

ORIGINAL ARTICLE

IMPACT India: Insights for Insulin Therapy in Routine Clinical Practice

V Mohan¹, Ashok Kumar Das², AG Unnikrishnan³, Siddharth N Shah⁴, Ajay Kumar⁵, Abdul Hamid Zargar⁶, Sanjay Kalra^{7*}

Abstract

Objective: Widely used in the management of diabetes, insulin therapy is influenced by several patient preferences and physician choices. This article reports the findings of the IMPACT survey, designed to assess insights on various factors which influence the choice of insulin therapy in India.

Methods: We administered a questionnaire which focused on the practice and patient profiles and the preferred regimens in specific clinical situations using a case scenario. Respondents were asked about preferred insulin regimens for various phases of life, comorbid conditions, dietary choices and psychological factors.

Results: Overall, 314 doctors participated in the survey. Majority were general physicians (51%) and diabetologists (37%). In clinical practice, the most preferred regimens included premix insulin BD in adults (59%) and elderly (53%), and basal bolus therapy in pregnant women (>47%) and in acute illness (62%). Both regimens were equally preferred for symptomatic patients (41% basal bolus and 38% premix insulin) and those with renal or hepatic failure (36% each). Premix insulin was preferred for patients with high carbohydrate intake (73%) while basal bolus was preferred for patients with variable meal timings (39%) and in pronounced postprandial glucose excursions (45%). Insulin co-formulation and high-mix insulins were not a part of the survey questionnaire.

Summary: Indian physicians exercise logic in the choice of insulin regimens. Preference is based on patient characteristics including glucophenotype, dietary patterns, psychosocial needs, clinical situations, and comorbid conditions.

Introduction

Poor glycemic control is common in routine clinical practice for diabetes.^{1,2} This reflects a delayed initiation of therapy, including insulin therapy.³ Several guidelines provide directions and rationale for the initiation and intensification of therapy with insulin. Based on the duration and severity of diabetes, these guidelines provide elaborate algorithms for insulin therapy.⁴⁻⁹ The American Association of Clinical Endocrinologists (AACE) and American Diabetes Association (ADA)^{6,7} recommend basal insulin while the Indian National Consensus Group (INCG)⁵ recommends premix insulin for the initiation of therapy in diabetes. The International Diabetes Federation (IDF), National Institute of Clinical Excellence (NICE), and

the Research Society for the Study of Diabetes in India (RSSDI) provide directions for initiation of therapy with basal or premix insulin depending upon the degree of hyperglycemia.^{4,5,8} However, most guidelines usually do not specifically describe the patient characteristics that determine the choice of insulin regimen in patients with diabetes.¹⁰

The adoption of insulin in routine practice is guided by several factors

including the patient preferences and overall health status of the patient. In addition, cost and accessibility are also common concerns. Due to the heterogeneity in diabetes, individualization and customization of therapy are needed to meet glycemic goals in routine practice.¹¹ These factors collectively explain the challenges for optimizing therapy in the management of diabetes in routine clinical practice. The Insulin Management: Practical Aspects in Choice of Therapy (IMPACT) India group comprising seven leading diabetologists of India developed a survey to objectively gain insights on various factors which influence the choice of insulin therapy in India. In this paper, we present the results of the pilot survey and explain the utilization of insulin regimens in routine clinical practice in India and the impact of clinical and psychosocial factors that influence clinical decision making.

Methods

The survey was made available to participants between August 29, 2018 and September 5, 2018 at <https://www.surveymonkey.com/r/IMPACTIND>. The initiative was promoted through e-mail communications and SMS to all participants of 12th National Insulin Summit 2018 (8th and 9th September 2018, Hyderabad, India), a scientific event under the auspices of the Indian College of Physicians, the academic wing of the Association of Physicians of India and Diabetes Research Society.

