the start of the study. Likewise, intensive glycaemic control reduced the mean adjusted risk of new microalbuminuria by 34% and reduced the progression of microalbuminuria if already present at the time of randomization, by 43%. Finally, similar effects were observed with regard to clinical appearance of neuropathy (reduced by 69%), or progression of neuropathy if already present (reduced by 57%). Thus, there is noncontroversial evidence that intensive glycaemic control can prevent the onset, and delay the progression, of microvascular complications in type 1 DM. It has been estimated that for every 1% rise in HbA1C above 8%, there is a 40-50% increase in the risk of developing retinopathy.

While setting the goal of treatment in an individual patient, it must, however, be remembered that hypoglycaemia is the most serious, and even life endangering complication of insulin treatment. In the DCCT, there was a threefold increase in the frequency of severe hypoglycaemia in the IT group. The risk of severe hypoglycaemia was inversely related to HbA1C levels. Taking into account the educational background of the patient, the likely level of patient compliance, the ready availability of family and medical support, and the socioeconomic status of the patient, the goals of management need to be individualized. For example, clinical practice guidelines from the Canadian Diabetes Association state that an optimal HbA1C is <7%, sub optimal 7.0 to 8.4%, and inadequate more than 8.4%. Taking cognizance of prevailing circumstances and available standards of health care delivery, the author recommended a target HbA1C of 7.5-8% in the South East Asian countries including India<sup>[15]</sup>. A similar recommendation is perhaps equally valid for GCC countries, including Kuwait. The evidence for such a recommendation is not robust, but certainly experiential.

### Type 2 DM

In contrast to type 1 DM, where the etiopathogenesis relates to an absolute lack of insulin, the type 2 DM associated with obesity is mainly due to a resistance to the action of insulin. In early stages, there is an attempt on the part of  $\beta$  cells to overcome this resistance by enhancing the

secretion of insulin, thereby maintaining normoglycaemia albeit with higher levels of circulating insulin. Subsequently, the compensatory mechanism by  $\beta$  cells may fail, especially in those with additional defect in the  $\beta$  cell, and hyperglycaemia results. Persistent hyperglycaemia, with basal fasting plasma glucose >150 mg/dl (8.3 mmol/L), further impairs  $\beta$  cell function due to 'glucose toxicity', with resultant decline in levels of circulating insulin<sup>[16]</sup>. Obviously, the rational approach to management of type 2 DM requires attempts at lowering of insulin resistance. This is easier to achieve at an early stage in a newly diagnosed case, or even at an earlier stage of the disease process (Impaired fasting glucose or impaired glucose tolerance). Attempts to further increase levels of circulating insulin (by administration of insulin or sulphonylureas) are unnecessary and may indeed be counterproductive.

### Nutritional Management

It must be considered axiomatic that the foundation of sound management of type 2 DM rests on nutritional counseling, and motivating the patient's compliance to the prescribed dietary plan. It is only over and above such a sound foundation that other nonpharmacological (physical exercise; stress reduction) or if required, pharmacological interventions are subsequently added. Admittedly, such an approach is time consuming for physicians and painstaking for the patients. Nevertheless, it ensures a better long-term prognostic outcome.

Approximately 80 to 90% of subjects with type 2 DM are obese; this is true for most parts of the world and more so for the GCC countries like Kuwait<sup>[17]</sup>. As obesity itself is a cause of insulin resistance, in obese type 2 DM the problem of insulin resistance is further amplified. The metabolic abnormalities associated with type 2 DM, including hyperglycaemia, hyperinsulinaemia, and dyslipidaemia, are all aggravated by obesity. Mortality rates in obese type 2 DM are higher than in the corresponding non-obese subjects.

Weight reduction, therefore, is a logical and rational approach. Weight loss reduces hyperglycaemia by its remedial effects on several of the pathophysiological defects discussed earlier. Weight loss reduces insulin resistance as demonstrated by euglycaemic-hyperinsulinaemic clamp technique, decreases hepatic glucose output, reduces hyperglycaemia, and in some patients may enhance insulin secretion<sup>[18]</sup>. Additional benefits of weight loss include a reduction in elevated triglyceride and low-density lipoprotein (LDL) cholesterol levels. Overtime, additional effects such as an increase in high-density lipoprotein

(HDL) cholesterol level may become manifest<sup>[19]</sup>. In those obese patients with dyslipidaemia at the time of diagnosis of type 2 DM, meticulous attention to the quantity and quality of fat content in the diet is warranted. With these measures, blood pressure may show a tendency towards normalization in those with borderline elevation. Collectively, all these effects assume significance in terms of risk reduction for coronary heart disease.

