Review Article

MANAGEMENT OF TYPE 2 DIABETES (NIDDM)

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During the past decade diabetes mellitus (DM), particularly type 2 diabetes has emerged as an important clinical and health problem. Several benefits to patients with diabetes are expected as a result of their treatment with improved patient education, availability of expertise, and sustained follow up and screening for the complications of diabetes. Several new groups of drugs have become available after initiation of historical UKPDS trial, thereby providing more flexibility in treatment and making the goal of glycemic control achievable. This article will outline current trends in the management of type 2 diabetes mellitus. However, managing diabetes is a difficult and time consuming task. It is common, serious, treatable and undertreated disease.

How common is it?

The epidemic is here in developing and newly industrialised nations. Between 1995 and 2025 there will be a 35% increase in the worldwide prevalence of diabetes. India will have second highest increase in prevalence of 59%. The greatest increase will be seen in India, 195% that is 19-57 million [1]. At both points India will have the largest number of diabetics. More important is that from present position of harbouring one tenth of total world diabetics, India will harbour one fifth of all diabetics in the world by 2025. More so, prevalence of diabetes is likely to increase with time in India, making the estimates even worse.

How serious is it?

Hyperglycaemia is the soil upon which CHD, CAD grow. Diabetic patients are at high risk of CAD progression, cardiovascular events and associated mortality. Females with diabetes had about four times and males 2½ times risk of developing CHD than nondiabetics [2]. Here is the setting of a CHD epidemic and disaster that will follow the epidemic of diabetes. The

ratio of the mortality rates for diabetic versus nondiabetic were highest for those aged 25-44 years with a value of 4.9 for men and 3.2 for women. The ratio declined with age but remained about 1½ times higher at the age group 65-74 years [3].

Microvascular complications add to morbidity related with diabetes duration and glycemic control. The 20 year prevalence of any type of retinopathy is about 80% in diabetics with poor glycemic control and 20% among those with acceptable diabetic control. The respective rates of proliferative retinopathy are 40% and 5%. The risk of clinically significant macular edema is 10-15% after diabetes has been present for 15-20 years [4]. Those diabetics who had acceptable glycemic control about 80% remain free of microalbuminuria. However, in a patient with poor glycemic control, genetic predisposition determines the progression of diabetic nephropathy with time [5].

Is it treatable?

First and foremost aim is to prevent, delay, arrest or reverse diabetic complications and to improve quality and if possible, quantity of life. Kumamoto study [6], UKPDS Study [7] and DIGAMI study [8], have proved beyond doubt that various complications of diabetes can be prevented, arrested and delayed in type-2 diabetics. It is also possible to improve quality and quantity of life. Kumamoto study though had a small number of patients was just parallel in result with DCCT in IDDM patients. It has showed that intensified glycemic control by multiple insulin injection can delay the onset and the progression of diabetic microvascular complications. In UKPDS Study [7] patients assigned to intensive treatment had a 25% risk reduction in microvascular end points compared with conventional treatment. There was significant reduction in retinal photocoagulation and cataract extraction but had no effect on vitreous haemorrhage. There were

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significantly less number of patients with microalbuminuria, proteinuria and decreased biothesiometer perception in intensive group at the end of nine years. There was 16% reduction in risk for acute MI in UKPDS, though not reaching statistical significance. This may highlight the fact that probably glycemic control was not tight enough for macrovascular disease either, or glycemic threshold for progression is not known. In DIGAMI Study [8], patients with AMI with BG>200 mg/dl were stratified in the control group and a group that received intravenous insulin infusion for first 24 hours and subsequently treated with subcutaneous insulin. Total mortality was 23% lower at 3 months and 29% at one year in insulin treated group.

Stages in management

Considering natural history of type-II diabetes, three stages can be defined in the management of diabetes with specific opportunity and tactics. These may be called public health care, primary physician care and specialist care. Public health care involves creating awareness about diabetes, conducting screening program for early diagnosis, and modifying life style of society to prevent or delay the onset of diabetes. Primary physician care till standard treatment protocols, fails to maintain acceptable glycemic control or intervention required for diabetes related complications. Specialised care to provide comprehensive care for complications and associated risk factors to decrease morbidity and mortality.

