## contents

### Editorial [Available in English]
New algorithm ADA-EASD for treatment of hyperglycemia: novel aspects and critical points

### Review [Available in English]
Atherogenic modifications of LDL particles in diabetic patients
Genetic manipulation of IRS proteins: animal models for understanding the molecular basis of diabetes

### Consensus Document
European guidelines on Cardiovascular Disease. Prevention in Clinical Practice: Spanish version from the CEIPC 2008 (I/III)
Consensus document for the harmonization of HbA1c results in Spain

### Original articles [Available in English]
The behaviour of glycemic parameters during the first trimester of pregnancy in women with type 1 diabetes mellitus

### Case report of diabetes discussed by experts [Available in English]
Type 2 diabetes and metformin intolerance

### New challenges in clinical practice
Oral drugs and weight gain in type 2 diabetes: is it clinically relevant?

### Therapeutic education in diabetes [Available in English]
The importance of adherence to the treatment in diabetes mellitus

### Historical Perspective
From pancreatic extracts to artificial pancreas: History, science and controversies about the discovery of the pancreatic antidiabetic hormone. I: The Pioneers

### Pictures in clinical diabetes [Available in English]
Grinspan’s syndrome in a diabetic woman

### News
The diffusion on October 22nd 2008 about the new ADA-EASD algorithm for the treatment of T2D hyperglycemia,¹ that will be published in January 2009, simultaneously by Diabetes Care and Diabetología, did not cause, by different reasons, the same adherence among the experts in diabetes than the first algorithm published in August 2006.² As the authors recognize, one of the most important current limitations of the treatment algorithms for the T2D is the shortage of randomized and controlled studies, well designed, that compare different treatment strategies, particularly different combinations of drugs among them. However, the authors did not doubt to come to the “clinical criterion” to argue on some of the recommendations included in the document, in spite of the lack of solid scientific evidences. Consequently, some therapeutic options have been favored in detriment of others, and the use of others has been ruled out based on the “lack of clinical experience”.

The most outstanding and the most controversial aspects of the new consensus are detailed below as regards to the authors’ opinion, prepared by relevant representatives of both scientific societies.

Innovative aspects
Glycemic control objectives
After the recent publication of the ACCORD and ADVANCE studies, a great controversy arouse about which should the glycemic control objectives be in patients with T2D. The current consensus confirms that the objective of the glycemic control should be to reach and keep a HbA₁c <7%. No other glycemic control indexes have been included (for ex. glycemic variability) for not having been studied systematically up to date. Moreover, it ratifies the need of optimizing the treatment in case of a HbA₁c ≥7%. No other glycemic control indexes have been included (for ex. glycemic variability) for not having been studied systematically up to date. Moreover, it ratifies the need of optimizing the treatment in case of a HbA₁c ≥7%, though it warns of the need to take into account other factors, as the life expectancy, the hypoglycemia risk and the presence of background cardiovascular disease,
considering the data arising from the last great published studies (ACCORD, ADVANCE).

**Metformin**
The metformin should be used from the beginning of the disease and as long as there is no intolerance or contraindication as regards to its use. Moreover, this consensus suggests that it can be used safely, without hypoglycemia risk in patients with “pre-diabetic hyperglycemia”, it means, before the disease starts in patients with high risk of developing T2D. Likewise, it is stated that the use of metformin is safe in patients with mild to severe renal failure and that it should not to be used in case of glomular filtration <30 mL/min.

**Insulin titration**
The insulin is still the most efficient drug for the hyperglycemia treatment. As in the first ADA-EASD consensus, the insulin has been placed in the second therapeutic step, after the failure of the monotherapy with metformin in combination with other non-pharmacological measures. The insulin titration algorithm turns out to be especially useful and updated, which is summed up in the document figure. A reasonable initial dose of basal insulin is recommended (10 or 0.2 IU/kg), the administration in the morning for long-acting insulin analogues is also admitted (glargine, detemir), a dose increasing scheme is stated by virtue of the fasting basal glycemia and the “basal-plus” strategy is recognized implicitly, that consists of adding a dose of prandial insulin in the main intake or, at least, in which there is a higher glycemic fluctuation, as a preferable option of the insulin treatment optimization. The use of premixed insulins is not recommended during the dose adjustment phase. Later, these ones should only be used in patients in whom the prandial/basal insulin proportion is kept stable at the moment of breakfast and/or dinner.

