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Chapter

Pathogenesis of Type 2 Diabetes Mellitus

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Abstract

Type 2 diabetes mellitus (DM2) results from the interaction between genetic and environmental factors which cause insulin resistance (IR) and deficit in insulin secretion. Genes encoding insulin-related enzymes or protein factors are candidates for the disease, most probably the insulin receptor substrate-1 (IRS-1), phosphoinositide 3-kinase (PI-3 K), calpain 10, and transcription factor 7-like 2 genes. Environmental factors that favor DM2 are android obesity, aging, glucotoxicity, and lipotoxicity. IR is the result of less insulin receptor binding, of less phosphorylation of the receptor, of IRS-1, of PI-3 K, and of glucose uptake by glucose transporters. At the hepatic level, glucose is produced by gluconeogenesis: in the muscle there is less glycogen deposition, and in adipocytes there is greater release of free fatty acids (FFA). Insulin secretion is the main pathogenic factor; relative insulin hyposecretion is not capable of compensating for the IR. Reduced incretin effect, hyperglucagonemia, and increased renal glucose reabsorption favor hyperglycemia. Disturbance of the microbiota releases proinflammatory adipocytokines which contribute to IR. Reactive oxygen species generation, caused by hyperglycemia and FFA, results in a decrease in insulin synthesis and action and also endoplasmic reticulum stress and mitochondrial dysfunction. Knowledge about the pathogenesis of DM2 has allowed the development of drugs for its treatment.

Keywords: type 2 diabetes, pathogenesis, environment, sleep disturbances, insulin resistance, glucotoxicity, lipotoxicity, microbiota

1. Introduction

Type 2 diabetes mellitus (DM2) is a complex metabolic and endocrine disorder resulting from the interaction between genetic and environmental factors, which cause different degrees of alteration in insulin functionality on peripheral tissues, as well as in the pancreatic β cell. Underlying pathologies such as excess weight and obesity, particularly of the android type, are the main factors that favor the development of DM2 [1, 2].

In absolute terms, insulinemia of diabetic subjects may be similar to those of euglycemic individuals but are proportionally insufficient in the hyperglycemia states. Reduced insulin action, for determined levels of the hormone, is known as insulin resistance (IR). When β cells undergo IR, initially there is insulin hypersecretion which compensates for the lack of hormonal action. Hyperglycemia only manifests when there exists a relative insulin hyposecretion to the glucose stimulus [3].

2. Natural history of DM2

DM2 is a progressive disease that develops in stages. Its natural history probably begins 10–20 years before its clinical onset, as a preclinical period with IR [4].

Hyperinsulinemia is initially capable of maintaining normal fasting and postprandial glycemias. This stage would be associated with increased levels of free fatty acids (FFA) in the obese IR patient.

Subsequently, and before DM2 manifests, IR is maintained, but the secretory capacity of the β cell begins to decline and glycemias rise, reaching abnormality levels for fasting glycemia and glucose intolerance, which are prediabetes stages. In these periods, chronic hyperglycemia is an important factor in the perpetuation of damage to the pancreatic β cells; as it increases and IR is maintained, glycemic levels progressively increase until finally clinical diabetes is established.

The stages of the pathogenesis of DM2 are shown in **Figure 1**.

The insulin secretory defects observed in DM2 contribute to IR. During the evolution of DM2, the IR state is maintained, and the insulin secretory capacity gradually decreases, arriving at an insulin hyposecretion in which it will be necessary, in some cases, to start insulin therapy.

Hyperglycemia in DM2 not only represents the biochemical manifestation of the disease, but it is rather, in itself, a permanent factor responsible for maintaining the diabetic state.

We will now refer to the multiple factors involved in the genesis of DM2.

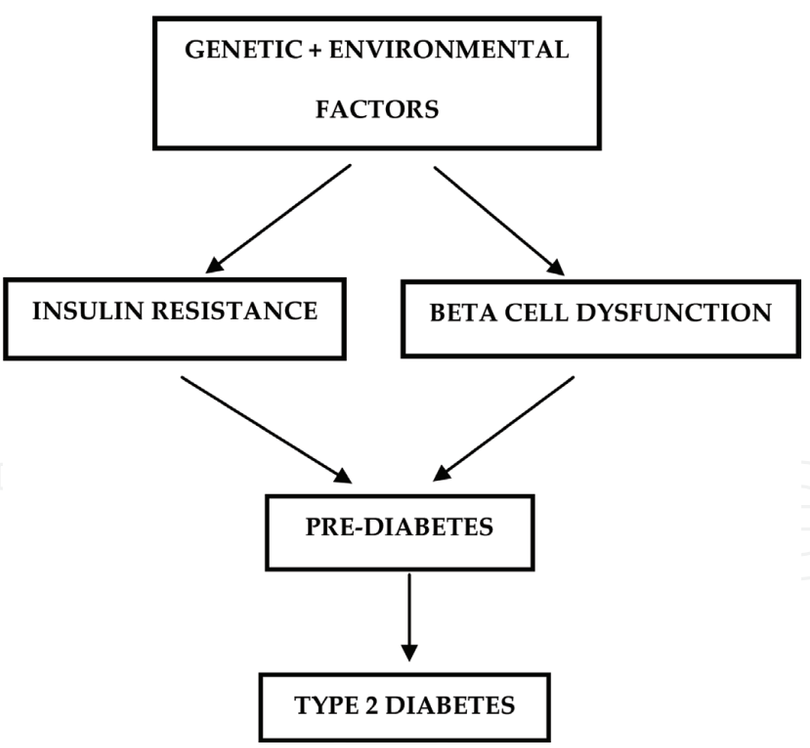

Figure 1.
Stages in pathogenesis of type 2 diabetes.

