Comments from the Brazilian Diabetes Society (SBD), subscribed by Brazilian Society of Endocrinology and Metabolism (SBEM), Intersectoral Forum of NCCs/NCDs in Brazil (ForumCCNT), Associação Nacional de Atenção ao Diabetes (ANAD), Federação Nacional das Associações e Entidades de Diabetes (FENAD), ADJ Diabetes Brasil, Instituto da Criança com Diabetes (ICD-RS) and Brazil Institute of Diabetes (IDB); on the submission for incorporation of rapid-acting insulin analogues (insulin lispro, insulin aspart, and insulin glulisine) to the WHO model list of essential medicines for the treatment of adults with type 1 and type 2 diabetes mellitus and for gestational diabetes and to the essential medicines list (EML) for children for the treatment of type 1 and type 2 diabetes

These technical-scientific societies of healthcare professionals and representative entities for people with diabetes would like to take this opportunity to contribute to the advancement of insulin therapy through the inclusion of rapid-acting insulin analogues in the WHO's essential medicines list. Regarding the indications for subgroups of people with diabetes, we recommend this insulin type for all PwT1D, all pregnant women with diabetes using bolus insulin, and, depending on the acquisition costs of rapid-acting insulin analogues, all PwT2D using bolus insulin or based on identification criteria described in the subsection related to T2D.

The advancement of insulin therapy for PwT1D in Brazil is outlined below and demonstrates how difficulties in achieving adequate diabetes management and glycemic targets are being minimized or resolved. Brazil is a vast country with a population of 203,080,756 people and significant regional and social class disparities in healthcare access (1), making it necessary to adopt national strategies to treat more evenly PwT1D across the country. The inclusion of rapid-acting insulin analogues was the first step toward this goal.

Our comments will be organized into the following topics:

- Inclusion of rapid-acting insulin analogues for PwT1D in the SUS (Brazilian Public Unified Health System)
- Benefits of rapid-acting insulin analogues for people with T2D

- Benefits of insulin analogues for pregnant women with DM (GDM, T1D, and T2D)

Inclusion of rapid-acting insulin analogues for people with T1D in the list of medicines in the Brazilian Unified Health System (SUS) (2):

In May 2016, the SBD submitted a dossier to CONITEC (National Commission for the Incorporation of Technologies in the Unified Health System) requesting the inclusion of rapid-acting insulin analogues in the treatment of people with type 1 diabetes mellitus (PwT1D). This request was endorsed by the Brazilian Society of Endocrinology and Metabolism (SBEM), Brazilian Society of Pediatrics (SBP), Associação Nacional de Atenção ao Diabetes (ANAD), Federação Nacional das Associações e Entidades de Diabetes (FENAD), ADJ Diabetes Brasil. In February 2017, rapid-acting insulin analogues were included in the SUS list of medicines for PwT1D who were already using regular human insulin but experienced severe hypoglycemia, nocturnal hypoglycemia, and inadequate glycemic control. The following documents were included in this request for incorporation (2):

1. Efficacy and safety of rapid-acting insulin analogues in the treatment of PwT1D.
2. Economic Analysis:
    a. Multicenter study on quality of life and utilities related to hypoglycemia in PwT1D within the Public Health System (SUS);
    b. Cost-Utility Model evaluating the use of rapid-acting insulin analogues for PwT1D;
    c. Budget Impact Analysis of rapid-acting insulin analogues for PwT1D in the Brazilian Unified Health System.

The key points of these extensive documents will be summarized next.

1) Efficacy and safety of rapid-acting insulin analogues in the treatment of PwT1D

We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to assess the effects of rapid-acting insulin analogues vs regular human insulin on hypoglycemia and postprandial glucose in PwT1D. Searches were run on the electronic databases MEDLINE, Cochrane-CENTRAL, EMBASE, ClinicalTrials.gov, LILACS, and DARE for RCTs published until August 2017. To be included in the study, the RCTs had to cover a minimum period of 4 weeks and had to assess the effects of rapid-acting insulin analogues vs regular human insulin on hypoglycemia and postprandial glucose levels in PwT1D. In this systematic review and meta-analysis, we originally report clinical evidence on therapeutical use of rapid-acting insulin analogues compared with regular insulin while focusing on the main possible benefits of these analogues, namely the reduction of hypoglycemia and postprandial glucose levels. Twenty-two articles met the inclusion criteria. Eight RCTs analyzed the effects of Aspart vs. regular human insulin, one analyzed the effects of Glulisine vs. regular human insulin, and 13 analyzed the effects of Lispro vs. regular human insulin. The selected studies contributed to a combined sample of 6.235 PwT1D for the meta-analysis (3).

