Recombinant Human Insulin in Global Diabetes Management – Focus on Clinical Efficacy

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Biosynthetic human insulin and insulin analogues are the mainstay of insulin therapy for both type 1 and type 2 diabetes although access to human insulin at affordable prices remains a global issue. The world is experiencing an exponential rise in the prevalence of diabetes presenting an urgent need to establish effective diabetes therapy in countries burdened by inadequate health care budgets, malnutrition and infectious diseases. Recombinant human insulin has replaced animal insulins and animal-based semisynthetic human insulin thereby available in sufficient quantities and at affordable prices able to provide global access to insulin therapy. In many patients, analog insulins can offer additional clinical benefit, although at a considerably higher price thus severely restricting availability in low income countries. The approval process for recombinant human insulins (i.e. biosimilars) and analogue insulins is highly variable in the developing countries in contrast to Europe and in North America, where it is well established within a strict regulatory framework. This review aims to discuss the future access to human insulin therapy in a global context with an ever increasing burden of diabetes and significant economic implications.

The International Diabetes Federation (IDF) estimated that the total number of adults (20–79 years) living with diabetes in 2015 was 415 million and that by 2040, the number is predicted to rise to 642 million (see *Figure 1*).[1] In countries with a low healthcare budget, biosynthetic human insulin is the mainstay of effective therapy, and is now available from an increasing number of suppliers, at an affordable price locally. However, the overall cost of diabetes care has been increasing due to the dramatic and relentless increase in prevalence globally. A significant part is related to cost of insulin in the form of human insulin, and the much more expensive option of analogue insulins. Insulin therapy is indispensable in type 1 diabetes (T1DM) and is essential for type 2 diabetes (T2DM), first presenting at an advanced stage or when orally active antidiabetic drugs (OAD) fail to maintain adequate glycaemic control with the many newer therapeutic options increasingly costly. The American Diabetes Association (ADA) estimates that the total cost of known diabetes in the US rose by about 40% over a five-year period from US$174 billion in 2007 to US$245 billion in 2012.[2] representing 20% of all healthcare dollars in the US. A significant part of this increase was attributed to the cost of new analogue insulins and new OAD drugs.

In contrast, worldwide, the cost of recombinant human insulin has been decreasing, due to large-scale production, competition between insulin manufacturers in different geographic areas (for example, India and Asian countries). In the US, human insulin formulations are now often available from drugstore pharmacies without a prescription. This includes the classically low-priced category of insulin vials and syringes, and also some insulin pen devices. Interestingly, in the US recently a price differential has developed between regular human insulin and intermediate-acting human neutral protamine hagedorn (NPH) insulin.

The situation is very different in low-income countries, where access to recombinant human insulin formulations at affordable price levels remains to be established and/or maintained. This is very obviously a question to be addressed by national and regional healthcare systems.

Figure 1: Estimated total number of adults (20–79 years) living with diabetes in 2015


<100 thousand
100–500 thousand
500 thousand – 1 million
1–10 million
10–20 million
>20 million
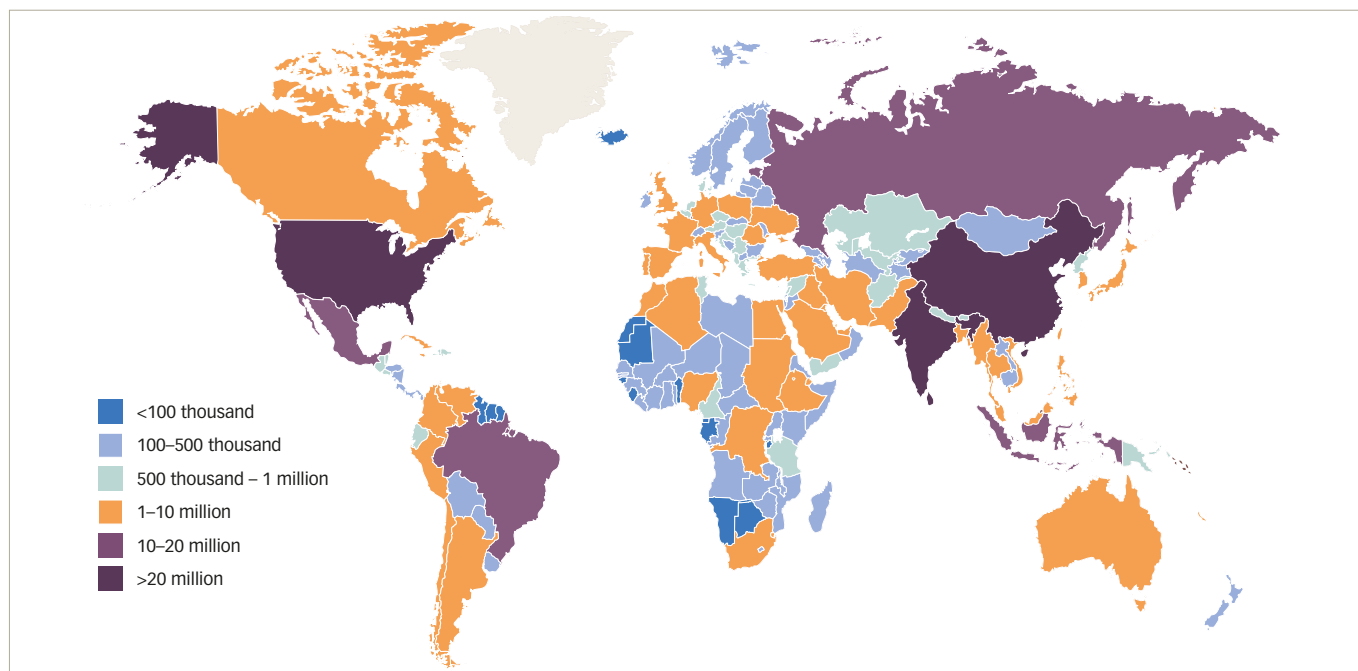
Source: International Diabetes Federation, 2015.[1]