3. Genetic factors of DM2

Presently, DM2 is considered to be a disease with a strong hereditary component. Thus, 35–50% of the patients have diabetic relatives, a number that is lower (15%) in subjects not having this pathology. If a survey for DM2 is conducted on the patients' parents, 10–30% of them have the disease in comparison to 1–6% in healthy controls.

In the Framingham Offspring Study, it was found that if one of the parents was diabetic, in the offspring the relative risk was 3.6; if both parents had the disease, it rose to 6.0. This study indicates that the risk for diabetes in sons or daughters of diabetic parents is similar regardless if it is the father or the mother who has the disease [5]. In monozygotic twins, there is up to 96% match for DM2, a percentage that falls to less than 50% in fraternal twins.

All genes that encode enzymes or protein factors associated with insulin secretion and action are possible candidates for the disease. It has been published that the hereditary factor is stronger than the environmental factor for the secretory defect. In IR, genetic and environmental factors have 50% participation each.

Table 1 shows the most relevant candidate genes for DM2, which are related to the insulin secretion defect and to IR.

Each gene has been found to be altered in approximately 10% of the DM2 patients studied. Therefore, it is necessary for the individual to have at least 10 defective genes for the disease to develop. Besides, in the various populations, different genotypes involved would exist, and differences would appear also in individuals of a same ethnic group.

3.1 Genetic defects of IR

Genetic mutations have been found in certain protein factors and enzymes associated with the transmission of the insulin signal inside the effector cell, which would allow to partly explain the IR of DM2 [6–8]. In the insulin receptor substrate-1 (IRS-1) gene, the mutation of glycine to arginine at codon 972 is twice more prevalent in Caucasian DM2 patients than in nondiabetic controls.

Insulin resistance genes
1. Directly associated with lower glucose uptake
• Insulin receptor substrate gene
• Phosphoinositide 3-kinase gene
2. Explaining the obesity-type 2 diabetes relationship
• β-3 adrenergic receptor gene
• Tumor necrosis factor alpha gene
• Peroxisome proliferator-activated receptor gene
3. Adipocytokines in obesity
• Leptin gene
• Resistin gene
• Adiponectin gene
4. Lipid metabolism
• Lipoprotein lipase gene
• Fatty acid-binding protein gene
5. The thermogenesis obesity relationship
• Uncoupling protein gene
Insulin secretion genes
• Insulin receptor substrate gene
• Calpain 10 gene
• K+ inwardly rectifier channel gene

Table 1.
Candidate genes of type 2 diabetes.

For phosphoinositide 3-kinase (PI-3 K), it has been demonstrated that in DM2 its synthesis is lower because the messenger RNA levels are lower.

In the relation of obesity with DM2, correlation, among the possible genes involved, mention is made of the tumor necrosis factor alpha (TNFα) gene, a polymorphism in its promoter consisting of the substitution of guanine to adenine at position 308, which originates higher TNFα synthesis in obese IR patients. The finding regarding leptin is very interesting, in studies on thousands of cases since only five have genetic mutations for the hormone, suggesting that obesity in DM2 humans would be associated with leptin resistance at the level of its receptors. On the other side, the adiponectin gene is located on chromosome 3q27, and in this position, a locus has been found which confers susceptibility to DM2. For resistin, it has been reported that its genetic expression is four times higher in abdominal adipose tissue than in subcutaneous adipose tissue.

The hereditary basis of IR in DM2 is extremely complex, moreover, when the obesity factor is included having its own polygenic component. DM2 patients have different degrees of IR with probably different genetic origins; this explains why their clinical behavior is singular.

3.2 Genetic defects in insulin secretion

In DM2, the genes encoding the different protein components that participate in the mechanism of insulin synthesis and secretion are potential candidates [9, 10]. Among the most likely ones is the IRS-2 gene, which is very interesting because a polymorphism has been described which predicts anomalies both in insulin secretion and action. In 2000, a false announcement was issued regarding the discovery of the gene of DM2, referring to the calpain 10 (CAPN10) gene that encodes a family of calpain enzymes, which are calcium-activated proteases that take part in the regulation of insulin exocytosis in β cells. It was published that in Pima Indians, a specific combination of CAPN10 alleles triplicated the risk of DM2. However, in recent years, the transcription factor 7-like 2 (TCF7L2) gene has appeared to be more relevant in the genetic susceptibility to DM2, since a polymorphism of this gene has been found in several ethnic groups of DM2 patients. This factor is associated to a reduced response to glucagon-like peptide-1 (GLP-1) because GLP-1 expression in enteroendocrine cells is regulated by TCF7L2, which would have as a final consequence, a failure in β cell proliferation and in insulin secretion; thus, variants of the TCF7L2 gene would contribute to the risk for DM2.

It can be said that DM2 is a polygenic disease with many susceptibility genes, each with a slight impact on its pathogenesis but giving origin to several subgroups of DM2 on account of their genetic differences. Thus, in the various individuals and in the different ethnic groups, genetic heterogeneity results in variable degrees of alterations both in insulin secretion and action.

4. Environmental factors of DM2

Environmental factors are considered to be all situations that favor the development of this type of diabetes.

