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Insulin treatment in type 2 diabetes

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Type 2 diabetes is a major health problem due to its high prevalence, its long-term complications and the implication of these in the quality of life of patients and the health costs originated. An adequate metabolic control can reduce microvascular and probably also macrovascular complications of the disease.

When, despite oral antidiabetic agents at correct doses and adequate compliance with treatment, the therapeutic goals are not reached, insulin should then be initiated promptly. One should not await for the disease to progress or for complications to arise to commence treatment with insulin.

Treatment regimens are made on an individual basis depending on the characteristics of the patient, stage of the disease, and the existence or not of complications. Moreover an early start in insulin therapy could slow down the progress of the disease. Many type 2 diabetic patients will need exogenous insulin at some point along the course of the disease, either in monotherapy or combined with oral antidiabetic agents.

Introduction

Diabetes mellitus (DM) can be defined as a "group of metabolic diseases" that are characterised by chronic hyperglycemia, resulting from a defect in the secretion of insulin, insulin action or both[1]. In type 1 diabetes, which accounts for 10% of patients with diabetes, there exists a deficit in the secretion of insulin. Type 2 diabetes patients account for nearly 90% of diabetic mellitus patients. In the latter, it is common to find both a deficit in insulin secretion and an alteration in insulin action (insulin resistance).

Due to its high prevalence, its long term complications and high mortality, diabetes represents one of the diseases that have great impact on public health and society[2,3]. According to the Diabetes Strategy of the Spanish National Health System *(Estrategia en Diabetes del Sistema Nacional de Salud)*, the prevalence in our context is about 6.5% of the population between 30 and 65 years of age. The same sources affirm that the mean health costs of the disease without complications comes to 883 euros per patient, which increases to 2,133 euros per patient with complications (data from 2002). The prevalence of DM is increasing, in great part due to the increase in the prevalence of obesity[4].

Microvasculature (retinopathy, nephropathy and neuropathy) and macrovascular complications (coronary, cerebrovascular and peripheral arterial disease) increase morbimortality and greatly reduce the quality of life[5].

Type 2 DM patients have a 3-4 times greater risk of cardiovascular death, which is the main cause of death in these patients (40% of al deaths are due to coronary disease, 15% due to other heart disease, and 10% due to cerebrovascular disease)[4].

Strict control of glycemia has proved effective in delaying the onset and progression of microvascular complications[6,7]. However, the role of intensive therapy on the apparition of cardiovascular disease is still unclear in type 2 DM patients, possible due to the strong influence of other associated risk factors. Results from the UKPDS study[6] showed no significant differences in cardiovascular events in the group with intensive treatment compared to the group with standard treatment. However, other studies have shown a relation between the levels of glycosylated haemoglobin and the existence of cardiovascular events[8,9,10]. These studies point towards an increased risk of cardiovascular disease with inadequate or poorly controlled glycosylated haemoglobin levels. Currently there are 2 studies that will hopefully shed some light on this issue. These are the ACOORD and the ADVANCE studies[11,12].

Objectives for patient control

Glycosylated haemoglobin (HbA1c) is the major parameter of glycemic control in the follow up of patients and correlates with the apparition and evolution of complications. The goals to target for, both glycemic and HbA1c levels have not been studied systematically. However in studies like the UKPDS[6,8] and the DCCT14 the aim was to reach glycemic levels similar to non diabetic patients. No study has shown achievement of HbA1c levels similar to non diabetic patients in the group with intensive therapy. Levels of HbA1c reached around 7% (4 standard deviations above the mean of non diabetic patients)[15].

The American Diabetes Association (ADA) recommends, in general, to aim for an HbA1c < 7. These levels should be individualised in function of the characteristics of the patients. In the European consensus "good control" based on HbA1c levels is considered <6.5%. Besides an adequate glycemic control, control of cardiovascular risk factors should be included in overall management: tobacco, blood pressure, weight and lipids. In the UKPDS, it was observed that adequate blood pressure control of hypertensive patients with DM reduced the risk of death related to diabetes, complications and the progression of diabetic retinopathy and deterioration of visual acuity[16]. Table 1 shows the ADA recommendations.

Treatment of diabetes mellitus

After diagnosis and evaluation of the diabetic patient, management should be approached adequately. Initially we would commence with lifestyle changes, diet and exercise, with metformin in all patients with no contraindications. If the therapeutic goals are not reached with these measures, then other oral agents should be associated (except in cases where insulin is clearly indicated, as in pregnancy, severe hyperglycemia, important weight loss or positive ketone bodies in urine). If, despite the additional measures, goals are not achieved then treatment with insulin is warranted.

