



## Point of View

# Why is Premixed Insulin the Preferred Insulin? Novel Answers to a Decade-Old Question

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### Abstract

A wide range of sources have been used to create an equally wide range of types of insulin (rapid acting, fast acting, premixed, intermediate acting and long acting). While some of these insulins are no longer in clinical use, others are being used extensively across the world. Premixed insulin is the most frequently prescribed and used insulin in Asia; basal insulin is more extensively used in USA. As compared with basal insulin alone, premixed regimens tend to lower HbA1c to a larger degree while providing enhanced convenience. It is a challenge for diabetologists to assess the conflicting guidelines and decide which one to follow. This is especially true with regard to choosing appropriate insulin for initiation of therapy. Besides, ethnicity may play a key role in determining choice of insulin therapy among different populations. Here, the authors discuss the various factors, pharmacological as well as psychological, that have made premixed insulins the preferred insulin for type 2 diabetes in India and the many parts of Asia. The authors utilize well known theories of psychology, namely generalization, cognitive dissonance and concordance to provide a rational explanation for the preference for premixed insulin that Indian people with diabetes, and their physicians, have.

### Introduction

Insulin has been an indispensable part of diabetes management since its discovery. Insulin has gone through various modifications, with the currently available range of insulin having a little resemblance to the brown crystalline powder produced in 1921. A wide range of sources (bovine, porcine, bovine-porcine, human, analogue) have been used to create an equally wide range of types of insulin (rapid acting, fast acting, premixed, intermediate acting and long acting). While some of these insulins are no longer in clinical use, others are being used extensively across the world.

The currently available insulins can be classified as rapid-acting, premixed, or intermediate/ long acting. All these can be of human or analog origin. A lot of controversy continues to exist regarding the ideal insulin for initiation and intensification. The position statement of the American Diabetes Association (ADA) and European Association for Study of Diabetes (EASD) recommend beginning therapy with basal insulin. In an interesting observation, they state that “a more convenient but

less adaptable method involves ‘premixed’ insulin, consisting of a fixed combination of intermediate insulin with regular insulin or a rapid analogue”. However, they conclude that in general, when compared with basal insulin alone, premixed regimens tend to lower HbA1c to a larger degree, usually at the expense of slightly more hypoglycaemia and weight gain.<sup>1</sup> In contrast, guidelines/algorithms from the International Diabetes Federation (IDF), and American Association of Clinical Endocrinologists (AACE) recommend initiation of treatment with either premixed or basal insulin.<sup>2,3</sup> This allows the treating physician (and his or her patient) a wider range to choose from. The Indian National Premixed guidelines go a step further and recommend use of premixed insulin as a preferred mode of initiating and intensifying therapy.<sup>4</sup> Similar views are echoed in national guidelines from Bangladesh. Looking at the available data, postprandial plasma glucose (PPG) peaks are the major factor leading to cardiovascular disease (CVD) and mortality. The association between mortality and PPG is much stronger than the one between mortality and fasting plasma glucose (FPG).<sup>5</sup> Any treatment that targets PPG is superior when we compare it with outcomes to therapy which targets FPG. In a study by Woerle *et al.* 94% of people achieving the postmeal target of <7.8 mmol/l (140 mg/dl) achieved an HbA1c <7%, while only 64% of those who achieved fasting plasma glucose <5.6 mmol/l (100 mg/dl) achieved the target HbA1c. Decreases in postmeal plasma glucose accounted for nearly twice the decrease in HbA1c compared with decreases in fasting plasma glucose.<sup>6</sup> This has also been recently highlighted in the IDF guidelines

