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Rising cost of insulin: A deterrent to compliance in patients with diabetes mellitus

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ABSTRACT

Background and aims: The rapid increase in burden of type 2 diabetes mellitus (T2DM), poses a huge medico-economic challenge, especially when the cost of care is funded by out-of-pocket expenses. The aim of this review is to highlight various issues associated with rising cost of insulin, prevalence of cost-related insulin underuse, insulin related cost-saving behaviors, and viable solutions for the benefit of patients with T2DM receiving insulin.

Methods: Electronic databases (PubMed and Google Scholar) from 2000 to 2020 were searched using the key terms uncontrolled diabetes mellitus, insulin therapy, glycemic control, direct cost, indirect cost, out-of-pocket expenses, cost-related insulin underuse, cost-saving behaviors, and biosimilar insulin in developed countries and India.

Results: In majority of the patients with T2DM on monotherapy, addition of another oral antidiabetic agent is required. Despite these measures, the target glycemic goals are not achieved in majority of the patients resulting in various complications. These complications can be prevented and target glycemic goals can be achieved with early initiation of insulin therapy. However, rising cost is a major deterrent to the lifelong use of insulin. This results in non-compliance and further deterioration of glycemic control. Recently, biosimilar insulins have revolutionized the management of T2DM and look promising from the economic point of view.

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Conclusions: Biosimilar insulins are likely to further enhance the compliance of patients and should be used whenever feasible in patients with DM. However, the patient, along with prescriber should be allowed to make shared, informed decisions regarding the insulin they wish to use.

1. Introduction

Plethora of anti-diabetic medications are available for the treatment of type 2 diabetes mellitus (T2DM). However, majority of the patients with T2DM are unable to attain the glycemic targets and thus, remain uncontrolled [1]. Uncontrolled T2DM results in a variety of micro- and macro-vascular complications, thereby resulting in increased morbidity, mortality, and healthcare spending [2–4]. Among all the treatment options available, insulin is the most efficient way of achieving glycemic control. As there is absence of maximum tolerated insulin dose, any HbA1c level can be decreased to the target range if adequate dose is used [5]. However, recent years have witnessed a steep rise in the cost of insulin, resulting in unaffordability even in some high-income countries [6]. This has resulted in decreased compliance [7], and subsequently increased cost of managing the complications resulting from uncontrolled diabetes mellitus (DM) [8]. Thus, in this article, we discuss various issues associated with rising cost of insulin, its effects on compliance, and viable solutions for benefit of the patients with T2DM receiving insulin therapy.

2. Health expenditure and economic burden: Global and India

DM inflicts considerable economic impact on nations, healthcare systems, and individuals and their families, especially when the cost of care is funded by out-of-pocket (OOP) expenses [9]. Around 79% of patients with DM reside in low- and middle-income countries [10]. The rapid rise of DM in individuals residing in developing nations poses a huge medico-economic challenge to economies already burdened by communicable diseases.

The economic impact of DM can be described in terms of direct and indirect cost. The direct cost includes the health expenditures incurred to patients, private or public payers, or government. Globally, between 2007 and 2019, the direct cost has increased significantly from 232 billion to 760 billion USD, respectively [10]. A systematic review focusing particularly on Indian patients with DM reported that costs to hospitals and other health providers comprises only a small fraction of the total cost. The cost of medication forms >50% of the total direct costs [11]. In India, with 87.9% of adults with DM in the South-East Asian Region, the average yearly expenditure per patient was found to be 92 USD [10]. An early study reported that median annual direct cost of managing DM among Indian patients was INR 9,996, ranging from INR 4724 to 25,391 [12]. A study from Delhi reported that the average annual direct cost of T2DM was 143.14 USD, of which >50% was cost of medication (76.59 USD) [13]. Another study reported a total direct cost of 114.4 USD over 6 months, of which 62% was cost of medication (70.88 USD) [14]. A systematic review reported that the annual median direct cost of managing DM in North, South, North-East, and West zones was INR 18,890, 10,585, 45,792, and 8,822, respectively [15]. Thus, DM poses a high economic burden on individuals or families and the cost of medication accounts for a major burden of the diabetes care.