Participation in the survey was free

¹Chairman and Chief of Diabetology, Dr. Mohan's Diabetes Specialities Centre, WHO Collaborating Centre, Non-Communicable Disease Prevention and Control and IDF Centre of Excellence in Diabetes Care and President and Chief of Diabetes Research, Madras Diabetes Research Foundation, ICMR Centre for Advanced Research on Diabetes, Chennai, Tamil Nadu; ²Department of General Medicine, Pondicherry Institute of Medical Sciences, Puducherry; ³Department of Endocrinology, Chellaram Diabetes Institute, Pune, Maharashtra; ⁴Department of Endocrinology, SL Raheja Hospital, Mumbai, Maharashtra; ⁵Department of Diabetology, Diabetes Care and Research Centre, Patna, Bihar; ⁶Department of Gynaecology and Obstetrics, Sheri-i-Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir; ⁷Department of Endocrinology, Bharti Hospital Karnal, Karnal, Haryana; *Corresponding Author
Received: 20.02.2019; Accepted: 01.03.2019

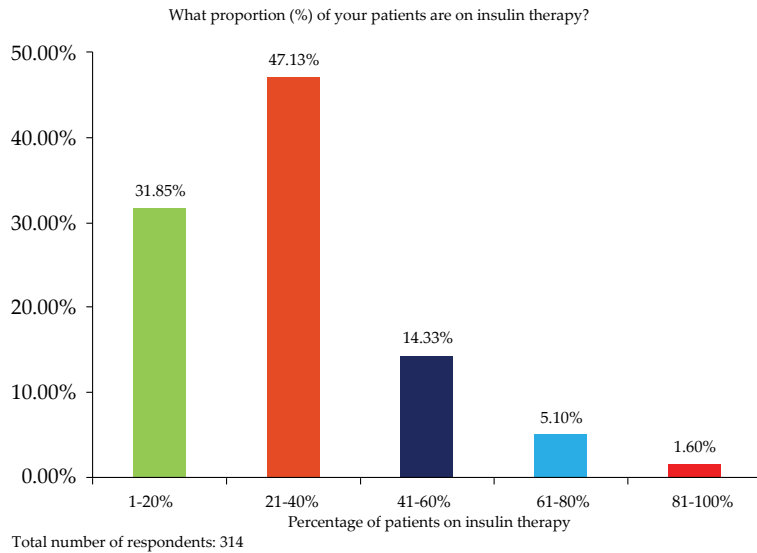
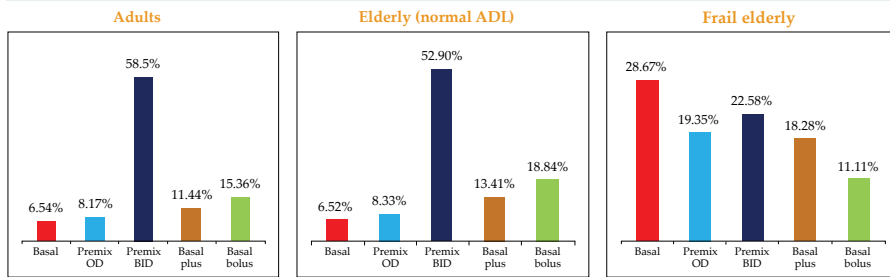


Fig. 1: Proportion of patients on insulin therapy



ADL: Activities of daily living

Fig. 2: Preferred insulin therapy in adults and elderly patients with diabetes

and the responders were anonymous. For details of the questionnaire, refer to supplementary materials. The development and administration of this survey was driven by the Scientific Committee of the National Insulin Summit.

Structure of questionnaire

The questionnaire was created on website host Survey Monkey® (Palo Alto, Calif, USA). The survey was anonymized, and the responses were confidential throughout the process of the survey. The questionnaire had 4 parts:

Practice profile

Two questions in this section sought to determine the specialty of physicians and the average numbers of patients with diabetes they saw every month in their clinical practice.

Patient profile

This section included questions (n=3) on the age and duration of diabetes of the patients seen in clinical practices. In addition, the respondents were asked about the proportion of patients on insulin therapy in their

practice.

