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Review Article

Classifying insulin regimens – difficulties and proposal for comprehensive new definitions

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Modern insulin regimens for the treatment of type 1 diabetes are highly individualized. The concept of an individually tailored medicine accounts for a broad variety of different insulin regimens applied. Despite clear recommendations for insulin management in children and adolescents with type 1 diabetes there is little distinctiveness about concepts and the nomenclature is confusing. Even among experts similar terms are used for different strategies. The aim of our review – based on the experiences of the Hvidoere Study Group (HSG) – is to propose comprehensive definitions for current insulin regimens reflecting current diabetes management in childhood and adolescence. The HSG – founded in 1994 – is an international group representing 24 highly experienced pediatric diabetes centers, from Europe, Japan, North America and Australia. Different benchmarking studies of the HSG revealed a broad variety of insulin regimens applied in each center, respectively. Furthermore, the understanding of insulin regimens has been persistently different between the centers since more than 20 yr. Not even the terms 'conventional' and 'intensified therapy' were used consistently among all members. Besides the concepts 'conventional' and 'intensified', several other terms for the characterization of insulin regimens are in use: Basal Bolus Concept (BBC), multiple daily injections (MDI), and flexible insulin therapy (FIT) are most frequently used, although none of these expressions is clearly or consistently defined. The proposed new classification for insulin management will be comprehensive, simple, and catchy. Currently available terms were included. This classification may offer the opportunity to compare therapeutic strategies without the currently existing confusion on the insulin regimen.

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Modern insulin regimens for the treatment of type 1 diabetes are highly individualized. The concept of an individually tailored medicine (1) accounts for a broad variety of different insulin regimens applied (2). Flexible, personalized insulin preparations and fixed premixed preparations are in use (3). Despite clear recommendations for insulin management in children and adolescents with type 1 diabetes (4, 5) there is little distinctiveness about concepts and the nomenclature is confusing. Even among experts similar terms are used for different strategies. The aim of this paper – based on the experiences of the Hvidoere Study Group (HSG) – is to propose comprehensive definitions for current insulin regimens reflecting current diabetes management in childhood and adolescence.

Historical development

Commonly accepted is the differentiation between 'conventional therapy (CT)' and 'intensive therapy' since the results of the Diabetes Control and Complications Trial (DCCT) study have been published in September 1993 (6). The terms, however, were already used earlier. Different types of treatment in the context of micro vascular complications were mentioned already in the 1960s (7). Even earlier, in the 1930s, the German pediatrician Karl Stolte, one of the pioneers of modern insulin therapy, differentiated between classical insulin concepts and more liberal strategies with dose adjustment to varying carbohydrate amount of meals (8). CT according to the DCCT definition means one or two daily insulin injections including premixed intermediate and rapid acting insulins and daily self-monitoring of urine or blood glucose. In contrast, intensive therapy is defined as administration of insulin three or more times daily by injection or external pump. The dosage is adjusted according to the results of self-monitoring of blood glucose performed at least four times per day, dietary intake and anticipated exercise (6). This definition already discloses one of the difficulties defining insulin regimens: the number of injections, the insulin types and blood glucose measurements can all be used as criteria for a classification.

Insulin preparations

As a consequence of the DCCT (6) and an implication of subsequent publications (9) intensive insulin management has been established as a standard for the treatment of children with type 1 diabetes. A broad variety of types of insulin is available (Table 1) to implement best tailored management to the individual need of each child or adolescent (10).

Experiences from the HSG

The Hvidoere Study Group (HSG) – founded in 1994 – is an international group representing 24 highly experienced pediatric diabetes centers, from Europe, Japan, North America, and Australia. The group established a research network to carry out multicenter investigations to compare data on childhood diabetes. They published several benchmarking studies that revealed considerable differences in metabolic outcomes among the participating centers (11–13). However, it was difficult to attribute these differences to the different insulin strategies applied (14, 15). Besides the proportion between short to intermediate-acting insulin, the circadian rhythm of insulin sensitivity, the principles of estimating or calculating carbohydrates, protein and fat, practical aspects such as the injection area or the device used (syringe, pen, pump) may all be significant parameters considered when comparing metabolic outcome cross centers. Other relevant key factors for therapy success are the quality and extent of education for patients and their families and the supportive behavioral management over a long time to improve self-efficacy in a child's life.

Consensus finding

Consensus of experts is considered to be the least credible form of evidence and thus usually is rated in the lowest category of evidence by most health systems, e.g., the U.S. Preventive Services Task Force (16) or the UK National Health Service (17). Using individual clinical expertise is not *per se* inconsistent with evidence-based medicine (18), however for the matter of comparisons and the development of recommendations individualized medical concepts are obstacles. The application and classification of different insulin regimens (19) discloses the dilemma between the striving for individually tailored concepts on the one hand and evidence-based concepts on the other hand.