The efficacy analysis was based on postprandial blood glucose levels, considering that the main objective of prescribing bolus insulin is to control postprandial glucose. Rapid-acting insulin analogues (Aspart, Glulisine, and Lispro) were associated with lower postprandial glucose levels when compared with regular human insulin (mean difference/MD − 19.44 mg/dL; 95% CI − 21.49 to − 17.39; 5031 PwDs, I2 = 69%). Also,

they were associated with lower postprandial glucose levels after all meals: breakfast (MD − 22.35 mg/dL; 95% CI − 23.52 to − 21.17; 4623 PwDs; I2 = 50%); lunch (MD − 10.86 mg/dL, 95% CI − 13.41 to − 8.31; 3675 PwDs; I2 = 54%) and dinner (MD − 19.52 mg/dL, 95% CI − 21.73 to − 17.31; 4530 PwDs; I2 = 90%) (3). Postprandial glucose peaks, as well as hypoglycemic events, are responsible for increasing cardiovascular events in PwD - and glycemic variability includes both events. Minimizing glycemic variability can prevent future cardiovascular events and adjusting it emerges as a goal to be persecuted in clinical practice to reduce, in addition to the average blood glucose, and its direct effects on DM-related vascular complications (4,5).

Safety analysis was based on the risk of hypoglycemic events (total, nocturnal and severe), one of the main barriers to achieving good glycemic control. Rapid-acting insulin analogues were associated with a decrease in total hypoglycemic episodes (risk rate 0.93, 95% CI 0.87–0.99; 6235 PwDs; I2 = 81%), nocturnal hypoglycemia (risk rate 0.55, 95% CI 0.40–0.76, 1995 PwDs, I2 = 84%), and severe hypoglycemia (risk rate 0.68, 95% CI 0.60–0.77; 5945 PwDs, I2 = 0%) (3). The Hypoglycemia Assessment Tool (HAT) study in Brazil demonstrated that the frequency and incidence of hypoglycemic events were higher in people living with diabetes under insulin therapy in Brazilian than those observed at the Global HAT study and Latin-American study group. (6,7). In addition, the incidence of severe hypoglycemia and nocturnal hypoglycemia were higher in Brazilian people with diabetes insulin-treated, compared with the people of the Global HAT (6,7). Therefore, there was a need of strategies to reduce the risk of hypoglycemic events among Brazilian PwD who were using insulin. The introduction of rapid-acting insulin analogues, in the list of medicines available for T1D, could help to achieve this goal, as demonstrated by us in the systematic review (3).

Our study showed that rapid-acting insulin analogues were associated with lower HbA1c when compared with regular human insulin (MD − 0.13, 95% CI − 0.16 to − 0.10; 5204 PwDs; I2 = 73%) (3). Postprandial glucose fluctuations contribute approximately 50% of the total hyperglycemia episodes in PwD on multiple doses of insulin (8). Therefore, rapid-acting insulin analogues were expected to be associated with lower HbA1c levels. However, the decreases were clinically irrelevant, even though the rapid-acting insulin analogues were indeed associated with lower HbA1c levels. This could be explained by the reduction in hypoglycemic episodes, mainly the nocturnal events that are longer, compared with the diurnal ones, leading to a HbA1c reduction.

Limited evidence analyzed in our systematic review suggests that, for PwT1D, the treatment with rapid-acting insulin analogues is more convenient than with regular human insulin. The higher satisfaction levels and greater flexibility associated with rapid-acting insulin analogues could be explained by the fact that they can be administered immediately before meals, as opposed to the anticipated 30 to 45 min when administering regular human insulin (3). In a study involving 1184 PwT1D, adherence to the correct timing of regular human insulin was 7% for the ones taking it 30 or more minutes before meals, 60% for those taking it 15-30 min before meals, and 33% for those taking it 15 min before meals. Regarding the administration of insulin Lispro, 98% of the PwD followed the orientation (0 to 15 min before meals) (9). Another reason why administering rapid-acting insulin analogues when the plate is ready or immediately

after the meal, as it may not always be possible to predict how much food (carbohydrates) the PwD will have eaten.

