Non-insulin therapy of type 2 Diabetes Mellitus: advantages...

Carla Silva, Zélia Lopes, J.A. Freire Soares

Abstract

Diabetes mellitus (DM) is a chronic disease that is increasing in prevalence worldwide. The therapeutic agents available for the treatment of this disease have increased significantly in the last decade, which is reflected in the clinical practice by more therapeutic options and the need to make increasingly complex decisions. The authors present a review of the mechanisms of action, side effects, efficacy and advantages of each class of drugs.

Key words: α-glucosidase inhibitors, secretagogues, biguanides, thiazolidinediones, incretin mimetics, DPP-IV inhibitors.

INTRODUCTION

Diabetes mellitus (DM) designates a group of metabolic disorders that share a common phenotype: hyperglycemia. There are various etiologies underlying this process, resulting from the interaction of genetic and environmental factors. Metabolic deregulation secondary to sustained hyperglycemia causes a progressive increase in resistance to the action of insulin in the peripheral tissues, and stimulation of hepatic neoglucogenesis, effects that induce physiopathological alterations in multiple organs and systems. The result of this process is the appearance of late complications that severely impair quality of life and survival of patients, as well as having high social and economic costs, imposing a heavy burden on individuals and society. With increasing prevalence and incidence, type 2 DM will continue to be one of the main causes of morbidity and mortality.

PHYSIOPATHOLOGY OF TYPE 2 DIABETES MELLITUS

Type 2 DM (DM2) is a metabolic disorder characterized by two major defects which complement and potentiate each other: reduction of insulin secretion by the pancreas β-cells and insulin resistance in the peripheral tissues (muscles, liver and adipose tissue), resulting in an inability to utilize glucose.

Various factors seem to contribute to its genesis: genetic factors, other associated pathologies – arterial hypertension, dyslipidemia, excessive visceral adipose tissue – as well as endovascular factors – stimulation of platelet aggregation, activation of vascular inflammation, endothelial dysfunction and early atherosclerosis. The molecular mechanisms of insulin resistance are not entirely defined. Multiple defects in the signaling processes of the transmembrane and/or intracell receptors of various organs and systems form the molecular basis of these events, generating, as a whole, a harmful environment of glucotoxicity, which is, in itself, self-potentiating.[1]

The β-cell represents a sustained elevation of glycemic values with a permanent state of hyperinsulinemia, which in the long term induces functional failure. The disease, therefore, is the result of the joint action of an environment of glucotoxicity, lipotoxicity, and chronic inflammation, associated to a genetic basis.

Diagnosis of DM2 is frequently made, whether just a few years or decades after the onset of insulin-resistance, in a late phase of evolution of the disease, when about half of the cases already present micro- and macrovascular complications associated with the disease itself.

Numerous studies have proven that the complications can only be prevented though proper glycemic control. A study by the United Kingdom Prospective Diabetes Study (UKPDS), in particular, demonstrated showed that a reduction of just 1% in the value of glycated hemoglobin (Hg A1c) is associated with a 21% reduction in the risk of micro- and macrovascular complications.[2] On the other hand, the American

Department of Medicine – Internal Medicine Service
Tâmega e Sousa Hospital Center, EPE –Padre Américo Unit
Received for publication on 20th October 08
Accepted for publication on 10th April 09

Diabetes Association (ADA) considers that Hg A1c values higher than 7% favor the emergence of these complications, and it therefore recommends that the therapeutic goal should be to lower these values, and keep them low.[3]

ORAL ANTI-DIABETIC AGENTS

The initial treatment of DM2 involves not only the establishment of an appropriate nutritional plan, but also a regular physical exercise program and the institution of a drug therapy in increasingly earlier stages of the disease.

The therapeutic agents available are varied and multiple, enabling action on various phases of the dysglycemia. Advances in DM2 therapy have continued to focus on the use of oral administration agents, which act in the different underlying pathological processes of the disease.

The therapeutic classes of oral antidiabetic agents now available include: α – glucosidase inhibitors, secretagogues, biguanides, thiazolidinediones and PPAR α/γ receptor agonists.

α-glucosidase inhibitors

α-glucosidase inhibitors have been available since 1990. Their single representative in Portugal is acarbose. Arcabose does not act on any physiopathological mechanism specific to diabetes. It acts competitively inhibiting the α–glucosidase of the enterocyte brush border, an enzyme that breaks down oligosaccharides and disaccharides into monosaccharides, a form in which they are absorbed by the intestinal lumen. In doing so, it delays and reduces the absorption of monosaccharides into the bloodstream, reducing the postprandial glycemia levels. Its effect is predominantly enteric and depends on the glycemic intake, therefore they do not induce the emergence of hypoglycemia. It reduces the Hg A1c value by 0.5%-1.0%, resulting in an efficiency that is clearly lower than that of most oral antidiabetic agents.[4]

The use of α – glucosidase inhibitors is recommended in combined therapy for diabetic individuals with high postprandial glycemia values, potentiating the effect of other drugs.

