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Optimizing Basal Insulin Dosing

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In January 1936, Hagedorn et al described "protamine insulinate," the first practical and stable long-acting insulin, developed in Copenhagen.[1] Even at that time, Hagedorn understood that severe insulin deficiency required insulin replacement during the "postabsorptive period," after carbohydrate absorption.[2] Several decades later, in 1960, it became possible to measure plasma concentrations of immunoreactive insulin under overnight fasting or "basal" conditions.[3] In 1987, Kruszynska et al reported C-peptide and insulin secretion rates in healthy normal weight individuals; C-peptide was used to estimate insulin secretion because the liver clears significant quantities of secreted insulin but not C-peptide.[4] These authors described remarkably stable serum insulin and C-peptide concentrations between 2:00 a.m. and 7:00 a.m. in all participants (although greater variability is reported in other studies[5]). They also compared this basal secretion with that secreted over the entire day. For the C-peptide derived insulin measurement, this ratio came to 50 ± 8%, whereas for insulin the ratio was 36 ± 11%. Based on these results, expert recommendations developed that basal insulin replacement should be 50% of an individual's total daily insulin dose, to replicate physiologic secretion.

The 50% basal view has been challenged, especially over the last decade. Methods to establish with this basal dose should be vary considerably. In 2007, 1 group used early continuous glucose monitoring technology to titrate basal insulin to maintain "basal glucose" within a tight range and established that basal requirements were 38.4% of the total daily dose.[6] Other investigators used retrospective data from individuals with well-controlled diabetes to develop algebraic models that suggested a basal that is 47% of the total daily dose.[7] A Japanese group titrated basal insulin doses needed to keep glucose stable (within 30 mg/dL) between meals and reported basal requirements that were 27.7 ± 6.9% of the total daily dose.[8] This same group postulated that higher basal recommendations might be due to high-fat dinners, which delay gastric emptying, or individuals setting basal rates higher than required to lower blood glucose over time but still resulting in reasonable overall glycemic

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control. The variability in these findings have led to professional organizations recommending that basal insulin should represent 30%−50% of the total daily dose.[9] However, this still signifies tremendous variability; for someone on 30 units/day of insulin this range represents a basal insulin dose from 9 units (0.375 units/hour) to 15 units (0.625 units/hour) a day.

It is not surprising that practice patterns and use of basal insulin among providers vary. Some attempt to mimic physiology and others use basal insulin in whatever way needed to achieve glycemic targets. For example, in individuals who consistently miss bolus doses, increasing basal doses can be enticing albeit risky if adherence improves. If the basal dose is increased above what is required to maintain stable glucose when fasting (ie, using basal insulin to compensate for meals not covered by boluses), then the risk for hypoglycemia increases if meals are delayed or missed, contributing to excess carbohydrate intake and eventual weight gain. It is commonly accepted that the safest tactic is to titrate the basal dose to keep blood sugars stable (±30 mg/dL) when there are no longer carbohydrates or bolus insulin in the system. This method decreases the risk of hypoglycemia and glucose variability. The difficulty is that, even with precise basal titration, insulin sensitivity varies and glycogen stores may be depleted during prolonged fasting, decreasing hepatic gluconeogenesis. In addition to these known challenges, the choice of basal insulin dosing may have a multitude of unknown clinical sequelae.

In this volume of *The Journal*, Rasmussen et al perform a cross-sectional analysis of 19 687 individuals from the international Better control in Pediatric and Adolescent diabete**S**: **W**orking to cr**E**ate C**E**n**T**ers of Reference (SWEET) registry age 18 years or under, with type 1 diabetes for 2 or more years to evaluate the relationship between percent basal insulin, hemoglobin A1c, body mass index SD score, and treatment modality.[10] The SWEET registry includes a robust sample of 76 centers, of which 65 were included in this study. The patients were on multiple daily injections (51%) or insulin pump (49%), including those with hybrid closed-loop features. Although the population was predominantly European (71%), there was representation from Asia, Africa, Middle East, South America, North America, Australia, and New Zealand. The percentage of basal insulin varied from 42% to 55% of the total daily dose, with a median of 43%. Even though the use of basal insulin of 50% or more of the total daily dose falls outside of current recommendations, this value served as a cutoff between groups in the present study. After adjustment for age, sex, and diabetes duration basal insulin of less than 50% of the total daily dose correlated with a lower hemoglobin A1c and body mass index SD score than basal insulin of 50% or greater of the total daily dose among pump users. In addition, the risk of severe hypoglycemia was higher in the group using a basal insulin of 50% or more of the total daily dose.

Disproportionately high basal rates—more than 50% of the total daily dose—are very likely to result in a slow downward trend in glucose over time. The consequence is that, if bolus doses are appropriate, then every correct bolus dose results in eventual hypoglycemia. This negatively reinforces goals, encourages consumption of excess calories with consequent weight gain increasing cardiovascular risk, and introduces a self-perpetuating cycle of hypoglycemia and rebound hyperglycemia that can increase the hemoglobin A1c.[11]

It is important to note that, in this study, basal to total daily insulin ratios are for 1 time point only, which may not reflect dosages over time. We are entering an era of more widespread use of hybrid closed-loop systems that modulate the basal rate to stabilize glucose, thereby invalidating the metric as a measure of true basal.[12] Additionally, insulin doses for those on multiple daily injections could be influenced by recall bias. Furthermore, there are certain minimum criteria needed to become a center in the SWEET registry and requirements for reporting in this particular study that may introduce a systematic bias to the sample. As should be noted for any cross-sectional observational study design, the relationships described are hypothesis generating, but do not indicate causality.

A relevant question is if those with doses closer to 40% differed from those closer to 50%, ratios that fall within established guidelines. Future studies should be performed that assign participants to randomized basal doses from 30% to 50%. The challenge is maintaining the assigned basal ratio and the expense of long-term follow-up, particularly for outcomes such as body mass index. Nevertheless, insulin dosing is at the core of clinical diabetes practice and evidence-based guidelines are needed.

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References

1. Hagedorn HC, Jensen BN, Krarup NB, Wodstrup I. Landmark article Jan 18, 1936: Protamine insulinate. By H.C. Hagedorn, B.N. Jensen, N.B. Krarup, and I. Wodstrup. JAMA 1984;251:389–92. [PubMed: 6361301]
2. Hagedorn HC. Protamine insulinate: (section of therapeutics and pharmacology). Proc R Soc Med 1937;30:805–14. [PubMed: 19991109]
3. Rodari T. Immunological determination of plasmatic insulin in normal subjects in basal conditions. Folia Endocrinol Mens Incretologia Incretoterapia 1960;13:96–101. [PubMed: 14438127]
4. Kruszynska YT, Home PD, Hanning I, Alberti KG. Basal and 24-h C-peptide and insulin secretion rate in normal man. Diabetologia 1987;30:16–21. [PubMed: 3552817]
5. Levy I, Recasens A, Casamitjana R, Figuerola D. Nocturnal insulin and C-peptide rhythms in normal subjects. Diabetes Care 1987;10: 148–51. [PubMed: 3556102]
6. King AB, Armstrong DU. A prospective evaluation of insulin dosing recommendations in patients with type 1 diabetes at near normal glucose control: basal dosing. J Diabetes Sci Technol 2007;1:36–41. [PubMed: 19888377]
7. Davidson PC, Hebblewhite HR, Steed RD, Bode BW. Analysis of guidelines for basal-bolus insulin dosing: basal insulin, correction factor, and carbohydrate-to-insulin ratio. Endocr Pract 2008;14:1095–101. [PubMed: 19158048]
8. Kuroda A, Kaneto H, Yasuda T, Matsuhisa M, Miyashita K, Fujiki N, et al. Basal insulin requirement is ~30% of the total daily insulin dose in type 1 diabetic patients who use the insulin pump. Diabetes Care 2011;34:1089–90. [PubMed: 21430086]
9. Danne T, Phillip M, Buckingham BA, Jarosz-Chobot P, Saboo B, Urakami T, et al. ISPAD Clinical Practice Consensus Guidelines 2018: insulin treatment in children and adolescents with diabetes. Pediatr Diabetes 2018;19(Suppl 27):115–35. [PubMed: 29999222]

10. Rasmussen. J Pediatr 2019, in press.
11. Corbin KD, Driscoll KA, Pratley RE, Smith SR, Maahs DM, Mayer-Davis EJ, et al. Obesity in type 1 diabetes: pathophysiology, clinical impact, and mechanisms. Endocr Rev 2018;39:629–63. [PubMed: 30060120]
12. Lal RA, Ekhlaspour L, Kook K, Buckingham B. Realizing a closed-loop (artificial pancreas) system for the treatment of type 1 diabetes. Endocr Rev 2019 [Epub ahead of print].