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Editorial
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Do we need yet another Insulin?

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Insulin is one of the most extensively studied proteins in many fields. Efforts in studying the molecule have been recognized widely, beginning with the Nobel Prize in 1923 to Banting and Macleod for the discovery of insulin [1]. Yet the pace does not appear to slacken on developing newer insulins. Do we need to work on the newer analogues or can we just exert ourselves in translating to clinical use of what we already have?

When insulin was discovered, it was felt that diabetes was curable: insulin lack results in diabetes, and once that was replaced, the disease was as good as gone. The operative word is 'replaced' and all efforts ever since have targeted methods and molecules to mimic physiological insulin replacement: viz match supply with need.

When insulin was first commercially available, for all its dramatic results, it contained many impurities with variable potency. Improved manufacturing processes led to better quality insulin extraction from the original bovine an dporcine sources. Next by the 1930's a longer acting preparation, protamine zinc insulin was developed,, which needed to beinjected fewer times. Initially it was given once a day, without being topped up by short acting insulin as we do presently. It took nearly two decades for lente and NPH insulin insulins to come into the market.

Understanding of the meal-related glucose spikes and persistent diabetic long-term microvascular complications with the use of once a day protamine zinc insulin led to twice daily split-mix regimen of regular insulin for meal related spikes and NPH for longer duration of action. The early 1980'2 saw the advent of purified pork insulin and later recombinant human insulin, the latter from recombinant DNA technology. Both these ensued purity and all but nearly obliterated immunological allergic reactions of the previous extracted insulins. In a way they slowed the pace of innovation in the development of insulin until the 1990's [2].

For all the good of earlier human short acting insulin, it had drawbacks: a relatively slow onset of action which did not match the speed at which ingested food was absorbed. It had to be therefore taken about 30 minutes before the anticipated meal as a compromise. Besides, at concentrations found in vials, it formed dimmers and hexamers, further slowing its absorption and action.

Landmark randomized clinical trials, the DCCT and UKPDS brought to the fore the importance of euglycemia to reduce or retard the risk of microvascular complications [3,4]. The DCCT also showed that conventional insulins were associated with a greatly increased risk of hypoglycemia. A need for insulins with physiologically matching pharmacokinetic properties was obvious [5].

Initial efforts were targeted at generating short acting analogs, which tended not to self-associate, by changing the amino acid sequences of human insulin, so that only the rate of absorption was altered, not its physiological actions.

Insulin lispro was developed by modification at the B26-30 regions of insulin. This altered the formation of insulin dimmers, not binding affinity to insulin receptor. Insuin lispro had the normal sequence of proline at position 29 of B chain and lysine at position 29 reversed. It was therefore absorbed faster and had a shorter duration of action: action started within 15 mins of injection, peaked by an hour and disappeared within four hours. Clinical studies showed it improved postprandial glucose control with a lower rate of hypoglycemia. When lispro was modified to a protamine formulation of neutral protamine lispro, it gave similar ovarall glycemic control, with improved postprandial glucose.

The next short-acting analogue was insulin aspart, in which proline was substituted with aspartic acid. It reduced the self-association and enhanced the absorption rate, while retaining the receptor interaction kinetics of human insulin. Twice as fast as human insulin, premixed aspart insulin is in widespread clinical use [6].

Insulin glulisine is the newest of the rapid acting insulin analogues. It was derived from human insulin by replcement of AspB3 by Lys and LysB29 by Glu. A decrease in isoelectric point is achieved by adding a positive charge at B3. Polysorbate 20 when added to the glulisine formulation acts as a surfactant at the hydrophobic interfaces [7]. The effect of glulisine insulin is indistinguishable from native insulin at tissue level [8].

Both glulisine and lispro are absorbed faster than regular insulin and both displayed non-inferiority of glycemic control in all types of diabetes. The fast year onset of action of glulisine was displayed independent of the injection site.

Cell function is affected by insulin analogs at a variety of sites including signal transduction, metabolic pathways, gene expression and stress tolerance.