The benefits mentioned above are most likely determined by the specific pharmacokinetic properties of these analogues, having a very rapid-acting activity, limiting the risk of late falls in glucose levels (10). The association between rapid-acting insulin analogues and a reduction of 7% in total hypoglycemic episodes, 32% in severe hypoglycemia, and 45% in nocturnal hypoglycemia levels is an important finding, as these episodes are particularly associated with lower quality of life and treatment nonadherence (11). It is important to highlight that the quality of life and treatment adherence of Brazilians with T1D are compromised, as evidenced by previous studies (12,13).

2) Economic Analysis

Hypoglycemia is a critical and limiting factor for metabolic control and can adversely affect the quality of life of PwD. A multicenter, cross-sectional and observational study with PwT1D, was conducted to evaluate the health-related quality of life and calculate utility values associated with hypoglycemia in Brazilian PwT1D. Demographic and clinical data were collected, besides details on the frequency and severity of hypoglycemia. Health-related quality of life was assessed using EQ-5D instrument and utility values generated (14). The study enrolled 221 PwD and most of them (96.8%) reported at least one symptomatic hypoglycemia in the last three months, 68% (n = 150) reported nocturnal episodes and 34.8% (n = 77) reported severe episodes. High frequency (daily or weekly) was observed in 38.6% and 26% of those reporting nocturnal or severe hypoglycemia, respectively. The median visual analog scale was 70 [60–85] for all PwDs, with differences between those with and without severe hypoglycemia (70 [60–80] vs 80 [61–90]; p = 0.006) and those with high and low frequency (62.5 [50–72.25] vs 70 [60–80]; p = 0.007). The median utility value was 0.801 [0.756–1.000] for all PwD, with difference between those with high and low frequency of severe episodes (0.737 [0.628–1.000] vs 0.801 [0.756–1.000]; p = 0.02). This study shows the high frequency of hypoglycemia in a sample of PwT1D treated in three reference centers of the Brazilian public health system and the impact of severe hypoglycemic episodes on health-related quality of life. Utility values generated were used for the economic analysis associated with treatments that could decrease hypoglycemia and consequently improve quality of life (14).

The next step in the preparation of the dossier for the inclusion of rapid-acting insulin analogues in the SUS medicine list for PwT1D involved developing a simplified cost-utility model to evaluate the use of rapid-acting insulin analogues for type 1 diabetes (T1D) compared to regular human insulin. A decision tree was constructed to compare the use of regular human insulin with rapid-acting insulin analogues. The model was based on different incidences of hypoglycemic episodes to estimate the incremental utility between therapeutic options.

For medication pricing, the Health Price Database maintained by the Ministry of Health (Ministério da Saúde 2016) (2) was consulted. The intervention’s effectiveness was derived from a systematic review previously described (3). Utility estimates were obtained from a study involving 221 PwT1D, detailed earlier (14).

The results demonstrate that the ICER (incremental cost-effectiveness ratio) is highly sensitive to minor variations in price and dosage strategies. Decision-making primarily hinges on the cost per unit (UI) difference between rapid-acting insulin analogues and regular human insulin. Consequently, the strategy favoring rapid-acting insulin analogues is hindered by the presence of high-cost options in the market, which increase the average cost per unit. Analyses considering only the cheaper available options result in more favorable ICER and budget impact assessments. An electronic auction by therapeutic class would address this issue, ensuring that the most economical rapid-acting insulin analogue is centrally procured by the Ministry of Health.

3) Current Treatment for PwT1D in Brazil, as Provided by the SUS (PCDT T1D) The Brazilian Unified Health System (SUS) offers the following treatments for individuals diagnosed with type 1 diabetes (T1D) (15):

- Regular human insulin;
- NPH human insulin;
- Rapid-acting insulin analogues;
- Long-acting insulin analogues;
- Glucometers, reagent strips, and lancets for digital puncture to facilitate self-monitoring of capillary glucose;
- Syringes and needles for insulin administration using insulin pens.

