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Insulin and Insulin Analogues in the Management of Diabetes Mellitus

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ABSTRACT

Diabetic mellitus is characterized by multiple metabolic disorders of carbohydrate metabolism, resulted chronic hyperglycemia with the insulin deficiency and resistance in the pancreatic β-cells. A new treatment paradigm for patient with diabetes to achieve and maintain normal glycemic control is necessary. Oral monotherapy for diabetes is initiated when diet and exercise do not control hyperglycemia. Insulin is the last therapeutic option used when multiple oral combination treatment fails. In recent years, there has been a marked rise in the prescribing of insulin analogues. Clinical trials have demonstrated equal or superior efficacy and safety outcomes of these analogues when compared with human insulin, particularly lower incidence of hypoglycemic events.

Key words: Insulin analogue, r DNA, aspart, NPH, insulin pump

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INTRODUCTION

Diabetic mellitus is one of the oldest disease affecting millions of people all over the world[1]. It can cause serious complications that result in disability and death. Three to four million deaths per year in the world are due to diabetes, corresponding to 8500 deaths per day, or about 99% of disease related deaths. The total number of people with diabetes is projected to rise from 171 millions in 2000 to 366 million in 2030[2]. Projections of the Global Burden of Disease study (GBD) reveal that by 2020 diabetes will rank among the top 20 diseases causing mortality. The key risk factors of obesity, unhealthy diets and physical inactivity are being highlighted in patient education and mass awareness programs on diabetes. Several different treatment options are available for achieving glycemic control in diabetes. These options include insulin, oral antihyperglycemic agents and newer injectables[3]. Despite the presence of these multiple treatment modalities, insulin remains an important therapy for patients with diabetes. Insulin therapy, when delivered appropriately, is almost always effective in achieving glycemic control in diabetes, even after other agents have failed. The ideal goal of insulin therapy is to mimic the pattern of physiologic insulin secretion to control both fasting plasma glucose and post-prandial glucose such regimens should help optimize glycemic control to minimize the risk of diabetes-related complications[4]. This review presents a brief description of the clinical benefits of insulin analogues in the treatment of diabetes mellitus.

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HYPERGLYCAEMIA

Diabetes has been a reduction in both insulin sensitivity and β-cell function. People with diabetes mellitus must take exogenous insulin for survival to prevent the development of ketoacidosis. Generally diabetes involves two functional deficits: insulin resistance by poor metabolic control and abnormalities of insulin secretion at the level of the β-cell, by poor glycemic control. Some patients are characterized by predominant insulin resistance and relative insulin insufficiency, while the others have a major defect in insulin secretion combined with insulin resistance. Insulin resistance which results in increased Hepatic Glucose Production (HGP), decreased glucose disposal and impaired β-cell secretory function (both basal and glucose stimulated) [5]. However, in patients with diabetes mellitus, phase 1 insulin secretion is markedly decreased or absent. As the disease progresses, phase 2 insulin release is also reduced, often by more than 50%[6].

The number of surviving β-cell function determines whether plasma concentrations of glucose remain normal or are increased. Patients with advanced diabetes manifest both insulin resistance and β-cell failure. In diabetes, the peak of insulin secretion is lower and delayed which results in an increased glycemic excursion after meals (hyperglycemia). The hyperglycemia itself incites further metabolic abnormalities since it reduces insulin actions

