

Premix Insulin: Initiation and Continuation Guidelines for Management of Diabetes in Primary Care



Indian National Consensus Group*

Abstract:

The role of insulin in providing good glycemic control and other systemic benefits is evidence based and irrefutable. In India a large proportion of patients with diabetes have to be cared for by the primary care physicians (PCPs). There exists some inhibition among PCPs regarding initiation and continuation of insulin therapy as it is perceived as complex, time consuming and need to have a team approach. Making the ideal (physiological) insulin therapy more acceptable to PCPs is a contemporary challenging need to contain diabetes in India. Premix insulin stands out as the a suitable & effective regimen to be used in primary care practice. Hence a national consensus group met with the objective of framing a guideline with simple and doable algorithm for using premix insulin therapy in primary care practice. This group recommended premix insulin may be used as a simple, safe, near physiological option and easy to start and stay regimen.

Introduction

India has the largest number of people with diabetes in the world. There were an estimated 42 million people with diabetes in 2007 and this number is predicted to rise to almost 70 million by 2025.¹ Indians are more prone to develop diabetes and its complications at a younger age. Consequently burden of uncontrolled diabetes in India is high with more than two third of the treated patients not achieving optimal glycemic target. This to some extent can be attributed to low purchasing power and inadequate access to health care facilities in remote areas of our country.^{2,3,4}

Type 2 diabetes is a progressive disease and is often diagnosed late. Patients are started on multiple oral anti-diabetics agents even when target glycemic control is not achieved. Although insulin therapy is most effective and suitable in most of these patients, it is usually started late, and more so intensified too slowly^{2,3}. Delayed Insulin is one of the often cited reasons of poor glycaemic control among type 2 diabetics in our country². This fundamentally stems from physician and patient inertia to initiate insulin on time.

About large proportion of the people with diabetes in India are being treated by Primary care physicians (PCPs). PCPs have reluctance in using insulin for treating type 2 diabetes. They often perceive initiation and continuation of insulin therapy complex,

time consuming and dependent upon a diabetes management team. Therefore, it is important to develop expertise in the use of regimens of insulin, that are less complicated yet enable patients to achieve target glycemic levels.

The objective of this guideline is to empower the PCPs with simple and doable algorithm for starting and titrating premix insulin therapy. Needless to mention this will immensely help the nation in reducing the huge burden of mortality and morbidity due to uncontrolled hyperglycaemia. Basal Long acting Insulin is also an recommended option which is available and practiced in some parts of the world but cost remains an important barrier for its widespread routine use and is not discussed in this document.

Indications

Even though regular premix insulins is the most commonly used insulin in our country we do not yet have a clear elucidation of its availability in various formulations and its unique advantages.

Indications for Insulin in Type 2 Diabetes

- At onset:
 - If the blood glucose values are very high i.e. Fasting > 250 mg/dl and postprandial > 300 mg/dl, HbA1c > 9%
 - If the newly diagnosed patient is having systemic infection, sepsis, acute myocardial infarction or unstable angina, diabetic ketoacidosis or has to undergo surgery or is pregnant
- Poor glycemic control in spite of optimal dose of two or three OADs (from dose response curve it has been observed that 80% of the response comes with half maximal dose)⁵:
 - Fasting >150mg/dL
 - Random or Postprandial >200 mg/dL
 - HbA1c > 8.5%
- Further insulin therapy is indicated in
 - Severe or Systemic Infection or Sepsis
 - Acute Myocardial Infarction or Unstable Angina

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Table 1 : Table depicting target glycemic goals of various Diabetic Associations

| Parameters | AACE ⁸ | IDF ⁹ | ADA ¹⁰ |
|-----------------------------|-------------------|------------------|-------------------|
| HbA1c (%) | ≤6.5 | ≤6.5 | <7.0* |
| Fasting/Preprandial (mg/dL) | <110 | <100 | 70-130 |
| Postprandial (mg/dL) | <140 | <135 | <180* |

AACE: American Association of Clinical Endocrinology

IDF: International Diabetes Federation

ADA: American Diabetes Association

- Diabetic Ketoacidosis or Hyperosmolar State
- Diabetic Kidney Disease.
- Pre-gestational or Gestational Diabetes.

Insulin: An optimal choice

Prandial insulin response is often blunted in people with type 2 diabetes^{6,7}. Glycemic targets set by American College of Endocrinology (ACE), International Diabetes Federation (IDF), American Diabetes Association (ADA) and Association of Physicians of India (API) not only include preprandial glucose targets, but also postprandial glucose (PPG) goals (Table 1)^{8,9,10}. Clinical and epidemiological studies have also correlated high PPG with increased cardiovascular risk¹¹. Growing body of evidence also suggests that reducing postmeal plasma glucose excursions is as important,¹³ or perhaps most important for achieving HbA1c goals.^{9,13}

Once-daily injection of long-acting insulin due to its inability to control post meal glucose excursions may not be the treatment option available to treat the insulin deficits and achieve glycemic targets especially in situations of post prandial hyperglycemia. However, premix insulin provides a combination of mealtime (rapid/short acting) and basal (intermediate/long acting) insulin in a preset ratio which may offer an advantage to offset the post prandial glycemic excursions.

It consists of premix human insulin or premix insulin analogue in ratio of 30:70 and 50:50. Rapid/short-acting component (30% or 50%) covers mealtime glucose excursions, while intermediate/long-acting insulin (70% or 50%) augments background insulin levels. This may take care of fasting (FPG), prandial (PPG) & HbA1c with a single insulin¹⁴. Globally, the usage of premix insulin is quite high. In some parts of the world and may currently represent 38% of the world market in human insulin.¹⁵

Premix insulin is the preferred insulin because of

- Simple start
- Option to intensify with same insulin
- Coverage of both FPG and PPG
- Effective HbA_{1c} control
- Low incidence of hypoglycaemia
- Available in vials & insulin delivery device

The rationale for using Premix insulin therapy in India

Basal insulin is a physiological option for diabetes used in the US and EU but cost is a major barrier for its routine use in PCP in India. The transition of Basal to basal plus and basal bolus is complex and PCP may find it complex to use. The classical basal bolus regimen is the most ideal insulin regimen. However, in India, there are some practical difficulties in implementing it at the PCP level. It requires highly motivated patients and a significant amount of time to be spent for patient education and

follow up. At the primary care level, there is absence of Team, Time, and Training. The concept of Diabetes Treatment Unit (DTU), carbohydrate count, self-mixing, judicious monitoring and adjustments is not feasible in our current primary care set up.

Further, the patient may be reluctant to start insulin therapy with four injections per day if a classical basal bolus option is offered. Thus Premix insulin offers the advantage of being simple regimen to be adopted in primary care practice. It addresses both fasting and postprandial insulin requirement in a single injection. It also avoids the disadvantages of traditional self mixing such as¹⁵: viz. need for proper sequencing, Chances of dosing errors, Chances of spillage in the vial base.

Premix insulin is an option which may be used in all the stages of disease progression. It provides an option of easy intensification from once to twice, and sometimes even to thrice daily dosing to achieve control. Risk of hypoglycemia is less with premix insulins, and may be decreased with premix insulin analogues^{16,17}. So this regimen may be scalable without any fear of less glycemia.

Moreover, a simple titration protocol involves less and simple monitoring. Thus it provides an easy and practical approach of treating diabetes by PCPs which may increase compliance, and convenience for the patients.

Premix Insulin: Is there published evidence base ?