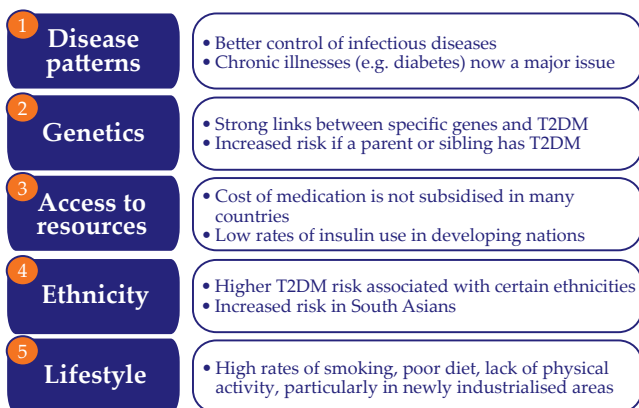


Fig. 1 : Regional and cultural concerns exist in developing nations

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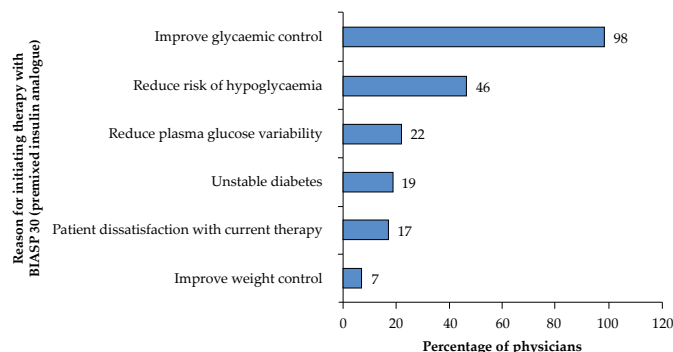
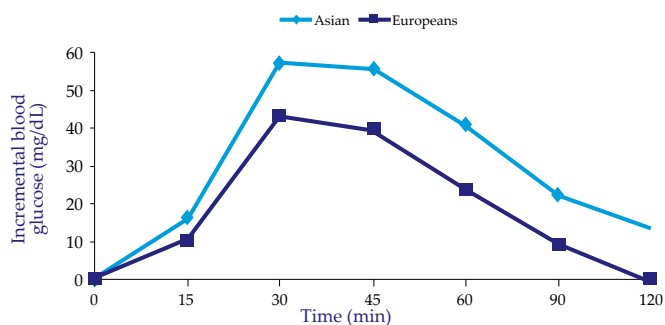


Fig. 2 : Reasons for initiating therapy with biphasic insulin aspart (BIAsp 30) in patients with type 2 diabetes in the Indian cohort of A\_cheive® study



**Fig. 3 : Different responses to cereals between the Asians and Caucasians for cereals (Adapted from reference 18)**

for the management of postmeal glucose in patients with type 2 diabetes.<sup>7</sup>

## Global Trends and Ethnopharmacy

Market differences add to this diversity. While premixed insulin is the most frequently prescribed and used insulin in Asia, basal insulin is more extensively used in USA. Some unique regional and cultural concerns existing in developing nations are summarized in Figure 1. The recently reported baseline results of A<sub>1</sub>cheive<sup>®</sup>, the largest global observational study in diabetes, reinforce this opinion. While premixed insulin is the initial insulin of choice in 75% of South Asian patients, basal insulin is used to initiate therapy in 54% of South American diabetics.<sup>8</sup>

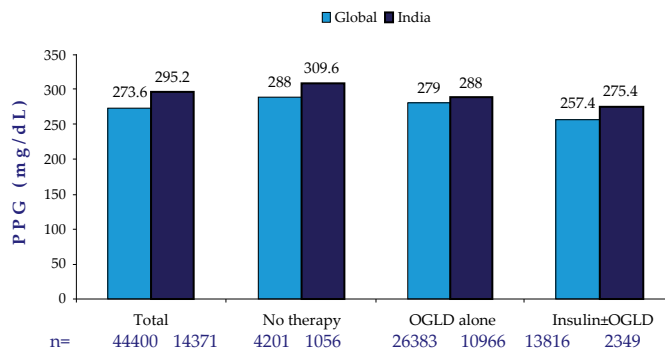
It is a challenge for diabetologists to assess the conflicting guidelines and decide which one to follow. This is especially true with regard to choosing appropriate insulin for initiation of therapy. Evidence is available in support of both premixed and basal insulin, though clinical trials have shown that the use of premixed insulin twice-daily provides superior glycaemic control versus basal insulin.<sup>9-10</sup> Biphasic insulin aspart 30 is a premixed insulin analogue that contains 30% rapid-acting insulin aspart and 70% protaminated insulin aspart. Its safety and efficacy has been demonstrated in numerous randomized clinical trials, meta-analyses and observational studies.<sup>8-15</sup> Traditionally, however, premixed insulin has always been thought of as twice daily insulin.

Evidence favoring use of once daily premixed insulin is a rather recent development. A multicentre study performed in 4 continents compared once daily premixed aspart insulin with once daily glargine insulin. With respect to HbA<sub>1c</sub>, BIAsp 30 fulfilled the statistical criteria for superiority to insulin glargine and, according to pre-defined criteria, the improvements in HbA<sub>1c</sub> are considered clinically equivalent.<sup>14</sup> Surprisingly, participants from India, Malaysia and the Philippines (n= 155) seemed to respond much better to premixed aspart insulin as compared to glargine insulin.<sup>15</sup> Differences in dietary patterns were suggested as a possible explanation for this observation.

## Ethnopharmaceutic Explanation

Following these findings, John et al. used the data regarding ethnic differences in glucose metabolism and glycemic index to suggest ethnicity as a factor for determining choice of insulin therapy.<sup>16</sup> These interesting observations paved the way for introduction of the term 'ethnopharmacy' to diabetology by John and Kalra.<sup>17</sup>

While this obvious difference remains a subject of much debate and discussion, the issue has not yet been systematically explored. There is no published literature exploring the reasons behind this variation in response across different ethnicity to the best of our knowledge. The umbrella term 'ethnopharmacy' has