**GLP-1 analogues**
Another novelty has been the incorporation of the GLP-1 analogues to the algorithm (exenatide), as therapeutic option in combination with other oral agents. This recognizes the GLP-1 analogues potential that, besides reducing the HbA1c in the region of 0.5-1%, reduces the weight and does not induce hypoglycemia, though the publication of isolated cases of severe pancreatitis in patients treated with these drugs is admitted.

**Criticizable points**
One of the most debatable points of the new algorithm is the division among basic and well-determined therapies (insulin, sulphonylureas), or first therapeutic option after the failure of the monotherapy with metformin, and less determined therapies, or second option. This arbitrary division seems to reply most to economists’ criteria than to the current knowledge of the disease physiopathology. The sulphonylureas, though they have a lower cost and their use has been recently revalidated (ADVANCE), induce weight gaining and a higher risk of serious hypoglycemias, and have a lower sustainability of the glycemic control (ADOPT).

**Rosiglitazone**
Since the revision of the first ADA-EASD algorithm in November 2007, published in January 2008, the contrary opinion of this group of experts to the use of rosiglitazone in T2D is known. However, the caution showed on these revision contrasts with the current frontal positioning against such drug, without having appeared since then new data that might justify this change of attitude. Notwithstanding that the authors recognize the lack of conclusive data about the potential cardiovascular risk associated to the rosiglitazone; these experts are against its use. Neither it results coherent nor reasonable that these experts point out with vehemence the use of pioglitazone (versus rosiglitazone), especially in the figure that depicts the algorithm, in spite of recognizing that the available data are “less than conclusive for … a cardiovascular disease benefit with pioglitazone”. Recent data (ACCORD, VADT) do not seem to confirm an increase of the mortality risk associated to the use of rosiglitazone. The
new studies (RECORD, BARI2D), currently ongoing, with more appropriate designs, should state the safety and efficacy of rosiglitazone definitively versus other oral agents used for the T2D treatment.

Finally, in spite of the fact that in the consensus it is stated as one of the basic principles for the selection of a particular option as regards to its capacity to allow reaching and keeping the glycemic targets, it results surprising that this advantage is not attributed explicitly to the rosiglitazone, which showed a higher sustainability of the glycemic control in monotherapy versus metformin and glibenclamide in the ADOPT study.

**DPP-4 inhibitors**

Like the GLP-1 analogues, the DPP-4 inhibitors or incretin potentiators (sitagliptine, vildagliptine), represent one of the most important therapeutic novelties of the latest months.
administered by oral route (unlike the GLP-1 analogues, that are administered by subcutaneous route), even in combination with fixed doses with metformin, to the ponderal neutrality and its safety, as it does not increase the hypoglycemia risk. Especially these last characteristics confer them clear advantages versus the sulphonylureas and other secretagogue drugs, as alternatives to combine with metformin or glitazones. Therefore, the non-inclusion of these drugs to the algorithm surprise, according to these experts, given the “potential for this class of compounds to interfere with immune function”,¹, which is neither defined not stated up to date.

To sum up, the new ADA-EASD algorithm for the treatment of hypoglycemia in T2D represents an update and the consolidation of the main principles collected in its initial version. However, in spite of its virtues, the arbitrary differentiation in the selection of the several therapeutic actions, the arguable positioning versus the rosiglitazone and the lack of inclusion of the DPP-4 inhibitors, turn it in an “evolving algorithm” since its creation. Other experts, as the ones of the American College of Endocrinology and the American Association of Clinical Endocrinologists (ACE/AACE) and those of the Canadian Diabetes Association, have been able to recognize these aspects and have submitted alternative algorithms. The treatment algorithm of the Canadian Diabetes Association is depicted in figure 1,⁴ a different view and probably more clinical and less dogmatic than the new ADA-EASD algorithm.

Declaration of potential conflict of interests
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References
Atherogenic modifications of LDL particles in diabetic patients

Clinical manifestations derived from atherosclerosis are the leading complications in patients with diabetes mellitus, being responsible of 50–70% of deaths in these individuals. The precise link between accelerated development and atherosclerosis and diabetes is not completely understood, although mechanisms related with hyperglycemia and diabetic dyslipidemia play an important role. Both mechanisms are closely related and frequently are two faces of the same coin. There are well-recognized qualitative modifications of low-density lipoproteins, such as an increased percentage of small, dense LDL particles with higher electronegative charge. These modifications disturbing physicochemical and biological characteristics of LDL particles are involved in the common mechanisms by which dyslipidemia and hyperglycemia promote increased atherosclerosis in diabetic patients.

