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Rising Prevalence of Diabetes in India and the Implications of ADA-EASD Consensus on the Management

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EPIDEMIOLOGY OF DIABETES IN INDIA

India has nearly 44 million diabetic subjects today, (Table 1) which is chiefly contributed by the urban population. The scenario is changing rapidly due to socio-economic transition occurring in the rural areas also. Availability of improved modes of transport, and less strenuous jobs as in the vicinity have resulted in decreased physical activities. Better economic conditions have produced changes in diet habits. The conditions are more favorable for expression of diabetes in the population, which already has a racial and genetic susceptibility for the disease. Recent epidemiological data show that the situations are similar throughout the country[1] (Table 2).

Prediabetic conditions like impaired glucose tolerance and impaired fasting glucose are also on the rise, indicating the possibility of further rise in the prevalence of diabetes. Metabolic syndrome, which is a constellation of cardiovascular risk factors, of which hyperglycemia and insulin resistance are components, is also widely prevalent[2].

The conversion to diabetes is enhanced by the low thresholds for the risk factors, such as age, body mass index and upper body adiposity. Indians have a genetic phenotype characterized by low body mass index, but with high upper body adiposity, high body fat percentage and high level of insulin resistance[3].

With a high genetic predisposition and the high susceptibility to the environmental insults, the Indian population faces a high-risk for diabetes and its associated complications. Early diagnosis of high-risk groups and appropriate intervention by lifestyle

Table 1: World population and South-East Asia at a glance

		World Population			*South East Asia*	
		2007	*2025*		*2007*	*2025*
Total	(billions)	6.6	7.9	(millions)	1336	1656
Adult population (age 20-79)	(billions)	4.1	5.2	(millions)	770	1083
World Diabetes and IGT (20-79 age group)						
Diabetes						
Regional Prevalence (%)					6.0	7.4
Comparative prevalence (%)		6.0	7.3		6.5	8.0
Number of people with diabetes (millions)		246	380		46.5	80.3
IGT						
Regional Prevalence (%)					5.9	6.5
Comparative prevalence (%)		7.5	8.0		6.0	6.7
Number of people with IGT (millions)		308	418		45.2	70.5

Diabetes Atlas, 3rd edition, 2006

Table 2: Studies on prevalence of diabetes in India

			Urban	*Rural*
1971	Tripathy et al	Cuttack (central)	1.2	
1972	Ahuja et al	New Delhi (North)	2.3	
1979	Gupta et al	Multicentre	3.0	1.3
1984	Murthy et al	Tenali **(South)**	4.7	
1986	Patel	Bhadran (West)	3.8	
1988	Ramachandran et al	Kudremukh **(South)**	5.0	
1989	Kodali et al	Gangavathi **(South)**		2.2
1989	Rao et al	Eluru **(South)**		1.6
1991	Ahuja et al	New Delhi (North)	6.7	
1992	Ramachandran et al	Madras **(South)**	8.2	2.4
1997	Ramachandran et al	Madras **(South)**	11.6	
2000	Ramankutty et al	Kerala (South)	12.4	2.5
2001	Ramachandran et al	National Urban(DESI)	12.1	
2001	SR Iyer et al	Dombivli	6.2	
2004	Sadikot et al	National	5.9 (4.3)	2.7
2006	Mohan et al	Chennai	14.3	
2006	Menon et al	Kerala Urban	19.5	

modification may offer a solution for the disease burden.

Prevalence of vascular complications is high in Indians. Our studies have shown that the economic burden of diabetes at personal and societal level escalates several fold when diabetic complications occur.

Availability of newer medications for lowering blood glucose, newer insulin, and better knowledge on the efficacy of life style modifications (LSM) have provided an increased number of choices, either used as a single or combination therapy in the management of diabetes.

The American Diabetes Association and the European Association for the Study of Diabetes consensus statement " Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy"[4].

Given below are the guidelines for therapy in type 2 diabetes.

GLYCEMIC GOALS OF THERAPY

Several systematic long-term prospective studies such as the Diabetes Control and Complications Trial (DCCT) and the Stockholm Diabetes Intervention Study in type 1 diabetes and the U.K. Prospective Diabetes Study (UKPDS) and Kumamoto Study in type 2 diabetes, have helped to establish the glycemic goals of therapy that result in improved long-term outcomes. All the studies support decreasing glycemia as an effective means of reducing long-term microvascular and neuropathic complications.

