Economics of Insulin

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Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by inherited and/or acquired deficiency in the production of insulin by the pancreas or due to insulin resistance of body tissues. Diabetes is an important metabolic disease which can affect every organ in the body. This devastating disease is an important cause of premature death and disability.

Poor glycemic control in diabetes is associated with chronic complications. Microvascular complications i.e. neuropathy, nephropathy and retinopathy are commonly seen in type 1 diabetics, while type 2 diabetics are more prone to macrovascular complications (cardiovascular, cerebrovascular and peripheral vascular disease). 1,5

Major multicentric studies have shown substantial decrease in the risk of micro and macrovascular disease in patients who achieve strict glycemic control.

Prevalence of Diabetes: Global Scenario

The World Health Organization in 1998 has projected an increase in global prevalence from an estimated 4% in 1995 to 5.4% by 2025. 1 This increase from 135 to 300 million patients due to changing lifestyle, longevity of life, obesity, sedentary work, changing dietary patterns, and low birth weight. Diabetes has reached epidemic proportions and it is projected that most of the increase in future will be contributed by developing countries.

Indian Scenario

Currently 10.4 million individual are affected by diabetes and equal number are believed to be undiagnosed. These numbers are expected to increase to 57.2 million by the year 2025 (one – sixth of the world total). 1 Indian diabetics tend to be younger and are more likely to fall prey to complications ranging from heart attacks and strokes to blindness and sexual dysfunction.

Earlier studies had reported high prevalence of insulin resistance2 and diabetes3 among migrant Indians compared to the native population. In 1970, prevalence of diabetes among urban Indians was reported to be 2.1%, which has now risen to 12.1%. 4 A similar though slower trend is also shown among periurban population and rural residents also. 10

Cost of Diabetes Mellitus

The economic burden of diabetes is substantial, as it currently accounts for an average of around 8% of total health care budgets in developed countries. 11

UKPDS Study – Intensive Treatment of Diabetes is ‘Cost Effective’

The UKPDS group has concluded that cost of intensive blood glucose control in type 2 diabetes is largely offset by significantly reduced costs of complications and the increased time free of complications. Intensive therapy would cost an additional £1,435 per patient (£140 per year) giving a total additional annual cost of £14,000-27,000. The cost would be offset by a saving of £10,000-18,000 on treating complication.

DCCT Study

The Diabetes Control and Complication Trial (DCCT) group for type 1 Diabetes reported in 1995 that the annual cost of intensive group ($ US 4000 and $ US 5800 per patient for multiple daily subcutaneous injections and continuous subcutaneous insulin infusion (CSII) respectively) was approximately 2-3 times that of conventional therapy ($ US-1700) in patients with type 1 diabetes. 4 However, this increased cost must be considered alongside potential future reductions in costs associated with decrease in long-term complications and improved quality of life for patients. Improved glycemic control leads ultimately to reductions in costs of managing complications and can be expected to increase length of life. Hence intensive insulin therapy was considered cost-effective. 5

Kumamoto Study

The study was done to evaluate the cost and effectiveness of intensive insulin therapy for type 2 diabetes on the prevention of diabetes complications in Japan. One hundred and ten patients with type 2 diabetes were divided into: (a) MIT – Multiple injection therapy and (b) CIT - Conventional insulin injection therapy

Economic evaluations were done for effectiveness of intensive insulin therapy and frequency of complications. MIT reduced relative risk in progression of retinopathy by 6%, photocoagulation by 77%, and progression of nephropathy by 66% relative to CIT. The total cost for MIT group as compared to CIT group was less mainly due to reduced costs for management of diabetic complications. 5

Early Initiation of Insulin for Type-2 Diabetes

In Sweden, beta-cell function, glycemic control and quality of life were monitored over 2 years in 39 patients with type 2 diabetes diagnosed 0-2 years before inclusion in the study. Patients were randomly assigned to pre-mixed insulin (2 injections daily) or glibenclamide. It was concluded that early insulin versus glibenclamide treatment in type 2 patients temporarily prolongs endogenous insulin secretion and promotes better metabolic control. 13

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UKPDS - 57

Sulphonylurea inadequacy - efficacy of addition of insulin ever 6 yrs in patients with type 2 diabetes.

The main objective of UKPDS – 57 was to evaluate the efficacy of the addition of insulin when maximum sulphonylurea therapy is inadequate in individuals with type 2 diabetes.14

The conclusion of this study was that early addition of insulin when maximal sulphonylurea therapy is inadequate can significantly improve glycemic control without promoting increased hypoglycemia and weight gain.

UKPDS 49 – Progressive requirement of multiple therapies for Type 2 Diabetes

The main objective of UKPDS – 49 was to assess how often therapy with diet, sulphonylurea, metformin or insulin in patients with type 2 diabetes can achieve the glycemic control target levels (fasting plasma glucose of <7.8 mm d/l pr 140 mg/dl or HbA1C below 7%). It was conducted that each therapeutic agent as monotherapy, increased 2-3 told the proportion of patients who attained HbA1C below 7% compared with diet alone. However the progressive deterioration of diabetes control was such that after 3 yrs approximately 50% of patients could attain this, declined to approximately 25%. The majority of patients needed multiple therapies including insulin to attain this glycemic target level in the longer term.15

Cost of Management of Diabetes per year, per patient in Rs.

The primary cost of diabetes treatment for medications only, vary from Rs.500 to Rs.5000 per patient per year depending on the type of oral hypoglycemic agent used. From Rs.3500 to Rs. 10,000 per year depending on the type of insulin and insulin devices used. In type 1 diabetic patients considering the cost of meters and monitoring strips, the outgoing would be Rs. 5,000 per year if monitored weekly.

Antioxidants are freely prescribed to diabetic patients for variety of reasons. This would add Rs. 750/- per patient per year to the treatment regimen. Effective management of hyperlipidemia costs Rs. 3000/- per year.

A type 2 diabetic patient without any complication will have to spend Rs. 6200-10,700/- per year. Type 1 diabetic will have to spend Rs. 4,500-14,000 per year. Cost of complication of diabetes would be more than cost of treating primary disease i.e. diabetes.

**Insulin Lispro**

Insulin Lispro is a recombinant insulin analogue with transposed amino acids (proline and lysine) at position 28 and 29 near the ‘C’ terminus of the B chain. The most prominent practical advantage of insulin Lispro over human soluble insulin lies in its very rapid onset of action; hence Lispro is injected immediately before meals. Numerous clinical studies have shown significant improvement in postprandial glycemic control16-18 with some evidence of reduced rates of severe or nocturnal hypoglycemia relative to conventional insulin in patient receiving Lispro insulin.19,20

Quality of life studies showed consistent preferences by patients for and increased treatment satisfaction with insulin Lispro over human soluble insulin, particularly with DTSQ (Diabetes Treatment Satisfaction Questionnaire).21-24 Willingness of patients to pay additional costs for insulin Lispro or a premixed Lispro-based formulation over conventional human insulin and costs have been shown in well designed studies in Australia and Canada.25,26 Spanish data suggest cost effectiveness in terms of episodes of severe hypoglycemia avoided.

**Insulin aspart**

Insulin aspart is a fast acting analog like lyspro with similar pharmacokinetic. It effects lasser hypoglycemic thought with quicker action.

**Insulin - Glargine**

Insulin analogue, insulin Glargine is designed to have a low solubility at neutral pH. At pH 4, insulin Glargine solution is completely soluble. After injection into subcutaneous tissue, the acidic solution is neutralized, leading to formation of micro-precipitates from which Glargine is released continuously – smooth, peakless with 24 hours duration of action. However it is expensive, hence cost-effectiveness has to be assessed.

