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Current medical treatment of diabetes type 2 and long term morbidity: how to balance efficacy and safety?

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Abstract

Current medical treatment of type 2 diabetes mellitus (T2DM) requires special attention to different comorbidities that often are associated with hyperglycemia, such as overweight or obesity, dyslipidemia, hypertension, microvascular or macrovascular complications, etc. .. The control of these factors risk to health is as important as the glucose control in diabetes type 2, it is essential for the antidiabetes drugs consider these risk factors. The consensus statement published by the ADA/EASD and AACE emphasizes that the potential effects of antidiabetes medications on CV risk factors besides hyperglycemia (ie, overweight/obesity, hypertension, and dyslipidemia) should be considered in pharmacotherapy selection. Since T2DM is a progressive disease with worsening HbA1C values over time, monotherapy, even with different agents, will eventually fail to maintain the glycemic target. Because insulin resistance occurs in a variety of organs and tissues, many patients may achieve fasting glycemic control but develop postprandial hyperglycemia. Other issues include the risk for hypoglycaemia or weight gain with traditional glucose-lowering medications. The AACE/ACE algorithm for glycemic control is structured according to categories of HbA1C and suggests an HbA1C goal of ≤6.5%, although that may not be appropriate for all patients.42 The algorithm recommends monotherapy, dual therapy, or triple therapy based on initial HbA1C level of 6.5% to 7.5%, 7.6% to 9%, and >9% and reserves initiation of insulin therapy until treatment with oral or other injectable agents has failed. GLP-1 receptor agonists and DPP-4 inhibitors are novel options to improve glycemic control and reduce the incidence of weight gain. Combination therapy with newer and traditional agents improves glycemic control with a low incidence of hypoglycemia.

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Key words: *Diabetes type 2. Comorbidities. Antidiabetes medications.*

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TRATAMIENTO MÉDICO ACTUAL DE DIABETES TIPO 2 Y MORBILIDAD A LARGO PLAZO: ¿CÓMO EQUILIBRAR EFICACIA Y SEGURIDAD?

Resumen

El tratamiento médico actual de la diabetes mellitus tipo 2 (DMT2) requiere una especial atención a las distintas comorbilidades que a menudo aparecen asociados a la hiperglucemia, como por ejemplo el sobrepeso u obesidad, la dislipidemia, la hipertensión, las complicaciones microvasculares o macrovasculares, etc.. El control de estos factores de riesgo para la salud es tan importante como el control de la glucosa en la diabetes tipo 2, por lo que es fundamental que los medicamentos contra la diabetes tengan en cuenta estos factores de riesgo. La declaración de consenso publicado por la ADA (American Diabetes Association) / EASD (European Association for the Study of Diabetes) y la AACE (American Association of Clinical Endocrinologists) hace hincapié en que los efectos potenciales de los medicamentos antidiabéticos sobre los factores de riesgo cardiovascular, el sobrepeso/obesidad, hipertensión y dislipidemia, deben ser considerados en la selección del tratamiento farmacológico. Dado que la DM2 es una enfermedad progresiva con empeoramiento de los valores de HbA1c en el tiempo, la monoterapia, aunque sea con diferentes medicamentos antidiabéticos, a largo plazo será incapaz de mantener el objetivo glucémico. Debido a que la resistencia a la insulina se produce en una gran variedad de órganos y tejidos, muchos pacientes pueden conseguir el control glucémico en ayunas pero desarrollar hiperglucemia postprandial. Además, algunos fármacos llevan asociados riesgos adicionales como hipoglucemia o aumento de peso. La AACE/ACE han establecido un algoritmo para el control glucémico que se estructura de acuerdo a los niveles de HbA1C y sugiere un objetivo para los valores de HbA1C ≤ de 6,5%, a pesar de que puede no ser apropiado para todos los pacientes. El algoritmo recomienda monoterapia, terapia doble, o triple terapia basada en el nivel inicial de HbA1C de 6,5% a 7,5%, 7,6% a 9%, y > 9% y se reserva el inicio de la terapia con insulina hasta que el tratamiento con agentes orales u otros agentes inyectables no sea efectivo. Los agonistas del receptor de GLP-1 e inhibidores de la DPP-4 son nuevas opciones para mejorar el control glucémico y reducir la incidencia de aumento de peso. La terapia combinada con agentes nuevos y tradicionales mejora el control glucémico con una baja incidencia de hipoglucemia.

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Palabras clave: *Diabetes tipo 2. Comorbilidades. Fármacos antidiabéticos.*

Introduction

The latest reports from the International Diabetes Federation (IDF) reveal that currently 366 million people have diabetes, 4.6 million deaths are due to diabetes and millions of euros are spent on care for diabetes *(http://www.idf.org/global-diabetes-plan-2011-2021)*. Despite all efforts to control the disease, microvascular complications such as retinopathy, nephropathy and neuropathy are quite common and cardiovascular disease remains the leading cause of death in patients with type 2 diabetes mellitus (T2DM). Consequently, the treatment of diabetic comorbidities like obesity, hypertension, hyperlipidemia, subclinical inflammation and hypercoagulability assumes major importance and must be coordinated with good glycemic control for morbimortality reduction in type 2 diabetes mellitus.