The most recent glycemic goal recommended by the American Diabetes Association, selected on the basis of practicality and the projected reduction in complications over time, is "in general" an A_{1C} level < 7%. For "the individual patient" the A_{1C} should be "as close to normal (< 6%) as possible without significant hypoglycemia. The most recent glycemic goal set by the European Union International Diabetes Federation is an A_{1C} level <6.5%.

This goal is not practical for some patients, and clinical judgment, based on the potential benefits and risks of a more intensified regimen needs to be applied. The risk of hypoglycemia need to be considered before intensifying therapeutic regimens.

MANAGEMENT OF HYPERGLYCEMIA IN TYPE 2 DIABETES

Metabolic management of type 2 diabetes is to achieve and maintain glycemic levels as close to the non-diabetic range as possible. Lifestyle interventions should be initiated concurrent with metformin therapy as the first step in treating newly diagnosed type 2 diabetic subjects in the absence of specific contraindications. Metformin treatment should be titrated to its maximally effective dose over 1-2 months.

If lifestyle intervention and maximal tolerated dose of metformin fail to achieve or sustain glycemic goals, another medication should be added within 2-3 months of the initiation of therapy. Choose among insulin, a sulfonylurea or a thiazolidinediones (TZD). If lifestyle, metformin and a second medication do not result in goal glycemia start or intensify insulin therapy with short – or – rapid – acting insulin given before selected meals to reduce postprandial glucose excursion. When prandial rapid – or very –rapid – acting insulin injections are started, insulin secretagogues (sulfonylurea or glinides) should be discontinued. Since they are not considered synergistic with administered insulin.

Insulin plus metformin and insulin plus a TZD are particularly effective means of lowering glycemia in patients requiring insulin. The increased risk of fluid retention with the latter combination must be considered. Both TZD's and metformin effectively increase sensitivity to insulin, they have different target organs and have been shown to have modest additive effects. Although three oral agents can be used, initiation and intensification of insulin therapy is preferred based on effectiveness and expense. Check A_{1C} every 3 months until < 7% and then at least every 6 months. The goal must be individualized and modified depending on the age and the clinical profile.

PRINCIPLES IN SELECTING ANTIHYPERGLYCEMIC INTERVENTIONS

Choosing specific antihyperglycemic agents is decided based on their effectiveness in lowering blood glucose, extraglycemic effects that may reduce long-term complications, safety profiles and tolerability. In India, special consideration may be given for the cost of medication.

EFFECTIVENESS IN LOWERING GLYCEMIA

Apart from their differential effects on glycemia, there are insufficient data at this time to support a recommendation of one class of glucose-lowering agent, or one combination of medications, over others with regard to effects on complications.

LIFESTYLE INTERVENTIONS

While there is still active debate regarding the most beneficial type of diet and exercise, weight loss almost always improves glycemic levels.

Lifestyle modification (LSM) program with healthy diet and physical activity promotes weight loss and should be included as part of diabetes management. The beneficial effects of such programs are usually seen rapidly, within weeks to months and often before there has been substantial weight loss. Weight loss of as little as 4 kg will often ameliorate hyperglycemia. However, in Indians, the Indian Diabetes Prevention Programme (IDPP) study has shown that moderate LSM helps to prevent conversion of impaired glucose tolerance (IGT) to diabetes, even without significant weight reduction. It helps to improve the sensitivity of insulin. A large majority of patients will require the addition of medications over a period of time, as the long-term practice of LSM is difficult.

MEDICATIONS

The glucose lowering effectiveness of individual therapies and combinations depends greatly on the baseline glycemia, duration of diabetes, previous therapy and other factors. When levels of glycemia are high (e.g. A_{1C} > 8.5%), classes with greater and more rapid glucose-lowering effectiveness or potentially earlier initiation of combination therapy, are recommended ; conversely, when glycemic levels are closer to the target levels (e.g., A_{1C} < 7.5%), medications with lesser potential to lower glycemia and / or a slower onset of action may be considered.

Therefore individualization of medication is mandatory.

METFORMIN

Its major effects is to decrease hepatic glucose output and lower fasting glycemia. Typically, metformin monotherapy will lower A_{1C} by ~ 1.5% points. Indians seems to require smaller doses of the drug and the drug is fairly well tolerated. In non obese Indian patients, metformin works well even as a monotherapy[5].

The major nonglycemic effect of metformin is modest weight loss. The UKPDS demonstrated a beneficial effect of metformin therapy on CVD outcomes.