**Anti-Inflammatory and Potential Anti-Atherogenic Effect of Insulin**

Atherosclerosis is now recognized as an inflammation of the arterial wall and thus the action of Nuclear Factor – kappa NF-kb is considered central to pro-inflammatory molecules.27

Insulin has a suppressive effect on NF-kb with a corresponding reduction in the expression of pro-inflammatory genes. It also suppresses activator protein – 1 (AP-1),28 the transcription factor which modulates matrix metalloproteinases (MMPS), expressed in the atherosclerotic plaque and could be responsible for plaque rupture.29,30 In addition, it suppresses early growth response gene – 1 (Egr –1),31 the transcription factor which modulates tissue factor (TF) which in turn activates thrombin generation.

These effects indicate that insulin could have a key inhibitory role in the regulation of factors which are central to atherogenesis, plaque rupture and thrombosis. The final events which precipitate acute cerebral ischaemia and myocardial infarction.

The successful use of insulin in acute MI with and without the use of thrombolitics in diabetic patients and non-diabetic subjects in improving clinical outcomes might reflect the profound anti-inflammatory and potential anti-thrombotic properties of insulin.

**DIGAMI Study (Diabetes mellitus Insulin Glucose infusion in Acute Myocardial infarction)**

In this study 620 patients with diabetes and acute myocardial infarction were randomized to intensive insulin treatment or to serve as controls given standard anti-diabetic therapy. Mortality was significantly reduced in the insulin group.

The cost–effectiveness ratio was estimated as the incremental cost per life–year and quality adjusted life-year gained due to intensive insulin treatment. The results of DIGAMI study indicate that intensive insulin treatment after an acute myocardial infarction in patients with diabetes has an ‘ACCEPTABLE’ level of cost-effectiveness.32
Newer Methods of Drug Delivery

1. Efficiency of insulin injection methods – In Spanish study 3 ways of injecting insulin were studied with traditional syringes, injector pens and preloaded injection syringes. The main aim of the study was to compare their efficiency in normal use, and the second to compare their effectiveness. The conclusion was that if there is similar efficacy, automatic systems are more efficient than traditional syringes and insulin vials.33

2. Implantable insulin pumps.
Implantable insulin pumps provide a basal rate of insulin secretion and can be directed by remote control to give bolus insulin at mealtime. These pumps are suited for patients with brittle diabetes who have unsatisfactory glycemic control despite intensive diabetes management with subcutaneous insulin. However these pumps are more costly.34

3. Inhaled insulin
Insulin–delivery devices that take advantage of lung as diffusion membrane i.e. intrapulmonary insulin, because of its lower bioavailability, will almost certainly be more expensive than injected insulin.

Conclusion
It has been shown by various studies that long-term intensive glycemic control is essential to prevent micro and macrovascular complications of diabetes. The cost of complications is much more than treatment of diabetes. Hence for type 1 diabetics intensive glycemic control by thrice-daily insulin regime and for type 2 diabetes by oral hypoglycemic agents and early initiation of insulin is recommended.

Finally, pharmaco-economic of insulin does not depend on total daily cost of insulin vis-a-vis OHA but on good glycemic control which will prevent the early onset of complications. It has been documented that in the long run the cost of complication would be greater than the management of diabetes if not done effectively.

References
6. Ahuja MMS – Epidemiology studies on diabetes mellitus in India. In Ahuja MMS, editor Epidemiology of Diabetes in Developing Countries, New Delhi: Interprint 1979;29-38.

Cost of Various Insulins available in Market

Table 1 : Cartridges

<table>
<thead>
<tr>
<th>Name of Insulin</th>
<th>In Form of</th>
<th>Price Per Unit in Rs</th>
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<tbody>
<tr>
<td>Novorapid (Aspart)</td>
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<tr>
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<tr>
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<td>Wosulin R</td>
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<tr>
<td>Wosulin N</td>
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All Cartridges are U-100 unless specified

Table 2 : Vials

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All Vials are U-40 unless specified