Case scenario

This section had a total of 13 questions. In the first question, respondents were asked about the preferred regimens for a patient with fasting plasma glucose (FPG) 150mg/dl, post prandial glucose (PPG) 300 mg/dl, and glycosylated hemoglobin (HbA1c) 9.5%. In next 12 questions, structured into 4 sections of 3 each, their preferred prescribing approaches were explored with regards to specific phases of life, clinical situations, dietary and psychological variables, and different glucophenotypes.

Phase of life

Questions were focused on approach in elderly, frail elderly and antenatal women or those planning pregnancy.

Clinical situation

Approach was confirmed for patients with symptoms (weight loss, asthenia or osmotic symptoms), intercurrent acute illness (infection, injury inflammation), and renal or hepatic failure.

Diet and psychological

Questions were designed to explore the approach in patients with high carbohydrate diet and two heavy meals a day, those with limited diabetes literacy and numeracy or those seeking to minimize the number of delivery devices, and those with variable meal times or need for flexibility in frequency or timing of injection.

Glucophenotype

Respondents were asked 3 questions about preferred regimens for patients with pronounced post prandial excursions of 400 mg/dl, fasting glucose of 200 mg/dl and post prandial glucose of 220 mg/dl, and those with a high risk of hypoglycemia and high glucose variability.

Statistical measures

Data retrieved from Survey Monkey® were analyzed using IBM Statistics Package for the Social Sciences (SPSS) version 14.0. Descriptive statistics were used to describe the analyses.

Results

A total of 314 physicians from across India responded to the survey. The respondents included endocrinologists (6.4%), diabetologists (37%), and physicians (51%). Most of the respondents (>60%) reported managing more than 100 patients with diabetes in a month.

Majority (44%) of the patients in clinical practice were aged between 41-60 years while >20% each were aged between 61-80 years and 21-40 years. More than 50% of patients had diabetes duration from 1-10 years. About 20% and 16% patients had diabetes duration of 5-10 years and 1 year, respectively. Majority of the respondents (47%) had 21-40% patients on insulin therapy while 31% had 20% patients on insulin therapy (Figure 1). Twice daily dosing of premix insulin was the preferred insulin regimen in adults and in elderly with no limitations of activities of daily living (Figure 2). In the frail elderly, basal insulin was the most preferred (29%) followed by twice daily premix (22.58%). In pregnant women, basal bolus therapy was the most preferred choice (>47%) followed by premix insulin twice daily (28%) or once daily (6%) dosing.

In symptomatic patients, both basal

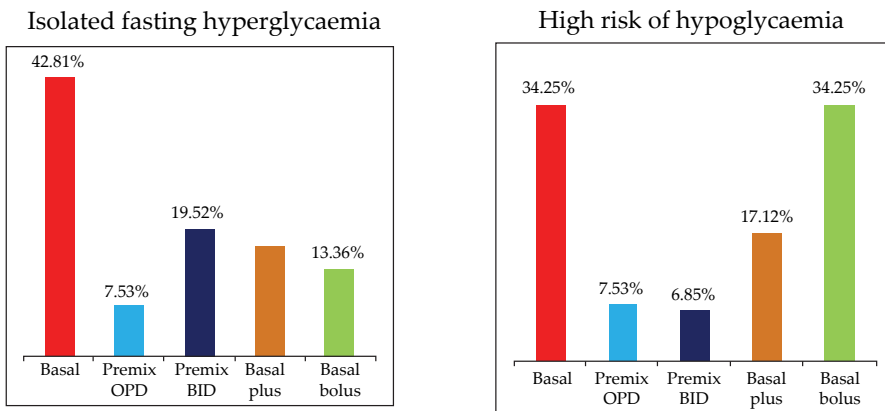


Fig. 3: Preferred insulin therapy in glycemic variability in routine practice

bolus (41%) and twice daily premix insulin (38%) were the preferred regimens, whereas there was a higher preference for basal bolus regimen in patients with intercurrent acute illnesses vs premix insulin (62% vs. 24%). The use of basal bolus and premix insulins were equally preferred (36%) for patients with hepatic or renal failure.