SULFONYLUREAS, α GLUCOSIDOSE-INHIBITORS

Sulfonylureas lower glycemia by enhancing insulin secretion. They appear to have an effect similar to metformin, and they lower A_{1C} by ~1.5% points. The major adverse side effect is hypoglycemia.

α-Glucosidase inhibitors reduce the rate of digestion of polysaccharides in the proximal small intestine, primarily lowering postprandial glucose levels without causing hypoglycemia. They are less effective in lowering glycemia than metformin or the sulfonylureas, reducing A_{1C} by 0.5-0.8% points.

In Indians, higher doses (more than 100 mg) seem to produce flatulence. Therefore, smaller doses are usually prescribed.

THIAZOLIDINEDIONES

Thiazolidinediones (TZD's or glitazones) are peroxisome proliferator-activated receptor γ modulators; they increase the sensitivity of muscle, fat and liver to endogenous and exogenous insulin. The limited data regarding the blood glucose – lowering effectiveness of TZDs when used as monotherapy have demonstrated a 0.5-1.4% decrease in A_{1C}. The most common adverse effects with TZDs are weight gain and fluid retention.

The TZDs either have a beneficial or neutral effect on atherogenic lipid profiles, with pioglitazone having a more beneficial effect than rosiglitazone.

Edema and weight gain are the common side effect especially in women. Beneficial effects of glitazone as a monotherapy in Indian patients has been reported[5].

INSULIN

Insulin is the oldest of the currently available medications and has the most clinical experience. Unlike the other blood glucose – lowering medications there is no maximum dose of insulin beyond which a therapeutic effect will not occur.

Insulin therapy has beneficial effects on lipid levels but results in weight gain of ~2-4 kg, probably proportional to the correction of glycemia and owing predominantly to the reduction of glycosuria.

Insulin analogs with longer, nonpeaking profiles may decrease the risk of hypoglycemia compared with NPH, and analogs with very short durations of action may reduce the risk of hypoglycemia compared with regular insulin.

Initiation and adjustment of insulin regimens should be designed taking lifestyle and meal schedule into account.

Insulin therapy can be initiated with 10 units or 0.2 units per kg body weight with bedtime intermediate – acting insulin or bedtime or morning long-acting insulin. Increment of insulin by 2 units every 3 days should be done until fasting target range of 70-130 mg / dl is achieved. If the fasting glucose is >180 mg / dl, increase insulin dose in larger increments of 4 units every 3 days. If HbA_{1C} value is < 7.0% and hypoglycemia occurs reduce bedtime dose by ≥ 4 units or 10%. Add a second injection when HbA_{1C} value is ≥ 7.0% after 2-3 months. Add approximately 4 units and adjust by 2 units every 3 days until blood glucose levels are in normal range. Add rapid acting insulin at breakfast, lunch or at dinner if the pre-lunch, pre-dinner or pre-bed blood glucose values are out of range respectively.

Continue the regimen and check HbA_{1C} values after 3 months. If HbA_{1C} value is ≥ 7.0%, recheck pre-meal blood glucose levels and if out of range, add another injection. If HbA1c value continues to be out of range, check 2hr postprandial levels and adjust preprandial rapid acting insulin. In Indians, the timing of meals are different from the western world. Therefore, the dose and timing of insulin injections should be adjusted.

GLUCAGON-LIKE PEPTIDE 1 AGONISTS (EX-ENATIDE)

Glucagon-like peptide 1 (GLP-1) 7-37, a naturally occurring peptide produced by the L-cells of the small intestine, stimulates insulin secretion.

Synthetic exendin-4 (exenatide) was approved for use in the U.S. in 2005 and is administered twice per day by subcutaneous injection.

It is not associated with hypoglycemia but has a relatively high frequency of gastrointestinal side effects, with 30-45% of treated patients experiencing one or more episodes of nausea, vomiting or diarrhea. The drug has not reached Indian market yet.

CONCLUSIONS/SUMMARY

The epidemic of diabetes in India causes enormous human suffering and economic burden, especially when it is associated with vascular complications. Better modalities of treatment and wider choices are available now.

The guidelines and treatment algorithm presented by the ADA–EASD consensus apply to diabetic patients in India which include:

- Achievement and maintenance of normal glycemic goals.
- Reinforcement of lifestyle modification when necessary.
- Rapid addition of medications and transition to new regimens, when target glycemic goals are not achieved or sustained; and
- Addition of insulin therapy in patients who do not meet target goals, considering the socio-economic setting.

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