Keywords: diabetes mellitus, atherosclerosis, modified lipoproteins, electronegative LDL particles.

Hyperglycemia and atherosclerosis

At present, it is broadly accepted that the atherosclerosis pathology starts with the onset of a dysfunction in the vascular endothelium, in response to an external aggres-
Inflammatory chronic condition promotes a migration of elements of the immune system whose activity at long term leads into the characteristic lipid accumulation in the intima layer of the arterial wall. An important increase of the cell proliferation follows this phase and, consequently, the thickening of the arterial wall. Finally, the cytotoxicity, the apoptosis and the activation of thrombosis processes arise leading to the complication of the atherosclerotic injury and the onset of clinical events. Therefore, the endothelial dysfunction and the associated inflammatory process are the key initial events in the development of the atherosclerotic injury.

The clinical manifestations of the atherosclerotic disease constitute the main complication in the population with diabetes mellitus, as they are responsible of over 50% of the mortality, and most of the patients with T2D without previous cardiovascular disease have the risk of suffering a coronary event similar to the patients without diabetes who had already shown a myocardial infarction. This risk increase can be explained in part by the higher prevalence and atherogenic effect of the classic cardiovascular risk factors. However, the prognosis of cardiovascular events from these risk factors does not exceed the 50% of the cases, stating clearly that the responsible mechanisms of the accelerated development of the atherosclerosis in diabetes is unknown. These patients have also hypercoagulability and there is an increased systemic inflammatory condition, as it can be observed from the major plasma concentration of reactive C-protein and, as it will be discussed below, other processes derived from the hyperglycemia and dyslipidemia situation that play an important role in the atherosclerosis development.

In spite of the advances carried out during the last decade about the molecular mechanisms involved in the diabetes atherosclerosis, it is still a reason of discussion if the glucose and the lipids exert independent effects on the development of the atherosclerotic injury. In fact, the glucose and lipids effects on the activation of different metabolic routes in the endothelial cell are surprisingly similar. The simple presence of a high concentration of glucose can cause endothelial dysfunction, basically due...
to the limited endothelial capacity of controlling the intracellular glucose levels. Several mechanisms have been suggested, as an increased consumption of NAPDH, the formation of advanced glycation end products (AGE), the activation of protein kinase C or specific transcription factors. The common link of these mechanisms is that the intracellular oxidative stress increase activating an inflammatory response by the vascular endothelium.

**Dyslypidemia and diabetes**

Besides the direct effect of the hyperglycemia on the endothelial dysfunction, other authors have suggested that the dyslipidemia associated to the diabetes is the main cause of atherosclerosis, especially in the T2D. The so-called diabetic or atherogenic dyslipidemia is characterized by the presence of hypertriglyceridemia, reduced concentration of high-density lipoproteins (HDL) and predominance of small and dense low-density lipoproteins (LDL). It is important to point out that these lipid alterations are not usually present in the patients with T1D and are neither exclusive of the T2D, but its association is indeed constant with the insulin-resistance or hyperinsulinemia condition, in which the plasma concentration of non-esterified fatty acids (NEFA) is high. The cause of these alterations is mainly due to the high NEFAs in the plasma promote the hepatic triglyceride synthesis. Simultaneously, the insulin resistance increases the expression of apoprotein B (ApoB) in the liver. The result of both phenomena is an hepatic hypersecretion of very low-density lipoproteins (VLDL) enriched in triglycerides. To this point, we have to add the fact that the insulin-resistance reduces the expression of the endothelial lipoprotein lipase, causing a reduced catabolism of VLDL and favoring the hypertriglyceridemia.

On the other hand, the reduced concentration of HDL is due to the reduction of the VLDL catabolism, as the lypolitic action of the endothelial lipoprotein lipase favors the formation of HDL from the surface material of the VLDLs. Finally, the T2D is characterized by a higher expression of the hepatic lipase as well as by an increase of the triglycerides interchange and the mediated cholesterol esters by the proteins that transfer them. Both enzymes take part in the maturation process of the VLDL, and its principal activity gives place to the formation of small and dense LDL particles (figure 2). On the other hand, the deficient clearance of the VLDLs by the previously mentioned mechanisms, gives place to the formation of residual lipoprotein particles that have an intermediate density (IDL) and, as the small and dense LDL, have an increased atherogenic potential as regards to the normal size LDL.