There is evidence that premix may be used as an option in situations like primary care. The INITIATE study showed that addition of premix insulin to Oral antidiabetic drugs (OADs) was more effective, than adding basal insulin for treatment of type 2 diabetes.¹⁸ The glycemic targets were attained in 66% of patients treated with premix insulin as compared to 40% in the basal insulin arm. In another study comparing premix insulin therapy with basal bolus therapy, it was found to have effect equivalent to basal-bolus therapy in insulin naïve patients¹⁹. Designer Insulin Regimen in Clinical Practice has been investigated as a pilot multi-center Indian Study²⁰. This study has depicted that both premix insulin analogues (two injections per day) and basal bolus analogue regimen (four injections per day) can be used as an equally effective way of initiating insulin therapy in type 2 diabetes. However, premix insulin analogue fared better than the basal-bolus regimen in lowering HbA1c (1.58 vs. 1.16%, p<0.05). Also 41% more patients in the premix insulin analogue group could achieve target HbA1c <7% at the end of study. Patient's adherence & compliance to the therapy was better with premixed insulin group. However large multicenter and global GCP trials addressing this issue are lacking. The "4T" trial did address this issue and came with conflicting results.

Various Guidelines for the Use of Premix Insulin

American Association of Clinical Endocrinologists (AACE) guidelines suggest premix insulin is indicated for patients with HbA1c above 8.0%⁸. International Diabetes Federation (IDF) suggests twice-daily premix insulin is recommended particularly for patients with elevated HbA1c, which is the case scenario in our country.²¹ ICMR diabetes treatment guideline recommends use of premix insulin twice a day as a choice for multiple injection therapy.²²

NICE type 2 diabetes treatment guideline 2008²³ for type 2 diabetes considers twice-daily biphasic human insulin (pre-mix) regimens when HbA1c is elevated above 9.0% though once-daily regimen may be an option when initiating this therapy. It suggests to consider the option of pre-mixed preparations

Table 2 : Table Indicating the Dosage Titration of Premix Insulin

| Pre-meal Blood Glucose (mg/dL) | Change in Insulin Dose (U) |
|--------------------------------|----------------------------|
| ≤100 | - 2 |
| 100-110 | 0 |
| 110-140 | + 2 |
| 140-180 | + 4 |
| ≥180 | + 6 |

of insulin analogues rather than pre-mixed human insulin preparations when

- immediate injection before a meal is preferred, or
- hypoglycaemia is a problem, or
- there are marked postprandial blood glucose excursions.

Despite of limitations due to compliance and convenience in primary care setting premix insulin still option which merits use in primary care.

Combination therapy - OAD with Premix Insulin

Use of insulin in combination with OADs is one of the main stay of type 2 diabetes therapy. Premix insulin can be combined with insulin sensitizers and secretagogues when initiated once daily, nonetheless, OADs can be continued with twice and thrice daily premix insulin therapy also.^{24,25}

Metformin / TZDs with Premix insulin: Addition of metformin to premix insulin is preferred to thiazolidinediones (TZDs) in patients not reaching the target. Metformin prevents weight gain and also reduces the dose requirement of insulin.^{26,27} TZDs also reduce the dose requirement of premix insulin but causes weight gain.²⁸ Studies have shown better achievement of glycemic targets with this combination. Therefore, premix insulin can be combined with Metformin or TZDs. The order in which these two sensitizers are added to insulin treatment is important; if metformin is added before a thiazolidinedione, weight gain may be avoided.²⁹

Secretagogues with premix insulin It is also recommended that premix may be combined with secretagogues. If a patient is already on sulfonylurea, it should be continued while adding premix insulin to the therapy. The effect of secretagogues is not class specific.^{26,29}

It has been observed that 30 to 40% of patients can achieve the glycemic targets by combination of once daily premix insulin with OADs.^{25,26} However, the therapy needs to be intensified with the decline of β -cell function (= insulin secretion) as disease progresses. In this case premix insulin should be scaled up to twice and thrice daily with or without one or multiple class of OADs.

