Choice of Insulin in Type 2 Diabetes: A Southeast Asian Perspective

Sanjay Kalra, Hong Quang Thai, Chaicharn Deerochanawong, Goh Su-Yen, Dato’ Dr Mafauzy Mohamed, Tint Swe Latt, Than Than Aye, Zafar Ahmed Latif, Prasad Katulanda, Touch Khun, Sum Satha, Vadsana Vongvandy

Department of Endocrinology, Bharti Hospital, Karnal, Haryana, India, 1Vietnamese Association of Diabetes and Endocrinology, Vietnam, 2Rajavithi Hospital, College of Medicine, Rangsit University, Ministry of Public Health, Bangkok, Thailand, 3Department of Endocrinology, Singapore General Hospital, Singapore, 4Universiti Sains Malaysia, Health Campus in Kelantan, Kelantan, Malaysia, 5Myanmar Diabetes Association, 6Department of Medicine, University of Medicine 2, Yangon, Myanmar, 7BIRDEM Academy, Dhaka, Bangladesh, 8Department of Clinical Medicine, Diabetes Research Unit, Faculty of Medicine, University of Colombo, Colombo, Sri Lanka, 9Diabetology Unit, Preah Kossamak Hospital, 10Department of Medicine, Calmette Hospital, Phnom Penh, Cambodia, 11Center of Diabetes, Mahosot Hospital, Vientiane, Laos

Abstract

Southeast Asia faces a diabetes epidemic, which has created significant challenges for health care. The unique Asian diabetes phenotype, coupled with peculiar lifestyle, diet, and healthcare-seeking behavior, makes it imperative to develop clinical pathways and guidelines which address local needs and requirements. From an insulin-centric viewpoint, the preparations prescribed in such pathways should be effective, safe, well tolerated, nonintrusive, and suitable for the use in multiple clinical situations including initiation and intensification. This brief communication describes the utility of premixed or dual action insulin in such clinical pathways and guidelines.

Keywords: Asia, basal insulin, biphasic aspart, biphasic lispro, diabetes, dual action insulin, patient-centered care, postprandial glycemia, premixed insulin

Diabetes in Southeast Asia

Southeast Asia is one of the hot spots of the diabetes pandemic and bears more than its fair burden of the disease. Belonging to the Western Pacific Region of the International Diabetes Federation, the zone reports a diabetes prevalence of 9.3% and a large number of deaths, most of which occur in individuals below the age of 60.[1] An earlier onset of diabetes, rapid development of complications, and longer life expectancy have led to an increase in the burden of diabetes and diabetes complications. This strains the existing health-care system, which finds it challenging to handle the twin burden of communicable and noncommunicable disease which Southeast Asian nations face.

Importance of Clinical Pathways

The role of clinical pathways and clinical recommendations is of utmost importance in such a scenario. Well-crafted pathways and algorithms, based on evidence, help in providing much-needed guidance to physicians and other health-care providers who deal with diabetes. Such documents are expected to offer a comprehensive management strategy, which includes screening and diagnostic tools, as well as nonpharmacologic and pharmacological interventions. They empower general physicians to tackle diabetes in peripheral clinical setups and encourage timely management of the disease, thus reducing preventable complications.

Detailed suggestions are available from professional bodies such as the American Diabetes Association, European Association for Study of Diabetes, American Association of Clinical Endocrinologists, and International Diabetes Federation.[2-4] There is criticism, however, regarding the actual patient centeredness of these publications and their pan-ethnic appropriateness.[5,6] The techniques of diagnosis, thresholds for intervention, targets of management, and tools...
used to achieve them (the four T’s) must be pragmatic, realistic, and concordant with dietary and lifestyle patterns. In view of this, many Asian countries have developed their own national guidelines, relevant to their local needs.[7] This is in tune with the national list of essential medicines that each country develops: the subtle differences in these lists reflect the peculiar needs and requirements of each country.[8]

**Need for Southeast Asia Specific Clinical Pathways**

In diabetes care, we often tend to follow a Western-oriented management strategy. Data and recommendations from the Western world are usually extrapolated directly to Southeast Asia, without realizing that unique anthropometry, lifestyle, and glucophenol type of Southeast Asia modulate responses to pharmacotherapy. It should also be recognized that many Southeast Asian countries, especially the more urbanized and multiracial ones, are experiencing increasing rates of obesity and diabetes

The Asian type 2 diabetes phenotype is well known.[9] Southeast Asians have a relatively lower body mass index, and insulin secretory defect plays a more important role in the pathogenesis of diabetes. Caucasians, on the other hand, present with predominant insulin resistance. Thus, insulin replacement, both prandial and basal, is needed at an earlier stage in Asians with diabetes. There is a unique Asian lifestyle, “diet type,” and health care-seeking behavior, which is prevalent across most of the continent. In many countries of Southeast Asia, persons present to the health-care system at a relatively later stage, with significant glucotoxicity and lipotoxicity. Reversal of this toxicity may entail the administration of adequate amounts of both prandial and basal insulin.

Animal studies have proven that malnutrition during pregnancy can lead to decreased β-cell function and mass in newborns. Mothers who had suffered the Dutch Famine gave birth to children who developed impaired glucose tolerance and type 2 diabetes in later life.[10] The Great Chinese Famine sufferers experienced an increase in the risk of hyperglycemia during adulthood. This association appears to be exacerbated by a nutritionally rich environment in later life.[11] While most countries in Asia have experienced chronic food shortages in the past and this pathophysiologic pathway may have contributed to diabetes in elder generations, food sufficiency has been achieved now.

Rice forms the staple diet of all of Southeast Asian countries, and the high carbohydrate load requires prandial insulin coverage in persons with diabetes. The Southeast Asian diet pattern is also peculiar. Many persons take two heavy meals in a day and find it difficult to adjust to a 3 + 3 meal pattern which is an essential correlate of a basal-bolus regimen.

The high postprandial glucose levels, observed in Asian populations, are due to the intake of high carbohydrate meals in large quantity, a relatively higher glycemic index of food staffs in this ethnic group,[12] delayed presentation of the patient, and acceptance of insulin therapy. The prescription and use of insulin therapy must correctly and appropriately address the Asian pathophysiology and lifestyle habits.

**Insulin for Type 2 Diabetes in Southeast Asia**

Such control can be achieved by various regimens including basal, premixed, basal bolus, basal plus, and different delivery devices, namely, vials/syringes and disposable/reusable pens, can be utilized this purpose. The choice of regimens, preparation, and delivery devices should be made in a patient-centered manner,[13] following the spirit of informed and shared decision-making.

In a national clinical pathway or algorithm, however, preference should be given to therapeutic options which have the potential to provide maximum benefit to the maximum number of intended beneficiaries. Choosing an inappropriate insulin may delay control, worsen complications, and negatively impact the patient’s (and community’s) trust in the health-care system. On the other hand, initiating an insulin which provides effective, safe, well-tolerated, convenient, and nonintrusive glucose control helps improve both biomedical and psychosocial outcomes.

Clinical pathways and algorithms designed for Southeast Asia should be based on pathophysiological abnormalities, dietary content, dietary pattern, lifestyle, and healthcare-seeking behavior. Thus, it is especially important with respect to guidance related to the choice of insulin for initiation. Asian evidence which proves the need for greater prandial insulin coverage,[14] and the advantages of specific insulin preparations should be taken into consideration.[15]

Most persons request for insulin therapy which does not interfere with, or intrude into, their lifestyle. In an overstretched health-care system, it also makes sense to use stock and dispense a minimum number of pharmaceutical preparations. Thus, an insulin which can be used both for initiation and intensification should take precedence over preparations which are limited to the use in only specific clinical settings.

**Premixed Insulin for Southeast Asia**

In the Southeast Asian content, this option seems to be premixed insulin. This class of insulin provides comprehensive glucose control, including both fasting and postprandial euglycemia, with a lesser number of injections. Premixed analogs, such as biphasic aspart and biphasic lispro (lispro mix), have the advantage of lower hypoglycemia, lower levels of postprandial glucose excursions, better adherence, improved quality of life, and higher patient satisfaction with treatment. The dual action coformulation, insulin degludec aspart, which is an improvement over existing insulin preparations, has added advantages of even lower hypoglycemia, nocturnal hypoglycemia, and greater flexibility.[16]

Premixed or dual action insulin is the insulin of choice across most of the Asian and African countries.[17] This is borne out
by statistics which reveal that premixed insulin is the most popular type of insulin used in the Southeast Asian Region.\textsuperscript{[18]} The A1chieve observational study also showed that premixed insulin analogs were the preferred mode of insulin use in Indonesia.\textsuperscript{[19]}

Premixed insulin can be used once daily, twice daily, or thrice daily, depending on the clinical situation. It can be used for initiation as well as intensification and lends itself to easy self-titration by the user and to physician-led dose titration. Various regimens, such as high-mix, hetero-mix, and reverse hetero-mix regimens,\textsuperscript{[20]} allow for control of difficult-to-control or refractory diabetes.

