Review

Type 2 diabetes mellitus: epidemiology, pathophysiology, unmet needs and therapeutical perspectives

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Abstract

In France, prevalence of drug-treated diabetes reached 3.60% in 2005, with 92% of type 2 diabetic patients. In 2007, there are probably nearly 3 000 000 diagnosed or undiagnosed diabetic patients. Ageing of the population and increase in obesity are the main causes of this “diabetes epidemic”. Type 2 diabetes is a multifactorial disease, defined as resulting from defects in insulin secretion (including abnormalities in pulsatility and kinetics, quantitative and qualitative abnormalities of insulin, β-cell loss progressing with time) associated with insulin resistance (affecting liver, and skeletal muscle) and increased glucagon secretion. The lack of compensation of insulin resistance by augmented insulin secretion results in rise in blood glucose. To achieve satisfactory glycaemic control in order to prevent diabetes related complications, drug therapy is generally required in addition to life style changes. Currently available oral therapies offer a large panel of complementary drugs, but they have several contraindications and side effects. In spite of major advances in the management of type 2 diabetes, and the strictness of new guidelines, some goals remain unachieved and the new family of insulin-secretors (DPP-IV inhibitors, GLP-1 analogues) should enrich therapeutic approaches.

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Résumé

Diabète de type 2 : épidémiologie, physiopathologie, problèmes non résolus et perspectives thérapeutiques

En France, la prévalence du diabète traité par médicaments atteignait 3,6 % en 2005, dont 92 % de diabète de type 2, et en 2007 existent probablement près de 3 000 000 de diabétiques connus ou ignorés. Le vieillissement de la population et l’obésité croissante sont les principales causes de ce développement « épidémique » du diabète. Le diabète de type 2 est une maladie multifactorielle, qui associe une dysfonction insulaire (qui comporte des anomalies de la pulsabilité et de la cinétique, des altérations quali- et quantitatives de l’insulinosécrétion, et une perte de la masse des cellules β s’aggravant avec le temps) d’origine génétique, un déficit de l’insulinosensibilité (touchant le foie et le muscle strié) lié à des facteurs d’environnement (sédentarité et excès pondéral) et une hypersécrétion de glucagon. Le défaut de compensation de l’insulinorésistance par un débit insulinosécrétoire insuffisant a pour conséquence l’élévation de la glycémie. L’obtention d’un contrôle glycémique satisfaisant dans le but de prévenir les complications liées au diabète, nécessite en général le recours à des agents pharmacologiques en plus du traitement hygiénodiététique. Les médicaments oraux actuellement disponibles offrent un large spectre sur le plan de leur mécanisme d’action, mais ils ont un certain nombre de contre-indications et d’effets indésirables. Malgré les progrès accomplis dans le traitement du diabète de type 2 et la rigueur des nouvelles recommandations, il reste des objectifs non atteints, et de nouveaux insulinosécréteurs, inhibiteurs du DPP-IV et analogues du GLP-1, pourraient contribuer à compléter advantageous l’arsenal thérapeutique.

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1. Epidemiology of type 2 diabetes in France

In 2007, type 2 diabetes represents a major public health issue all over the world, becoming a “diabetes epidemic” as stated by Zimmet [1]. A few years ago, the concern of the “diabetes epidemic” was restricted to the US while the other parts of the world were not considered as threatened. Unfortunately, the picture has moved and nowadays no country escapes the diabetes invasion. In the world, diabetes prevalence in adults aged 20 and over was 4.0% in 1995 and it is expected to increase to 5.4% in 2030, slightly higher in the developed than in the developing countries [2]. Expressed in number of patients, the expected evolution of diabetes is more striking and spectacular, as the total number of adult diabetic patients (roughly type 2 diabetic patients) in the world should increase from 135 to 300 million between 1995 and 2030, mainly due to a tremendous increase of 171% in developing countries, from 84 to 228 million, while it should increase only of 41% in developed countries, from 51 to 72 million [2]. At the present time, the rank of countries for the number of diabetic patients is yet, in decreasing order, India, followed by China then the US. The ranking should be similar in 2030. In 2030, more than 75% of all the diabetic patients in the world will live in the developing countries, compared to 62% in 1995. In addition, these projections calculated by the WHO experts are probably underestimated as they are based only on the expected demographic evolution and do not take into account the evolution of obesity in the near decades. Therefore, the reality of diabetes in 2030 should be quite far over these figures.

1.1. Prevalence of type 2 diabetes in France

In France, diabetes prevalence has been well known for drug-treated patients from 1998 on [3], when the database of the National Public Health Insurance System (CNAMTS) containing all the files of patients’ claims for drug reimbursement was computerized (SIAM). Thus, thanks to the specificity of the drugs used for diabetes treatment (oral antidiabetic drugs [OAD] and insulin), the prevalence rate of diabetes could be calculated in 1998 then measured every year up to 2005. It increased from 2.78% in 1998 to 2.96% in 2000 [3] then 3.6% in 2005 [4], indicating an average annual increase of 3.2% between 1998 and 2000 then of 5.7% between 2000 and 2005, with around 92% of type 2 diabetic patients. French diabetic patients in 2005 were aged 64.7 ± 14.0 years (m ± SD) and had an annual death rate of 2.3%, with a mean age at death of 75.2 years [4]. When adding the type 2 diabetic patients only treated by lifestyle intervention (diet and physical activity), the prevalence of known diabetes was probably over 3% in 1998–2000 and could reach 4% in the very near future. In addition, there are undiagnosed diabetic patients whose number cannot be given precisely by definition, probably no more than 500 000 subjects as systematic diabetes screening is widely performed in France [5]. Therefore, overall, there are probably around 2 500 000 known diabetic patients and nearly 3 000 000 diagnosed or undiagnosed diabetic patients in metropolitan France at the present time. Concerning the French Overseas Departments, recent data indicated a prevalence of pharmacologically treated diabetes in 2005 equal to 10.1% in Guadeloupe, 7.9% in Martinique and 7.4% in La Reunion Island, confirming the previous figures, yet quite higher than in metropolitan France. Therefore, the label “diabetes epidemic” can probably be also applied to France.