Evaluating the magnitude of the problem

Complex pathophysiology and difficult management

Unlike what occurs in type 1 diabetes mellitus treatment based on the combination of insulin replacement, diet and exercise, T2DM is highly heterogenous, depending on the patient characteristics and the disease evolution stage. Treating type 2 diabetes patients ranges from the non-use of drugs (only dietary treatment and exercise) to the use of different types of drugs (oral or parenteral) or insulin, all alone or in some combinations.

There are some clinical clues, phenotypic changes and laboratory data that can help us to identify the main physiopathological mechanism underlying each specific patient in the clinical practice. These signs can help us to deem the disease evolution stage of each patient, in order to choose the most appropriate therapy. Weight status (obese or normal weight) is one of the most important determinants of therapy, since insulin resistance secondary to overweight is present in more than 80% of patients with T2DM. So that, most of diabetic patients will need an insulin sensitizer (metformin), besides diet and exercise, as the first line therapy approach. Time from diagnosis of T2DM is a very good predictor of residual insulin secretion; the longer the evolution, the lower the insulin reserve. When a patient is diagnosed of T2DM there is already a loss of beta cell mass and function between 30 to 70%. The combination of normal-low weight (suggesting minimal insulin resistance), long history of diabetes (more than 5 years) and high basal HbA1c values, is a very good indicator of advance beta cell loss and dysfunction and indicates that we should use not only an insulin sensitizer but a secretagogue from the beginning (dual therapy) or insulin, if the patient is symptomatic (poluric and losing weight).[1,2,3]

Accordingly with the ADA/EASD 2012 Position Statement on the Management of Hyperglycemia in T2DM[68] for most patients, initial treatment includes diet, physical activity, education and drug therapy with metfomin. If these measures are inadequate to get HbA1c bellow 7%, after 3-6 months, you should progress to combination therapy with 2 agents (Metformin plus either a sulphonylurea, GLP-1 analog, DPP4 inhibitor or pioglitazone). If necessary, during the following 3-6 months you can use a third drug or initiate basal insulin therapy in combination with oral agents. Finally, if you cant t get a good individualized metabolic control, you will need to use a complex multidose insulin approach.

Changes in treatment, based on the values of HbA1c should be early to prevent complications or delay its progression if they are already present.[4,5] Even with treatment, over 60% of patients do not achieve HbA1c normal (approx. 7%). Most should be treated with 2-3 drugs and insulin therapy schemes are increasingly more complex.[1,2,3]

Complications of type 2 diabetes

People with diabetes are at increased risk for multiple and complex complications related to macrovascular disease (coronary heart disease, stroke, and peripheral arterial disease) and microvascular disease (nephropathy, retinopathy, and neuropathy).[6,7] Diabetes complications begin early in the disease process and well before a clinical diagnosis. Patients who finally develop clinical diabetes have 2-4 times higher risk of cardiovascular disease, cardiac insufficiency and death, than those who did not develop diabetes.[8] It is well accepted that diabetic macrovascular disease is more related to coexistent insulin resistance, dyslipidemia, hypertension, hypercoagulability, endothelial dysfunction and subclinical inflammation, typical of T2DM, than due to hyperglycemia per se. One of the biggest challenges in the management of T2DM is to prevent the disease or to make an early diagnosis since by the time of its clinical appearance, patients already have some kind of dysfunction (e.g. diabetic retinopathy 20-30%, microalbuminuria 10-20%, Arterial hypertension > 50%, dyslipidemia > 66%, endothelial dysfunction 80-100%)[2] related to the complications mentioned above. Early treatment can delay the progression or reduce macrovascular and microvascular complications.[4]

How to Measure Glycemic Control?

Role of the HbA1c

Glycated haemoglobin (HbA1c) was initially identified as an "unusual" haemoglobin in patients with diabetes over 40 years ago.[69] After that discovery, numerous small studies were conducted correlating it to glucose measurements resulting in the idea that HbA1c could be used as an objective measure of glycaemic

control. The A1C-Derived Average Glucose (ADAG) study included 643 participants representing a range of A1C levels. It established a validated relationship between A1C and average glucose across a range of diabetes types and patient populations.[70] HbA1c was introduced into clinical use in the 1980s and has become a cornerstone of clinical practice.

HbA1c reflects average plasma glucose over the previous eight to 12 weeks.[71] It can be performed at any time of the day and does not require any special preparation such as fasting. These properties have made it the preferred test for assessing glycaemic control in people with diabetes. More recently, there has been substantial interest in using it as a diagnostic test for diabetes and as a screening test for persons at high risk of diabetes.[72]

A diabetic person with good glucose control as a HbA1c level that is close to or within the reference range Accordingly to for four of the major organizations involved in the control of diabetes, *American Diabetes Association (ADA), American College of Endocrinology (AACE/ACE), International Diabetes Federation (IDF) and European Association for the Study of Diabetes (EASD)* the use glycosylated hemoglobin (HbA1c) value is the best reducing risk indicator as it correlates with the appearance of micro and macrovascular complications in the long term and because it provides information on the control degree in the previous 2-4 months.

