Classification of Distinct Baseline Insulin Infusion Patterns in Children and Adolescents With Type 1 Diabetes on Continuous Subcutaneous Insulin Infusion Therapy

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OBJECTIVE — We hypothesized systematic differences in the patterns of programmed basal insulin infusion rates in children and adolescents with type 1 diabetes on continuous subcutaneous insulin infusion (CSII). We aimed at classification of basal insulin infusion rate regimens and comparing patients' underlying clinical characteristics.

RESEARCH DESIGN AND METHODS — The German/Austrian diabetes data acquisition system for prospective surveillance database for quality control and scientific surveys in pediatric diabetology served as the primary data source. Latest (September 2004) basal insulin infusion rates of all 1,248 patients with type 1 diabetes on CSII (0.38–18 years) were analyzed (dataset 1). Basal insulin infusion rates per hour were expressed relative to mean basal insulin infusion rates per 24 h. Unsupervised clustering was used to classify basal insulin infusion rate patterns. Clinical characteristics of patients falling into distinct basal insulin infusion rate clusters were compared by Kruskal-Wallis test. Changes of basal insulin infusion rates in 64 patients were followed from initial settings before CSII to latest programming in an independent dataset 2.

RESULTS — Seven different basal insulin infusion rate patterns occurred in dataset 1. A dawn-dusk pattern was used in 708 patients (14.9 ± 2.4 years) with the peak basal insulin infusion rate at 5 A.M. Additional patterns showed only one basal insulin infusion rate oscillation per 24 h with a backshift of peak basal insulin infusion rates in younger children ($P < 0.000001$) (1 A.M.: $n = 152$, 12.4 years and 9 P.M.: $n = 117$, 8.9 years). All but two patients in dataset 2 were initially set on dawn-dusk patterns but showed a comparable diversification of basal insulin infusion rates during follow-up with backshift of peak basal insulin infusion rates in younger children ($P < 0.01$).

CONCLUSIONS — Pediatric diabetologists shape distinct basal insulin infusion rate profiles during treatment of CSII patients, mainly reflecting differences in age. Our data strongly suggest that age-dependent endocrine changes during childhood (e.g., puberty) affect circadian distribution of insulin needs in CSII, which should be kept in mind when considering basal insulin infusion rate strategies in children and adolescents.

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Continuous subcutaneous insulin infusion (CSII) therapy has become an increasingly used, effective, safe treatment in children and adolescents with type 1 diabetes (1–5). A growing number of even very young children are treated with CSII (6–8). CSII has been demonstrated to effectively reduce hypoglycemia (3,9–12), while ketoacidotic events are not increased (2,3,6,10). Several studies have demonstrated improvement of metabolic control due to CSII as assessed by A1C (2, 9–13). Compared with multiple daily injections, CSII allows for higher flexibility in timing meals and snacks, which is of particular importance in young children with often unpredictable food intake, enabling intensive treatment with painless insulin delivery.

In addition to the above features and in contrast to multiple daily injection regimens, CSII provides the unique opportunity to program an hourly basal insulin infusion rate, reflecting individual circadian distribution of basal insulin needs. This is of documented (2,10,14) effectiveness in overnight glycemic control in the presence of a "dawn phenomenon" in older children and adults. Children and adolescents undergo dramatic sex-, age-, and puberty-related changes in their endocrine system from birth to adolescence (15,16), involving hormones antagonizing insulin, e.g., IGF-1 (16). Also, sleep patterns and sleep duration change with age during childhood (17,18). Sleep in turn is important for normal growth hormone secretion (19) controlling IGF-1 production. In view of this and of the technical options for basal insulin infusion rate modification in CSII, surprisingly little is known about distinct basal insulin infusion rate patterns in children

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Abbreviations: CSII, continuous subcutaneous insulin infusion; DCCT, Diabetes Control and Complications Trial; DPV, diabetes data acquisition system for prospective surveillance; SDS, SD score.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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with type 1 diabetes on CSII. Interestingly, very recently, patient age has been associated with use of different basal insulin infusion rate distributions (4,8). Based on a large, nationwide, German, multicenter cohort of 1,248 pediatric CSII patients, we here present a two-step strategy in which we first identify and characterize existing basal insulin infusion rate patterns (basal insulin infusion rate "phenotypes") and subsequently analyze the clinical characteristics of the CSII patients falling into these patterns.