**Fig. 4 : Post-prandial glucose (post-breakfast) values by pre-study therapy (adapted from reference 8)**

been utilized by John and Kalra to explain the reasons behind this differential use of insulins in various regions of the world.<sup>16</sup> It is postulated that as we consume a higher carbohydrate load, and have a higher glycemic response to calorie intake, we need prandial insulin earlier on in the natural history of disease. Appreciable difference in glycaemic responses to a glucose load and to a commonly consumed breakfast cereal in the communities was recently demonstrated by Venn and coworkers.<sup>18</sup> Similarly, Valensi et al. have shown that PPG is higher among Indians at the time of initiation of insulin therapy as compared to other populations.<sup>13</sup> Similar results have also appeared in the baseline data of the A<sub>1</sub>cheive<sup>®</sup> study (Figure 4).<sup>8</sup> As we (Indians) consume lesser number of meals, we do not need, and may not tolerate a basal bolus regimen in many instances. Premixed insulin provides a convenient way of administering both basal and prandial insulin in a safe and well tolerated manner.

## Biopsychobehavioural Explanation

There are alternate explanations to describe the ethnic differences noted in insulin usage. These alternate explanations are based in bio-psycho-behavioral concepts of medicine. Insulin usage in America and Europe dates back to the 1920's when it was a treatment for type 1 diabetes, rather than type 2 diabetes. Successive generations of endocrinologists were trained to use insulin, in a prandial, and later, basal-bolus regimen in patients with type 1 diabetes with absolute insulin deficiency. Sparingly available insulin was initially used sparingly in type 2 diabetics, who were considered for insulin therapy only during life threatening complications. In contrast, insulin usage came much later to the developing world including India. First recorded use of insulin in India was in 1935- around a decade later than in the USA.

## Necessity is the Mother of Invention

Logistic factors such as availability of the product often guided the changing trends in type of insulin used in the country. At times, patients on prandial insulin had to be shifted to premixed insulin as insulin shortages hit the country.<sup>19</sup> At other times, such decisions were guided by convenience as well. Though this may be termed improvisation, it actually led to innovation, when it was noted that both type 1 and type 2 patients responded well to premixed insulin. The use of premixed insulin was associated with less number of infections and monitoring thus cutting down costs dramatically. This 'innovative improvisation' led to effective results, which strengthened the popularity of premixed insulin as the insulin of choice in the country.

## Generalization

Theories of learning could also help explain certain aspects

of the behavior related to choice of type of insulin among the endocrinologists.

*Generalization* is a concept from classical conditioning that helps explain pairing of conditioned response with stimulus having close resemblance to the conditioned stimulus. Consequently closely resembling stimuli tend to induce same response in spite of a lack of repeated pairing of the relatively novel stimulus. Thus in a western outpatient department (OPD), when the conditioned stimulus of a patient of type 1 diabetes (which formed a large proportion of early diabetes clinics) was replaced by an unconditioned stimulus of uncontrolled type 2 diabetes, the response of the physician was the same basal insulin, with or without bolus insulin. On the other hand, the Indian physician was conditioned to the stimulus in form of type 2 diabetes (as type 1 formed a minuscule proportion of his practice). Consequent to the initial response of use of premixed insulin the same response was generalized to other diabetes types. It must be mentioned here that use of a specific insulin type was strengthened by a positive reinforcement in form of clinical response, i.e. diabetes control and patient satisfaction offered by a particular insulin type. Had a satisfactory therapeutic response not occurred, generalization or use of premixed insulin would not have continued. Indian physicians/ endocrinologists had a much shorter experience with exclusive use of bolus and prandial insulin and hence its use was less deeply ingrained.

## Cognitive Dissonance vs. Concordance

Another concept that could help understand this observation is that of cognitive dissonance. Cognitive dissonance is a state of discomfort caused by holding conflicting ideas simultaneously. Physicians, much like other fellow human beings, tend to rationalize their previous behavior and thoughts in order to avoid cognitive dissonance. Hence it is possible that a physician who has learnt to use basal bolus insulin in type 1 diabetes continues to use the same regimen in type 2 diabetes. This may be done subconsciously in order to avoid discrediting his earlier effort of using a particular type of insulin that was deemed to be effective. The same could be used to explain another interesting observation of prescription of premixed insulin to people with type 1 diabetes in certain centers in India in spite of the obvious differences between these two conditions. This occurs because subconsciously, the treating physician achieves cognitive concordance by prescribing the same type of insulin to all people with diabetes. One should endeavor, however, to emphasize the subtle (and not so subtle) differences between the various forms of diabetes, to ensure optimal therapy of diverse patients. This can be done successfully during postgraduate training and through continuing medical education programmes.

## Conclusion

Ethnicity may play a key role in determining choice of insulin therapy among different populations. Introduction of the concept of ethnopharmacy to diabetology can help systematically study this interesting aspect of diabetes care. Various bio-psycho-behavioral concepts can also be used to understand and explain these observations across different regions of the world with regards to choice of type of insulin in treatment of diabetes. There is a need to systematically study these possible hypotheses in order to have a clear understanding on these issues.

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