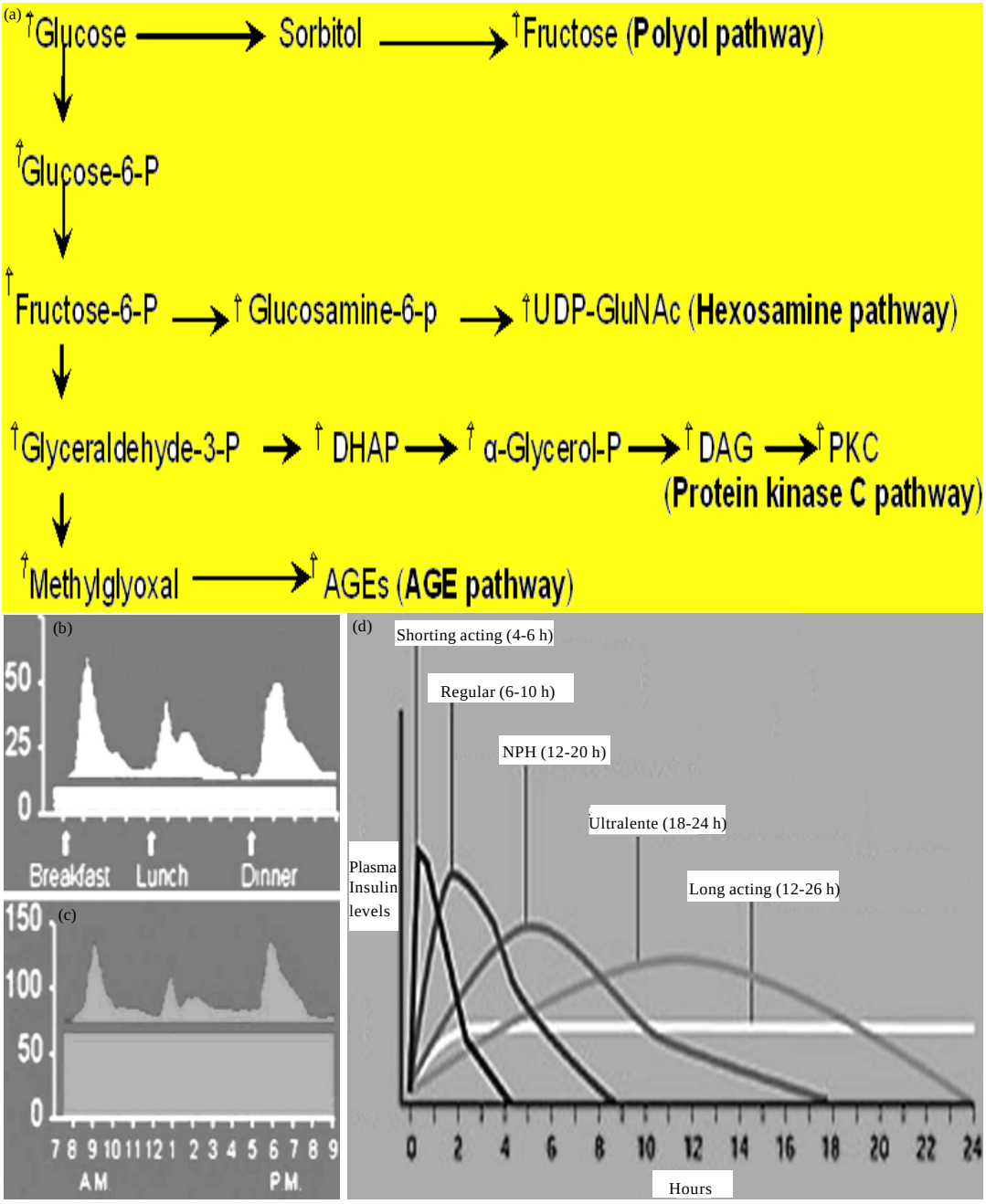

Fig. 1(a-d): Illustrate basic mechanism of glucose metabolism in diabetes (a) Basal insulin (b) Basal glucose (c) Release patent in plasma and (d) Pharmacokinetic profile of insulin analogues

at post receptor mechanisms. Four main hypotheses about how hyperglycaemia causes diabetic complications have generated a large amount of data, as well as several clinical trials based on specific inhibitors of these mechanisms. The four hypotheses are: increased polyolpathway flux, increased advanced glycation end-product formation, activation of protein kinase C isoforms and increased hexosamine pathway flux (Fig. 1a). Sustained elevation of blood glucose also further reduces β-cell insulin secretion. As a result chronic hyperglycemia leads to more chronic hyperglycemia, because hyperglycemia alters both the

aspects of metabolic control that are essential for regulating glucose insulin actions and insulin secretion.