Weight loss can be achieved primarily by reducing energy intake (calorie restriction) and by increasing energy expenditure (physical exercise). Both constitute the key to a successful planning and management of type 2 DM. The United Kingdom Prospective Diabetes Study (UKPDS) is to-date the largest well designed study, which investigated the effect of weight loss in newly presenting type 2 DM patients<sup>[20]</sup>. The study was planned and initiated in 1977 primarily to establish whether intensive blood glucose control in such patients reduced the risk of micro- and macrovascular complications. A total of 3044 patients, with a mean fasting glucose of 218+67 mg/dl ( $12.1 \pm 3.7$  mmol/L), were inducted in the initial diet phase of the study. Caloric restriction was prescribed according to the patient's weight and activity level; the mean caloric intake was 1,361 kcal/d obtained from a diet of 50% carbohydrate, 30% fat and 20% protein. In 2597 patients (~85%), who dieted for three months, there was an average loss of 7% of bodyweight. Most significantly, this weight loss was associated with a decrease in fasting glucose from mean 205 to 146 mg/dl (11.4 mmol to 8.1 mmol/L). The patients with higher fasting glucose at the time of induction achieved the greatest decreases in blood glucose ( $r = .76$ ;  $p < .001$ ), although those with only modest elevation of blood glucose were more successful in achieving normoglycaemia (FPG <108 mg/dl or 6 mmol/L) at the end of three months of dietary management. It is noteworthy that in this multicentre study, those centers with better facilities of nutritional counseling and greater contact time with patients for education and motivation, achieved higher weight loss and better glycaemic responses. Indeed 482 patients (11%) achieved 11% body weight loss and became normoglycaemic (fasting glucose < 108 mg/dl or 6 mmol/L). Along with the outcome of other studies aimed at weight control in type 2 DM, there is thus strong evidence for prescribing caloric restriction as the first step in the management of type 2 DM, especially in subjects who are overweight and obese. While the UKPDS study provided evidence of a strong correlation between weight loss and

decrease in blood glucose over a period of three months, other studies, extended over longer time duration, also provide supportive evidence. A correlation between weight loss and HbA1C changes both at 6 months, and over a period of 12-16 months has been reported<sup>[21,22,23]</sup>. In summary, there is strong and unequivocal evidence that an average weight loss of 5-10% body weight enhances improvement in glycaemic control through one year, but weight loss of higher magnitude (~20% of body weight) may be associated with still greater benefit in terms of glycaemic control.

To ensure successful compliance, dietary prescription for diabetes must permit the patient to continue to consume, as far as possible, staple items of food without a major departure from the usual pattern of food consumption. As majority of patients with type 2 DM are obese, they must be motivated to attain realistic targets for weight reduction, even though it may take a longtime to reach the target. A sustained weight loss of 1kg/2 weeks (2 kg/month) is achievable in a majority of such patients by reducing the daily caloric intake to about 500 Kcal/day below that required for 24 hrs. The daily caloric requirements are calculated on the basis of desirable weight and the nature and type of activities (sedentary; moderately active, or heavy duty work). Generally, basal caloric requirements equal ideal weight (Kg)  $\times$  25. To this are added 10%, 20% or 30-40% calories in case of sedentary, moderately active, or more strenuous work, respectively. In addition, pregnant and lactating women need 300-500 extra calories per day. In contrast, in subjects over the age of 50-60 years, a 10-20% reduction in calorie intake is recommended. In general, a nutritionally balanced, weight reducing diet should not be less than 1200 Kcal for women and 1400 Kcal for men. Although very low-calorie diets (VLCD) of less than 500 Kcal per day are sometimes recommended<sup>[23]</sup>, such a dietary management should at best be left to experts, to be practiced under their strict supervision after admitting the patient to a metabolic ward.