1.2. Causes of the increase in type 2 diabetes prevalence

Obesity, mainly when fat is distributed predominantly at the abdominal level as shown in the fifties by Jean Vague, is the main risk factor for type 2 diabetes. In France as in all over the world, the diabetes epidemic is due to the increase in prevalence of obesity, linked to “westernized” lifestyle, namely changes in nutritional habits, with increased intake of saturated fats, refined sugars and alcohol, and reduced intake of fibres, and at the same time, reduction in physical activity. The impact of “coca-colonization” has been nicely shown by the comparison between Pima Indians from Arizona and Pima Indians from a remote area in Mexico, and native Mexicans (Fig. 1), showing the major role of environmental factors compared to genetic factors in the occurrence of diabetes [6]. The role of environment has also been demonstrated from many years by urban–rural comparisons of diabetes prevalence, higher in the urban areas inside any ethnic group, in a lot of epidemiological studies all around the world.

The increase in obesity is not only restricted to the US, but is becoming a major Public Health concern in France. In our
country, in adults aged 18 and over, obesity prevalence (body mass index (BMI) ≥ 30 kg/m²) increased from 8.2% in 1997 to 9.6% in 2000 then 11.3% in 2003 and, in the meanwhile, overweight (25 kg/m² < BMI < 30 kg/m²) increased from 28.5 to 29.4% then 30.4% according to the OBEPI surveys [7]. In addition, in children, obesity defined by the cut-off point corresponding to the 97th percentile in 1965 was present in 15% of the young population in 2003. With obesity, ageing of the population is the other cause of the type 2 diabetes epidemic, and the longer life expectancy of diabetic patients is also another reason for the increase in diabetes prevalence. In 2005, in France, the highest diabetes prevalence rate was observed in the 70–79 years age class, 17.7% in males and 11.5% in females.

1.3. Treatment of type 2 diabetes and associated cardiovascular risk factors in France

In 2005, 23.9% of the French diabetic patients were treated by insulin, alone (13.5%) or combined with OAD (10.4%) versus 21.0% in 2000 (13.0% alone and 8.0% combined with OAD) [4]. In 2005, among OAD, biguanides were the most commonly used drug (58.1% vs. 50.1% in 2000), preceding sulfonylureas for the first time (54.6 vs. 66.1% in 2000). Thiazolidinediones (TZDs), launched in France in 2002, were used by 1.5% of the patients in 2003, then 4.2% in 2004 and 8.9% in 2005. 11.9 and 8.1% used α-glucosidase inhibitors and glinides of the patients respectively, in 2005 versus 18.3 and 2.1% in 2000. Concerning the patients treated by OAD alone, in 2005, monotherapy was used by 51.5%, bitherapy by 36.0% and tritherapy or more by 12.4% versus, respectively, 54.4, 34.9 and 10.7% in 2000. Antihypertensive treatment was used by 73.8% in 2005 versus 68.7% in 2000, including 57.0% of ACE-inhibitors or sartans versus 45.0%. Hypolipemic agents were used by 54.9% in 2005 versus 42.7% in 2000, including 40.3% of statins versus 23.9%. Anti-platelet agents were used by 32.2% in 2005 versus 25.8% in 2000, including low-dose aspirin in 25.6 versus 22.4%. The costs for glycaemic and cardiovascular risk factors treatments per patient were estimated respectively at 312 and 448 € in 2005 versus 237 and 301 € in 2000, indicating an annual increase of the financial burden for drug treatment of diabetes equal to 7.1%, with two thirds represented by cardiovascular risk factors treatment. The total cost of drug treatment increased from 0.9 billion € in 2000 to 1.8 billion € in 2005.

In conclusion, in spite of some recent improvements in the treatment of diabetic patients, type 2 diabetes represents in France evaluated at 4.862 billion € in 2000 to 5.710 billion € in 2005.

2. Pathophysiology of type 2 diabetes

2.1. Abnormalities in insulin secretion

According to WHO, type 2 diabetes is defined as resulting from a defect in both insulin secretion and in insulin sensitivity. β-cell dysfunction includes abnormalities in pulsatility and in kinetics of insulin secretion, quantitative and qualitative abnormalities of insulin, β-cell loss and its progression.

2.1.1. Alterations in pulsatile insulin release and in insulin secretion kinetics

In normoglycaemic subjects, insulin displays rapid variations in blood concentrations, with secretory peaks every 5–10 min, and larger oscillations every 60–120 min. In overt type 2 diabetic patients, a reduction or an absence of rapid secretory peaks is observed [9,10]. Normal insulin secretion stimulated by intravenous glucose is characterized by a biphasic pattern, with an early peak rising abruptly 3–5 min after the beginning of the test, and lasting for 10 min, then followed by a slower and more progressive phase, which lasts as long as the glucose infusion. In type 2 diabetes, first-phase insulin secretion is abolished [11,12], and late phase is reduced and delayed. Early phase insulin secretion is pivotal in the transition from fasting state to fed state, as it suppresses hepatic glucose production [13], and lipolysis [14], and crosses the endothelial barrier, preparing target cells to the action of insulin [15]. Decrease in first-phase takes place early in the course of the disease, as it has been reported in impaired glucose tolerance (IGT) [16], as well as normoglycaemic first-degree relatives of type 2 diabetics [17].

2.1.2. Quantitative and qualitative alterations in insulin secretion

In type 2 diabetes, a decrease in basal and stimulated insulin plasma levels has been reported, whatever the BMI [18]. Specific immunoradiometric assay has distinguished true insulin deficiency, masked in type 2 diabetes by an excess in circulating prohormones: pro-insulin, split 32-33 and 64-65 pro-insulin, accounting for more than 40% of the circulating peptides (5% in non-diabetics) [19]. This excess in proinsulin is not a consequence of hyperstimulation of the β-cell, as it is absent from the states of secondary hyperinsulinism, such as obesity and liver diseases.

2.1.3. Progression of abnormalities of insulin secretion with time

Worsening of insulin deficiency has been evidenced by longitudinal studies while insulin sensitivity remained unchanged. Studies in the control group of the UKPDS indicated that residual insulin secretory capacity was decreased by 50% at the time of diagnosis, with a further decrease of 15% 6 years later (Fig. 2) [20]. This decrease is linear during this 6-year follow-up. If one prolongs the line toward the left, the actual onset of the disease may have happened 10 years before, consistent with the results drawn from the retinal status at diag-
sible for the susceptibility variants (PPARG and E23K in KCNJ11) increased only slightly the risk. Recently, a major type diabetes 2 susceptibility gene, accounting for 20% of cases, TCF7L2, has been identified [32]. Studies conducted in European Caucasian, Asian Indian and Afro-Caribbean populations [33] have confirmed the ubiquitous distribution of the association. TCF7L2 is associated with alterations in insulin secretion. Genotype–phenotype relationship studies disclosed severely impaired insulin secretion in carriers of susceptibility variants [34].