MANAGEMENT OF DIABETES

Patients with diabetes mellitus can be treated initially with oral medications that increase insulin secretion throughout the day (secretagogues or incretins), enhance insulin action (sensitizers), or reversibly inhibit carbohydrate breakdown (α-glucosidase inhibitors). Also, oral agents may slowly lose durability and therefore fail to control glucose levels in the majority of patients, even when given in combination, making exogenous insulin necessary.

INSULIN SECRETION

In a person with a healthy pancreas, demonstrate two components basal and stimulated insulin secretion. Basal insulin is continuously secreted between meals and throughout the night. Stimulated insulin on the other hand, is secreted in response to a meal that is variable in terms of quantity, duration and depends on individual needs (propandial insulin secretion)[7]. Normal healthy subjects demonstrated that insulin secretion returned to base line after each meal and equal quantities of insulin were secreted in about four hours after each meal. Basal insulin is continuously released at low levels in response to hepatic glucose output, while prandial (bolus) insulin is released intermittently in response to elevated glucose levels following a meal. Twenty within seconds of food ingestion, there is an initial release of insulin which peaks in 1 to 2 minutes and lasts about 10 minutes[8]. First phase is responsible for suppressing hepatic glucose output, limiting post-prandial glucose elevations and stimulating phase 2 insulin release of newly manufactured insulin. The post-meal pattern of the insulin secretion was a damped oscillation with two pulses after breakfast and three pulses after lunch and dinner. The study concluded with the important finding that insulin secretion is oscillatory in nature. This pulsatile secretory response is present in response to meals, as well as in the absence of secretory stimuli. Second phase lasts 1 to 2 h until normoglycemia is restored[5] (Fig. 1b, c).

PHARMACOKINETICS

The factors related to pharmacokinetics of insulin are important to keep in mind while individualizing treatment protocols in diabetic patients. The pharmacokinetics of insulin comprises the absorption process, the distribution including binding to circulating insulin antibodies, insulin receptors and its ultimate degradation and excretion (Fig. 1d). The distribution and metabolism cannot be actively changed, except in case of circulating insulin antibodies which in rare cases also may cause insulin resistance. Various injection techniques, changes in blood flow of injected tissue are also contributing factors (Injection into various regions: thigh or abdominal wall, cause differences in blood flow).

INSULIN ANALOGUES

To overcome the shortfalls and limitations in the action of regular insulin, the amino acid structure of human insulin was modified in a way that it remained as monomers or dimmers in the solution. These were synthesized by rDNA techniques, as a result of these genetic modifications human insulin analogs have enabled insulin therapy to more closely mimic normal physiologic insulin secretion[9]. An insulin analog is an altered forms of insulin, different from any occurring in nature, but still available to the human body for performing the same action as human insulin in terms of glycemic control[10]. Standard insulin's do not replicate endogenous insulin secretion[11], so insulin analogues have been developed to address this and to offer more convenient and flexible insulin injection schedules[12]. The key issues to consider in the design aspects of insulin analogues are: (1) should be better than existing ones in both pharmacokinetically and pharmacodynamically. (2) Insulin analogues provide an overall view of structural-activity relationships in insulin biochemistry and insulin action. (3) The insulin structure thus provides many options for the modification of newer variables and at the same time equal amount of caution needs to be exercised in making such modifications considering the adverse affects related to it. (4) IGF-1 has A and B domains in a single chain which is almost similar to the A and B chains of insulin. However, the A and B regions of IGF-1 are connected through a C domain and the C terminal end of the A domain contains a D region extension. The IGF-1 receptor is capable of distinguishing between basic residue at positions B28 and B29. Therefore this insulin analogue has a very high magnitude of affinity for the IGF-1 receptor[13]. It is concluded that the increased duration of interaction of insulin analogue with the receptor induces sustained activation of the insulin receptor tyrosine kinase which may be the cause of the disproportionately high mitogenic potency. Thus, analogues dissociating very slowly from the insulin receptor showed a disproportionate increase in the mitogenic potency[14]. (5) Another principle for protracting a soluble insulin action is a modification which promotes the binding to serum proteins like albumin. The rationale is that subcutaneous albumin binding and consequently increased plasma half-life will prolong the action profile (Fig. 2a).