Screening of Diabetes [9]

To increase the cost effectiveness of testing undiagnosed diabetics, screening should be considered in high risk population eg. age >45 years, family history of diabetes (parent or sibling), obesity, hypertension, dyslipidemia or previous history of impaired glucose tolerance (IGT) or gestational diabetes mellitus (GDM). The screening test of choice is fasting plasma glucose (FPG). Fasting is defined as no consumption of food or beverages other than water for at least eight hours before testing. Here it should be noted that glucometer based capillary blood glucose is not recommended for screening. Screening of high-risk individual should be considered at 3 yearly intervals. The rationale for this interval is that there is little likelihood of an individual developing any complications of diabetes to a significant degree within 3 years of a negative screening test result. American Diabetes Association (ADA) has recommended three criteria for diagnosis of DM-FPG $\geq$ 126, 2hPG $\geq$ 200, & RPG $\geq$ 200 if symptoms are present. But it should be

confirmed on a subsequent day by measurement of FPG or 2hPG again.

What treatment modalities are available?

There are four treatment modalities available, namely Medical Nutrition Therapy (MNT), exercise, oral drugs and insulin. Fifth modality though practised by almost every diabetic in India i.e. Ayurvedic, Homeopathic, advice of relatives and friends etc, hardly has thorough scientific basis. Moreover, diabetes is a progressive and life long disease hence any transitory experimental treatment should be discouraged.

Management of type 2 diabetes should follow staged and stepped approach beginning with life style modifications, oral hypoglycemic agents (OHA) should then be added singly or in combination [10]. Coalition therapy with OHA and insulin [11] and pure insulin therapy [12] should be given last to achieve appropriate glycemic control (Table-1).

TABLE 1
Metabolic control (ADA recommendation)

Biochemical index	Good	Acceptable	Poor
Fasting/preprandial plasma glucose	80-120	$\leq$ 140	> 140
Postprandial plasma glucose	80-160	< 180	> 180
Glycosylated Hb	< 8.5%	8.5 - 9.5%	> 9.5%

Life style modifications

MNT and exercise are essential components of any treatment modality for diabetes mellitus. Without going into details of MNT, it is sufficient to stress that ethnicity of diet should be maintained rather than giving ready-made prescription. Diet should be modified with lowering caloric value, encouraging complex carbohydrate and fibres, and avoiding refined and free sugar. Daily brisk walk for half an hour should be encouraged in all after assessing underlying cardiac status.

Single Oral Agents

These consist of five groups of drugs - sulphonylurea, metformin, acarbose, thiazolidinediones and repaglinide.

Sulphonylureas : Sulphonylureas bind to an area of the beta cell plasma membrane associated with ATP dependent K⁺ channels referred to as sulphonylurea receptor (SUR). Closure of K⁺ channel depolarises the membrane and opens voltage dependent Ca⁺² channel leading to exocytosis of insulin. The sulphonylureas differ in their potency per milligram, extent of hepatic metabolism, hypoglycemic activity, renal excretion, peak and duration of action, side effects and cost (Ta-

ble-2). Each pharmaceutical company attempts to differentiate its sulphonylurea to increase market share but the differences are subtle and there is little evidence that they have major impact on success of therapy. Sulphonylurea therapy should be started with lowest recommended dose except in very symptomatic and hyperglycaemic patient. Glibenclamide, glipizide and gliclazide are better absorbed and more effective if given 30 minutes before meals. Common side effects include hypoglycaemia and weight gain.

TABLE 2

Drug	Daily dose	Duration	Renal excretion	Cost (Rs)
Glibenclamide	2.5 - 20	16 - 24	50	0.50
Glipizide	2.5 - 20	12 - 16	85	0.50
Gliclazide	80 - 320	10 - 20	70	3.00 (6.50)
Glimepiride	1 - 8	24	60	11.00

Two newer sulphonylureas require special mention in view of tall claims made by the drug companies. Gliclazide molecule has azabicyclo-octyl ring attached which is said to impart beneficial effects on platelet function and vascular phenomenon related to atherosclerosis in patients with diabetes, however, better and clinically established effect can be obtained by half a tablet of aspirin with much lower cost. Glimepiride [13], new in Indian market, binds to a 65-kDa protein on the beta cell rather than to the 140-kDa protein targeted by other sulphonylureas. There is less interaction of glimepiride than glibenclamide with cardiovascular ATP dependent K^+ channel, rendering it more pancreatic specific than other sulphonylureas. Glimepiride results in lower insulin and C-peptide levels with similar glucose control, supposedly as a result of greater insulin-mimetic effect in peripheral tissue. Gastro intestinal absorption is complete without interference from concurrent meals and drug accumulation is not seen with decreased renal function. However, importance of these differences in general clinical use needs to be determined.