Non genetic factors, particularly insufficient supply of nutrients and amino-acids during the foetal life and the first years of life, may also be involved in a defective development of the islets. This defect may result in a reduced β-cell mass, and/or a reduction in the ability to compensate when insulin resistance is present (pregnancy, excess weight or obesity, low physical exercise level, aging). In this respect, Hales and al. [35] have shown that subjects with birth weight in the lowest quintiles are more prone to IGT and type 2 diabetes in adulthood. This hypothesis has been supported by animal models studies [36].

2.1.5. Compensation of insulin resistance by the β-cell

In non-diabetics, the β-cell adapts its secretion rate to the level required by insulin sensitivity, plasma glucose concentrations thus remaining normal, with a hyperbolic relation between insulin secretion and sensitivity [37–39]. If compensation is impaired, plasma glucose rises gradually. Inability of the β-cell to adjust its secretion rate to increased demand explains why glucose intolerance appears in the physiological setting of aging [40], and gestational diabetes.

2.1.6. Origin of β-cell dysfunction

β-cell dysfunction is present at the early stages of the disease, i.e. IFG or IGT, and in normoglycaemic first-degree relatives of patients with type 2 diabetes [17,41,42]. These results rule out the hypothesis of a hyperinsulimism state preceding type 2 diabetes, which was evoked from results of studies with non-specific insulin assay (over-estimating “true” insulin concentrations), or from pseudolongitudinal studies describing the “Starling curve of the pancreas”. In fact, simultaneous plasma glucose levels, and insulin-sensitivity status were not taken into account in these studies. The phenomenon of compensation of insulin resistance by the β-cell has permitted to restore the correct sequence of events leading to the gradual decrease in insulin secretory capacities in type 2 diabetes [38].

2.2. Respective roles of insulin resistance and of the defect in insulin secretion

Type 2 diabetes occurs when 2 major abnormalities co-exist (Fig. 3):

- a reduction of insulin effects (insulin resistance) on target tissues (liver and skeletal muscle);
- a quantitative and qualitative (first phase, pulsatility) reduction of insulin secretion [43–46].

Fig. 2. Insulin deficiency in type 2 diabetes. Studies in the control group of the UKPDS indicated that residual insulin secretory capacity was decreased by 50% at the time of diagnosis, with a further decrease of 15% 6 years later. If one prolongs the line toward the right, the line crosses the x-axis 10–12 years after the date of diagnosis of diabetes [20].

Different explanations have been proposed to explain the progressive reduction in insulin secretion, including glucotoxicity [22] and lipotoxicity [23]. The role of advanced glycation, particularly of the insulin promotor gene [24], has been proposed, as well as the role of deposits in the islets of amylin [25]. More pertinent is the toxic role of reactive oxygen species, produced in excess in uncontrolled diabetes, and responsible for β-cell apoptosis [26,27]. β-cell apoptosis has been evidenced by results of post mortem studies [27,28], and supported by in vitro studies [29]. In the β-cell, mitochondrial production of superoxides ions induced by hyperglycaemia activates uncoupling protein 2 (UCP2), resulting in a decrease in ATP/ADP intracytosolic ratio, and of insulin secretion evoked by glucose [27,30]. Insulin secretion, decreased cytosolic ATP and ATP/ADP ratio, abnormal hyperpolarisation of the mitochondrial membrane, together with hyperexpression of UCP2, of complexes I and V of the respiratory chain, and high levels of a marker of oxidative stress, nitrotyrosine are present in diabetic islets [31]. A 20–40% reduction in the β-cell mass, which determines the amount of insulin released by the pancreas, is present in type 2 diabetes [28]. It contrasts with the β-cell hyperplasia observed in insulin-resistant states without diabetes, such as rodent models of obesity, and human obesity. Reduction in β-cell mass is an early event, as a reduction by 40% is present yet in IGT [27,28].

2.1.4. Genetics and/or environment in the early life

Until now the search for the gene or genes responsible for type 2 diabetes mellitus has failed, except for monogenic subtypes of diabetes (MODY, MIDD, neonatal diabetes). A weak association between type 2 diabetes and the calpain 10 gene had been demonstrated, and the rare known type diabetes 2 susceptibility variants (PPARG and E23K in KCNJ11)
Type 2 diabetes is also associated with an increase in glucagon secretion, which is frequently forgotten, but which has important consequences on hepatic glucose production both in the postabsorptive and the postprandial states. Insulin resistance is characterized by an overproduction of glucose by the liver and a reduction of glucose utilization by skeletal muscle. Insulin resistance results from a defect in insulin signalling pathway in target tissues, secondarily to a dysfunction of adipose tissue. Type 2 diabetes never occurs as long as pancreatic \( \beta \)-cells are able to compensate for insulin resistance by an over-secretion of insulin (prediabetic state). The passage from pre-diabetic state to patent type 2 diabetes is characterized by three major changes. The first one is a reduction of pancreatic \( \beta \)-cells and of compensatory insulin secretion. It is not known whether if this functional defect in \( \beta \)-cells is genetically programmed and/or acquired (glucotoxicity and/or lipotoxicity). This transition is crucial in the natural history of type 2 diabetes. The second one is an overproduction of glucose by the liver, probably secondarily to the oversecretion of glucagon, to an excessive release of free fatty acids and adipocytokines by the adipose tissue. The third one is an increase of insulin resistance in skeletal muscles, frequently linked to the presence of obesity and an excessive release of free fatty acids and adipocytokines. The aim of the present chapter is to summarize the knowledge of biochemical mechanisms responsible for the anomalies of pancreatic hormone secretion and of insulin action and to try to identify the cellular steps, which should be the basis for a pharmacological approach for the treatment of type 2 diabetes.

