

Current Status of Diabetes in India and Need for Novel Therapeutic Agents



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Abstract

The prevalence of diabetes is rising all over the world due to population growth, aging, urbanisation and an increase of obesity and physical inactivity. Unlike in the West, where older persons are most affected, diabetes in Asian countries is disproportionately high in young to middle-aged adults. This could have long-lasting adverse effects on a nation's health and economy, especially for developing countries. The International Diabetes Federation (IDF) estimates the total number of people in India with diabetes to be around 50.8 million in 2010, rising to 87.0 million by 2030.

The primary goal in the management of diabetes mellitus is the attainment of near-normal glycaemia. In India, more than half of patients have poor glycaemic control and have vascular complications. Therefore, there is an urgent need to develop novel therapeutic agents of diabetes without the development and progression of complications or compromising on safety.

Glucagon-like peptide-1 (GLP-1) analogues and dipeptidyl peptidase-4 (DPP-4) are novel agents that show promising results. Exenatide is the first in the incretin mimetic class and liraglutide is a once-daily human GLP-1 analogue. Once-daily liraglutide was effective and well tolerated when used as monotherapy or in combination with oral antidiabetic drugs (OADs) in patients with type 2 diabetes, and is therefore a promising new treatment option for the management of type 2 diabetes.

Epidemiology of Diabetes in India

According to recent estimates, approximately 285 million people worldwide (6.6%) in the 20–79 year age group will have diabetes in 2010 and by 2030, 438 million people (7.8%) of the adult population, is expected to have diabetes.⁽¹⁾ The largest increases will take place in the regions dominated by developing economies.¹

The global increase in the prevalence of diabetes is due to population growth, aging, urbanisation and an increase of obesity and physical inactivity. The primary determinants of the epidemic are the rapid epidemiological transition associated with changes in dietary patterns and decreased physical activity. Unlike in the West, where older populations are most affected, the burden of diabetes in Asian countries is disproportionately high in young to middle-aged adults.^{2,3} This could have long-lasting adverse effects on a nation's health and economy, especially for developing countries. Healthcare expenditures on diabetes are expected to account for 11.6% of the total healthcare expenditure in the world in 2010. Estimated global healthcare expenditures to treat and prevent diabetes and its complications are expected to total at least 376 billion U.S. Dollars (USD) in 2010. By 2030, this number is projected to exceed some USD490 billion.¹

The "Top 10" countries in the world, in terms of the number of people with diabetes, for 2010 and 2030, are shown in Table 1. At both time points, the three countries with the largest number of people with diabetes are India, China and the U.S.¹ This picture is likely to change soon, in light of the recent escalation in prevalence of diabetes (92.4 million adults) in China.⁴ Roughly

80% of people with diabetes are in developing countries, of which India and China share the larger contribution.³ It is estimated that the total number of people with diabetes in 2010 to be around 50.8 million in India, rising to 87.0 million by 2030.¹ According to the World Health Organization (WHO) criteria, the prevalence of known diabetes was 5.6% and 2.7% among urban and rural areas, respectively.⁵ Ramachandran et al. reported that age-standardised prevalence of diabetes and impaired glucose tolerance (IGT) in urban India in 2000 were 12.1% and 14.0%, respectively, with no gender difference.⁶ Diabetes showed positive and independent associations with age, body mass index (BMI), waist-to-hip ratio, a family history of diabetes, monthly income and sedentary physical activity. Age, BMI and a family history of diabetes showed associations with IGT.

More recent reports from various parts of India showed further increases in diabetes prevalence in urban areas (Table 2).⁷ Moreover, the prevalence of diabetes was also found to be increasing rapidly in rural areas, as a result of the recent socio-economic transitions.⁷

Table 1 : Top 10 countries for estimated numbers of adults with diabetes, 2010 and 2030¹

Rank	Country / Territory	2010 (millions)	Country / Territory	2030 (millions)
1	India	50.8	India	87.0
2	China	43.2	China	62.6
3	U.S.	26.8	U.S.	36.0
4	Russian Federation	9.6	Pakistan	13.8
5	Brazil	7.6	Brazil	12.7
6	Germany	7.5	Indonesia	12.0
7	Pakistan	7.1	Mexico	11.9
8	Japan	7.1	Bangladesh	10.4
9	Indonesia	7.0	Russian Federation	10.3
10	Mexico	6.8	Egypt	8.6

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Table 2 : Prevalence of diabetes in urban India since 2000⁷

Region	Year	Age of subjects (years)	Prevalence (%)		
			Diabetes	IGT	IFG
National					
Ramachandran et al	2000	> 20	12.1	14.0	--
Reddy et al.	2003	20-69	8.4	--	6.4
Sadikot et al	2004	> 20	5.9	6.3	4.8
Northern India					
Ramachandran et al	2000	> 20	11.6	8.6	--
Gupta et al	2003	> 20	8.6	--	5.3
Prabhakaran et al [†]	2005	20-59	15	37	
Southern India					
Ramachandran et al	2000	> 20	13.5	16.8	--
Mohan et al	2004	> 20	14.3	10.2	--
Menon et al	2005	18-80	19.5	4.1	7.0
Ramachandran et al	2006	> 20	18.6	7.4	--

