

# Number-Based Approach to Insulin Taxonomy

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## ABSTRACT

This article describes a number-based system for the classification of insulin regimes. It utilizes a patient-centered variable (number of injections per day) and pharmacokinetic/dynamic characteristics to craft a taxonomic system that is able to incorporate all available insulin preparations and coformulations. This framework of systematics is robust enough to include various molecules that have been recently developed. It serves to enhance understanding of the subject, and facilitates the practical or clinical usage of theoretical knowledge. We propose that number-based insulin taxonomic models should be used in clinical guidelines and recommendations rather than restricting ourselves to pharmaceutical-based classifications. PubMed articles including both review articles and

clinical trials published since the year 1990 were searched, to gather evidence and information on the various types of insulins available, and how they can be used, based on the number or frequency of injections prescribed per day.

**Keywords:** Aspart; Basal insulin; BiAsp; Coformulation of insulin; Degludec; Glargine; Glulisine; Insulin; Intensive insulin; Lispro; LisproMix; IDegAsp; IDegLira; LixiLan; Premixed insulin; U300

## INTRODUCTION

The term “taxonomy” is used to describe the classification of various things, so the term “drug taxonomy” refers to the science of listing and describing drugs, according to various properties, in a manner which allows easy comprehension and understanding of their usage.

Traditionally, only pharmaceutical properties (e.g., chemical structure and pharmacodynamic and pharmacokinetic characteristics) have been used to separate

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drugs into various groups. Increasingly, however, the end user (i.e., the patient's or community's perspective) is considered when studying pharmacology [1, 2]. In the present work, we provide a balanced, syncretic approach to insulin taxonomy, using both patient-centered and pharmacokinetic aspects, to craft a number-based classification of insulin regimes.

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

## CURRENT INSULIN TAXONOMY

Endocrinology and diabetology textbooks provide comprehensive coverage of various insulin preparations and then utilize these to discuss different insulin regimes. The current American Diabetes Association (ADA)/European Association for Study of Diabetes (EASD) 2015 guidelines use the terms “basal,” “basal plus,” “premixed,” “split-mix,” and “intensive” to describe insulin regimes [3]. Other terms used for regimes involving 3 or more injections per day are “multiple” and “intensified” insulin therapy. This drug-centered or pharmaceutical-based terminology served diabetology practitioners adequately in the past; the corresponding taxonomic methodology was able to incorporate the limited insulin preparations available, which included both traditional and modern insulins. This pharmaceutical classification of insulin regimes is not, however, syntactic with the current emphasis on a patient-centered approach. It must be reemphasized here that it is patient-centeredness which forms the basis for recent advances in drug development and improvements in treatment guidelines.

## PATIENT-CENTERED INSULIN TAXONOMY

Most patients of diabetes do not appreciate the pharmacodynamic or kinetic nuances of insulin preparations. What is more relevant to the person requiring insulin is the number of injections to be taken per day, the timing of administration, and the flexibility with which these timings can be adjusted. Based upon these factors, it is important to craft a fresh synopsis of insulin regimes, using the number of injections per day as the framework for systematic study. At the same time, such a classification system must address the nature of insulin preparations, whether basal, premixed, or prandial.

Modern clinical trials are available which support the use of premixed insulin in once-daily and thrice-daily dosages, as opposed to the traditional twice-daily regime. The basal insulins detemir and glargine often need to be prescribed twice daily in order to achieve adequate glycemic control. Innovative regimes utilizing combinations of rapid-acting and premixed/coformulated insulins with varying frequencies of administration have also been documented. These factors also provide important reasons to revisit current classifications of insulin preparations.

