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ASPECTS OF INSULIN THERAPY IN DIABETES MELLITUS

OBJECTIVE: To provide an update on insulin therapy in diabetes mellitus (DM). MATERIALS AND METHODS: A review was performed of current insulin therapy guidelines and their application in clinical practice: The American Society of Diabetes guidelines (ADA) "Medical Care Standards in Diabetes" 2019, which provides recommendations for the detection, diagnosis, and treatment of diabetes; the Diabetes Update Guide of the RedGDPS Foundation, which summarizes the latest evidence-based clinical guidelines; UptoDate®, an evidence-based clinical decision support resource that provides the fundamentals of insulin therapy in DM; and drug and therapeutics bulletins with the latest updates on new insulin therapies. Based on the evidence provided, we gathered guidelines for the administration, monitoring, and prevention of medication errors. RESULTS AND CONCLUSIONS: All patients with type 1 mellitus diabetes (DM1) and many patients with type 2 mellitus diabetes in advanced stages of the disease (DM2) receive insulin. It is recommended to initiate insulin therapy in patients with DM2 when glycemic targets are not met despite non-pharmacological interventions and the administration of double/triple non-insulin therapy. Background human insulin analogs have proven to be associated with a lower risk for hypoglycemia and are a therapeutic option for at-risk patients. Insulins are high-risk drugs that may cause severe adverse events including hypoglycemia, weight gain, and lipodystrophy. Therefore, prescription errors can have serious consequences. The provision of information to healthcare professionals and patient education will prevent insulin misuse. KEYWORDS: type 1 diabetes mellitus, type 2 diabetes mellitus, insulin.

MARIA TERESA ACÍN GERICÓ
Primary Care Pharmacist. Pharmacy Management Service. SNS-O

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Introduction

Insulin is the gold standard therapy for type 1 diabetes mellitus (DM1). Moreover, insulin is frequently administered to patients with type 2 diabetes mellitus when glycemic control is not achieved with combined oral antidiabetic therapy, or when hyperglycemia at diagnosis is severe.[1] Insulin is also administered for the treatment of patients with gestational diabetes and hyperglycemia.

The purpose of this bulletin is to assess the use of insulin therapies in DM1 and DM2, which includes the monitoring of glycemic control, the classification of insulins by their pharmacokinetics, the pharmaceutical forms available, and the relevance of preventing prescription errors.

What patients need insulin?

Insulin is a natural hormone made by the pancreas with a polypeptide structure and glucose-lowering activity mediated by the inhibition of liver gluconeogenesis that regulates the use of glucose in peripheral tissues. The need for insulin depends on the balance between insulin secretion and insulin resistance.[2]

Insulin therapy in DM1

Insulin therapy is the only treatment available for DM1. In general, the starting dose of insulin is calculated as a function of body weight, with total insulin doses ranging from 0.4 and 1.0 units / kg / day. Higher doses are required during puberty. It is recommended to administer prandial and background insulin or the administration of a short-acting insulin analog pump therapy to reduce the risk for hypoglycemia.[1]

Insulin therapy in DM2

The therapy of choice for DM2 is metformin, unless it is not tolerated or contraindicated.[3] Metformin can be administered in combination with other drugs, including insulin.[1]

Insulin therapy is administered to DM2 patients whose beta cells have lost their ability to produce sufficient levels of insulin;[3] recently-diagnosed DM2 patients (weight loss, polyuria, polydipsia); with HbA1c ≥10% (86 mmol / mol); and / or glycemia ≥300 mg / dL (16.7 mmol / L) (1). Combination therapy of insulin + metformin must be considered in patients with recently diagnosed DM2 with HbA1c≥9% (75 mmol / mol).[1,4]

It is important that insulin therapy is started as soon as possible to prevent the adverse effects of prolonged hyperglycemia. Patients must be informed on the risks of delaying insulin therapy and the necessity of overcoming prejudices about the use of insulin. Patients should not interpret their starting on insulin as a personal failure and must be aware that all DM2 patients will ultimately require exogenous insulin for the inability of their pancreas to produce endogenous insulin.[1]