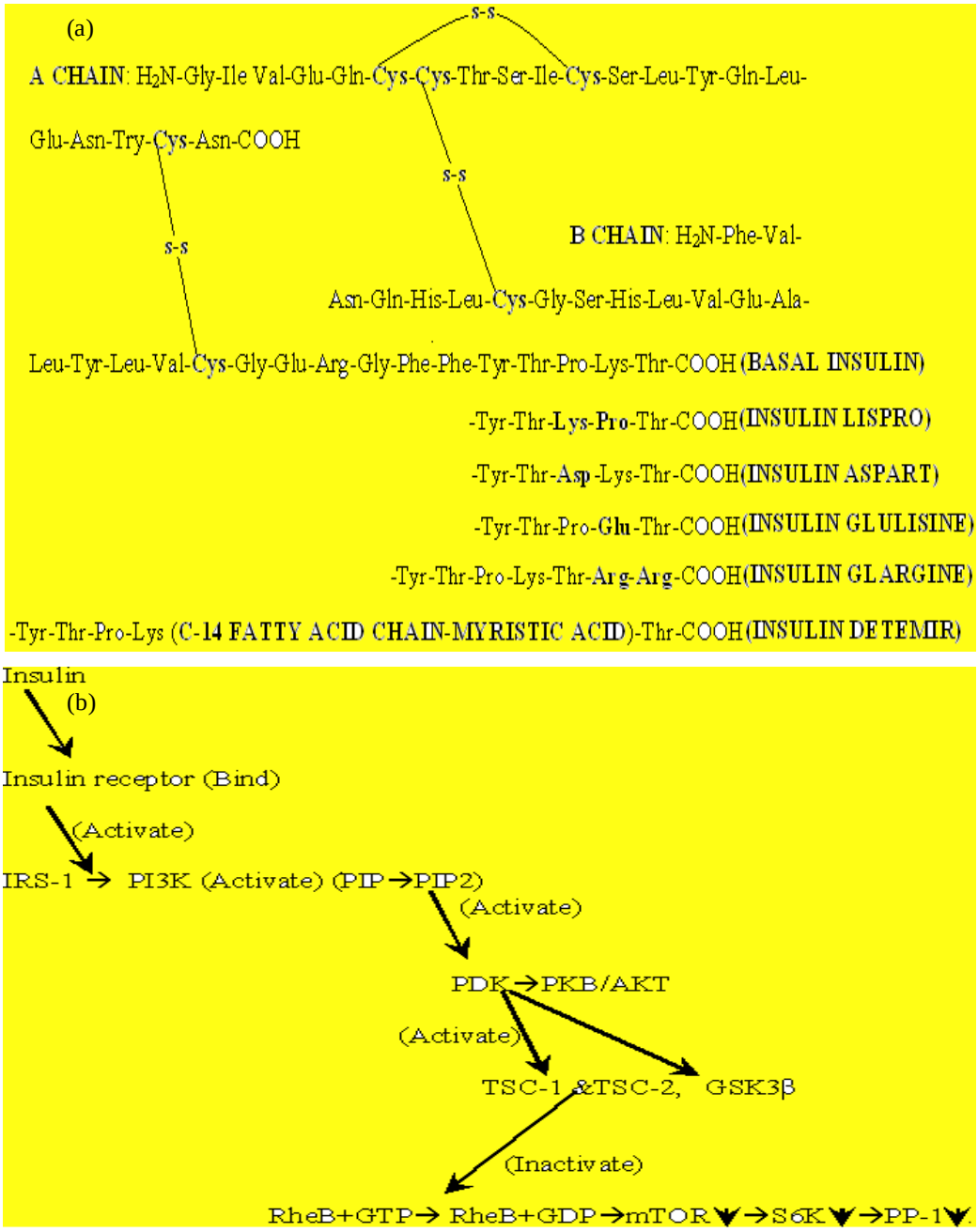

Fig. 2(a-b): (a) Insulin analogues and its basic aminoacid sequences and (b) Human insulin metabolic process