Metformin (Rs.0.65 per 500 mg tab): Metformin reduces appetite and glucose transport across intestinal mucosa. Its main effect is to reduce endogenous hepatic glucose output, which is contributed by increased hepatic insulin sensitivity and inhibition of gluconeogenesis. It also increases peripheral insulin mediated glucose uptake and decreases fatty acid oxidation [14]. There is also antiatherogenic effect, which appears to be independent of the changes in glycaemia; it includes improved lipid profile with decrease in triglyceride 10-20%, total & LDL cholesterol by 5-

10%, and increase in HDL cholesterol, increased fibrinolytic activity (reduces PAI-1), decreased platelet aggregation, increased erythrocyte deformability, decreased arterial wall smooth muscle cell growth and decrease in insulin resistance [15]. Clinical evidence of this is 39% lower risk ($p=0.01$) of myocardial infarction (MI) in metformin treated group in UKPDS [16]. It is preferred initial therapy in obese type-2 diabetics, however, it is also found equally effective in non-obese diabetics. Metformin is best started with 500 mg twice or thrice daily with meal, gradually increased to 2-3 gm. Gastrointestinal side effects like nausea, metallic taste and increased bowel frequency are common. Metformin therapy should be avoided in patients with renal, hepatic and cardiac impairment due to increased risk of lactic acidosis. Almost all brands cost 65 paise per 500-mg tablet.

Acarbose (Rs 5.50 per 50 mg tab) : It competitively binds to the carbohydrate binding region of alpha-glucosidase enzymes i.e. sucrase, maltase, dextrinase, and glucomylase, and interferes with digestion of oligosaccharides. Undigested carbohydrate spills into large intestine where bacteria metabolise carbohydrate to short chain fatty acid leading to flatulence, diarrhoea and abdominal discomfort. An approximate mean decrease in FPG of 20 mg/dl, PPPG of 50 mg/dl, and HbA1c of 0.86% is to be expected with maximum dose of 100 mg three times during meals. It is most effective with high carbohydrate diet. It should be titrated as per Table-3 to avoid side effects. Acarbose also causes significant fall in blood ammonia, increase in gut peristalsis, leading to improvement in clinical signs of encephalopathy when administered to patients with type 2 diabetes and cirrhosis [15].

TABLE 3

Acarbose dosing schedule [10]

Week	BF	Lunch	Dinner
1	—	—	1/2 tab
2	1/2 tab	—	1/2 tab
3-4	1/2 tab	1/2 tab	1/2 tab
5	1/2 tab	1/2 tab	1 tab
6	1 tab	1/2 tab	1 tab
7-8	1 tab	1 tab	1 tab
9	1 tab	1 tab	2 tab
10	2 tab	1 tab	2 tab
11-12	2 tab	2 tab	2 tab

Thiazolidinedione (TZD) [17]: The TZD are a unique class of compounds that exert direct effect on the mechanism of insulin resistance and result in improved insulin action and reduced hyperinsulinemia.

TZD binds to PPAR- γ (peroxisome proliferator activator receptor) and regulates transcription of various molecules required for insulin action and lipid metabolism in adipocyte, skeletal muscle and liver. The biological potency of various TZDs is highly correlated with their binding to receptor. Rosiglitazone (RST) binds 10 fold more strongly than pioglitazone, which in turn binds 10-fold more strongly than triglitazone, paralleling the clinical doses of 2-8 mg, 30-50 mg, and 200-800 mg. TZDs also oppose the action of tumour necrosis factor- α , a potential mechanism in insulin resistance state. Troglitazone has been withdrawn from world market due to its hepatotoxicity. Presently pioglitazone and rosiglitazone are being used world over. RST is likely to be introduced in Indian market shortly. Maximum response with RST monotherapy is seen at 8 weeks, with fall in FPG of about 75 mg/dl almost equivalent to sulphonylureas. It also lowers free fatty acid, triglycerides, and increases HDL and LDL cholesterol. However, LDL particles become larger, more buoyant, and less prone to oxidative modification. Its beneficial effect on the development of atherosclerosis remains to be determined. RST is not metabolised by the hepatic cytochrome, hence in clinical studies abnormal liver chemistry appears about one-tenth the rate of troglitazone [18].