## NUMBER-BASED CLASSIFICATION OF INSULIN REGIMES

While a number-based terminology has already been proposed [4], it is inadequate to cover the current range of insulin preparations and the large number of regimens that they are used in. With the newer insulin analogues available, a modern, number-based classification is required. Table 1 lists the various insulin

**Table 1** Insulin preparations that are currently on the market, along with the prescription patterns for them

Frequency of injection	Name of regimen	Insulin preparations used	Timing of administration
1 (once a day)	Basal	NPH, IDet, IGLar, Iglar U300	At bedtime or the same time every day
	Basal	IDeg	At any time of the day
	Premixed	BIAsp, LisproMix	With major meal
	Coformulation	IDegAsp	With major meal
	Basal + GLP1RA	IDeg + liraglutide IGlar + lixisenatide	At any time of the day
2 (twice a day)	Basal	NPH, IDet, IGLar	At bedtime and in the morning
	Premixed	BHI, BIAsp, LisproMix	With major meals <sup>a</sup>
	Coformulation	IDeg Asp	With major meals <sup>b</sup>
	Basal plus	Basal + prandial	At bedtime + with major meal
3 (thrice a day)	Prandial	Regular, aspart, lispro, glulisine	With meals
	Bolus–bolus–premixed	Prandial + premixed	With meals
	Premixed–bolus–premixed	Prandial + premixed	With meals
	Bolus–bolus–coformulation	Aspart + IDegAsp	With meals
4 or 5 (four or five times a day)	Basal–bolus	Any combination of basal and bolus	With meals [3], and at bedtime or twice daily
CSI (continuous insulin infusion pump)	Alternative to multiple injection		

<sup>a</sup> Antipodal meal (i.e., meals spaced roughly 12 h apart)

<sup>b</sup> Minimum 8-h gap between 2 doses

regimes and preparations as well as the frequency and timing of administration for each. All regimes enumerated in this table are backed by randomized controlled trials, as shown in Table 2.

Newer ultralong-acting basal insulins and coformulations of ultralong-acting insulin analogues with either rapid-acting insulin analogues, or with GLP-1RA (glucagon-like peptide-1 receptor agonists), have recently been introduced. While these newer preparations are a combination of two

preparations, they definitely do not fit into the earlier category of premixed insulins. They differ from previous molecules in their kinetic properties as well as their versatility. Other molecules, such as PEGylated lispro, are also in advanced stages of development, and will soon be available for clinical use.

Once-daily injections include all basal, premixed, and coformulation insulins. If necessary, these can be used in a twice-daily regime. Basal insulins were initially thought to be used once a day. As NPH, glargine, and

**Table 2** Prescription patterns of currently available insulin preparations, supported by evidence from various published clinical studies

Insulin preparation/ frequency of injections	Once a day	Twice a day	Thrice a day	More than thrice a day
Insulin degludec	Zinman et al. Diabetes Care 2012. (BEGIN Once Long). T2DM patients ( $n = 1030$ ) [5]	NA	NA	NA
	Heller et al. Lancet 2012. (BEGIN Basal–Bolus Type 1). T1DM patients ( $n = 629$ ) [6]	NA	NA	NA
Insulin glargine U 300	Riddle et al. Diabetes Care 2014. Edition I. T2DM ( $n = 807$ ) [7]			
	Yki-Jarvinen et al. Am Diabetes Assoc 2014. Edition II. ( $n = 811$ ) [8]			
Insulin glargine	Fritsche et al. Ann Intern Med 2003. T2DM ( $n = 695$ ) [9]	Ashwell et al. Diabetes Medicine 2006. T1DM ( $n = 20$ ) [10]	NA	NA
	Riddle et al. Diabetes Care 2003. T2DM ( $n = 756$ ) [11]	Hassan et al. Pediatrics 2008. T1DM ( $n = 19$ ) [12]	NA	NA
Insulin detemir	King. Diabetes Obes Metab 2009. T2DM ( $n = 29$ ) [13]	Kolendorf et al. Diabetic Medicine 2006. T1DM ( $n = 130$ ) [14]	NA	NA
	Russell-Jones et al. Clin Ther 2004. T1DM ( $n = 749$ ) [15]	Home et al. Diabetes Care 2004. T1DM ( $n = 408$ ) [16]	NA	NA
Insulin degludec + insulin aspart	Onishi et al. Diabetes Obes Metab 2013. T2DM ( $n = 296$ ) [17]	Fulcher et al. Diabetes Care 2014. Intensify premix I. T2DM ( $n = 446$ ) [18]	NA	NA