Usually, indirect costs are not taken into account. However, they form a considerable burden on the individual and society. Studies suggest that indirect costs primarily include labor-force drop out, presentism, absenteeism, and mortality. In 2015, this indirect cost constituted 34.7% of their total global estimate of managing DM (1.31 trillion USD) [16]. Apart from direct cost, the median annual indirect cost of managing DM among Indian patients at the individual/household level was estimated to be INR 5,237, ranging from INR 2435 to 12,756 [12]. Moreover, another study reported a total of 48.09 USD as indirect costs over a 6-month period. The loss of patient income accounted for 61% of the total indirect cost (29.10 USD), while the remainder 39% (18.96 USD) was due to loss of income of the care taker [14]. A systematic review suggested that the annual median indirect cost of managing DM in North, South, North-East, and West zones of India were INR 18,146, 1,198, 18,707, and 3,949, respectively [15]. These findings suggest that indirect costs incurred in managing DM result in considerable loss of revenue.

3. Proportion of patients with uncontrolled T2DM requiring insulin

In majority of the patients with DM, monotherapy with an oral antidiabetic (OAD) is initiated. However, over the period, addition of another agent is required in nearly half of the patients by 3 years, and in three-fourth by 9 years [17]. Failure of the OADs due to any reason results in higher number of uncontrolled patients with DM. In Diab-care Asia-India study, 50% patients with DM were poorly controlled [18]. Another study reported that, compared to the percentage of patients with DM at target at baseline (45%), only 55% patients achieved target HbA1c level at 6 months [19]. These findings highlight that a large percentage of patients with DM fail to achieve the HbA1c goal.

Among all the hypoglycemic agent known, insulin is most effective. It has been documented that early initiation of insulin therapy results in good clinical outcomes in terms of both short- and long-term glycemic control [20]. Early initiation of insulin therapy helps overcome the glucotoxic effects of hyperglycemia, thus resulting in β-cell rest, and preserving their mass and function. Simultaneously, it improves insulin sensitivity. Moreover, insulin has antioxidant and anti-inflammatory action that may provide resistance against endothelial dysfunction and damage leading to vascular disease [21]. Thus, earlier initiation of insulin therapy not only provides good glycemic control, but also results in long-term protection to end organs through metabolic memory, regardless of ensuing treatments and amount of glycemic control [21,22].

It is further reported that early initiation of insulin therapy in newly diagnosed patients with DM presenting with clinical symptoms and having HbA1c > 8.5–9% leads to achievement of near normal glucose control and demonstrates long-lasting remissions in up to half of the patients. Long-term studies such as UKPDS-Legacy, DIGAMI 1, and ORIGIN indicate considerable advantage in microvascular disease, cardiovascular events, and improved life expectancy [22].

Though majority of the patients with DM prefer OADs over insulin, initiation of insulin in patients receiving oral therapy is a preferred approach found effective in several patients [23]. This is supported by the findings of a study involving patients with T2DM poorly controlled on oral therapy. In this study, over a period of 24-

weeks, the use of glargine plus OAD regimen enabled ~50% of patients with DM to reach HbA1c goal, while <30% of patients receiving 70/30 insulin achieved HbA1c goal [24].

4. Inclusion of insulin in national list of essential medicines and proportion of Indian patients with DM receiving insulin

Nearly a century since its discovery, insulin remains out of reach for millions due to poor accessibility and unaffordability [25]. However, it is an essential medicine (EM), due to its lifesaving nature in patients with DM. The World Health Organization (WHO) refers EMs as those which fulfil the global health requirements of most of the individuals and encourages cost-effective use of healthcare resources [26]. The latest Edition of the Model List of Essential Medications (2021) issued by the WHO includes various insulins, including long-acting degludec, detemir, and glargine [27].

The last revision of the Indian National List of Essential Medicines (NLEMs, 2015) was a significant improvement over the 2011 NLEMs. From the endocrinology point of view, the recommendations are quite clear, and insulin in fixed ratio combinations [30:70 combination of soluble and Neutral Protamine Hagedorn insulin] was included. This inclusion suggests the trends in prescription and management of Indian patients with DM. The point worth appreciation is the absence of insulin trade name in the present NLEM [28].

With respect to the Indian public healthcare sector, the inclusion of insulin products in the national and state EMs lists is free-of-charge [29]. Additionally, the patients have the option to get the medications from the private-sector online pharmacies and/or government schemes including Jan Aushadhi Scheme, which intends to furnish quality medicines at economical cost to every individual [30]. Despite these initiatives, the last decade has witnessed an exponential rise in the cost of insulin. This has resulted in a corresponding rise in insurance co-pays and OOP costs for the individuals [31].