What is the Goal of HbA1c?

Lowering A1C to below or around 7% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes it is associated with long-term reduction in macrovascular disease. Therefore, a reasonable A1C goal for most adults is < 7%.

- The goal of HbA1c, according to the ADA, is ≤ 7%.[7] Failure to achieve this percentage should review and adjust the patient's treatment plan.
- The goal of EASD guidelines for HbA1c is < 6.5% for both type 1 diabetes and for type 2.[12]
- The goal of International Diabetes Federation (IDF) is < 6.5%,[13] a value that does not seem to perform better than goal of the ADA.[7]
- The goal of American College of Endocrinology is < 6.5%.

Providers might reasonably suggest more stringent A1C goals (such as,6.5%) for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Appropriate patients might include those with short duration of diabetes, long life expectancy, and no significant CVD.

Less stringent A1C goals (such as 8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, and extensive comorbid conditions and for those with longstanding diabetes in whom the general goal is difficult to attain despite self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin.[7]

The benefits of early and tight glycemic control

Landmark clinical trials have established that glycemic control is critical for the prevention or delay of diabetic microvascular complications and may also help diminish macrovascular complications of the disease. The most important studies related to diabetes control like *Diabetes Control and Complications Trial (DCCT)*[9] and its follow-up observational study, the *Epidemiology of Diabetes Intervention and Complications (EDIC) study,*[15,20] *Multifactorial Intervention Steno-2 study,*[16] *United Kingdom Prospective Diabetes Study (UKPDS)*[10] and its follow up study,[73] *Action to Control Cardiovascular Risk in Diabetes (ACCORD) study,*[17] *Action in Diabetes and Vascular Disease: Preterax and Diamicron modified release Controlled Evaluation (ADVANCE) study,*[18] and *Veterans Affairs Diabetes Trial (VADT)*, agree that an early and tight glycemic control of hyperglycemia can prevent microvascular complications.[19] Some of these studies have explored the issue of intensive blood glucose control in patients with diabetes type 2 and have also addressed whether other therapeutic options such as blood pressure reduction and/or lipid lowering can act in concert with improved glycemic control to reduce the incidence and progression of vascular complications particularly the macrovascular complications.

Studies like the *Diabetes Control and Complications Trial (DCCT)*[9] designed to evaluate the impact of an Intensive Insulin based approach to decrease HbA1c have shown that from values above 8% there is an proportional increase in micro and macrovascular complications.[9] Moreover, in the DCCT trial a reduction from HbA1C of 9% in the conventional treatment arm to 7.2% in the intensive treatment arm, decreased the relative risk for retinopathy (63%), nephropathy (54%), neuropathy (60%) and microalbuminuria. Studies such as the *United Kingdom Prospective Diabetes Study (UKPDS)*[10] demonstrated a direct relationship between the intensity of HbA1c reduction and the lowering in the risk of complications in T2DM patients. A reduction of HbA1c from 7.9% (Conventional Treatment Arm) to 7% (Intensive Treatment Arm) was translated into a 25 % reduction ($p = 0.0099$) in all microvascular complications, 22% reduction in the risk of any diabetes-related complication ($p = 0.029$), 6% decrease in total mortality ($p = 0.44$) and a 16% less incidence of Myocardial Infarction ($p = 0.052$) at the end of 8 years of active intervention.[10]

As mentioned above, there were no significant effects of blood glucose reduction on cardiovascular complications. Despite the observed effect of increased body weight with insulin and sulphonylureas, it is interesting to note that there was no increase in cardiovascular events in the intensive arm of UKPDS.

In the original UKPDS Trial patients whose body weight was more than 120% of their ideal weight could be randomised to an intensive glucose control policy with metformin instead of diet, sulphonylurea or insulin.[74] At the end of 8 years of active intervention, reductions in the risk of myocardial infarction of 39% (p = 0.01) and of death from any cause of 36% (p = 0.01) were observed.