Several studies carried out in non-diabetic patients stated that the hypertriglyceridemia and the reduced HDL are cardiovascular risk factors (CVR). However, these alterations do not explain more than 25% of the CVR excess that the patients with T2D show, and much less in the case of T1D, which in general the lipid plasma concentrations are practically normal. On the other hand, the cholesterol bound to the LDLs (cLDL) is considered by the National Cholesterol Education Program/Adult Treatment Panel III of the United States (NCEP-ATP-III) as the main risk factor and the first therapeutic objective. The cLDL is usually normal even in patients with T2D and diabetic dyslipidemia, but it is the most potent prognosis factor of coronary disease in patients with or without diabetes. This apparent paradox is attributable in the diabetes mostly to the qualitative characteristics of the LDL than the plasma concentration may be most important. According to this hypothesis, there are several processes that converge in the diabetes and contribute to a series of modifications that the LDL suffers and that might cause it to be a more atherogenic particle.

**Small/dense LDL (sdLDL)**

It has already been mentioned that the presence of LDL particles of smaller size and higher density, due to an increase of the protein/lipid, takes place frequently in situations of hypertriglyceridemia and cholesterol bound to the reduced HDL (cHDL). Since in general these abnormalities come together, it is difficult to determine which proportion of the increase of CVR corresponds to each of them. Some studies have indicated that the CVR is increased in subjects with sdLDL predominance regardless of the triglycerides concentration or the LDL/HDL ratio, though other studies have not found this association. On this regard, several authors are posing that a better measure than the cLDL to determine the CVR might be the number of LDL particles by means of magnetic resonance imaging, or even the ApoB concentration or the total ApoB / cholesterol ratio. These parameters might reflect the presence of sdLDL particles, which is ignored by the simple cLDL measure. In this sense, assuming that the cLDL underestimates the cholesterol from the atherogenic lipoproteins (VLDL, IDL, LDL and sdLDL) –which is specially important in...
hypertriglyceridemia situations—than the non HDL and ApoB cholesterol reflect better the cholesterol and the total mass of atherogenic particles, and there are more and more data that support that the non HDL cholesterol and the ApoB are better predictors of cardiovascular events than the cLDL; these parameters are included in the recommendations of the NCEP-ATP-III, the American Diabetes Association and the American Heart Association (AHA).

Beyond its association with the CVR, the sdLDL present a series of physicochemical characteristics that make it potentially atherogenic (figure 2). Its smaller size makes it cross the vascular endothelium more easily than the bigger sized LDL, favoring the cholesterol subendothelial accumulation. Moreover, the sdLDL is more susceptible to the oxidation, increasing its atherogenic potential, as the oxidative modification of the LDL is a key factor in the triggering of the vascular inflammatory response. The sdLDL has less affinity for the LDL receptor, reducing its plasma clearance rate and increasing its time of permanence in blood. In a hyperglycemia condition, the LDL that remains more time in circulation has more possibilities of suffering non-enzymatic glycation process. As it will be mentioned below, the glycated LDL has several proatherogenic characteristics. Other characteristics of the sdLDL are a higher negative electric load and an increased content in proteins different from the ApoB. All these factors make that a series of characteristics that increase its atherogenicity converge in sdLDL.