Type of insulin

Short acting insulin (Aspart, Lispro and Glulisine): Short acting insulin includes regular soluble insulin and the newer ones like aspart, lispro and glulisine. Short acting insulin analogues have been developed to improve glycemic control in patients with diabetes mellitus. These rapid insulin analogues improve postprandial glycemic control. Several studies have shown that the risk of hyperglycemia is also reduced with short acting analogues. Native insulin monomers remain in an associated form of hexamers which is a stable form of insulin. Hexamer molecules are slowly absorbed as

compared to monomers and the postprandial peak remains slow. Short acting analogues like insulin lispro and insulin aspart retain their structure in a monomeric or dimeric configuration on subcutaneous injection and are thus absorbed three times more rapidly than human insulin. As a result there is a rapid increase in plasma insulin levels and early onset of hypoglycemic action[15]. Short acting insulin injected about 30 to 45 min before a meal and it peaks at about two or three hours. This insulin can be injected right before meals and its effect can last for as long as six hours.

Insulin aspart: The neutral proline at position B28 is replaced by negatively charged aspartic acid[11]. A subcutaneous injection of insulin aspart dissociates to rapidly acting dimmers and monomers. The absorption of insulin aspart was be twice as fast and twice as higher levels reached when compared to unmodified human insulin. Thus, the pharmacodynamic response is more superior to unmodified human insulin in meal related insulin therapy. The affinity for the IGF-I receptor by insulin aspart was similar to that of human insulin.

Insulin lispro: The structure is a heterodimer consisting of an A chain with 21 amino acids and a B chain with 30 amino acids. The normally occurring Pro-Lys sequence at position B28 and B29 is reversed, that is Lys-Pro[16]. When compared to regular insulin, insulin lispro injected subcutaneously gives rise to peak serum insulin concentrations twice as high and within half the time of regular dose of human insulin. Thus the action of insulin lispro is faster, forms a peak higher and disappears faster when compared to regular human insulin. Insulin lispro was found to be either equipotent or slightly less potent than regular human insulin in binding to the human insulin receptor and slightly more potent than regular human insulin in binding to the human IGF-I receptor. The dissociation rate of insulin lispro from the insulin receptor was equal to that of native insulin is approximately 50% of regular human insulin and insulin lispro[17]. Studies showed that insulin lispro was equipotent to regular human insulin at stimulating metabolic processes such as glucose and amino acid transport and at activating different arms of the insulin signaling pathway, namely the Phosphoinositol (PI) 3-kinase/p70 S6 kinase and the extracellular signal-regulated kinases signalling cascades.

Insulin glulisine: Lys B3, Glu B29 activates the IRS-2 pathway that is involved in mitogenic activity and may have safety issues with its use[18]. It is intended for meal time insulin delivery either through subcutaneous injection or the external infusion pump. The pharmacodynamics are similar to insulin aspart and lispro, it also demonstrated a more rapid onset and shorter duration of action when compared to regular human insulin. Using euglycemic clamp technique, it was found to be safe, effective and well tolerated in diabetic patients[19].

Intermidate acting insulin (NPH and Lente): The commonly used intermediate acting insulins are neutral protamine Hagedorn (NPH) insulin and lente insulin. NPH and lente is added with protamine or zinc increasing the absorption time for insulin. It is a cloudy suspention and has to be mixed before it is injected. These formulations dissolve slowly on subcutaneous administration and hence act for a longer period of time. Differences in crystal size and inadequate resuspension cause changes in absorption kinetics and dosing precision result in unpredictable glucose levels[20]. NPH insulin has been the most frequently used basal insulin, usually administrated in the evening. It is characterized by peaks in plasma insulin concentrations 5 to 10 h after administration, increased risk of hypoglycemia during the night, duration of action of approximately 12 to 18 h that may contribute to hyperglycemia in the morning. Dosing with NPH insulin is not precise and high range of variability is common due to inadequate re-suspension[21]. Lente insulin is a combination of crystallized (ultra lente) and amorphous insulin (semi lente) in an acetate buffer. Lente lasts even longer, it peaks at 4 to 12 h after injection and its effects are seen upto 12 to 18 h. The duration of action being shorter fails to provide glycemic control throughout the night.

Last acting insulin (Glargine and Detemir): Insulin glargine and detemir are long acting insulins are usually taken in the morning or before bed, these have a slow onset and prolonged action. They provide low basal concentration of insulin continuously throughout the day. It is difficult to quantify the optimal dosage of this insulin due to their long duration of action. Various approaches are used to retard the absorption and prolong the metabolic action of long acting insulins. This includes shift of the isoelectric point of the insulin (i.e., the pH at which insulin is least hydro soluble), by substitution of amino acids at the C-terminal portion of the B-chain from 5.4 to a neutral pH of 7.4. After injection of acid preparations of these insulins, in which the insulin is available in solution, a precipitation of relatively small crystals having a similar size at a physiological pH in the subcutaneous depot occurs. Another retarding mechanism employed within this analogue (apart from shifting the isoelectric point) is an enhancement of the cohesive forces between the six insulin molecules of a hexamer.

Insulin glargine: Insulin glargine was the first clinically available DNA-recombinant long-acting human insulin analogue. It differs from native human insulin by virtue of amino acid substitutions in both A and B chains of the protein. In the A chain, asparagine is substituted for glycine at position 21. The B chain is elongated at the C-terminus by the addition of two arginine residues. The changes in the A chain increase the stability of the molecule, while those in the B chain result in a more neutral isoelectric point. As a result of these structural changes, insulin glargine is soluble in the acidic (pH = 4.0), this pH is suitable for making a hexamer molecules stable and forms amorphous micro-precipitates. This is providing rapid precipitates into stable hexamers after injection owing to the neutral pH in the subcutaneous tissues. This greatly slows the absorption of insulin glargine[22]. Glargine, like insulin can induce phosphorylation of both extracellular-regulated kinase and AKT and this suggested that the analog was able to stimulate both the Ras-Raf-mitogen-activated protein kinase (MAPK) and PI3K-AKT pathways. Furthermore, glargine induced both insulin receptor and Insulin Growth Factor-insulin receptor phosphorylation (Fig. 2b).

Insulin detemir: Insulin detemir is the result of acylation of a 14-carbon chain fatty acid (myristic acid) to the lysine residue at the position B29 of the insulin molecule[23]. This change provides a low, constant and reproducible plasma insulin supply for up to 24 h, resulting in delayed absorption due to both increased self association at the injection site as well as a high degree of reversible albumin binding. The data suggest that insulin detemir is hexameric following injection, but that hexamer-dihexamer equilibrium is established as pharmaceutical preservatives (phenol and cresol) are depleted from the injection site and exchanged for physiological electrolytes. Dihexamers are thought to form via contact between the myristic acid groups which are situated at the poles of the hexameric complex. Self-associated insulin is more slowly absorbed into the circulation than monomeric insulin and dihexamerisation is likely to delay dissociation of the complex into monomers. Insulin detemir is bound to albumin in both self-associated and monomeric states that self-associated insulin detemir may bind more than one albumin molecule[24]. There is strong binding to albumin at the injection site, in the plasma (98% remains bound to albumin) and in the target tissue (96% remains bound to albumin). This protects insulin detemir from liver clearance which is only about 1/500 or 8% of the single pass extraction of human insulin[25].

