Challenging the 50-50 rule for the basal-bolus insulin ratio in patients with type 2 diabetes who maintain stable glycemic control

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Background

It is widespread clinical practice to aim for a 50-50 ratio between basal and total daily bolus insulin doses in patients with diabetes mellitus who are using basal-bolus insulin therapy, although titration guidelines do not mandate it.[1] However, it appears this practice is based on a classic 1988 study of endogenous insulin levels in individuals without diabetes,[2] which may not be applicable to patients with diabetes. Only one published study has assessed the validity of the 50-50 rule in patients with type 2 diabetes (T2D) treated with basal-bolus insulin therapy, but the frequency of insulin titrations was not stated and, more importantly, glycemic control was suboptimal during that study,[3] outside of conventional treatment goals.

To assess the validity of the 50-50 rule in real-world practice in patients with T2D under stable control within conventional glycemic guidelines, we analyzed clinical data from patients with T2D who were treated with basal-bolus insulin therapy that was adjusted at least weekly.

Insulin dose adjustments for these patients were performed by an artificial intelligence (AI)-driven titration within the d-Nav® Insulin Management Technology (d-Nav). Treatment was optimized and maintained over time, while basal and bolus insulin requirements of these patients were closely tracked and recorded, thereby providing a unique longitudinal dataset for investigation. The d-Nav titration follows conventional guidelines in insulin titration without mandating the 50-50 rule; therefore, the resulting basal-bolus ratios are driven solely by real-time adaptation to achieve glycemic control.[1, 4]

Methods

The d-Nav® Insulin Management Technology

Descriptions and validations of the d-Nav technology as a standard of care in insulin management have been described elsewhere.[4-8] Briefly, patients referred to the d-Nav service are provided with a phone application (“app”) or a separate handheld device called d-

Nav. Patients use their own glucometer or the d-Nav device to measure glucose before each insulin injection. In turn, the d-Nav app or device provides a recommended dose for the upcoming insulin injection. The AI within the app or device assesses each patient's responses to his or her current insulin doses by analyzing glucose patterns. Unlike typical diabetes management, d-Nav titrates insulin therapy at least weekly, rather than during outpatient clinic visits that occur just a few times per year. The AI autonomously adjusts each patient's insulin doses, to find a clinically achievable balance between preventing hyperglycemia and preventing hypoglycemia. If insulin requirements drop or hypoglycemia ensues, the AI within d-Nav makes immediate autonomous adjustments as often as needed, following the safety-first approach of prioritizing the avoidance of hypoglycemia. The d-Nav AI adjusts most types of insulin regimens, including basal-bolus therapy with insulin analogues.[1, 4]

Trained healthcare providers, periodically follow up with patients through telephone calls and formal consultations, in-person or virtually, to boost user confidence, correct usage errors, and identify uncharacteristic clinical courses.[5, 6] These d-Nav specialists do not perform insulin titrations. Additional software is available to provide further insights regarding insulin dynamics.[9] The d-Nav service is linked to the wider healthcare system so that each patient's data are always available for review by the patient's physicians, who handle all other medications for diabetes and any comorbid conditions.

Outcomes

The primary outcome of this study was the average percent of the total daily dose of insulin that was basal insulin ("basal insulin fraction"), which we calculated for each patient each week. The secondary outcome was the fold variation in the basal insulin fraction in each patient over time, defined here as the ratio of the patient's highest divided by that patient's lowest basal insulin fraction.

Description of patients and statistical analysis can be found in the supplementary material.

Results

We acquired a cohort of 306 patients who were followed for 3.4±1.8 years (mean±SD), corresponding to about 180 autonomous insulin dose titrations and 5,000 individual autonomous dose recommendations per patient. Supplementary Table 1 shows demographics and key clinical characteristics during enrollment. Duration of T2D was 19.0±7.4 years, and time on exogenous insulin injections was 13.3±7.2 years (means±SDs).

Insulin titrations occurred, on average, every 6.8±1.5 days to enable cohort-wide HbA_{1c} maintenance close to 7%, which remained stable over time after the initial run-in period (Figure-1). HbA_{1c} values at the end of the study were 7.3%±1.0% (56.3±7.7mmol/mol).

Surprisingly, in just over three-quarters of the patients (231/306, 75.5%), the average basal fraction was <50% (meaning basal-bolus ratios less than 50-50; Figure-2A). Half of the cohort (153/306) had a mean basal insulin fraction <41.2% (basal-bolus ratios below 41-59). In one-quarter of the patients, the basal insulin fraction was less than 33.6% (basal-bolus ratios less than 34-66).

Moreover, the basal insulin fraction did not remain static in each patient over time (Figure 2B). In half of the patients, the basal insulin fraction varied by a factor of 1.9 or greater, in order to maintain glycemic control (e.g., when a patient's basal-bolus ratio rises over time from 30-70 to 62-38). In 25% of the patients, the basal insulin fraction varied by a factor of 2.5 or greater.