In accordance with the Clinical Protocol and Therapeutic Guidelines for T1D, established by the Brazilian Ministry of Health (PCDT T1D), the criteria for inclusion in treatment involving rapid-acting insulin analogues are as follows (15):

- Prior usage of NPH insulin and regular insulin for a minimum duration of three months.
- Evidence presented within the preceding six months of at least one of the criteria outlined below, contingent upon the exclusion of causal factors for hypoglycemia (e.g., reduced food intake without adjustment of insulin dosage, physical activity without insulin adjustment, review of insulin injection sites, excessive doses of insulin, or excessive alcohol consumption):
    - Severe hypoglycemia, defined by the necessity for emergency medical assistance or third-party intervention for resolution, substantiated by emergency care reports, records in software systems, logs, or glucometer data where available;
    - Recurrent non-severe hypoglycemia (≥ 2 episodes per week), characterized by capillary glucose levels of <54 mg/dL with or without symptoms, or <70 mg/dL accompanied by symptoms such as tremors, cold perspiration, palpitations, or fainting sensations;
    - Recurrent nocturnal hypoglycemia (>1 episode per week);
    - Persistent poor glycemic results, demonstrated through laboratory analysis of HbA1c criteria over the past 12 months;
    - Self-monitoring of capillary blood glucose (SMBG), performed no fewer than three times/day;
    - Regular medical follow-ups (at least biannual) with physicians and multidisciplinary teams, ideally including endocrinology specialists.

The inclusion criteria for treatment with long-acting insulin analogues, as per the PCDT T1D, are (15):

- Previous administration of NPH insulin combined with rapid-acting insulin analogues for a minimum duration of three months;
- Evidence presented within the preceding six months of at least one of the criteria outlined earlier, adhering to similar exclusions of causal factors for hypoglycemia.

Concerning the cost associated with the acquisition of rapid-acting insulin analogues in Brazil, it is noteworthy that electronic auctions have significantly reduced the prices of these insulin analogues in comparison to regular human insulin within the framework of government procurement. Recent government purchases revealed that the disposable pens containing the three rapid-acting insulin analogues (Aspart, Lispro, and Glulisine) were priced at R$16.47 (USD $2.80) (16), the same cost of disposable pens for regular human insulin.

Given these developments, it is evident that maintaining restrictive inclusion criteria for the utilization of rapid-acting insulin analogues for PwT1D is no longer justified. An update to the PCDT T1D is anticipated to redefine the eligibility criteria for both rapid-acting and long-acting insulin analogues.

Benefits of Rapid-Acting Insulin Analogues for Individuals with T2D

In 2024, the Department of Pharmaceutical Assistance within the Ministry of Health submitted a request for the inclusion of rapid-acting insulin analogues (RAIAs) for individuals with type 2 diabetes mellitus (T2D). This request arose due to difficulties in procuring NPH and regular human insulin (RHI) (17), which represent the basal and bolus insulin classes, respectively, as recommended in the Clinical Protocol and Therapeutic Guidelines for Type 2 Diabetes Mellitus (PCDT T2D) (18). The incorporation of RAIAs aimed to mitigate the risk of bolus insulin shortages for individuals with T2D within the SUS inventory. Therefore, the incorporation request only necessitates evidence of efficacy and safety equivalence between RAIAs and regular human insulin (RHI), currently provided by the SUS.

During the evaluation conducted by CONITEC, the department of the Ministry of Health responsible for incorporating technologies into the SUS, systematic reviews with meta-analysis published in 2018 and 2021 (19,20) were included to assess the efficacy and safety of RAIAs (aspart, lispro, and glulisine) for individuals with T2D compared to RHI. These evaluations revealed no differences between RAIAs and RHI regarding changes in glycated hemoglobin (HbA1c) levels or occurrences of total, severe, or nocturnal hypoglycemia during the studies (17,19,20).

Nevertheless, despite postprandial glucose control being the primary objective of prescribing bolus insulin, systematic reviews assessing the efficacy of these insulins typically do not employ postprandial glucose control as either a primary or secondary endpoint. Only one systematic review, involving individuals with T1D and T2D, included postprandial glucose as a secondary endpoint. For the T2D subgroup of this review, it was demonstrated that individuals treated with IAsp achieved better glycemic control

compared to counterparts in the RHI arms (WMD, –0.22%; 95% CI, –0.39 to –0.05). One RCT demonstrated that the mean postprandial blood glucose level in individuals treated with IAsp was 0.96 mmol/L lower compared to the RHI group ($p < 0.05$). Two additional studies reported lower postprandial glucose levels in the IAsp arm (0.44 mmol/L and 3.40 mmol/L in respective studies) (21). Therefore, RAIAs demonstrated superior efficacy compared to RHI about the intended prescription objective: postprandial glucose control.