When choosing an oral antidiabetic agent various aspects should be considered including its effica-

Table 1. Recommendations for adults with diabetes (adapted from ADA 2007)[17]

Glycemic control	HbA1c < 7.0%[a] Pre-prandial capillary plasma glycemia: 90–130 mg/dL (5.0–7.2 mmol/L) Postprandial capillary plasma glucose[b]: <180 mg/dL (<10.0 mmol/L)	HbA1c is the primary target for glycemic control. Goals should be individualized Certain groups (children, pregnant women and the elderly) require special considerations More strict goals (eg: HbA1c <6% can reduce future complications. However, they increase the risk of hypoglycemia.) Less strict goals can be indicated in those patients with frequent or severe hypoglycemias.
Blood pressure	< 130/80 mmHg	
Lípids [c]	LDL < 100 mg/dL (<2.6mmol/L) Triglycerides < 150 mg/dL (<1.7 mmol/L) HDL > 40 mg/dL (>1.0 mmol/L)[d]	

(a) Refers to normal HbA1c levels between 4-6 %.

(b) Postprandial glucose should be measured 1-2 hours after commencement of the meal.

(c) Currently, the NCEP/ATP III suggests that in patients with TGL >200 mg/dL (2.26 mmol/L), values of "non-HDL cholesterol" (Total cholesterol minus HDL), with a goal of <130 mg/dL (3.38 mmol/L)[28].

(d) In women, the recommended levels of HDL should be increased by 10 mg/dL (0.25 mmol/L).

cy in reducing glucose levels, the presence of extra-glycemic effects that can reduce long term complications, safety.and tolerance of the agent[15].

In a document issued by the ADA and the EASD (European Association for the Study of Diabetes), the following guideline was recommended (figure 1).

Treatment with insulin

Indications of insulin therapy

The initiation of insulin therapy is often unnecessarily delayed due to the reluctance on the part of the patient or the doctor. Insulin can be necessary in type 2 diabetic patients in different situations:

Basal glycemia > 250 mg/dL (13.9 mmol/L). At diagnosis, and if glucose levels are high, insulin may be necessary, generally only temporarily, to combat glucotoxicity. The reduction in glucotoxicity can be beneficial to preserve function of the beta cell[19].

Glycemia ≥ 300 mg/dL (16.7 mmol/L), with positive ketonuria and/or symptoms of severe hyperglycemia (polyuria and polydipsia) and/or weight loss. When these symptoms appear a severe deficit of insulin should be suspected. It is important to recall that 1% of type 1 diabetic patients debut after 35 years of age, frequently with a positive response to markers of autoimmune pancreatic injury (anti-GAD antibodies). When confronted with a patient with a brief clinical onset, suggestive symptoms, and a possible association of other autoimmune endocrine pathology, then we should suspect type 1 diabetes mellitus of the adult or LADA type diabetes (Latent Autoimmune Diabetes in the Adult)[20] which requires close follow up to detect the need for insulin.

Deficient metabolic control despite adequate pharmacological agents (secondary failure) and good compliance with diet and exercise. In the guidelines for diabetes management of the Navarre Regional Health Service in Spain (Servicio Navarro de Salud), insulin is inexcusably recommended when HbA1c ≥ 10%[20]. However, in other guidelines recommended values for initiating insulin are HbA1c ≥ 8%[21], an approach which is more recommendable.

During pregnancy.