It needs to be reiterated that 10-15% of type 2 patients may be of normal weight and a few may be underweight at the time of diagnosis. They have only mild to moderate insulin resistance, along with a low and delayed insulin response due to a secretory defect of the  $\beta$  cell resulting in deficient insulin secretion. The amount of circulating insulin is adequate to regulate lipolysis (and prevent ketogenesis), but is insufficient to control hyperglycaemia. In those subjects, there is no need to reduce caloric intake. Instead, nutritional

management includes optimization of the composition, form, content, and timing of food intake with due consideration to the type and timing of drug administration. These general principles equally apply to type 1 DM where inter-relationship between food intake, physical activity, and administration of insulin assumes critical significance. In a child with type 1 DM, assessment of growth pattern is an essential prerequisite for caloric and insulin prescription. Maintenance of a regular record of height and weight data on a standardized growth chart (relevant to age-matched controls in the same ethnic population) is as important as monitoring and maintaining blood glucose record. Any deviations need appropriate remedial action regarding calorie and insulin prescription.

Distribution of calories into dietary source needs careful consideration. During the last two decades, there has been a consistent shift towards liberalization of the amount of carbohydrate in the diabetic diet<sup>[24]</sup>. From the standard textbook recommendation that 40% of energy should be derived from carbohydrate sources in the diabetic diet, opinion has gradually changed to increase the carbohydrates to provide 50-60% of dietary energy, thus bringing it in line with the traditional patterns of oriental diets. The evolution of global thinking is reflected in a change in emphasis in the two WHO reports. The WHO Expert Committee on Diabetes Mellitus in 1979 (the author was its Vice-Chairman) recommended<sup>[25]</sup> that 'selective carbohydrate restriction is rarely necessary but rapidly absorbed sugars are best avoided', and emphasized that 'the use of low-carbohydrate diets is being questioned and re-examined'. In contrast, the WHO Study Group in 1985 (the author was its Co-Chairman) made more definitive recommendations and stated: 'dietary fat should be limited to approximately 30% of total daily energy intake ... protein should account for approximately 15-20% of the daily intake, and carbohydrate, rich in natural fibre, should constitute the remaining food energy'. Explicit in the above statement is the fact that carbohydrate may constitute 50-55% of total daily energy intake. More importantly, taking cognizance of the traditional dietary patterns in several Asian and some African countries, the WHO Study Group further emphasized that "the fat content of the normal diet in some populations may be as low or lower than that recommended above, and intake of unrefined carbohydrate may be as high or higher; diabetics in these populations can be well controlled with such diets"<sup>[26]</sup>.

While recommending high carbohydrate diets providing 50-55% of daily intake caloric requirement, two important considerations must

always be remembered: (i) it must be ensured that only complex carbohydrates are permitted; and (ii) there is a high fiber content (not <30gms/day) in the diet. Several studies have clearly shown that increasing complex dietary carbohydrates through the intake of foods also high in soluble fiber (e.g. legumes, lentils, chickpeas, barley, oat, whole-grain breads, green vegetables, some fruits etc.) not only improves glycaemia but may also benefit dyslipidaemia by reducing LDL-cholesterol. Green vegetables and fruits are a rich dietary source of antioxidants which are also made available through spices like turmeric, ginger, garlic, cumin and cloves, commonly used in oriental cooking<sup>[24]</sup>.

In pursuance of the WHO recommendations, dietary fat should be limited to approximately 30% of total daily energy intake. Of this, saturated fat intake should be less than one-third of the total fat, providing less than 10% of total energy intake. Substantial reduction of saturated fats will generally reduce dietary cholesterol daily intake to < 300 mg. The remaining fat calories are derived from unsaturated fatty acids, preferentially monounsaturated fatty acids (MUFA), which also constitute a significant part of the Mediterranean pattern of diet with beneficial effects in lowering the incidence of stroke, coronary heart disease and certain types of cancer<sup>[27]</sup>. While both MUFA and PUFA (Polyunsaturated fatty acids) lower LDL-cholesterol, MUFA has the added advantage that unlike PUFA, there is hardly any reduction in HDL-cholesterol with the intake of MUFA. Sesame, peanut, olive, and canola oils are a rich source of MUFA. Along with MUFA providing ~10-15% total energy intake, some long chain PUFA of n-3 series ( $\omega$  3 fatty acids), derived largely from fish, may also be beneficial as they prolong platelet aggregation and bleeding time by decreasing production of thromboxane A<sub>2</sub>, thereby reducing the risk of thrombosis<sup>[28,29]</sup>. Furthermore, dietary fish oil may affect basal fat oxidation in healthy adults<sup>[30]</sup>. Although supplementation with eicosapentaenoic acid and docosahexaenoic acid has been recommended by ardent advocates of long chain  $\omega$  3 fatty acids, it is equally beneficial, safer and more appropriate in the context of Kuwait and GCC countries to increase fish consumption by replacing 3-4 meals a week containing red meat (lamb, bacon) with meals containing non-fried (grilled, steamed or baked) fish.

It needs to be reiterated that most of the benefits of nutritional management remain theoretical if the patient is unable or unwilling to meticulously follow and adhere to the prescribed diet plan.

Compliance can be ensured only if the specific dietary intervention including dietary menu and meal planning for each patient is individualized, taking into consideration type of diabetes, current nutritional status, presence and absence of complications or co-morbidity, as well as cultural, religious, ethnic and socioeconomic aspects of the patient<sup>[24]</sup>. This is best achieved through a close interaction between the physician and dietician, each reinforcing the other and ensuring appropriate behavioral modifications and long-term compliance.

### Physical Exercise

The combination of diet therapy with restricted energy intake, and physical exercise with increase in energy expenditure, is essentially complimentary. There is complete agreement among international diabetologists that diet in combination with exercise must constitute the first line of therapy, prior to the consideration of any pharmacological intervention in obese type 2 DM.

Health benefits of physical exercise are well documented. Physical exercise, in combination with caloric restriction, facilitates weight loss in obese type 2 DM. Even prior to achieving significant weight loss, acute exercise improves insulin sensitivity over short term in these subjects; long-term aerobic exercise maintains enhanced insulin sensitivity over an extended period of time<sup>[31]</sup>. The metabolic effects of exercise include increase in glucose uptake by muscle, due to an enhanced transmembrane increase in glucose transport related to an increase in the number, activity and translocation of glucose transporters and an increase in glycogen synthase activity<sup>[32]</sup>. Additional metabolic effects include an increase in non-oxidative glucose disposal and an improvement in lipid profile by increasing HDL-cholesterol and decreasing LDL-cholesterol. Long-term effects on lipid metabolism include a possible redistribution of body fat due to a preferential reduction in central (visceral) adiposity. Following moderate aerobic exercise over a period of six months, loss of fat from visceral fat depots was demonstrable by whole body magnetic resonance imaging (MRI) even when there was no significant change in body weight, BMI, and waist-to-hip ratio<sup>[33]</sup>. These effects are more easily demonstrable when diet and exercise are combined. Additional beneficial effects include improved fibrinolysis, a reduction in blood pressure, and a more efficient myocardial performance. Collectively, these effects may lead to a significant risk reduction for cardiovascular co-morbidity<sup>[34]</sup>.

Unlike in subjects with type 2 DM, where exercise therapy can be prescribed after ensuring physical fitness and absence of significant coronary heart disease, severe hypertension, or microvascular complications including proliferative retinopathy or advanced nephropathy, such a course of management in type 1 DM needs, in addition, a most judicious evaluation of the degree and state of metabolic control. In the absence of optimal glycaemic control, patients with type 1 DM may suffer acute metabolic decompensation during or following a bout of physical exercise<sup>[35]</sup>. The main reason for such acute metabolic decompensation resulting in ketosis, is the lack of critical amount of circulating insulin, which is essential to inhibit the production of ketones in the liver. In the presence of insulin deficiency, and with an increase in the level of counter-regulatory hormones such as glucagon and catecholamines during exercise, ketogenesis is exacerbated. Thus, a fine adjustment of the dose, type and timing of exogenously administered insulin is essential not only to avoid hyperglycaemia and ketoacidosis but also to prevent exercise induced hypoglycaemia due to over-insulinization. Nevertheless, with proper education, guidance, and supervision, a prescribed programme of exercise can be initiated and continued safely and successfully in such patients.