Insulin pens: The discomfort and insulin injection phobia faced by the patient fuelled research towards an easier, less painful insulin delivery systems. The routinely used conventional subcutaneous insulin injections are painful and inconvenient. Insulin delivery with these devices is slow combined with high inconsistent pharmacokinetics. The conventional syringes cannot be turned off once delivered into the skin. This has lead to the development of novel insulin devices like insulin pens and insulin pump devices. Better and improved insulin delivery systems like the insulin pens help not only in achieving target glycemic levels, but also overcome the fear associated with multiple daily injections intensive insulin therapy. This pen device was accepted easily by most patients, device also provides accurate dosage delivery[26].

Insulin pump therapy: Current goals of therapy in type 1 and 2 diabetes are to achieve near glycemia, minimize the risk of severe hyperglycemia, limit excessive weight gain, delay or prevent late vascular complications thereby improve quality of life in these patients. Instead of the multiple daily injection regime used in intensified, continuous subcutaneous insulin infusion (CSII) therapy provides a treatment option that can achieve all of the management goals. CSII uses only rapid acting insulin providing a greater flexibility in timing of meals by a variable programmable basal rate delivered as bolus doses to optimize overnight glycemic control reducing the risk of hypoglycemia. This is done via a small indwelling cannula attached to a pump device. The number of users of the pump device is rapidly growing, especially in young patients across the world[27].

CONCLUSION

All the health interventions are providing a better quality of life to achieve proper glycemic control and improve the quality of life in diabetic patients by reducing the risk of diabetic complications. Insulin provides the glycemic control that is necessary in the control of diabetes and prevention of diabetic complications. A need for the ideal insulin fuelled researchers to develop newer, safer insulin must match the profile of normal insulin secretory pattern. Various preparations of insulin exhibit different profiles with respect to their onset, peak and duration of actions. Recombinant DNA techniques enable modifications to the amino acid sequence of insulin in such a way as to provide stable, effective forms of insulin closely mimicking physiological patterns in achieving metabolic control. Insulin pen and pumps that retain insulin stability, that produce the less toxic reaction and over comes the iso-electric precipitation and fibrillation.