The significant economic burden of managing DM is suggested by the fact that a substantial number of Indian patients with DM need insulin therapy to achieve and/or maintain target HbA1c levels. DiabCare India study (2011) concluded that around 35% patients with DM require insulin therapy. Among them, most of the patients with DM received human insulin (71.1%), and remaining received insulin analogues (32%) and a combination of both (3.1%) [32]. Another study involving database of the Apollo Sugar Clinics suggested that most of the patients with DM were on OADs (68.2%) followed by OADs + insulin (22.8%) and insulin alone (9.0%). Thus, approximately 31% patients with DM required insulin [33]. Additionally, the dependence on insulin for attaining the glycemic control increases with the chronicity of DM. This is supported by a study in which only 1.8% of the patients with DM (duration of DM: 0–5 years) required insulin therapy, while when the duration of DM was >20 years, this proportion reached 46.2% [34].

5. Average use of insulin per patient

As per the American Diabetes Association (ADA), patients with Type 1 DM (T1DM) usually require two different varieties of insulin every day. They generally initiate with 2 injections/day and progress to 3–4 doses/day. While, patients with T2DM might initiate with 0.5–0.8 U/kg/day and progress to 1–2 U/kg/day. Thus, an individual weighing 68 kgs and 80 kgs would require 68–136 U/day and 80–160 U/day, respectively [35]. Based on these facts, a patient with T1DM and T2DM would require 2–3 vials/month and ≥6 vials/month, respectively. Patients with T2DM usually have insulin resistance and thus, require higher doses of insulin. Patients with DM requiring >1 U/kg/day are recognized to have insulin resistance, and those requiring >2 U/kg/day have severe insulin resistance. Alternatively, severe insulin resistance is regarded as the requirement of >200 U/day. The requirement of this large daily dose leads to practical problems related to delivery of insulin, as a standard U-100 insulin given in a large quantity can be very painful and results in altered onset and duration of insulin action [36].

6. Higher cost of insulin and its analogues

Globally, the cost of insulin is increasing, especially in the USA. The high prices for insulin are ironic given the intentions of the original insulin discoverers. In 1923, Banting, Best, and Collip filed the first patent related to the process of separating the insulin, and gave it, for 1 USD each, to the University of Toronto on the premise that this patent and license would result in easy availability of insulin to all the patients with DM. However, in the following century, older insulins have been successively succeeded by newer, significantly upgraded insulins that are protected by multiple supplementary patents. Thus, in the USA, >90% of privately insured patients with T2DM on insulin therapy are prescribed the most recent and costly insulin analogues [37].

The steady and exponential rise in the cost of insulin is a result of the complexities involved in the manufacturing, supply chain, and mechanism of pricing [38]. With specific reference to India, the latest and costly insulins are aggressively promoted and prescribed (e.g., at INR 1800 [30 USD] per vial, degludec is more costly in India than Europe, and 50% more expensive than human insulins versus NPH, sold at INR 133 [2.2 USD]) [39]. Moreover, the mean list price of insulin has shot-up and nearly tripled from 2002 to 2013 [6]. Between 2001 and 2015, lispro and human insulin have become costly by 585% (from 35 to 234 USD per vial) and 555% (from 20 to 131 USD per vial), respectively [39]. Fig. 1 illustrates significantly higher median consumer prices of analogue insulin compared to human insulin [25]. Following the similar trend, OOP expenses of patient for insulin has doubled over the last decade. This skyrocketed cost has resulted in unaffordability of insulin, even for few high-income patients with DM [6]. Thus, patients are compelled to make a choice of either paying for other daily needs or buying their medications, thereby endangering them to both short- and long-term complications [8].

7. Reasons for increasing cost of insulin and its analogues

Several factors have led to rise in the cost of insulin, including: 1. As of 2009, insulin analogues represented two-thirds of all insulin used in high-income countries. However, on an average, they cost more than two times as much as conventional human insulins, in terms of per unit cash price [40]; 2. Insulin supply chain, from manufacturer to consumer, is complex and involves multiple