Since their action takes places at intestinal level, they can cause the emergence of gastrointestinal disorders in about 20% of patients (flatulence, abdominal discomfort, diarrhea and bloating). These effects that are minimized by their administration in low, gradually titered doses. Their use is contraindicated in the presence of intestinal inflammatory disease, irritable bowel, or in cases of moderate to severe renal and hepatic insufficiency.

Secretagogues

Secretagogues include sulfonylureas and the biguanides, available since 1955 and 1998, respectively. This type of antidiabetic agent acts on the insulin secretion mechanisms that release endogenous insulin, sharing the same action mechanism, differing only in the binding site with the receptor.

Sulfonylureas activate the ATP channel, which is sensitive to K+ of the β cells. Its binding to the SUR1 receptor of the tetrameric transmembrane protein closes it, stopping the efflux of potassium and stimulating the influx of calcium, which enables the exocytosis of the pre-formed insulin vesicles.

Sulfonylureas exert their insulin secretion capacity independently of the serum glycemic value, therefore they easily induce hypoglycemia, but they do not interfere in the peripheral sensitivity of tissues to insulin. They are recommended as a first line therapy in non-obese individuals recently diagnosed with DM2, and who still present capacity to produce residual insulin. Sulfonylureas enable Hg A1c values to be reduced to levels of between 1.0 and 1.5%. Their metabolism process is liver-based and they are eliminated mainly by the kidneys. They should therefore be avoided in patients with moderate to severe hepatic insufficiency, and are contraindicated in patients with severe renal insufficiency. The second generation of these drugs shows a better safety profile, better pharmacokinetic, and less side-effects compared to the first generation.

Metiglinides stimulate the SUR-1 transmembrane receptor in its benzathine locus, promoting the exocytosis of insulin granules through the same mechanism as sulfonylureas. Repaglinide and nateglinide have been commercialized since 1998 and 2001, respectively.

Metiglinides have a faster onset of action in sensitizing the receptor, but a shorter half-life than sulfonylureas, resulting in a more ephemeral release of insulin granules, and consequently a lower risk of hypoglycemia. This characteristic enables it to be easily adapted to meal times, hence they should be administrated after eating, according to the amount of food ingested. Their efficiency is demonstrated in

inter- and postprandial glycemic control, reducing Hg A1c by 0.5 to 1.0%.[5]

The efficacy of secretagogues is ephemeral, as they gradually induce the failure of β cells and the consequent inefficiency of these cells.[6] They also have no recognized benefit in the prevention of cardiovascular events, this fact being probably attributed to the sustained hyperinsulinemia that they induce, which is frequently associated with increased body weight. They even suggest increased risk for events, with a harmful action on the myocardium in the context of ischemia. The UKPDS showed a reduction of microvascular complications, but did not demonstrate any benefit in any of the cardiovascular parameters evaluated – mortality and prevention of macrovascular complications.[2]

Biguanides

In the 1920s and 1930s, guanidine derivatives, precursors of the biguanides, were used in the treatment of DM2, but these had major side effects. The biguanides, synthesized in 1929 were introduced as antidiabetic drugs between 1957 and 1959. Only metformin continued, after decades of experiments and evaluation of the safety profile, in which it was proven to reduce hepatic gluconeogenesis, absorption of intestinal glucose, and peripheral resistance to insulin.[7]

Metformin activates hepatic and muscular monophosphate protein kinase (AMPK), inducing the inhibition of the acetyl-coenzyme A carboxylase and promoting oxidation of the fatty acids. The concomitant inhibition of the SREBP-1 transcription factor also enables a reduction in expression of lipogenic enzymes, the synthesis of triglycerides and hepatic steatosis. It also has a sensitizing action on the insulin intracellular transporters.

These mechanisms result in a glycemic control capable of reducing the Hg A1c values by 1.0-2.0% of the pre-treatment value, through a glucose-dependent effect, promoting weight stabilization/loss, improving lipid profile and reducing prothrombotic factors. These particularities ensured its recommendation in the UKPDS, either in the control of the metabolic syndrome or in the reduction of cardiovascular risk. [8]

Despite its good profile of tolerability, side-effects might occur, particularly gastrointestinal effects in about 15% of patients, caused by a reduction of intestinal glucose absorption (flatulence, abdominal discomfort, diarrhea, bloating), effects that are reverted with the use of gradually increased titered doses.[9]

The possibility of occurrence of lactic acidosis is a limiting effect, particularly when associated with situations that induce or promote it, and for this reason, its use is contraindicated in patients with renal insufficiency (creatinine clearance <60 mL/min), hepatic or cardiac insufficiency, severe infections and chronic alcoholism.[10,11] Metformin is not an insulin-secreting drug, and for this reason, the risk of hypoglycemia is practically non-existent if used in monotherapy.