Figure 2: Mean annual health expenditure per person with diabetes by region, 2010

Region	Mean Annual Expenditure/Person US$
North America	5751
Europe	1991
Western Pacific	508
South America and Central America	458
Eastern Mediterranean	210
Africa	112
Southeast Asia	53

Source: Nainggolan L, 2013.[3]

Figure 3: Utilisation of human, animal, and analogue insulin among type 2 diabetes patients in the US who had at least one prescription for insulin[25]
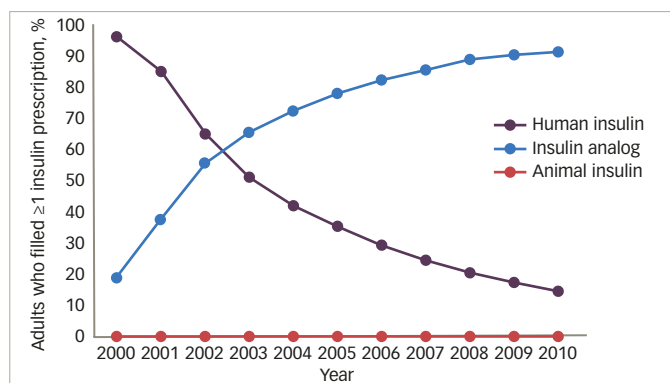
Source: Lipska KJ, et al., 2010.[25]

Globally, 12% of health expenditure is currently consumed by diabetes and diabetes-related complications with major differences related to the access to diabetes care and provision of effective medication.[1]

The mean annual health expenditure per person with diabetes in 2010 was highest in North America and lowest in South-East Asia (see *Figure 3*).[3] The capital expenditures on diabetes per person per year also differed among different countries of the world,[4] with half of all nations spending less than US$400, 42% of countries less than US$300 and 20% allocating less than US$100 per person per year.[5] The fraction of capital expenditure attributed to insulin therapy is particularly high in countries with low health budgets, because there are no other therapeutic options for persons with T1DM.

Many regions of the world, such as Asia, are currently experiencing a disproportionally large increase in the prevalence of diabetes, both T1DM and T2DM, due to more effective screening, enhanced early diagnosis, and changes in lifestyle due to rapid economic growth and urban development. In Asia, T2DM tends to develop at a younger age and in those with a lower body mass index than in Europe and North America.[6] According to the World Health Organization (WHO), the western Pacific region has 153 million adults with diabetes, which is substantially more than either in China (109.6 million) or India (69.2 million). On the continent of Africa, the expected rate of increase in prevalence of diabetes is amongst the highest in the world.[7] In an assessment of the treatment options, the WHO has addressed issues on how to support the production of pharmaceuticals in Africa.[8,9]

Insulin by injection remains the most effective component of diabetes management.[6,10] Therapy in T1DM needs to be initiated at or near the time of diagnosis. Therapy by insulin in T2DM is most often initiated when OAD drugs no longer achieve effective glycaemic control. Metformin is the most common first-line therapy,followed by the addition of a sulfonylurea, dipeptidyl peptidase 4 (DPP-4) inhibitor, an insulin sensitiser, a sodium-glucose co-transporter-2(SGLT2) inhibitor or a glucagon-like peptide 1 (GLP-1) receptor agonistas second line. Insulin-based therapy is usually the third line when orally active drugs fail.[11] Insulin may be commenced at an early stage if on presentation the person with T2DM is markedly hyperglycaemic (glycated haemoglobin [HbA$_{1c}$] >8%) with symptoms. Clinical evidence suggests

that the introduction of insulin earlier in the treatment of patients with T2DM can modulate the disease process and significantly improve glycaemic control.[12,13] Where there is a strong rationale to initiate insulin therapy at an early stage of T2DM, selecting an affordable biosynthetic human insulin (or animal insulin) should be considered in preference to analogue insulins. Initiation of insulin therapy is often delayed, despite the evidence of chronic poor glycaemic control ('clinical inertia') or simply due to limited access. A GLP-1 receptor agonist is advocated when the body mass index exceeds 35 kg/m prior to or as add-on to insulin therapy. Therapy change always needs to take into consideration both the clinical situation and the patient's preference. There are clinical situations when analogue insulins have important advantages, in paediatrics,[14] in pregnancy[15] and in Ramadan.[16] Many people with diabetes unfortunately remain in poor glycaemic control[17,18] due to barriers such as compliance to therapy, patient and healthcare professional preferences, and resource allocation, all of which must be addressed.[19]

Global availability of insulin

The global supply situation for insulins has improved steadily since the early period, when animal insulins were gradually replaced by chemical synthesis of human insulin and semisynthetic human insulin,[20] due to concerns about future limitations of supply. The global supply of recombinant human insulin and analogue insulins has improved steadily (*Table 2*). A recent market survey on global insulin supply concluded that at the moment, insulin production has been able to sustain the increase in demand.[21] Significant inequalities exist in the global availability of human insulin at affordable cost in developing countries, often limiting access to this crucial therapy[22] despite its inclusion in the WHO's Essential Medicines List. Based on the International Insulin Foundation's (IIF's) assessment, the root cause relates to distribution, tendering and government policies which are all aimed at reducing diabetes-related expenditures.[23] The situation is critical in countries with limited resources, where human insulin (formulations of soluble and NPH insulin) is the only affordable option. The introduction of analogue insulins[24,25] and new injectable and orally active diabetic agents have contributed significantly to the steadily increasing cost of diabetes care in Europe and North America, with reimbursement an increasing problem restricting their availability.[26] In the US, the use of insulin among privately insured adults with T2DM mellitus increased by approximately 50% between 2000 and 2010 (see *Figure 3*),[27] which coincides with the widespread prescription of analogue insulins and recently developed coformulations, due to specific advantages of personal convenience and a reduced risk of hypoglycaemia.[28] In Europe, cost and re-imbursement remain critical issues for patient-related decisions. However, many healthcare schemes retain human insulin on their essential drug lists and continue to encourage their use due to long-term established therapeutic efficacy.[29] The three essential medicines for T2DM are metformin, sulfonylureas and human insulin.[30] Metformin is available in generic form, with sulfonylureas and biosynthetic human insulin also now widely available. The global market for human insulin is dominated by three major insulin manufacturers including Eli Lilly, Novo Nordisk and Sanofi. Prescribing human insulin formulations is a logical and practical approach to reducing costs, with the recent option of considering biosimilar insulin analogues, which involves complex and evolving approval procedures ongoing in Asia, India and Africa.[22]

The global insulin market

When considering the cost of human insulin formulations (see *Table 1*), there is a clear cost benefit in favour of the classical vial and

Table 1: Median prices per 10 ml of recombinant human insulin compared with 10 ml of analogue insulin[8]

Price per 10ml 100 IU/ml	Public sector				Private sector	
	Tender price human	Tender price analogue	Patient price human	Patient price analogue	Patient price human	Patient price analogue
Minimum	2.24	6.88	2.16	6.41	1.67	5.89
Maximum	43.51	81.67	36.70	124.90	50.57	250.73
Median	5.99	34.20	7.64	45.03	16.65	39.35
Ratio analogue: human		5.71		5.89		2.36

Source: Beran D, et al., 2016.[8]

syringe formulations and the more convenient human insulin pen presentations. The cost difference of adopting formulations of analogue insulins has little justification for the vast majority of insulin-treated persons with diabetes. The price is on average fivefold higher for insulin analogues, although it is decreasing gradually in certain markets with the availability of biosimilar analogue insulins (for example, insulin glargine). However, currently the costs involved remains out of range for many developing countries. For basal insulin therapy, analogue insulins[22] have advantages over NPH human insulin but cost remains a prohibiting factor in such countries.