4.1 Obesity

General obesity, and in particular the android type, is the main environmental factor in the genesis of DM2. In our experience, at diagnosis of DM2, 80% of the patients are obese.

Historically, it was believed that fat tissue was metabolically neutral, being only an energy reservoir. In recent years, it is considered to be a real endocrine organ with a huge importance in the pathogenesis of DM2 and IR [11].

The increase in visceral adipose tissue results in higher levels of FFA that activate the β isoform of protein kinase C (PKCβ) and inhibit glucose transport-4 (GLUT-4) translocation to the cell membrane, reducing glucose entry into insulin target tissues. TNFα and interleukin-6 (IL-6), by phosphorylating IRS-1 on serine/threonine residues and not on tyrosine, disrupt the correct transmission of the insulin signal.

Adipose tissue also secretes several hormones known as adipocytokines; among them we will refer, in relation to the increase in IR, to leptin, adiponectin, and resistin. DM2 patients exhibit elevated leptin levels, favoring obesity due to greater food intake and lower caloric expenditure. In humans, the defect is a resistance to leptin action at the hypothalamic receptor level, with obesity developing as these receptors become insensitive to leptin. Adiponectin is the only adipocytokine whose circulating levels are diminished in obesity. It is interesting to point out that the low adiponectin levels are observed particularly in coronary patients, constituting a risk marker for this pathology. In respect of resistin, there has been much controversy regarding its role in obesity and DM2. Its overexpression is associated to IR, dyslipidemia, and DM2, through inhibition of cell glucose uptake.

4.2 Aging

The influence of age on the development of DM2 is indisputable only by reviewing the universal epidemiology of this type of diabetes, which shows a progressive increment of its prevalence rates with increasing age. Glucose tolerance deteriorates with aging, which has been attributed to the loss of muscular mass and increase in adipose tissue (sarcopenia), especially in sedentary individuals, increasing IR in susceptible subjects [12].

It has been proposed that at an older age, mitochondrial functions decline favoring IR and, on the other side, leptin resistance rises intensifying visceral fat deposition, increasing IR and inducing DM2.

4.3 Psychological stress

Acute psychological stress has been acknowledged for many years as a factor which favors the onset of diabetes. This is because sympathetic activation reduces the functionality of the pancreatic β cell, diminishing insulin secretion.

At the same time, in the muscle there is a decline in insulin sensitivity, glucose uptake, and glycogen deposition, all of which elevates glycemia and clinically favors the development of DM2.

Among the psychosocial factors related to this type of diabetes, depression in its different degrees has been widely studied, and a bidirectional association has been found between both disorders. It is bidirectional in the sense that depression induces DM2 and diabetics suffer from 30% more depressive states than nondiabetics [13].

The Cardiovascular Health Study demonstrated, in elderly adults, that those who reported strong depressive symptoms developed DM2 more frequently than their non-depressive peers. This association cannot be totally explained by differences in the risk factors for DM2. It is likely that both disorders have a common feature [14].

Although the intimate mechanism of this association is not known, it has been speculated that it could be related to inflammation, considering that inflammatory markers are present in diabetes and in depressive states. Some authors have found elevated C-reactive protein levels in these cases, but this has not been confirmed by others.

It has been established that depressive subjects are physically less active and that, due to their psychic disorders, also have poor eating habits, both behaviors favoring obesity, IR, and DM2. Diabetics are highly sensitive to the effects of physical stress, which is related to adrenergic stimulation that could reduce insulin secretion and glucose utilization.

In recent years, abnormal glucose metabolism has been correlated with various sleep disturbances, such as duration, fragmentation, quality, respiratory function, obstructive sleep apnea, hypoxemia, and circadian rhythm. This situation is explained by an increase in cortisol, growth hormone, inflammatory markers, and adipocyte function. There also exists a reduction in brain glucose utilization, with an increase in ghrelin, a situation that leads to obesity. This is reflected in an increase in IR and a reduction in β cell function, ultimately favoring hyperglycemia and DM2 [15].

4.4 Glucotoxicity and lipotoxicity

The concepts of glucotoxicity and lipotoxicity, related to DM2, appear in the 1990s, supported by experimental studies in animals which have been subsequently confirmed in humans. At present, glucotoxicity is defined as the adverse effects produced by chronic hyperglycemia on cell structures and functions. Hyperglycemia would cause an inhibition of the hormone synthesis through a decrease in messenger RNA for insulin; therefore, glucose would be capable of inducing damage at the level of the genetic information which is indispensable for a correct insulin synthesis [16].

Other mechanisms involved in glucotoxicity would be the lower activity of phospholipase C, an enzyme necessary for the formation of inositide phosphates which participate in insulin secretion by increasing the intracellular calcium level. Cytotoxicity to the β cell by glucose, acting as a free radical, is also possible, causing greater β cell apoptosis.

In 1963, Randle proposed that the increase in FFA, as a result of the degradation of triglycerides, causes peripheral IR. A great FFA mobilization due to greater lipolysis induces an increase in FFA oxidation in the muscle and the liver, with less glucose utilization in the former and higher hepatic gluconeogenesis; this leads to hyperglycemia plus inhibition of insulin secretion, which further elevates serum glucose levels. FFA are deposited in the muscle as triglycerides, ectopic deposits which favor IR. In the β cells, reactive oxygen species (ROS) increase, thus reducing insulin gene expression and secretion [17]. Therefore, a dual mechanism is acknowledged to lipotoxicity in the pathogenesis of DM2: it favors IR and has a direct deleterious effect on β cells. Probably, ROS produce less insulin secretion due to a lower GLUT-2 activity.