There are few studies with a sufficiently long follow-up to enable comparison between metformin and other drugs (new sulfonylureas, meglitinides or glitazones). However, there is evidence that metformin shows better results on glycemia, body weight, lipid profile and diastolic blood pressure, particularly in patients with a high body mass index.[12] Its use is recommended in first line therapy for obese individuals with proven insulin-resistance, as well as in the treatment of type 1 DM (DM1) and DM2 in association with insulin therapy, making use of its "insulin sensitizing" effect and thereby reducing insulin need.

Thiazolidinediones

The thiazolidinediones, available since 2000, are known as "external sensitizing" agents, since they reduce glycemic levels, promoting sensitivity of the peripheral tissues to insulin, with no evidence of any capability of insulin secretion. These drugs act as synthetic ligands for PPAR γ (peroxisome proliferator-activated receptor γ) nuclear receptors of adipocytes, myocardial cells, skeletal muscle cells, and hepatocytes, which activate specific regions of the DNA. Their action induces the expression of genes of carbohydrate and lipid metabolism, synthesis of transcription factors and stimulation of the differentiation of preadipocytes into adipocytes. These effects result in the catabolism of serum triglycerides and the reduction of the amount of free fatty acids, factors that indirectly promote the use of glucose by the cells.[13] The process of adipocyte differentiation promotes redistribution of the visceral adipose tissue to the subcutaneous cell tissue, contradicting the trend in visceral obesity.

Thiazolidinediones show great efficacy in the control of hyperglycemia, reducing the HgA1c by 1.0-1.5%, through a glucose-dependent effect.[14] Besides

their hypoglycemic action and their stabilizing action on the lipid profile, thiazolidinediones interfere in many other metabolic processes, promoting a reduction in urinary excretion of albumin, lowering blood pressure, and also showing some anti-thrombotic effect, promoting fibrinolysis.[15]

The process of thiazolidinedione metabolization occurs mainly in the liver, in the P450 cytochromes, therefore their use is contraindicated in individuals with hepatic insufficiency. Their use in a therapeutic regimen requires regular assay of markers of hepatic cytolysis, and they should be discontinued the transaminase values rise to three times higher than normal levels.[16,17] However, these drugs show relative safety in patients with renal insufficiency.

From clinical experience, a tendency was observed of these drugs to promote a reduction in renal excretion of sodium and water, with consequent fluid overload and a tendency to form peripheral edema, factors that can cause a risk of cardiac decompensation in susceptible individuals. This fact is even more evident when these drugs are associated with other antidiabetic agents, therefore their use is contraindicated in individuals with class II-IV cardiac insufficiency of the NYHA.[18,19]

The pharmacodynamic evaluation and histological investigation of the action of thiazolidinedione were at the origin of a new concept: functional preservation of the pancreatic γcell, which was later associated with that of the induction of endocrine cell neogenesis. These characteristics, due to their relevance and value, started to be considered and called upon in the valuation of their clinical application, although they are still the object of investigation. Within this context, markers for evaluating the level of functionality and quantification of cell mass were identified, particularly the levels of serum insulin, HOMA-S (homeostasis model assessment) as markers of pancreatic secretion, as well as C peptide and molecular precursors on insulin (post-insulin fractions 32 and 33), as indicators of β cell funtion.[20] The reduction in levels of C peptide, the molecular precursors insulin, and in serum insulin levels, through the use these drugs, reveals the capacity to yield available insulin, avoiding overstimulation of the β cells and thereby promoting cell preservation. The PROactive study (PROspective pioglitaAzone Clinical Trial in macroVascular Events) demonstrated these data in relation to pioglitazone.[21] Similarly, the capacity of rosiglitazone to inhibiting apoptosis, maintaining cell proliferation, was also indicated. Nevertheless, it is not known whether this effect is the result of a direct action, activation of pancreatic cell PPAR γ, or an indirect action through normalization of metabolic parameters, and a consequent reduction of insulin requirements.[22]

PPAR α/γ agonists

PPAR α/γ agonists act, like the glitazones, on the PPAR. Their concomitant action in the α and γ receptors produces a reduction in insulin resistance, lipid profile optimization and reduction of body weight, characteristics that are not present in glitazones. Initial studies carried out with these drugs registered a reduction of the Hg A1c value by 1.05-1.23%, as well as a reduction of triglycerides, apolipoprotein B, LDL cholesterol and an increase in HDL cholesterol.[23,24]

The clinical use of tesaglitasar showed renal, hepatic toxicity patterns, also acting as a hematogenesis inhibitor, facts that jeopardize its clinical use.[25-26] Muraglitasar will be the first of this new class of drugs to be commercialized, and it has shown good tolerance.[27]

NEW PERSPECTIVES, NEW DRUGS

Clinical experience has shown that the different groups of effective drugs currently available not only induce, in many cases, side-effects that compromise their tolerability, but also provide conditions for a progressive loss of efficacy, since they are not capable of preserving pancreatic endocrine tissue. For these reasons, it is necessary to choose a combined therapy and/or administrate exogenous insulin. These factors have led to an ongoing need to search for and create new therapies.