RESEARCH DESIGN AND METHODS

— The German/Austrian diabetes data acquisition system for prospective surveillance (DPV) database for quality control and scientific surveys in pediatric diabetology (20,21) served as a primary data source. In all participating centers, data collection was in compliance with the hospital data protection agency. Only anonymized data were transmitted for central analysis. Only the most recent (September 2004) basal insulin infusion rates of all documented 1,248 patients with type 1 diabetes on CSII (0.38–18 years) were considered (dataset 1). Basal insulin infusion rates per hour were expressed relative to mean basal insulin infusion rate per 24 h in percent. We therefore focused on the patterns of basal insulin infusion rate oscillation but not on absolute dosages per hour. To be able to properly compare basal insulin infusion rate values of patients on normal insulin as opposed to fast-acting insulin, analogs were shifted forward by 1 h.

We subsequently performed unsupervised hierarchical average linkage clustering adopted from functional genomics bio-mathematic strategies (22–24) using cluster software (22) to sort the 1,248 individuals according to their basal insulin infusion rate patterns. Results were displayed with TreeView software (22) generating a dendrogram, which reflected the degree of similarity of individuals' basal insulin infusion rates. This in turn makes it possible to distinguish major subgroups of basal insulin infusion rate patterns. Mean ± SD for basal insulin infusion rate patterns were calculated for each of the identified basal insulin infusion rate subgroups.

The following clinical characteristics of patients were extracted from the DPV database: age, sex, duration of diabetes, age at manifestation, height SD score (SDS), weight SDS, BMI SDS, total prandial insulin per day, bolus insulin per kilogram per day, total basal insulin per day, basal insulin per kilogram per day, total insulin per day, total insulin per kilogram per day, relative fraction of bolus insulin compared with basal insulin, and A1C (Diabetes Control and Complications Trial [DCCT] corrected). Subsequently, we used the Kruskal-Wallis test and Holm correction for multiple testing to assess differences between patient groups.

To test whether basal insulin infusion rate patterns were initially programmed or shaped throughout the course of therapy, data on initial basal insulin infusion rate programming just before the first onset of CSII is needed. As DPV has no systematic information in this respect, we generated a different, independent dataset of 64 patients (dataset 2) in which initial basal insulin infusion rates were retrieved from patients' files. These patients were derived from eight different centers for pediatric diabetology scattered throughout Germany. The initial basal insulin infusion rate and most recent basal insulin infusion rates were considered and clustered as described above for dataset 1.

RESULTS

— Clustering revealed the existence of seven major basal insulin infusion rate patterns, which we named A through G (n = 1,208). The remaining patients did not clearly fall into any of these patterns and were not considered for further evaluation. As pattern E consisted of only 23 of the 1,248 patients, it was also not included in the further discussion. Figure 1 demonstrates cluster analysis, revealing the basal insulin infusion rate patterns. Most patients fell into cluster B (n = 708, 56.7%), demonstrating a clear dawn-dusk pattern with a higher insulin peak in the early morning than in the late afternoon. Mean age was 14.9 ± 2.4 years, indicating mainly pubertal and postpubertal developmental stages of the patients with this basal insulin infusion rate pattern. A smaller cluster, C (n = 83, 6.7%), could be distinguished from B, also showing a dawn-dusk pattern but with a less pronounced morning insulin peak. Mean age was slightly younger than in cluster B (13.9 ± 3.9 years). In addition to these biphasic patterns, four patterns with only one oscillation per 24 h were observed. In pattern D (n = 152, 12.2%), a broad insulin peak was present with a maximum peak immediately after 12 A.M (12 A.M.-1 A.M.), while in pattern F (n = 117, 9.4%), the maximum peak was observed before 12 A.M. (9–10 P.M.). Mean age was 12.4 ± 3.6 years and 8.9 ± 4.3 years (pubertal and prepubertal, respectively). Patterns B, C, D, and F all shared the common feature of relatively low insulin during daytime around 12 A.M. Projecting the curves of patterns B, C, D, and F over each other reveals that decreasing age seems to shift the programmed peak basal rate back in time, leading to a virtual "fusion" of the dawn peak with the dusk peak in the two monophasic patterns D and F (Fig. 2). In contrast, two patterns, A (n = 63, 5.1%) and G (n = 62, 5.0%), demonstrated the inverse basal insulin infusion rate distribution with high insulin rates during the daytime but lower insulin during the night (Fig. 1). Mean ages were 13.9 ± 4.0 years and 11.6 ± 5.2 years for patterns A and G, respectively. A and G differed from each other with respect to maximum insulin rates, which occurred during early morning in the older group (A) but in the early evening in the younger group (G).