HbA1c measurement

The 2019 ADA guide recommends measuring HbA1c at least twice a year in patients meeting their therapeutic targets with stable glycemic control. In patients who have changed treatment or who are not meeting their glycemic targets, HbA1c should be determined on a quarterly basis.[1]

The standard target in patients younger than 65 years is HbA1c <7% for adults, and <7.5% for children and adolescents. However, these targets must be individualized based on the comorbidities of each patient, the risk for hypoglycemia, and life expectancy.[3,7]

Less strict HbA1c targets (<8.0% [64 mmol / mol]) can be appropriate for patients with a history of severe hypoglycemia, a limited life expectancy, micro or macrovascular complications, severe comorbidity or a long history of diabetes, who do not meet their target despite having been informed on the measures to be adopted for controlling diabetes.[1]

Therapeutic decision-making criteria for the optimization of HbA1c targets

The target HbA1c is established as a function of the duration of the disease, life expectancy, comorbidities, vascular complications, potential risks associated with hypoglycemia, adverse events caused by drugs, patient's attitude, and healthcare and social resources available.[1]

Age	Duration of DM, presence of complications or comorbidities	HbA1c Target
≤ 65 years	No severe complications or comorbidities	< 7.0 %*
	> 15 year history of diabetes or with severe complications or comorbidities	< 8.0 %
66-75 years	≤ 15 year history of diabetes without severe complications or comorbidities	< 7.0 %
	> 15 year history of diabetes without severe complications or comorbidities	7.0 - 8.0 %
	With severe complications or comorbidities	< 8.5 %**
> 75 years	—	< 8.5 %**

(*) A target HbA1c ≤ 6.5 % can be established for younger patients with a short history of diabetes on non-pharmacological therapy or monotherapy.
(**) Whatever the target HbA1c is, efforts should be made to control symptoms of hyperglycemia.
Drawn from reference.[3]

A 7.5-8.5% HbA1c target can be established for frail older patients, patients with a long history of diabetes, a history of severe hypoglycemia, micro and macrovascular complications, severe comorbidities, short life expectancy and/or psychological disorders.[3]

Rationale for recommendations

The benefit/risk balance of intensive glucose-lowering is unclear. No conclusive evidence has been provided to date that intensive glucose-lowering reduces cardiovascular/ all-cause mortality vs conventional control. Intensive glucose-lowering therapies to maintain HbA1c < 6 % for 3.5 years have been associated with increased mortality, whereas cardiovascular events were not reduced significantly.[5] These results indicate that intensive glycemic control in high-risk DM2 patients has deleterious effects on health.

Further trials are needed to evaluate critical outcomes in specific groups of patients –such as younger, recently-diagnosed or older patients– to set thresholds for the initiation of therapy.[6]

The RedGDPS proposes an algorithm for the initiation of insulin therapy. These guidelines recommend starting with long-acting background insulin, considering basal glycemic adjustment to achieve the therapeutic target.[3]