Biomolecular investigation and in-depth knowledge of physiopathological mechanisms of DM2 have enabled the identification of precursors, inducers and inhibitors of this whole complex metabolic process, enabling synthesis via molecular biology of mimetics, inhibitors and genetic and molecular modelers, with the aim of creating new drugs. In recent years, various studies have been designed and carried out, some are still underway or in different stages of development, which will enable the introduction of new drugs to clinical practice. Thus, various other antidiabetic drugs are still being tested and studied. Since they represent a new approach to the treatment of DM2,

the following are highlighted: incretin mimetics, inhibitors of dipeptidyl peptidase-IV (DPP-4) and amylin mimetics.

Incretin mimetics

Incretins are peptide hormones secreted by the endocrine cells of the gastrointestinal tract, stimulated by the presence of food in the small intestine. GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (glucagon- like peptide-1) are two identified incretin hormones. Their action on the pancreatic β cells activates adenylcyclase, inducing an increase of the AMPc levels and intracellular calcium, and triggering the exocytose of insulin granules. Studies on the development of clinical application of these physiopathological mechanisms have focused particularly on the GLP-1, as it has revealed greater power of action.[28]

The effect of intestinal peptides on postprandial insulin secretion was identified after noticing that the administration of a bolus of oral glucose causes an increase in insulin level higher than that obtained by intravenous administration of the same amount of glucose. This effect is integrated to the action of the "enteroinsular axis", i.e., the production of postprandial insulin directly stimulated by neurotransmitters and incretins. This amplification of the insulin response associated with the contribution of oral glucose, was termed the "incretin effect".

GLP-1 exerts its effect on various areas: it enables active insulin secretion, triggers the transcription of genes that induce its synthesis, and inhibits the secretion of glucagon, delays gastric emptying and thereby reducing sensation of hunger and ingestion of food.[29] In addition, it maintains functional integrity and induces the proliferation of β cells, suppressing apoptosis.[30-31]

The main obstacle associated with the therapeutic use of these compounds is their short half-life after intravenous administration, since they are quickly neutralized by DPP-4 (dipeptidyl peptidase IV) - transmembrane peptidase present in lymphocyte T and B cells and free plasma, which act by cleaving proline residues.

The creation of mimetic substances and inhibitors of the GLP-1 route therefore becomes an objective.

Exatinide is a peptide of 39 amino acids, derived from the saliva of the Gila monster lizard, which mimics the action of incretins (mainly GLP-1), yet is resistant to neutralization of DPP-4. It is the first of a generation of injectable antidiabetics, with proven efficacy in glycemic homeostasis, promoting sensitivity to insulin and stabilizing the weight. The insulinotropic action of GLP-1 is glucose-dependent, being activated for values of glycemia higher than 5 mmol/l, which gives it a low risk of hypoglycemia.[32] It reduces the Hg A1c value by 0.7-1.1% and its characteristics led to its approval in combined therapy with metformin and/or sulfonylureas. Its capacity to preserve and induce the proliferation of β cells, as well as neogenesis of pancreatic islets from the precursor cells, in *in vitro* and *in vivo* models, gave it clear benefits.[33]

Available for about two years only, the initial evaluation of its tolerability and its safety profile have demonstrated good acceptance, the only undesirable effect described being higher incidence of nausea in the initial phase of treatment, which spontaneously recedes with more prolonged use.

Evaluation of the results after 82 weeks of treatment shows a reduction in Hg A1c levels in about 48% of patients, to values lower than 7%, with sustained glycemic control in the preliminary results. A progressive reduction in body weight was also evident (-4.4%± 0.3Kg).[34] Its use is contraindicated in patients with terminal chronic renal insufficiency (Creatinine clearance <30 mL/ min).[35]

Liraglutide is also a GLP-1 analogue, performing many of the endogenous actions of this incretin: It reduces fasting and postprandial hyperglycemia and suppresses glucagon production. A phase 2 trial showed a reduction in Hg A1c of 0.8%, compared with the placebo.[34]

DPP-4 inhibitors

Sitaglipine, saxagliptine and vidagliptine, are inhibitors of the proteolytic enzyme (DPP-4). Their action induces an increase of GLP-1 levels and a consequent reduction of postprandial glycemic peaks, inhibiting glucagon and the hepatic production of glucose. They also promote the process of cell regeneration and differentiation and neogenesis of the pancreatic β cells. Treatment with sitagliptin leads to an increase in the proinsulin:insulin ratio and in the capacity of β cell to produce this hormone.[36] However, it did not show any effect on the reduction of body weight or insulin-resistance, unlike the incretin mimetics. It enables the Hg A1c value to be reduced by around 0.7-1.1%, also

resulting in low hypoglycemia risk. Gastrointestinal symptoms were also the most commonly reported side effects (delay in gastric emptying, nausea and vomiting).