2.3. Mechanisms of insulin resistance in skeletal muscle and liver

The use of various methods, particularly the euglycaemic hyperinsulinaemic clamp, has allowed identifying a state of insulin resistance in type 2 diabetic subjects \[44,45\]. As 80% of type 2 diabetic subjects are obese, and as insulin resistance also characterized obesity, it is important to distinguish the part due to type 2 diabetes and the part due to obesity. As insulin resistance is observed both in lean diabetic subjects compared to lean non-diabetics and as obese type 2 diabetics are more insulin resistant than non-diabetics with the same degree of obesity, insulin resistance of type 2 diabetes is specific of the diabetic state \[44,45\]. For simplicity, we will use the term “type 2 diabetes” in the text even when diabetes is associated with obesity. In type 2 diabetic subjects, hepatic glucose production is less reduced and peripheral glucose utilization is less stimulated in response to insulin, indicating that both liver and peripheral tissues are responsible for insulin resistance. In man, skeletal muscles are the major tissue responsible for the insulin effect on glucose uptake by peripheral tissue \[44,45\]. It was rapidly established that insulin resistance in skeletal muscle and liver did not result from a decrease in insulin receptor number but from a defect in the insulin-signalling pathway \[44,45,47\], new technologies, based upon nuclear magnetic resonance, have allowed to identify in vivo the cellular steps defective in skeletal muscle of type 2 diabetics \[48\]. It was clearly demonstrated that insulin resistance in skeletal muscle resulted from a defect in insulin-dependent glucose transport. This defect resulted from the inhibition of the phosphorylation of insulin receptor substrate (IRS) on tyrosine inducing a decrease in the association of IRS with the regulatory subunit (p85) of phosphatidylinositol 3 kinase (PI 3 kinase) and a decrease in the signalling cascade responsible for the stimulation of glucose transport. Glucose transport is the rate-limiting step of glucose metabolism in skeletal muscle. The stimulation of glucose transport in response to insulin results from the translocation of glucose transporters (Glut4) localised in membranes of intracellular vesicles to the plasma membrane. The stimulation of glucose transport in response to insulin is reduced by 50% in skeletal muscle of type 2 diabetics and it is correlated with the severity of diabetes \[49,50\]. As the concentration de Glut4 in skeletal muscles of type 2 diabetes is modestly altered \[48,50\], a defect in the translocation (or traffic) of Glut4 is responsible for the decrease of glucose transport.

One of the mechanisms, which could explain the decrease in insulin signalling, is the intracellular accumulation of lipid metabolites (acyl-CoA, diacylglycerol) in skeletal muscle and in the liver \[48\], resulting from the excessive release of FFA from the adipose tissue. Indeed, lipolysis in adipose tissue of type 2 diabetics is less sensitive to insulin than in control subjects, and adipose tissue releases large amounts of FFA, particularly when diabetics are obese. The accumulation of acyl-CoA and of diacylglycerol stimulates a protein kinase C, which phosphorylates IRS on serine residues and induces a decrease in the insulin-signalling pathway \[48\] (Fig. 4). The other mechanism is the oversecretion by adipose tissue of obese diabetics of adiponectins (TNF-\( \alpha \), IL-6, resistine) having anti insulin action (Fig. 5). The lower secretion of adiponectins (adiponectin, visfatin) having insulin like action by adipose tissue of obese diabetics contributes also to insulin resistance. Indeed, in vivo and in vitro studies performed in rodents have clearly shown that adiponectin stimulated glucose transport (muscle) and fatty acid oxidation (muscle, liver) via the activa-
tion of AMP-activated protein kinase, a kinase dependent on the energy state of the cells.

Type 2 diabetic patients have an overproduction of glucose during the post-absorptive period and there was a correlation between the degree of hyperglycaemia and the rate of hepatic glucose production [45]. Glucose overproduction by the liver in type 2 diabetics results from an increase in hepatic gluconeogenesis, glycogenolysis remaining unchanged. Two factors could contribute to enhanced hepatic gluconeogenesis in type 2 diabetics. The first one is chronic hyperglucagonaemia, which stimulates the expression of genes encoding key enzymes of gluconeogenesis, such as phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G-6-Pase) [51]. Suppression of hyperglucagonaemia reduced hepatic glucose production in type 2 diabetic subjects and transgenic overexpression of phosphoenolpyruvate carboxykinase (PEPCK) in liver of mice induced a state of glucose intolerance, but not type 2 diabetes. This suggested that glucose overproduction by the liver contributed to the development of glucose intolerance but was not responsible alone for the appearance of type 2 diabetes. The second factor could be the chronic increase in plasma FFA in type 2 diabetic subjects. Increased hepatic fatty acid oxidation provides co-factors (ATP, acetyl-CoA, NADH) necessary for an active gluconeogenesis [51]. The inhibition of hepatic fatty acid oxidation in type 2 diabetics induced a decrease in hepatic glucose production. Finally, gluconeogenesis being much less sensitive to insulin action than glycogenolysis, the presence of overactive gluconeogenesis in type 2 diabetics could explain the insulin resistant state of the liver. During the postabsorptive or after oral glucose administration (postprandial), hepatic glucose production is not decreased in type 2 diabetics, in contrast to what occurs in non-diabetic subjects [52]. As intestinal glucose absorption and peripheral glucose utilisation (due to hyperglycaemia) of type 2 diabetic subjects are unchanged compared to non-diabetic subjects, the failure to inhibit glucose production is responsible for postabsorptive hyperglycaemia. Several factors could contribute to this failure in type 2 diabetic subjects:

● the inability to inhibit glucagon secretion and the release of FFA from adipose tissue and the disappearance of the first phase of insulin secretion [52];
● the absence of inhibition of hepatic glucose production in response to hyperglycaemia.

As intestinal glucose absorption and peripheral glucose utilization after an oral glucose load are similar in type 2 diabetics (due to hyperglycaemia) and non-diabetics, the absence of suppression of hepatic glucose is responsible for the postprandial hyperglycaemia [53]. Several factors could contribute to this phenomenon:

● the non-suppression of glucagon secretion, the insensitivity of lipolysis to insulin and the delayed secretion of insulin;
● absence of suppression of hepatic glucose in response to hyperglycaemia in type 2 diabetic patients [54].

In conclusion, studies performed in the last few years allowed identifying a number of mechanisms that could explain the defects of insulin secretion and insulin action in type 2 diabetics. The defect in pulsatility and of the first phase of insulin secretion in response to glucose seems to be partly related to an abnormal function of glucokinase and ion channels. Insulin resistance in type 2 diabetes is linked to a defect in the insulin-signalling pathway, secondarily to an excess FFA and a disturbed adipocytokine secretion by adipose tissue. The overproduction of glucose by the liver results both from an increased gluconeogenesis due to an oversecretion of glucagon and to an active fatty acid oxidation in liver. There is probably a very small number of type 2 diabetic patients (< 5%) that suffer from a monogenic defect (glucokinase, insulin receptor, K-ATP channel, mitochondrial DNA), but a large majority of diabetic subjects suffer from polygenic defects and a dysregulation of metabolism in response to chronic hyperglycaemia and dyslipidemia. This is well illustrated by the work
performed using transgenic rodents [55]. Overexpression of key hepatic gluconeogenic enzymes, reduction of glucokinase in pancreatic β-cells, overexpression of a tyrosine kinase deficient insulin receptor in skeletal muscle, invalidation of glucose transporter GLUT4 in skeletal muscle and adipose tissue produce a state of glucose intolerance but never overt diabetes. This is in agreement with the studies on aetiology of type 2 diabetes, which suggest that the development of overt diabetes needs both a defect in insulin sensitivity in target tissues, but also an incapacity of pancreatic β-cells to compensate this defect. Part of the anomaly of insulin secretion and of insulin resistance seems to be linked to the chronic state of hyperglycaemia and dyslipidemia. This is illustrated by the fact that the anomalies of insulin secretion and action are corrected by strict control of glycaemia (exercise, loss of weight, insulin therapy, oral antidiabetic drugs). The identification of biochemical steps, which are altered in type 2 diabetes is crucial for the development of pharmacological agents targeting these steps.