Glucotoxicity and lipotoxicity, disclosed separately for didactic reasons, coparticipate in the genesis of DM2 and interact together causing structural and functional damage in β cells and in target organs. Thus, glucotoxicity describes more accurately the reality of the chronic deleterious process. Glucolipotoxicity is capable of causing inflammation in pancreatic β cells and in the peripheral tissues where insulin acts. In the β cells, an activation of the nuclear factor kappa beta (NF-kβ) pathway occurs, increasing the production of NF-kβ which is an inflammatory cytokine. In the visceral adipose tissue, there is a decrease in adiponectin which is anti-inflammatory (insulin-sensitizing) and an increase in the proinflammatory cytokines: leptin, TNFα, and IL-6.

This chronic low-grade inflammatory state is referred to as a metainflammation [18].

4.5 Oxidative stress

ROS, generated both by hyperglycemia and increased FFA levels, would have the most important role in the onset and progression of DM2. In β cells, ROS [18] cause a

decrease in insulin synthesis and secretion; since β cells have a low antioxidant capacity, excessive ROS production results in an imbalance of the redox state, tilting the balance toward oxidation. In peripheral tissues that are targets for insulin, ROS favor inactivation of insulin signal transmission. It has also been observed that inflammation, mainly through the increase in IL-6 and TNFα, favors IR and β cell dysfunction.

On the other side, the production of chemicals used worldwide in different activities including the food industry, probably through ROS generation, has increased progressively since 1940. In the USA, a direct relationship has been found between the production curves of synthetic organic chemicals and the prevalence of diabetes and other pathologies [19]. The Environmental Protection Agency has defined as endocrine-disrupting chemicals, exogenous agents that interfere with the production, secretion, transport, metabolism, binding, action, or clearance of hormones.

4.6 Endoplasmic reticulum stress and endothelial dysfunction

The endoplasmic reticulum actively participates in protein synthesis, producing the correct folding of proteins by means of chaperones, which are helpers of this process. Activating signals such as hyperglycemia increase the demand for insulin synthesis, causing endoplasmic reticulum stress in β cells; this induces apoptotic pathways as a normal adaptive metabolic response to a metabolic load. In DM2, the endoplasmic reticulum stress caused by glucotoxicity and inflammatory cytokines can lead to β cell dysfunction and death [20].

The β cell mitochondrion participates in insulin synthesis and in exocytosis. In diabetes, a mitochondrial dysfunction occurs: the mitochondrial membrane proteins are diminished, and transcriptional changes occur in their formation. Mitochondrial dysfunction, induced by glucotoxicity, results in β cell failure, increase in ROS, and oxidative stress.

In IR, the excess of circulating fatty acids associated with the reduction in the number of mitochondria causes an increment in the level of intracellular FFA and also of diacylglycerol. These molecules activate PKC which in turn activates the serine kinase cascade, leading to an increment in the phosphorylation of the serine residues in IRS-1 and preventing the phosphorylation of tyrosine residues, which in turn inhibits PI-3 K activity, finally resulting in the suppression of insulin-induced glucose transport [21].

4.7 Diet and nutrients

In recent years, a special interest has aroused for studying the influence of the diet in general and of different nutrients in particular, on the development of DM2.

There is a consensus in that a healthy diet with no caloric excess and a suitable physical activity are the most effective measures for preventing DM2. There is also clinical and biological evidence that excessive sugar consumption promotes the development of DM2 and of cardiovascular disease [22].

The effect of dietary fat on the risk for DM2 is not absolutely clarified, and some studies have even provided contradictory results; but there exists a consensus in that the quality of the fat is more important than the total amount. Dietary fat is not only a source of energy, but also fatty acids affect cell metabolism. Monounsaturated fatty acids and trans-fatty acids would not be associated with a higher incidence of DM2.

In relation to dietary fats, arrives at more categorical conclusions indicating that a diet high in monounsaturated fatty acids (olive oil) and polyunsaturated fatty acids of marine origin is associated with low risk of DM2 [23]. This is confirmed by the fact that consumption of Mediterranean diet, high in monounsaturated fatty acids from vegetable oils and polyunsaturated fatty acids from fish, reduces the risk for DM2.

For a long time, it was believed that free consumption of fructose had no negative effects on the body, since it does not require insulin for its metabolism. Recent studies demonstrate the exact opposite, stating that excessive intake favors metabolic syndrome. In recent years, the high fructose consumption in corn syrups in the USA is correlated with the increased prevalence of DM2, obesity, and cardiovascular disease.

The so-called fructose hypothesis postulates that a high fructose content in the diet induces activation of peroxisome proliferator-activated receptor gamma (PPAR-ϒ) responsible for IR, lipogenesis, and DM2 [24]. Besides, the fructose load with the resulting hepatic stress causes the release of proinflammatory cytokines such as TNFα that induces IR and favors the development of DM2.

The association between gluten intake and DM2 has been the subject matter of recent studies. In US healthy men and women, an inverse correlation has been found between gluten intake and incidence of DM2.

Subjects receiving a diet with high gluten content, followed up for 20–28 years, exhibit low DM2 rates [25]. The cause would be in that subjects who eat gluten-rich foods also receive an elevated supply of cereal fiber. The mechanism through which gluten reduces the risk of DM2 is unknown but is probably related to favorable changes in gut microbiota.