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REFERENCES

1. Andallu, B. and N.C. Varadacharyulu, 2002. Control of hyperglycemic and retardation of cataract by mulberry (*Morus indica* L.) leaves in streptozotocin diabetic rats. Indian J. Exp. Biol., 40: 791-795.
2. Wild, S., G. Roglic, A. Green, R. Sicree and H. King, 2004. Global prevalence of diabetes. Diabetes Care, 27: 1047-1053.
3. Sicat, B.L. and L.A. Morgan, 2007. New therapeutic options for the management of diabetes. Consult. Pharm., 22: 45-56.
4. Robertson, C., 2006. Physiologic insulin replacement in type 2 diabetes: Optimizing postprandial glucose control. The Diabetes Edu., 32: 423-432.
5. Chan, J.L. and M.J. Abrahamson, 2003. Pharmacological management of type 2 diabetes mellitus: Rationale for rational use of insulin. Mayo. Clin. Proc., 78: 459-467.
6. Bonadonna, R.C., M. Stumvoll, A. Fritsche, M. Muggeo, H. Haring and E. Bonora, 2003. Altered homeostatic adaptation of first and second-phase β-cell secretion in the offspring of patients with type 2 diabetes. Diabetes, 52: 470-480.
7. Davidson, M.B. and A.L. Peters, 1997. An overview of metformin in the treatment of diabetes mellitus. Am. J. Med., 102: 99-110.
8. Davis, S. and D. Granner, 1996. Insulin, Oral Hypoglycemic Agents and the Pharmacology of the Endocrine Pancreas. In: Goodman and Gilman's: The Pharmacologic Basis of Therapeutics, Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon and A.G. Gilman (Eds.). 9th Edn., McGraw-Hill, New York, pp: 1487-1518.
9. Hartman, I., 2008. Insulin analogs: Impact on treatment success, satisfaction, quality of life and adherence. Clin. Med. Res., 6: 54-67.
10. Bolli, G.B., R.D, Dimarchi, G.D, Park, S. Pramming and V.A. Koivisto, 1999. Insulin analogues and their potential in the management of diabetes mellitus. Diabetologia, 42: 1151-1167.
11. Gomez-Perez, F.J., S. Hernandez-Jimenez, C.A. Aguilar-Salinas and J.A. Rull, 2002. Insulin analogs: A critical review. Rev. Invest. Clin., 54: 527-541.
12. Singh, S.R., 2009. Efficacy and safety of insulin analogues for the management of diabetes mellitus: A meta-analysis. Canadian Med. Associat. J., 180: 385-397.
13. Simpson, D., 2007. Insulin lispro: A review of its use in the management of diabetes mellitus. Drugs, 67: 407-434.
14. Einhorn, D., M. Rendell, J. Rosenzweig, J.W. Egan, A.L. Mathisen and R.L. Schneider, 2002. Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: A randomized, placebo-controlled study. Clin. Therapeutics, 22: 1395-1409.
15. Janka, H.U., G. Plewe, M.C. Riddle, C. Kliebe-Frisch, M.A. Schweitzer and H. Yki-Jarvinen, 2005. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. Diabetes Care, 28: 254-259.
16. Davis, S.N., 2006. Insulin, Oral Hypoglycaemic Agents and Therapeutic Pharmacology of Endocrine Pancrease. In: Goodman and Gilman's the Pharmacological Basis of Therapeutics, Brunton, L., J. Lazo and K. Parker (Eds.). 11th Edn. McGraw-Hill, New York, USA., ISBN-13: 9780071608916, pp: 1625-1628.
17. Slieker, L.J., G.S. Brooke, R.D. DiMarchi, D.B. Flora and L.K. Green *et al.*, 1997. Modifications in the B10 and B26-30 regions of the B chain of human insulin alter affinity for the human IGF-I receptor more than for the insulin receptor. Diabetologia, 40: S54-S61.
18. Hennigne, A.M., R. Lehmann, C. Weigert, K. Moeschel and M. Schauble *et al.*, 2005. Insulin glulisine: Insulin receptor signaling characteristics *in vivo*. Diabetes, 54: 361-366.
19. Garg, S.K., S.L. Ellis and H. Ulrich, 2005. Insulin glulisine: A new rapid-acting insulin analogue for the treatment of diabetes. Expert Opin. Pharmacother., 6: 643-651.
20. Jehle, P.M., C. Micheler, D.R. Jehle, D. Breitig and B.O. Boehm, 1999. Inadequate suspension of Neutral Protamine Hagendorn (NPH) insulin in pens. Lancet, 354: 1604-1607.
21. Hermansen, K., P. Fontaine, K.K. Kukolja, V. Peterkova, G. Leth and M.A. Gall, 2004. Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. Diabetologia, 47: 622-629.
22. Garber, A.J., 2005. Pharmacologic modifications of hormones to improve their therapeutic potential for diabetes management. Diabetes Obesity Metab., 7: 666-674.

23. Heinemann, L., R. Linkeschova, K. Rave, B. Hompesch, M. Sedlak and T. Heise, 2000. Time-action profile of the long-acting insulin analog insulin glargine (HOE901) in comparison with those of NPH insulin and placebo. Diabetes Care, 23: 644-649.
24. Havelund, S., A. Plum, U. Ribel, I. Jonassen, A. Volund, J. Markussen and P. Kurtzhals, 2004. The mechanism of protraction of insulin detemir, a long-acting, acylated analog of human insulin. Pharm. Res., 21: 1498-1504.
25. Dea, M.K., M. Hamilton-Wessler, M. Ader, D. Moore and L. Schofer *et al*., 2002. Albumin binding of acylated insulin (NN304) does not deter action to stimulate glucose uptake. Diabetes, 51: 762-769.
26. Bohannon, N.J.V., 1999. Insulin delivery using pen devices. Simple-to-use tools may help young and old alike. Postgraduate Med., 106: 57-58.
27. Torreance, T., V. Franklin and S. Greene, 2003. Insulin pumps. Arch. Dis. Childhood, 88: 949-953.