Premix insulin twice daily dosage was the most preferred regimen for patients with high carbohydrate intake (73%) and those with limited diabetes literacy (44%) while basal bolus (39%) followed by basal plus (24%) were the preferred choice for patients with variable meal timings.

There was a higher preference for basal and basal bolus therapy in patients with isolated fasting hyperglycemia (42.81%). In those at high risk of hypoglycaemia both basal and basal bolus insulin were preferred (Figure 3). In patients with pronounced postprandial glucose excursions, there were preference for basal bolus (45%) followed by basal plus (27%) and premix insulin twice daily dosing (21%).

There was a higher preference for twice daily dosing when compared to the once daily dosing of premix insulin in adults (59% vs. 8%), elderly (53% vs. 8%), frail elderly (23% vs. 19%), and pregnant women (28% vs. 6%). Similar trends were reported for patients with symptoms (38% vs. 5%), acute illness (24% vs. 3%), hepatic or renal impairment (25% vs. 11%), high carbohydrate diet (73% vs. 1%), limited diabetes literacy (44% vs. 16%), variable meal timings (17% vs. 7%), pronounced post prandial excursions (21% vs. 7%), and isolated fasting hyperglycemia

(20% vs. 8%). However, the two were equally used in patients with higher risk of hypoglycaemia (7% vs. 8%).

Discussion

Internet- and web-based applications are increasingly being used to guide the provision of care in diabetes and to assess the impact of the clinical practices.^{12,13} We present the survey results for assessment of choice of insulin regimens in routine clinical practice by Indian physicians. This was a comprehensive survey capturing important aspects of use of insulin regimens in diabetes management. The survey questionnaire was peer reviewed and was subjected to a pilot before approval. Designed by experts in the management of diabetes, the survey was simple and easy to administer and understand. The survey had a good geographical coverage with responses from physicians of various specialties across India.

The objective of our survey was to determine trends in insulin therapy in routine clinical practice. Studies with similar objectives include the A1chieve and the IMPROVE study (Shah 2010; Valensi 2008). The A1chieve was a prospective, open-label, non-interventional, 24-week study in patients of diabetes (n=60,000) across four continents (Asia, Africa, South America, and Europe). The study reported the utilization of premix (biphasic insulin aspart 30), basal (insulin detemir), and meal-time (insulin aspart) insulin analogs in people with type 2 diabetes.¹⁴ The IMPROVE study was an open-label, non-randomised, 26-week observational study assessing the safety and effectiveness of biphasic insulin

aspart 30 (BIAsp 30) in type 2 diabetes (n=51286).³ Unlike these studies, our study is a survey focused on assessing the choice of insulin regimens and the factors influencing the choice for insulin therapy.

Delayed initiation of insulin is common in India. The case scenario in the survey is focused around glycemic levels reported in A(1)chieve, i.e. fasting (140-160 mg/dL) and postprandial (300-350 mg/dL) levels of blood glucose and glycosylated hemoglobin (HbA1c: 9.5%).

The 12 questions included key factors determining therapeutic choices, i.e. patient characteristics, presenting symptoms, diversity in meal patterns and patient preferences, severity and patterns of hyperglycemia, and diversity in meal patterns. The survey enabled assessments for the influence of stage of life, clinical situation, diet and psychosocial factors, and glucophenotype on the choice of insulin regimens in routine clinical practices.

Physicians in India prefer premixed insulin in the elderly population. This choice is logical and rational due to the ease of administration reported for premixed preparations in the elderly with diabetes.¹⁵ Further, the premixed preparations of insulin are reported to be safe in patients at risk of hypoglycaemia.¹⁶ This makes premixed insulin a preferred choice for the management of diabetes in the elderly.