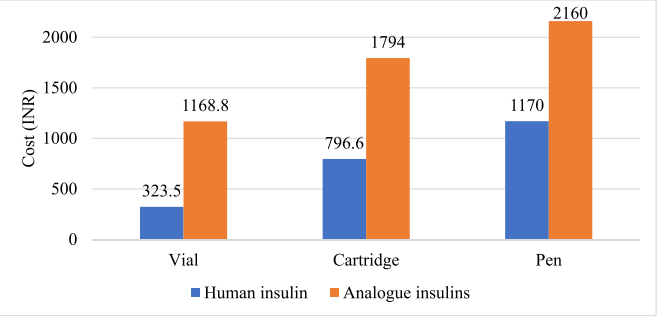

Fig. 1. Median consumer prices (adjusted to 10 ml 100 IU/ml) by insulin type (adapted from findings of Satheesh et al. [26]).

parties – including wholesalers, pharmacy benefit managers, employers, insurance health plans, and pharmacies in between – that make profit or loss on the basis of insulin sales; 3. Insulin, a biologic drug, is obtained from recombinant DNA technology, thereby making it costly to manufacture; 4. Biologic drugs require unique conditions to manufacture that are proprietary and difficult to exactly replicate; and 5. Insulin being a biological product cannot be produced as generic in the same way as other drugs [41].

8. Prevalence of cost-related insulin underuse and insulin-related cost-saving behaviors

The high cost of insulin has an impact that is beyond the budgets of government health insurance programmes. The rate of increment in OOP payments has crossed the inflation for majority of insulin products. This has led to, among patients with T2DM, use less dose of insulin than prescribed, or completely avoid it, as they can no longer afford insulin [37]. It is generally stated that the cost of medication is inversely related to the compliance [31]. A study highlighted that around 25% of patients with DM confessed about cost-related underuse of insulin and this is clearly related to poor glycemic control. The study also stated that >33% patients with DM with cost-related underuse never discuss this issue with their diabetologists. The cost-related underuse of insulin was mostly reported by individuals with lower incomes and around 66% of these individuals also faced hardship in purchasing diabetes equipment, suggesting wider cost barriers in management of DM [41].

As per Insulin Affordability Survey (2018), 39% individuals suggested increased insulin costs over the last year, while 27% stated that the increased cost has affected the use or purchase of insulin in some way. Among those affected, 26% confessed about taking less than prescribed dose regularly, 23% had switched to more economical brands or types, and further 23% confessed about missing doses weekly. Apart from these insulin rationing behaviors, these individuals also reported having to give up their other requirements including daily utilities, transport, hospital visits, other medications, or housing [7].

Various ways by which patients with DM indulge in cost-related insulin underuse are using less insulin than prescribed, trying to stretch out one's prescribed insulin, stopping the use of insulin, not filling an insulin prescription, and/or not starting insulin at all. According to a study, one-fourth of the respondents accepted that they had indulged in at least one of these underuse behaviors in the last 1 year due to higher OOP cost of insulin. These patients had lower income; 60.8% patients discussed the cost of insulin with their diabetologists and 29.4% changed the type of insulin due to cost [41].

9. Cost, non-compliance, and poor glycemic control: An entangled triplet

Several patients with DM have comorbid conditions that require the use of prescription medication; thus, these patients have higher mean monthly OOP medication costs compared to patients with most other chronic conditions. Higher OOP costs can result in a considerable hindrance to compliance to prescription medication. Studies have demonstrated that certain patients cut back on medication use because of higher cost, and this decreased compliance has been associated with serious adverse events, including emergency department visits, hospitalization, and mortality [42,43].

As per an estimate, there would be addition of an OAD every 4–5 years, and the drug count for OAD seems to stabilize after 15 years of diagnosis of DM and three OADs. This plateauing effect is most likely due to the addition of insulin. Moreover, need of non-diabetic drugs tend to rise suggesting an increased need of medications for comorbid conditions. For OADs alone, the mean lifetime cost is around INR 1.5 million [34].

Various ways of estimating the compliance are medication possession ratio of ≥80% over the period of observation, discontinuation rates, and medication persistence (as no gap in prescription drug supply for at least 30 days) [44]. It is suggested that the risk of poor medication compliance may be higher when it is estimated in terms of patients who failed to fill the first prescription. Depending on the methodological approach used, the reported incidence of poor medication compliance in patients with T2DM ranges from 38 to 93% [45].

In patients with T2DM, non-compliance is among the major factors associated with poor outcomes. The ADA defines adequate compliance as 80% compliance. In their first year of therapy, around half of the patients with T2DM fail to take at least 80% of prescribed doses [46]. Various studies have reported wide variation in the percent of patients being non-compliant and this ranges from 13 to 64%, and 19–46% for users of OADs and insulin, respectively [47]. It is further reported that 47.8% patients with T2DM do not meet the HbA1C goal of <7%, suggesting that poor glycemic control is a common occurrence [46]. Moreover, patients with DM involved in cost-related underuse of insulin are 3 folds more likely to have poor glycemic control [41].