Presently, the effect of vitamin D supplements at pharmacological dosages in the prevention of both type 1 and type 2 diabetes is being debated. Epidemiologic studies demonstrate a relationship between vitamin D deficiency and DM2, as well as the higher frequency of this type of diabetes in areas with low sun exposure. In prospective studies of up to 20 years in humans, it has been demonstrated that the incidence of DM2 decreases by providing a daily supplement of 800 IU of vitamin D [26]. However, other studies do not show the same results; it could be concluded that supplying vitamin D to persons at risk for diabetes is an advisable measure, even though there is still not enough scientific evidence to support this position.

5. Deficit in insulin secretion

In DM2 patients, deficit in insulin secretion is the building block of its pathogenesis. It has been found that the disturbances caused are both quantitative and qualitative and are present in variable degrees in the patients.

When the secretory disorder appears, hyperglycemia manifests. It has been demonstrated that, in general, individuals exhibiting the most severe hyposecretion have the highest glycemias. The graphic relationship of fasting and postprandial glycemias versus insulinemias is very well known and gives origin to the inverted U or Starling curve; at low glucose values, insulinemias are also low and then the relationship is inverse, and at higher glycemias, there are lower insulinemias [27].

In DM2 patients, the lack of insulin response to glucose worsens with the years of evolution of the disease and is accentuated with the persistent hyperglycemias (glucotoxicity). Once glycemia rises, a vicious circle is produced because glucose on its own causes changes in β cells, paradoxically slowing down insulin secretion [28].

DM2 patients exhibit changes in the biphasic insulin secretion curve under a stimulus of intravenous glucose; the first phase is lost, the second phase shows less elevation and is more prolonged in time than in the normal curve. These alterations, which are present since the prediabetes state, reduce the effectiveness of insulin. Besides, in DM2 patients, there are a lower number of pulses of insulin secretion under glucose stimulus [29]. Similar to other hormones, insulin is more effective when secreted in pulses that released continuously.

At the anatomical level, in the pancreas of DM2 patients, there is a 40% reduction of the β cell mass, which on its own does not explain the hyposecretion. In this respect, the theory of low birth weight, also called the theory of the thrifty gene or of feast and famine, is very attractive. In those patients, their reduced pancreas does not allow to compensate the insulin demand when they are obese, subsequently developing DM2 [30]. The reduction in β cell mass could be due to an increase in apoptosis and autophagy that would exceed the islet regenerative capacity.

In DM2, a morphological change that has been extensively studied is the amyloid deposition in the islets of Langerhans, a disturbance that may lead to accelerated death of β cells with the consequent decrease of insulin secretion. It has been reported that the presence of amyloid coincides with or precedes hyperglycemia, favoring β cell apoptosis [31].

Amyloid is constituted by a peptide initially named amylin and presently referred to as islet amyloid polypeptide (IAPP), normally produced by β cells. This amyloid forms fibrils that are cytotoxic to these cells through an oxidative stress mechanism; IAPP overexposure would favor DM2 development. It has not yet been clarified whether the excess of amyloid deposition is caused by the hyperglycemia or precedes the diagnosis of DM2.

At present, epigenetics is considered to be a factor of DM2 and other diseases; these are interactions between genes and environment that occur in individuals through small chemical modifications that are capable of regulating the expression of the DM2 genes especially related to insulin secretion [32].

6. Insulin resistance

IR, defined as a lower biological activity of the hormone in its different metabolic actions for a certain concentration, is the first abnormality detected in the evolution of DM2 and is already present in the prediabetes state.

IR plays a main role in DM2 development together with the insulin secretion defect, both disorders having genetic bases that have been extensively studied but not well defined to date, influenced by epigenetic factors that can act since intrauterine life.

IR, obesity, and DM2 are highly interrelated. In 95% of the cases, IR presents in subjects with excess weight or obesity will subsequently develop DM2. Although IR is present in almost all patients with DM2, the degrees of IR are very variable in different individuals; besides, a proportion of IR comes from obesity itself, and the other is characteristic of DM2.

IR is expressed in the liver, muscle, and adipose tissue with different intensities in the different individuals.

In DM2 due to IR, hyperglycemia occurs through three mechanisms: excessive hepatic production of glucose (gluconeogenesis), decrease in its uptake by peripheral tissues (muscle and adipose tissue), and increase in FFA resulting from a greater lipolysis in the adipocytes. FFA competes with glucose as a source of energy contributing to increase glycemia and inhibit glucose entry through the cell membrane [3].

6.1 IR in the liver

A positive correlation has been demonstrated between fasting glucose and hepatic gluconeogenesis, such that as the latter descends, basal glycemia levels also descend. Therefore, the hepatic gluconeogenesis that produces glucose in an environment of elevated glycemia levels is abnormal and of very important in maintaining fasting hyperglycemia in DM2 patients. The mechanism through which hepatic glucose production increases would be an elevated supply of FFA from adipose tissue, which

through the metabolites of the Krebs cycle, serve as a substrate for gluconeogenesis. In the liver, at least two types of alterations have been found: the already mentioned increase in hepatic gluconeogenesis and an incapacity both of insulin and of glycemia to inhibit glucose production. In individuals with IR, the hepatic glucose cycle is increased due to a higher activity of glucose-6-phosphatase that dephosphorylates glucose-6-phosphate, which once dephosphorylated cannot be metabolized in the glycolysis such that glucose enters the circulation favoring hyperglycemia.