The phenomenon of ongoing beneficial effects on diabetic complications after a period of improved glycemic control followed by a return to usual (often poorer) metabolic control was described as representing "metabolic memory" by the DCCT/EDIC investigators and as the "legacy effect" by the UKPDS investigators.[20,73] Following conclusion of original UKPDS Study, there was a post-trial monitoring to determine whether the improved microvascular outcomes observed during the active glucose control trial persisted and whether such therapy had a long-term effect on macrovascular outcomes.[73] Patients were asked to attend annual UKPDS clinics for 5 years, and all patients in years 6 to 10 were assessed through questionnaires but no attempts were made to maintain their previously assigned therapies. After 10 years of follow up (mean 18 years from initial aleatorization), the relative risk reduction in the sulfonylurea-insulin group was 9% for any diabetes-related endpoint (p = 0.04) and 24% for microvascular disease (p = 0.001) but most important, in the sulfonylurea-insulin group there were also achieved a reduction in relative risk for death related to diabetes (17%, P = 0.01), myocardial infarction (15%, P = 0.01), and death from any cause (13%, P = 0.007). In the Obese-Metformin treatment arm of UKPDS after 10 more years of follow up (for a total of 18 years), there was a drop in the risk for any diabetes-related endpoint to 21% (P = 0.01), diabetes-related death in 30% (P = 0.01), myocardial infarction in 33% (p = 0.005), microvascular disease in 16 % (p = 0.31) and death from any cause in 27% (p = 0.002).

"Metabolic memory" and "legacy effect" are terms used to describe the fact that an early and appropriate control of glucose levels has a great influence on the diabetes complications reduction and disease progression. Most patients with type 2 diabetes eventually require insulin to achieve glycemic targets. Early use of insulin therapy may help normalize blood sugar and HbA1C levels and thus improve the prognosis of the disease by preventing further vascular damage. For this purpose, the American Diabetes Association (ADA) established HbA1c values (depending on the group of patients) at which it is recommended initiation of appropriate therapy (according to their recommendations) to prevent an increase in vascular damage (table I).

Table I
Goals of glycemic control (HbA1c)

Standards of Medical Care in Diabetes 2009		
Goals of Glycemic Control (HbA1c)		
Prevention	*Hb1Ac*	*Recommendation*
Microvascular and Neuropathy: In general[1]	< 7%	A
Macrovascular: In general[2]	< 7%	B
Subgroup Strict Control[3,4]: Short duration of DM Hb1Ac low at the beginning, not CVD	6-6.5%	B
Subgroup Laxo Control[4]: Short life expectancy History of severe hypoglycaemia Advanced Microvascular Disease Long-term DM Atherosclerotic load	> 7%	C

[1] = DCCT, Stockholm Diabetes Study, UPPDG, Kumamoto.
[2] = DCCT CDIG UKPDS Follow-up.
[3] = Subgrupos de DDCT y UKPDS ADVANCE.
[4] = ACCORD, ADVANCE, VADI.
Nathan DM et al. *Diabetes Care* 2000; 12: 193.

Therapeutic management as a pathophysiological approach

The core pathophysiological defects in T2DM are marked by insulin resistance in the liver and skeletal muscle and, beta-cell failure in the pancreas. In addition to this "triumvirate," adipose tissue, the pancreatic alpha cell, the kidney, the brain, and the gastrointestinal (GI) tract play important roles in the development of glucose intolerance and hyperglycemia. The members of this "ominous octet" all have an interdependent role in the pathophysiology and the development of T2DM that represent targets for current and emerging therapies. These therapies include a range of antidiabetic drugs that are classified as:

Insulin secretagogues

– Sulfonylureas (glibenclamide, gliclazide, glipizide, glimepiride). The sulphonylureas act to enhance the sensitivity of the beta-cell to glucose and, when bound to the transmembrane sulphonylurea receptor (SUR-1), mediate the closing of the potassium-sensitive ATP channels on the cell membrane. Cellular efflux of potassium is reduced and membrane depolarisation takes place. Calcium influx is mediated by the opening of voltage-dependent Ca2+-channels that promote the release of pre-formed insulin granules which lie just adjacent to the plasma membrane. The net effect is increased responsiveness of beta cells to both glucose and non-glucose secretagogues (such as amino acids), resulting in more insulin being released

at all blood glucose concentrations. Thus, sulfonylureas are useful only in patients with some beta cell function.[75]

Insulin sensitizers

– Biguanides (metformin). Biguanides are generally considered the drugs of choice in obese type 2 diabetics. Metformin can be used in combination with any other class of oral antidiabetic drug or with insulin. The principal function of metformin is to reduce hepatic glucose production thtough a reduction in glyconeogenesis as well as glycogenolysis, and to improve peripheral insulin sensitivity, thus ameliorating hyperglycemia. So that, hepatic sensitivity to insulin is increased, thereby contributing to basal plasma glucose lowering effects. Skeletal muscle and adipocytes undergo up-regulation of the insulin-sensitive GLUT- 4 and GLUT-1 transporters to the cell membranes, thereby increasing glucose uptake and reducing postprandial glycemia.[21] Metformin has been shown to activate AMP activated protein kinase (AMPK). AMPK is a well-known serine/threonine kinase that functions as an intracellular energy sensor and has been implicated in the modulation of glucose and fatty acid metabolism.[76,77] Once activated, AMPK inhibit the expression of two key hepatic gluconeogenic genes, PEPCK and G6Pase, which, in turn, suppresses gluconeogenesis and lipogenesis while promoting both fatty acid oxidation and lipolysis.[21,76,77] Glucose metabolism in the splanchnic bed also increases. Further metabolic effects include suppression of fatty acid oxidation as well as triglyceride lowering.[21,22]