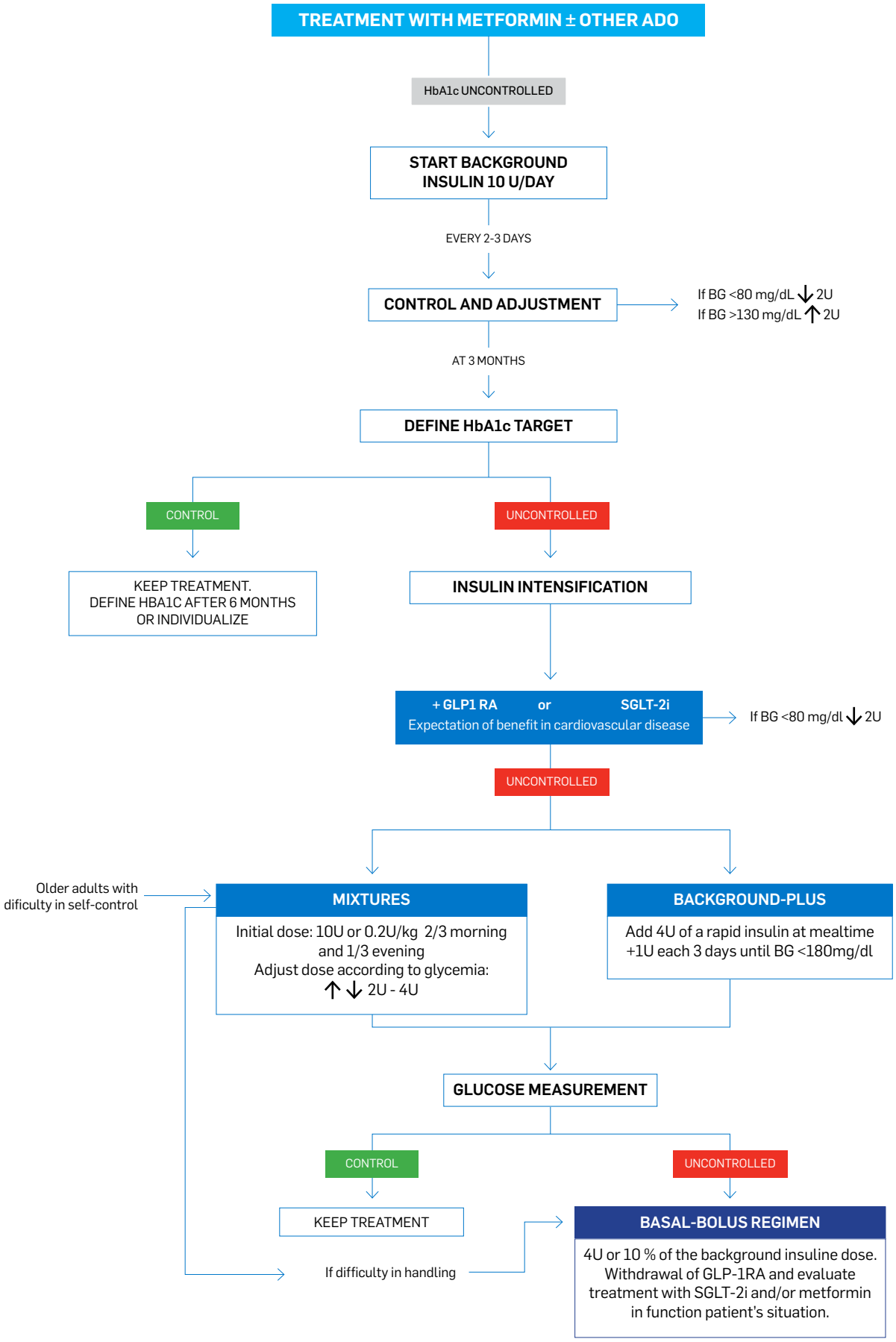
Use of insulin in chronic kidney disease

Chronic kidney failure is associated with impaired renal insulin metabolism. For this reason, glycemic levels must be closely monitored in patients with kidney failure receiving insulin therapy.[7]

Insulin therapy can be used in any stage of chronic kidney disease.[3] The insulin regimen will be adapted to the control target and it can be either a conventional or an intensive therapy. You can find below some initial thresholds that must be adapted to each patient, glomerular filtrate (GF) > 50 mL/min/1,73 m^2: dose adjustment is

Characteristics of the patient/disease	Approach to glycemia target individualization HbA1c = 7.0%		
	Stricter	↔	Less strict
Potential risk associated with hypoglycemia and other adverse effects	Low	–	High
Duration of the disease	Recent diagnosis	–	Long history
Life expectancy	Long	–	Short
Severe comorbidities	Absent	Some	Severe
Known vascular complications	Absent	Some	Severe
Patient's preferences	Motivated, excellent self-care skills	–	Preference for a less unpleasant therapy
Resources and support network	Easily accessible	–	Limited

Adapted from reference.[3]



GLP-1RA Glucagon-like peptide 1 receptor agonists **SGLT-2i** Sodium-glucose cotransporter-2 inhibitors
ECV Enfermedad cardiovascular **BG** Basal glycemia **HbA1c** Glycosilated hemoglobin **U** Units ↑ Increase ↓ Decrease

Adapted from reference[3].

not required; GF 50-10 mL/min/1.73 m^2: will require a 25% dose reduction with respect to the previous insulin dose; GF < 10 mL/min/1.73 m^2: will require a 50% dose reduction with respect to the previous insulin dose.[8]

Glucose measurement

The purpose of measuring glucose is to prevent glucose levels < 70 mg/dL and fasting glycemia > 140 mg/dL, as well as long-term complications such as retinopathy, nephropathy or diabetic polyneuropathy; and to make adjustments to pharmacological treatment, diet, and physical activity as necessary.