Kruskal-Wallis with Bonferroni step-down (Holm) correction for multiple testing revealed that patients in the different basal insulin infusion rate groups differed primarily by age ($P < 0.000001$). In addition, duration of diabetes ($P < 0.000001$), age at manifestation ($P < 0.000001$), BMI SDS ($P < 0.01$), total prandial insulin per day ($P < 0.000001$), prandial insulin per kilogram and day ($P = 0.00005$), basal insulin per day ($P < 000001$), total insulin per day ($P < 0.00001$), total insulin per kilogram per day ($P < 0.000001$), and A1C (DCCT corrected, $P = 0.00004$) differed significantly between the different cluster groups. In contrast, sex ratio was not significantly associated with specific basal insulin infusion rate patterns.

Patients in cluster B were significantly older than patients in clusters C–F ($P < 0.0001$ for all comparisons, P values Bonferroni adjusted). Cluster C patients were younger than B. Cluster D patients were younger than B and older than F. Patients in cluster F were significantly younger than all other groups (all $P < 0.0001$, Bonferroni adjusted). Cluster A patients were older than groups F and G.

Multiple logistic regression analysis revealed that age ($P < 0.0001$), standardized BMI ($P = 0.0002$), and bolus insulin requirements ($P < 0.001$) were independent significant predictors of basal insulin infusion rate profiles, while sex, duration of diabetes, and metabolic control did not contribute to this.