It may be associated with biguanides, sulfonylureas or thiazolidinediones. Its simultaneous use with compounds that present complementary action mechanisms is, without doubt, the best course of treatment. Its neutrality in relation to body weight and the low risk of inducing hypoglycemia seem to be attractive within this context. The concept of preservation and regeneration of pancreatic cells that is inherent to these drugs may lead to their use in first line therapy, even in an early phase of the disease, maintaining the good functioning of the cell tissue for as long as possible.[37] However, establishing its priority in the therapy line depends on long-term studies that will enable the durability of glycemic control to be evaluated, and its real effectiveness in preserving cell functionality.

Amylin mimetics

Amylin can be referred to as the "twin sister" of insulin, since they are segregated together in response to the hyperglycemic stimulus. A reduction in this hormone is also manifest in patients lacking insulin, whether with DM1 or DM2, with non-functioning β cells. The action of these two hormones is complementary, with amylin modulating the speed of glucose influx to the interior of the cell in the postprandial period, suppressing glucagon production and slowing gastric emptying, increasing the feeling of fullness. Amylin replacement provides better control of postprandial glycemia.

The pramlintide is a synthetic analogue of amylin, producing the same physiological effects and in an equipotent way, but contrary to the endogenous hormone, it has no tendency to aggregate insoluble particles. It has an anti-hyperglycemic and non-hypoglycemic effect, reducing the values of postprandial glycemia to intervals considered physiological. Pramlintide favors a reduction in body weight proportional to body mass index (BMI), maintaining stability in individuals with low indices, even under the concomitant effect of a restrictive diet and regular practice of physical exercises. Its efficacy enables a reduction in the Hg A1c value by 0.3-0.6 %. It is indicated as an adjuvant therapy in insulin-treated patients (together with insulin administered at mealtime), whether in association or not with sulfonylureas and/ or metformin.[38]

Hypoglycemic events, although rare, can take place in the first 4- 6 weeks of treatment, particularly in patients with DM1, coinciding with the phase of highest intolerability to the drug and the emergence of side effects (nausea, vomit, anorexia).

Replacing the amylin hormone with its analogue at meal times, as an insulin adjuvant therapy, improves the glycemic profile and reduces body weight, without the need to increase the dose of the insulin therapy, through mechanisms that complement each other.[39]

A PRACTICAL LINE...

The UKPDS, the longest trial carried out with oral antidiabetic agents, is still a milestone reference in this area. The comparative study of therapy with metformine *vs* sulfonylurea *vs* insulin, lasted 10.7 years, showing that in all areas the best glycemic control was achieved with the overlapping effectiveness of various classes of drugs.[40] When compared in relation to the incidence of vascular events, the patients treated with metformin had a lower number of events than the groups treated with sulfonylureas or insulin, revealing significant differences, either in global mortality or in death by myocardial infarction.[41]

A comparative study of the efficacy and safety of the antidiabetic agents (between second generation sulfonylureas, biguanides, thiazolidinediones, meglitinides and α- glycosidase), reassessing various intermediary parameters, -Hg A1c, lipid profile, weight and side effects -, concluded that the groups treated with metformin and sulfonylureas presented more advantages. In addition, they had the benefits of lower cost, better documentation with scientific studies, and long experience in the clinical practice.[42] Based on these criteria, it was shown that metformin is at least as effective as the other antidiabetics and second generation sulfonylureas confirmed their profile of efficacy and safety, despite the higher risk of hypoglycemia. Thiazolidinediones are a unique class of drugs in the treatment of type 2 DM, acting primarily in the insulin-resistance process. They revealed the smaller tendency to hypoglycemia and a beneficial effect on HDL cholesterol, but lower effectiveness on metabolic control, weight gain, and higher incidence of cardiac decompensation.

The PROactive study (PROspective pioglitAzone Clinical Trial in macroVascular Events) demonstrated

the benefit of the pioglitazone in reducing various cardiovascular factors.[43] The same result was demonstrated in the RECORD study (Rosiglitazone Evaluated for Cardiovascular Outcomes), in which no increase of cardiovascular risk was recorded for rosiglitazone, compared with metformin or sulfonylureas.[44] The evaluation of the action of various drugs in relation to cardiac parameters (mortality and morbidity), does not reveal any significant differences among them, except for a higher risk of cardiac insufficiency in patients treated with thiazolidinediones.

In the DREAM study (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication), rosiglitazone showed benefits in the prevention of the evolution of the disease, data corroborated by comparing this drug with metformin and glyburide in the ADOPT study (Diabetes Outcome Progression Trial).[45] However, in all of them the effect of this class of drugs still remains also revealing also an increase in body weight by fluid retention and consequently higher incidence of cardiac insufficiency, factors that jeopardize the long-term maintenance of the treatment. Clinical trials have unequivocally shown this characteristic across the various risk groups: pre-diabetic patients, with or without cardiovascular pathology, in diabetic patients with documented cardiac insufficiency, with or without structural alteration. However, this does not seem to reflect in an increase in mortality rate.[19] Thus, in the current context, pioglitazone and rosiglitazone should not be considered as first line therapy, being indicated in the treatment of DM2, in monotherapy, in patients who do not tolerate metformin or when it is contraindicated, or in combined therapy with sulfonylureas and metformin.