The Indian National Consensus Group (INCG) recommends premixed insulins, preferably analogue formulations, for the management of all stages of diabetes as these offer a simple and safe option for the initiation of treatment.¹⁷ According to our survey, Indian physicians prefer to use twice daily dosing of premix insulin in adults, elderly with no limitations of activities of daily living, and the frail elderly. Similar results have been reported in the IMPROVE study wherein therapy was initiated with a twice-daily regimen of BIAsp 30 in more than 80% patients of diabetes.³ Premixed insulins are best options in patients who are unwilling or are unable to adhere to the frequency of injections or the frequent monitoring required with basal-plus or basal-bolus regimens.¹⁸

Our findings suggest that physicians prefer premix insulin in twice daily dosing for patients with high

carbohydrate intake. This synchronizes with the INCG recommendations for initiation of therapy with premixed insulin in Asians who show high glycemic response to meals.⁵ This can be explained by the high carbohydrate components of diets in the Indian population. This preference can also be driven by various cultural practices in Asian countries.¹⁹

In India, the basal bolus therapy is the most preferred therapy for pregnant women. Indian physicians also make efforts to individualize therapy for optimal glycemic control during pregnancy. Available evidence suggests that basal/bolus combination of long- and short-acting insulin preparations are the best options in pregnant women requiring insulin therapy.^{20,21} Premixed insulins are virtually not used in pregnancy in the west. In our study, 28% of respondents used premixed insulins during pregnancy and reported good results with this regimen.

In this survey, physicians report preference for basal bolus regimen for patients with intercurrent illnesses. Basal bolus regimens are reported to be efficacious and safe for use in patients of diabetes with medical and surgical complications.^{22,23} However, twice daily dosing of premix insulin was preferred over once daily dosing. The recently updated Indian Council of Medical Research (ICMR) Guidelines also recommend the use of premix insulin twice a day as an alternative to multiple insulin injection regimen.²⁴ The twice daily regimen also offers a convenient approach to intensification of premix insulin therapy to achieve glycemic targets.²⁵

The limitations of the survey include the recall bias of respondents and the potential influence of the sponsor. By design, the results reflect the opinions of survey participants which could be different from those of the non-responders. We are also aware that the responses given by 314 physicians are not sufficient to generalize the results to a large country like India. The survey was limited to physicians in India and hence this may not be generalized to others. Further, the survey does not differentiate preferences across primary care practices and tertiary centers. We also need to consider the fact that differences in treatment algorithms across practices which could be a possible bias for respondents with

greater familiarity of the algorithms. The survey does not provide any details for diet or lifestyle though these are key factors that influence the choice of insulin in patients with diabetes. The likelihood for preference of an insulin regimen has not been assessed on a probability scale.

The survey questionnaire prompts for the use of only select insulin formations and did not include some popular regimens, e.g. high-mix (50:50), insulin co-formulations, and delivery devices of insulin that are increasingly being used to individualize treatment in people with diabetes.^{26,27}

There is increasing evidence in support of the usage of insulin co-formulations which are convenient and are preferred by many clinical practitioners for the initiation and intensification of treatment.²⁸ Insulin co-formulations make a logical choice in several scenarios with advantages of similar efficacy to basal bolus or basal plus regimens along with proven reduction in hypoglycemia events as well as reducing burden of injections.²⁹ Unfortunately, insulin co-formulations were not part of the survey questionnaires. This should be explored in further research when determining the factors for choice of insulin in various glucophenotypes encountered in patients in routine clinical practice.

Nevertheless, despite these limitations, the insights gained through this study for the factors influencing the choice of insulin therapy in routine clinical practice among Indian physicians can help to guide future research for the use of insulin to optimize glycemic control in diabetes.

Summary

The results of our survey suggest that the Indian physicians follow a fairly logical approach in choosing various insulin regimens used in treatment of type 2 diabetes. Physicians appear to practice glucophenotype guided-flexibility in their approach to diabetes. When choosing an appropriate insulin regimen and dosage pattern, Indian physicians also assess stage of life, clinical situation, diet, and psychosocial factors as well.