Initiation and titration of Premix insulin

Premix insulin can be started once daily with 10 U either in the morning (AM), if night-time glucose is high or in the night (PM), if the morning glucose is high. If the total insulin dose exceeds 20 U, then premix insulin can be given twice daily, before breakfast and before dinner (AM & PM), distributed as two third in morning and one third in evening.

However, premix analogues should be distributed in two equal halves in morning and evening when single dose exceeds 30 units. Also premix insulin may be started twice daily in case of patients with higher HbA1c, or if blood glucose control is suboptimal.

Table 3: Table Showing the Advantages of Premix Insulin Analogue over Premix Human Insulin.

| Parameters | Premix human insulin | Premix insulin analogue |
|------------------------------|----------------------|-------------------------|
| Postprandial glucose control | + | +++ |
| Fasting glucose control | ++ | ++ |
| HbA1c control | + | ++ |
| Less hypoglycaemia | + | ++ |
| Meal-time flexibility | + | +++ |

The “nuts and bolts” of achieving control with Premix insulin

The usual initiating dose is about 10 units of premix insulin either morning (AM) or night (PM). The dose can be titrated as given below (Table 2). The blood sugar levels need to be monitored every week and the dose titrated. The simple principle of “starting low and scaling slow” must be applied. Second dose to be given if

- daily insulin requirement > 20 units or
- pre dinner blood glucose persists > 150 mg/dl

Simple monitoring procedure while on Premix insulin

Premix insulin can be given once daily before breakfast or dinner. Then it can be intensified to twice or thrice daily. Night (PM) or morning (AM) dose needs to be titrated based upon pre-breakfast or pre-dinner blood glucose respectively. Dosage adjustments based on pre-meal blood glucose should be done as depicted in the table 2. Titration should be done at regular interval (at least weekly) until glycemic goals are achieved.

Premix Human Insulin and Premix Insulin Analogue – A comparative evaluation

Premixed insulin analogues contain a fixed proportion of soluble, rapid-acting insulin analogue along with protaminated analogue like human premix insulin. Analogue premixes have more physiological pharmacokinetic and therapeutically more desirable pharmacodynamic profiles than premixed human insulin.³⁰

Consequently, postprandial glycaemic control is better with premixed insulin analogues than with premixed human insulin. Minor and major hypoglycaemia appears to be rare with these modern insulins.^{15,17} The premixed insulin analogues, also allow flexibility relative to meal timing, thus improving adherence, compliance and quality of life compared with premixed human insulin.³¹

Overall, the evidence for its safety and effectiveness suggests that premixed insulin analogues are cost effective and have useful advantages (Table 3) over premixed human insulin for the treatment of type 2 diabetes. Switching from premix human insulin to premix Insulin analogue should be done on unit for unit basis.

Premix insulin in special situations

a. Pregnancy

There is adequate evidence and experience that the Premix human insulin can be used in pre-gestational and gestational diabetes in our country. These insulins are safe and effective with favourable outcomes. For women with postprandial hyperglycemia on premixed human insulin, recommending premix insulin analogue though appears rational, it has not yet received a formal approval by Indian regulators. Hence use of premix insulin analogues in pregnancy

should be based on individual patients need and physicians experience.

b. Adolescents

Premix insulin (human/analogue) has been proved to be beneficial in pediatric/adolescents patients with type 1 and type 2 diabetes. It has been recommended that premixes, in particular, premix insulin analogue, should be investigated as a therapeutic option, when treating poor glycaemic control in adolescents and children with type 2 and type 1 diabetes.³² Basal Bolus strategy may be ideal but not always practical in many resource constrained environments or special situations.