Approved and marketed human insulin products

In the WHO Essential Drugs List, insulin (soluble) and intermediate acting insulin (NPH) are listed without further detail or reference to products.[31] Brand names differ considerably by global region and a search using the international non-proprietary names (INN, insulin human) as well as careful identification of the specific formulations is recommended. In each case, the active pharmaceutical ingredient (API) is recombinant human insulin.

There are currently three groups of recombinant human insulin formulations available for clinical use,[32] which are characterised by their onset, peak action and duration of action which determines their clinical use. The groups are:

- Regular human insulin (short-acting soluble).
- Intermediate-acting human insulin (NPH) suspension with delayed onset and protracted duration of action.[33,34]
- Premix formulations provide both meal time and basal insulin supply, they contain a fixed ratio of soluble regular insulin and of NPH insulin suspension, in a range of 15–50% of soluble insulin.[33]

Widely available recombinant human insulin brands include Insuman® (Sanofi, Paris, France), Humulin® (Lilly, Indiana, United States) and Novolin® (Novo Nordisk, Bagsværd, Denmark).[33] These insulin formulations are of consistent quality, with globally available documentation of product details.

The premix formulations of recombinant human insulin with variable ratios of regular and NPH insulin, i.e. Humulin M2, M3 and M5, Insuman Comb 15, 30 and 50; and related Novolin premix formulations, such as Novolin 70/30, Novolin 60/40 and Novolin 50/50 need thorough re-suspension immediately before injection.[25]

In the last decade, an increasing number of 'biosimilar' recombinant human insulins have emerged from different pharmaceutical companies

Table 2: Global supply, demand and surplus of insulin 2012–2014

	2012	2013	2014
Demand (Million Pieces)	1580.0	1850.0	2150.0
Production/ Supply (Miillion Pieces)	1828.9	2000.0	2217.6
Surplus (Million Pieces)	248.9	150.0	67.7

Source: Wirtz et al. 2016[21]

in India, United Arab Emirates (UAE), Egypt, Mexico and Poland, which were subsequently approved by their respective drug regulatory authorities. This provides an ever-increasing number of recombinant human insulin formulations (common INN insulin human), often marketed locally under different brand names and with limited supporting published documentation. All prescriptions need to include brand names to avoid mistakes when exchanging products (interchangeability). There is an ever-increasing number of formulations which do not provide either medical and/or pharmaceutical information.

Biosimilars of analogue insulins (recombinant)

There is currently considerable interest in the development and approval of biosimilar analogue insulins,[29] in part due to patent expiration and the opportunity to substantially decrease clinical development costs and eventually the cost to the consumer.[29] However, there is the need for rigorous documentation relating to the production process, pharmacokinetics (PKs), clinical efficacy and safety when compared with marketed analogue insulin products.[35] The global access to 'biosimilar' analogue insulins is now relatively easy due to an ever-increasing number of manufacturers and production facilities involved.[29,36] The decreasing cost of analogue insulins will encourage market competition and can eventually result in a further expansion of the global access to insulin therapy.[37]

A panel of certified diabetes educators (CDEs) found that many patients would definitely use the more affordable biosimilar analogue insulin products, after strict evaluation to determine that they are equivalent to currently marketed insulin products in terms of safety and clinical efficacy based on rigorous quality, pharmacovigilance and risk-assessment procedures.[31] Details of the procedures will differ considerably depending on established regulations.

The European Medicines Agency (EMA) approval procedure refers to the need for preclinical, clinical and pharmaceutical information, including pharmacovigilance and a risk management plan.

- Detailed documentation for process of manufacturing and consistent quality assurance (details of biosynthesis process, purification and final insulin product).
- PK and pharmacodynamic (PD) studies are required to be conducted for bioequivalence using the glucose clamp technology.
- Evidence of consistent glucose control by HbA_{1c}, pre-meal and post-meal blood glucose profiles, seven-point blood glucose profiles, etc.
- Self-monitored plasma glucose (SMBG) profiles recorded by patients.
- Hypoglycaemia rates, by predefined criteria including plasma glucose monitoring where available, and by clinical evidence
- Comparative studies in patients with T1DM, versus approved marketed products.
- Comparative studies in patients with T2DM, versus approved marketed products and in other specific populations (paediatric, pregnancy etc.)
- Specific clinical studies on antigenicity and local reactions in people with T1DM.