As for any drug therapy, prescribing physical exercise for any patient requires full understanding and knowledge of its relative and absolute contraindications, the type, intensity, duration, and frequency of exercise regimen being prescribed, the risk of possible adverse effects, and the likelihood of any interactions with insulin or any other drug, which the patient may be taking. In general, after ensuring absence of any contraindications, a formal exercise testing may be undertaken. Such a procedure must include a pulse and blood pressure response, as well as ECG monitoring if clinically indicated, a record of post-exercise orthostatic blood pressure, post-exercise blood glucose concentration, and urinary protein excretion. Following a careful evaluation of data, recommendations regarding type, intensity, duration, and frequency of exercise regimen can be rationally prescribed. In general, aerobic activities including brisk walking, cycling, and running are recommended. Resistance exercise can be subsequently combined with aerobic activities. Most exercise programs start at 40-50% of maximal aerobic capacity, generally derived from maximal pulse rate. As a rough approximation, the patient's maximal pulse rate

is estimated by subtracting his/her age from 220 (e.g. Age 60: max. pulse rate= 220-60 i.e. 160). Starting at 50% of the maximal pulse rate, progress is monitored and gradual increments are allowed over 4-8 weeks to reach target heart rate at about 60-70% of the aerobic work capacity (in the above example the target pulse rate at 70% will be 112/mt)<sup>[12]</sup>. As improved glucose disposal is a function of the intensity and duration of exercise (i.e. total work performed), longer sessions of moderate intensity are equivalent to shorter sessions of high intensity. It must be remembered, however, that exercise should be performed at least every other day to maximize its glucose lowering effect, as there is an add-on of the residual effect of each bout of exercise. The timing of exercise must take cognizance of the convenience of the patient, working hours, the time of food intake, and the timing of intake of drugs, especially the time of administration and type of insulin therapy.

As in the case of diet therapy, compliance with the exercise regimen can be enhanced with intensive behavior modification, reinforced by support by the family, especially the spouse.

### Prevention of Long-term Complications

The principal long-term complications of Type 1 and Type 2 include micro- and macroangiopathy, both accounting for a significant increase in the morbidity and mortality of diabetes mellitus. Along with the efforts aimed at normalization of weight, rational caloric intake, and optimization of physical activity, the life-style modifications must include cessation of smoking.

### Smoking and Diabetes

In addition to the possibility that smoking may be associated with the subsequent development of diabetes<sup>[36,37]</sup>, there is evidence to suggest that insulin resistance was significantly increased among those type 2 DM subjects who smoked<sup>[38]</sup>. Smoking also appears to be associated with android obesity (visceral adiposity) which may be a marker of insulin resistance and clinical diabetes<sup>[39]</sup>. While these observations are at best suggestive, they do provide appropriate context for considering the role of smoking in the causation and progression of vascular complications of diabetes mellitus.

The relationship of cigarette smoking with cardiovascular morbidity and premature mortality in non-diabetic subjects is well established. There is strong evidence to support the role of smoking as a risk factor for excess morbidity and mortality due to cardiovascular disease in both type 1 and type 2 DM. Cigarette smoking was observed as a significant risk factor

for death in subjects with type 2 DM in the Multiple Risk Factor Intervention Trials (MRFIT)<sup>[40]</sup> as well as in the Finnish and the Paris Perspective Studies<sup>[41]</sup>. In addition to excess mortality, smoking in type 2 DM also increases the incidence of coronary heart disease as well as stroke<sup>[42,43]</sup>.

What is true for macrovascular disease is equally applicable to microangiopathy. Evidence is available from several studies regarding the relationship of smoking with the development and progression of nephropathy both in type 1 and type 2 diabetes mellitus<sup>[44,45]</sup>. Smoking is also a recognized risk factor for the development and progression of neuropathy<sup>[39]</sup>. In contrast, the relationship with retinopathy, remains somewhat speculative although there is suggestive evidence that smoking reduces retinal blood flow and therefore may aggravate the hypoxic environment of diabetic retina<sup>[46]</sup>.

Thus, there is enough evidence of adverse effects of smoking on physical and mental health in general, and in its contribution to long-term complications of diabetes in particular. Undoubtedly, therefore, smoking cessation is one of the few cost-effective and safe interventions that can be strongly recommended for all patients with diabetes, and rigorously reinforced at all encounters between such patients and any member of the diabetes health care delivery team. This therapeutic goal is particularly relevant in the context of Kuwait and other GCC countries, where an alarming rise both in the prevalence of smoking<sup>[47]</sup> as well as of type 2 DM<sup>[48]</sup> is being witnessed in the recent years.