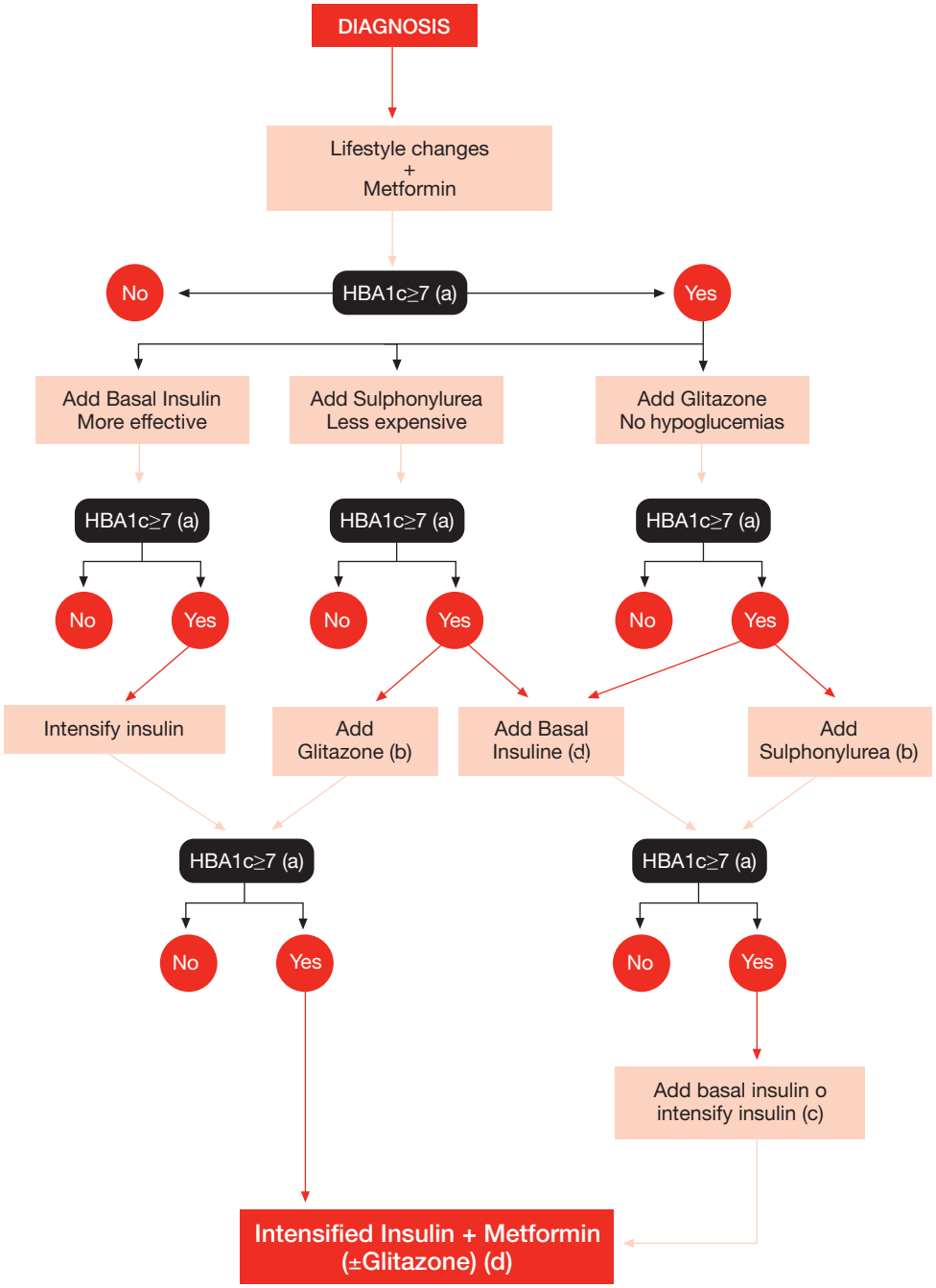
When an intercurrent illness descompensates metabolic control. Certain patients such as those with myocardial infarction, or critical patients in intensive care can benefit from insulin therapy, even though they previously were not treated with insulin.

It is the role of health professionals to make patients understand that the indication for insulin is not the result of personal failure, and that along the course of the illness, insulin may be required either temporarily of permanently.

The UKPDS study showed that deterioration of the beta cell is progressive[6]. At diagnosis, only 50% of the beta cells function, and in the following years, the deterioration continues. After 6 years of treatment with sulphonylureas, 53% of the patients required insulin and, after 9 years, 80% of

A good control of DM is vital to avoid the apparition and progression of complications.

Figure 1. Consensus algorithm for the treatment of type 2 DM.



a) Glycosylated hemoglobin should be measured every 3 months until levels <7% are reached, after which levels are controlled every 6 months.

b) Other secretagogues can be associated (glinides), though at a greater cost.

c) Even though 3 oral agents can be employed, it is preferable to use insulin because of its effectiveness and cost.

d) In Spain, the association of pioglitazone and insulin has been approved since July 2007 (however there is no clear indication and it should be considered of high risk). In a notice published recently by the European Medicines Agency (EMEA), emphasis was made on the risk of administration of combined rosiglitazone with insulin and indicating that its use be restricted to exceptional cases and under close medical supervision, given the increased risk of liquid retention and heart failure.

patients[21]. With an early diagnosis, and a strategic management plan, including early insulin, these periods will be prolonged.

In those patients treated with 2 oral agents who do not achieve adequate control, it may be tempting to associate a third agent. There are studies that show a similar metabolic control achieved with metformin + insulin though the combination was much more expensive[22]. It thus seems more adequate to initiate insulin therapy, but it is not as yet clear whether it should be associated with an oral agent or in monotherapy. In a Cochrane review[23] it was concluded that insulin associated with oral hypoglycemic agents produced an equivalent glycemic control than with insulin alone, and if the agent was metformin then there was less weight gain[24]. Moreover, if insulin is associated with oral agents, insulin requirements are reduced.

Characteristics of insulin

Insulin is the oldest pharmaceutical agent we have to treat diabetes and of which most experience is available. It has been used for over 80 years, and is one of the greatest medical advances of the 20th century. Though initially it was used in type 1 diabetic patients, it soon extended to overcome insulin resistance in type 2 diabetes[15].

It is the most effective agent in reducing glycemic levels. Moreover, an early start in treatment with insulin can preserve beta cell function and improve lipid metabolism[15]. In contrast to what occurs with other hypoglycemic agents, there is no maximum effective dose above which insulin shows no effect or produces unacceptable toxicity. In type 2 diabetes patients, higher doses of insulin may be required than in type 1 diabetic patients to overcome insulin resistance, reduce HbA1c levels and achieve therapeutical goals[15,21].

The principal side effects include weight gain and the risk of hypoglycemia. Generally, on initiating insulin, weight can increase by 2-4 kg. This increase is proportional to the reduction in glycemia and is mainly due to a correction in glycosuria. The increase in weight, could have an adverse cardiovascular effect[15], though in the UKPDS trial, insulin was seen as a safe agent with regards to cardiovascular risk[6].