Repaglinide : (Rs3.50 per 0.5 mg tablet) Repaglinide a carbamoylmethyl benzoic acid derivative, is a non-sulphonylurea short acting insulin secretagogue. It stimulates insulin secretion by binding to ATP sensitive potassium channel on pancreatic beta cells, distinct from that of sulphonylurea. It is absorbed quickly (5-10 min), making it suitable for preprandial dosing. Maximum plasma levels are reached in 30-60 min, and action is terminated rapidly due to short half-life (1 hour), hence reduces the risk of postprandial hypoglycaemic events. It is mainly metabolised by liver (98%) and excreted via bile (90%), hence can be used effectively in patients with mild to moderate renal insufficiency. It is started in the dose of 0.5-2 mg preprandially. In view of short duration of action it can be given according to number of meals providing more flexibility, hence will be useful in diabetics with irregular food habits. Maximum clinical effect is evident within one week of repaglinide therapy [19].

Combination Oral Therapy

Initial successful treatment with single oral agent is likely to fall in 3-5 years, or desired glycemic control may not be achieved by single agent when initial FPG

is > 200 mg/dl, hence the obvious next step is to add a second agent. Above group of drugs have different mechanisms of action and therefore can be combined to obtain additive effect. Moderate doses of two agents may achieve equal glycemic effect with fewer side effects than full doses of either agent alone. Most widely used oral combination is sulphonylurea with metformin. There are fewer studies of sulphonylurea plus acarbose, metformin plus acarbose, and others [10]. However, lack of studies should not deter the physician to use combination of drugs with different mechanisms of action in a given patient to achieve glycemic control.

Coalition Therapy (OHA and Insulin)

During last two decades combination therapy with insulin and OHA has become popular. There are two aspects of coalition therapy [11]. One, additional insulin therapy, patient with unacceptable glycemic control with OHA can be prescribed additional night time insulin therapy. Another, adjunctive OHA therapy, patients uncontrolled with or requiring high doses of insulin monotherapy can be given OHA in the hope to achieve better glycemic control and decrease in the doses of insulin. Additional insulin therapy has more patient acceptance, improved glycemic control, rapid glycemic control, improved lipid profile, decreased insulin requirement, less weight gain and cost effectiveness [20-29].

Indication for Coalition

Sulphonylurea treatment undergoes secondary failure at the rate of 5-20% yearly. Consequently, treatment fails in 5-20 years. Hence patients on maximum doses of OHA therapy when not able to maintain glycemic control to the acceptable level for 3-6 months should be started on coalition therapy.

Coalition Regimes

Sulphonylurea and insulin therapy : It decreases fasting serum glucose by 50-80 mg/dl and glycosylated haemoglobin by 1-2% [20-24]. Glycemic control improves in patients who have the worst glycemic control except when fasting blood glucose level is more than 300 mg/dl and in patients with the greatest degree of obesity.

Metformin and Insulin Therapy : A recently conducted study compared metformin plus insulin with sulphonylurea plus insulin in obese and non-obese patients with type-2 diabetes [28]. In the non-obese group, metformin treatment gave similar glycemic control, but with lower insulin doses and with lower weight gain. In obese patients, glycemic control was

better and weight loss was more in metformin group.

Insulin Regimens

There has been no consensus about the form of insulin, and dose of insulin used. Various studies have definitely pointed towards beneficial effects of evening use of insulin. However, time and form of the insulin used varied in different studies.

Fixed Low Dose : Single night-time intermediate acting insulin e.g. lente insulin or NPH insulin, at the dose of 0.1-0.2U/kg subcutaneously at 10.00 PM. It can be increased by 2-5 units fortnightly to maintain fasting plasma glucose level [25]. If more than 30-36 units of insulin are necessary to obtain good glycemic control, consider stopping OHA treatment and continue on insulin monotherapy. Two studies have reported requirement of insulin about 20-30 units with this regime [21,23]

Maximum Tolerated Dose : Starting insulin in the dose of 10 units, increased fortnightly by 5-10 units till fasting blood glucose is controlled [22]. Insulin doses required with this regime ranges from 30-70 units.

Monitoring of blood glucose : Monitoring of blood glucose should be done fortnightly, fasting and predinner. Blood glucose measurement at 3.00 AM is indicated with symptoms suggestive of night time hypoglycaemia.