– Thiazolidinediones (pioglitazone, rosiglitazone). Thiazolidinediones (TZDs) mediate their function through binding to the PPAR-γ receptor that is expressed predominantly in adipocytes. It is expressed to a lesser extent in muscle and liver tissue. Binding of the PPAR receptor in turn mediates binding to the retinoic-X receptor (RXR-receptor). This heterodimer then binds to a nuclear response element which then switches on gene transcription. Many of the genes that are activated play a central role in carbohydrate and lipid metabolism. Interestingly, the thiazolidinediones also suppress the expression of TNF-α by adipocytes.[80]

Glycosidase inhibitors (Acarbose)

Acarbose, inhibit the activity of the glycosidase enzymes which are present in the brush border of enterocytes in the intestinal villi. Disaccharide and oligosaccharide cleavage is prevented with a net decrease in intestinal carbohydrate absorption. Overall, the α-glycosidase inhibitors reduce postprandial insulin concentrations through the attenuated rise in postprandial glucose levels.[81]

New drug modalities (Incretin based therapies)

Pharmacologic administration of GLP-1 is not practical because it is metabolized in minutes by the enzyme dipeptidylpeptidase-4 (DPP-4), but two strategies have been developed to take advantage of this hormone's beneficial properties. GLP-1 mimetics (Exenatide and Liraglutide) are protein derived injectable products, resistant to DPP4 action, that duplicate the effects of GLP-1 and demonstrate significant reductions in HbA1c in patients with type 2 diabetes. Also of interest as an incretin therapy is the use of DPP-4 inhibitors, which can be given orally and produce near-physiologic levels of GLP-1. These agents have been shown to have a prolonged inhibitory effect on DPP-4, enhancing half life of native GLP1 and GIP and stimulating insulin secretion in the presence of glucose and producing significant decreases in HbA1c. They have the added advantage of inducing moderate weight loss. Because they are peptide hormones, they have to be injected subcutaneously. There appears to be a significant frequency of nausea and vomiting with these agents, which for most patients is transient.

– Exenatide. The synthetic 39-amino acid peptide sequence overlaps with that of GLP-1, but has a longer half-life than native GLP-1. This incretin mimetic improves glycemic control mainly by stimulating glucose-dependent insulin secretion and suppressing postprandial glucagon secretion. It also delays gastric emptying, reduces food intake and facilitates weight loss.

– Liraglutide. Liraglutide has 97% homology with GLP-1 and resists DPP-IV degradation by FA acylation and albumin binding. Single-dose kinetic studies in DM2 subjects revealed a half-life of 13-14 hrs, allowing for single daily-dose administration, whereas native GLP-1 with a very short half-life of 1-3 min has limited clinical value. Liraglutide enhanced several β-cell function parameters and the enhancement was correlated with the improvement in glycemic control. The mechanisms of Liraglutide action, as expected, appear to be analogous to those exerted by endogenous incretins and others incretin mimetics like exenatide.

– DPP4 inhibitors (Vildagliptin, Sitagliptin, Saxagliptin, Linagliptin). Inhibition of dipeptidyl peptidase-IV stimulates the secretion of insulin in a glucose-dependent way, so minimising possible hypoglycemic side-effects. Inhibition of DDP-IV is dose-dependent. Recent data suggest restorative effects on pancreatic islet cells, thereby fuelling the hope that the DDP-IV inhibitors could potentially slow or reverse the course of beta-cell failure.[23,24] These drugs can be used as monotherapy in type 2 diabetes or in combination with metformin, SUs, TZDs or Insulin if the existing regimen no longer provides adequate glycaemic control. Sitagliptin, Saxagliptin and Linagliptin can be taken orally once daily and Vildagliptin must be taken twice daily. All have shown to reduce HbA1C levels by a

Table II
Oral Antidiabetic Agents (OAA) effect on T2DM pathophyisiologic defects

Parámeter	*SU*	*Glinides*	*Met*	*TZD*	*I-DPP-IV a-GLP1*
Insulin secretion	⇑	⇑			⇑
Insulin resistance			⇓	⇓	
Hepatic gluconeogenesis			⇓⇓	⇓	
Hypoglycemia risk	⇑⇑	⇑	⇓		⇓
Edema and ICC risk				⇑	
Weight change	⇑	⇑	⇓⇔	⇑	⇔⇓
Gastrointestinal effects			⇑		⇑
Use in renal insufficiency	⊘	⇔	⊘	⇔	⇑

SU = Sulphonylareas; TZD = Thiazolidinediones.

mean of 0.6-1%. Since the best predictor of hypoglycaemic effect of any drug is basal level of HbA1c, all DPP4-inhibitors can decrease HbA1c up to 3% if the A1C is high enough. Unlike the GLP-1 analogues, they have no effect on weight, but have the advantage of not being associated with the occurrence of nausea.

