Review Paper

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Diabetology

ROLE OF RECOMBINANT HUMAN PREMIX INSULIN (RHI 50/50) IN THE MANAGEMENT OF TYPE 2 DIABETES MELLITUS IN ASIAN POPULATION: AN EXPERT REVIEW

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KEYWORDS :

Introduction:

The prevalence of type 2 diabetes (T2D) is increasing at exponential rates, the estimated prevalence of diabetes in adults aged 20–79 years has more than tripled, from an estimated 151 million (4.6% of the global population at the time) to 537 million (10.5%), 643 million people will have diabetes by 2030.[1]). If trends continue, the number will jump to a staggering 783 million (12.2%) by 2045,[1] almost 90% of people with undiagnosed diabetes live in low- and middle-income countries.[2] India accounts for 1 in 7 of all adults living with diabetes worldwide.[1] Asian Indians have a higher predilection for T2DM, and this is due to the 'Asian-Indian phenotype.[3] Dietary carbohydrates form the major source of energy in Asian diets. There have also been rapid changes in the dietary composition of Asian Indians such that diets today are high in refined carbohydrates, sugars, fats, and salt. All these factors contribute to the rising prevalence of diabetes, hypertension, and cardiovascular diseases (CVDs).[4] The carbohydrate quantity and quality play a vital function in the management of diabetes. High glycaemic index foods elicit higher glycaemic and insulinemic responses and promote insulin resistance and type 2 diabetes (T2D) through beta-cell exhaustion. The higher the plasma glucose level with which a patient goes to bed as a result of postprandial hyperglycemia, the higher will be the fasting hyperglycemia in the morning. Similarly, the higher the fasting hyperglycemia in the morning, the higher the postprandial level during the day.[5]

High Carbohydrate diet and Asian population

Diets in Asian countries including India continue to derive two-thirds of carbohydrate calories from cereal staples and this has not changed during the last three decades in India.[4]

If attempts with simple lifestyle changes have not produced a satisfactory response, pharmacologic intervention is indicated. Of all antidiabetic agents available, only the non-sulfonylurea secretagogues (the meglitinides), the α-glucosidase inhibitors (acarbose and miglitol), and few types of insulins and GLP-1 analogues specifically target postprandial hyperglycemia, control of postprandial hyperglycaemia is an important part of the control of diabetes.[6] Both the quantity and type of carbohydrates could affect insulin secretion and postprandial glycaemia. Multiple insulin regimens are available to control the post-prandial glycaemic surges. A practical and feasible option is to initiate insulin with one or more biphasic preparations at mealtimes, thus providing both basal and prandial coverage.

High carbohydrate Diets

The quality and quantity of carbohydrates are the main predictors of glycaemic response. Carbohydrate-rich foods that are rapidly broken down and absorbed into the bloodstream are categorized as high-GI foods. High-GI foods lead to a rapid increase in blood glucose and insulin responses following food ingestion. In the past, these carbohydrates have been derived from whole grains. However, today, they are replaced with refined carbohydrates, predominantly from rice, due to modern milling technology.[7] . It is known that high-carbohydrate diets raise plasma glucose, insulin, TAG, and NEFA and thus contribute to insulin resistance. Sakurai et al in their cohort study evaluated the risk of developing T2D in Japanese men, based on the percentage of energy intake contributed by carbohydrates and the level of obesity.[8] They reported that higher carbohydrate intake was linked with an increased risk for new-onset T2D in obese individuals rather than in non-obese individuals. [8] In urban Indians in Chennai (10 yr follow-up study), Anjana et al showed that a higher diet risk score which included a larger intake of refined grains and reduced intake of vegetables and fruits, dairy, and nuts doubled the incidence of new-onset T2D.[9]

Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE) by Dehghan et al a prospective cohort study showed that higher carbohydrate intake was associated with an increased risk of total mortality.[10] The Chennai-based epidemiology study, CURES-17 by Mohan et al which looked at the secular trends in the prevalence of diabetes and impaired glucose tolerance, stated that the overall crude prevalence of diabetes using WHO criteria was 15.5% (age-standardized 14.3%), while that of IGT was 10.6% (age-standardized 10.2%). Within a span of 14 years, the prevalence of diabetes increased by 72.3%.[11] The prevalence of IGT increased by 9.6% from 1989 to 1995 and by 84.6% between 1995 and 2000. However, it decreased by 39.3% between 2000 and 2004. There was a shift in the age at diagnosis of diabetes to younger age in CURES compared with NUDS (national urban diabetes survey).[11]