Premixed insulin is included as an insulin of choice for initiation as well as intensification in guidelines from the International Diabetes Federation,\textsuperscript{[21]} Australasia,\textsuperscript{[22]} Cambodia,\textsuperscript{[23]} India,\textsuperscript{[7]} Japan,\textsuperscript{[24]} Myanmar,\textsuperscript{[25]} South Africa,\textsuperscript{[26]} and Vietnam.\textsuperscript{[27]} This reinforces the utility of this preparation in diabetes care. Premixed insulin is also mentioned in the national lists of essential medicines of various Southeast Asian countries\textsuperscript{[28]} including Cambodia,\textsuperscript{[29]} Myanmar,\textsuperscript{[26]} and Vietnam.\textsuperscript{[29]} The comprehensive Laotian formulary of essential medicines\textsuperscript{[30]} also mentions “insulin zinc (mixed)” as an essential drug. This preparation therefore seems optimal for inclusion in various national clinical pathways and guidelines across Southeast Asia.

Data from DiabCare Asia suggest that conventional strategies and practices are ineffective in achieving good glycaemic control. In Malaysia, for example, only 41% of participants achieved a target HbA1c <7.0%, with a mean HbA1c of 7.8 ± 2.2%.\textsuperscript{[31]} Indonesia reported a mean HbA1c of 8.2 ± 2.0%, with 32.1% participants achieving target.\textsuperscript{[32]} Results from Bangladesh showed a mean HbA1c of 8.6 ± 2.0%, with only 23.1% of the patients achieving the target of <7.0%.\textsuperscript{[33]} Surveys in Thailand show similar trends, with 29.7%–41.3% participants reaching HbA1c goal in various studies.\textsuperscript{[34]} These figures suggest that we need to enhance efforts for timely initiation of insulin, with preparations that are effective in controlling both fasting and postprandial glucose.

**Southeast Asian Leadership**

Southeast Asia is recognized as a global leader in the provision of essential medicines for chronic disease, with best practices from Vietnam being highlighted by the World Health Organization website.\textsuperscript{[35]}

It seems natural, therefore, for Southeast Asian nations to continue their proactive and patient-centered approach toward the management of diabetes. This is accomplished by ensuring publication and adoption of updated national clinical pathways and guidelines, which reflect and respond to the lifestyle, dietary patterns, and biomedical as well as psychosocial needs of their citizens.

**Acknowledgment**

This paper is being published simultaneously in the *Vietnamese Journal of Endocrinology and Metabolism.*

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Regional Fact Sheet. Available from: http://www.diabetesatlas.org. [Last accessed on 2016 Nov 24]
2. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes, 2015: A patient-centered approach: Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:140-9.
3. Global Guideline for Type 2 Diabetes. Available from: http://www.idf.org/guideline-type-2-diabetes. [Last accessed on 2016 Nov 24]
4. Handelsman Y, Bloomgarden ZT, Grunberger G, Umpierrez G, Zimmerman RS, Bailey TS, et al. American Association of Clinical Endocrinologists and American College of Endocrinology – Clinical practice guidelines for developing a diabetes mellitus comprehensive care plan – 2015 – Executive summary. Endocr Pract 2015;21:413-37.
5. Kalra S, Balhara YS, Das AK. The bio-psycho-social model and the American Diabetes Association European Association for the Study of Diabetes position statement on management of hyperglycemia. J Soc Health Diabetes 2013;1:53-5.
6. Kalra S, Bantwal G, John M. The ADA-EASD patient-centered guidelines for management of hyperglycemia: Are they patient-centered enough? J Soc Health Diabetes 2013;1:41-3.
7. Madhu SV, Saboo B, Makkar BM, Reddy GC, Jana J, Panda JK, et al. Guideline Development Group. RSSDI clinical practice recommendations for management of type 2 diabetes mellitus, 2015. Int J Diabetess Dev Ctries 2015;35:1-71.
8. Kalra S, Gupta Y, Saboo B. Essential drugs in diabetes: South and South East Asian perspective. J Soc Health Diabetes 2015;3:4.
9. Chan JC, Yeung R, Luk A. The Asian diabetes phenotypes: Challenges and opportunities. Diabetes Res Clin Pract 2014;105:135-9.
10. de Rooij SR, Painter RC, Phillips DI, Osmond C, Michels RP, Godland IF, et al. Impaired insulin secretion after prenatal exposure to the Dutch famine. Diabetes Care 2006;29:1897-901.
11. Li Y, He Y, Qi L, Jaddoe VW, Feskens EJ, Yang X, et al. Exposure to the Chinese famine in early life and the risk of hyperglycemia and type 2 diabetes in adulthood. Diabetes 2010;59:2400-6.
12. Venn BS, Williams SM, Mann JI. Comparison of postprandial glycaemia in Asians and Caucasians. Diabet Med 2010;27:1205-8.
13. Kalra S, Gupta Y. Choosing an insulin regime: A developing country perspective. Afr J Diabetes Med 2014;22:17-20.
14. Ji L, Min KW, Oliveira J, Lew T, Duan R. Comparison of efficacy and safety of two starting insulin regimens in non-Asian, Asian Indian, and East Asian patients with type 2 diabetes: A post hoc analysis of the PARADIGM study. Diabetes Metab Syndr Obes 2016;9:243-9.
15. Kalra S, Plata-Que T, Kumar D, Mumtaz M, Søndergaard F, Kozlovski P, et al. Initiation with once-daily BIasp 30 results in superior outcome compared to insulin glargine in Asians with type 2 diabetes inadequately controlled by oral anti-diabetic drugs. Diabetes Res Clin Pract 2010;88:282-8.
16. Kalra S. Insulin Degludec Aspart: The first co-formulation of insulin analogues. Diabet Ther 2014;5:65-72.
17. Kalra S, Balhara YP, Sahay BK, Ganapathy B, Das AK. Why is premixed insulin the preferred insulin? Novel answers to a decade-old question. J Assoc Physicians India 2013;61 1 Suppl: 9-11.
18. Matsuba I, Sawa T, Kawata T, Kanamori A, Jiang D, Machimura H, et al. Cross-national variation in glycemic control and diabetes-related distress among East Asian patients using insulin: Results from the MOSAic Study, Diabetes Ther 2016;7:349-60.
19. Indonesia. Available from: http://www.a1chieve.com/en/reports-generator/indonesia. [Last accessed on 2016 Nov 24].
20. Kalra S, Farooqi MH, El-Houni AE. High-mix insulins. Indian J
Kalra, et al.: Premixed insulin in Southeast Asia

Endocrinol Metab 2015;19:686-90.

21. Wu T, Betty B, Downie M, Khanolkar M, Kilov G, Orr-Walker B, et al. Practical guidance on the use of premix insulin analogs in initiating, intensifying, or switching insulin regimens in type 2 diabetes. Diabetes Ther 2015;6:273-87.

22. Clinical Practice Guidelines for the Treatment of Type 2 Diabetes at NCD Clinics/RHs, Department of Preventive Medicine, Ministry of Health, Cambodia; 2015. p. 20.

23. Treatment Guide for Diabetes; 2014-2015. Available at: http://www.jds.or.jp/modules/en/index.php?content_id=1. [Last accessed on 2016 Nov 25].

24. Myanmar Guideline for Insulin Therapy. 1st ed. Yangon: Myanmar Diabetes Association; 2014. p. 18-9.

25. Amod A, Berg G. The 2012 SEMDSA guidelines for the management of type 2 diabetes. JEMDSA. 2012; 17:S1-95.

26. Vietnam: Local Guideline for Diagnose and Treatment in T2DM. Hanoi: Ministry of Health of Vietnam; 2014.

27. Essential Medicines List (CPA 2); 2012. p. 28 Available from: http://www.ddfcambodia.com/document/68-essential-medicines-list.html. [Last accessed on 2016 Nov 28].

28. Essential and Complementary Medicines and Vaccines for MYANMAR. 2014. p. 24. Available from: http://www.moh.gov.mm/file/NLEM.pdf. [Last accessed on 2016 Nov 28].

29. Viet Nam. National Medicines List/Formulary/Standard Treatment Guidelines. Available from: http://www.who.int/selection_medicines/country_lists/vnm/en/. [Last accessed on 2016 Nov 25].

30. 1406186221National Medicine Formulary Lao.pdf. p. 307. Available from: http://www.fdd.gov.la/download/contents_documents/. [Last accessed on 2016 Nov 28].

31. Mafauzy M. Diabetes control and complications in public hospitals in Malaysia. Med J Malaysia 2006;61:477-83.

32. Soewondo P, Soegondo S, Suastika K, Pranoto A, Soeatmadji DW, Tjkroprawiro A. The DiabCare Asia 2008 study-Outcomes on control and complications of type 2 diabetic patients in Indonesia. Med J Indones 2010;19:235.

33. Latif ZA, Jain A, Rahman MM. Evaluation of management, control, complications and psychosocial aspects of diabetics in Bangladesh: DiabCare Bangladesh 2008. Bangladesh Med Res Counce Bull 2011;37:11-6.

34. Deerochanawong C, Ferrario A. Diabetes management in Thailand: A literature review of the burden, costs, and outcomes. Global Health 2013;9:11.

35. Country Stories. Available from: http://www.who.int/medicines/about/country-stories/en/. [Last accessed on 2016 Nov 28].