Weight control is an important aspect in the management of diabetes mellitus. Various classes of drugs are associated with increase of body weight: secretagogues, thiazolidinediones and insulin itself. Only metformin, incretin mimetics, DPP-4 and α-glycosidase inhibitors have a stabilizing or reductive effect on body weight, effects which are more significant, particularly in the case of metformin, when in combined therapy with sulfonylurea or insulin.[46]

The ADOPT trial showed that women treated with rosiglitazone presented a higher incidence of bone fracture when compared with patients using metformin or sulfonylureas.[47] These data still require confirmation. However, there is increasing evidence that the lack of metabolic control directly interferes in hormonal balance. The hyperinsulinemia resulting from insulin resistance induces exaggerated production of testosterone and reduces the synthesis of hepatic globulins, increasing the concentration of serum total and free testosterone levels. Treatment with metformin reduces hyperinsulinemia and testosterone levels, increasing estradiol levels and enabling a reduction of hirsutism, normalizing menstrual cycles, and inducing ovulation in patients with polycystic ovary syndrome. Glitazones also seem to present some beneficial effect in these patients.

Metformin still remains the first line therapy, due to its safety profile, efficacy and tolerability, and long clinical experience, as well as its accessible cost. The new drugs are more expensive and present similar or worse effects, either in relation to metabolic control or in the incidence of micro- and macrovascular complications.[12,42]

Oral antidiabetic agents, when used in association, give better metabolic control, but at the same time, trigger a higher incidence of side effects, except when used in low doses.[42]

Studies on the new drugs are still rare, inconclusive and contradictory. There is greater consensus in relation to results of studies carried out with monotherapy, with divergence on multiple variables when compared in combined therapies.

The first studies have shown that when the association sitagliptin *vs* glipzide is compared to a metformin monotherapy regimen in DM2 patients, a reduction of Hg A1is verified, which is similar in both after 52 weeks of treatment. In addition, sitaglipin registered the lower incidence of hypoglycemia and weight reduction (difference of about 2.5 kg) in relation to glipizide.[48]

The association of sitagliptin and pioglitazone (*vs* sitagliptin and placebo) has also shown an improvement in the glycemic profile, as well as an increase in the proinsulin:insulin ratio. However, in both cases, weight gain was also observed.[49]

The 24-week treatment with tesaglitasar *vs* piogitazone achieved the same results in the metabolic control, highlighting only the elevation of serum creatinine in patients treated with tesaglitasar, this being a dose-dependent effect.[50]

The place given to each drug in the lines of treatment of diabetes mellitus still depends on a long, hard work, to be defined and prepared by clinical research

trials, allied with evidence from clinical experience. Knowledge on this reality enables us to rigorously select, for each individual, the therapeutic plan that best fits their inherent characteristics and special features, particularly their "metabolic phenotype".

CONCLUSION

Guidelines point to Hg A1c values of 7% or lower (< 6.5%), in about 6- 12 months of treatment, after initial diagnosis, as target values for adequate metabolic control of patients with DM2. A multidisciplinary approach is important for achieving the recommended goals, with changes in habits and lifestyle being a fundamental requirement, the milestone of the whole process, which should never be discouraged. The combined therapy of antidiabetic agents, and of these with insulin, should be considered increasingly earlier, since the combination of drugs in sub-therapeutic doses has been proven to be more effective in the metabolic correction than the use of a maximum dose regimen in monotherapy. It is also more effective in delaying micro and macrovascular complications, which lead to dramatic consequences for the patient. ■

References

1. Fonseca VA. Management of diabetes mellitus and insulin resistance in patients with cardiovascular disease. Am J Cardiol 2003; 92(suppl):50J-60J.

2. American Diabetes Association. Implications of the United Kingdom Prospective Diabetes Study. Diabetes Care. 2003;26 (suppl 1): S28-S32.

3. American Diabetes Association. Standards of medical care in diabetes - 2007. Diabetes Care. 2007 Jan;30 Suppl 1:S4-S41.

4. Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes. JAMA 2002;287:360-72.

5. Cheng AY, Fantus IG. Oral antihyperglycemic therapy for type 2 diabetes mellitus. CMAJ 2005;172(2):213-226. Review

6. Del Prato S, Bianchi C, Marchetti P. beta-cell function and anti-diabetic pharmacotherapy. Diabetes Metab Res Rev 2007;23(7):518-27. Review

7. Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: an update. Ann Intern Med 2002; 137:25-33.

8. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352:854-865.

9. Koski RR. Practical review of oral antihyperglycemic agents for type 2 diabetes mellitus. Diabetes Educ. 2006 ;32(6):869-876. Review.