Table 1. Insulin type and activities (Steck et al. 10)

Type of insulin	Onset of action	Peak effect	Total duration
Short and rapid acting			
Regular	30–60 min	2–4 h	6–9 h
Aspart, lispro, and glulisine	10–15 min	30–90 min	3–4 h
Intermediate acting			
NPH	1–2 h	3–8 h	12–15 h
Basal insulin			
Glargine	1–2 h	No peak	24 h
Detemir	1–2 h	No peak	20 h
Premixed insulins			
70/30 NPH/regular	30–60 min	3–8 h	12–15 h
75/25 NPH/lispro	10–15 min	30 min–8 h	12–15 h

NPH, Neutrale Protamine Hagedorn.

Currently applied terms

Different benchmarking studies of the HSG revealed a broad variety of insulin regimens applied in each center, respectively (14, 20). Furthermore, the understanding of insulin regimens has been persistently different between the centers since more than 20 yr. Not even the terms 'conventional' and 'intensified therapy' were used consistently among all members. However, most of the group agreed that CT nowadays means: 1–2 injections per day, insulin types, and doses determine when and what the patients need to eat. In contrast, intensified conventional insulin therapy (ICT) consists of three or more injections per day; insulin administration is adjusted to mealtime (circadian rhythm of insulin sensitivity) and amount of food.

Besides the concepts 'conventional' and 'intensified', several other terms for the characterization of insulin regimens are in use: Basal Bolus Concept (BBC), multiple daily injections (MDI), and flexible insulin therapy (FIT) are most frequently used, although none of these expressions is clearly or consistently defined.

Available recommendations

Frequently used regimens are described in detail by the International Society for Pediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines (4, 5). Injection frequency, insulin formulations and preparations, dose adjustments are part of this report. The American Diabetes Association (ADA) Recommendations concentrate on MDI (3–4 injections per day of basal and prandial insulin) for the treatment of type 1 diabetes (21). The International Diabetes Federation (IDF) Guidelines emphasize the dynamic relationship between carbohydrate intake, physical activity, and insulin using the term basal bolus regimen (22).

Table 2. Classification of insulin regimens (according to administration)

Category I: Fixed insulin dose regimens
Definition: set insulin dosage not or minimally adjusted to daily varying meals. Insulin dosage defines the subsequent mealtimes and their amount of carbohydrates.
Insulin administration: 1–2 injections per day.
Included: Basal insulin only/premixed insulin only/free-mixed insulin combinations.
Category II: Glucose and meal-adjusted injection regimens
Definition: administration of insulin according to results of self-monitoring of glucose and intended time of meal intake (no set dose). Insulin dosage allows a varying amount of carbohydrates following the injections.
Insulin administration: three or more injections.
Included: ICT/BBC/MDI/FIT.
Category III: Pump therapy
Definition: continuous subcutaneous insulin infusion and administration of insulin according to results of self-monitoring of glucose and intended time of meal intake. Insulin dosage allows a varying amount of carbohydrates following the injections.
Insulin administration: continuous insulin administration for basal insulin.

BBC, Basal Bolus Concept; FIT, flexible insulin therapy; ICT, intensified conventional insulin therapy; MDI, multiple daily injections.

In some countries the category I regimen is relatively uncommon. In previous studies of the Hvidoere Study Group category II was the regimen most frequently applied. The option to adjust insulin for the glucose but using a fixed or prescribed meal content may be considered a simplified version of category II.

Difficulties defining insulin regimens

The criteria for characterizing different strategies are diverse. Whereas some are focused on insulin administration, others include the proportion of short- to intermediate-acting insulin in their definition. For none of the definitions there is a clear and scientifically proven association to glycemic control. For matters of comparison and benchmarking studies, however, it is crucial to characterize the insulin strategy applied in each center respectively. These difficulties and the need for a generally accepted definition are obvious.

Proposal for classifying insulin regimens

A new classification should be comprehensive, simple, and catchy. Currently available terms should be included. On the basis of experience of former benchmarking studies among different international centers of excellence, a new classification of insulin regimens is proposed. Insulin regimens were divided into three categories (fixed insulin dose regimens, glucose and meal-adjusted regimens, pump therapy) according to the administration of insulin (Table 2).

Perspectives

This proposed classification for insulin management may offer the opportunity to compare therapeutic strategies without the currently existing confusion on the insulin regimen.

Best therapeutic strategies will depend on the regimen and the implementation of these regimens. Cornerstone remains the quality and extent of patient education and skill training (carbohydrate counting, home monitoring of blood glucose values, etc.), ensuring the patients' efficacy in realizing all steps of these different therapies in their daily life.

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