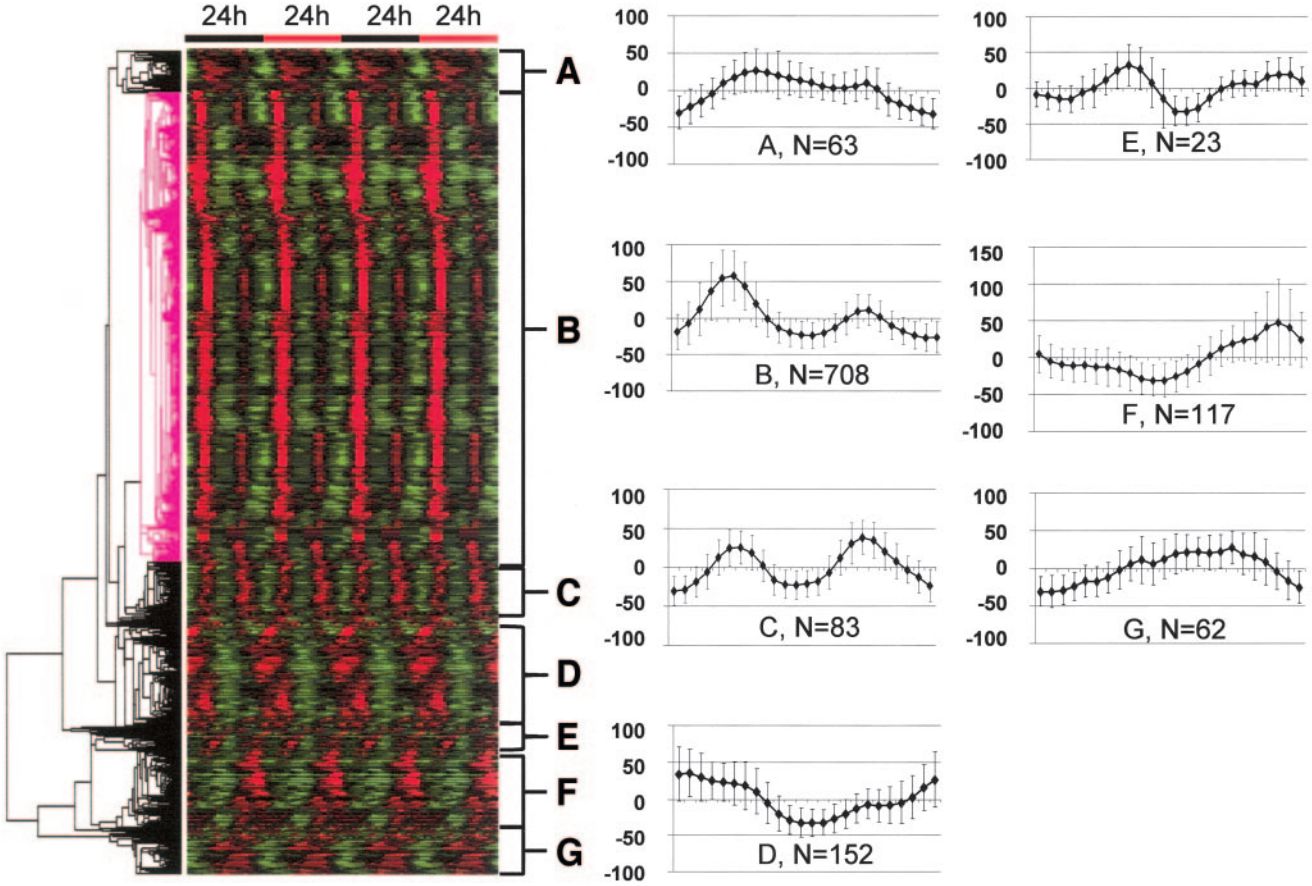

Figure 1— *On the left hand side, the clustering diagram of basal insulin infusion rates of 1,248 different individuals in dataset 1 is displayed (Y-axis). The time course of the basal insulin infusion rates (BRs) is displayed from left to right (X-axis) over four periods of 24 h to show the BR patterns and their rhythms. Increasing red intensity reflects increasing BR while increasing green intensity reflects decreasing BR. Blackish colors reflect BRs near an individual's mean BR. The order of the BRs has been calculated hierarchically by average linkage clustering. The tree in the left margin of the cluster diagram displays the degree of similarity of BR patterns. The most similar BRs cluster right next to each other, thus forming clusters. The pink part of the tree displays an example of a node depicting the dawn-dusk cluster B. The names of the identified BR clusters are displayed in the right margin of the clustering diagram. On the right side of the figure, the mean BRs of all patients in clusters A-G were calculated and are displayed in percent variation from mean BR ± SD per cluster.*

To achieve more evidence as to whether basal insulin infusion rate patterns were arbitrarily set initially before first treatment and remained unchanged or whether they were successively shaped during treatment and could therefore reflect individual distribution of basal insulin needs, we identified 64 patients (2.4–17.6 years) in eight of the collaborating pediatric diabetes centers in whom the first pump settings had been documented. This is not regularly the case in DPV documentation. Figure 3 demonstrates that most patients were initially set on dawn-dusk basal insulin infusion rates. However, diversification of basal insulin infusion rate patterns evolved during treatment (mean duration 1.1 ± 1.2 years), demonstrating three distinct clusters. We named these clusters α, β, and γ. Most of the patients fell into the dawn-dusk group (α) (n = 28, 43.8%, 13.3 ±

