Clinical, Economic and Healthcare Constraints and Challenges Using Insulin Analogues in the Treatment and Control of Diabetes in Vulnerable Populations

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Abstract
Insulin constitutes the most superior, effective and consistent substance for blood glucose level control in diabetes. Insulin analogues are forms of insulin which have undergone molecular alteration. The approximate global acceptance of the transition to analogue insulins in recent decades has resulted in elevated costs, but devoid of pellucid posited evidence of the advantages in persons presenting with diabetes. Pregnancy impacts on both maternal and foetal metabolism in both diabetic and non-diabetic women; thus, insulin requirements increase at pregnancy due to progressive augmentation of insulin resistance. Universal constraints and challenges with respect to insulin access have been reported in low-income and middle-income countries as well as high-income countries in vulnerable populations and others.

Keywords:
Aspart, Detemir, Lispro, Degludec, Glargine, Pregnancy

1. Introduction
Insulin constitutes the most superior, effective and consistent substance for blood glucose level control in diabetes. Neutral protamine Hagedorn, NHP has preponderated as the basal insulin in clinical care since 1946. There is perspicuous absorption variability, though due to the unavoidable requirement for re-suspension and the time-action profile of peak activity of circa 4-6h following subcutaneous administration that confers a significant propensity for between-meal and nocturnal hypoglycaemia. During the 1980s, recombinant DNA technology provided the latitude to modify the insulin molecule leading to the development of soluble long-acting insulin analogues, glargine and detemir. They both present lower hypoglycaemia risk in comparison to NPH regarding improved time-action profiles and decreased daily glucose variability [1].

Insulin analogues are forms of insulin which have undergone molecular alteration. The approximate global acceptance of the transition to analogue insulins in recent decades has resulted in elevated costs, but devoid of pellucid posited evidence of the advantages in persons presenting with type 2 diabetes, T2D. Short-acting insulin analogues ostensibly provide more flexible dosing and convenience, while long-acting analogues are related to decreased risk for hyperglycaemia in comparison to synthetic human insulin, but their cost is grossly higher [2]. Universal constraints and challenges with respect to insulin access have been reported in low-income and middle-income countries [3] as well as high-income countries [4] in vulnerable populations and others.

2. Type 1 diabetes, T1D and Type 2 Diabetes, T2D
The treatment and control of type 1 diabetes mellitus, T1D encompasses exogenous and extraneous imposition of the functionalities of beta cells to achieve blood glucose concentrations which are proximate to the normal range. This strategy indicates that glucose sensing has to be replaced and insulin contents must give a semblance of physiologic insulin-action profiles, as well as basal coverage and alterations at meals. In addition to the training and education available to diabetic patients, it is necessary to provide and achieve adequate glycaemic control from insulin preparations with action profiles and latitude for stable basal insulin coverage and conventional mealtimes insulin peaks for desirable quality of life without compromising stringent glycaemic control in the face of type 1 diabetes or other. Insulin analogues of diverse modifications or regimens [5].

Type 2 diabetes is a progressive disorder that requires insulin therapy in several instances to ensure continuous and adequate blood glucose control [6]. At the onset, basal insulin is efficacious in several T2D patients for control sustenance, but in certain individuals, post-prandial glucose concentrations are elevated or become exacerbated with the further reduction of endogenous insulin concentrations. Supplementation with a meal-time insulin becomes pertinent for the provision of better post-prandial glucose control. The post-prandial glucose control is pertinent even at high concentrations of bA1c (>10.0% or 86 mmol/mol) in the absence of optimized basal insulin, with intended supplementation of up to 30% of subsequent cumulative glucose control [7]. Supplementation with a meal-time insulin to basal insulin therapy is reasonable utilizing T2D treatment guidelines as a strategy for optimum precise and flexible insulin procedure [8]. Insulin analogues have been formulated for greater physiological pharmacokinetic/pharmacodynamic profiles as compared to normal human insulins [9]. It was shown that conventional unaltered human insulin has slower onset and longer action duration than rapid-acting insulin analogues; and the analogues precipitate better post-prandial glucose control in randomized controlled trials, RCTs [10,11].