6.2 IR in the muscle

Glucose utilization by the skeletal muscle is mainly mediated by insulin and reaches about 5 g/hour in the postabsorptive state. In DM2 patients, this process is severely disrupted, glucose uptake is decreased, and the amount of stored glycogen is reduced.

Glycogenesis is approximately 60% lower due to a lower activity of the muscle glycogen synthase (GS) [33]. In the IR state, insulin is incapable of stimulating muscle GS; there is excess glucose in the postabsorptive state, but it is not deposited in the form of glycogen, such that this genetic defect directly contributes to post-prandial hyperglycemia.

6.3 IR in adipose tissue

In DM2 patients with IR and low insulin levels, a greater lipolysis occurs in the adipocytes increasing the concentration of circulating FFA, particularly during the night; the capacity of insulin, in these cases, is being insufficient to maintain the FFA plasma levels within the normal range.

FFA, as already mentioned, contribute to elevate fasting glycemia through gluconeogenesis, which would be the main defect, and additionally reduce glucose uptake and oxidation in the muscle.

Increased FFA inhibits the activity of pyruvate dehydrogenase, an enzyme that participates in the final stage of glycolysis, thus slowing down glucose degradation and energy production by glucose metabolism.

The higher supply of long-chain FFA by the fatty acid-binding protein-2 (FABP-2) for their oxidation as a source of energy is another mechanism of competition with glucose.

Regulation of FFA metabolism is highly sensitive to insulin levels and is probably one of the first actions that are lost when insulinemia decreases and the individual is IR.

The metabolic pathways of IR in the liver, muscle and adipose tissue of DM2 patients is seen in **Figure 2**.

6.4 Cellular mechanisms

In DM2 patients, IR is caused by alterations in the insulin receptor, and mainly postreceptor changes subsequent to insulin receptor binding. Disturbances at the receptor level would be caused by obesity of the patients and postreceptor ones would be more specific to DM2.

Normally, insulin action in relation to glucose uptake occurs by insulin binding to its receptor which is a tyrosine kinase that is activated by autophosphorylation on tyrosine, this being the first step. Subsequently, second messengers are produced, among others IRS and PI-3 K, which are also activated by phosphorylation on tyrosine; then, GLUT migrate from the intracellular space to the cell membrane to take up glucose from the blood stream through facilitated diffusion, which is a selective

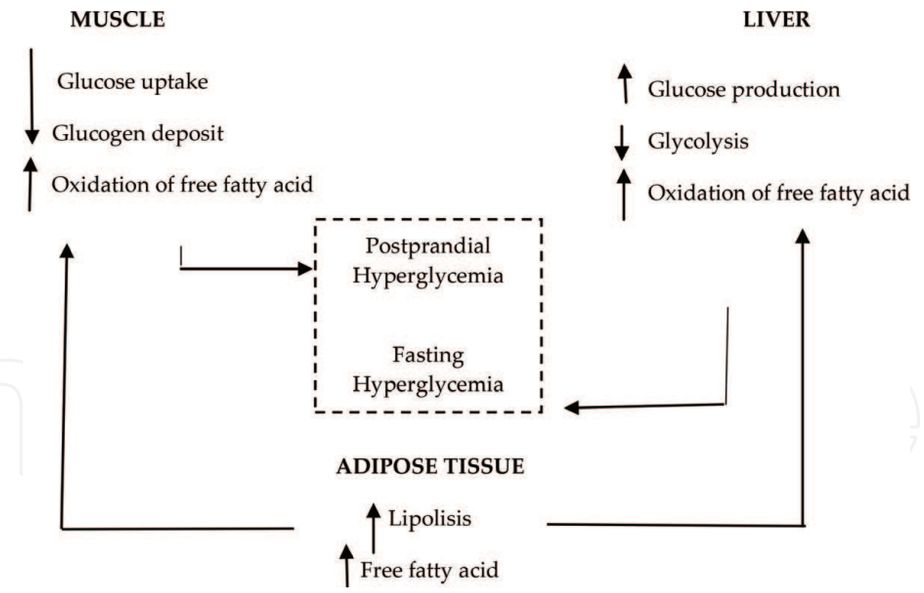

Figure 2.
Mechanism involved in insulin resistance in the liver, muscle and adipose tissue.

translocation of a molecule against its gradient by transporters. As a last stage for ending the signal transmission, the receptor is inactivated by a dephosphorylating mechanism, a process in which protein-tyrosine phosphatase-1B (PTP-1B) participates.

In DM2, part of the IR is caused by a reduction of insulin binding to its receptors; however, defects in the protein substrates and in the enzymes, inside the cells, would be of greater importance, and they correspond to postreceptor defects. The abnormalities of the receptor do not explain the great IR of DM2 patients; therefore, postreceptor defects are considered to contribute in higher proportion to cause this disturbance.

Numerous studies have demonstrated that insulin receptor binding in the various tissues of DM2 patients is decreased by 50% in obese subjects and by 20% in normal weight subjects. Besides, the autophosphorylation capacity of the receptor is 40% less than in nondiabetic individuals. The decrease in kinase activity of the receptor is a relatively specific damage of the diabetic state, which can be due to an intrinsic enzymatic defect of the receptor. In DM2, only a small fraction of the total receptors is capable of autophosphorylation under insulin stimulus; therefore, the activity of the receptors is reduced leading to lower action of the hormone, which is IR.