### Tight Glucose Control and Complications

The evidence for significant reduction in microvascular complications because of intensive insulin therapy in type 1 DM has already been highlighted (DCCT). A mention has also been made of UKPDS in type 2 DM and the effects of a three-month dietary regimen in terms of blood glucose control. To pursue the main objective of the UKPDS regarding the relationship, if any, between tight glucose control and micro- and macrovascular complications, following a three month dietary run-in, 3867 patients were considered eligible for random assignment to either intensive treatment (IT) group (2729 patients), or to conventional treatment (CT) group (1138 patients). The therapeutic goal in IT group was to achieve and maintain fasting plasma glucose (FPG) <6 mmol/L. The aim in CT group was the best achievable FPG with diet alone: drugs were added only if there were symptoms of hyperglycaemia or if the FPG was greater than 15

mmol/L. The median follow-up for endpoint analyses was 10.0 years (7.7 - 12.4 years)<sup>[49]</sup>.

There was a median 0.9% difference in HbA1C between the intensive (7.0%; range 6.2 - 8.2%) and conventional (7.9%; range 6.9 - 8.8%) groups over 10 years indicating a mean HbA1C reduction of 11%. The UKPDS data unequivocally demonstrated that such a lowering of HbA1C in IT group, over the first 10 years after diagnosis of type 2 DM, reduced the risk by 12% for any diabetes related endpoint as defined in the study (sudden death; death from hyperglycaemia or hypoglycaemia; fatal or non-fatal myocardial infarction; angina; heart failure; stroke; renal failure; amputation of at least one digit; vitreous hemorrhage, retinopathy requiring photocoagulation; blindness in one eye or cataract extraction). Most of the risk reduction for any diabetes-related endpoint was due to a 25% risk reduction in microvascular endpoints, which in turn was mainly due to fewer patients requiring photocoagulation<sup>[49]</sup>.

As in the DCCT, the proportion of patients with one or more major, or any, hypoglycaemic episode in a year was significantly higher in the IT group as compared to the CT group. Within the IT group the number of major hypoglycaemic episodes was higher in patients on insulin (2.3%) as compared to those on chlorpropamide (0.4%) or glibenclamide (0.6%). Weight gain was significantly higher in the IT group than in the conventional group. Patients receiving insulin gained most in weight (mean 4.0 kg). None of the individual drugs (insulin, sulphonylureas) had an adverse effect on cardiovascular outcomes. On the contrary, there was a trend, not reaching a level of statistical significance, indicating a reduction in diabetes-related mortality or myocardial infarction. The investigators plan to carry out post-study monitoring for a further five years, in order to establish whether the improved glucose control will substantially decrease the risk of fatal and non-fatal myocardial infarction during the extended period of follow-up.

Although tight glucose control did not significantly reduce diabetes-related mortality or incidence of myocardial infarction, it is well recognized that hyperglycaemia, in association with hypertension, dyslipidaemia, central adiposity and smoking, does contribute to a progressive increase in the incidence of macrovascular disease. Attempting to achieve and maintain good glucose control is therefore, therapeutically rational.

## Control of Hypertension

Hypertension in Diabetes Study (HDS) was an embedded study within the UKPDS. This study, which started in 1987 and included 1148 patients, randomly allocated hypertensive patients to a tight blood pressure control treatment (758 patients). The aim for this group was to achieve and maintain a blood pressure of 150/85 mm Hg or lower with either an ACE inhibitor captopril (400 patients) or a  $\beta$ -blocker atenolol (358 patients). The remaining patients were allocated to a less tight blood pressure control treatment (390 patients) that aimed for a blood pressure of 180/105 mm Hg or lower but avoided the use of captopril or atenolol. Over a follow-up mean period of 8.4 years, mean blood pressure in tight control group was 144/82 mm Hg as against 154/87 mm Hg in less tight control group. In the tight control group, there was a 24% reduction in diabetes-related endpoints; a 32% reduction in deaths related to diabetes mellitus; a 44% reduction in strokes; and a 37% reduction in microvascular endpoints. Reduction in all cause mortality did not reach a level of significance<sup>[50]</sup>.