Our survey reports that premix insulins are the preferred option by most physicians in India. Further, the survey affirms this preference

to be guided by factors such as high carbohydrate diet, high levels of post-prandial glycemic excursions, and delayed insulin initiation. Basal insulin is more preferred in patients with isolated high FPG and higher risk of hypoglycemia. The basal-bolus regimen was more preferred in patients with intercurrent illness, pregnancy and other special situations.

This survey forms the foundation for further research on the preferences of other insulin regimens including insulin co-formulations and various insulin delivery devices.

Acknowledgments

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work, and have given final approval for the version to be published.

Medical writing and editorial support in the preparation of this article was provided by Dr Tarveen Jandoo and Dr. Punit Srivastava of Mediception Science Pvt. Ltd.

Conflict of interest

Viswanathan Mohan has received honoraria and research grants from Novo Nordisk, Sanofi and meeting support from Eli Lilly. Sanjay Kalra has received lecture fees and honoraria from Eli Lilly, Novo Nordisk and Sanofi. Unnikrishnan AG has received research grants/honoraria from Novo Nordisk, Eli Lilly, Sanofi and other pharmaceutical companies.

References

1. Anand Moses CR, Seshiah V, Sahay BK, Kumar A, Asirvatham AJ, Balaji V, et al. Baseline results indicate poor glycemic control and delay in initiation and optimization of insulin therapy: results from the improving management practices and clinical outcomes in type 2 diabetes study. *Indian J Endocr Metab* 2012; 16, Suppl S2:432-3.
2. Anjana RM, Pradeepa R, Deepa M, Datta M, Sudha V, Unnikrishnan R, et al. Prevalence of diabetes and prediabetes (impaired fasting glucose and/or impaired glucose tolerance) in urban and rural India: Phase I results of the Indian Council of Medical Research-India DIABetes (ICMR-INDIAB) study. *Diabetologia* 2011; 54:3022-7.
3. Valensi P, Benroubi M, Borzi V, Gumprecht J, Kawamori R, Shaban J, et al. IMPROVE Study Group Expert Panel. The IMPROVE study—a multinational, observational study in type 2 diabetes: baseline characteristics from eight national cohorts. *Int J Clin Pract* 2008; 62:1809-19.
4. International Diabetes Federation. IDF diabetes atlas. 8th ed. 2017. Available on: <http://diabetesatlas.org/resources/2017-atlas.html>. Accessed on 13 October, 2018.
5. Indian National Consensus Group. Premix Insulin: Initiation and Continuation Guidelines for Management of Diabetes in Primary Care. *J Assoc Physicians India* 2009; 57(Suppl):42-6
6. American Diabetes Association. Standards of Medical Care in Diabetes-2017: Summary of Revisions Diabetes Care 2017;