In DM2 patients, there could exist deterioration in insulin-mediated IRS-1 phosphorylation when a proportion of these protein factors that phosphorylate on serine (not on tyrosine) are inactivated. Consequently, the insulin signal transmission is lower inside the cell [34], and glucose transport is reduced due to diminished PI-3 K activity. There is also a significant reduction in the number of glucose transporters available in the cell membrane, which would be due to a disorder in their distribution as they remain within an inactive intracellular pool, the final result being hyperglycemia. Increased FFA reduces glucose transport translocation through inhibition of PKCβ activity and lower GLUT phosphorylation.

The β cell is in charge of responding to these higher demands caused by IR, increasing insulin synthesis in order to preserve normal levels of fasting and postprandial glycemias. In DM2, insulin is incapable of responding to the demands of IR; it is evident that the ability of the β cell for secreting insulin under the glucose stimulus for maintaining glycemic homeostasis is lost in DM2.

DM2 does not develop if there is no β cell dysfunction even if there exists IR.

7. Other pathogenic alterations of DM2

7.1 Hyperglucagonemia

It has been found that in DM2 patients, fasting and postprandial glucagon levels are increased and directly correlated to the higher glucose production; such that in DM2 patients, hyperglucagonemia contributes to fasting hyperglycemia through hepatic gluconeogenesis. The bihormonal theory in DM2, insulin deficit and glucagon increase, was proposed in 1981 by Unger and is widely accepted today [35].

7.2 Diminished incretin effect

It has been demonstrated that orally administered glucose induces greater insulin secretion than intravenously injected glucose; this is called the incretin effect.

Incretins are peptides secreted in the digestive tract that have a role in the regulation of glycemia. These are GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). These peptides, synthesized in the ileum and the jejunum, are released after oral glucose intake, stimulating endogenous insulin secretion and reducing glucagon secretion; also, they slow down gastric emptying and reduce appetite. GLP-1 is much more important, contributing with 90% to the total effect.

Decreased incretin effect is associated with the lower GLP-1 levels exhibited by DM2 patients in the postabsorptive state; GLP-1 deficit is related to lower insulin secretion, and consequently glucose production in the liver after meals is not inhibited either [36].

7.3 Microbiota

The digestive tract hosts a complex bacterial ecosystem of nearly 100 trillion microorganisms, with about 1000 species having multiple nutritional and metabolic functions. In DM2 patients, compared with nondiabetic subjects, a proportional increase of Gram-negative bacteria has been found, which would participate in the chronic inflammation state of this pathology [37].

Several mechanisms are proposed to explain the influence of gut microbiota (GM) on the onset of IR and DM2; the best founded mechanism postulated is the change in intestinal permeability with increase of endotoxemia.

It has been observed that since the beginning of the development of obesity and DM2, there exists an alteration in GM that is capable of inducing a disturbance in the intestinal barrier, causing the person to absorb more toxic substances. This metabolic endotoxemia, characterized by an increase in serum levels of lipopolysaccharides, contributes to the low-grade chronic inflammatory state that is associated to IR and to DM2 [38].

Lipopolysaccharides derived from the cell membrane of the Gram-negative bacteria of GM are known inflammation stimulators, which could be explained because they bind to Toll-like receptor 4 (TLR4) present in adipocytes, stimulating the production of proinflammatory cytokines, particularly TNFα and IL-6. These TLR4 favor NF-kβ activation, which regulates the synthesis of inflammatory molecules [39]; activation of TLR4 would cause an increase in the activity of the NF-kβ transcription factors of proinflammatory cytokines which prevent the interaction of insulin with its receptor, contributing to DM2 through lower insulin action.

7.4 Increased renal glucose reabsorption

It is presently accepted that alterations in the renal mechanisms of glucose regulation would be involved in the pathogenesis of DM2. In experimental studies, it has

been demonstrated that in DM2 there exists a poor adaptive response of the kidney, through higher renal glucose reabsorption, favoring hyperglycemia [40].

Glucose reabsorption is mediated by sodium glucose-linked transporters (SGLT), a family of membrane transporters widely distributed throughout the body, of which SGLT1 and SGLT2 are expressed in the proximal convoluted tubule of the kidney. SGLT2 has a high capacity and reabsorbs 90% of the filtered glucose; this physiological mechanism is produced through a process of sodium/glucose active cotransport, such that when sodium is absorbed, an energy gradient is produced that permits the entry of glucose into blood circulation independently of insulin [41].

In DM2 patients, a higher synthesis and absorption capacity of SLGT2 have been demonstrated, increasing maximal glucose transport from a glycemia of 180 mg/dl in healthy subjects to 240 mg/dl in DM2 patients. Thus, glucosuria begins at higher glycemic levels, originating a greater glucose reabsorption which contributes to maintaining the hyperglycemia. On the other side in DM2, increased renal gluconeogenesis has been found, resulting in higher glucose production and favoring even more the hyperglycemia of these patients [42].

Considering all the above, in relation to the pathogenesis of DM2, DeFronzo [30] describes what he called the ominous octet, because the alterations exhibited by these patients are eight. These are in pancreatic β cells, less insulin secretion; IR in the liver with increase in gluconeogenesis; IR in muscular tissue with less glucose uptake; IR in adipose tissue with greater FFA production; in the gut, reduction in GLP-1 release with decreased incretin effect; hyperglucagonemia due to greater production in pancreatic α cells; in the kidney, increase in glucose reabsorption; and in the brain, IR with a non-clarified effect.