Pharmacovigilance studies are required for each biosimilar insulin product, for the lifetime of production, to detect any clinical effects which may be related to the methods used for production of the specific recombinant biosimilar analogue insulin preparation. Discussions on the price of recombinant insulin formulations are based on legal and governmental considerations in different countries worldwide.

Interchangeability

One important practical consideration when choosing biosimilar human insulin products is its interchangeability, i.e. can a patient be switched from an approved product to a biosimilar formulation? Such a substitution when initiated and authorised by pharmacists may require identification by the INN and specific formulation (short-acting or regular, intermittent-acting, long-acting or premixed human insulin).

Traceability

After a change from one approved insulin product to another biosimilar, traceability is also very important. This requires identification of the initial and subsequent insulin product, both by the approved WHO INN and brand identification. Traceability is essential for any pharmacovigilance programme. This information is available from drug regulatory systems established by the country of origin (manufacturing site) and the Ministry of Health in that country or region.

Future evolution of insulin therapy requires a full understanding by patients and healthcare professionals on the subject of human insulin biosimilars (a small, restricted group) and analogue insulin biosimilars. The majority of patients (66%) in a recent market research survey would consider using such biosimilar insulins, provided that the cost is decreasing but that efficacy and safety is maintained and confirmed.[38] The adoption of biosimilar insulin products is clearly a responsibility of the governmental authorities and/or health insurance systems. In clinical terms, there may be a benefit when changing from a recombinant human insulin to more expensive analogue insulins, e.g. in special populations of patients who require a faster onset, and/or a longer duration of action, a reduced risk of hypoglycaemia, less weight gain and improved stability in insulin delivery systems. Implementation of such decisions then depends on local cost considerations.

Conclusions and future perspectives

The world is experiencing an exponential rise in the number of patients diagnosed with diabetes and requiring insulin therapy (diabetes pandemic). This is the main driving force behind the increased economic burden of diabetes in low-income countries.[39] The rising cost of therapy in developed regions of the world such as North America and Europe is predominantly attributed to the introduction of the much more expensive new insulin analogues, the widespread introduction of continuous glucose monitoring systems e.g. continuous subcutaneous glucose monitoring (CSGM), and the ever-increasing number of expensive injectable and OAD drugs for T2DM.

Clinical efficacy of recombinant human insulin has been well established over approximately 35 years of clinical use. Clearly, in low-income countries the critical factor is to provide affordable access to recombinant human formulations. With respect to insulin therapy and improved management of T1DM and T2DM, validated diabetes education for patients and healthcare professionals alike is essential.[8] A key issue is the earlier introduction of insulin treatment in T2DM, which has been shown to improve glycaemic control and thereby to retard and reduce the onset and progression of diabetes-related complications. These complications include amputations, visual loss and blindness,

coronary artery disease and cerebrovascular accidents (stroke), nerve and kidney damage and complications during diabetic pregnancy. In 2012, a report from the London School of Economics estimated that the cost of prescribing medication for the complications of diabetes is around three to four times greater than the cost of prescribing effective diabetes medication early after establishing the diagnosis.[40]

Very distinct problems remain relating to insulin therapy, which includes its safe and effective application, glucose monitoring, management of hypoglycaemia and adherence to therapy.[41] The problem of non-adherence is very real in low-income countries without fully developed patient support systems in place. One important aspect of improving adherence is to establish consistent access to human insulin at an affordable price level.

Recombinant human insulin therapy is a confirmed and effective therapeutic option when supported by appropriate patient education.[36] The increasingly broad range of 'biosimilar' human insulin preparations now available in many countries requires specific education for healthcare professionals on prescribing and dispensing, when selecting human insulins products for clinical practice.[42] In developed countries biosimilar human and analogue insulins are assessed by well-defined preclinical procedures and clinical studies, supported by post-marketing pharmacovigilance programmes.[43] Clinical awareness of any changes in insulin quality is very important. Self-monitoring of blood glucose for several weeks after a change to or between biosimilar insulins will help to identify any batch-to-batch differences, thus enabling dose adaptation. Diabetologists are fully aware that patients' insulin requirements change under different real-life situations and they should take this into consideration. Therefore, individual guidance, counselling and monitoring, while often elusive, remains an essential requirement to achieve better and safer glycaemic control, especially in patients requiring insulin therapy. Global availability of recombinant human insulin of consistent high quality is an important future step in the quest to improve the outcome for people with diabetes. ❑

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