Conversely, studies have demonstrated that improved compliance is linked to better glycemic control and reduced use of healthcare resources [46]. Higher compliance has been reported to be related with overall reduced costs, particularly lower acute care costs that results in total cost reduction [48]. Review of literature suggests that higher compliance is associated with improved glycemic control, lesser rate of hospital admission, and fewer visits to emergency department [49].

10. Uncontrolled DM and its consequences

Over the period of time, uncontrolled DM progresses to result in various complications that may decrease the health-related quality of life and increase the risk of premature death [2]. In the short-term, cessation of insulin primarily results in diabetic ketoacidosis. If left untreated, it can result in coma and death [50]. A study based in US reported that about 33% of patients with DM who developed diabetic ketoacidosis due to withdrawal of insulin stated that they were short of funds to procure insulin [51]. These findings suggest a critical need to focus on the affordability of insulin.

The long-term complications resulting from non-compliance due to self-rationing of insulin are microvascular (such as nephropathy, neuropathy, and retinopathy) and macrovascular (such as coronary artery disease, stroke, and peripheral vascular disease) [2]. These complications are a cause of increased economic burden of T2DM. Around 20% cost of commercial insurance or Medicare is due to diabetes-related complications [3]. Among these Medicare beneficiaries, an increase in complications has been reported to be associated with increased total costs [4].

To reduce the risk of diabetic complications, it is recommended to achieve and sustain the glycemic targets [2]. Importance of achieving the glycemic targets was highlighted by a study in US, according to which each 1% increment in HbA1c results in a 4.4% rise in costs of managing the DM, translating to an increment of 250 USD per year [52]. As suggested from the above-mentioned findings, complications related to DM results in significantly increased costs, not only at the time-point at which they occur, but during the period that follows [53].

11. Concept of interchangeability

Biosimilar insulins are approved versions of and highly similar to already marketed reference biological insulin with respect to potency, safety, and quality [54]. They were introduced with an objective to replicate the structure and clinical functions of the reference biological insulin and thus, provide an alternative to existing biological insulins that are no longer protected by the patents [55]. This has resulted in reduced cost and time required to bring a new biosimilar insulin in to the market, as it has to be demonstrated biosimilar to the reference biological insulin through analytical, chemical, and pharmacokinetic or pharmacodynamic studies without the requirement of longer-term clinical trials [54].

The highly similar nature of biosimilar insulin allows them to be used interchangeably with reference insulin, as they are expected to result in identical clinical effects as the reference insulin in every patient. Moreover, they are devoid of safety issues or loss of efficacy when used over a period of time and interchanged with reference insulin [56]. The evidence gathered over a period of 11 years demonstrate that biosimilars approved by regulatory agencies can be used as safely and effectively in all their approved indications as other biological drugs [57]. Over the last decade various biosimilar insulin have been approved by Drugs Controller General of India and US Food and Drug Administration. Table 1 depicts the biosimilar insulin approved in India and US with their availability in respective markets [58].

12. Biosimilar insulin: The way ahead?

The introduction of biosimilar insulins has changed the landscape of insulin market. This has enabled wider access of insulin with reduced price that is expected to be in the range of 20–40%. Moreover, in the long run, the increased competition between insulin manufacturers might result in further decrease in the price of insulin [55,59]. Fig. 2 illustrates the comparative cost of innovator and biosimilar insulin brands marketed in India and it can be observed that biosimilar insulins are relatively more economical than innovator insulin.

Moreover, with rising costs of insulin, biosimilar versions might be the best option to make healthcare more economical (Fig. 3)

Table 1
Biosimilar insulin approved in India and US with their availability.