In 2016, Schwartz [43] published that the alterations in DM2 patients are 11, thus adding to those mentioned above, gut microbiota, deregulation of the immune system, and increase of glucose uptake in the gut. The object of this description is to find similarities between the pathogenesis of DM2 and the pathogenesis of type 1 diabetes and in the future create a new β cell-centric classification of diabetes.

8. Therapeutic implications of the pathogenesis of DM2

The present knowledge on the pathogenesis of DM2 has permitted the development of various drugs for the treatment of this type of diabetes, which act on the different disturbances presented by these patients to correct the multiple pathogenic disorders.

Sulfonylureas (SU), the first drugs used (1954), act on the β cells stimulating insulin secretion by closure of the ATP-sensitive K channels and elevation of intracellular calcium.

Later, in 1997, meglitinides appear they are insulin-secreting drugs with a shorter action than SU, which are employed as prandial regulators of glycemia. Their mechanism of action is similar to that of SU; they bind to specific receptors in the β cells, different from those of SU. Their use has been very limited due to their lower effectiveness and higher cost.

Metformin, introduced in the USA in 1955, is an insulin-sensitizing drug belonging to the biguanide family, widely used as a monodrug or associated with other hypoglycemic drugs. Metformin reduces IR and fasting hyperglycemia by slowing down gluconeogenesis; it also increases glucose uptake by the muscle and favors glucose utilization by the gut. Several mechanisms of action have been postulated; however, they are still not exactly known.

Another group of insulin-sensitizing drugs is constituted by thiazolidinediones (TZD), incorporated into the drug therapy in the year 2000 with the object

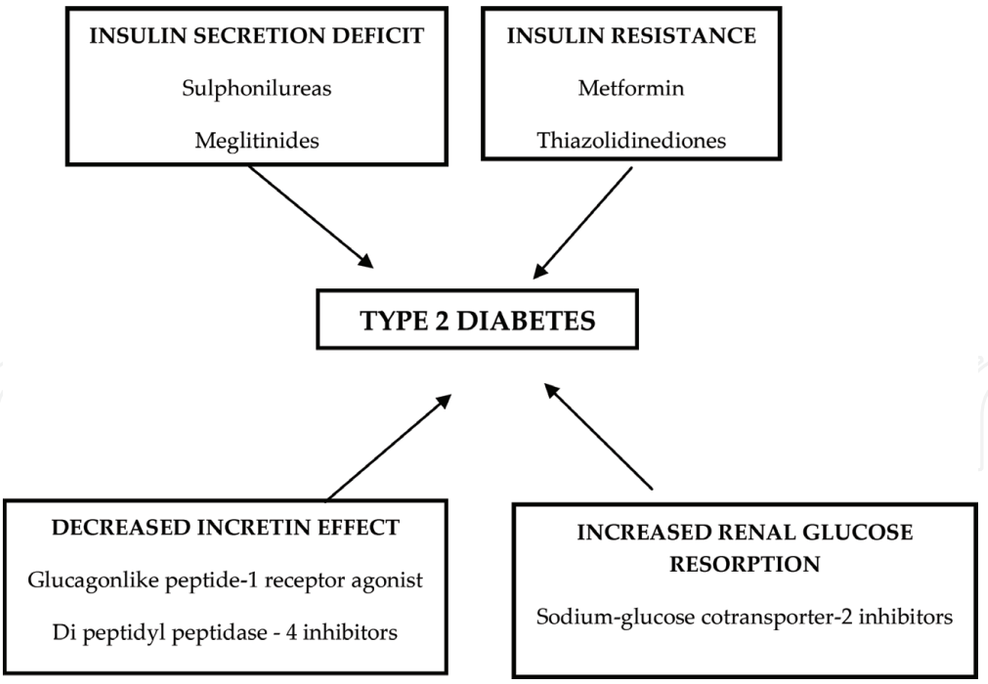

Figure 3.
Pathogenic alterations of type 2 diabetes and pharmacotherapy.

of reducing IR, especially in adipose tissue. They act by binding to the PPAR-ϒ nuclear receptors, also known as glitazone receptors. Their use is restricted and has been questioned because of their adverse effects, among others, heart failure and possible vesical cancer.

In 2005, GLP-1 receptor agonists (GLP-1 RA) were incorporated. These are drugs that improve the diminished incretin effect of DM2 patients. They are resistant to the action of dipeptidyl peptidase-4 (DPP-4) enzyme which degrades native GLP-1 in 1–2 minutes. Through an action similar to GLP-1, they stimulate insulin secretion. GLP-1 RA are injectable and very expensive, and, in addition to their hypoglycemic action, they have other effects as mentioned above.

One year later DPP-4 inhibitors (DPP-4i) appeared, which are at present extensively used. DPP-4i also act restoring the diminished incretin effect; they inhibit the rapid degradation of GLP-1 by the enzyme and indirectly favor insulin secretion.

The most recently incorporated group of hypoglycemic drugs (2013) are the SGLT2 inhibitors that partially block renal glucose reabsorption which is increased in DM2 patients. Their effect is to lower glycemia by causing glucosuria independently of insulin. Several of these drugs are available, and other benefits have been described for them, the most important being a lower risk of cardiovascular disease [45].

Figure 3 shows, together with the main pathogenic alterations of DM2, the corresponding hypoglycemic drugs employed in the usual clinical practice [44].

We hope that in the near future, even better new drugs will be developed that will be able to stop the natural evolution of DM2, slowing down the destruction of the β cell mass and thus reducing the important public health problem of this pathology.

Conflict of interest

The authors declare that they have no conflict of interest associated with this chapter.

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