There are two methods for measuring glucose:

Monitoring glucose in blood

Patients on intensive glucose-lowering therapy (multiple daily injections or insulin pump therapy) must measure insulin in the blood before meals, at bedtime, occasionally after meals, before exercise, on suspicion of hypoglycemia, after treatment for hypoglycemia until normal glucose levels are reached, and before critical activities such as driving.

There is evidence supporting a correlation between the frequency of self-monitoring glucose levels in blood and lower HbA1c levels in patients on insulin. In any case, supervision of how patients measure their glucose and evaluation of the frequency and need for self-monitoring is recommended.[1]

Continuous glucose monitoring

Continuous real-time monitoring systems have been developed to measure glucose in interstitial fluid of subcutaneous cellular tissue. It is correlated with glucose in plasma.[1] Continuous monitoring of glucose throughout the day may prevent episodes of hypo- and hyperglycemia, as compared with the conventional self-monitoring system, by which glycemia is measured in capillary blood. Differing results have been obtained on the prevention of hypoglycemia using this method. In multicentre trials, a decrease in HbA1c levels was maintained for 24 weeks in patients under continuous monitoring vs conventional tests, and hypoglycemia was reduced in patients with DM1 treated with multiple injections. Time with biochemical hypoglycemia (<70 mg/dL) was 43 minutes/day in the group under continuous monitoring vs 80 min/day in the control group. The incidence of severe hypoglycemia was very low and similar in the two groups.[9] In another 26-week follow-up trial in patients with DM1 treated with multiple daily insulin injections, the group under continuous glucose monitoring (63 mmol/mol) maintained lower mean HbA1c values vs those under conventional treatment (68 mmol/mol). Of the 142 patients included, severe hypoglycemia was reported for 5 patients receiving conventional treatment vs 1 patient on continuous glycemic monitoring.[10]

Glucose targets will be more or less strict based on the presence or not of complications or comorbidities

The devices currently available on the market for continuous glucose monitoring are: Dexcom® G4/G5 de Dexcom, Enlite® de Medtronic and FreeStyle Libre® of Abbott, a flash glucose detection system.

A healthcare evaluation report on the effectiveness, safety, and cost-effectiveness of the flash system (FreeStyle Libre®) for continuous glucose monitoring in DM1 and DM2 revealed that, in general, these devices are safe. Only mild adverse effects were reported in the puncture site used to insert the sensor. The evidence provided was of moderate quality in terms of its effectiveness in reducing hypoglycemia and time with biochemical hypoglycemia.[11]

In the light of the results obtained, more studies are needed to assess the long-term effectiveness, clinical outcomes and adverse events of continuous glucose monitoring using these systems.

Nevertheless, it should be taken into account that there is a time delay between plasma and interstitial glucose (5 to 20 minutes), a phenomenon known as physiological time delay. This delay increases when glucose levels are unstable or change rapidly, which compromises the accuracy of sensor-based measurements.[12]

The American Association of Diabetes (ADA) considers that continuous glucose monitoring is useful for meeting HbA1c targets in DM1 when glycemic targets are not met, provided that disease control and patient's self-care are adequate.[1]

Classification of insulins

According to their origin, insulins are classified as human insulins or human insulin analogs. The latter are obtained using genetic recombination techniques to change their 3D structure and improve their pharmacokinetics. Short-acting analogs are less likely to bind in hexameric complexes than human insulin and are absorbed more easily. Therefore, their onset of action, peak activity, and clearance occur more rapidly.[15]

Prandial insulins

This type of insulin is delivered before meals to mimic the insulin peak that usually occurs after the intake of food.[3,19]

Ultra-rapid action:

Insulin lispro (Humalog®), aspart (Novorapid®) and glulisin (Apidra®) are analogs of human insulin which amino acid sequences are modified to accelerate absorption. The time of dissociation of amino acids determines the onset of action of rapid-acting insulins.[15] Ultra rapid-acting insulins have similar characteristics: their action starts at 3-15 minutes from subcutaneous administration, time to peak is 45-70 minutes, and their duration of action is 2-4 hours. These insulins must be administered before meals .[16]

Nicotinamide (vitamin B3) has been added to the conventional formula to develop a new formulation of insulin aspart (Fiasp®). This new formulation increases the speed of initial insulin absorption, as compared to NovoRapid®. It is available as an injection solution delivered using a pre-filled pen. Fiasp® has been proven to be effective in reducing glucose levels in patients with diabetes in three main studies. Two of these studies demonstrated that Fiasp® was at least as effective as NovoRapid®. Another study revealed that glycemic control improved when Fiasp® used before meals was added to long-acting insulin + metformin therapy. Approval of Fiasp® is based on comparative studies with insulin aspart (NovoRapid®) (which was already authorized). Glucose levels decrease faster with Fiasp®, although its total effect size is similar to that of insulin aspart.[17]

The most frequent adverse effect (can affect more than 1 in 10 patients) of Fiasp® is hypoglycemia, which can occur earlier with this formulation than with other prandial insulins. According to safety studies, 94- 98% of patients in the two trials experienced at least one episode of hypoglycemia. In both DM1 and DM2, the rate of confirmed or severe hypoglycemias 1 or 2 hours after the start of the meal was higher for Fiasp® than for NovoRapid®, although no statistically significant differences were observed in other post-meal times.[18]

A concentrated formulation of ultra-rapid-acting insulin lispro 200 U/mL (Humalog KwikPen®200) is available on the market. These concentrated formulations are more convenient for patients and improve adherence in those requiring higher insulin doses.[19]

Rapid action:

The onset of action of regular or human insulin (Actrapid®) occurs 30 minutes after administration. Its peak action occurs at 2-4 hours, and the duration of action is 5-8 hours.[19]

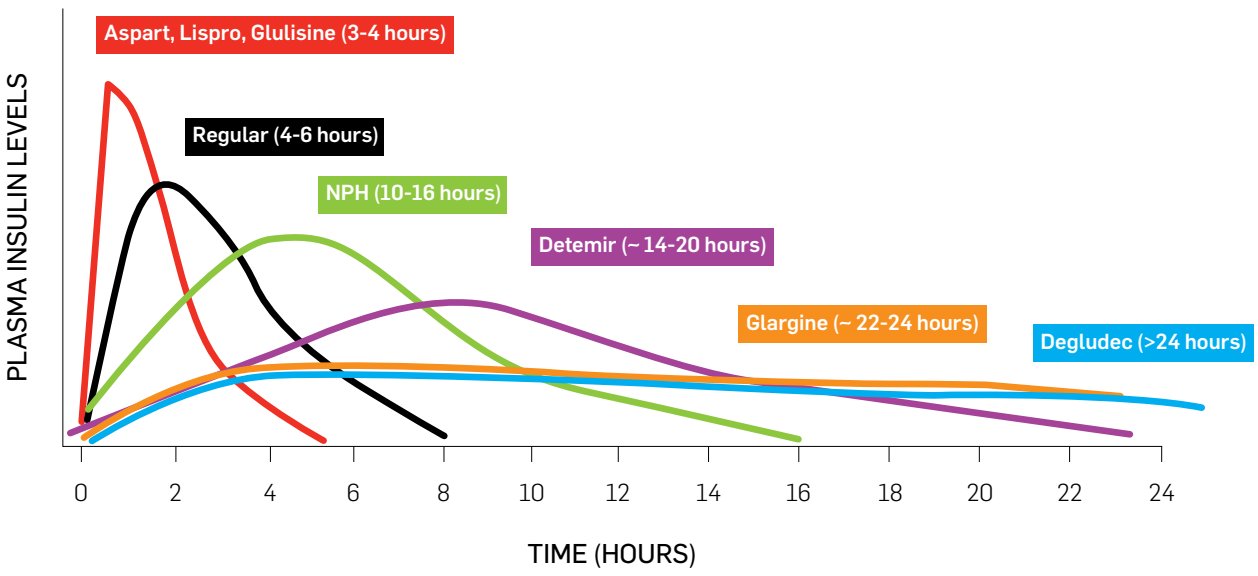
Background insulins

Background insulins are used to meet insulin needs between meals.[19]

Intermediate action:

Isophane or Neutral Protamine Hagedorn insulin (NPH) is obtained by adding protamin to regular human insulin. It can be administered in combination with oral drugs. This

Pharmacokinetic profiles of insulins (from: https://www.diabepedia.com.ar/nueva-insulina-degludec-tresiba).