- 40(Suppl. 1):S4–S5.
7. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm - 2018 Executive Summary. *Endocr Pract* 2018; 24:91-120.
 8. Bajaj S. RSSDI clinical practice recommendations for the management of type 2 diabetes mellitus 2017. *International Journal of Diabetes in Developing Countries* 2018; 38:1-15.
 9. NICE guideline [NG28]. Type 2 diabetes in adults: management. 2017. Available on: <https://www.nice.org.uk/guidance/ng28>. Accessed on 13 October 2018.
 10. Kalra S, Czupryniak L, Kilov G, Lamptey R, Kumar A, Unnikrishnan AG, et al. Expert Opinion: Patient Selection for Premixed Insulin Formulations in Diabetes Care. *Diabetes Ther* 2018; 9:2185-2199.
 11. Merino J, Florez JC. Precision medicine in diabetes: an opportunity for clinical translation. *Ann N Y Acad Sci* 2018; 1411:140-152.
 12. Spearson CL, Mistry A. Several Aspects of Internet and Web-Based Technology in Diabetes Management. *Diabetes Spectrum : A Publication of the American Diabetes Association*. 2016; 29:245-248.
 13. Gallo M, Mannucci E, De Cosmo S, Gentile S, Candido R, De Micheli A, et al. Algorithms for personalized therapy of type 2 diabetes: results of a web-based international survey. *BMJ Open Diabetes Research and Care* 2015; 3:e000109.
 14. Shah SN, Litwak L, Haddad J, Chakkarwar PN, Hajjaji I. The A1chieve study: a 60 000-person, global, prospective, observational study of basal, meal-time, and biphasic insulin analogs in daily clinical practice. *Diabetes Res Clin Pract* 2010; 88 Suppl 1:S11-6.
 15. Coscelli C, Calabrese G, Fedele D, Pisu E, Calderini C, Bistoni S, et al. Use of premixed insulin among the elderly. Reduction of errors in patient preparation of mixtures. *Diabetes Care* 1992; 15:1628-30.
 16. Bretzel RG, Arnolds S, Medding J, Linn T. A direct efficacy and safety comparison of insulin aspart, human soluble insulin, and human premix insulin (70/30) in patients with type 2 diabetes. *Diabetes Care* 2004; 27:1023-1027.
 17. Ashok Kumar Das, Binode Kumar Sahay, V Seshiah, V Mohan, A Muruganathan, Ajay Kumar, et al. INCG Group. Indian National Consensus Group: National Guidelines on Initiation and Intensification of Insulin Therapy with Premixed Insulin Analogs. API India, medicine update. 2013; Chapter 51: 227-236.
 18. Wu T. Premixed insulin analogues: A new look at an established option. *Diabetes and Primary Care Australia* 2016; 1:129-33.
 19. Pathan F, Latif ZA, Sahay RK, Zargar AH, Raza SA, Khan AK, et al. Update to South Asian consensus guideline: Use of newer insulins in diabetes during Ramadan Revised Guidelines on the use of insulin in Ramadan. *JPMA. The Journal of the Pakistan Medical Association* 2016; 66:777-8.
 20. McElduff A, Moses RG. Insulin therapy in pregnancy. *Endocrinol Metab Clin North Am* 2012; 41:161-73.
 21. Blum AK. Insulin Use in Pregnancy: An Update. *Diabetes Spectrum : A Publication of the American Diabetes Association*. 2016; 29:92-97. doi:10.2337/diaspect.29.2.92.
 22. Umpierrez GE, Smiley D, Zisman A, Prieto LM, Palacio A, Ceron M, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT 2 trial). *Diabetes Care* 2007; 30:2181-6.
 23. Umpierrez GE, Smiley D, Jacobs S, Peng L, Temponi A, Mulligan P, et al. Randomized study of basal bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). *Diabetes Care* 2011; 34:256-61.
 24. Indian Council of Medical Research. Guidelines for Management of Type 2 diabetes. 2018. Available on: https://medibulletin.com/wp-content/uploads/2018/05/ICMR_diabetesGuidelines.2018.pdf. Accessed on 21 Jan, 2019.
 25. Garber AJ, Wahlen J, Wahl T, Bressler P, Braceras R, Allen E, 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). *Diabetes Obes Metab* 2006; 8:58-66.
 26. Cahn A, Miccoli R, Dardano A, Del Prato S. New forms of insulin and insulin therapies for the treatment of type 2 diabetes. *Lancet Diabetes Endocrinol* 2015; 3:638-52.
 27. Meneghini L. New insulin preparations: A primer for the clinician. *Cleve Clin J Med* 2016; 83(5 Suppl 1):S27-33.
 28. Giugliano D, Chiodini P, Maiorino MI, Bellastella G, Esposito K. Intensification of insulin therapy with basal-bolus or premixed insulin regimens in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Endocrine* 2016; 51:417-28.
 29. Sheu WH, Ji L, Lee WJ, Jabbar A, Han JH, Lew T. Efficacy and safety of premixed insulin analogs in Asian patients with type 2 diabetes: A systematic review. *Journal of Diabetes Investigation* 2017; 8:518-534.