Indications for Referral

- Not able to produce optimal targeted Control.
- Brittle Diabetes (rarely the fluctuations are very wide).
- Complications like DKA (suspect if a person complains of abdominal pain and vomiting lasting for >6 to 8 hr), severe infections etc.
- Pre gestational & gestational diabetes where control is not achieved (fasting <90 mg/dL and any time of the day <120 mg/dL).
- Advanced Diabetic Complications like diabetic nephropathy (proteinuria, serum creatinine > 1.5 mg %), myocardial infarction, etc.
- Foot ulcer not healing in 3 days

Availability of Insulin in delivery devices:

Any successful antidiabetic therapy must involve recognition of the lifestyle and quality-of-life issues that the patient encounters in the daily management of this disease. The perceived patient barriers of insulin therapy include the psychological discomfort of self-injection, fear of gaining weight, and fear of hypoglycemia.³³

Insulin is normally delivered from syringes, necessitating accuracy of insulin doses drawn up from insulin vials under suitably hygienic conditions. Also it involves equipment to carry and store, which might be inconvenient for patients who travel or are physically active.³⁴

Modern pen injector devices obviate most of these problems and offer a convenient and safe means of carrying around injection equipment. A study comparing a pen with a conventional syringe and vial found that setting and drawing up the dose of insulin was significantly easier for patients using the pen ($p=0.0490$).³⁵

The insulin injection devices have easy-to-read dial, large button for injection and audible clicks for units injected, Also the needles used with these devices are fine (31G) which cause significantly less pain than with syringes and vials ($p=0.0018$).³⁵ Even patients with motor dysfunction and/or visual problems have found device more convenient to the vial and syringe. In all studies comparing pens with conventional syringes more patients stated a preference for the pens over the conventional syringe and vial.^{36,37}

Advantages of insulin pen devices over conventional insulin syringes³⁵⁻³⁸

- More convenient insulin delivery
- More discreet

- More accurate dosing
- Less pain because finer-gauge needles are used
- Easier compliance with insulin regimen
- Simpler for specific populations to use (e.g., older adults, children and adolescents, pregnant women)
- Improved social acceptability, especially at school, work place or social gatherings
- More flexibility because of disposable or reusable options
- Better quality of life

Storage and administration of Premix Insulin

It is ideal to keep insulin at 2°C - 8°C in a refrigerator (not too near the freezer compartment), the insulin vial or pen devices should never freeze. In absence of this facility, the vial/pen device/penfills may be kept in a cool place (eg. Near a pitcher in kitchen), away from heat and direct sunlight. However, such a vial or delivery device has to be used within a period of 4 weeks.

The necessity of resuspending the premix insulin preparation immediately before use is to be stressed to the patient. The resuspended liquid must appear uniformly white and cloudy. Excess agitation should be avoided to prevent loss of potency, clumping, frosting or precipitation.

Conclusion

Premix insulins are a reasonable option which is effective in all the stages and offers unique advantage of simplicity and convenience. These regimens may be used throughout the course of the disease. Availability of these insulins in pens has reduced the time needed to learn injection technique. There may be a lower index of intrusion into patient's personal life with premix regimen option compared to conventional basal bolus which may have a positive impact on the quality of life.

Acknowledgement, Methodology of the Preparation and Conflict of Interest

This document was prepared with the help of 27 diabetologist, physician and endocrinologists who took the challenge of disseminating this information among the PCPs and physicians in a structured format and developed this guideline. This group of 27 experts (Core committee and extended core committee members) discussed and defined the problem of insulin usage in primary care. Evidences in this regard were searched systematically and critically appraised. A recommendation was made based on these evidences and the clinical experience. A primary draft was prepared.

This was circulated among the committee members and edited for consistency of style and terminology. Then the draft was sent to 250 diabetologist and physicians across the country for their perusal and suggestions. These suggestions were incorporated to the maximum extent and final draft was prepared. This development of guideline is supported by an unrestricted educational grant from Novo Nordisk India Pvt Ltd.

References

1. Sicree R, Shaw J, Zimmet P. Diabetes and impaired glucose tolerance in India. Diabetes Atlas. Gan D Ed. International Diabetes Federation, Belgium. pp 15-103, 2006.