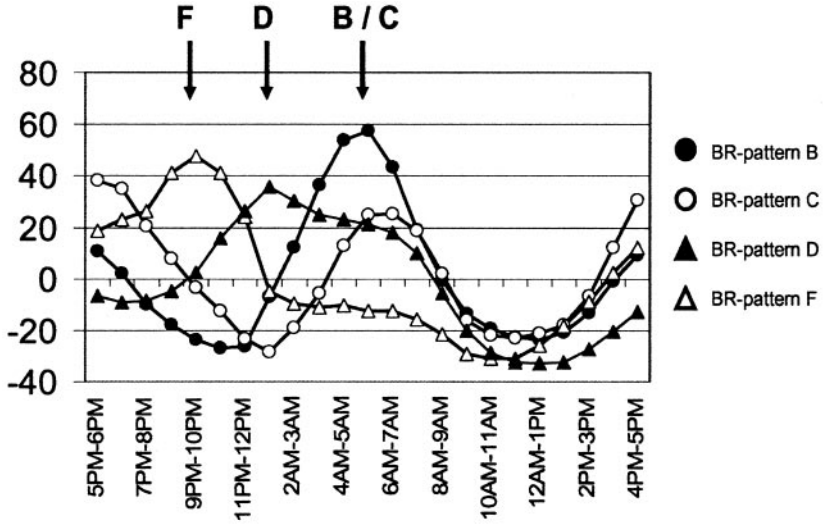

Figure 2—*The calculated mean basal insulin infusion rates (BRs) from clusters B, C, D, and F were projected over each other. The Y-axis displays the percent deviation of hourly BRs from the mean BR while the X-axis displays a time interval from 5 P.M. to 5 P.M. The right hand side of the figure shows the BR curves. The arrows depict the shift of BR maximum from patterns B/C over D to F back in time with younger age.*