Diabetes and Postprandial hyperglycemia:

After meals, several mechanisms (sequence/composition of meals, gastric emptying/intestinal glucose absorption, gastrointestinal hormones, hyperglycemia mass action effects, insulin/glucagon secretion/action, de novo lipogenesis, and glucose disposal) operate in concert for optimal regulation of postprandial glucose fluctuations. [12] Many factors can influence postprandial glucose: the GI of different foods combined in a meal; the carbohydrate content; the size of a meal; the presence and the percentage of the other three macronutrients (fat, protein, and amount and type of dietary fiber) in a meal; and also factors such as hormonal secretion, gastric emptying and the sequence of all macronutrients being ingested, and meal timing.[12]

The American Diabetes Association has established postprandial glucose (PPG) as an independent contributor to both HbA1c and diabetes complications, and increasing evidence suggests that all three glycaemic parameters of HbA1c, FPG, and postprandial glucose (PPG) are independently important. [13] Increased PPG is also followed by a rise in postprandial insulin in people who do not have diabetes. Hence in people with type 2 diabetes, the post-meal insulin response is diminished leading to postprandial hyperglycemia. Postprandial hyperglycemia is more detrimental to the development of T2D complications because it contributes greatly to microvascular and macrovascular damage. As hyperglycaemic spikes during the postprandial state have been shown to trigger endothelial dysfunction, inflammation, and increase oxidative stress, controlling postprandial hyperglycemia should be the focus of all nutritional interventions for T2D. The importance of addressing postprandial glucose control in insulin regimens has been highlighted by Monnier et al.[14] They determined that 70% of overall glycaemic control as represented by

HbA1C relates to postprandial glucose when A1C values are < 7.3%, and 50% of overall glycaemic control relates to postprandial glucose when A1C values are 7.3-8.4%.[14] Post-prandial hyperglycaemia is one of the independent risk factors for macrovascular complications in diabetic patients. There is also evidence suggesting that postprandial hyperglycemia may be an independent risk factor for cardiovascular disease, stroke, retinopathy, renal failure, and neurologic complications in both diabetic and nondiabetic individuals. One of the proposed mechanisms of diabetic vascular disease is the increase in oxidative stress that occurs following the consumption of high carbohydrate diet that causes post-prandial hyperglycemia. This oxidative stress has been shown to induce endothelial dysfunction and increase inflammation, vasoconstriction, and carotid intima-media thickness. PPG control is important not only for regulating glycemia, but also because reducing postprandial hyperglycemia may mitigate cardiovascular risks. Further, the most recent guidelines from the International Diabetes Federation recognize the importance of PPG control in mitigating cardiovascular risks and include strategies for cardiovascular risk reduction as a major focus of therapy.[1]In the early stages of prediabetes and diabetes, the deleterious effects of an imbalance between impaired insulin secretion and insulin resistance are more apparent in the postprandial state than in the fasting state. PPG levels increase earlier and faster than FPG levels because more insulin is needed after meals than in the fasting state to maintain glucose homeostasis. In addition, most PPG metabolism occurs via insulin-dependent pathways; however, in the fasting state, most glucose disposal is not dependent on insulin.[14]

Often by the time diabetes is diagnosed based on elevated FPG levels, the β-cell function has decreased by approximately 50%. Vascular endothelial dysfunction has been recognized as a key step in the early development of cardiovascular disease. Endothelial dysfunction results in an impairment of endothelium-dependent vasodilation, as well as an increase in proinflammatory, pro-coagulatory, and proliferative responses, all of which are associated with the development of atherosclerosis. It has been observed that pharmacologic strategies that target PPG to slow the progression of type 2 diabetes have reduced cardiovascular morbidity and mortality

Premixed Insulin

Insulin plays a primary role in the regulation of glucose homeostasis via its effects on insulin-sensitive tissues: blood levels of glucose are regulated simultaneously by the rates of glucose production from the liver (and kidneys), and the rates of disposal to peripheral tissues (mainly skeletal muscle).[15] Premixed insulin provide both basal and postprandial coverage starting with 1 injection, but they are generally administered twice daily (BID), one injection at breakfast, and one injection at supper depending on glucose profile. Physicians may recommend adding further injections, depending on the patient's individual needs

Choosing an appropriate insulin type and regimen should also be based on specific patient attributes, rather than taking a 'one-size-fits-all' approach, and many guidelines now recognize both basal and premix insulin as options for initiating/intensifying insulin therapy in T2D.[15] Indeed, the loss of the first-phase insulin release is one of the earliest detectable defects of -β cell function in individuals destined to develop T2D. The resultant postprandial hyperglycemia is to be addressed to mitigate the progression of diabetes complications. Unlike basal insulin, premix insulin targets both FPG and PPG, which is essential for addressing this glycaemic defect and achieving optimal glycaemic control, especially in the Indian context.