2. Joshi SR, Das AK, Vijay VJ, Mohan V. Challenges in Diabetes care in india: Sheer numbers, lack of awareness and inadequate control. *JAPI* 2008; 56: 443-450
3. Yoon K-H, Lee J-H, Kim J-W, Cho JH, Choi Y-H, Ko S-H, Zimmet P, Son H-Y. Epidemic obesity and type 2 diabetes in Asia. *Lancet* 2006; 368: 1681-88
4. Mohan V, Sandeep S, Deepa R, Shah B, Varghese C. Epidemiology of type 2 diabetes: Indian Scenario. *Indian Journal of Medical Research* 2007;125:217-30.
5. Dailey GE 3rd. Early insulin: an important therapeutic strategy. *Diabetes Care*. 2005 Jan;28(1):220-1
6. Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 1999; 104(6):787-794.
7. Gerich JE. Pathogenesis and treatment of type 2 (noninsulin-dependent) diabetes mellitus (NIDDM). *Horm Metab Res* 1996; 28(9):404-412.
8. American Association of Clinical Endocrinologists. Medical Guidelines for clinical practice for the Management of Diabetes Mellitus. *Endocr Pract*. 2007; 13(Suppl. 1): 40-82
9. International Diabetes Federation. Guideline for management of postmeal glucose. IDF 2007. www.idf.org.
10. American Diabetes Association. Clinical Practice Recommendations. *Diabetes Care*. 2008;31(Suppl. 1):S12-S54.
11. DECODE Study Group. Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and noncardiovascular diseases? *Diabetes Care* 2003; 26(3):688-696.
12. Sorkin JD, Muller DC, Fleg JL, Andres R. The relation of fasting and 2-h postchallenge plasma glucose concentrations to mortality: data from the Baltimore Longitudinal Study of Aging with a critical review of the literature. *Diabetes Care* 2005;28(11):2626-2632.
13. Hanefeld M, Cagatay M, Petrowitsch T, Neuser D, Petzinna D, Rupp M. Acarbose reduces the risk for myocardial infarction in type 2 diabetic patients: meta-analysis of seven long-term studies. *Eur Heart J* 2004; 25(1):10-16.
14. Garber AJ, Ligthelm R, Christiansen JS, Liebl A. Premixed insulin treatment for type 2 diabetes: analogue or human? *Diabetes Obes Metab*. 2007 Sep;9(5):630-9.
15. Turner HE, Matthews DR. The use of fixed-mixture insulins in clinical practice. *Eur J Clin Pharmacol* 2000; 56: 19-25
16. Boehm B, Home P, Behrend C, et al. Premixed insulin aspart 30 vs. premixed human insulin 30/70 twice daily: a randomized trial in type 1 and type 2 diabetic patients. *Diabet Med* 2002;19:393-9.
17. Boehm BO, Vaz JA, Brondsted L, et al. Long-term efficacy and safety of biphasic insulin aspart in patients with type 2 diabetes. *Eur J Intern Med* 2004; 15: 496-502
18. Raskin P, Allen E, Hollander P, et al. for the INITIATE Study Group. Initiating insulin therapy in type 2 diabetes: a comparison of biphasic and basal insulin analogs. *Diabetes Care* 2005;28:260-5.
19. Liebl A, Prager R, Kaiser M, Binz K, and Gallwitz B. Biphasic Insulin Aspart 30 (BIAsp30), Insulin Detemir (IDet) and Insulin Aspart (IAsp) allow patients with Type 2 Diabetes to Reach A1c Target: The PREFER Study. *Diabetes* 2006; 55 (Suppl. 1): A123
20. Joshi SR, Kalra S, Badgandi M, Rao YS, Chawla M. Designer Insulins Regimens in Clinical Practice - Pilot Multicenter Indian Study. *JAPI* . 2005;53:775-779.
21. International Diabetes Federation. Global Guideline for Type 2 Diabetes. Clinical Guidelines Task Force. IDF 2005. www.idf.org
22. Guidelines for Management of Type 2 diabetes by the Indian Council of Medical Research. 2005. http://www.icmr.nic.in/guidelines_diabetes/guide_diabetes.htm