3. Therapeutic overview: present and perspectives

Appropriate diet, weight reduction and physical activity are the cornerstones of the treatment of type 2 diabetes, but the achievement of optimal glycaemic control, which is essential for the prevention of diabetes related complications, generally requires the use of antidiabetic drugs. None of these are able to correct all the anomalies involved in the pathogenesis of type 2 diabetes. So, they generally fail after a few years of evolution of the disease [56]. Combination therapies and even insulin also rarely achieve durable glycaemic control and expose the patient to side effects, particularly hypoglycaemia and weight gain. This explains the intensive pharmacological research of new drugs targeting β-cell function and the response of insulin sensitive tissues, with the aims to reduce therapeutic side effects, to preserve β-cell function and to prevent diabetes related complications.

3.1. Sulfonylureas

The oldest class of oral antidiabetic agents has dominated the market for many years. Presently, sulfonylureas (SU) are no longer recommended as first line therapy in the majority of type 2 diabetic patients, but they remain indispensable in the later stages of the disease. The effect of SU on insulin secretion is known since the early experiments of Loubatières, but their mechanism of action at the cellular level has only been discovered 12 years ago [57]. They act by binding to the sulfonylurea receptor (SUR-1) associated with the proteic units of the K+ channel of the β-cell (Kir 6.2) [58]. This leads to the closure of the K+-channel, an effect, which is physiologically induced by the increase of the ATP/ADP ratio resulting from the metabolism of glucose in the β-cell. The reduction of the K+ efflux depolarizes the β-cell membrane resulting in an opening of voltage dependent Ca++ channels. The increase of intracellular Ca++ concentration triggers the exocytosis of insulin granules.

Sulfonylureas do not promote the synthesis of proinsulin. They potentiate the physiological effect of glucose, but are able to stimulate insulin secretion at low glucose concentrations. Within the SU family, drugs differ in their reversibility of binding to the receptor and β-cell selectivity.

The hypoglycemic effect of SUs is rapid and potent, and an absolute decrease of 1 to 1.5% in HbA1c is usually obtained during the first year of evolution of type 2 diabetes [59]. Several studies have however shown that this effect is less durable than that obtained with metformin [60] and even more with thiazolidinediones (TZDs) [60,61]. The cause of this secondary failure of SU therapy seems to be related to the decrease in β-cell function and mass.

Hypoglycaemia is the major adverse effect of SUs [62]. The risk depends on the pharmacokinetic characteristics (elimination time, activity of metabolites) [63], the reversibility of the binding to the receptor and the potential for drug interactions. Severe hypoglycaemia can occur, particularly in elderly patients, in the case of reduced metabolism or elimination of the drug (hepatic or renal impairment), in the case of drug-drug interactions. Other adverse effects like immune-allergic accidents, digestive intolerance, dilution hyponatremia or alcohol flushing are very rare and drug dependent.

The hypothesis of potential cardiac side effects remains debated. Although SUR-2A, the protein associated to the K channel in cardiomyocytes and vascular muscle cells is expressed at a lower level and binds SUs with a lower affinity than SUR-1 present on the β-cell membrane, some insulin secreting agents considered as poorly selective for SUR-1 or able to bind directly to Kir 6.2 (gliblenclamide, repaglinide) could exhibit, in ischaemic conditions, some deleterious effects which are not observed with more selective SUs (gliclazide, glibenpiride) [64]. Indeed, in normal conditions, the myocardial K channels are maintained closed because of the high ATP/ADP ratio in the cell. In ischaemic conditions however, the channels open as a consequence of the drop in intracellular ATP concentration, reducing Ca++ influx and so decreasing myocardial contractility and oxygen consumption. Non-selective SUs impair this protective mechanism in experimental models [65]. The UKPDS [66] and more recently ADOPT [60] however did not show any increase in coronary events or mortality in the gliblenclamide-treated patients. On the contrary, data from a Danish [67] and an Italian [68] registry suggest a lower relative risk of coronary events or mortality in gliclazide and glimepiride users in comparison to older SUs. A French study in cardiologic intensive care units similarly showed a decrease of the inhospital mortality rate in SU versus non-SU treated diabetics hospitalized for acute myocardial infarction (HR: 0.52; $p = 0.025$) [69], but the mortality rate of the gliblenclamide treated patients (7.8%) was similar to that of non-SU users, while it was reduced in glimepiride and gliclazide users (3.0%) [70].

3.2. Repaglinide

Repaglinide is the only meglitinide derivative available in France. Its pharmacokinetical characteristics, with a rapid con-
centration peak and elimination time after oral absorption explain that the drug has a more pronounced effect on post-prandial glucose levels and a lesser effect on fasting plasma glucose levels than conventional SUs [71]. Because of its almost completely biliary elimination, repaglinide can be used in patients with renal insufficiency.

The mechanism of action of repaglinide is similar to that of SUs, but the drug has two binding sites, one on SUR-1 and one directly on Kir 6.2 [72]. The effect of repaglinide on insulin secretion seems to be more strongly glucose dependent than that of glibenclamide [73,74], but the slow dissociation of the drug from its receptor [75] probably explains that despite its fast elimination time, the risk of hypoglycaemia is only marginally [75,76], or not significantly [77–81] reduced in comparison to conventional SUs.

Medications interfering with CYP 2C8 and to a lesser degree with CYP 3A4 are susceptible to modify the pharmacokinetics of repaglinide.

Lesser weight gain is another supposed benefit of repaglinide in comparison to SUs. There is however no long-term controlled study to evaluate the benefit of repaglinide on weight, or on β-cell function and diabetes related complications.

Nateglinide, a phenylalanine derivative available in some countries, belongs more clearly than repaglinide to the family of postprandial glucose regulators, because of its much shorter duration of action [82].

3.3. Metformin

Since the results of the UKPDS cohort of overweight patients, which showed a beneficial effect of metformin on cardiovascular events [83], this drug is recommended as a first line drug therapy in the majority of type 2 diabetic patients. The major effect of metformin is the reduction of hepatic glucose production, and to a lesser extent improvement of peripheral insulin sensitivity [84]. However, despite five decades of clinical use, the mechanism of action of the drug at the molecular level remains largely unknown [85]. In recent years, it has been attributed to the stimulation of adenosine monophosphate activated protein kinase (AMPK) [85]. Metformin circulates in unbound form and is eliminated by the kidney in unchanged form [85]. Clinically significant drug–drug interactions are rare, but cimetidine has been reported to reduce the renal clearance of metformine. Inversely, the coadministration with acarbose reduces the bioavailability of metformin [84]. Overall, metformin decreases HbA1c to an extent similar to SUs.

Hypoglycaemia is rare in the absence of combination with sulfonylureas, glinides or insulin [83]. Metabolic side effects, particularly abdominal discomfort, anorexia and diarrhea are the most frequently observed adverse events and lead to drug discontinuation in about 5% of patients. They are dose-dependent and can be partly prevented by progressive dose increase [84]. Impairment of cobalamin absorption has been reported, but it rarely leads to frank anaemia. Other adverse effects like cholestasis or immune-allergic manifestations are very uncommon. Lactic acidosis is the most severe adverse effect of metformin therapy, although it is much rarer (1/30 000 patients years) than it had been reported with phenformin in the past [84]. Lactic acid overproduction probably results from the activation of the non-oxidative glucose metabolism by biguanides. When other conditions of increased lactate production (tissue hypoxia, severe cardiac or respiratory insufficiency) or decreased lactate clearance (hepatic or renal dysfunction, including iodinated radiocontrast use), lactic acidosis, a life-threatening complication, can occur.

3.4. Alpha-glucosidase inhibitors (AGI)

Acarbose, miglitol and voglibose (not available in Europe) are competitive inhibitors of the α-glucosidases, the enzymes located in the brush border of enterocytes, which are responsible of the cleavage of saccharose, maltose, maltotriose and several other oligosaccharides. This inhibitory effect delays glucose absorption and consequently decreases the post-prandial glucose peak and insulin response to the meal [86]. Acarbose, a pseudotetrasaccharide, is partly degraded in the bowel and some of its fragments are absorbed and eliminated in urine, while miglitol is totally absorbed and eliminated in unchanged form in urine. Both drugs regulate post-prandial glucose levels and only moderately lower fasting plasma glucose and HbA1c.

The most frequent side effects are digestive: flatulence, abdominal distension, and diarrhea result from the fermentation of unabsorbed carbohydrate in the bowel. They can be partly prevented by limitation of dietary sucrose load and progressive drug dosing. Treatment cessation or poor compliance are however frequent [87].

Except for several cases of increased liver enzymes reported with high doses of acarbose, other side effects are rare. AGIs do not cause hypoglycaemia in the absence of coadministration with SUs or insulin, but in that case, the patient should be advised to use glucose for the correction of hypoglycaemia. In the absence of long-term clinical end point studies and considering the cost and modest effect of AGI on HbA1c, this therapeutic class still has a limited place in therapeutic guidelines.

3.5. Thiazolidinediones

The insulin sensitizing agents thiazolidinediones (TZDs) are agonists of the nuclear peroxysome proliferator activated receptor γ (PPAR-γ), which plays a major role in the metabolism of adipose tissue and indirectly controls glucose metabolism in diabetic patients by reducing free fatty acid levels and favourably altering the secretion of several adipokines involved in insulin sensitivity [88]. By contrast with metformin, TZDs act mainly at the peripheral level and to a lesser degree on hepatic glucose production. In Europe, rosiglitazone and pioglitazone are licensed for the treatment of type 2 diabetes in monotherapy in overweight patients who have a contra-indication or are intolerant to metformin, in combination therapy with metformin in overweight patients or with sulfonylur-
eas, but only if metformin cannot be used, or in triple therapy associated with metformin and SUs. TZDs do not increase the risk of hypoglycaemia when they are given as monotherapy or in combination with metformin. They may have specific cardiovascular protective effects [89], but despite some favourable results of the Proactive study [90], additional proof is needed since a recent meta-analysis of the rosiglitazone trials was suggestive of an increased risk of myocardial infarction and cardiovascular death [91]. This might be related to the differences between both drugs in the lipid profile with an increase of LDL particles with rosiglitazone [92].

The most frequent side effects of TZDs are related to fluid retention which can lead to heart failure in the case of preexisting cardiac disease [93,94] and sometimes anaemia. Oedemas, which frequently occur during TZD treatment, are usually not linked to cardiac failure; they are attributed to the fluid retention and an increased vascular permeability [93]. Another major concern with long term TZD treatment is weight gain [95,96]. Several studies have shown that the weight increase, related to fluid retention but also to fat deposition, predominantly concerns the subcutaneous fat and that the waist/hip ratio slightly decreases during treatment, while insulin sensitivity improves. DREAM [97] and ADOPT [60] have shown that slope of mean weight gain remains constant over time (+0.7 kg per year in ADOPT). Very recently, the increased risk of distal fracture evidenced by ADOPT [60] in rosiglitazone treated women has been confirmed by a re-analysis of the Proactive data. TZDs could reduce osteoblastic differentiation and consequently bone turnover in animals [98,99], and recently an observational study showed bone loss in older female diabetic patients treated with TZDs [100]. Several cases of macular oedema have been reported during TZD treatment and seem to correlate with fluid retention and weight gain [101]. Other side effects like elevated creatinine kinase, and myalgias [102,103] are rare. Finally, large-scale studies and post-marketing observational studies did not find any hepatotoxic potential of rosiglitazone and pioglitazone as it had been reported with troglitazone. On the contrary, a decrease in ALT is observed, indicating an improvement of liver steatosis [60, 90]. In conclusion, current oral therapies of type 2 diabetes offer a large panel of complementary drugs with a good efficacy to control basal and post-prandial hyperglycaemia and reduce HbA1c. They have however several contraindications and side effects, particularly hypoglycaemia and weight increase and do not, with the exception of TZDs, slow the loss of glycaemic control over time. The challenge for new insulin secreting and insulin sensitizing agents will be to offer an equivalent efficacy to available drugs with less side effects and a better durability of effect.

3.6. Are new drugs able to reach some unachieved targets?

Although huge advances have been obtained in the management of type 2 diabetes by the currently available pharmacological arsenal as much as the new and more stringent guidelines [104], new agents should provide better approaches and particularly some unachieved targets or allow new strategies of treatment.