We found no statistically significant correlations of basal insulin fraction or range of its changes in each patient with any demographic or clinical characteristics. These included patients age, duration of diabetes, duration of insulin usage, and initial and latest HbA_{1c} levels. We found no statistically significant differences in basal insulin fraction or range of its changes between genders.

Supplementary Figure 1 provides examples of the dynamics of insulin therapy, including basal insulin fractions, for three representative patients over time.

Conclusions

In this report, we have shown that the overwhelming majority of patients with T2D who successfully maintain stable glycemic control during frequently adjusted, AI-driven basal-bolus insulin therapy, require ratios between basal and bolus insulin analogues that are not 50-50. To our knowledge, there are no prior published studies of basal-bolus ratios in patients with T2D under stable control within conventional glycemic guidelines. We found that the basal-bolus ratio varies considerably amongst patients, and the ratio for any given patient varies considerably over time. These data complement our previous reports showing that patients' insulin requirements are highly dynamic, highly individual, and never achieve static doses.[10, 11]

Our current finding of an unequal ratio between exogenous basal and bolus requirements in patients with T2D treated with insulin may be explained by defects in the secretion or action of endogenous basal insulin compared with endogenous prandial insulin, or effects of endogenous glucagon in different patients and at different times (reviewed in [12]). It is plausible that non-insulin antidiabetes medications or the use of insulin analogues play a role as well, although neither of these factors seems likely to explain high variability from patient-to-patient and over time.

The study limitations include its observational design, limited ethnic diversity, lack of information on additional antidiabetes medications, possible dietary changes, physical activity, and lack of a negative control group. On the other hand, the 50-50 rule that has been used by providers for years is based on a 1988 study on a few patients without diabetes, on whom we do not have additional background data, nor did this prior study show mechanisms behind the findings.

In summary, our data show that a 50-50 ratio of basal-to-bolus insulin does not generally apply to patients with T2D who successfully use this therapy to maintain stable glycemia. Therefore, the 50-50 ratio should not serve as an ongoing treatment guide, and in particular, insulin titration of each regimen component should consider only the pattern of glycemia and not the ratio between basal and bolus. In view of the variability and dynamics in insulin requirements and basal insulin fraction in each patient over time, our results emphasize the importance of frequent dose titrations when administering insulin to patients with T2D.

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Figure legends

Figure 1: Cohort-wide glycated hemoglobin (HbA_{1c}) values over time in our Cohort of 306 patients with type 2 diabetes mellitus during long-term management by frequent artificial intelligence-driven insulin titration within the d-Nav® service. Displayed are means±SDs. The x-axis shows years on the d-Nav service, with numbers of patients on the service for each time point. This panel includes data from the initial six-month run-in period, before glycemia had stabilized. Because we used rolling enrollment of this Cohort, patients who started the service later during the period had shorter follow up, indicated by decreasing patient numbers along the x-axis.

Figure 2: Basal-bolus insulin dosing in our cohort of 306 patients with type 2 diabetes mellitus during long-term management by frequent artificial intelligence-driven insulin titration within the d-Nav® service. A) Primary outcome: Percent of the total daily dose of exogenous insulin that was basal insulin ("Basal insulin fraction") for each of the 306 patients in our cohort. Data are arranged from the patient with the lowest to the highest mean value. The graph depicts the mean (heavy black line) and SD (thin vertical gray lines) for each patient. These parameters were assessed weekly for each patient while on d-Nav during a period of 3.4±1.8 years (about 180 autonomous insulin dose titrations and about 5,000 autonomous individual doses recommendations per patient). The red horizontal line indicates a basal insulin fraction of 50% (meaning a basal-bolus ratio of 50-50). The three vertical dashed lines divide the patients into quartiles.

B) Secondary outcome: Fold variation in basal insulin fraction for each patient over time, defined as the patient's highest divided by that patient's lowest basal insulin fraction. Data are arranged from the patient with the lowest to the highest fold variation in basal insulin fraction during long-term follow-up. The three vertical dashed lines divide the patients to quartiles. As

noted in the Methods, panels 2A and 2B do not include data from the first six months of management by d-Nav, owing to the time it takes to achieve stable glycemia.[10]

Figures

Figure 1:

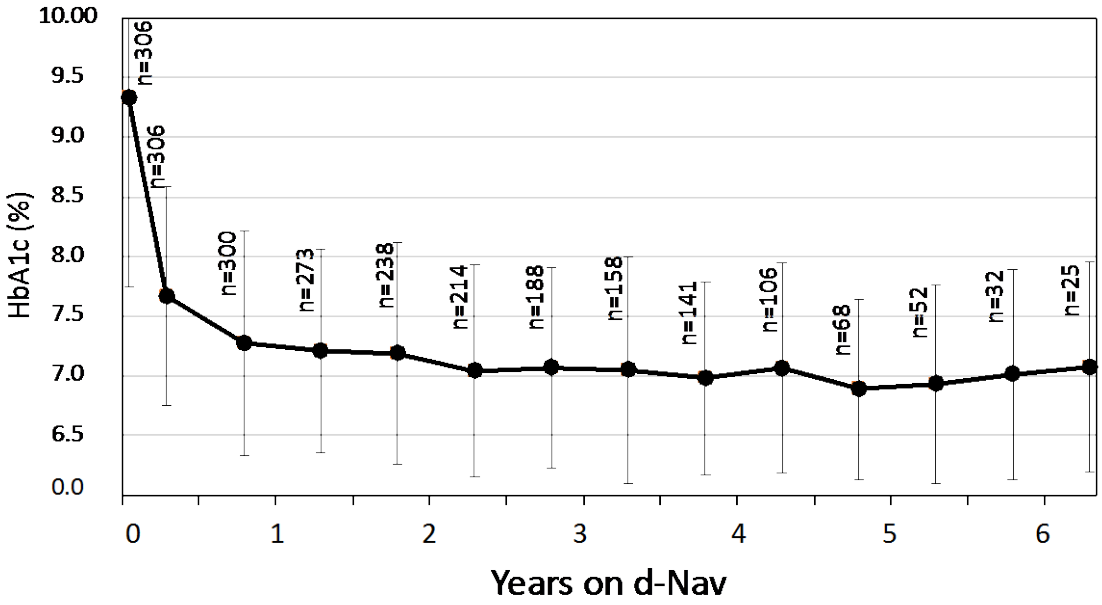

Figure 2A:

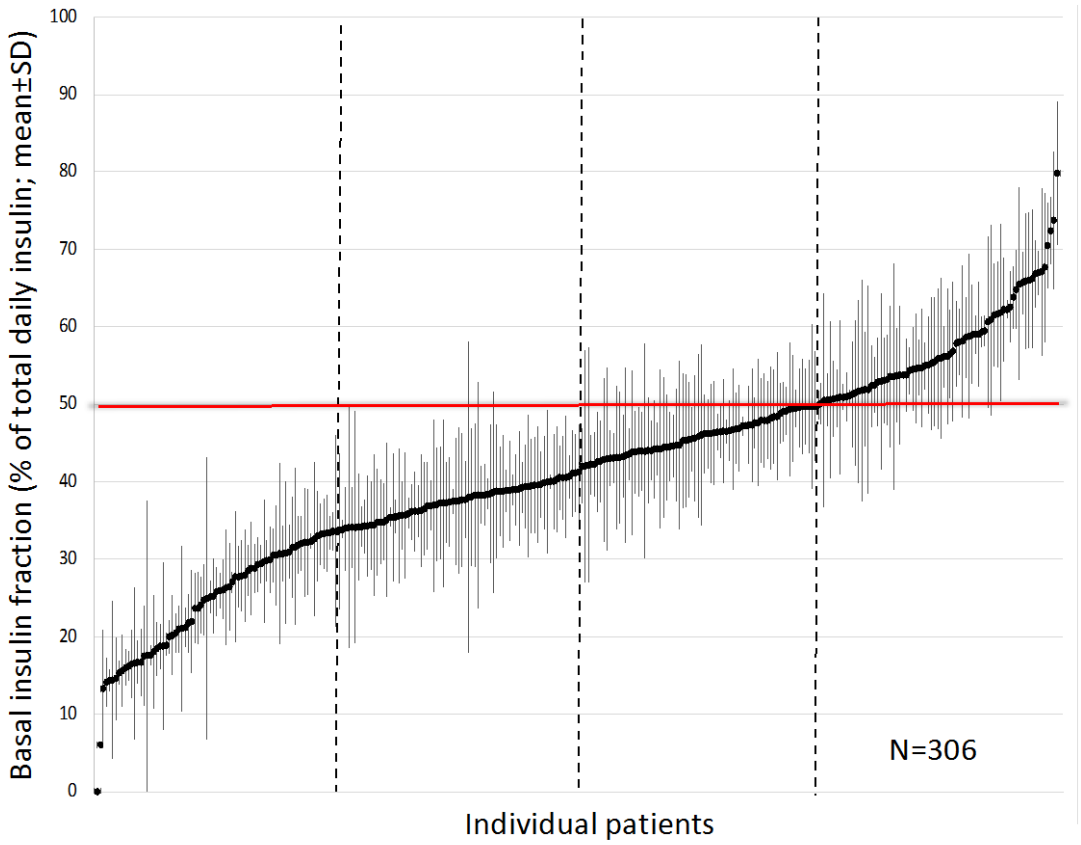

Figure 2B: