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Diabetes - old therapies revisited

Abstract

Today, there are many therapeutic options for the treatment of type 2 Diabetes, which means that therapeutic decision making has become increasingly challenging and complex. With the recent introduction in clinical practice of new classes, with different mechanisms of action, what is the role of the older drugs? This article reviews these drugs, with recently published data update. Today, recommendations are not based on a simple algoritm, but in a patient centered approach. Besides the phenotypic heterogeneity of patients with type 2 diabetes, there is also a great diversity in response to treatment. This concept of personalized medicine has changed in recent years. The new era of personalized medicine evolves in order to identify molecular and clinical signs that can predict therapeutic response, reducing uncertainty in decision making. The "old" drugs may resurface, with more precise indications, in selected groups of patients.

Keywords: type 2 diabetes, treatment, old therapies, phenotypic heterogeneity, guanidine, gluconeogenesis, hypoxia, hypoglycemia, glyburide, glucotoxicity, insulin

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Joana Guimaraes
Department of Endocrinology, Centro Hospitalar do Baixo Vouga, Portugal

Correspondence: Joana Guimaraes, Graduated Assistant of Endocrinology and Nutrition, Endocrinology Department, Centro Hospitalar do Baixo Vouga, EPE, Portugal, Email joanaguimaraes.endoc@gmail.com

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Abbrevations: IRS-2, insulin receptor substrate; ACC, acetyl-coa carboxylase; UKPDS, united Kingdom prospective diabetes; TFG, the glomerular filtration; SU, sulfonylureas; SUR1, sulfonylurea receptor 1; SUR, su receptors; UGDP, university group diabetes program; EMA, european medicines agency; FDA, food and drug administration; RECORD, rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes; EMA, european medicines agency; ADA, american diabetes Association

Introduction

Today, there are many therapy options for managing type 2 Diabetes. The recommendations are published and often updated,[1] emerged in an attempt to assist clinicians in the best decision, which must be individualized, patient-centered, taking into account numerous factors such as effectiveness and side effects of drugs, the objective to be attained and the co-morbidities and patient preferences. With the emergence of new therapeutic classes, with different mechanisms of action, what is the role of the older drugs?

Metformin

Metformin is used since 1957 in Europe and 1995 in the USA and currently, is the drug of choice recommended by all international associations. Is a derivative of Guanidine, discovered in 1920, in plant extracts Galega officinalis, used for centuries in the treatment of diabetes.[2] G. officinalis is known from the middle ages to relieve the symptoms of diabetes mellitus. Georges Tanret identified a plant alkaloid, galegine, which was less toxic, and this has been evaluated in clinical trials without success in patients with diabetes between 1920 and 1930. Other related compounds have been investigated clinically, biguanide derivative. This work led finally, to the discovery of metformin.[3]

Metformin is known and widely used throughout the world for its antidiabetic action, but has gained importance by other effects:[4] reduces food intake and weight, influence cardiovascular risk markers, inflammatory markers and possibly reduces the risk of cancer.[5]

Antidiabetic action-mechanism of action

The antihyperglycaemic action of biguanides is mainly a consequence of reduced glucose output owing to inhibition of liver gluconeogenesis[6] and, possibly to a lesser extent, increased insulin-mediated glucose uptake in the skeletal muscle.[7]

Metformin increases the activity of insulin receptor and insulin receptor substrate 2 (IRS-2) and enhances glucose uptake via increased translocation of glucose transporters, such as GLUT-1 (also known as SLC2A1), to the plasma membrane and, as a result, enhances the insulin-mediated supression of gluconeogenesis. Furthermore, metformin opposes the gluconeogenic action of the peptide hormone glucagon. The effect of these interactions is the inhibition of gluconeogenic enzymes and stimulation of glycolysis by altering the activity of multiple enzymes.[8]

Gluconeogenesis accounts for 28-97% of overall hepatic glucose output in nondiabetic individuals and in patients with advanced type 2 diabetes mellitus, s rate is superior. In these patients, metformin is responsible for reducing hepatic glucose production in 75%.[9] Metformin improves insulin sensitivity and glucose uptake by skeletal muscle mediated by an increase in activity of tyrosine kinase on insulin receptor of insulin and enhanced activity and translocation of glucose transporters, such as GLUT-4.[9]

Also interacts with incretin axis by stimulating the expression of GLP-1 's receptor in the pancreas and increasing plasma levels.[10] The primary target in the cell is the mitochondria, where metformin inhibits complex I of the mitochondrial electron transport chain, resulting in a reduction of ATP production and increased levels of ADP and AMP.[11] The increased levels of AMP explain the activation of AMPK, which is the major regulator of cellular energy homeostasis. The central role of activation of AMPK in the mechanism of metformin action was demonstrated in 2001 by Zhou et al.,[12] which showed that metformin stimulated activation of AMPK in hepatocytes of rats and that it was essential for inhibition of hepatic glucose production. However, Foretz Gacon et al.,[13] have shown that metformin inhibited liver production in transgenic mice, without activation of AMPK. So,

although AMPK activation is the main mediator of metformin action, there are independent mechanisms.

One of the targets of AMPK is acetyl-CoA Carboxylase (ACC), precursor of lipogenesis, and regulator of expression of multiple lipogenic genes, which contributes to the increased sensitivity to insulin. On the other hand, the gluconeogenesis is a process that requires ATP and once that metformin lowers levels of ATP, the hepatocytes respond by reducing glucose production.[14] One of the other proposed mechanism, independent of AMPK, is the inibition of the protein kinase activity, AMPc-dependent, an important signal of glucagon action and glucagon-induced gluconeogenesis.[15]

The intestinal microbiota plays a sigificant role in energy balance and seems to have responsibility in the pathogenesis of obesity and diabetes. Previous studies have shown that the intestine plays an important role in the glucose-lowering effect of metformin, facilitating uptake and utilization of glucose. Metformin increases the abundance of Akkermansia, Gram-negative bacteria, associated with the restoration of reduced regulatory T cells and improves the degree of inflammation of adipose tissue.[16]

GLP-1 levels (not GIP or péptideo YY), are increased in obese subjects and diabetic treated with metformin, and this increase is not related to the inhibition of DPP-4, but probably with the muscarinic acetylcholine receptor.[17] Autophagy has implications in metabolism, particularly in cases of energy deficiency and has implications on turnover and function of mitochondria and endoplasmic reticulum. Metformin can enhance Autophagy, through APMK activation, which may also explain the protection of beta cells against the lipoapoptose and improvement of structural changes on cardiomyopathy.[18]

Efficacy

Efficacy of metformin, alone or in combination with sulfonylurea, was evidenced in the United Kingdom Prospective Diabetes (UKPDS). After 3 years, 79% of the 207 obese patients initially randomized to received metformin, remained with the same drug and 10% required addition of another drug. Mean of Hemoglobin A1C in this group of patients was 7.1% and 7.8% in the control group.[19]

In the UKPDS, metformin has proved to be higher than the insulin or sulfonylurea, for any diabetes-related complication, mortality and stroke [20], and there was significant reduction of myocardial infarctions, compared with conventional treatment [relative risk (RR): 0.61; $P < 0.010$], which persisted after 10 years [RR: 0.67; 95% confidence interval (CI): 0.51-0.89].[21] However, the UKPDS included individuals with newly diagnosed type 2 diabetes and were excluded patients with heart or kidney complications. Subsequently, several studies have evaluated the safety and risk-benefit of metformin.

Heart disease

In patients with acute coronary syndrome (NSTE or revascularization), metformin is associated with better short and long term prognosis, when compared with other antidiabetic, so Should not to be considered a contraindication, unless if circulatory insufficiency is present.[22]

Cardiovascular disease is the first cause of death in patients with type 2 diabetes and to reduce this risk is necessary a multifactorial approach, the remaining risk factors, but cardiovascular protection represents a primary goal. Although controversial, metformin can confer such protection in newly diagnosed patients and in patients with more advanced disease treated with insulin, maybe because the beneficial effects on lipids, inflammation, endothelial and platelet function, haemostasis and blood vessel abnormalities.[23]

Side-effects and contraindications

The most common adverse effects are gastrointestinal (diarrhea, nausea, abdominal pain and flatulence), reported by more than 30% of patients during the first 2 weeks, but resolve spontaneously in the majority and only 5% keeps intolerance.[24] Despite not having been validated in clinical trials, it is recommended to start metformin with low doses and gradually increase. Metformin alters the absorption of vitamin B12 and deficiency may occur (< 150 pmol/L) in 9.9% of patients.[24]

Lactic acidosis, although rare, is an important side effect because it can be fatal. The risk is higher in situations that promote the formation of lactate due to hypoxia (circulatory and respiratory failure, severe), which alter the metabolism via gluconeogenese (liver failure) or that increase levels of metformin (renal insufficiency).[25] A recent Cochrane review, from 347 prospetived or observational studies, metformin was not associated with increased risk of lactic acidosis, when compared with other antidiabetic drugs.[26] However, clinical trials excluded patients at high risk and probably with known contraindications known, different scenario of daily practice.

Recently, Inzucchi et al.,[27] in a review of studies published from 1950 to 2014, to assess the risk of lactic acidosis in patients with type 2 diabetes and chronic kidney disease, revealed that lactate levels are often normal in patients treated with metformin and with discreet renal insufficiency (creatinine clearance 60-90 ml/min) to moderate (creatinine clearance 30-60 ml/min) and when high, not reached the criteria of lactic acidosis (lactates > 5mmol/L and pH 7.35 <). In the cases of lactic acidosis, there were associated causes like infection, liver failure, acute renal failure or severe circulatory. In view of these results, the authors suggest maximum dose of metformin of 2550mg when the glomerular filtration (TFG) estimated more than 60ml/min/1.73m^2; maximum dose of 2000 mg of metformin when the TFG is estimated 45 to 59mL/min/1.73m^2 and 1000mg/day in the case of GFR of 30 to 44mL/min/1.73m^2.

Recommendations

Metformin is considered the first line pharmacological therapy in type 2 diabetes, as soon as the diagnosis or non-pharmacological measures are not sufficient to achieve the goal, unless there are any contraindications. This recommendation is based on the neutral effect on weight, absence of hypoglycaemias, good tolerability and low cost.

Sulfonylureas

The capacity of synthetic sulfur containing compounds to lower blood glucose levels was reported in 1941 and later with the occurrence of episodes of severe hypoglycemia with antibacterial administration for typhoid fever in 1942.[28] In 1956 it was marketed in Germany, the 1st sulfonylurea (tolbutamide), as antidiabetic, followed by chlorpropamide, acetohexamida and tolazamida (1st generation). Later, Italian investigators have developed the sulfonylureas of 2nd generation, glyburide and glipizide, approved in the U.S.A in 1984 and years later in Europe. Later, were introduced glimepiride and gliclazide. Although all sulfonylureas (SU) have the same mechanism of action, the intrinsic antidiabetic activity and binding affinity to the SU receptor varies considerably, such as the onset and duration of action.

Mechanism of action

The sulfonylureas (still widely used in clinical practice) mecanism of action, involves binding to the pancreatic islet cell sulfonylurea receptor 1 (SUR1), which results in closure of the cell membrane ATP-sensitive potassium channel (K1 ATP), thereby causing membrane depolarization, influx of calcium ions, and subsequent release of insulin from storage.[29] Potassium channels (K+)-ATP are widely distributed throughout the body, but are heterogeneous with respect to protein composition. All consist of 4 units of K+ (Kir) and 4 SU receptors (SUR). There are 2 isoforms of Kir (Kir 6.1 and Kir 6.2) and 3 isoforms of SUR (SUR1, SUR2A and SUR2B). Pancreatic β cells express predominantly SUR1, SUR2A in the cardiomyocytes and skeletal muscle and vascular smooth muscle cells SUR2B.[30]

In adition to SUR1 binding, sulfonylureas likely exert a portion of their effect through binding with exchange protein directly activated by cAMP (Epac2).[31] In experimental models without the expression of Epac2A, the glucose-lowering effect of tolbutamide is reduced, so Epac2A is essential for the secretion of insulin. Despite the essential role of K+channels/ATP for the stimulation of insulin secretion by SU's, enabling the Epac2A/Rap1 signaling is required for the full effect, in the exocytosis of insulin granules, except with gliclazide.

The effect of glucose-lowering stems essentially from the stimulation of insulin secretion, but there are extra-pancreáticos effects,[32] such as reduced clearance of insulin (no-observed-effect with glibenclamide); reduction of glucagon (probably subsequent to stimulation of insulin secretion) and increased insulin sensitivity (small to be clinically significant effect).

Efficacy

In the UKPDS, more than 50% of patients with newly diagnosed diabetes, reached the objective of Hemoglobin A1C 7 <%, with SU monotherapy, but 9 years after, just 24% kept that goal in monotherapy and already 3 years later, 50% not reached the goal.[33] A recent Cochrane review,[34] totaling 22,000 patients and including SU 1st and 2nd generation, identified 1.0% HbA1C reductions in monotherapy. In patients naive, monotherapy with SU can achieve reductions in HbA1C of 1 to 2%.[35]

Adverse effects and contraindications

The 1st generation sulfonylureas had a high incidence of adverse reactions such as severe and prolonged hypoglycemia, water retention and hiponatrémia by inappropriate secretion of antidiuretic hormone and alcohol-induced flush.[36] However, even with the 2nd generation SU, there are relevant side effects.

Hypoglycemia

As insulinosecretagogos, one of the most clinically significant adverse effects is the occurrence of hypoglycemia, with negative implications on the quality of life, risk of falling and fractures, coma, cardiovascular consequences and costs. Severe hypoglycemia occurs in every 100 patients treated with 1:00 pm SU.[37] year.

In UKPDS study, 17.7% of patients treated with glibenclamide had 1 or more episodes of hypoglycemia per year and 0.5% severe hypoglycemia [38], later a meta-analysis showed a 52% higher risk of hypoglycemia secondary to glyburide, when compared with other SU (RR 1.52 [95% CI, 1.21-1.92]).[39] Despite more frequent with the sulfonylureas of long duration of action such as glyburide, any SU can cause hypoglycemia, when used in high doses or in certain situations.

Several studies have shown an association between severe hypoglycemia and a two-fold higher risk of cardiovascular events, and a recent meta analysis with 903,510 patients showed that this association is independent of the coexistence of severe co-morbidities.[40] Due to the increased risk of hypoglycemia, most SU must be discontinued when the estimated glomerular filtration rate is less than 45-60 ml/min.[41] Other factors such as the omission of meals, overdose, malnutrition, heart failure or liver, alcohol intake, age, interactions with other drugs (aspirin, sulfa, gemfibrozil, warfarin, etc.) increase the risk.

Weight gain

Weight gain is a common effect and in UKPDS, during 6 years, patients treated with SU increased an average of 5.3 Kg and although occur with all SU's, glimepiride is associated with the smallest increase.[42]

Beta cell exhaustion

Pre-clinical and clinical studies are inconsistent with regard to the negative impact of SU in β cell function.[43] Glbenclamide enhances apoptosis in human islets and an observational study showed a decrease in the concentration of C-peptide in patients treated with SU.[44] In the ADOPT study (A Diabetes Outcome Progression Trial) trial, monotherapy failure after 5 years of treatment was 34% for glyburide, 21% for metformin, and 15% for rosiglitazone, but also demonstrated that 5 years later, β cell function was similar in all groups.[45]

However, glucotoxicity (a consequence of persistent hyperglycemia) is more harmful to the function of the cell that the SU-induced chronic hyperstimulation.[46] More important, but widely overlooked, aspect of the kinetics-effect relations of sulfonylureas is the fact that treatment promoting continuous exposure to high sulfonylurea plasma levels impairs rather than improves therapeutic efficacy, seemingly due to downregulation of SUR. The dose-response curve of SU during chronic treatment is a bell -shaped and not sigmoidal, so using high doses can cause a vicious cycle of hyperglycemia, with consequent increase of the dose of SU and therapeutic failure.[47]

Cardiovascular safety

The cardiovascular safety question of SU class has questioned first time after the publication of the study University Group Diabetes Program (UGDP), in 1970. In this study, designed to compare the efficacy of tolbutamide, insulin and diet in monotherapy, showed an increased number of deaths in the group treated with tolbutamide, which led to the suspension of treatment.[48]

Almost 3 decades later, the UKPDS intensive treatment compared SU (glyburide, glipizide or chlorpropamide) or insulin with conventional treatment with diet, in newly diagnosed diabetics and 10 years later, the intensive treatment was associated with lower morbidity and mortality, and there was no evidence of increased mortality with the SU's.[38]

In 2007, after the publication of cardiovascular adverse results of Thiazolidinediones,[49] cardiovascular safety scrutiny of sulfonylureas returned to the debate and investigation. There are several studies that assess the association between SU and cardiovascular events, but with limitations. Eight meta-analyses were carried out and published recently.[50] Observational studies suggest a high risk, but randomized trials suggest that there is no difference in risk. These discrepancies are result of several limitations: randomized trials and controlled are

the most suitable to assess causality relationships, but in the case of SU´s and cardiovascular risk, the majority was not designed with this goal, involve a limited number of patients and are short-lived.

Regardless of these limitations, there will be biological justification for the association between SU and cardiovascular risk? The K+-ATP, essential for the glucose-lowering effect of SU´s, also exist in another tissues and inhibition of these channels in the heart and vascular smooth muscle, can contribute to adverse effects, particularly for glibenclamide, which is not selective for the pancreatic SUR1 (such as gliclazide and glipizide), which already showed change the ischemic preconditioning.[51] Hypoglycemia is related with cardiovascular adverse events, but the risk is less with gliclazide and glimipirid.[52] Also weight gain, which cause insulin resistance, hypertension and increase proinsulin/insulin ratio, can justify an increased cardiovascular risk.

After so many years, the cardiovascular safety question that has dogged the SU class remains unresolved. Two studies that are taking place, the TOSCA. IT[53] and[54] Carolina may clarify by comparing the sulfonylureas with pioglitazone and linagliptin, respectively. Other studies will be needed to evaluate the differences between the various types of SU´s.

Recommendations

Sulfonylureas have 60 years record of use, so that there is enough evidence about its efficacy and safety. They are considered one of several second-line options for most people with type 2 diabetes, or as first line alternative for patients who cannot tolerate metformin. Of the various SU available, glyburide, for interfering with ischemic preconditioning is associated with greater mortality and is not recommended.[55] Regarding the cardiovascular safety of other sulfonylreas, the results of several studies are inconsistent, for the reasons already pointed out. These therapies offer the advantage of ease of administration, good tolerance and low cost. However, due the risk of hypoglycemia, should not be used in the elderly, when there is a history of hypoglycemia, renal dysfunction or when there are other comorbities that increase the risk of hypoglycemia.

Glinides

Glinides (in Portugal, is only marketed the nateglinide) are insulinosecretagogos with a mechanism of action similar of SU´s, however the association and dissociation of nateglinide with the SUR1 receptor-KATP complex is more rapid that that of sulfonylureas and even repaglinide.[56] Oral ingestion of 60mg of nateglinide in patients with type 2 diabetes, leads to increased insulin secretion in 10 to 60 minutes and blood glucose declines within 20 minute of the drug ingestion,at minimum by 60 min. Recommended an initial dose and maintenance of 120mg 3id, ideally 10 minutes before meals.It is not necessary adjust the dose in liver and kidney failure.

Although promising, because they work mainly on postprandial glycemia and with fewer side effects than the SU´s, was not proven to reduce cardiovascular risk, or the progression of intermediate hyperglycemia to diabetes in the NAVIGATOR study.[57]

Thiazolidinediones

Rosiglitazone (ROSI) and pioglitazone (PIO), the only available in Portugal, bind to PPARγ recetor, to form heterodimers with retinoid-X receptors, which then bind to various elements of the genome, resulting in transactivation of gene products that increase the action of insulin and transrepression of nuclear signal pathways generally unfavorable to insulin action (notably, nuclear factor kappa B [NF-kB]).[58] In adipose tissue, receptor PPARγ activation, blocks the release of free fatty acids reduces tumor necrosis factor alpha (TNF-alpha) and increases adiponectin. Promote the expansion of subcutaneous adipose tissue and decrease the visceral, which is associated with increase water retention, conditions that lead to weight gain.

Althought both metformin and glitazones decrease hepatic glucose production, only the glitazones decrease the fat content in the liver, reduces the concentration of free fatty acids and increases adiponectin levels.

Efficacy

In ADOPT study, rosiglitazone was higher than the glibenclamide and metformin, in terms of durability, the Hemoglobin A1C was less than 7% for a longer period of time.[45] Due to their insulinsensitizing activity, glitazones are not associated with an increased risk of hypoglycemia and reduce the incidence of type 2 diabetes in patients with intermediate hyperglycemia[59] possibly by reduction of lipotoxicity and inflammatory state which improve insulin resistance, but can also improve the function of β cell and in vitro studies have shown that PPARγ agonists prevent amyloid-induced apoptosis.

Thiazolidinediones are not inferior to other therapeutic approaches, have a greater durability and a very low risk of hypoglycemia.

Cardiovascular disease

Several experimental studies suggested a potential protective effect of this class at cardiovascular level. Ironically, it was precisely the opposite that prompted the suspension of the marketing of rosiglitazone by the EMA (European Medicines Agency)[60] and the restriction on use in 2010 by the FDA (Food and Drug Administration), which in 2013 was reviewed and cancelled.[61] In 2007, Nissen et al.,[49] published a meta-analysis suggesting a high cardiovascular risk in patients treated with rosiglitazone, confirmed in other subsequent meta-analyses,[62] but pioglitazone showed to have a beneficial effect.[63] PROactive was a large prospective cardiovascular outcomes study of 5238 T2DM patients with prior cardiovascular disease and pioglitazone showed 10% risk reduction of mortality, non-fatal MI, acute coronary syndrome, stroke, major amputation and revascularization of the MI, though non-significant [64] and in patients with prior EAM, significantly reduced the risk of re-infarction by 28%[65] and stroke 47%.[66]

The reason for these discrepante effects of ROSI and PIO on cardiovascular outcomes remains unclear. One hypothesis is a more favorable effect of PIO on the plasma lipid profile when compared to ROSI (decrease in LDL-C and TG, increase in HDL-C). PIO improves both established and emerging cardiovascular risk factors, with, for instance, a significant decrease in arterial blood pressure, C-reactive protein, fibrinogen, plasminogen activator inhibitor-1 and MMP-9.

Non-alcoholic estatohepatite

PIVENS study, conducted in patients with non-alcoholic steatohepatitis and without cirrhosis or diabetes, pioglitazone was associated with significant reductions in fatty liver, and inflammation and a large proportion of patients showed resolution of steatohepatitis.[67] These effects are also evident in diabetic patients.

Adverse effects and contraindications

Weight gain: Glitazones are associated with weight gain, in order of 2 to 5% and is more marked when associated with SU or insulin. The reasons for this increase in weight are not fully clarified, but water retention and fat deposition contribute to this increase.

Water retention and heart failure: In 7% of patients occurs swelling of the lower limbs, more pronounced with the associated insulin therapy (>15%). The mechanisms underlying this water retention are not entirely clear, but may increase the risk of macular edema[68] and risk of heart failure.

The RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes) trial of 4447 patients T2DM compared rosiglitazone plus either metformin or SU, versus the combination of metformin and SU, specifically for cardiovascular outcomes. Analysis of RECORD trail data identified an increased risk of heart failure among rosiglitazone users (hazard ratio 2.1 [95% CI, 1.35–3.27], vs nonusers), but no significant advantage with regard to microvascular disease, or cardiovascular event-related hospitalization or death and in PROactive, 5.7% of patients with severe heart failure had pioglotazone treatment.[69] Although the risk is less than with pioglitazone, cardiac function should be monitored.