The preference for premix insulin regimens over other insulins in India may be due to the following reasons:[16]

1. Indians with typical Asian Indian Phenotype i.e., higher waist circumference, higher total and visceral fat, hyperinsulinemia, and likely insulin resistance respond better to premix insulins.

2. High intake of carbohydrates, resulting in higher glucose excursions after every meal.

3. Several observational studies have demonstrated high baseline post-prandial glucose (PPG) levels and diminished insulin response.

4. There is often a delay in the initiation of insulin therapy, resulting in a higher risk of failure of basal insulins.

5. Convenience and simplicity with premixed insulins, allowing physicians to intensify the treatment with the same insulin

The premixed insulins have pharmacokinetics that favour both efficacy (Prandial and Basal components) and patient convenience. This explains the high adherence rates and better glycaemic control with premixed insulins. The conventional premixed biphasic human insulin is a combination of regular human insulin and neutral protamine Hagedorn (NPH) in ratios of 30/70 or 50/50. These are administered 30 min prior to meals, and the action lasts for about 10–16 h.[17]

Role of recombinant Human insulin 50/50:

The rHI 50/50 insulin has 50 % of rapid-acting insulin and 50% of Neutral Protamine Hagedorn. The 50 % of rapid-acting insulin helps in curbing the prandial glycaemic surge and 50 % of NPH supports the basal insulin component.[18] Choosing the most appropriate insulin regimen for the patient when choosing an insulin regimen for initiation, it is imperative to bear in mind the long-term progressive nature of T2D and the likely need for intensification. Premixed 50/50 have a more time-action profile and produce greater reductions in the magnitude of postprandial glucose excursions than human insulin 70/30. More specifically, it is essential to suppress post-prandial blood glucose elevation and to stabilize the diurnal variation of blood glucose levels for the improvement of HbA1c levels and pre- and post-prandial blood glucose levels

Guidelines and recommendations[18,19,15,20]:

- RSSDI consensus recommendations on insulin therapy in the management of diabetes states that Premixed insulins will take care of both the basal and meal-related insulin requirements.
- Journal of The Association of Physicians of India: Consensus on Initiation and Intensification of Premix Insulin in Type 2 Diabetes Management, states that in the setting of high carbohydrate consumption in India, or in patients with predominant postprandial hyperglycaemia, premix insulin/co-formulation can offer effective and convenient glycaemic control.
- The Indian National Consensus Group (INCG) has provided guidance for the initiation and intensification of therapy with premixed insulin in the management of diabetes in primary care.
- The Royal Australian College of General Practitioners (RACGP) and RSSDI have provided guidance for the initiation, titration, and intensification of therapy with premixed insulin.
- According to these guidelines, premixed insulin may be an appropriate and simple option for glycaemic control when fasting and postprandial glucose levels are consistently elevated. Patients may be switched to premixed insulin if target HbA1c levels are not achieved with basal insulin alone or therapy intensified to basal plus or basal-bolus. It is important to emphasize appropriate nutrition and physical activity at all stages of treatment initiation and intensification.

Dose and dose titration

- Treatment with premixed insulin (10 U or 0.1–0.2 U/kg/day immediately before the largest meal, usually the evening meal) can be started in insulin-naïve persons with diabetes.
- The dose is then titrated once or twice a week depending upon the lowest blood glucose levels (fasting/prandial) over the last 3 days.

Conclusion:

Asians have relatively higher post-prandial glucose levels due to the consumption of carbohydrate-rich diets and the early onset of β-cell dysfunction. Premixed insulins are the preferred preparation in Southeast Asian countries and are included in the National List of Essential Medicines of various countries. rHI 50/50 has an equal component of basal and bolus insulin helps to plummet in the postprandial surge which is an affordable and accessible option to many Indian patients

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