	Marketing authorisation holder	Availability in India/Date of DCGI approval	Availability in US/Date of US FDA approval	Name of the Product approved in India	Cost in India (INR) [58]
Insulin Glargine	Wockhardt	22-02-2007	Not available[b]	Glaritus	1525 (900 IU)
	Biocon	28-08-2018	Not available[b]	Basalog	610.53 (300 IU)
	L. G. Lifesciences[c]	20-12-2011	Not available[b]	Insulin Glargine	Not applicable
	Lupin	13-02-2015	Not available[b]	Basugine	594.8 (300 IU)
	Eli Lilly	21-08-2017	16-12-2015	Basaglar	665 (300 IU)
	Sanofi	Available[a]	25-02-2015	Toujeo Max Solostar	Not applicable
	Sanofi	Available[a]	25-02-2015	Toujeo Solostar	3906 (1350 IU)
Biphasic Isophane Insulin	Wockhardt Limited	March 24, 2003	Not available[b]	Wosulin 30/70	640.5 (900 IU)
	Wockhardt Limited	July 14, 2003	Not available[b]	Wosulin 50/50	640 (900 IU)
	Wockhardt Limited	March 24, 2003	Not available[b]	Wosulin N	640 (900 IU)
	Gland Pharma[c]	09-08-2011	Not available[b]	Biphasic Isophane Insulin	Not applicable
	Gland Pharma[c]	09-08-2011	Not available[b]	Biphasic Isophane Insulin	Not applicable
	Gland Pharma[c]	09-08-2011	Not available[b]	Isophane Insulin Injection	Not applicable
	MJ Biopharma[c]	14-06-2018	Not available[b]	Human Insulin	Not applicable
	Epygen Biotech[c]	21-05-2021	Not available[b]	Biphasic Isophane Insulin	Not applicable
	Aventis Pharma	07-05-2002	Not available[b]	Insuman Basal	140.07 (400 IU)
	Novo Nordisk[c]	14-05-2009	Not available[b]	Biphasic Isophane Insulin	Not applicable
	Novo Nordisk	14-05-2009	07-01-1991	Insulatard	350.9 (300 IU)
	Novo Nordisk	Available[a]	25-06-1991	Mixtard 30	350.9 (300 IU)
	Novo Nordisk	Available[a]	Not available[b]	Mixtard 50	350.9 (300 IU)
	Biocon[c]	12-02-2018	Not available[b]	Biphasic Isophane Insulin (30/70)	Not applicable
	Biocon	12-02-2018	Not available[b]	Insugen N	214.41(300 IU)
	Biocon	Available[a]	Not available[b]	Insugen 50/50	258.96 (300 IU)
	Lupin	Available[a]	Not available[b]	Lupisulin M 30	319 (300 IU)
	Lupin	Available[a]	Not available[b]	Lupisulin M 50	290.15 (300 ml)
	Lupin	Available[a]	Not available[b]	Lupisilin N	264.6 (300 IU)
	Shreya life sciences	Available[a]	Not available[b]	Recosulin M 30	143.43 (400 IU)
	Shreya life sciences	Available[a]	Not available[b]	Recosulin M 50	180.62 (400 IU)
	Shreya life sciences	Available[a]	Not available[b]	Recosulin N	140.7 (400 IU)
Human regular insulin	Wockhardt	24-03-2003	Not available[b]	Wosulin R	582.5 (900 IU)
	Shantha Biotechnics[c]	14-11-2013	Not available[b]	Human insulin	Not applicable
	Scigen Biopharma[c]	03-02-2015	Not available[b]	Recombinant Human Insulin	Not applicable
	Eli Lilly	18-04-1998	28-10-1982	Huminsulin R	389 (300 IU)
	Biocon	20-12-2016	Not available[b]	Insugen R	235.63 (300 IU)
	Novo Nordisk	14-05-2009	25-06-1991	Acrapid	350.9 (300 IU)
	Aventis Pharma	07-05-2002	Not available[b]	Insuman Rapid	333.8 (300 IU)
	Gland Pharma[c]	09-08-2011	Not available[b]	Soluble Insulin injection IP	Not applicable
	Wockhardt	24-03-2003	Not available[b]	Consegna R	398 (600 IU)
	Koye Pharma	Available[a]	Not available[b]	Equisulin R	242.62 (300 IU)
	USV	Available[a]	Not available[b]	Human-Fastact	143.42 (400 IU)
	Cadila Pharma	Available[a]	Not available[b]	Humarap	147.74 (400 IU)
	Sun[a]	Available[a]	Not available[b]	Insucare R	149.4 (400 IU)
	Shreya life sciences	Available[a]	Not available[b]	Recosulin-R	147.06 (400 IU)

[a] Available in the Indian market, however date of market authorization not found in public domain.
[b] Data on brand name not available in public domain, however possibility of its market authorization by other brand name could not be refuted.
[c] Brand name not available in public domain.