Table 2 continued

Insulin preparation/ frequency of injections	Once a day	Twice a day	Thrice a day	More than thrice a day
BiAsp	Hirsch et al. Diabetes Care 2012. T1DM ( $n = 548$ ) [19]	Kaneko et al. Diabetes Res Clin Pr 2015. Intensify all. T2DM ( $n = 424$ ) [20]	NA	NA
	Yang et al. Curr Med Res Opin 2013. T2DM ( $n = 521$ ) [21]	Raskin et al. Diabetes Care 2005. T2DM ( $n = 209$ ) [22]	Garber et al. Diabetes Obes Metab 2005. The 1–2–3 study. T2DM ( $n = 100$ ) [23]	NA
	Kalra et al. Diabetes Res Clin Pr 2010. T2DM ( $n = 155$ ) [24]	Yang et al. Diabetes Care 2008. T2DM ( $n = 321$ ) [25]	Ligthelm et al. Exp Clin Endocrinol Diabetes 2006. T2DM ( $n = 394$ ) [26]	NA
LisproMix	Koivisto et al. Diabetes Care 1999. T2DM ( $n = 22$ ) [27]	Roach et al. Clinical Therapeutics 2001. T2DM ( $n = 172$ ) [28]	Jia et al. Lancet Diabetes Endocrinol 2015. T2DM ( $n = 402$ ) [29]	NA
	NA	Tirgoviste et al. Rom J Intern Med 2003. T2DM ( $n = 175$ ) [30]	NA	NA
Biphasic human insulin	NA	Clements et al. Diabetes Obes Metab 2008. T1DM/T2DM ( $n = 664$ ) [31]	Shanmugasundar et al. Indian J Med Res 2012. T2DM ( $n = 50$ ) [32]	NA
	NA	McNally et al. Diabetes Care 2007. T2DM ( $n = 160$ ) [33]	NA	NA
Insulin NPH	Raskin et al. Diabetes Care 2000. T1DM ( $n = 619$ ) [34]	Hassan et al. Pediatrics 2008. T1DM ( $n = 19$ ) [12]	NA	Rossetti et al. Diabetes Care 2003. T1DM ( $n = 51$ ) [35]
	Yki-Jarvinen et al. 2000. Diabetes Care. T2DM ( $n = 426$ ) [36]	Rostami et al. Iran J Pediatr 2014. T1DM ( $n = 40$ ) [37]	NA	NA

Table 2 continued

Insulin preparation/ frequency of injections	Once a day	Twice a day	Thrice a day	More than thrice a day
Regular human insulin	NA	NA	Home et al. Diabetes Research and Clinical Practice 2006. T1DM ( <i>n</i> = 753) [38] Danne et al. Pediatric Diabetes 2007. T1DM ( <i>n</i> = 26) [39]	Bernard et al. Journal of Hospital Medicine 2011. T2DM ( <i>n</i> = 176) [42]
Insulin aspart	Mathieu et al. Diabetes Obes Metab 2014. T2DM ( <i>n</i> = 413) [40]	NA	Garber et al. Lancet 2012. T2DM ( <i>n</i> = 1006) [41]	NA
Insulin lispro	Rodbard et al. Lancet 2013. ( <i>n</i> = 401) [43]	NA	Umpierrez et al. J Clin Endocrinol Metab 2009. T2DM ( <i>n</i> = 130) [44] Bretzel et al. Lancet 2008. T2DM ( <i>n</i> = 415) [46]	NA
Insulin glulisine	Tinahones et al. Diabetes Obes Metab 2014. T2DM ( <i>n</i> = 476) [45]	NA	Bowering et al. Diabet Med 2012. T2DM ( <i>n</i> = 426) [47] Urata et al. J Ren Nutr 2015. T2DM ( <i>n</i> = 18) [50]	NA
IDegLira	Riddle et al. Diabetes Obes Metab 2014. T2DM ( <i>n</i> = 588) [48] Choe et al. Diabetes Metab J 2012. T2DM ( <i>n</i> = 87) [51]	Ito et al. Drug Des Devel Ther 2014. T2DM ( <i>n</i> = 27) [49]	Fritsche et al. Diabetes Obes Metab 2010. T2DM ( <i>n</i> = 310) [52]	NA
	Gough et al. Lancet Diabetes Endocrinol 2014. T2DM ( <i>n</i> = 1663) [53]	NA	NA	NA