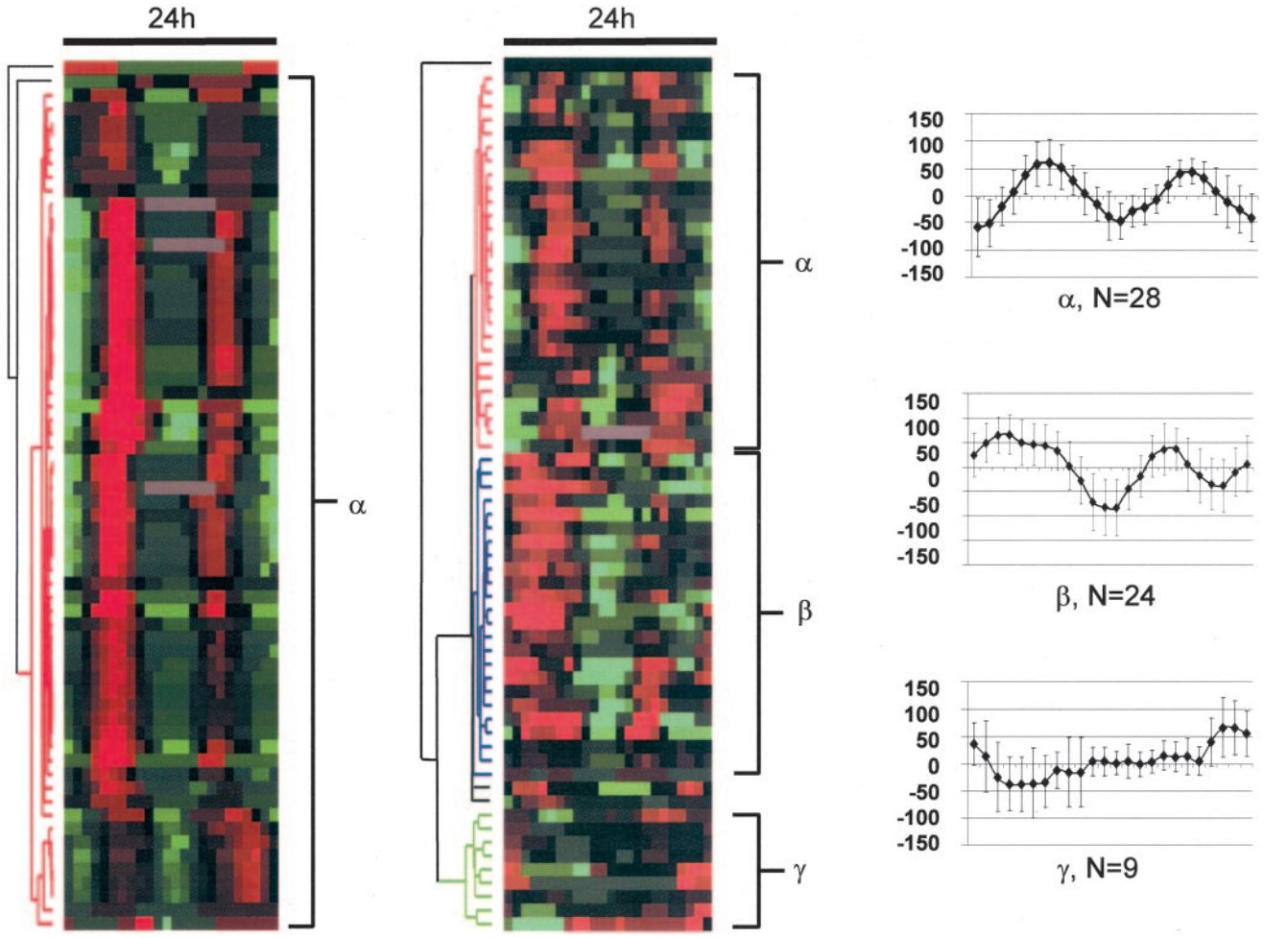

Figure 3—*On the left hand side of the figure, the clustering diagram of initial basal insulin infusion rates (BRs) before first onset of CSII of the 64 patients in dataset 2 is displayed (Y-axis). The color code and description of the tree is the same as in Fig. 1. In the middle part of the figure, only the very last documented BRs were clustered, demonstrating diversification of patterns compared with initial settings. The names of the identified BR clusters are displayed in the right margin of the middle clustering diagram. On the right hand side, the mean BRs of all patients belonging to clusters α, β and γ (red, blue, and green, respectively) were calculated and are displayed in percent variation from mean BR ± SD per cluster.*

4.4 years), supporting our findings in dataset 1. However, a further biphasic dawn-dusk–like cluster (β) revealed a backshift of the early morning insulin peak to ~3–4 A.M. (n = 24, 37.5%, age 12.9 ± 2.8 years). A third cluster (γ) revealed a monophasic basal insulin infusion rate with a broad insulin peak at 9–10 P.M. These children were only 8.2 ± 3.7 years old. While the difference in age between α and β was not significant, t tests revealed that differences between β and γ and between α and γ were highly significant ($P < 0.001$ and $P < 0.01$, respectively). Therefore, basal insulin infusion rate patterns changed during treatment and changes reflected age, supporting analysis in dataset 1.

CONCLUSIONS — Using an unsupervised clustering strategy based on a large cohort of pediatric patients with type 1 diabetes on CSII from Germany and Austria, we demonstrate for the first time the existence of distinct strategies of basal insulin infusion rate distribution over 24 h in the form of defined basal insulin infusion rate clusters. The fact that basal insulin infusion rate regimens change over the course of therapy in our smaller dataset (64 patients) also suggests that basal insulin infusion rate distribution reflects, at least to some extent, individual basal insulin needs. We further show that age is the most important determinant of basal insulin infusion rate clustering. Prandial insulin requirement and age-adjusted BMI are additional, independent, statistically significant contributing factors. In contrast, duration of diabetes or metabolic control achieved (DCCT-adjusted A1C) were not independently related to basal insulin infusion rate clustering, presumably due to their association with age. Our data are in accordance with two recent studies (4,8) demonstrating age-specific differences in the usage of basal insulin infusion rate patterns in CSII patients.

Children and adolescents undergo comprehensive changes with increasing age from birth to adolescence including circadian rhythms (25), sleep patterns (17,18), growth, and pubertal development sequentially interfering with or altering the endocrine background (15,16,19). These changes are likely to interact in an age-dependent manner with the pattern of insulin sensitivity, thus giving rise to age-dependent differences in the basal insulin needs and consequently in the programmed basal insulin infusion rates, as observed in our study. We suggest that pediatric diabetologists should be aware of the existence and shape of these different patterns in order to opti-

mize basal insulin infusion rate regimens in their patients. Prospective studies starting with linear basal rates at initiation of CSII could help to clarify the role of differences in basal insulin infusion rate patterns.

Two patterns (clusters A and G) displayed an unexpected, inverse insulin distribution, with a broad relative insulin peak covering the whole daytime but lower insulin at nighttime. Patients in these clusters were of similar ages to patients in clusters B and D, indicating that factors other than age alone play relevant roles in establishing the particular basal insulin infusion rate patterns in individual patients. We hypothesized that patterns A and G cover the prandial insulin needs in part during the day in addition to the given bolus insulin, thus reflecting individual lifestyle. Unfortunately, it is not possible to retrieve exact underlying information from the anonymized DPV dataset 1 to pin down this phenomenon. In dataset 2, we could not observe this pattern. This is likely due to the small sample size of dataset 2 compared with dataset 1.

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