Frequent hypoglycemia, particularly nocturnal and severe episodes, represents a major barrier to achieving adequate glycemic control. A retrospective cohort study leveraging the electronic medical records of the Cleveland Clinic Health System (CCHS) involving 50,439 individuals with T2D evaluated the relationship between severe hypoglycemia events and PwD characteristics. Logistic regression analysis confirmed an increased likelihood of severe hypoglycemia with insulin usage, sulfonylureas, a higher number of diabetes medications, a history of non-severe hypoglycemia, HbA1c < 6%, Black race, and higher Charlson comorbidity index scores. Compared to individuals without severe hypoglycemia episodes, those experiencing severe hypoglycemia included a greater proportion of older individuals (71.9 vs. 64.1 years, $p < 0.001$) and those with lower BMI (29.2 vs. 31.7 kg/m2, $p < 0.001$), although median HbA1c levels were similar (6.8% vs. 6.7%, $p = 0.925$) (22). Notably, published studies on insulin therapy in individuals with T2D predominantly involve individuals with obesity who fail to achieve adequate glycemic control. However, clinical practice indicates that individuals with lower BMI are more insulin-sensitive, thus carrying a heightened risk for hypoglycemic events.

Considering the equivalent acquisition cost of regular human insulin and rapid-acting insulin analogues, it is reasonable for all individuals with T2D undergoing basal-bolus insulin therapy to utilize RAIAs. However, practical challenges surrounding prescription updates and guidance for dispensing professionals necessitate a less aggressive implementation strategy. In light of this situation, the SBD recommends:

- Initially selecting populations likely to benefit most from RAIA usage until 100% of individuals with T2D transition to RAIAs:
    - a. Individuals with poorer postprandial glucose control;
    - b. Individuals with high glycemic variability;
    - c. Individuals with nocturnal and severe hypoglycemia;
    - d. Individuals with BMI < 30 kg/m2;
    - e. Older individuals with longer diagnosis duration;
    - f. Pregnant women with T2D (aspart, risk category A), discussed in the following item;
    - g. Individuals with impaired renal and hepatic function; h. Individuals unable to anticipate the administration of RHI.

Benefits of Rapid-Acting Insulin Analogues for Pregnant Women with Diabetes

Women with T2D, including those previously glycemic controlled with oral agents, will require insulin during pregnancy due to its safety and efficacy. Pregnant women with T2D should discontinue non-insulin treatments before or immediately after the onset of pregnancy, ensuring an immediate transition to insulin therapy. During pregnancy, glycemic levels, particularly postprandial levels, tend to increase, making the use of

Regular insulin or rapid-acting insulin analogues (RAIAs) recommended during this phase.

A randomized controlled trial comparing insulin Lispro with Regular insulin in 33 pregnant women with T1D found no evidence of differences between these insulins regarding the risk of maternal hyperglycemia and hypoglycemia episodes (RR 0.21, 95% CI 0.01 to 4.10) (23). Another randomized study comparing insulin Aspart with RHI in 322 women with T1D using NPH insulin reported lower postprandial glycemic excursions at the end of the first and third trimesters among Aspart users ($p = 0.003$ and $p = 0.044$, respectively), as well as lower mean glucose levels 90 minutes after breakfast ($p = 0.044$ and $p = 0.001$, respectively) (24). No adverse maternal, fetal, or neonatal effects have been reported with the use of RAIAs during pregnancy. Although specific studies in pregnant women with T2D are lacking, the efficacy and safety findings observed in women with T1D can be extrapolated to this population.

The SBD considers that the recommendation for the use of rapid-acting insulin analogues during pregnancy is supported by their potential to better glucose metabolism profile during this phase of a woman's life. In Brazil, insulin Aspart is classified as category A risk during pregnancy, insulin Lispro as category B, and insulin Glulisine as category C.

Conclusion

The demonstrated superiority of rapid-acting insulin analogues in postprandial glycemic control, reduction of hypoglycemic events (particularly severe and nocturnal episodes), modest reductions in glycated hemoglobin, flexibility in timing of administration relative to meals, quality of life and improved treatment adherence underscores their value. We urge the WHO to reconsider the inclusion of this class of insulins in its essential medicines list (WHO-EML). The cost of rapid-acting insulin analogues can be reduced through therapeutic class-based procurement, as has been implemented in Brazil, resulting in these insulins being priced equivalently to regular human insulin.

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