[†]This study was conducted in industrial workers (men only)

Glycaemic Control based on Recent Studies

The Diabetes Control and Complications Trial (DCCT) demonstrated that good metabolic control, resulting from intensive insulin therapy, reduced the risk of progression or development of retinopathy, nephropathy and neuropathy in type 1 diabetes.⁸ The United Kingdom Prospective Diabetes Study (UKPDS) showed that intensive glycaemic control in type 2 diabetes significantly reduced the risk of development and deterioration of microvascular complications.⁹ The primary goal of the management of diabetes mellitus is the attainment of near normal glycaemia. The target for good glycaemic control recommended by the American Diabetes Association (ADA)¹⁰ is glycated hemoglobin A_{1c} (HbA_{1c}) < 7.0%.

Unmet needs with existing drugs

Lifestyle modification is the most cost-effective intervention for prevention of diabetes in high-risk groups in India.¹¹ However, control of diabetes with diet, weight control and physical activity has been difficult and will not be sufficient for most of the patients. Moreover, the steady increase in the incidence of type 2 diabetes has significant socioeconomic implications.¹²

OADs

An oral antidiabetic drug (OAD) is the first line of drug treatment for type 2 diabetes. However, the progressive nature of type 2 diabetes usually requires a combination of two or more oral agents in the long term, often as a prelude to insulin therapy. Safety and tolerability (notably hypoglycaemia), and weight gain often limit the optimal use of OADs. Insulin treatment is the cornerstone of diabetes management. It is the only means of achieving good glycaemic control in insulin-deficient patients with type 1 diabetes. Insulin is also used as an intermittent or permanent therapy in some patients with type 2 diabetes. The UKPDS data showed that the current available treatment modalities were not satisfactory as evidenced by

the high morbidity and mortality among subjects with type 2 diabetes.⁹ Both OADs and insulin treatment increased the risk of hypoglycaemia. Weight gain was significantly higher in the intensive group with a sulphonylurea (SU) (chlorpropamide, glibenclamide or glipizide) or with insulin than in the conventional group with diet, and patients assigned insulin had a greater weight gain than those assigned chlorpropamide or glibenclamide.

Studies in India indicate that more than 50% of people with diabetes have poor glycaemic control (HbA_{1c} > 8%), uncontrolled hypertension and dyslipidaemia, and a large percentage have diabetic vascular complications.¹³⁻¹⁶ Overall, diabetes care in India leaves much to be desired. Increased awareness amongst health professionals to improve the standard of diabetes care is urgently needed, along with the development of novel therapeutic agents that can effectively control diabetes and prevent the development and progression of its complications without compromising on safety.

Type 2 diabetes is a complex, multifactorial disease. It is associated with progressive deterioration of β -cell function and insulin resistance.⁹ The UKPDS and DCCT data showed that tight control of diabetes can significantly prevent the development of vascular complications.^{8,9} The UKPDS also suggested that 53% of type 2 patients would require insulin 6 years after diagnosis, and 75% of patients would require multiple treatments after 9 years.⁹ Although insulin treatment is effective, its long-term use can lead to gains in fat mass, especially abdominal obesity, which may worsen insulin resistance. Moreover, repeated episodes of hypoglycaemia may cause major problems.

Need for novel therapeutic agents

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted from the L cells in the lower gut. GLP-1 secretion is strongly correlated to gastric emptying rate, and GLP-1 secretion throughout the day is highly correlated to insulin release.¹⁷

Byetta[®] (exenatide) is the first in the incretin mimetic class (GLP-1 receptor agonists) that offers effective treatment for patients with type 2 diabetes. The dose is initially 5 μ g subcutaneously twice daily and may be titrated to 10 μ g subcutaneously twice daily to achieve the desired goal. Clinical trials have shown benefits by adding exenatide to metformin and SUs. The weight loss seen with exenatide is also an advantage over most of the current treatments. However, it is difficult to determine if nausea plays a role in weight loss. The concern for exenatide's use in type 2 diabetics is the reduction in gastric emptying. Also of interest is the preservation of the β cells of the pancreas and the conversion of non-insulin-secreting cells to insulin-secreting cells *in vitro*. Studies are ongoing that will hopefully elucidate the true effect that exenatide has on the β cells.

The NICE has updated the guidelines for the management of type 2 diabetes, which also gives guidance on use of exenatide.¹⁸ Though exenatide is not recommended for routine use in type 2 diabetes, it should be considered as an option in subjects with obesity who have HbA_{1c} \geq 7% with conventional oral agents or if another high-cost medication or insulin is recommended.