Insulin is also associated with hypoglycemia, though to a less extent than in type 1 diabetic patients. In clinical trials whose main objective was normalization of glycemia and HbA1c levels <7%, it was observed that the risk of severe hypoglycaemia (defined as that which requires aid from another person) oscillates between 1 and 3 cases per 100,000 patient-years[25,26]. The incidence is much lower than that observed among type 1 diabetic patients in the DCCT trial, 61 cases per 100,000 patient-years[14].

Interventions must be made on cardiovascular risk factors.

In those patients with retinopathy, another possible side effect of insulin is the worsening of the degree of retinopathy, or the development of maculopathy coinciding with a rapid improvement in glycemia (approximately 5% of the patients). Patients with an HbA1c>10% are at greater risk. In these patients, HbA1c levels should be reduced gradually (2% per year) and ophthalmologic revisions should be done more frequently[21].

Types of insulin

Different types of insulin are available based on the chemical properties of the molecule and pharmokinetics: onset of action, maximum peak, duration of action and mode of administration. They proceed from biosynthesis in laboratories, employing genetic engineering methods to generate so-called “recombinant insulin” with a similar formulation to human insulin, or slightly modified to improve pharmokinetic properties (insulin analogs). Table 2 shows current commercial types of insulin available.

New insulins: what have they to offer?

Rapid-acting insulin analogs

Regular human insulin has been used historically to treat postprandial hyperglycemia, but its action profile is far from the postprandial peak of pancreatic secretion. Onset of action is 30-60 minutes after administration and maximum effect is reached at 2-3 hours.

At some point many type 2 DM patients will need insulin either temporarily or permanently.

Table 2. Types of insulin.

Insulin	Onset	Peak	Duration	Presentation		Price[1]
Subcutaneous insulin						
Monocomponent insulin						
Rapid acting						
Human						
Regular	30-60 min	2-3 hours	5-8 hours	Vial: Prefilled pens:	Actrapid® Actrapid Innolet® Humulina reg Pen®	1.49 2.59 2.53
Analogs						
Lispro	5-15 min	30-90 min	5 hours	Vials: Prefilled pens:	Humalog® Humalog Pen®	2.14 3.13
Aspart	5-15 min	30-90 min	5 hours	Prefilled pens:	Novorapid Flexpen®	3.07
Glulisine	5-15 min	30-90 min	5 hours	Prefilled pens:	Apidra Solostar®	3.13
Intermediate acting						
Human						
NPH	1.5-3 hours	4-10 hours	10-16 hours	Vials: Prefilled pens:	Insulatard NPH® Humulina NPH® Insulatard Flexpen® Humulina NPHPen®	1.49 1.55 2.59 2.53
Analogs						
NPL (Insulin lispro protamin)	1-2 hours	4-8 hours	10-18 hours	Prefilled pens:	Humalog NPL Pen®	3.25
Long acting						
Analogs						
Glargine	2-4 hours	No peak	20-24 hours	Vials: Prefilled pens:	Lantus Vial® Lantus Optiset® Lantus Opticlik® Lantus Solostar®	5.13 5.13 5.13 5.13
Detemir[2]	3-5 hours	No peak	20 hours	Prefilled pens:	Levemir Flexpen® Levemir Innolet®	5.23 5.23
Insuline mixtures						
Human						
70% NPH - 30%Regular	30-60 min	Dual	10-16 hours	Vials: Prefilled pens:	Mixtard 30® Humulina 30/70® Mixtard 30/70 Innolet® Humulina 30/70 Pen®	1.50 1.51 2.59
Analog mixtures[3]						
70%Aspart prot -30%Aspart	5-15 min	Dual	10-16 hours	Prefilled pens:	Novomix30 Flexpen®	3.19
75%NPL-25% Lispro	5-15 min	Dual	10-16 hours	Prefilled pens:	Humalog Mix 25®	3.25
50%NPL-50% Lispro	5-15 min	Dual	10-16 hours	Prefilled pens:	Humalog Mix 50®	3.25
Inhaled insulin						
Short acting						
Inhaled human insulin	10-20 min	2 hours	6 hours	Exhubera®:	Kit+90 blister 1 mg 270 blister de 1 mg 90 blister de 3 mg	161.68[4] 148.78 118.52

(1) Price: €/100 Unit

(2) In some texts Detemir insulin is classified as an intermediate acting insulin[25], though in the majority of references it is considered a long acting insulin[28,29].

(3) These insulins include the rapid delayed analog with Protamin (Lispro-protamin: NPL or aspart-protamin) together with the a rapid acting analog.

(4) The price of inhaled insulins is price per box. 1 mg of insulin is equivalent to 3 units of subcutaneous insulin, and 3 mg of inhaled insulin is equivalent to 8 units of subcutaneous insulin. In clinical trials with inhaled insulin, requirements of inhaled insulin were 2-3 times higher than the subcutaneous form[30].

The new analogs, lispro, aspart and glulisine have a similar pharmacokinetic profile. Onset of action takes place 5-15 minutes after administration and peak effect is reached between 30 and 90 minutes. They have a shorter duration of action than regular insulin and their action profile approximates the physiological secretion of insulin. Moreover, individual variability in the duration of peak effect is lower than regular insulin[27,31]. For of all these reasons, there is a lower risk of hypoglycaemia than with regular insulin[15].

Long-acting analogs

These analogs are used as basal insulin, just like NPH. The arrival of NPH insulin supposed an advance in the treatment of diabetes given that, comparing the administration of 2 doses of NPH with a single dose of ultralente insulin, in the former hypoglycemias were less frequent and less severe, patients showed better metabolic control and higher levels of satisfaction[32].

The advantage offered by the new analogs compared to NPH insulin is that, on not having a peak effect, the risk of hypoglycemia is greatly reduced (mostly nocturnal hypoglycemias) and the flexibility of the regimen is greater[15,33,34,35]. In addition, the analogs possess less individual variability in absorption and this is not influenced by the site of injection[28,36]. Their pharmacokinetic profile is less variable than NPH insulin.

Glargine insulin has a duration of 24 hours, and thus a single administration dose is recommended per day. The hour of administration should be individualized, but it is important that it takes place at the same hour every day[27,37]. In studies comparing glargine with NPH insulin, levels of control in patients were similar[33,34]. In these studies a single dose of glargine administered daily was compared to a single dose of NPH administered at night *(bedtime),* which in the majority of type 2 DM patients is sufficient. In those patients who required 2 doses of NPH insulin, glargline insulin had the additional advantage of a single daily dose. However in some patients the duration of glargine insulin´s action was lower (about 15 hours) and 2 doses were required thus losing this potential advantage[31].

The insulin detemir has a half-life of approximately 20 hours. In many patients with type 2 diabetes a single dose is sufficient but, when insulin requirements are high, then two daily doses are necessary[27,31]. This form of insulin presents less hypoglycemias than NPH, as in the case of glargine insulin and moreover, there are studies that show that there is less weight gain with detemir than with either NPH or glargine[38].

On the contrary, the disadvantage of these two analogs is the higher cost compared to NPH insulin. Recently, a Cochrane review was published that compared long acting insulin analogs with NPH insulin in type 2 diabetes. The authors concluded that the benefit obtained on employing the analogs was small (reduction in hypoglycemias). Until more long-term evidence is obtained on efficacy and safety, they suggest that analogs should be used with caution[39]. Other authors also question whether the lower incidence of hypoglycemias and the higher level of satisfaction of patients are sufficient to warrant the additional cost that supposes employment of analogs[40].

The long-acting analogs cannot be mixed with other insulin forms, and they are not apt for intravenous administration or continuous pump infusion. If they are used in conjunction with other insulins then they should be injected at different sites[29,37].

Inhaled insulin

Inhaled insulin was commercialised in Spain in June 2007 but a few months later the manufacturer decided to withdraw it from the market. It is a rapid-acting recombinant insulin indicated in type 1 and type 2 diabetes patients. It can be used solely or associated with oral antidiabetic agents and/or subcutaneous intermediate or long-acting insulin[41]. This agent requires a hospital-based prescription and approval from pharmaceutical inspection. The approved indications by the Spanish Ministry of Health are:

- Patients over 18 years of age with type 1 diabetes with no contraindications
- Type 2 diabetes mellitus patients *only in the following situations*:
  - Severe lipodistrophy at the site of injection.
  - Patients that reiteratively do not comply with treatment due to uncontrolled phobia of subcutaneous injections.

Contraindications include: allergy to the main substance or excipients, asthmatic patients with a

Metformin and a single dose of an intermediate or long-acting insulin is the usual form of initiating combined treatment.

sever condition, unstable or poor control; severe chronic obstructive pulmonary disease, COPD (GOLD grade III or IV); active smokers or smoking during the last 6 months. It also should be suspended in cases of deterioration in pulmonary function (infections, pneumonia, etc.).

Inhaled insulin just like rapid-acting insulin analogs has a faster onset of action than subcutaneous regular human insulin. The duration of action is longer than most of the analogs, and is comparable to regular insulin. Its bioavailability is inferior to injected insulin and in the clinical trials performed, 2-3 additional units by inhalation were required than by subcutaneous administration.

A periodic and exhaustive control of lung function is necessary during therapy with inhaled insulin. In studies that compared inhaled insulin with subcutaneous insulin the results showed that the level of control obtained was similar. Inhaled insulin presents an improvement in quality of life indicators and greater satisfaction in patients[30,42,43,44,45].

Inhaled insulin, when compared to oral antidiabetic agents, showed better HbA1c control but the incidence of hypoglycemias was much higher[46]. In the short term no important pulmonary side effects were reported with inhaled insulin, but all studies insisted on the need for long term evaluation for safety and efficacy and the need for a cost-effective analysis[30,47].

Regimens of insulin therapy

Treatment should always be individualised (on the basis of patient characteristics, age, previous treatment, years of evolution, glycemic profile, etc). Two forms of insulinisation can be employed: standard insulin therapy (1-2 injections of insulin per day, of the same type of insulin) and intensive insulin therapy (basal-bolus): multiple doses of insulin per day, of two or more types of insulin.

Standard insulin therapy

This is a non-physiological regimen since it does not mimic the normal secretion of insulin, which consists of a continuous basal secretion of insulin with peak effects in response to food ingestion. This therapy has proved useful especially when associated with oral agents.

Intensive therapy is justified in young patients and at the onset of microvascular complications.

When a patient is under treatment with 2 oral antidiabetic agents (sulphonylureas and metformin generally) and has a poor metabolic control, a single daily dose of an intermediate or long-acting insulin should be associated. If either NPH insulin or detemir are used, then administration should be nocturnal. Glargine can be used indifferently in the morning or at night. If there are no contraindications, metformin should be maintained as an oral agent given that, even though metabolic control is similar, there is less weight gain, less requirements of insulin dose and a lower incidence of hypoglycemias than with only insulin or insulin associated with sulphonylureas[48]. Thus, metformin and insulin prove to be the best combination for the majority of patients[21].

If metformin is contraindicated or there is no indications of insulin resistance (patients with either normal weight or moderately overweight) then insulin should be associated with sulphonylureas (with lower doses). This combination is effective and produces less weight gain and lower incidences of hypoglycemia than only insulin[49]. Sulphonylureas augments secretion of endogenous insulin during the early stages of the disease but, when endogenous insulin secretion declines and/or HbA1c levels are high (>10%), then the combination of insulin with sulphonylureas is hardly effective[21].

Glinides are secretagogues with a shorter period of action than sulphonylureas. Theoretically, they can be combined with insulin but there is no sufficient evidence to approve its use[21]. They can be useful in cases of moderate renal failure.

Whenever insulin therapy is initiated caution should be taken to detect hypoglycemias. The patient and/or family should be instructed on how to detect, manage and treat hypoglycemias. The profile of these patients usually is hyperglycemic before breakfast but with acceptable glycemias throughout the day. With the dose of insulin administered, the aim is to maintain morning glycemia within the control levels. In these patients, the pancreas still maintains a response to postprandial hyperglycemia.

If the goal is not achieved then the dose of insulin should be increased. If the NPH insulin is used, then administration should be in two doses: 2/3 of the total dose before breakfast and 1/3 before dinner. Detemir can also be given in two doses, though the proportion is not quite clear. To adjust the morning dose, attention should be paid to the glycemia before dinner, with the precaution of not

provoking hypoglycaemia before lunch. To adjust the nocturnal dose, basal glycemic levels should be evaluated.

However, we might find that despite increases in insulin doses, goals are not achieved or the glycosylated haemoglobin remains high. In these cases, postprandial glycemias should be evaluated because if they are high then the patient may require rapid-acting insulin.

At this point, it is necessary to decide whether to maintain a basal regimen (with a long-acting insulin combined with a preprandial rapid-acting insulin) which will require 4-5 doses of insulin daily or a standard regimen of pre-combined insulin (in 2-3 doses per day). If the alternative is to use premixed insulin, normally 70-75% NPH insulin and 25-30% rapid-acting insulin (regular or analog), then the combination of analogs in general are safer because they produce a lower incidence of hypoglycaemia[19]. It should be taken into account that, in patients with renal failure, normally a lower dose of insulin is needed while the risk of hypoglycemias is higher.

Doses of insulin

Insulin NPH: start with 5-10 units before dinner or 0.2 units/kg. Doses should be adjusted every 3 days initially according to basal glycemia.

Insulin glargine: start with 10 units at night. It can be administered in the morning if hypoglycaemias occur or if the patient prefers a morning dose, but always at the same hour. It is not necessary to administer the dose before eating as it does not possess a peak effect. Adjustments in dose should be made in function of basal glycemia and every 3 days.

Insulin detemir: start with 10 units at night. It is not necessary to administer it before dinner. This insulin was initially considered to be administered as a basal-bolus (intensive therapy) but new studies have shown its usefulness in combination with sulphonylureas and metformin[35].

Intensive insulin therapy (basal-bolus)

When the combination of oral agents and insulin are not effective, management should be directed towards only insulin therapy, except in cases of important obesity where a low to moderate dose of metformin is recommended. Generally these are patients who have a long history of diabetes and their insulin reserve is low due to pancreatic beta cell exhaustion.

Intensive insulin therapy should be individualised and should be reserved for those young patients where this form of management provides greater benefits. However in elderly patients and in those with no complications, intensive therapy may present more risk than benefit[21]. These regimens of insulin are similar to those given to type 1 diabetic patients: basal-bolus therapy. They combine intermediate or long-acting insulin with rapid-acting insulin (generally analogs) before each meal.

Table 3. Titration schedule for basal insulin.

Fasting blood glucose (mg/dL)	Adjustment of basal insulin (units)
>9.90 (>180)	8
8.80 to 9.90 (160-180)	6
7.70 to 8.75 (140-159)	4
6.60 to 7.65 (120-139)	2
5.50 to 6.55 (100-119)	1
4.40 to 4.45 (80-99)	Maintain dose
3.30 to 4.35 (60-79)	-2
<3.30 (<60)	-4

Adapted from reference 27.

This form of therapy requires a more careful surveillance on the part of both patient and health care provider. The patient must learn to administer insulin, monitor and modify doses in relation to ingestion (especially carbohydrates). These treatments are prone to higher risk of hypoglycaemia and in general weight gain is greater.

Basal insulin: Either intermediate insulin (NPH) in 2-3 doses, detemir in 2 doses, or glargine in one daily dose can be used. Adjustments on dosage can be done as expounded earlier.

Prandial insulin. A regimen of rapid-acting insulin is indicated (usually analogs, given their more predictable profile and better adjustment to prandial insulin secretion) based on the pre-prandial glycemias and the quantities of carbohydrates to be eaten. Generally, to start 5-6 units are suitable and adjustments can be made according to the individual response[27].

Recently, results of the first phase of the 4-T study were published, comparing the association of oral agents with different regimens of insulin therapy[50]

In elderly patients or those with no complications, treatment is usually more conservative.

(basal insulin, prandial insulin and insulin mixtures). The results suggest that the majority of patients, will not need more than one type of insulin to achieve goals in glycemia. These are results after one year and the trial has a planned duration of 2 years more. Once completed, more information will be available on the usefulness of complex regimens of insulin therapy in these patients.

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Conclusiones

An adequate control in diabetic patients is fundamental to avoid the incidence and progression of complications. A multi-factorial management intervention on risk factors (especially cardiovascular) should be carried out to minimise the risk.

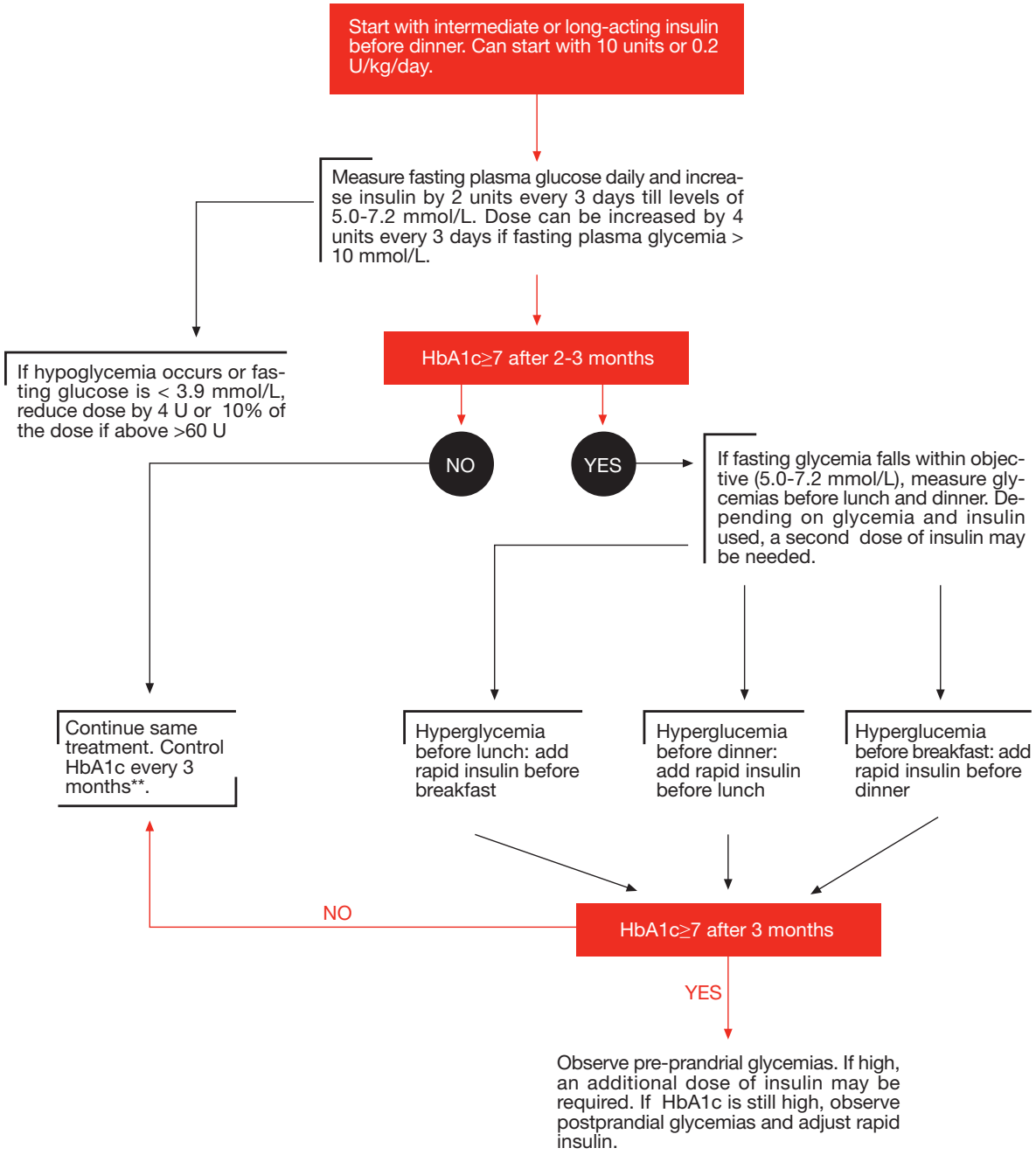
The natural evolution of the disease is a reduction in pancreatic beta cells and thus, a reduction in the quantity of endogenous insulin secreted. Therefore many diabetic patients will need at some point exogenous insulin to provide for the deficit.