10. Salpeter S, Greyber E, Pasternak G, Salpeter E. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. [Cochrane review]. In: The Cochrane Library; Issue 4, 2004.

11. Stades AM, Heikens JT, Erkelens DW, Holleman F, Hoekstra JB. Metformin and lactic acidosis: cause or coincidence? A review of case reports. J Intern Med 2004;255 (2): 179-187.

12. Sáenz Calvo A, Fernández Esteban I, Mataix Sanjuán A, Ausejo Segura M, Roqué M, Moher D. [Metformin for type-2 diabetes mellitus. Systematic review and meta-analysis] Aten Primaria 2005; 36(4):183-91. Review. Spanish

13. Peters AL. Using thiazolidinediones: rosiglitazone and pioglitazone in clinical practice.Am J Manag Care 2001; 7(3 Suppl):S87-95; quiz S96-7. Review.

14. Luna B, Feinglos MN.Oral agents in the management of type 2 diabetes mellitus. Am Fam Physician 2001; 63(9):1747-1756.

15. Tack CJ, Smits P. Thiazolidinedione derivatives in type 2 diabetes mellitus. Neth J Med 2006; 64(6):166-174. Review.

16. Avandia. In: Physicians' Desk Reference [electronic version]. Greenwood Village, Colo: Thomson Micromedex 2006.

17.Actos. In: Physicians' Desk Reference [electronic version]. Greenwood Village, Colo: Thomson Micromedex 2006.

18. Nesto RW, Bell D, Bonow RO et al. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. Diabetes Care 2004; 27:256-263.

19. Lago RM, Singh PP, Nesto RW.Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomized clinical trials. Lancet 2007; 370(9593):1129-1136. Review.

20. Donnelly R. Effect of pioglitazone on the drivers of cardiovascular risk in type 2 diabetes.Int J Clin Pract 2007; 61(7):1160-1169. Epub 2007 May 18. Review.

21. Wilcox R, Kupfer S, Erdmann E; PROactive Study investigators. Effects of pioglitazone on major adverse cardiovascular events in high-risk patients with type 2 diabetes: results from PROspective pioglitAzone Clinical Trial In macro Vascular Events (PROactive 10). Am Heart J. 2008 Apr; 155(4):712-7. Epub 2008 Feb 21. Erratum in: Am Heart J. 2008; 156(2):255.

22. Gastaldelli A, Ferrannini E, Miyazaki Y, Matsuda M, Mari A, DeFronzo RA. Thiazolidinediones improve beta-cell function in type 2 diabetic patients.Am J Physiol Endocrinol Metab 2007; 292(3):E871-883. Epub 2006 Nov 14.

23. Fagerberg B, Schuster H, Birketvedt GS, Tonstad S, Ohman KP, Gause-Nilsson I; SIR Study Group. Improvement of postprandial lipid handling and glucose tolerance in a non-diabetic population by the dual PPARalpha/gamma agonist, tesaglitazar. Diab Vasc Dis Res 2007; 4(3): 174-180.

24. Fagerberg B, Edwards S, Halmos T, Lopatynski J, Schuster H, Stender S, Stoa-Birketvedt G, Tonstad S, Halldórsdóttir S, Gause-Nilsson I. Tesaglitazar, a novel dual peroxisome proliferator-activated receptor alpha/gamma agonist, dose-dependently improves the metabolic abnormalities associated with insulin resistance in a non-diabetic population. Diabetologia 2005; 48(9): 1716-1725.

25. Göke B, Gause-Nilsson I, Persson A; GALLANT 8 Study Group. The effects of tesaglitazar as add-on treatment to metformin in patients with poorly controlled type 2 diabetes. Diab Vasc Dis Res 2007; 4(3): 204-213.

26. Ratner RE; The Diabetes Prevention Program Research. An update on the Diabetes Prevention Program. Endocr Pract 2006;12 Suppl 1:20-24. Review.

27. Buse JB, Rubin CJ, Frederich R, Viraswami-Appanna K, Lin KC, Montoro R, Shockey G, Davidson JA. Muraglitazar, a dual (alpha/gamma) PPAR activator: a randomized, double-blind, placebo-controlled, 24-week monotherapy trial in adult patients with type 2 diabetes. Clin Ther 2005; 27(8): 1181-1195.

28. Barnett A. DPP-4 inhibitors and their potential role in the management of type 2 diabetes. Int J Clin Pract 2006;60 (11):1454-1470. Review.

29. Meier JJ, Gallwitz B, Salmen S et al. Normalization of glucose concentrations and deceleration of gastric emptying after solid meals during intravenous glucagon-like peptide 1 in patients with type 2 diabetes. J Clin Endocrinol Metab 2003;88: 2719-2725.

30. Drucker DJ. Glucagon-like peptide-1 and the islet beta-cell: augmentation of cell proliferation and inhibition of apoptosis. Endocrinology 2003; 144: 5145–5148.