Liraglutide is a once-daily human GLP-1 analogue. Studies in animals and humans have demonstrated promising blood glucose-lowering effects as well as a favourable safety profile. In India, Victoza[®] (liraglutide [rDNA origin] injection) is approved for "use in type 2 diabetes". Once-daily liraglutide was effective and well tolerated when used as monotherapy or in combination

with OADs in patients with type 2 diabetes, and is therefore a promising new treatment option for the management of type 2 diabetes. A double-blind, randomised, parallel-group, placebo-controlled trial with an open-label comparator arm was conducted among 193 outpatients with type 2 diabetes.¹⁹ A once-daily dose of liraglutide provided efficacious glycaemic control and was not associated with weight gain. Adverse events with the drug were mild and transient, and the risk of hypoglycaemia was negligible. Another randomised, double-blind, parallel-group, placebo-controlled trial showed that eight weeks of 0.6 mg liraglutide treatment significantly improved glycaemic control without weight gain in subjects with type 2 diabetes compared with those on placebo.²⁰ No influence on 24 hour energy expenditure was detected. Adverse events were mainly mild and related to the gastrointestinal system. No episodes of hypoglycaemia were observed. Subjects with a history of pancreatitis should not be given these agents.

DPP-4

DPP4 inhibitors such as sitagliptin and vildagliptin are novel agents for treatment of type 2 diabetes. They target both prandial and fasting glucose concentrations, and work by improving β -cell sensitivity to glucose, whereby it increases glucose-dependent insulin secretion. Gliptins can be used as monotherapy or combined with metformin or SUs. Gliptins are largely weight neutral. No serious adverse events were noted during the clinical trials. Vildagliptin is not recommended in patients with hepatic impairment. Long-term safety regarding cardiovascular outcomes needs to be assessed.

A variety of newer agents now available for treatment of type 2 diabetes gives further choice of treatment options. Their protective effect on β -cell function is a major benefit.

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References

1. *IDF Diabetes Atlas, 4th edition*. International Diabetes Federation, 2009.
2. Chan JC, Malik V, Jia W, et al. Diabetes in Asia: Epidemiology, risk factors, and pathophysiology. *JAMA* 2009;301:2129–40.
3. Ramachandran A, Wan Ma RC, Snehalatha C. Diabetes in Asia. *Lancet* 2010;375:408–18.
4. Yang W, Lu J, Weng J, et al. Prevalence of diabetes among men and women in China. *N Engl J Med* 2010;362:1090–101.
5. Mohan V, Pradeepa R. Epidemiology of diabetes in different regions of India. *Health Administrator* 2009;22:1–18.
6. Ramachandran A, Snehalatha C, Kapur A, et al. High prevalence of diabetes and impaired glucose tolerance in India: National Urban Diabetes Survey. *Diabetologia* 2001;44:1094–101.
7. Ramachandran A, Snehalatha C. Current scenario of diabetes in India. *J Diabetes* 2009;18–28.
8. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993;329:977–86.
9. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:837–53.
10. Goldstein DE, Little RR, Lorenz RA, Malone JJ, Nathan DM, Peterson CM. Tests of glycemia in diabetes. *Diabetes Care* 2004;27(Suppl 1):S91–S93.
11. Ramachandran A, Snehalatha C, Yamuna A, Mary S, Ping Z. Cost-effectiveness of the interventions in the primary prevention of diabetes among Asian Indians: Within-trial results of the Indian Diabetes Prevention Programme (IDPP). *Diabetes Care* 2007;30:2548–52.
12. Zimmet P. The burden of type 2 diabetes: Are we doing enough? *Diabetes Metab* 2003;29:6S9–6S18.
13. Raheja BS, Kapur A, Bhoraskar A, et al. DiabCare Asia—India Study: Diabetes care in India—Current status. *J Assoc Physicians India* 2001;49:717–22.
14. Nagpal J, Bhartia A. Quality of diabetes care in the middle- and high-income group populace: The Delhi Diabetes Community (DEDICOM) survey. *Diabetes Care* 2006;29:2341–8.
15. Ramachandran A, Mary S, Sathish CK et al. Population based study of quality of diabetes care in southern India. *JAPI* 2008;56:513–16.
16. Rema M, Premkumar S, Anitha B, Deepa R, Pradeepa R, Mohan V. Prevalence of diabetic retinopathy in urban India: The Chennai Urban Rural Epidemiology Study (CURES) eye study, I. *Invest Ophthalmol Vis Sci* 2005;46:2328–33.
17. Holst JJ. On the physiology of GIP and GLP-1. *Horm Metab Res* 2004;36:747–54.
18. Alder AI, Shaw EJ, Stokes T, Ruiz F. Newer agents for blood glucose control in type 2 diabetes: Summary of NICE guidance. *BMJ* 2009;338.
19. Madsbad S, Schmitz O, Ranstam J, Jakobsen G, Matthews DR. Improved glycemic control with no weight increase in patients with type 2 diabetes after once-daily treatment with the long-acting glucagon-like peptide 1 analog liraglutide (NN2211): A 12-week, double-blind, randomized, controlled trial. *Diabetes Care* 2004;27:1335–42.
20. Harder H, Nielsen L, Tu DT, Astrup A. The effect of liraglutide, a long-acting glucagon-like peptide 1 derivative, on glycemic control, body composition, and 24-h energy expenditure in patients with type 2 diabetes. *Diabetes Care* 2004;27:1915–21.