Pharmacokinetics of insulins[13, 14].

Insulin			Trade names	Onset of action	Maximum effect	Effect-Duration
Pandrial	Ultra rapid-acting	Lispro*	Humalog®	3-15 min	45-75 min	2-4h
		Aspart*	Novorapid® Fiasp®			
		Glulisine*	Apidra®			
	Rapid	Regular	Actrapid® Humulina®	30 min	2-4h	5-8h
Background	Intermediate-acting	NPH or isophane insuline	Insulatard®, Humulina®	2h	4-12h	8-18h (normal duration of action of about 12h)
	Long-acting	Detemir*	Levemir®	2h	3-9h	6-24h
		Glargine*	Lantus® Toujeo®	2h	No peak	20->24h
		Degludec*	Tresiba®	2h	No peak	>40h
Mixtures		Regular + NPH or isophane insulin	Humulina® Mixtard®	30 min	2-8h	24h
		Lispro + NPL*	Humalog®	15 min	1-8h	24h
		Aspart + NPA*	Novomix®	10-20 min	1-3h	24h

(*) Insulin analogs. NPH: Human Isophane insulin; NPL: Neutral Protamine Lispro; NPA: Neutral Protamine Aspart

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therapy is generally started at bedtime to reduce the risk for nocturnal hypoglycemia.[19]

Long or prolonged action:

The pharmacokinetics of long-acting analogs provide more consistent insulin plasma levels and a longer action with respect to NPH, thereby reducing injections to once or twice daily in a high proportion of patients.[19]

Insulin detemir (Levemir®) can be used as basal insulin alone or in combination with bolus insulins. It can also be used in combination with oral antidiabetics and/or GLP-1 receptor agonists.

When detemir is administered in combination with oral antidiabetics or is added to GLP-1 receptor agonists, it is recommended that it be administered once daily at an initial dose of 0.1–0.2 units/kg or 10 units in adult patients; this dose should be titrated based on the individual patient's needs. When a GLP-1 receptor agonist is added to detemir, it is recommended that the insulin dose be reduced by 20% to minimize the risk of hypoglycemia. Subsequent dosages should be adjusted individually.[19,20]

Glargine 100 units/mL (Lantus®) is a long-acting insulin that is administered once daily at any time every day at the same time.[19]

In patients with DM2, glargine insulin can be administered in combination with oral antidiabetics. Its potency is expressed in exclusive glargine units, which are not the same as the units used to express the activity of other insulin analogs. The prolonged duration of action of subcutaneous glargine insulin is directly related to a lower absorption rate, which explains why it is administered just once daily. In studies assessing the secretion and resistance of glargine in health subjects and DM1 patients, its onset of action was slower, its activity profile was more consistent without peaks, and the duration of its effects was longer, as compared with NPH insulin.[21]

The biosimilar insulin glargine 100 units/mL (Abasaglar®) is similar to the reference biological medicine (Lantus®), with a comparable action profile and efficacy.[22]

Insulin glargine (Toujeo®)is a concentrated formulation of 300 units/mL. The pre-filled pen contains 450 units, which allows the administration of a higher dose in a lower volume.[2] In studies comparing glargine insulin 300 units/mL with glargine insulin 100 units/mL in patients with DM2 poorly controlled with glucose-lowering drugs and/or insulin, similar HbA1c reductions were obtained in the two glargine groups. In contrast, no significant differences were observed in severe hypoglycemia and only slight differences in nocturnal hypoglycemia.[23]

The safety profile of glargine insulin 300 units/mL is largely similar to that of 100 units/mL , although they are not equivalent or interchangeable without dose titration.[24,25]