**Table 2** continued

Insulin preparation/ frequency of injections	Once a day	Twice a day	Thrice a day	More than thrice a day
LixiLan	Buse et al. Diabetes Care 2014. T2DM (n = 413) [54] Riddle et al. Diabetes Care 2013. T2DM (n = 446) [55] Ahren et al. Diabetes Care 2013. T2DM (n = 680) [56]	NA NA NA	NA NA NA	NA NA NA

*Basal*/NPH, glargine, detemir, degludec, *BHI* biphasic human insulin, *BLAsp* biphasic insulin aspart, *LisproMix* biphasic insulin lispro, *LAsp* insulin aspart, *IDeg* insulin degludec, *IDegAsp* insulin degludec and insulin aspart, *IDegLira* insulin degludec and liraglutide, *LixiLan* lixisenatide and insulin glargine, *IDet* insulin detemir, *IGlar* insulin glargine, *IGlu* insulin glulisine, *NPH* neutral protamine Hagedorn, *Prandial* regular, lispro, aspart, glulisine, *NA* not applicable

detemir do not provide adequate 24 h coverage, they may need to be used twice daily in certain patients, especially those with type 1 diabetes. The novel ultralong-acting insulin degludec provides adequate 24-h glycemic control and can be used once daily at any time of the day. These factors need to be reflected in an updated taxonomic profile of insulin.

While basal insulins are able to achieve adequate fasting control in many cases, they are unable to provide prandial coverage. Initiation of a once-daily premix or coformulation with the major meal or meal with highest glycemic excursion allows control of postprandial glucose after one meal as well. The frequency of administration of these insulin preparations can, if required, be intensified to twice or thrice daily. While biphasic human insulin or premixed analogue insulin need to be administered at antipodal meals (i.e., meals spaced roughly 12 h apart), *IDegAsp* (insulin degludec aspart) may be administered at two consecutive meals, provided an 8-h gap is maintained. All of these patterns of use find a place in a number-based umbrella of insulin taxonomy, as opposed to the traditional regime classification, which proposes only twice daily use of premixed insulin.

If the twice-daily regime does not achieve 24-h euglycemia, intensive insulin therapy (defined as that including 3 or more than 3 injections per day) may be required in the form of either three premix insulin injections or a basal bolus regimen. Various regimes are available in this group. Depending upon the needs of the patient, one can prescribe prandial insulin thrice a day; premixed twice and prandial once; or prandial twice and premixed/coformulation once. Basal–bolus regimes involving 3 bolus doses and 1 or 2 basal doses can also be used in refractory patients and in type 1 diabetes.

## CONCLUSION

The number-based taxonomy is able to include all of these regimes as subclasses (Table 1), based upon published randomized controlled trials (Table 2). This arrangement makes it much simpler for the student to understand the subject of insulin pharmacotherapeutics. It helps the practitioner to appreciate the versatility of insulin and the many ways in which this life-saving molecule can be used. This system also allows the physician to choose the appropriate regime for a particular patient while following person-centeredness in letter and spirit. At the same time, choice of regime should take biomedical factors such as severity of hyperglycemia, risk of hypoglycemia, and diabetes indices into account.

Such a codification would promote appropriate choice of therapy based upon the individual's glucophenotype, motivation level, and psychosocial limitations, ease of use, and acceptance of insulin, by sensitizing the diabetes care professional to the patient's needs. It also facilitates the gradual intensification of therapy with the same insulin.

We therefore propose that future guidelines and recommendations utilize this person-centered arrangement of insulin regimes, rather than straitjacketing preparations according to traditional criteria.

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**Compliance with ethics guidelines.** This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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