Thus, even if it represents the universal and unquestionable current first line therapy of all guidelines, metformin does not address the first disorder causing type 2 diabetes, β-cell dysfunction. Moreover the UKPDS showed a progressive failure of insulin secretion and a need for protecting β-cells against decline and apoptosis. Traditional treatments for type 2 diabetes do not address the progressive decline in β-cell function and therefore, despite therapy; patients continue to advance in their disease state. Only TZDs are supposed to be able to play such a role [60]. Sulfonylureas, which effectively stimulate insulin secretion, may cause hypoglycaemic attacks particularly in patients with mild hyperglycaemia or older subjects by inappropriate insulin secretion (i.e. whatever the glycaemic levels). Except metformin, all the oral drugs, sulfonylureas and TZDs as insulin injections favour weight gain and/or stimulate appetite [56]. Lastly, in addition, in type 2 diabetic patients, glucagon production by α-cell, which normally maintains hepatic glucose production during fasting periods, is not suppressed by meal ingestion. This increased glucagon secretion leads to inappropriate levels of hepatic glucose output in the post-prandial state and consequently to hyperglycaemia. In summary, pancreatic islet dysfunction (α- and β-cells) is a rational target for the treatment of type 2 diabetes [105,106].

The search for new and effective therapies for type 2 diabetes has led to the identification of a novel therapeutic target, the “incretin” hormones, which play a role in mediating glucose homeostasis via effects on glucagon and insulin secretion from pancreatic islet α- and β-cells, respectively. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are hormones secreted by the enteroendocrine cells of the gut in response to the ingestion of nutrients. These incretin hormones, so called because they increase insulin secretion, are key modulators of pancreatic islet hormone secretion and, thus, glucose homeostasis. Moreover GLP-1 decreases glucagon secretion. Studies demonstrating that incretin activity is impaired in type 2 diabetes have led to investigations into incretin-based new therapies such as incretin-mimetics, analogues of GLP-1 (i.e. a long-acting GLP-1 receptor agonist) as exenatide, a long-acting GLP-1 analogue (liraglutide) and inhibitors of dipeptidyl peptidase-IV (DPP-IV), a ubiquitous enzyme that rapidly inactivates both GLP-1 and GIP, increase active levels of these hormones and, in doing so, improve islet function and glycaemic control in type 2 diabetes [107,108].

4. DPP-IV inhibitors

These inhibitors of dipeptidyl peptidase-IV (DPP-IV) have been recently launched in the US and will be soon on the European market after many large preclinical and clinical studies (mainly three pharmaceutical companies and drugs: sitagliptin vildagliptin and saxagliptin). DPP-IV inhibitors stabilize endogenous GLP-1 at physiological concentrations, and induce insulin secretion in a glucose-dependent manner; therefore, they do not demonstrate any hypoglycaemic effects since their effects, on the β-cell, end when glycaemia reaches a normal value. Furthermore, they are orally bioavailable. In addition to their ability to protect GLP-1 against degradation, DPP-
IV inhibitors also stabilize other incretins, including gastric inhibitory peptide and pituitary adenylate cyclase-activating peptide. They also reduce the antagonistic and desensitizing effects of the fragments formed by truncation of the incretins. On the other hand, potential risks associated with DPP-IV inhibitors include the prolongation of the action of other peptide hormones, neuropeptides and chemokines cleaved by the protease, and their interaction with DPP-IV-related proteases. Thus, a high specificity of enzyme inhibitor is required for reducing the risk of some deleterious side effects [109]. Another major concern is represented by the long-term stimulation of pancreatic cells. However, DPP-IV inhibitors increase incretin levels toward normal and not pharmacological values, by contrast to some other drugs [110].

In clinical studies, when used for the treatment of type 2 diabetic patients over a 1-year period, DPP-IV inhibitors show improved efficacy over time. This finding can be explained by a GLP-1-induced increase in the number of beta cells [111]. The oral DPP-4 inhibitors vildagliptin, sitagliptin and saxagliptin are being evaluated as both monotherapy and in combination with the most commonly prescribed oral anti-diabetic drugs (OADs).

4.1. Preclinical studies

Studies with vildagliptin and sitagliptin have shown increased levels of active GLP-1 both at baseline and in response to a meal. Only one-third to one-half of the postprandial GLP-1 in the plasma of healthy subjects and patients with type 2 diabetes consists of active GLP-1. By contrast to incretin-mimetics (analogues of GLP-1, i.e. exenatide) raising the proportion of active GLP-1 rather than the total GLP-1 concentration, DPP-4 inhibition results in only modestly elevated plasma levels of GLP-1, supporting the physiological role of GLP-1 without producing GLP-1 concentrations that induce the GLP-1-related side effects. Several studies have demonstrated increased insulin secretion with DPP-IV inhibitors leading the investigators to suggest that DPP-4 inhibitors may be able to improve β-cell function in humans [112].

4.2. Clinical studies with DPP-IV inhibitors

Many DPP-IV inhibitors have entered clinical trials, vildagliptin, sitagliptin, and saxagliptin, for those in late-stage development. The DPP-IV inhibitors have been currently evaluated as monotherapy and as combination therapy with previous OADs in patients with type 2 diabetes. To date, about 11 000 patients have been enrolled in vildagliptin and sitagliptin phase 2 and 3 studies until for > 52 weeks in some of them.

4.3. Vildagliptin monotherapy

Monotherapy with vildagliptin during 12 weeks improves HbA1c in patients with type 2 diabetes [113]. The effect is more pronounced in patients having the higher baseline HbA1c, from baseline to endpoint −0.6 ± 0.2% or the whole cohort (baseline 8.0%) and −1.2% for subjects with baseline HbA1c 8.0–9.5%. Vildagliptin at a dose of 100 mg for 4 weeks reduced fasting and postprandial glucose concentrations, as well as plasma glucagon levels, while the ratio of insulin to glucose increased [114] A large 52-week study of vildagliptin 50 mg twice daily versus metformin 1000 mg twice daily (baseline HbA1c 8.7%) showed a mean change in HbA1c from baseline to endpoint of 1.0% for vildagliptin and 1.4% for metformin sustained throughout 1-year of treatment. However this difference in HbA1c did not establish non-inferiority of vildagliptin 100 mg per day versus metformin 2000 mg per day but a clinically significant sustained reduction in HbA1c was obtained throughout 1-year of treatment with vildagliptin. [115,116]. In an other study vildagliptin monotherapy (100 mg daily) was compared to rosiglitazone alone (8 mg daily) baseline HbA1c was 8.7% with a similar decrease after 24 weeks treatment, with most of the HbA1c reduction achieved by weeks 12 and 16, respectively. At end point, vildagliptin versus rosiglitazone improved HbA1c by −1.1 and −1.3%, respectively, meeting the statistical criterion for non-inferiority. In patients having the lowest BMI (< 30 kg/m²) vildagliptin reduced HbA1c more than rosiglitazone (1.3 vs. 1.08). In this study, in patients with the highest BMI (> 35 kg/m²), a difference of 2.8 kg was observed between groups (−1.1 in the vildagliptin vs. +1.7 in the rosiglitazone group) [116]. Similar results have been obtained after 24 weeks, with sitagliptin 100 mg per day in monotherapy, about −1% HbA1c and excellent tolerance mainly regarding the hypoglycaemic risk [117].