To determine whether tight control of blood pressure with either captopril or atenolol has a specific advantage or disadvantage in preventing the macro- or microvascular complications of type 2 DM, data were further analyzed. Captopril and atenolol were equally effective in reducing blood pressure in the two groups to a mean of 144/83 and 143/81 mm Hg, respectively. There was also an equal effectiveness in reducing the risk of macrovascular or microvascular endpoints. There was no evidence that either drug has any specific beneficial or deleterious effect, suggesting that blood pressure control in itself may be more important than the mode of treatment employed<sup>[51]</sup>.

The data from the HOPE (Heart Outcomes Prevention Evaluation) study and MICRO-HOPE substudy<sup>[52]</sup> where an ACE inhibitor, ramipril, was used in a dose of 10 mg/day in a group of 1808 subjects with diabetes mellitus, aged 55 years or older. These subjects were randomly assigned out of a group of 3577 subjects with diabetes, who had a previous cardiovascular event or at least one other cardiovascular risk factor but with no clinical proteinuria or heart failure. The treatment group was compared with a placebo group of 1769 subjects, randomly allocated. There was no significant difference in the systolic (mean 141.7 in the treatment and 142.3 mm Hg in the placebo group) or the diastolic blood pressure (80 mm Hg vs. 79.3 mm Hg) during the study of baseline characteristics of participants. The combined

primary outcome was myocardial infarction, stroke, or cardiovascular death. Ramipril lowered the risk of combined primary outcome by 25%, myocardial infarction by 22%, stroke by 33%, and cardiovascular death by 37%. The investigators conclude that the cardiovascular benefit was greater than that attributable to the minimal decrease of blood pressure observed in the study.

In contrast to the UKPDS data discussed previously, the beneficial effects were attributable to the administration of ramipril, and not to the minimal reduction in blood pressure in the treated group. Furthermore, the demonstrable benefit was apparent irrespective of whether participants had a history of cardiovascular events, hypertension or microalbuminuria, or were taking insulin or oral hypoglycaemic agents, or had type 1 or type 2 DM. These results, therefore, point to the possibility of a protective effect of ACE inhibitors on the arterial wall<sup>[52]</sup>. Supportive evidence is provided by the results of recent studies, which demonstrate a distinct advantage of an ACE inhibitor against a calcium channel blocker<sup>[53]</sup> as well as a  $\beta$ -blocker-diuretic regimen<sup>[54]</sup>. The latter study, which is a subanalysis of the Captopril Prevention Project (CAPPP), has provided evidence for a significant reduction in fatal and nonfatal myocardial infarction, stroke as well as other cardiovascular deaths in a randomly assigned group of 309 subjects with type 2 DM treated with captopril for an average of 6.1 years, as compared to a group of 263 subjects with similar baseline characteristics assigned to a conventional treatment regimen with diuretics and/or a  $\beta$ -blocker<sup>[54]</sup>. These results support those of HOPE and MICRO-HOPE studies, which showed that subjects with multiple risk factors are likely to benefit from therapeutic intervention with ACE inhibitors for reasons other than a minimal reduction in blood pressure. Some of these reasons may include: (i) improvement of whole-body glucose uptake with captopril<sup>[55]</sup>; (ii) improvement of endothelial dysfunction<sup>[56]</sup>; (iii) reduced sympathetic activity<sup>[57]</sup>; bradykinine accumulation resulting in the enhanced production of prostaglandin E<sub>2</sub> and nitric oxide<sup>[58]</sup> and (v) improvement in coronary reserve<sup>[59]</sup>. Based on these data, studies are now in progress using angiotensine II (Ang II) receptor blockers (ARB<sub>s</sub>) and initial results indicate a promising trend<sup>[60]</sup>.

In summary, the benefits of tight control of blood pressure in type 2 DM are firmly established, and the use of ACE inhibitors is presently favoured. Irrespective of the type of drug therapy used, the role of dietary sodium restriction (< 3 gm/d) along with other dietary interventions and

life style changes, as also indicated for type 2 DM, play a significant role in the management of hypertension<sup>[61]</sup>.