Algorithm for glycemic control according to HbA1c

The AACE/ACE algorithm for glycemic control is structured according to categories of HbA1C and suggests an HbA1C goal of ≤ 6.5%, although that may not be appropriate for all patients.[25] The algorithm recommends monotherapy, dual therapy, or triple therapy based on initial HbA1C level of 6.5% to 7.5%, 7.6% to 9%, and > 9%. Insulin therapy can be initiated as first-line treatment if the patient is symptomatic and A1C > 9% ("rescue insulin") or later on when treatment with oral or other injectable agents have failed.[26]

Initial treatment in T2DM with diet and physical activity is very common insufficient for blood glucose control, so that, at the time of diagnosis most patients will need pharmacological therapy with metformin or other drugs if the patient is metformin intolerant or has a contraindication for its use. After about 3 to 6 months without getting an acceptable metabolic control, a dual oral drug treatment must be established. The best predictor of the antidiabetic effect of any drug is basal hyperglycemia level and there is a difference in the potency and efficacy of distinct hypoglycaemic agents.[27] Therefore, insulin should always be considered when the patient has severe hyperglycemic symptoms, fasting glucose above 300 mg/dl or when he is ketotic. Frequently once achieved acceptable metabolic control with insulin and due to the resultant reduction of glucotoxicity and improvement in insulin sensitivity and secretory capacity, the use of insulin can be suspended and replaced with oral drugs. When initiating oral monotherapy treatment, up to 30% of patients respond inadequately. This phenomenon, known as "primary failure" and attributed initially only to sulphonylureas, has also been reported with other oral agents and is related to the degree of hyperglycemia and duration of diabetes.[28] In most cases, however, we can achieve an acceptable control that can last several years and thereafter there is a progressive metabolic control deterioration independently of the drug used. This phenomenon, known as "secondary failure" is due to a progressive loss of insulin secretion (Beta cell apoptosis) which is part of the natural evolution of T2DM, commonly genetically determined. It is estimated that up to 10% of patients/year fail to respond to monotherapy.[10,29,30,31,32] Most patients sooner or later, will need combination therapy with 2 or more drugs and finally with insulin since a heterogenous disease like diabetes mellitus, with multiple pathophysiologic dysfunctions, can t be addressed with one single drug that do not correct theses multiple deffcets (table II).

The justification for combination therapy is based not only to the high incidence of long term monotherapy failure, but in fact, supported by several studies; it is feasible to use the synergistic effect of different drugs action mechanisms.[5,33] A study has been shown that combination therapy with OAAs is more effective than intensified monotherapy.[34] In combination therapies, we must consider the use of new drugs based on the incretins (GLP-1 mimetics and DPP-IV inhibitors).

Among the defects that are involved in the pathophysiology of T2DM are abnormalities in the secretion of the incretin hormones GLP-1 and the glucose-dependent insulinotropic polypeptide (GIP).[35] GLP-1 and GIP are small peptides, having 30 and 42 amino acids and released by the enteroendocrine L cells located in the distal ileum and colon and by the K cells in the duodenum, and proximal jejunum respectively. Both rapidly stimulate the release of insulin only when blood glucose levels are elevated, thereby enhancing the glucose-sensing and insulin secretory capacity of the beta cells.[36] GLP-1 controls blood glucose via other actions besides stimulating glucose-dependent insulin release, and it is by inhibiting glucagon secretion and suppression of hepatic glucose output as well as by decreasing the rate of gastric emptying. On the other hand, GIP decreases gastric emptying to a much lesser degree and does not inhibit glucagon secretion.[36,37] GLP-1 also activates regions in the central nervous system important for control of satiety.[38] However, GLP-1 and GIP have also been shown in preclinical studies to exert significant cytoprotective and proliferative effects on the islets of Langerhans.[36,39,40] The incretin hormones elicit their actions through direct activation of distinct G protein-coupled receptors expressed on islet β-cells.[40] The short circulating half-life of bioactive intact GLP-1 and GIP initially limited enthusiasm for the potential use of incretin hormones in the treatment of diabetes. However, incretin analogs have been developed with significantly increased half-lives due to modification of the DPP-IV cleavage site and/or conjugation to large circulating proteins, such as albumin (i.e., liraglutide) or by inhibiting the DPP4 enzymes and prolonging endogenous GLP-1 and GIP. Nowadays, the majority of pharmacological efforts to develop incretin-based therapies are focused on GLP-1R agonist and DPP-IV inhibitors.

It is well accepted that the GLP-1R agonist liraglutide has more efficacy in lowering A1c than exenatide. In a head to head study liraglutide decreased A1c 0.3% more than exenatide with less nausea and with modest but more weight loss.[78] Single-dose studies of DPP-IV inhibitors, sitagliptin, saxagliptin, linagliptin and vildagliptin indicate that all compounds have similar clinical efficiency in reducing glucose excursion after oral glucose administration.[41,79] The use of these new drugs in monotherapy and combination therapy with metformin, sulphonylureas or TZDs, have shown at least not be inferior to the results obtained with the traditional antidiabetic drugs.