Bone fractures: The suggestion that these therapies are associated with an increased risk of bone fractures in women, emerge with the ADOPT and PROactive studies. More recently, Habib et al.,[70] showed an increased risk in women >65 years, but not in men and Dormuth et al.,[71] showed a higher risk with pioglitazone, affecting men and women.

The mechanism that results in the reduction of bone density is not fully clarified, but adipocytes and osteoblasts derive from a common progenitor and PPAR-γ receptor activation may increase the adipocyte differentiation at the expense of osteoblats, but can also induce osteocyte apoptosis. Caution must be used in prescribing a thiazolidinedione for a menopausal woman.

Cancer: In 2011, the European Medicines Agency (EMA), published a warning that pioglitazone was associated with risk of bladder carcinoma in men,[72] based on various epidemiological studies that pointed to a risk of 1.12 to 1.33, particularly in patients treated with pioglitazone for a long time and in high doses. Although the absolute risk of bladder cancer remains low (10,620 per year patients need to be treated before one bladder cancer case), it is recommended to avoid the use of pioglitazone in patients with bladder carcinoma (present or former) or with macroscopic hematuria.

Recommendations

Glitazones were a very promising class, but subsequently of great controversy, since the suspension of troglitazone for hepatotoxicity, later of rosiglitazone and cardiovascular risk, even with pioglitazone, by association with bone fractures, bladder carcinoma and heart failure. Despite the use have declined substantially, are still considered therapeutic recommendations, although third or fourth line, always considering the balance of risk and potential benefit.

Conclusion

Today, there are many therapy options for managing type 2 diabetes. This multiple choices also means that therapeutic decision making has become more difficult and the question if the oldest therapies still have a role, is actual and challenging. Metformin remains the first line therapy. The American Diabetes Association (ADA) and the European (EASD) in 2012, published new recommendations that are not based on a simple algorithm, but in a patient-centred approach, in which the different therapies can be used, considering the efficacy and safety of the same, and the characteristics and preferences of the patient.

Besides the phenotypic heterogeneity of patients with type 2 diabetes, there is also a great diversity in the response to treatment and these recommendations also state that in the absence of glucose reduction, should be investigated the patient's adherence to treatment and consider another drug with different mechanism of action.

These concepts of personalized medicine have changed in recent years.[73] Cancer therapy is one example. Treatment for monogenic forms of diabetes is is a very good example of how dissecting the aetiology of diabetes leads to personalized treatment, for example, if mutations in the gene HNF1A (MODY 3) are present; patients are particularly sensitive to sulfonilureias.[74] This most likely relates to the fact that the defects in the β cell caused by HNF1A mutations are in glycolysis and mitochondrial metabolism, and are therefore largely bypassed by sulphonylurea treatment, which acts downstream on the KATP channel. This work has resulted in the successful transition off insulin treatment and improved patient care for this subgroup of patients.

Pharmacogenetics studies focus on potential genes involved in drug metabolism and transport and in the case of diabetes, cytochrome P450 2c9 and SU efficay has been investigated and carrier OCT1 and tolerance to metformin. SU are inactivated in the liver by the cytochrome P450 2c9, but 6% of the population have polymorphisms in the gene that encodes the enzyme, SU in those individuals are not inactivated and the risk of hypoglycemia is high. The GoDARTS study showed that this population of individuals reaches more often A1C 7 <% (3.44 times more), but with higher risk of hypoglycemia.[75]

In the case of metformin, 8% of Europeans carry a variant of the carrier OCT1 and are more often intolerant (2x more than individuals with normal function). Other common drugs (for example, proton pump inhibitors, verapamil, diltiazem, spironolactone, rosiglitazone, trimethoprim, etc) that inhibit this carrier and when used in combination with metformin increases four-fold the risk of gastrointestinal intolerance.[76]

The new era of personalized medicine evolves in order to identify molecular and clinical signs that can predict therapeutic response, reducing uncertainty in decision making. The "old" drugs may ressurge, with more precise indications in selected groups of patients.

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None.

Conflicts of interest

The author declares there is no conflict of interest.

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