23. National Collaborating Centre for Chronic Conditions. Type 2 diabetes: national clinical guideline for management in primary and secondary care (update). London: Royal College of Physicians, 2008.
24. Goudswaard AN, Furlong NJ, Rutten GE et al. Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews* 2004;(4):CD003418.
25. Garber A, Wahlen J, Wahl T et al. Attainment of glycaemic goals in type 2 diabetes with once-, twice-, or thrice-daily dosing with biphasic insulin aspart 70/30 (The 1-2-3 study) *Diab Obes Metab* 2005;8:58-66
26. Bebakar WMW, Chow CC, Kadir KA, on behalf of the BIAsp-3021 study group. Adding biphasic insulin aspart 30 once or twice daily is more efficacious than optimizing oral antidiabetic treatment in patients with type 2 diabetes *Diabetes Obes Metab*. 2007 Sep; 9(5): 724-32.
27. Douek IF, Allen SE, Ewings P et al. Continuing metformin when starting insulin in patients with type 2 diabetes: a double-blind randomized placebo-controlled trial. *Diabetic Medicine* 2005;22(5):634-640.
28. Phatak, HM; Yin, DD. Factors associated with the effect-size of thiazolidinedione (TZD) therapy on HbA1c: a meta-analysis of published randomized clinical trials. *Curr Med Res Opin*, November 2006;22 (11); 2267-2278
29. Can glycemic targets be achieved - in particular with two daily injections of a mix of intermediate- and short-acting insulin? ACE/AACE Diabetes Conference. *Endocr Pract*. 2006;12(Suppl 1):52-55.
30. Garber AJ. Premixed Insulin Analogues for the treatment of Diabetes Mellitus. *Drugs* 2006; 66 (1): 31-49
31. Rizvi AA, Ligthelm RJ. The Use of Premixed Insulin Analogues in the Treatment of Patients with Type 2 Diabetes Mellitus: Advantages and Limitations. *Insulin*. 2007;2:68-79
32. Mortensen H, Kocova M, Teng LY, Keiding J, Bruckner I, Philotheou A. Biphasic insulin aspart vs. human insulin in adolescents with type 1 diabetes on multiple daily insulin injections. *Pediatric Diabetes* 2006; 7: 4-10
33. Hanas SR, Carlsson S, Frid A, Ludvigsson J. Unchanged insulin absorption after 4 days' use of subcutaneous indwelling catheters for insulin injections. *Diabetes Care*. 1997 Apr;20(4):487-90.
34. Korytkowski M, Bell D, Jacobsen C, Suwannasari R for the FlexPen Study Team. A multicenter, randomized, open-label, comparative, two-period crossover trial of preference, efficacy and safety profiles of a prefilled, disposable pen and conventional vial/syringe for insulin injection in patients with type 1 or 2 diabetes mellitus. *Clin Ther* 2003;25:2836-48.
35. Kadir A, Chraibi A, Marouan F et al. Comparison of NovoPen 3 and syringes/vials in the acceptance of insulin therapy in NIDDM patients with secondary failure to oral hypoglycaemic agents. *Diabetes Research & Clinical Practice* 1998;41(1):15-23.
36. Coscelli C. Safety, efficacy, acceptability of a pre-filled insulin pen in diabetic patients over 60 years old. *Diabetes Research & Clinical Practice* 1995;28(3):173-177.
37. Fox C, McKinnon C, Wall A et al. Ability to handle, and patient preference for, insulin delivery devices in visually impaired patients with type 2 diabetes. *Practical Diabetes International* 2002;19(4):104-107.
38. Bohannon NJV, Jack DB. Type II diabetes: tips for managing your older patients. *Geriatrics* 1996;51:28-35.