Balancing Efficacy *vs.* Safety of Oral Antodiabetic Agents (OAAs)

OAAs are by definition the starting point of pharmacologic treatment of T2DM. The modes of action of the five classes described are different, and offer an opportunity to "tailor treatment" addressing the likely pathogenetic mechanisms involved in this heterogeneous disease. "Failure" of one level of treatment should be monitored for at all times by appropriate checks on well being, fasting and post prandial blood glucose (self-monitoring), HbA1c, safety issues like weight, hypoglycaemia, edema and G-I tolerance (nausea, diarrhea, flatulence.

Cardiovascular safety of OAAs

Probably, the most important safety aspect is long term cardiovascular effects. A "safe OAAs" at least, should not increase CV risk. On the long term, insulin in Type 1 DM (DCCT / EDIC Trial);[20] sulphonylureas (UKPDS-FU Study, ADVANCE, VADT Trial),[18,19,73] metformin (UKPDS Obese-Metformin Arm),[74] and insulin in T2DM[73] have demonstrated CV safety in the treatment of hyperglycemia.

Hypoglycemia as a limiting factor in the treatment of T2DM

Glucose counterregulatory mechanisms have generally been found to be intact early in the course of type 2 diabetes.[51,52] However, as also noted above, iatrogenic Hypoglycemia becomes progressively more limiting to glycemic control over time,[47,53] and the frequencies of severe iatrogenic hypoglycemia have been reported to be similar in type 2 and type 1 diabetes matched for duration of insulin therapy.[54] Given progressive insulin deficiency in type 2 diabetes,[47] these findings indicate that iatrogenic hypoglycemia becomes a progressively more frequent clinical problem as patients approach the insulin-deficient end of the spectrum of type 2 diabetes.

In T2DM treatment, incidence of hypoglycemia is very difficult to predict due to the extreme heterogeneity of these patients, age, diabetes duration, renal function, treatment modality but what quite certain is that with sulphonylureas, meglitinides and insulin use, there is an increased risk.

In UK Hypoglycaemia Sludy Group trial,[55] about 7% of people with type 2 diabetes who were followed for an average of 8 yeras, had experienced at least one episode of severe hypoglycaemia in the first 2-3 years of insulin therapy, a proportion similar to those treated with sulfonylurea.[56] A retrospective study has reported 15% severe hypoglycemic episodes in type 2 insulin treated patients directly related to the duration of insulin use > 5 years.[57] People with type 2 diabetes constitute a disparate group, the ability of each patient to secrete glucagon in response to hypoglycaemia being related to the degree of insulin deficiency.[58] Glucagon secretion was almost absent in type 2 diabetic patients who exhibit total insulin-deficiency. By contrast, glucagon secretion is intact in OAAs-treated patient and in type 2 diabetic patients who have

recently started insulin. These patients do not experience hypoglycaemia more frequently than patients taking SU at similar HbA1c levels.[10] In a retrospective cohort of Medicaid patients, recent hospital discharge was the strongest predictor of subsequent hypoglycaemia in SU or insulin treated patients aged ≥ 65 years.[59] In the Fremantle Diabetes Study severe hypoglycaemia frequency was studied in older patients with cognitive impairment.[60] Hypoglycaemia requiring health services assistance was three times higher in patients with cognitive impairment or dementia. These patients were older, 76 4.6 years, 27.5% treated with insulin + OAD and 45% by SU, 46.4% having an HbA1c ≤ 7%. Dementia was present in 9.3% and cognitive impairment without dementia in 19.9%. Summarising, many studies support that the risk factors for hypoglycaemia with the treatment of T2DM patients are: older age, duration of diabetes, decreased food intake, unhealthy lifestyle habits, depression, cognitive dysfunction, dementia, fragile low weight patients, exercise, alcohol use, renal impairment, and use of secretagogues (sualphnylueas, meglitinides) and insulin.[61,68]

Other potential adverse effects of OAAs

– Sulphonylureas (SUs): Hypoglycemia is the most troublesome side-effect. It is very important to keep in mind that since all sulphonylureas are highly bound to plasma proteins, they can potentially interact with other protein-bound drugs. Displacement from plasma proteins because of drug interactions has been implicated as a cause of severe SU-induced hypoglycaemia. This adverse effect is more likely in the presence of impaired renal function and in the underweight elderly patient. Use of the sulphonylurea types that bind the SUR-2 A and B receptors (glibenclamide, glipizide, glimepiride) should be avoided in high-risk patients suspected of having significant coronary artery disease CAD.[43,44] Another side-effects that have been described include, weight gain (1-4 kg over 6 months), skin reactions, acute porphyria and, rarely, hyponatraemia.[45,46] There have been reports in the literature of glimepiride-induced acute cholestatic hepatitis.[47]

– Thiazolidinediones (TZDs): The main negative effect related to use of TZD is the fluid retention. Which includes several potential mechanisms such as increased vascular permeability, decreased urinary sodium excretion, increased sympathetic tone and altered interstitial ion transport? It has also been postulated that TZDs may actually unmask previously undiagnosed cardiac dysfunction owing to their effects on salt and water retention.[48] The use of TZDs in patients with New York Heart Association (NYHA) class III or IV heart failure is not recommended in view of the side-effects of fluid retention and weight gain. There are studies showing an increased risk of bone fractures in women.[49] The TZD effect on bone appears to be an inhibition of osteoblast differentiation, with a resultant negative effect on cortical bone formation without a change in bone resorption.