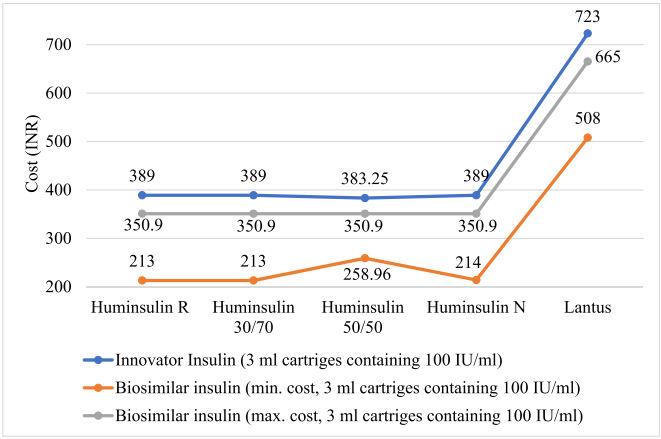

Fig. 2. Comparative cost of innovator and biosimilar insulin brands marketed in India.

[60]. In a recent study, biosimilar glargine has been shown to be non-inferior to innovator glargine in glycemic control with comparable immunogenic response and safety in patients with T2DM uncontrolled on OADs. There was no significant difference in percent change in the anti-insulin antibodies (AIA) titer, change in the HbA1c level at the end of six months, and the incidence of adverse events between the two treatment arms. Overall results suggested no significant difference in terms of immunogenicity, reduction in HbA1c, and tolerability profile of biosimilar and innovator glargine [61].

Addressing the cost issues of insulin, a position statement of Endocrine Society also recommends accelerating the approval of biosimilar insulin so as to create competition in the market [62]. Some pharmaceutical companies have taken aggressive steps towards this and have provided cost-effective biosimilar insulins and insulin analogues such as glargine to patients with T2DM. Even more cost saving attempts beyond this such as providing 50% extra human insulin and insulin analogues at the same price have made a huge difference in insulin adherence of patients with T2DM.

13. Shared decision making and insulin

It is recommended to practice informed, and shared decision making with the patients in every sphere of diabetes management to achieve optimal therapeutic outcomes. Such combined decision-making approach should be extended to the choice of insulin preparations. It is recommended that based upon the available evidence, and socioeconomic reality, patients should be able to make an informed decision regarding the choice of originator or biosimilar molecule. Also, to enable this, it would be an appropriate move by the manufacturer to make public all the factors which may influence this decision, including robustness of clinical data, quality of cold chain maintenance, and availability of post-marketing pharmacovigilance activities [63]. Based on the consensus statement, it is recommended that the physician should be highly vigilant and sure about the quality of the molecule and ensure that while using a biosimilar molecule he has access to and knowledge of the complete comparative profile validating its quality, safety, and efficacy [64]. In terms of quality standards of biosimilar insulins, health care professionals need to be vigilant about quality comparison to the innovator and assess the acceptability of

Fig. 3. Introduction of biosimilar and their effect on healthcare delivery.

biosimilar insulins for their specific patients' needs and by closely monitoring patients at time of initiation of and transition to a biosimilar insulin.

14. Conclusion

A majority of patients with T2DM are uncontrolled on OADs. Delay in initiation of insulin therapy leads to a variety of micro- and macro-vascular complications, thereby increasing the cost of managing the DM. Thus, insulin should be initiated at an early stage to attain and maintain the target glycemic goals. Though, the current cost of insulin therapy is a major deterrent to initiate and continue the lifelong use of insulin, introduction of biosimilar insulin is expected to decrease the cost and increase the affordability of therapy. Lot of discussion and debate on biosimilar insulin have been held to expect at par quality of biosimilar insulins as per the stringent rules by the regulators. With biosimilar insulin complying to the Indian and global regulatory norms with respect to quality, efficacy, and safety to that of innovator, these cost effective biosimilar human insulin and insulin analogues will further enhance the compliance of patients and should be practiced whenever applicable in Indian T2DM patients. However, the patient, along with prescriber, (and payer, if relevant) should be allowed to take shared, informed decisions regarding the insulin they wish to use. This practice will then be "patient-centered" in its true spirit.

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Declaration of competing interest

Dr. Shahu Ingole and Dr. Sanjay Kamble are the employees of Wockhardt Ltd. (India). All other authors declare no conflict of interest.

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