Insulin treatment should be given on an individual basis. The type of regimen employed will depend on the characteristics of the patient, the evolution of the disease, and the existence or not of complications.

In the majority of patients initial treatment can be started with a combination of oral agents with a single daily dose of intermediate or long-acting insulin. If there is no contraindication, the most recommended combination is metformin with insulin. If this is not possible, then insulin should be associated with sulphonylureas. The combination of insulin with glitazones is not recommended due to the high risk of heart failure, and there are no sufficient studies that support the combination of insulin with glinides.

When metabolic goals are not reached then intensive insulin therapy can be employed. Such treatments are usually complex in management and there is a higher risk of hypoglycemia. They are more appropriate in young patients and at the onset of microvascular complications. In elderly patients or patients with no complications, treatment should be more conservative.

APPENDIX 1. Algorithm on initiating and adjustments of insulin*.



* Every 6 months, according to the guidelines of the Navarre Regional Health Service in Spain.

** Adaptaded from reference 4.

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Patient-"information" by Big Pharma. A threat to public health

THE INTERNATIONAL SOCIETY OF DRUG BULLETINS

The European Commission is supporting the demand of the pharmaceutical industry to get direct influence on patients[1,2]. It is expected that a legislative proposal having this effect will be introduced by the Commission around September 2007. A foretaste of the bad quality be expected gives a 'patient information' on diabetes recently drafted by the Pharmaceutical Forum with heavy company involvement.

The International Society of Drug Bulletins (ISDB) warns that industry is not a source of reliable and trustworthy information and that it is a mistake to confuse advertising with information. In the contrary there is a need to limit industry influence on patients and prescribers alike. What is needed is to improve drug use with reliable, independent and comparative information so that patients and the public can make informed choices[3].

There are only two countries in the world that allow direct-to-consumer-advertising (DTCA) of prescription drugs: the USA and New Zealand. In both countries it has been shown that DTCA has detrimental effects on health. Pharmaceutical companies' messages are focused on relatively few top sellers, exaggerating effects and concealing risks, confusing patients and putting pressure on doctors to prescribe drugs they would not use otherwise. Lack of comparative information in advertising means people cannot choose among several options.

It is only 5 years ago that the attempt to introduce direct to consumer advertising of prescription drugs in the European Union was voted down by the parliamentarians with an overwhelming majority (494 against, 42 in favour). Most of today's members of European Parliament (MEPs) are newly elected and know little about these discussions[4].

The new move to introduce DTCA comes disguised as a means "to improve the quality of information available to the public". The main actor behind this move is the Pharmaceutical Forum, a working group without any democratic legitimacy that consists of two EU commissioners, three EU parliamentarians, Member State ministers, no less than five pharmaceutical industry associations, representatives of health professionals and insurers. Patients are "represented" by the industry sponsored European Patients' Forum.

Why should one sit together with industry to develop patient information? Health professionals, consumer and patient groups that are independent of pharmaceutical companies, health authorities and funding bodies have not waited for the pharmaceutical companies to take an interest in patient information. Many quality sources of information are now available to the public in Europe and worldwide[3].

Industry feels very confident that DTCA or an equivalent will be allowed: marketing companies already offer seminars how to make best use of this new opportunity to make more money. Pharmaceutical companies should rather do their homework and supply properly labeled medicinal products accompanied by improved Patient Information Leaflets (PILs).

The route chosen by the Commission and the Pharmaceutical Forum goes into the wrong direction. It will further the indiscriminate use of drugs, increase overall consumption of drugs, will be detrimental to health (more adverse reactions, more medical errors), and result in higher health costs. The health products market is not a market like any other. Patients are not consumers.

So, how to increase pharma companies competitiveness? By making medicines which offer real therapeutic advantage as defined in the ISDB Declaration on therapeutic advance[5]. In contrast to pseudo-innovations such products do not need big marketing efforts.

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