– Biguanides: Side-effects of these drugs can include lactic acidosis. Metformin increases lactate production in the splanchnic bed and portal venous system due to a reduction in the activity of pyruvate dehydrogenase enzyme, thereby shifting the metabolism towards the anaerobic spectrum. However, the incidence of metformin induced lactic acidosis is rare, with only 0.03 cases per 1,000 patient-years reported in the literature. Abdominal discomfort and diarrhoea are the most frequent side-effects. Vitamin B12 deficiency owing to decreased GUT absorption can occur.[50] Its gastrointestinal side effects are made worse usually by too large a dose initially, and increasing doses too quickly.

– Glucosidase inhibitors: Exist a high rate of gastrointestinal intolerance to these drugs, perhaps related to prescribing too large a dose initially, not taking it with appropriate meals and increasing the dose too quickly. Side-effects include flatulence, abdominal discomfort and diarrhoea, but tolerance of the side-effects quickly develops. Hypoglycaemia can occur only if used in conjunction with a sulphonylureas, meglitinides or insulin.

Selection criteria for hypoglycemics drugs

The management of patients with type 2 diabetes has been given a firm evidence base in recent years through the results of randomised clinical trials, notably the UKPDS. An improved understanding of the pathogenesis and natural history of this complex metabolic disorder has facilitated the application of new therapeutic agents. Attainment and maintenance of near-normal glycemic control, while minimising the risk of iatrogenic hypoglycaemia, is a central long-term objective of therapy; however, this is often difficult to achieve in practice. Many outcomes besides HbA1c are important when evaluating and comparing oral diabetes medications, such as blood pressure control, weight and lipid changes, adverse events, quality of life, micro and macrovascular disease, and mortality. It is critical to evaluate adverse events, since these affect adherence as well as morbidity and mortality. Additionally, certain diabetes medications may be less safe for patients with certain comorbid conditions.

Evidence based medicine (EBM) shows that most diabetes medications reduced HbA1c levels to a similar degree. Metformin, TZDs, GLP-1 mimetics and SPU are more effective than other medications (acarbose, meglitinides, DPP4-i) as monotherapy as well as when used in combination.[68] Metformin has a beneficial trend in body weight, blood pressure and plasma lipid levels. It was difficult to draw conclusions about the comparative effectiveness of type 2 diabetes medications on all-cause and cardiovascular mortality,

cardiovascular and cerebrovascular morbidity, and microvascular outcomes because of low-quality of the trials or because of insufficient evidence. EBM shows that the risk for hypoglycemia with sulfonylureas exceeds the that of metformin or thiazolidinediones and that the combination of metformin plus sulfonylureas is associated with 6 times more risk for hypoglycemia than the combination of metformin plus thiazolidinediones. Moderate-quality evidence shows that the risk for hypoglycemia with metformin and thiazolidinediones is similar. Metformin is associated with an increased risk for gastrointestinal side effects. Thiazolidinediones are associated with an increased risk for heart failure, and both rosiglitazone and pioglitazone are contraindicated in patients with serious heart failure.[62,63]

Surgical Approach of T2DM

Today, the most common surgical procedures are performed laparoscopically and include adjustable gastric band (LAGB), sleeve gastrectomy (LSG), Roux-en-Y gastric bypass (RYGB), One Anastomosis Gastric By-pass (BAGUA) and biliopancreatic diversion (BPD). BPD often includes duodenal switch (BPD/DS) and sleeve gastrectomy. RYGB, BAGUA and BPD show the best long-term results in terms of fat loss[64,65] and diabetes resolution.[66] Whereas LAGB and LSG exert their effects through mechanical gastric volume and food intake reduction, RYGB and BPD (with sleeve gastrectomy) combine this effect with malabsorption of nutrients by means of bypassing a substantial part of the small intestine. In addition, the intestinal reconfiguration results in a rapid improvement of diabetes within days in most patients, which cannot be entirely ascribed to energy restriction or fat loss.

Bariatric surgery has been demonstrated to have an extremely beneficial effect on T2DM. There are at least two distinct mechanisms for this effect. In the early postoperative period following operations involving gastrointestinal bypass (RYGB biliopancreatic diversion with/without duodenal switch) and probably sleeve gastrectomy, there is an increase in the incretin response, which leads to augmentation of insulin secretion from beta cell mass. This effect is independent of weight loss. In later follow-up, progressive weight loss from any bariatric procedure leads to improved peripheral insulin sensitivity.

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