In this regard, the A1chieve sub-group investigated populations starting the analogue insulin aspart in combination with basal insulin, with or without oral glucose reducing drugs; insulin aspart added to extant basal insulin, n=519 at various modifications [12]. The findings undergird the utilization of basal in addition to prandial insulin regimens in routine clinical practice in persons presenting with T2D having inadequate glycaemic control as compared or related to other regimens of diabetes treatment and control. Clinically significant improvements were detected in serum lipids alongside quality of life in the populations investigated. Also, the A1chieve sub-group investigated and analysed the clinical safety and effectiveness of biphasic insulin
aspart 30 in T2D individuals with switch from biphasic human insulin 30 [13] demonstrated improved glycaemic control and decreased hypoglycaemia rates devoid of tolerability or safety concerns. Thus, it is suggested that biphasic insulin regimens provide the latitude to configure the requirements of both basal and prandial glucose reduction, as they make provision of both intermediate and rapid/short-acting insulin ingredients in a sole injection. Therefore, biphasic insulin preparations give the latitude for an easy strategy to handle both fasting plasma glucose, FPG and post-prandial glucose, PPG for the achievement of glycated haemoglobin, Hba1C targets [14,15]. It has been determined that PPG constitutes an independent risk factor for complications of diabetes [16] and, therefore, becomes pertinent to target both FPG and PPG at every Hba1C concentration for the achievement of glycaemic targets, and to mitigate diabetic sequelae [17] as well as improved glycaemic control and decreased hyperglycaemia risk [18] by selecting insulin with respect to individual insulin requirements, jointly or severally, constituting part of routine clinical care [19].

3. Diabetes and Pregnancy

Insulin requirements increase at pregnancy due to progressive augmentation of insulin resistance broadly related to weight gain due to reduction in physical activity, with a transient drop in necessary insulin doses in the first trimester, ostensibly resulting from nausea and vomiting [20]. Relevant safety concerns on the employment of insulin analogues in pregnancy are related to pregnancy and coupled with their capacity of being aetiological agents of immunogenicity, mitogenicity, exacerbated risk of teratogenicity and embryotoxicity as well as transplacental passage of the antibody-analogue complex [21-23].

Rapid-acting insulin analogues used in pregnant diabetic patients include insulin lispro [24], insulin aspart, glulisine and detemir [25,26]. The insulin analogues constitute superior benefits in lowering nocturnal hypoglycaemia risks and promoting an enhanced physiologic glycaemic profile in pregnant women having T1D, T2D or gestational diabetes. The rapid-acting analogues lispro and Aspart are ostensibly safe and efficacious in the reduction of postprandial glucose concentrations in comparison to conventional human insulin, and portends decreased hypoglycaemia [27]. The long-acting insulin analogues do not present marked peak effect as HPH insulin, and are predicted to produce minimal nocturnal hypoglycaemia in particular, and generally minimal diurnal hypoglycaemia [28].

Pregnancy impacts on both maternal and foetal metabolism in both diabetic and non-diabetic women. Circa 2% to 14% of pregnant women develop gestational diabetes. Women with T2D on oral hypoglycaemic agents are required to change to insulin therapy, while those having pre-existing T1D need to commence intensive glycaemic control. It is pertinent to evaluate the use of generic basal insulin analogues in pregnancy for safety and efficacy [29].

4. Determinants and information-base in the accessibility of care in diabetes

With regard to socioeconomic status and income as facilitator as well as ingrained constraints and challenges, it is pertinent that public health and national economy modify the allocation of healthcare expenditures to presenting social programmes [30]. As much as 30% of USA medical expenditure does not enhance individual or population health. To an expansive magnitude, the available excess expenditure emanates from elevated costs or prices and consequent administrative wastage or dissipation of resources. In the public domain with particular emphasis on the State level with concomitant diverse budget constraints and reluctance to increase taxes, this concurrent expenditure overwhelms educational, public and social health ventures. In the long term, healthcare expenditure rises, while expenditure on sustainable enhancement to health social determinants are obliterated. Simultaneous reallocating of ineffectual healthcare spending to determined and cost-effective public health and social programmes tend to be difficult, but potential cognizance provided to improve public health while saving taxpayers enormous amount of pecuniary needs is liable to provide political platform to those likely to be involved in full and proper administrative all-encompassing reform.

It has been determined that Latinos are susceptible to increased risk for type 2 diabetes, T2D, as properly designed information technology, IT interventions have exhibited efficacious improved diabetes self-management, with a paucity of published IT intervention studies concerning Latinos, though. There are few studies on the most feasible approach to strategize on the discrete and unique sociocultural linguistic features which are liable to optimize adoption, utilization and benefit between Latinos. Sustainable e-health programmes associated with frequency in communication, bidirectionality or feedback and multimodal delivery of the intervention provide successful approach to the strategy. The utilization of community health workers, CHWs has consistently improved T2D outcomes in Latinos. The inclusion of CHWs in e-health interventions facilitates to mitigate the barriers associated with the difficulty in technology awareness and literacy with concomitant improvement in patient activation, satisfaction, adherence and compliance. Also, purposeful directed approach or tailoring to suit their needs in these interventions tend to be highly successful for improving patient activation. It is crucial to realize that tailoring is not merely linguistic translation, but involves intervention to the Latinos populace with optimum need to focus on educational language, literacy and acculturization contents simultaneously with discrete and unique illness beliefs, customs and attitudinal disposition concerning T2D in the Latino sociomedical concept in the community. Interventions ought to be expansive as to reach beyond solitary participants by inculcating shared decision-making models of friends, family and others in the community [31].