In addition to insulins with shorter onset and duration of action, there was need for other insulin analogues having longer duration of action; this was achieved primarily by retarding or stabilizing the absorption of insulin from the injection site.

Insulin glargine was developed by elongating the C terminal of insulin B chain by two arginine residues: A21 aspargine residue was substituted with glycine, which shifts isoelectric point to 6.7, making it less soluble at physiological pH. At neutral pH, this analogue

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precipitates in the subcutaneous tissue, delaying its absorption and thereby increasing the duration of action to 24 hours. Insulin glargine binds to the insulin receptor and has metabolic effects similar to regular human insulin. It has a greater affinity to IGF-1 receptor than human insulin. There is no difference in duration of action with different injection sites.

When insulin analogues have so many advantages, why aren't they used more extensively? The answer: cost. Analogues are more expensive than regular insulins. But looking at it from a different perspective, one realizes that the cost of treating diabetes is associated with treating diabetic complications. Improved glycemic control reduces vascular complications, the major cause of disease and death in diabetes. The costs relate directly to drug use, hospital services and management of complications; indirect costs cover loss of productivity and impaired quality of life. A cost-benefit analysis should give insights whether the higher cost of medications is offset by reduction of more expensive long-term diabetic complications [9].

Based on published evidence, what is the status of analogues compared to regular insulins? A Cochrane Collaboration reviewed on short acting insulins analogues versus regular human insulin concludes 'our analysis suggests only a minor benefit of short acting insulin analogues in the majority of diabetic patients treated with insulin. Until long term efficacy and safety data are available we suggest a cautious response to the vigorous promotion of insulin analogues [10]. Similarly, comparing long-acting insulin analogues versus NPH insulin (human isophane insulin for type 2 diabetes mellitus), the report concludes that 'our analysis suggests, if at all only a minor clinical benefit of treatment with long-acting insulin analogues for patients with diabetes mellitus type 2 treated with 'basal' insulin regarding symptomatic nocturnal hypoglycemic events [11].

However one should bear in mind that Cochrane Reviews synthesize information that is already available, and performance of head to head well designed studies with insulin analogues are likely to uncover the likely advantages with newer insulins. As an analogy, good glycemic control was a central aim of diabetic treatment much before the DCCT and UKPDS were conducted.

Indeed a recent meta-analysis of insulin analogues has shown that biphasic or prandial insulin analogues resulted in HbA1c <7% compared with basal insulin [12]. A proof of concept trial showed that a solube co-formulation of insulin analogs (insulin degludec and insulin as part) given once a day was well tolerated and provided comparable overall glycemic control to insulin glargine [13].

There has been much recent attention on the putative link between insulin use and the risk of malignancy [14,15]. The potential mechanistic links relate to obesity and insulin per se being related to tumors through activation of insulin receptor; activation of insulin like growth factor, through action of growth and apoptotic signals [16]. Diabetes and cancer are related through other ways as well. In women breast cancer occurs due to inhibition of sex hormone binding globulin, which leads to increased estradiol and testosterone levels. Colon cancer may be related to decreased bowel transit time and increased bile acids in diabetes. A recent consensus statement on the link between cancer and diabetes concluded that type 2 diabetes is associated with increased risk of several cancer types [17]. A complex interconnecting network of factors that vary with time might underpin the associations. 'Cancer risk should not be a major factor in choosing between available diabetes therapies for the average patient. For selected patients with a very high risk of cancer occurrence, these issues may require more careful consideration.'

Excitement has been generated by animal experiments, which employed a supramolecular insulin assembly which had a very long duration of action [18]. Utilizing the property of insulin to aggregate into an oligomeric intermediate on the path to amyloid formation, an insulin formulation was devised that led to controlled and sustained release for extended periods.

Insulin reached its current status by the coordinated evolution over 80 years of protein chemists, clinical researchers, clinical practitioners and millions of individuals with diabetes. The Holy Grail for physiological insulin delivery is leading to insulin analogues. They have provided better efficacy, safety and versatility. Subjects with diabetes now have more flexibility in the timing of meals, snacks and exercise, better quality of life. The Grail still leads on, towards new technologies that will help optimize insulin replacement.

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