4.4. Sitagliptin monotherapy

Similar results were found with 100 and 200 mg sitagliptin monotherapy during a 24 weeks study versus placebo HbA1c −0.79 and −0.94%, respectively [118]. Only one trial has compared a DPP-IV inhibitor, sitagliptin, and a sulfonylurea, glipizide, in monotherapy in a long-term (12 weeks) study, in order to assess both drugs in patients with type 2 diabetes who have inadequate glycaemic control on diet and exercise (baseline HbA1c 7.9 ± 1%). Glipizide exhibited a more pronounced glycaemic lowering effects versus sitagliptin 100 mg (50 b.i.d), −1 versus −0.77% HbA1c. But it remains difficult to interpret this small a difference, because the up-titration of glipizide was not stringently described. However in these conditions less hypoglycaemic attacks (1.6 vs. 17.1%) and no or limited weight gain (0.4 vs. 0.9 kg) were found in the sitagliptin group by contrast to glipizide [119].

In general, for all these studies, relative to baseline, body weight did not change significantly, or moderately decreased in any of the “gliptin” groups and the drugs were well tolerated, better than metformin or TZD in the comparator groups. Thus initial monotherapy with a DPP-IV inhibitor is equivalent or rather a bit less effective when compared to the recommended first line therapy, metformin or its alternate if not tolerated, TZD.
4.5. Vildagliptin combination therapy

Adding vildagliptin to metformin in patients with type 2 diabetes resulted in a decrease in HbA1c after 12 weeks compared with placebo, with a 1.1 ± 0.2% difference in HbA1c in the 40-week extension study [120]. Insulin secretion (post-meal 0–30 minutes C-peptide), was increased in the vildagliptin group compared with metformin alone [121].

In a 6-month study, type 2 diabetic patients received vildagliptin 100 mg per day plus pioglitazone 30 mg per day or a monotherapy. In these patients a statistically significant reduction in HbA1c (−1.9%) was observed, compared with patients randomized to pioglitazone 30 mg alone (−1.4%). Among patients with higher baseline HbA1c values (≥9%) the combination of vildagliptin and pioglitazone produced a reduction in HbA1c of 2.8%. Furthermore, two-thirds (65%) of patients on vildagliptin plus pioglitazone achieved the EASD-ADA consensus HbA1c target of ≤7% [122]. Vildagliptin has been added for 24-weeks in type 2 diabetic patients with a long history of insulin therapy inadequately controlled (HbA1c 7.5-11%) by insulin versus a control group continuing insulin therapy alone. Baseline HbA1c averaged 8.4 ± 0.1% in both groups. The adjusted mean change from baseline to endpoint in HbA1c was −0.5 ± 0.1% and −0.2 ± 0.1% in patients receiving vildagliptin or placebo, respectively (P = 0.01). In patients aged ≥65 years, the delta HbA1c was −0.7 ± 0.1% in the vildagliptin group versus −0.1 ± 0.1% in the placebo group (P < 0.001). The incidence of adverse events was similar in the vildagliptin (81.3%) and placebo (82.9%) groups. However, hypoglycaemic events were less common (P<0.001) and less severe (P < 0.05) in patients receiving vildagliptin than in those receiving placebo [123].

4.6. Sitagliptin combination therapy

In a 52-week study of adjunctive sitagliptin 100 mg once daily was compared to glipizide up to 20 mg per day in patients with HbA1c 7.5% (baseline) on metformin monotherapy. Both groups showed significant reductions in HbA1c of −0.67% compared with baseline, which confirm for non-inferiority versus glipizide and few side effects mainly less or no hypoglycaemias with sitagliptin [124]. Efficacy and safety of 100 mg sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone has been studied in a large 24 week study. This bitherapy was efficacious (−0.67% HbA1c) and well tolerated in patients with type 2 diabetes inadequately controlled with metformin alone [125].

5. Long-acting GLP-1 analogues, and GLP-1-receptor agonists

Long-acting glucagon-like peptide 1 analogue (liraglutide), and GLP-1-receptor agonists (exenatide) are more powerful on glycaemic control compared to DPP-IV inhibitors. Effect of GLP-1 analogues starts later, after a few weeks, and produces a more marked benefit on weight. However, DPP-IV inhibitors compared with GLP-1 analogues are orally administered and cause little effects on gastric emptying, and subsequently few or no gastrointestinal side effects.

6. Conclusion

If one considers the international guidelines and the clinical results obtained with DPP-IV inhibitors, it is possible to suggest their integration in the following way. Admittedly, whether in the future, one can imagine DPP-IV inhibitors as an alternative first line of treatment for type 2 diabetes, metformin will probably remain, for years, the most evidence-based, recommended, less expensive and most used first line OAD. Long-term studies considering safety, durability on glycaemic effects and glucagon inhibition, β-cell preservation, will be necessary before reconsidering this classic initial strategy. Thus, it is obvious that it is rather logical to use DPP-IV inhibitors in combination with OADs acting on insulin-resistance, mainly when HbA1c is moderately elevated (i.e. efficiency and no hypoglycaemic risk). Indeed one of the most promising results of this new class of drugs is the absence of hypoglycaemic events and/or weight gain when compared to sulfonylureas, glitazones and insulin. Nevertheless, in contrast to metformin and sulfonylureas, this new class has not yet evidenced its safety and its efficacy on “events” (microangiopathy and cardiovascular prevention) on long-term studies beyond their benefits on “intermediate criteria”. Their alleged β cell protection must be demonstrated by human trials. For the moment, their profile allows for earlier combination therapies in the many moderately hyperglycaemic (≥6.5% to < 7.5% HbA1c) type 2 diabetics, and possibly in some fragile or older subjects. This new class should help clinicians apply the new and more stringent guidelines. Tritherapies, combining metformin/TZD–DPP-IV inhibitors, must be considered as promising. However, until the results of ongoing trials are available, such combinations are not yet recommended.

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