Although, the USA presents an increased level of medical care expenditure, the population has extant shorter life expectancy and poorer health indices than available in several OECD countries [32]. The current USA health disadvantage may be associated with certain cross-country disparities, however, price differentials and administrative lapses are expansive contributory factors in exacerbating costs in the USA healthcare system which are invariably controlled by policy objectives resulting in significant discordant and incongruent costs for standard medical care services in the USA as opposed to certain high-income nations. Interventions in education, public health, early childhood development, housing, transportation, diet and nutrition, as well as curbing smoking and other inimical behaviours are liable to enhance financial returns. These sustainable programmes may generate high tax revenues from increased earnings and decreased spending in law enforcement which overwhelm the programme costs [33]. Regarding the shift from social expenditure and public health, it is suggestive that health outcomes have deteriorated relative to the expectancy as envisaged. Evidence demonstrates that in addition to lagging behind other high-income countries in life expectancy, irrespective of higher endowment of national wealth and resources, that enhancement in life expectancy in the USA has been both retarded and incongruent in recent decades [34]. There is extant perspicuous uncertainty regarding the potential savings in healthcare and effectiveness of the educational and public health programme in the instant case. It is pertinent to consider a point estimate of the tradeoffs of elevated healthcare expenditure with that associated with social and public health. As is evident in medical care, it is not all expenditures on social services which result in intended benefits and impacts with resultant cost effectiveness. Studies have elucidated the potential and practical advantages of shifting expenditures based on comparative advantage, such as from low-value ventures to
high-value activities. It is suggested that high-value interventions are amenable in public health, early childhood education, development and other sectors, without encouraging categorical expenditure shifts from a sector to another in the absence of evidence on the associated effectiveness and programme costs [35]. Medical care prices could be genuinely decreased by circa 15% in the long term as progress needs proper latitude in conjunction with political will and fundamental reduction in wastage, dissipation of pecuniary resources and unwarranted increase in the USA healthcare system [35].

5. Discussion and Conclusion

Diabetes without adequate supply of insulin is presently expanding globally with debilitating impact in low- and middle-income countries, LMICs with special effect in certain conurbation [36]. One major constraint is that a vast majority of the data on the epidemiology of the interface between diabetes and insulin usage with undergirding socioeconomic factors emerge from developed countries, whereas the population at risk are in low- and middle-income countries, LMICs. Research, preventive, newfangled therapeutic strategies are required in a global scale, particularly in LMICs where there is vast emergence of the greatest risk coupled with least availability of detection, treatment and control. The adverse sequelae of diabetes without appropriate insulin treatment and control may present deranging impacts on the global burden of diseases.

The basal insulin agents currently in the market do not optimally have a semblance of endogenous insulin secretion. These unmet criteria have created the lacunae with need to fill them via the production of newfangled basal insulin analogues to enhance their pharmacokinetics/pharmacodynamics profile [37]. Degludec is a prolonged-acting insulin that constitutes elongated subcutaneous multimers with resultant absorption procrastination. Phase trials in T1D and T2D exhibit the non-inferiority of degludec to comparators, such as glargine with a less albeit inconsistent decrease in total hyperglycaemia and a slight absolute disparity in nocturnal hypoglycaemia. Other developmental analogues include LY2605541 that comprises insulin lispro coupled with polyethylene glycol, culminating in elevated hydrodynamic size and retarded absorption via the subcutaneous tissue. Another agent is glargine U300 that is formulated from glargine with resultant flatter and more elongated time-action profile in excess of its predecessor [38].

These novel insulin analogues must be stringently monitored for adverse signals irrespective of their advantages of inter alia increased molecular hydrodynamic size, reduction in absorption and clearance after subcutaneous administration, formation of compact subcutaneous depot, and smaller surface area to form gradual and prolonged release. Future research is mandatory inter alia to develop insulins which are in compliance with physiologic insulin profiles at pregnancy and other diabetic conditions.

References