31. Brubaker PL, Drucker DJ. Minireview: glucagon-like peptides regulate cell proliferation and apoptosis in the pancreas, gut, and central nervous system. Endocrinology 2004; 145: 2653–9. 2006; 445: 9–18.

32. Kim D, MacConell L, Zhuang D, Kothare PA, Trautmann M, Fineman M, Taylor K. Effects of once-weekly dosing of a long-acting release formulation of exenatide on glucose control and body weight in subjects with type 2 diabetes. Diabetes Care. 2007; 30 (6): 1487-1493.

33. Gleeson JM, Berenbeim DM, Gilkin RJ. Incretin mimetics: promising new

therapeutic options in the treatment of type 2 diabetes. J Manag Care Pharm. 2005 ; 11 (7 Suppl):S2-13; quiz S14-15.

34. Hinnen D, Nielsen LL, Waninger A, Kushner P. Incretin mimetics and DPP-IV inhibitors: new paradigms for the treatment of type 2 diabetes. J Am Board Fam Med. 2006; 19 6):612-620. Erratum in: J Am Board Fam Med 2007; 20(2):240.

35. Linnebjerg H, Kothare PA, Park S, et al. Effect of renal impairment on the pharmacokinetics of exenatide. Br J Clin Pharm 2006 In press.

36. Florentin M, Liberopoulos EN, Mikhailidis DP, Elisaf MS. Sitagliptin in clinical practice: a new approach in the treatment of type 2 diabetes.Expert Opin Pharmacother. 2008; 9(10):1705-1720. Review.

37. Barnett A. DPP-4 inhibitors and their potential role in the management of type 2 diabetes. Int J Clin Pract. 2006; 60(11):1454-1470. Review.

38. Singh-Franco D, Robles G, Gazze D. Pramlintide acetate injection for the treatment of type 1 and type 2 diabetes mellitus. Clin Ther 2007; 29(4):535-562. Review.

39. Ratner RE, Dickey R, Fineman M, Maggs DG, Shen L, Strobel SA, Weyer C, Kolterman OG. Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in Type 1 diabetes mellitus: a 1-year, randomized controlled trial. Diabet Med 2004; 21(11):1204-1212.

40. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA 1999 ;281 (21): 2005-2012.

41. Schnell O, Standl E. Impaired glucose tolerance, diabetes, and cardiovascular disease.Endocr Pract 2006;12 Suppl 1:16-19. Review.

42. Bolen S, Wilson L, Vassy J, Feldman L, Yeh J, Marinopoulos S, et al. Comparative Effectiveness and Safety of Oral Diabetes Medications for Adults with Type 2 Diabetes. Rockville, MD: Agency for Healthcare Research and Quality; 2007

43. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefèbvre PJ, Murray GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Korányi L, Laakso M, Mokán M,Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schernthaner G, Schmitz O, Skrha J, Smith U, Taton J; PROactive investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 2005;366 (9493): 1279-1289.

44. Komajda M, Curtis P, Hanefeld M, Beck-Nielsen H, Pocock SJ, Zambanini A, Jones NP, Gomis R, Home PD; RECORD Study Group. Effect of the addition of rosiglitazone to metformin or sulfonylureas versus metformin/sulfonylurea combination therapy on ambulatory blood pressure in people with type 2 diabetes: a randomized controlled trial (the RECORD study). Cardiovasc Diabetol 2008; 7:10.

45. [Glitazones and congestive heart failure: update on PROactive, ADOPT, DREAM and RECORD clinical trials]Rev Med Suisse. 2007;3(122):1876, 1878-83. Review. French.

46. Golay A. Metformin and body weight.Int J Obes (Lond). 2008; 32(1):61-72. Epub 2007 Jul 24. Review

47. Kahn SE, Zinman B, Lachin JM, Haffner SM, Herman WH, Holman RR, Kravitz BG, Yu D, Heise MA, Aftring RP, Viberti G; Diabetes Outcome Progression Trial (ADOPT) Study Group. Rosiglitazone-associated fractures in type 2 diabetes: an Analysis from A Diabetes Outcome Progression Trial (ADOPT). Diabetes Care. 2008; 31(5):845-851. Epub 2008 Jan 25.

48. Nauck MA, Meininger G, Sheng D, Terranella L, Stein PP; Sitagliptin Study 024 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. Diabetes Obes Metab 2007; 9(2):194-205.

49. Rosenstock J, Brazg R, Andryuk PJ, Lu K, Stein P; Sitagliptin Study 019 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing pioglitazone therapy in patients with type 2 diabetes: a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Clin Ther 2006; 28(10): 1556-1568.

50. Bays H, McElhattan J, Bryzinski BS; GALLANT 6 Study Group. A double-blind, randomised trial of tesaglitazar versus pioglitazone in patients with type 2 diabetes mellitus. Diab Vasc Dis Res 2007;4(3):181-193.