

Diabetes and Cardiovascular Diseases (IV)

Treatment of Diabetes Mellitus: General Goals and Clinical Practice Management

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Diabetes mellitus is associated with a marked increased of cardiovascular events. The treatment strategy of diabetes has to be based on the knowledge of its pathophysiology. Thus, insulin is essential for treatment of type 1 diabetic patients because there is a defect in insulin secretion. However, treatment of type 2 diabetic patients is more complex because a defect in both insulin secretion and insulin action exists. Therefore, the treatment selection will depend on the stage of the disease and the individual characteristics of the patient. This article examines the general goals of the treatment and reviews the management of type 2 diabetes.

Key words: *Diabetes treatment. Oral drugs. Insulin.*

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Tratamiento de la diabetes mellitus: objetivos generales y manejo en la práctica clínica

La diabetes mellitus se asocia a un importante incremento de acontecimientos cardiovasculares. La estrategia terapéutica de la diabetes debe fundamentarse en el conocimiento de su fisiopatología. Así, la administración de insulina es esencial en el tratamiento de la diabetes mellitus tipo 1, ya que en estos pacientes existe un importante déficit en la secreción de insulina. Sin embargo, el tratamiento de los pacientes con diabetes tipo 2 es más complejo porque existe un déficit tanto de la secreción como en la acción de la insulina. Por tanto, la selección del tratamiento dependerá del estadio de la enfermedad y las características individuales del paciente. En este artículo se exponen los objetivos generales del tratamiento y se revisa el manejo terapéutico de la diabetes mellitus tipo 2.

Palabras clave: *Tratamiento de la diabetes. Antidiabéticos orales. Insulina.*

INTRODUCTION

Diabetes mellitus is a chronic disease with one of the highest social and healthcare costs and is associated with a 3-fold to 4-fold increment in cardiovascular morbidity and mortality. In fact, ischemic heart disease is the main cause of death in diabetic patients.^{1,2} This article places special emphasis on the therapeutic management of type 2 diabetes, which is the most prevalent type and, consequently, the modality that will cause the greatest cardiovascular morbidity and mortality in absolute figures.

The treatment of diabetes must be based on an understanding of its pathophysiology. Thus, in type 1

diabetes mellitus a severe insulin secretion deficit exists and the only treatment, at present, is the administration of insulin or insulin analog. However, type 2 diabetes mellitus is a much more complex disease, in which insulin resistance predominates in the early stages. In more advanced stages, insulin resistance persists but the deficit in insulin secretion is more evident. Therefore, the therapeutic approach will depend on the stage of the disease and characteristics of the patient.

GOALS OF TREATMENT

The general goals of the treatment of diabetes are to avoid acute decompensation, prevent or delay the appearance of late disease complications, decrease mortality, and maintain a good quality of life. As for chronic complications of the disease, it is clear that good control of glycemia makes it possible to reduce the incidence of microvascular complications (retinopathy, nephropathy, and neuropathy),^{3,4} whereas good

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TABLE 1. Therapeutic objectives for the prevention and treatment of vascular disease in diabetic patients

	Objective	At onset or when modifying pharmacological treatment
Blood glucose profile		
Preprandial glycemia mg/dL*	80-120	<80/>140
Postprandial glycemia mg/dL*	80-140	>140
Glycemia at bedtime mg/dL*	100-140	<100/>160
HbA _{1c} %	<7	>8
Lipid profile		
C-LDL mg/dL	≤100	>100**/>130
C-HDL mg/dL	>45 (M)	55 (W)
Triglycerides mg/dL	<200	>200-400***
Blood pressure	<130/85 mm Hg >140/90 mm Hg	

*Capillary blood; **in the case of previous cardiovascular disease (CVD) and in diabetic patients without previous CVD but with some other risk factor (low C-HDL, smoking, arterial hypertension, family history of CVD, microalbuminuria or proteinuria); ***based on clinical judgment. M indicates men; W, women. These objectives are recommended by the American Society of Diabetes,⁵ and are similar to those prepared by the European⁶ and Spanish⁷ Diabetes Societies.

control of glycemia *per se* does not seem to be as determinant in the prevention of macrovascular complications (ischemic heart disease, cerebrovascular disease, peripheral arteriopathy).⁴ In this sense, the treatment of hyperglycemia should be contemplated as part of an integral approach to the combined risk factors present in these patients (arterial hypertension [AHT], dyslipidemia, smoking). Thus, a treatment designed to obtain optimal glycaemic control that neglects other cardiovascular risk factors is not very rational. In fact, it will surely be more beneficial to the diabetic patient to address cardiovascular risk factors overall, even if goals are not strictly reached for any of them. The therapeutic objectives are listed in Table 1.⁵⁻⁷ Glycosylated hemoglobin (HbA_{1c}) is the best index of the control of diabetes, since it provides information about the degree of glycaemic control in the last two to three months and should remain below 7%. Nevertheless, in older patient or persons with a very limited life expectancy, it is not necessary to reach this therapeutic target since it entails a high risk of causing severe hypoglycemia. As for the target values for the lipid profile and blood pressure, it should be remembered that ischemic heart disease is the main cause of mortality in diabetic patients^{1,2} and that the cardiovascular risk of diabetic patients is similar to that of nondiabetic patients who already have ischemic heart disease.⁸ Therefore, the target values required in the diabetic population should be strict and similar to those demanded in patients with established coronary artery disease.

TABLE 2. Risks of physical exercise in patients with diabetes

1. Hypoglycemia, if the patient is treated with insulin or oral hypoglycemic agents Induced by exercise Delayed onset after exercise (6-15 h later)
2. Hyperglycemia after extenuating exercise
3. Hyperglycemia and ketosis in patients with an insulin deficit
4. Triggering or exacerbation of cardiovascular diseases Ischemic heart disease Arrhythmia Sudden death
5. Aggravation of late complications of diabetes Proliferative retinopathy Vitreous hemorrhage Retinal detachment Nephropathy Increased proteinuria Peripheral neuropathy Soft tissue and joint lesions Neuropathy of the autonomic nervous system Reduction of cardiovascular response to exercise Decrease in maximum aerobic capacity Deterioration of response to dehydration Postural hypotension

GENERAL PRINCIPLES OF TREATMENT

Diet and exercise are fundamental in the treatment of diabetes. Dietary recommendations must be customized for each individual to achieve the general objectives of treatment. It should be remembered that obesity is common in type 2 diabetics so one of the main objectives should be weight reduction. The calorie content of the diet should be adjusted in each individual in accordance with the body mass index and regular physical activity. As far as the nutrient proportions of the diet, it is recommended that proteins should constitute 10%-20% of calorie intake and fats less than 30%, with less than 10% saturated fats. With regard to carbohydrates, emphasis should be placed on total intake rather than on their origin, although rapidly absorbed carbohydrates should be avoided.⁹

Physical exercise, aside from constituting a mainstay of the treatment of diabetic patients, helps to prevent the development of diabetes in adult life.¹⁰⁻¹⁴ In patients with type 2 diabetes, moderate regular exercise (30 min/day) is very beneficial, since it reduces glycemia by increasing sensitivity to insulin, improves the lipid profile, lowers blood pressure, contributes to weight loss, and improves cardiovascular state (decreased heart rate at rest, increased systolic volume, and decreased cardiac work). In addition, it gives the patient a sense of well being and better quality of life. The main disadvantage of exercise in diabetic patients is hypoglycemia, which can occur several hours later and should condition adjustments in the therapeutic re-

gimen. In addition, in patients with type 1 diabetes and poor metabolic control, especially after anaerobic exercise, hyperglycemic decompensation or even ketoacidosis can take place. Aside from disturbing glucose metabolism, physical exercise can entail other risks, which are detailed in Table 2. Therefore, the patient's exercise program must be planned individually taking into consideration physical capacity and potential risks.¹⁵

The diabetological education that the patient receives from qualified healthcare personnel is essential in achieving therapeutic objectives. For example, self-testing of capillary blood glucose informs the patient about the time of day when glycemic control is worse and helps to identify undetected hypoglycemia. Therefore, self-tests are fundamental for making opportune modifications in therapy. In addition, the patient who knows how to modify treatment based on capillary blood glucose measurements and has received advice on how to handle various situations, such as hypoglycemia or hyperglycemic-ketotic decompensation, will require fewer hospital admissions and have a better quality of life.

TREATMENT OF TYPE 2 DIABETES MELLITUS. GENERAL PRINCIPLES AND THERAPEUTIC APPROACH

The diet—which generally must be low-calorie due to the frequency of associated obesity—and a program of regular exercise are the basis of the treatment of type 2 diabetes mellitus. When acceptable metabolic control is not achieved, either because the patient does not adapt to changes in life style or because, in spite of complying with the diet and exercising regularly, therapeutic objectives are not attained, pharmacological treatment must begin. Figure 1 shows a diagram of the therapeutic approach to type 2 diabetes mellitus.

Pharmacological treatment

Sulfonylureas

In the mid-1950s the first sulfonylureas (SU) were developed for commercial use (carbutamide and tolbutamide). In the mid-1960s there were already four SUs on the market (tolbutamide, acetohexamide, tolazamide and chlorpropamide), which are currently known as the first-generation SUs. At the end of the 1960s, second-generation SUs were introduced (glibenclamide, glipizide, gliquidone, and gliclazide). In 1970, the results of the University Group Diabetes Program (UGDP)¹⁶ were published, where it was concluded that tolbutamide was ineffective in the treatment of the diabetes and also increased cardiovascular mortality. This study had a major impact not only in the U.S., but also in various European countries, and resulted in a consi-

derable decrease in the use of SUs. Nevertheless, since the results of the UGDP were much criticized regarding the methodology of the study,¹⁷ and there was evidence of its clinical effectiveness, in 1979 the American Diabetes Society decided to end restrictions of the use of SUs and they have been marketed in the U.S. since 1984. More recently, a new long-acting SU has been introduced: glimepiride.¹⁸

Mechanism of action. The SUs stimulate the second phase of insulin secretion by pancreatic beta cells, that is to say, the release of preformed insulin.¹⁹ Therefore, the SUs require the presence of a critical mass of beta cells with insulin secretory capacity in order to act. Therefore, the SUs will not be effective in patients who are pancreatectomized or have type 1 diabetes mellitus. The SUs act through high-affinity receptors located in the pancreatic beta cells.²⁰ Binding to these receptors inhibits the opening of ATP-sensitive potassium channels and avoids potassium outflow from the cell, thus triggering cell membrane depolarization. As a result, the calcium channels open, increasing intracellular calcium content and calcium binding to calmodulin, which produces microfilament contraction and the exocytosis of insulin granules (Figure 2).

In the heart and throughout the cardiovascular system there are also SU receptors and ATP-sensitive potassium channels, which have an important cardioprotective effect against ischemia. Closure of these channels by SUs could contribute to ischemia.²¹ Nevertheless, although this possible harmful effect seems evident in experimental studies in which high doses of SUs are administered acutely,²² this does not seem to be clinically relevant, as has been shown in the UKDPS study.⁴

Clinical pharmacology. The SU differ in potency, duration of action, metabolism, undesirable effects, and other pharmacological properties.²³ Some of the main pharmacological characteristics of the SUs are summarized in Table 3. The second-generation SUs are more potent and have less toxicity than the first-generation SUs. All the SUs are absorbed quickly in the digestive tract, reaching peak plasma level 2-4 h after ingestion. They bind mainly to albumin, from which they can be displaced by other drugs. The metabolism is fundamentally hepatic and its metabolites are eliminated in urine and, to a lesser extent, in bile. Gliquidone is eliminated mainly in bile, so it can be used in cases of moderate kidney failure (creatinine <2 mg/dL).

Undesirable effects. SUs are generally well tolerated. Hypoglycemia is the most frequent adverse effect and is directly related with the potency and duration of the effect of the drug administered.²⁴ Thus, it is more frequent with chlorpropamide or glibenclamide than with tolbutamide. Hypoglycemia due to SU is less frequent than with insulin, but it is often more prolonged and can require treatment with intravenous glucose in-

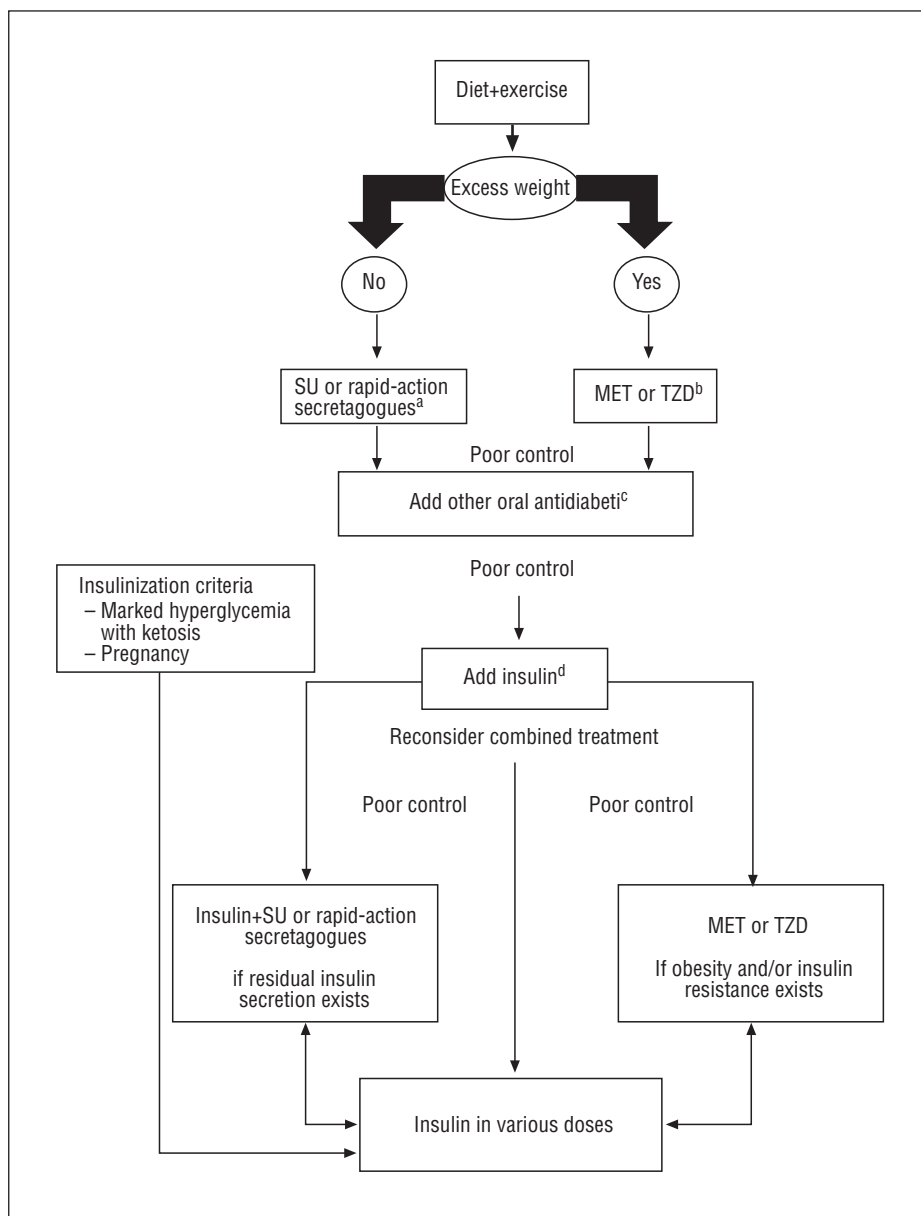


Fig. 1. Scheme of the therapeutic approach proposed for type 2 diabetes mellitus. ^aFast action secretagogues are repaglinide and nateglinide. ^bAt present, the thiazolidinediones (TZD) cannot yet be prescribed in monotherapy. ^cBased on patient characteristics. Thus, for example, if baseline hyperglycemia predominates and the patient was treated with sulfonylureas (SU), metformin (MET) can be added. However, if the patient follows treatment with MET and poor control is at the expense of postprandial hyperglycemic peaks, a secretagogue or alpha-glycosidase inhibitor should be added. ^dIt is recommended that insulin treatment begin with a single nocturnal dose.

fusion for several days. Kidney and liver failure are risk factors for SU-induced hypoglycemia. The decrease in intake and the use of drugs can potentiate the action of SUs²⁴ (e.g., aspirin, MAO inhibitors, pyrazolones, fibrates). All these factors often coincide in diabetics of advanced age. In addition, in such patients the typical symptoms of hypoglycemia may be absent and manifested only by psychiatric or neurological symptoms. Other undesirable effects are infrequent (<5%), generally well-tolerated, and reversible²⁵ (Table 4).

Indications, drug selection, and contraindications

SUs are considered drugs of first choice for the treatment of type 2 diabetes mellitus when the patient is

not overweight, as long as the therapeutic objectives are not achieved by means of an individualized program of diet and exercise. The second-generation SUs are the most frequently used and there is none that clearly surpasses the others, which is why it is more important that the physician prescribe the preparation she is most experienced with. Tolbutamide and glimepiride have been recommended for older persons due to the lower risk of serious hypoglycemia. Treatment should begin with small doses (generally half a tablet) to avoid hypoglycemia and to increase the dose at weekly intervals until good metabolic control has been achieved or the recommended maximum dose has been reached. When an adequate response is obtained, the possibility of reducing the doses should be reviewed. If a lower dose can be given, it likely that good

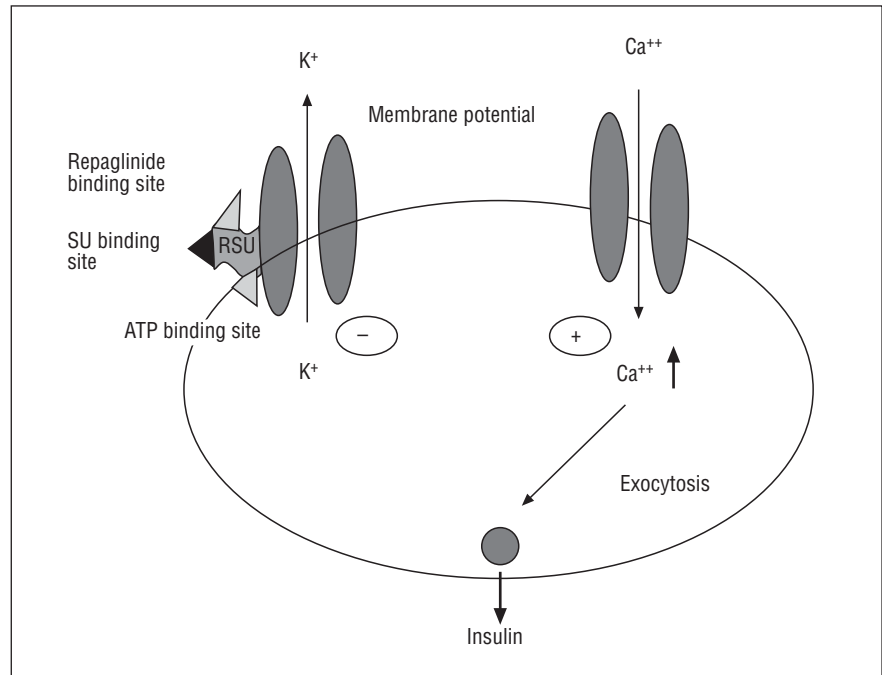


Fig. 2. Schematic representation of the mechanism of action of the sulfonylureas (SU). The SU receptor regulates the opening and closing of K⁺ channels and contains specific binding sites for ATP, SU, and repaglinide.

control will be obtained with diet alone. If good glyce-mic control is not achieved with the maximum dose of SU used, combined treatment with metformin can be tried or the patient can be switched to insulin.

SUs are contraindicated in patients allergic to sulfo-namides and, of course, in type 1 diabetics and in pan-creas-deficient diabetes (e.g., after pancreatitis or pan-createctomy), since they are only effective when the patient has some insulin-secreting capacity. They can-not be prescribed during pregnancy and breastfeeding

because they can cross the placental barrier and be se-creted in maternal milk. Its use in situations that cause important stress is not recommended since, in these cases, the SUs will not be capable of meeting insulin needs. Thus, in situations such as acute myocardial in-farction (AMI), severe trauma, or infectious processes of certain importance, it is preferable to switch to insu-lin treatment and then reassess SU treatment after overcoming the period of stress. They should not be used in the case of major surgical interventions,

TABLE 3. Major pharmacological characteristics of the principal sulfonylureas

Sulfonylurea	Half-life	Duration of action	Renal elimination	Daily dose
Tolbutamide Rastinon®	6-12 h	6-12 h	100%	500-3000 mg
Chlorpropramide* Diabenese®	>24 h	24-60 h	80%	125-500 mg
Glibenclamide Daonil®	3-5 h	16-24 h	50%	2.5-15 mg
Euglucon-5® Norglicem-5®				
Glicazide Diamicron®	6-12 h	12-24 h	70%	40-240 mg
Glipizide Diabenese® Minodiab®	1-5 h	12-24 h	70%	2.5-15 mg
Gliquidone Glurenor®	12-24 h	12-24 h	5%	15-90 mg
Glimepiride Amaryl® Roname®	10 h	16-24 h	50%	1-8 mg

*Not recommended due to the high risk of side effect.

TABLE 4. Main side effects of the sulfonylureas

Hypoglycemia
Gastrointestinal disturbances: nausea, vomiting, bloating, diarrhea, abnormal liver function tests, and cholestasis
Skin reactions: rash, itching, erythema nodosum, erythema multiforme, exfoliative dermatitis, photosensitivity
Hematological disturbances*: hemolytic anemia, agranulocytosis, thrombocytopenia, bone marrow aplasia
Disulfiram-like effect**
Hyponatremia**

*These effects occur occasionally, generally within the 6 first weeks after beginning treatment; **only with chlorpropamide. Hyponatremia can be severe and occurs as a result of an increase in the sensitivity of the renal tubule to antidiuretic hormone (ADH). These side effects make the use of chlorpropamide inadvisable.

which, aside from constituting a stressful situation, also entails the need for fasting. Therefore, patients should be switched to insulin treatment and intravenous glucose infusion.

The presence of liver disease is a relative contraindication. Most SUs are metabolized by the liver into compounds with little or no activity. Therefore, when impaired liver function exists, deactivation of the SUs decreases, the half-life becomes longer, and the hypoglycemic action increases. Hypoalbuminemia is an aggravating factor since a larger amount of SU will be present. If the patient also consumes alcohol, the risk of hypoglycemia will increase.

Kidney failure results in a decrease in the elimination of SUs and their metabolites, prolonging their action and increasing the risk of hypoglycemia. Therefore, their use in patients with kidney disease is not recommended. As has been mentioned, gliquidone, which is eliminated preponderantly in bile, could be an alternative in the case of moderate kidney failure whenever therapeutic objectives are strictly met; if not, patients should be passed immediately to insulin treatment.²⁴⁻²⁶

Other secretagogue drugs: repaglinide and nateglinide

Repaglinide and nateglinide are new secretagogues characterized by a selective action on the first phase of insulin secretion. From the clinical vantage point, they have a shorter but more intense action than the SUs, which produces into a smaller postprandial glucose elevation and less intense later hypoglycemic action, meaning that beta-cell stimulation is avoided during periods of fasting.^{27,28} This is especially important in avoiding nocturnal hypoglycemia. These fast-acting secretagogues, like the SUs, are indicated in type 2 diabetes mellitus when therapeutic objectives are not reached with diet and exercise.

Repaglinide. Repaglinide (Novonorm®) is a derivative of carbamoyl methyl benzoic acid (meglitinide family). It has a mechanism of action very similar to that of the SUs, but differs in the specific binding site to the SU receptor²⁹ (Figure 2). Its insulin-releasing action begins within the first 30 min of administration and the effect disappears in approximately 4 h. Therefore, it should be taken about 15-30 min before eating; it is fundamental to coordinate its administration with the meal schedule. This adjustment reduces the probability of hypoglycemia when meals are skipped or delayed, in contrast with conventional SU treatment.³⁰ The dose is 0.5-4 mg before each meal and can be adjusted in accordance with the type of meal ingested. In general, it is a well tolerated drug and its clinical effectiveness in monotherapy is similar to that of SUs. It also has been shown to be very effective in combination with metformin.^{31,32} It is metabolized by the liver and 90% is excreted in bile as inactive metabolites. Hepatic toxicity has not been described, but the transaminases can rise temporarily. Therefore, the dose would have to be reduced in patients with clinically significant liver disease. It is not contraindicated in the case of mild or moderate kidney failure, but in severe kidney failure (creatinine clearance 20-40 mL/min) the dose should be reduced.^{29,33}

Nateglinide. Nateglinide (Starlix®) is a derivative of D-phenylalanine that directly stimulates the beta cell. Its action is based on the fact that although the response to glucose is lost in the first phase of insulin secretion, the response to certain amino acids like phenylalanine is conserved. Its pharmacokinetics are very similar to those of repaglinide, but with a still more rapid onset and disappearance of action, which causes an earlier and intense peak insulin secretion that disappears sooner. Therefore, the preprandial delay is shorter, as are possible late hypoglycemic crises.²⁸ Although experience is limited, it has been shown to be effective at a dose of 60-180 mg taken before each meal. The best dose-response effectiveness is obtained with 120 mg.^{34,35}

Biguanides

The history of the biguanides dates back to the Middle Ages, when the legume *Galega officinalis*, whose active principle is guanidine or galegin, was used for the treatment of diabetes mellitus.³⁶ Nevertheless, it was not until 1918 that its utility as a hypoglycemic treatment was discovered.³⁷ Three derivatives of guanidine have been identified: monoguanidines (galegin), diguanidines (sintalin) and biguanides, formed by the union of two guanidine molecules and the elimination of an amino radical. Sintalin was introduced in Germany in 1926 but its toxic effects made it unusable. Between 1957 and 1960, the biguanides were introduced on the market (fenformin, buformin,

and metformin) and became very popular.³⁸ Nevertheless, in 1976 these drugs were discontinued in the U.S. and some European countries (Germany, Scandinavia) due to their association with lactic acidosis.³⁹⁻⁴¹ Nonetheless, cases of lactic acidosis had only been communicated with fenformin, so metformin and buformin continued to be prescribed regularly in most European countries and Canada. It should be noted that the incidence of lactic acidosis with metformin use is three cases per 100 000 inhabitants/year, a figure similar to the rate of deaths due to hypoglycemia attributed to glibenclamide.⁴²⁻⁴⁴ Because of its effectiveness and safety, metformin (Dianben[®]) is currently the only biguanide recommended for therapeutic use. Since 1995 metformin has again been made available on the U.S. market. At present it is one of the drugs most used in the treatment of type 2 diabetes.^{42,25}

Mechanism of action. The biguanides, unlike the SUs, do not stimulate insulin secretion by the pancreatic beta cells. Therefore, strictly speaking they cannot be considered hypoglycemic agents because they only reduce glycemia in diabetic patients. Their main mechanism of action is to reduce hepatic glucose production by decreasing both glyconeogenesis and glycogenolysis.^{42,46,47} They also increase glucose uptake by the skeletal muscle. Thus, it has been demonstrated that metformin favors the action of insulin in muscle tissue at different levels: by increasing the number of receptors and the affinity of insulin for its receptors, facilitating glucose transport through an increase in the expression, or activity, of GLUT-4, and stimulating non-oxidative glucose metabolism, which translates into an increase in glycogen deposits. It is clear that metformin improves sensitivity to insulin and is a drug of first choice when insulin resistance is the predominant mechanism in the etiopathogenesis of diabetes.

Aside from reducing glycemia levels, the biguanides exercise other effects that are especially beneficial for diabetic patients. Thus, it has been demonstrated that they reduce triglyceride concentrations by 20%-25% and C-LDL by 5%-10%, whereas C-HDL levels do not vary or rise discretely.^{42,46,48} Other effects that have been reported are the improvement of various rheological variables in blood (decreased platelet aggregability, increased erythrocyte deformability, decreased blood viscosity) and increased fibrinolytic activity.⁴² Finally, it has been demonstrated that treatment with metformin is accompanied by weight loss, especially compared with patients treated with insulin or SU.⁴⁹

Clinical pharmacology. The biguanides are absorbed quickly in the small intestine and only fenformin binds to plasma proteins and suffers partial hepatic metabolism. Buformin and metformin do not bind to plasma proteins and are eliminated unchanged by the kidney. Peak plasma metformin concentration is reached 2-3 h after it is taken. Its plasma half-life ranges

from 2 to 6 h and within 12 h 90% will be eliminated in urine. It can be given two or three times a day.^{23,42}

Undesirable effects and contraindications. The most frequent adverse effect of the biguanides are gastrointestinal disturbances, which occur in 30% of cases. These effects include anorexia, nausea, vomiting, abdominal discomfort, and a metallic taste, but undoubtedly the most frequent of them is diarrhea.^{23,48,50} Symptoms generally appear when treatment begins and are short-lived. A disorder in vitamin B₁₂ absorption has been reported in patients treated during prolonged periods. However, it has scant clinical repercussions.⁴⁸ Lactic acidosis is the most feared adverse effect of the biguanides since it is lethal in 30%-50% of cases.^{38,42} Nevertheless, this effect is very rare with metformin, being necessary an overdose of the drug and/or coexistence of impaired elimination or situations that produce an increase in lactic acid production for it to occur. Consequently, it is better not to recommend metformin in patients with kidney failure (creatinine >1.4 mg/dL), advanced liver disease, serious respiratory and/or cardiac insufficiency, alcoholism, and situations of major stress (AMI, severe trauma, or major infectious processes). It is also prudent to discontinue the drug temporarily when radiological contrast is injected, due to the risk of acute kidney failure. Although no studies have demonstrated teratogenic capacity or the ability to cross the placenta, its use is not recommended during pregnancy or breastfeeding. Age is not a limiting factor as long as creatinine clearance is >70 mL/min.^{42,48}

Drug selection and indications. As has been mentioned, the only biguanide recommended for clinical use is metformin. It is the drug of choice in overweight type 2 diabetics, since insulin resistance generally predominates over deficient insulin secretion in such cases.^{6,51,52} Of course, it should only be prescribed if therapeutic objectives are not achieved with a suitable diet and exercise program. It is recommended that treatment begin with a single low dose (500-850 mg) coinciding with food intake, and that it be gradually increased at 2-week intervals until therapeutic goals or a maximum dose of 2550 mg/day is reached (3 tablets/day). This minimizes side effects, especially diarrhea and other digestive problems, which are the main cause of withdrawal from treatment. Even so, 5% of patients do not tolerate it.^{48,50}

The therapeutic effectiveness of metformin is unquestioned and is comparable to that of the SUs.^{42,53} Metformin has a series of advantages over SUs, such as the absence of hypoglycemia, improvement of the lipid profile, and reduction of insulinemia levels. In addition, it is not associated with weight gain. In the UKDPS study, metformin was the only medication associated with a reduction in mortality in diabetic patients. Aside from reducing microangiopathic compli-

cations, it also significantly reduced the risk of AMI and cerebrovascular accidents.⁵⁴ If the therapeutic objectives are not attained after reaching the maximum dose, an SU or fast-acting secretagogue (repaglinide or nateglinide) can be added. Although this association has been demonstrated to be very effective,^{42,53,55,56} due to the progressive nature of diabetes, the secretory capacity of the beta cell will deteriorate with time and many patients will require insulin. In these cases, as long as a certain insulin secretion capacity persists, it is preferable to use combined therapy with oral drugs and to add insulin as a nocturnal dose administered before bedtime. Another option is to discontinue treatment with secretagogues and to use treatment with metformin and insulin.⁵⁷

Thiazolidinediones

This group of drugs of recent appearance have an action based on increasing sensitivity to insulin. In 1982 the first drug in this group, ciglitazone, was discovered, but it was not marketed due to its elevated toxicity. Since the mid-1990s, derivatives with a better safety profile have been developed: troglitazone, pioglitazone, and rosiglitazone.⁵⁸ Nevertheless, troglitazone has been withdrawn due to its hepatotoxicity⁵⁹ and in Spain pioglitazone (Actos®) is not yet available on the market, although its commercialization is imminent. Therefore, rosiglitazone (Avandia®) is only thiazolidinedione (TZD) that we can prescribe at present and, for the moment, its use is only authorized in combination therapy.

Mechanism of action, indications, and clinical effectiveness. The mechanism of action involves binding to specific nuclear receptors called PPAR- γ (*peroxisome proliferator-activated gamma receptor*), whose stimulation regulates the transcription of specific genes that will lead to an increase in the number and affinity of insulin receptors, especially the glucose transporters GLUT-4. This causes an increase in insulin-mediated peripheral uptake of glucose by muscle and adipose tissue. PPAR- γ stimulation also causes the transformation of preadipocytes into adipocytes with less capacity to respond to the action of tumor necrosis factor alpha (TNF- α). This reduces lipolysis and results in a decrease in circulating free fatty acids, consequently improving insulin resistance.⁶⁰⁻⁶³

Since they act as insulin-sensitizing agents or, what is the same, reducers of insulin resistance,⁶⁴⁻⁶⁶ their clinical effectiveness is clearly related with the presence of an insulin reserve. They do not reduce glucose levels in healthy subjects or in diabetics with clear insulinopenia unless they are administered in association with insulin.⁶⁷ Therefore, like metformin, their main indication will be patients with type 2 diabetes mellitus in which insulin resistance predominates.

The recommended dose of pioglitazone is 30 mg/day, whereas the recommended dose of rosiglitazone is only 4-8 mg/day, since it has more affinity for PPAR- γ receptors.⁶³ As we have mentioned, at present rosiglitazone is the only TZD that can be prescribed in Spain. Its maximum concentration is reached within an hour of intake, plasma half-life is 3.7 h, and it is metabolized in liver.⁶³ Nevertheless, it is necessary to consider that, since its mechanism of action is through the activation of gene transcription, metabolic effects are not fully reached until 3 to 6 weeks after beginning treatment.⁵⁸ Its pharmacokinetics are practically unchanged by kidney failure⁶⁸ or age.⁶⁹ It can be given in one or two daily doses and it does not matter if it is administered before or after meals.⁷⁰

Its hypoglycemic action is dose-dependent and, in theory, it can be used in monotherapy or combined with secretagogues, metformin, or insulin. Nevertheless, the European Agency for the Evaluation of Medicinal Products so far has only approved its clinical use in combination with metformin in obese patients, or with SUs in cases in which metformin is contraindicated or not tolerated.⁷¹ In fact, the effectiveness of TZDs is superior when they are used in combination with SUs or metformin than when they are used in monotherapy. Let us remember that the TZDs, metformin, and SUs act through different mechanisms. The TZDs stimulate glucose uptake by insulin-sensitive tissues, whereas the main mechanism of action of metformin lies in the inhibition of hepatic glucose production and that of the SUs is based on an increase in endogenous insulin levels. Therefore, it is logical that the combination of TZD with either metformin or SU has been shown to be very effective.^{47,72-74} It also is used in association with insulin therapy in patients with type 2 diabetes mellitus who require high doses of insulin, improving metabolic control and appreciably reducing insulin needs.⁷⁵

Aside from significantly reducing baseline glycemia, postprandial glycemia, insulinemia, and HbA_{1c}, they change the lipid profile. Thus, they reduce the mean value of free fatty acids and triglycerides by 15%-20% and produce a slight increase (5%-15%) in C-LDL and C-HDL.⁵⁸ It is also known that the TZDs can have potentially beneficial effects on the development or progression of arteriosclerosis that are under study.^{76,77}

Side effects and contraindications. The most serious toxic effect of the TZDs has been hepatotoxicity. Thus, an increase in transaminases was observed with troglitazone in around 2% of patients. In sporadic cases, severe hepatocellular lesions that caused the death of the patients was documented, so it was withdrawn from the market.^{59,78} Severe hepatotoxicity has not been reported with pioglitazone and rosiglitazone, although isolated cases of nonfatal hepatic lesion have been communicated.^{79,80} Therefore, for the moment it seems

prudent not to prescribe them in patients with liver disease and it is advisable to closely monitor liver enzymes when it is administered to patients without liver disease. Mild decreases in hematocrit and hemoglobin levels have been reported that do not seem to be related to disturbances in erythropoiesis and could be attributed to an increase in plasma volume.⁶³ In this sense, it has been demonstrated that troglitazone produces water retention, which causes hemodilution and edema due to a vasodilator effect. In addition, structural and functional cardiac disorders have also been communicated, but these effects have not been observed with rosiglitazone.^{81,82} In any case, until more experience with the use of TZDs is available, it would be prudent to avoid administering it to patients with anemia and/or established heart disease. At present, studies in humans have not included women who were pregnant or breastfeeding, or patients under the age of 18 years; therefore, TZDs cannot be used in such patients. However, since the metabolism of TZDs is hepatic, they can be prescribed in cases of mild or moderate kidney failure. Hypoglycemia is infrequent and it has been communicated in less than 1% of cases with rosiglitazone in monotherapy.⁸³ Finally, due to improvement in the use of glucose by adipose tissue, these drugs are lipogenic and weight gain is another undesirable effect that must be considered.

Alpha-glycosidase inhibitors

The inhibitors of the alpha-glycosidases (acarbose –Glucobay®, Glumida®– and miglitol –Diastabol®, Plumarol®-) competitively and reversibly inhibit intestinal alpha-glycosidases, thus delaying and partly impeding carbohydrate absorption. Consequently, their main effect is to reduce postprandial hyperglycemia. Their effectiveness in reducing HbA_{1c} is less than that obtained with the drugs commented above, and would be especially indicated in patients with an acceptable baseline glycemia and postprandial hyperglycemia.⁵⁷ In order to minimize side effects, it is recommended that treatment begin with 25-50 mg (one-half or one tablet), which should be swallowed without chewing before meals. The dose can be increased weekly until it reaches 300 mg/day, which is the usual dose, and its maximum effect is observed at 3 months.⁸⁴ The most important side effects, which are responsible for the largest number of withdrawals, are flatulence (30%) and diarrhea. They are contraindicated in patients with chronic intestinal disease, pregnancy, breastfeeding, liver cirrhosis, and kidney failure.

Combined treatment with oral antidiabetics

In up to 30% of cases, an insufficient response to any of the above mentioned drugs takes place within 3 months of initiating treatment; this is known as primary

failure.^{7,57} It is more frequent in diabetics with high baseline hyperglycemia and the main causes are the lack of compliance with diet and/or a scant insulin reserve due to a severe disturbance in insulin secretion capacity by pancreatic beta cells. On other occasions, patients stop responding after enjoying good metabolic control for at least 6 months; this is called secondary therapeutic failure. Every year 5% to 10% of patients cease to respond favorably. This reflects the progressive deterioration of the capacity for insulin secretion by the beta cell and forms part of the natural evolution of type 2 diabetes mellitus. It is important to distinguish between true secondary failure and a transitory loss in the effectiveness of oral drugs due to an intercurrent disease. In the latter case, good control can return with oral therapy after temporary insulin treatment.

In the case of primary or secondary failure, the option of combined therapy with other oral antidiabetics or insulin exists. The basis for this treatment is to take advantage of the synergic or complementary effects of their mechanisms of action. Besides from improving glycemic control, combined treatment makes it possible to reduce the doses of drugs used in monotherapy, which can help to minimize side effects. The choice of the second oral drug must be made after analyzing the main causes that condition poor metabolic control after considering the patient's individual characteristics. The pathophysiological bases for combined therapy and the clinical effectiveness found in the most representative studies are summarized in Tables 5 and 6.^{6,7,31,53,55,57,72-74,85-97}

TREATMENT OF TYPE 1 DIABETES MELLITUS

Insulin administration is the fundamental treatment of type 1 diabetes mellitus. Although insulin has been available for more than 75 years, in the last two decades there have been important changes due to the generalized use of reflectometers by patients to self-monitor capillary blood glucose. Control of blood glucose levels by patients includes adjustment by the patient of insulin doses based on algorithms prepared by the endocrinologist and allows patients more flexibility in their habits and, without a doubt, an improved quality of life. As mentioned, this article focuses on the therapeutic management of patients with type 2 diabetes mellitus, which is why we will not discuss specific aspects of the treatment of type 1 diabetics in detail. Therefore, the information given below on insulin treatment is applicable to patients with either type 1 or type 2 diabetes.

Types of insulin and administration pathways

At present, in Spain the only insulins used are biosynthetic human insulins that are obtained by genetic recombination techniques from cultures of bacteria

(*Escherichia coli*) or yeasts. Insulin is administered subcutaneously using «pen syringes» with refillable cartridges, disposable pens, or infusion pumps. Nevertheless, in situations of severe metabolic decompensation insulin can be administered intramuscularly or intravenously. According to their action profile, the various types of insulin can be classified into the three large groups specified in Table 7.

In recent years fast-acting insulin analogs have begun to be used (lispro insulin), which are obtained by changing an amino acid in the insulin sequence.⁹⁸ These analogs have the same hypoglycemic potency as regular insulin, but they are absorbed faster and have an earlier (1 h), higher, and briefer (4 h) insulinemia peak than is observed with regular insulin, which is why they can be administered immediately before eating. Due to the brief duration of their action, they produce less delayed hypoglycemia but, for the same reason, it will often be necessary to give an additional dose of intermediate action insulin. There are also premixed insulins with established percentages of fast-acting and intermediate action insulin on the market. They are especially useful and convenient for type 2 diabetic patients but, in general, do not adapt to the changing insulin needs of patients with type 1 diabetes. In addition to the insulins that are currently available, in the near future new subcutaneous analogs will be marketed, including both fast-acting (aspart, Novorapid®, glulisin) and slow acting (glargine, Lantus®) products, as well as inhaled fast-acting insulin.

Generally speaking, insulin therapy can be divided into conventional and intensive therapy. Conventional insulin therapy includes the use of one or two injections of insulin (sometimes more), sporadic blood sugar self-testing and occasional modifications by patients in the insulin regimen depending on blood glucose measurements, variations in the diet, or physical activity.

Intensive insulin therapy includes diet and an individualized physical exercise program, multiple doses of insulin (3-4 injections/day), frequent blood sugar readings (4-7 self-tests/day) and, especially, changes in the insulin dose in relation to variations in blood glucose, diet, and physical activity. This intensive treatment requires a highly motivated patient, good diabetological training, and the possibility of frequent contacts with the healthcare team. This type of treatment is indicated especially in patients with type 1 diabetes without advanced diabetic complications and during pregnancy. Some examples of multiple insulin injection regimens are outlined in Table 8. Strict blood glucose control is associated with more frequent hypoglycemia but, despite this and the greater effort dedicated to metabolic control, the quality of life of the patients seems to be as good or better in patients with intensive treatment than in patients undergoing conventional treatment.

The mean dose of insulin used varies widely (0.2-1 U/kg/day) since it depends on endogenous insulin secretion (which is practically null in patients with type 1 diabetes and variable in type 2 patients) and the presence of insulin resistance. It is recommended that tre-

Guidelines for insulin therapy

TABLE 5. Pathophysiological basis and effectiveness of combined treatments with oral antidiabetics

	Sulfonylureas+metformin*	Repaglinide+metformin
Pathophysiological principle	Sulfonylureas: stimulate insulin secretion MET: ↓ hepatic glucose production	Repaglinide: stimulates insulin secretion MET: ↓ hepatic glucose production
Additional decrease in HbA _{1c}	1.5-2.5 Independent of the first drug used	1.4%* In patients treated previously with MET
	Sulfonylureas+alpha-glycosidase inhibitors	Metformin+alpha-glycosidase inhibitors
Pathophysiological principle	Sulfonylureas: stimulate insulin secretion Alpha-glycosidase inhibitors: reduce postprandial hyperglycemia	MET: ↓ hepatic glucose production Alpha-glycosidase inhibitors: reduce postprandial hyperglycemia
Additional decrease in HbA _{1c}	1.5%-2% when sulfonylurea is added 0.5%-1% when an α-glycosidase inhibitor is added	1.5%-2% when MET is added 0.5%-1% when an α-glycosidase inhibitor is added
	Sulfonylureas+TZD	Metformin+TZD
Pathophysiological principle	Sulfonylureas: stimulate insulin secretion TZD: ↑ sensitivity to insulin	MET: ↓ hepatic glucose production TZD: ↑ sensitivity to insulin
Additional decrease in HbA _{1c}	0.5%-1% when low-dose rosiglitazone is added 0.7-1.7 when troglitazone is added (600 mg)	1% when rosiglitazone is added

*This is the association with which most experience has been acquired and that is presently the most effective. TZD indicates thiazolidinediones; α-glycosidase inhibitors, alpha-glycosidase inhibitors.

TABLE 6. Pathophysiological basis and effectiveness of combined treatment with insulin and oral antidiabetics

	Sulfonylureas+insulin*	Metformin+insulin*
Pathophysiological principle	– Sulfonylureas: stimulate insulin secretion – Nocturnal insulin: ↓ baseline glycemia by inhibiting hepatic glucose production	– MET: ↓ hepatic glucose production and increases sensitivity to insulin – Nocturnal insulin: ↓ hepatic glucose production
Additional decrease in HbA _{1c}	0.7%-1.1% when insulin is added to SU treatment	1,1%-2,5%
	Lα-glycosidase inhibitors**+insulin	TZD+insulin*
Pathophysiological principle	Improved metabolic control and reduction of insulin requirements due to improved postprandial glycemia	Improved metabolic control and reduction of insulin requirements due to improved sensitivity to insulin
Additional decrease in HbA _{1c}	0.69% when Lα-glycosidase inhibitors are added to insulin treatment	0.8%-1.4% when TZD are added to insulin treatment

*The most effective and advisable way to initiate insulin treatment in patients already receiving SU or MET is by administering a nocturnal dose of insulin.

**Alpha-glycosidase inhibitors.

atment begin with low doses (0.3-0.5 U/kg/day) administered in one or two injections/day of intermediate action insulin. The total dose is increased and/or the type of insulin is modified in accordance with the glycemic profile. In type 1 diabetic patients, a regimen of 3-4 insulin injections/day combining fast and intermediate action insulin is recommended from the beginning. In hospitalized patients who do not know that they are diabetics or in known diabetics with poor glycemic control, often motivated by circumstances that increase their insulin demand (e.g., AMI, surgery, infections, corticoid treatment, emotional stress, etc.), a good therapeutic approach is to administer subcutaneous insulin regularly in relation to blood glucose readings obtained every 6 h, together with a meal containing 50 g of carbohydrates. Depending on the amount

of insulin required every 6 h, the units/day that the patient requires can be estimated and the total dose can be administered in a single dose or divided it into several insulin injections (intermediate action or intermediate associated with fast action).

TREATMENT IN SPECIAL SITUATIONS

Treatment in acute myocardial infarction or unstable angina

As a result of metabolic response to stress and the elevation in counter-regulatory hormones (e.g., cortisol, catecholamines) that takes place immediately after an AMI, hyperglycemic decompensation often occurs in a known diabetic patient, or diabetes may even be

TABLE 7. Classes of human insulin commercialized, by spectrum of action. In addition, premixed preparations with established percentages of regular insulin/NPH insulin (10/90, 20/80, 30/70, 40/60, 50/50) and insulin lispro/NPL (25/75, 50/50) are marketed

	Onset of action	Peak	Duration
Fast action insulin			
Regular insulin Actrapid® Humulin Regular®	30-60 min	2-4 h	6-8 h
Rapid insulin analogs Humalog®	15-30 min	30-90 min	3-6 h
Intermediate action insulin			
NPH	2-4 h	6-10 h	14-18 h
NPL*	2-4 h	6-10 h	14-18 h
Slow Humulin®	2-4 h	6-8 h	22 h
Monotard®	2-3 h	7-15 h	24 h
Prolonged action insulin**			
Ultratar®	3-6 h	8-24 h	28 h
Ultralow Humulin®	3-6 h	8-16 h	36 h

*Analog obtained from the union of insulin lispro to protamine; **only injectable preparations are available.

TABLE 8. Multiple-dose insulin regimens

Breakfast	Lunch	Dinner
Fast	Fast	Fast+intermediate*
Fast+intermediate	Fast	Fast+intermediate*
Fast+intermediate	Fast+intermediate	Fast+intermediate*
Fast	Fast	Fast+prolonged
Fast+prolonged	Fast	Fast

*Intermediate action insulin can be administered before dinner or at bedtime.

TABLE 9. Protocol for the treatment of diabetic patients undergoing major surgery

1. Prepare an insulin solution with 0.5 U/mL fast action insulin (250 U of regular insulin in 500 mL of saline solution) and administer by infusion pump.
2. Infuse 5% glucose solution (GS) by pump. *In patients at risk of volume overload, infuse 50% of GS by central venous catheter.
3. Determine glucose concentrations in capillary blood at 1-h intervals.
4. Adjust infusion using hourly glycemia determinations, according to the following scheme:

Glycemia (mg/dL)	Insulin infusion, mL/h	5% GS infusion, mL/h	50% of GS infusion,* mL/h
<70	1	150	25
71-100	2	125	22
101-150	3	100	20
151-200	4	100	17
201-250	6	100	12
251-300	8	75	10
>300	12	50	0

TABLE 10. Control of diabetes on the day of a minor surgical intervention or invasive diagnostic procedure

Intervention that requires fasting	Intervention that does not require fasting												
<ol style="list-style-type: none"> 1. Do not administer the morning dose of insulin or oral antidiabetic 2. Determine capillary blood glucose every 4-6 h 3. Administer fast action insulin subcutaneously every 4-6 h according to the following scheme: <table border="1"> <thead> <tr> <th>Glycemia (mg/dL)</th> <th>Insulin (U)*</th> </tr> </thead> <tbody> <tr> <td><150</td> <td>0</td> </tr> <tr> <td>151-200</td> <td>2</td> </tr> <tr> <td>201-250</td> <td>3</td> </tr> <tr> <td>251-300</td> <td>5</td> </tr> <tr> <td>>300</td> <td>6</td> </tr> </tbody> </table> <ol style="list-style-type: none"> 4. Administer the usual dose of insulin or oral antidiabetic when the patient begins to eat lunch again 	Glycemia (mg/dL)	Insulin (U)*	<150	0	151-200	2	201-250	3	251-300	5	>300	6	<ol style="list-style-type: none"> 1. Given the normal morning dose of insulin or oral antidiabetic 2. Determine blood glucose and administer 4-8 U of fast action insulin subcutaneously if glycemia >250 mg/dL 3. Administer the next dose (lunch or dinner) of insulin or oral antidiabetic according to the usual dose and schedule
Glycemia (mg/dL)	Insulin (U)*												
<150	0												
151-200	2												
201-250	3												
251-300	5												
>300	6												

*The dose of insulin will depend on the amount of insulin that the patient usually requires. For example, a type 2 patient who requires <50 U of insulin per day or oral antidiabetics can be controlled with these doses, whereas a type 1 or type 2 diabetic patient who requires more than 50 U/day of insulin would need higher doses.

diagnosed for the first time. The stress-induced hyperglycemia that accompanies AMI is associated with an increment in intrahospital mortality in both diabetics and nondiabetics.⁹⁹ The therapeutic approach should aim at achieving glycemia values of 100-150 mg/dL (5.5-8.3 mmol/L). Hypoglycemia must be avoided because of the important cardiovascular risks in the period immediately after AMI. The catecholamine discharges caused by insulin-induced hypoglycemia have an arrhythmogenic potential that can be fatal during the phase of increased myocardial irritability that accompanies infarction.

In a prospective study (DIGAMI Study Group) it has been demonstrated that the energy control of glycemia achieved by infusing glucose, insulin and CIK (GIK) in the period immediately after AMI significantly improves long-term survival.^{100,101} Similar results have been communicated in nondiabetic patients,¹⁰² so this beneficial effect of GIK perfusion cannot be attributed to an improvement in glycemic control. The pathophysiological mechanisms by which GIK infusion improves post-AMI survival are not exactly known. Nevertheless, it should be noted that free fatty acids, the substrate of choice for the healthy myocardium, are toxic for the ischemic myocardium. Free fatty acids can injure the membrane of cardiac cells and cause a calcium overload and arrhythmias.¹⁰³ In addition, in studies of experimental animals it has been demonstrated that free fatty acids increase oxygen demand by the ischemic myocardium and reduce myocardial contractility.¹⁰⁴ Insulin administration reduces circulating free fatty acid levels and facilitates myocardial glucose uptake. In addition, it reduces protein degradation of the myocardium and coagulability by reducing thromboxane A2 production and PAI-I activity.^{105,106} Evidently, all of this would be beneficial for the myocardium and could explain why patients treated with an intrave-

nous infusion of GIK have a better evolution, but studies confirming the mechanisms involved in this cardioprotective effect are lacking.

Treatment during surgery

The treatment to be applied during the perioperative period will depend on the type of diabetes, degree of previous glycemic control, treatment that the patient is receiving, and type of surgery.¹⁰⁷ Patients with previous insulin treatment will always be given glucose and fast-acting insulin. Nevertheless, in patients not treated with insulin it is not usually necessary to administer insulin for minor surgery or noninvasive diagnostic processes, although it may be required for major surgery. In major surgery, when insulin treatment is needed, the most advisable approach is continuous intravenous insulin administration, which allows more exact and faster glycemia adjustments. Nevertheless, this requires hourly capillary blood glucose determinations to regulate the rate of infusion of glucose and insulin. Another alternative that could be indicated in patients with acceptable metabolic control before surgery, especially when strict monitoring cannot be guaranteed, is to administer subcutaneous insulin every 4-6 h in combination with the infusion of glucose solution. In any case, it should be remembered that the aim of treatment is not to achieve normoglycemia, and target blood glucose levels of 125 to 200 mg/dL are recommended in the perioperative period. Examples of protocols for major and minor surgery are shown in Tables 9 and 10.

Recently, it has been demonstrated that intensive treatment with insulin (GIK infusion to maintain a blood glucose level of 80-110 mg/dL) significantly reduces the morbidity and mortality of critically ill surgical patients.¹⁰⁸ Nevertheless, the mechanisms implicated in this beneficial effect of GIK treatment, which is unrelated to the existence of a previous history of diabetes, still have to be clarified.

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