Failure of Coalition therapy : Failure of coalition therapy is indicated by uncontrolled predinner blood glucose level (>180 mg/dl) despite acceptable levels of fasting blood glucose.

Insulin Therapy

Insulin has a definite role in treatment of NIDDM as coalition therapy or monotherapy [12]. It can control hyperglycaemia in almost all cases when given in appropriate doses. There is a general trend in improvement of metabolic state with change towards normalization of blood glucose and lipid levels. It also increases sense of physical and psychological well being. Insulin therapy in NIDDM may be required regularly or intermittently (Table-4).

Insulin Regimes

Mixed Split Regime : On failure of coalition therapy a mixture of intermediate and short acting insulin can be given twice daily half an hour before breakfast and dinner. Usual starting dose is 0.5 unit/kg, divided as two-third of total dose in the morning and one-third in the evening. Each dose consists of two-third of intermediate acting insulin and one-third short acting insulin. Adjustment of doses is done as per blood glu-

TABLE 4

Indication of insulin therapy

Regular therapy	Intermittent therapy
1. Non obese NIDDM < 40 years	1. NIDDM with poor control
2. OHA failure	2. Infection
(i) Primary - 30%	3. Perioperatively
(ii) Secondary - 5-10% per year	4. Pregnancy
3. Allergy and intolerance to OHA	5. Acute medical emergencies
4. Renal and hepatic disease	6. Acute surgical emergencies
	7. Acute metabolic complications

cose monitoring performed premeal once a week. This regime is quite popular due to its simplicity and adequacy to achieve good glycemic control. It is ideally suited for patients with regular life style.

Multiple Subcutaneous Regime : This regime is superior to conventional regime as demonstrated by Kumamoto study [6]. Those who are motivated educated and lead erratic life style, glycemic control can be achieved by multiple subcutaneous injection of short acting insulin before meals and at night time intermediate acting insulin.

Control of Post Prandial Hyperglycemia

Postprandial hyperglycaemia may be associated with a significantly increased risk of adverse cardiovascular events, even in the presence of normal FBG levels. Many options for reducing postprandial hyperglycaemia are available [30] :-

1. Reduction of carbohydrate intake
2. Ingestion of complex carbohydrate, mixed meal and fibres
3. Alpha glucosidase inhibitors
4. Metformin
5. Thiazolidinediones
6. Glucagon like peptide -1
7. Insulin secretagogues-Repaglinide
8. Preprandial insulin-insulin analogue (Insulin Lispro)

Future prospects [31-33]

Diabetes mellitus is a complex, and heterogeneous disorder with a variety of pathophysiological processes resulting in alteration in several metabolic pathways eg. glucose overproduction because of enhanced glycogenolysis and gluconeogenesis and glucose under utilisation due to diminished insulin production and insulin ineffectiveness. With the benefit of strict blood glucose control, there was a surge in search for more effective and safer hypoglycaemic agents. With better understanding of the metabolic derangements in diabetes mellitus in recent years, it became possible to

develop agents that act at various stages of the altered hormone fuel homeostasis. Some of the agents which have been tried in human and animal experimental studies are as follows :

1. Inhibitors of Gluconeogenesis : Hydrazomopropionic acid
Acyl CoA derivatives
Pyruvate analogues
2. Inhibitors of glycogenolysis : Dichloacetate
3. Inhibitors of fatty acid oxidation : Acipimox, Clomoxir
4. Gut Lipase inhibitors : Orlistat
5. Alpha glucosidase inhibitors : Miglitol, Voglibose
6. Increase incretin effect : GLP-1 and related peptides
7. Short acting nonsulphonylurea insulin secretagogues : BTS 67582, A -4166
8. Insulin sensitisers : SDZ PGU 693, NN 2344,
NN622, Oxadiazolidinedione
analog YM440
9. Minerals : Vanadyl Sulphate,
Magnesium, Chromium
Picolinate
10. Prolongation of insulin action : Phosphotyrosine
phosphatase inhibitors IRTK Activators.
11. Enhancement of GLUT-4 translocation/expression

How much is undertreated ?

In a recently conducted cross sectional Diabcare-Asia-India study, which included 26 specialised diabetic centres across the country, involving 2269 patients, central laboratory HbA1c data was categorised according to ADA guidelines. The proportion of patients with HbA1c >1% above the upper limit of normal range (ULN) was 77%, and >2% above ULN was 50% for type-2 patients [34].

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