### Management of Dyslipidaemia

Dyslipidaemia is a major risk cardiovascular factor. Both type 1 and type 2 DM have abnormalities of plasma lipids and lipoproteins. However, the pattern of these abnormalities in type 1 DM<sup>[62]</sup> differs significantly from that observed in type 2 DM<sup>[63]</sup>. Furthermore, dyslipidaemia is commonly present in type 2 DM, especially in patients with central adiposity and hypertension. In contrast, lipid abnormalities are much less common in type 1 DM, and are generally present in patients with poor metabolic control.

It is in the context of the cardiovascular risk in type 2 DM that the recognition and management of dyslipidaemia constitutes a significant component of the comprehensive management strategy. Several clinical trials during the last decade have provided evidence of risk reduction following appropriate management of dyslipidaemia: 1% decrease in serum total cholesterol may reduce coronary heart disease mortality by 2%, while a similar reduction in mortality may follow a 1% increase in HDL cholesterol. Hypertriglyceridaemia may also be an independent risk factor, especially in type 2 DM in South East Asian and other neighboring countries, and its management may bring additional risk reduction in morbidity and mortality due to coronary heart disease. As a general principle, the target should be a serum LDL cholesterol < 130 mg/dl or 2.6 mmol/L (optimal: in the presence of CHD) and 100-129 mg/dl or 2.6-3.4 mmol/L (near optimal: acceptable in the absence of CHD or risk factors for CHD); triglycerides < 150 mg/dl or 1.7 mmol/L and HDL cholesterol > 45 mg/dl (> 1.7 mmol/L) in the male and > 55 mg/dl (> 1.46 mmol/L) in the female patient. Any significant deviation warrants institution of appropriate management. However, in the presence of a pre-existing cardiovascular disease in a patient with type 2 DM, management should be initiated at a level of LDL cholesterol > 100 mg/dl or 2.6 mmol/L. The initial management is through life style modifications and appropriate nutritional intervention aimed to achieve weight loss by restricting energy intake, and by dietary modification with total dietary fat providing < 30% of prescribed energy intake through low amounts of saturated fats (<7-10%), moderate amounts of PUFA mainly of  $\omega$  3 series, and higher amounts of MUFA. In case of failure to achieve defined targets of serum lipids after meticulously following such an approach for 6 - 8 weeks and optimizing metabolic control of diabetes, specific pharmacological intervention with lipid-lowering agents may be instituted. The drugs

of first choice for LDL reduction in type 2 DM are HMG-CoA reductase inhibitors (statins), while for elevated triglyceride levels, fibric acids are preferred<sup>[64]</sup>. A combined approach may sometimes be of greater benefit<sup>[65]</sup>.

## CONCLUSION

A comprehensive goal of management, irrespective of the type of diabetes mellitus, must include: absence of symptoms due to hyperglycaemia or hypoglycaemia; meticulous attention to the achievement of normoglycaemia (target: fasting plasma glucose < 110 mg/dl or 6.2 mmol/L and postprandial - 2 hrs - plasma glucose < 140 mg/dl or 7.8 mmol/L; HbA<sub>1c</sub> < 7.0%); prevention of microvascular complications; maintenance of normal blood pressure and correction of hypertension, if present (target: systolic <130 mm Hg, diastolic: <85 mm Hg); maintenance of normal lipid profile, and correction of dyslipidaemia, if present (target: LDL cholesterol <100 mg/dl or 2.6 mmol/L, in the presence of CHD and <130 mg/dl or 3.4 mmol/L) in the absence of CHD or pre-disposing risk factor(s), TG <150 mg/dl or 1.7 mmol/L and HDL cholesterol >45 mg/dl (1.18 mmol/L) in the male and >55 mg/dl (1.46 mmol/L) in the female); attainment and maintenance of ideal body weight (target : < 110%) through prescribed energy intake; a progressive increase in physical activity, and cessation of smoking. In the ultimate analysis, the objective is to optimize motivation, in a well informed and empowered patient who is enthusiastically, effectively and efficiently participating in a diabetes management program aimed at not only reducing disability-adjusted life years (DALY)<sup>[66]</sup>, but also for enhancing quality-adjusted life years (QALY), and thus, achieving and enjoying a socially well adapted and economically productive life.

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