Glargine insulin cannot be used in combination with rapid acting insulins, as this combination would interfere with their pharmacokinetics.[2]

Insulin degludec (Tresiba®) is an insulin analog in which the amino acid sequence has been modified to confer a long duration of action (< 40 hours) that provides consistent plasma levels with a single dose.[2]

In clinical trials, degludec was non-inferior to glargine or detemir in reducing HbA1c. The advantage of degludec vs glargine in the reduction of nocturnal events (1.5 fewer events per patient per year in DM1 and 0.45 fewer events in DM2) disappears when the nighttime period is extended by 2 hours (0 to 8 h instead of 0 to 6 h), as demonstrated in a meta-analysis performed by the FDA.[14,26]

Pre-mixed insulins

Mixed insulins are suspensions composed of a rapid-acting prandial analog and its corresponding intermediate-acting protamin insulin similar to NPH (brackground).

The combination of a rapid-acting insulin and an intermediate- or long-acting insulin in different proportions facilitates a rapid and long-lasting action and a reduction of postpandrial glycemia.[27]

The use of pre-mixed insulins can be considered in patients with high HbA1c (≥ 9 %) prior to insulin therapy or when background insulin dose has been optimized and requires prandial control.[28]

Hypersensitivity reactions to insulins

There are several reports of hypersensitivity reactions to pre-mixed insulins such as irritation in the puncture site or atopic dermatitis. These reactions can be caused by insulin itself or the excipients used. Although hypersensitivity reactions to insulin are rare, they can be severe or hinder the management of diabetes.[29]

Preventable errors in the use of insulins

Insulin is classified as a high-risk drug by the Institute for the Safe Use of Drugs. Errors can occur at any stage of the insulin administration process. The wide range of pharmaceutical forms of insulin and look-alike packagings are a source of confusion in the prescription, dispensing and administration of insulin. Errors can also occur due to the use of abbreviations in prescriptions or the use of non-standardized abbreviations.

Insulin is a high-risk medicine

Errors can result in insulin overdosing (hypoglycemia) or underdosing (hyperglycemia). Symptoms of hypoglycemia range from hunger, anxiety, irritability, palpitations or sweating, to more severe symptoms such as convulsions, loss of consciousness and coma.

In all settings, including gestational diabetes, it is recommended that patients always have a source of rapid glucose and, if appropriate, intramuscular glucagon.[30-31]

Dosing errors can be prevented by abstaining from using a syringe to extract insulin from a pre-filled pen, a cartridge or a pump.[32] Another common error is using a tuberculin syringe instead of an insulin syringe.[33] Using the same pen to inject insulin to several patients poses a risk of viral infection.[30]

These errors are preventable. Therefore, healthcare professionals must ensure that all patients (children and adults) clearly understand how to control their diabetes and use insulin, and how dose titration is performed.[31]

As new pharmaceutical forms with insulin concentrations above 100 units/mL have emerged, such as insulin lispro 200 units/mL (Humalog® Kwikpen) or insulin glargine 300 units/mL (Toujeo®), patients must be aware that these forms can only be administered using pre-filled pens. These pharmaceutical forms are administered differently than standard insulin, which may lead to confusion and administration errors. There is no bioequivalence that allows replacement of highly-concentrated insulin with standard insulin. Therefore, dose titration must be performed based on the target glucose. For example, insulin glargine 300 units/mL is not bioequivalent to insulin glargine 100 units/mL, which means that these insulins are not interchangeable. When glargine 100 units units/mL is changed for 300 units/mL, it can be done from unit to unit, but a higher dose of glargine 300 units/mL (approx. 10-18%) may be required to reach the target glucose level in plasma.[34]

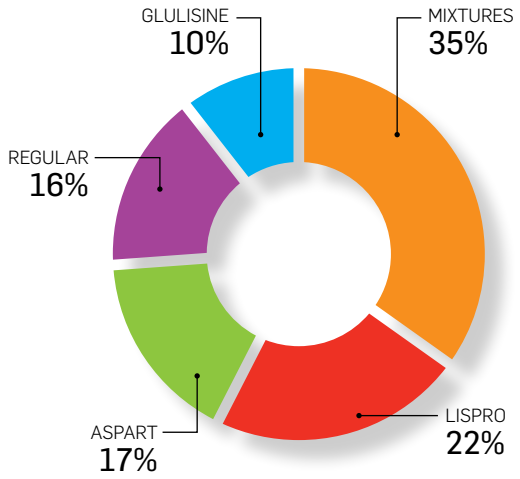
Common insulin interactions

Insulin needs may be lower when glucose-lowering drugs are used in combination, i.e. dipeptidyl-peptidase inhibitors (sitagliptin, vidagliptin, saxagliptin, linagliptin, alogliptin), GLP-1 (exenatide analogs, liraglutide, lixisenatide, dulaglutide), SGLT-2 inhibitors (dapaglifozin, empaglifozin, canaglifozin) and pioglitazone. Heart failure can be exacerbated when used in combination with pioglitazone. Other drugs that may interact with insulin

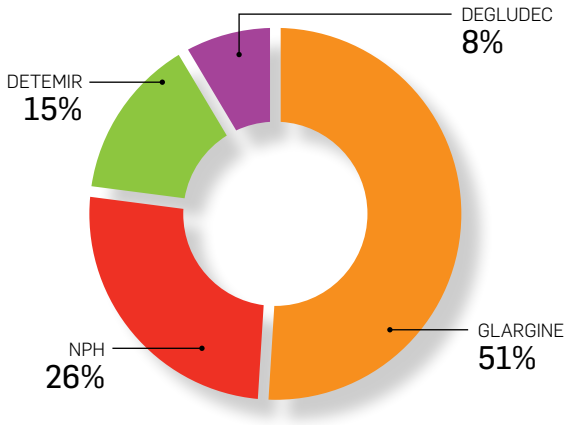
include androgens (nandrolone, testosterone, oxandrolone), beta-blockers, MAOIs, quinolones, salicylates, SSRIs, thiazide diuretics. Insulin can also interact with plants with glucose-lowering properties such as alfalfa, aloe, cranberry, bitter melon, celery, garlic, ginger, ginseng (American), marshmallow, or nettle.[35]

Prescription of insulins in Navarre (2018)

Rapid insulins (%DDD)



Background insulins (%DDD)



Data extracted from the Pharmaceutical Service information system. Navarre Health Service.

Reflections and Conclusions

Insulin is the gold standard therapy for all patients with DM1 and some patients with DM2. With regard to short-term outcomes –as HbA1c levels or risk of hypoglycemia–, rapid-acting insulin analogs may have a negligible advantage over regular insulin in patients with DM2, but not in patients with DM2. In DM2, long-acting insulins (glargine, detemir and degludec) may have some trivial clinical advantages over NPH in symptomatic and nocturnal hypoglycemia.

The involvement of healthcare professionals and patients is crucial for the safe use of insulin

Insulins are high-risk drugs that may cause severe adverse events including hypoglycemia, weight gain, and lipodystrophy. Healthcare professionals must be provided with sufficient updated information on the types of insulin available on the market, their mechanisms of action, pharmaceutical forms and potential adverse events for their adequate prescription, dispensing and use, thereby preventing administration errors. Therapeutic education is crucial to motivate and train patients and their families in the management of diabetes. Patient education should also address self-care and self-control skills aimed at achieving attitudinal changes leading the patient to assume responsibility for their disease. HbA1c levels, lipid profile, weight control, knowledge about diabetes, and healthy lifestyle improve with patient education.[31]

Conflicts of interest for the guidelines used

The conflict of interest statement of the authors of the 2019 ADA guidelines is available at: Diabetes Care 2019 Jan; 42 (Supplement 1): S184-S186. https://doi.org/10.2337/dc19-Sdis01

The authors of the redGDPs Foundation's guidelines for type 2 diabetes declared no conflicts of interest.

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INFORMATION AND SUSCRIPTION
Servicio Navarro de Salud / Osasunbidea
Plaza de la Paz, s/n
31002 Pamplona
T 848429047
F 848429010

E-mail
farmacia.atprimaria@cfnavarra.es

Web site
www.dtb.navarra.es