Modifications of the LDL in the arterial wall

Oxidative stress

Though several factors have been described that might trigger the inflammatory process associated to the atherogenesis, probably one has the most determining role is the oxidative modification of the LDL in the intima layer of the arterial wall. (figure 3). This is a pro-oxidative environment compared to the plasma, taking in account that the concentration of anti-oxidative molecules is lower and the release of free radicals produced by the metabolism of the cells that surround this micro-environment, mainly endothelial, smooth muscular cells and macrophages. The peroxidation cascade induced by free radicals in LDL generates multiple lipid products with inflammatory potential, among which the following ones are included: lysophosphatidylcholine, oxidized phospholipids, cholesterol oxides, aldehydes, and ketones. All these compounds are able to induce, by different routes of signalizing mediated by kinases, the activation of transcription factors that might start an inflammatory response, as the nuclear factor kappa B, the activator protein 1, or the peroxisome proliferators-activated receptor alpha and gamma. Thus, oxidized LDL might induce the expression and the release of most of the inflammatory mediators that have a relevant role in the atherosclerosis, such as adhesion molecules, chemokines, cytokines, growth factors, matrix metalloproteinases, and receptors for modified lipoproteins. Moreover, the oxidized LDL inhibits the production of nitric oxide and alters the balance in the synthesis routes of prostaglandins, reducing the production of prostacyclin I2 and increasing the thromboxane A2. Another characteristic of oxidized LDL is that accumulates with no control in the cytoplasm of macrophages and smooth muscle cells, inducing the formation of foam cells. This accumulation takes place as they...
are recognized and internalized through scavengers, as the LOX1, the SRA and the CD36,\textsuperscript{51,55} inducing cytotoxicity and apoptosis.\textsuperscript{56} Therefore, the oxidized LDL intervenes in all evolving phases of atherosclerosis, from the endothelial dysfunction, the recruitment of leukocytes, the cellular proliferation, the accumulation of lipids or the apoptosis up to the final phases of breakage of the atherosclerotic plate and the onset of thrombosis events.

In diabetes, this outlook might be worse given the chronic hyperglycemia. The atherogenic characteristics have been commented previously regarding to sdLDL predominating in the diabetic dyslipidemia, specially its high susceptibility to oxidation. On the other hand, hyperglycemia increases the intracellular oxidative stress through many mechanisms. It reduces the availability of NADPH,\textsuperscript{57} cofactor necessary for the activity of several anti-oxidative enzymes of the glutathione cycle. Other antioxidants, as Vitamin E, superoxide dismutase or catalase, have lower tissue concentrations in diabetic subjects.\textsuperscript{58} It also stimulates protein kinase C, that activates the pathway of cyclooxygenase and other peroxides, generating free radicals.\textsuperscript{59} The result is an increase of the sub-endothelium oxidative stress that favors the modification of the LDL retained in the arterial wall.\textsuperscript{8,60}

Non-enzymatic glycosylation

Another aspect that should be taken into account is the non-enzymatic glycosylation process that might affect both the LDL and other proteins of the arterial wall. The non-enzymatic glycosylation of proteins have some reversible initial phases (Schiff base, Amadori products) that derive into irreversible products, denominated AGE, some of which require an oxidative environment for its formation.\textsuperscript{57} These products are very frequent in diabetic patients, especially in structural proteins that have a long life period. The proteoglycans and the collagen of the arterial wall in diabetic patients are more glycated than in the normoglycemic individuals.\textsuperscript{62} This has a great importance in the atherosclerosis associated to the diabetes, as the lipoproteins are bound more greedily to the proteins of the extracellular glycated matrix, favoring its sub-endothelial retention, its later modification though different mechanisms and the starting of the inflammatory process.\textsuperscript{52,63} This process is also inverse, it means, the glycated LDL binds with more affinity to the sub-endothelial proteoglycans.\textsuperscript{64}

As regards to the LDL, it is frequent that in a situation combined of hyperglycemia and oxidative stress glycoxidation phenomena takes place, and modified LDL have been detected with AGE (AGE-LDL, or LDL glycosylated) in injuries of diabetic patients.\textsuperscript{62,65} Moreover, hyperglycemia stimulates the lypoperoxidative processes in LDL.\textsuperscript{66} In general, glycosylated LDL presents proatherogenic effects similar to those that the oxidized LDL show, though its intensity is usually higher.\textsuperscript{67} It has been described that the glycosylated LDL induces endothelial dysfunction\textsuperscript{68} and favors the production of chemokines,\textsuperscript{69} and chemokine receptors,\textsuperscript{70} adhesion molecules\textsuperscript{71} and receptors for modified lipoproteins,\textsuperscript{72,73} inducing cytotoxicity and apoptosis [además de inducir citotoxicidad y apoptosis].\textsuperscript{74,75} It is likely that the products of lipid oxidation, also present in the oxidative LDL, induce part of the atherogenic effects of the glycosylated LDL, but other molecules intervene also. The AGE play a determining role, as several experiments show in which the inflammatory effect and the progression of the atherosclerosis induced by the glycosylated LDL are partially inhibited by specific antibodies that block the binding to the receptor AGE (RAGE), implying this receptor in the inflammatory action.\textsuperscript{76} In this sense, it has to be pointed out that the glycosylated LDL is not only recognized by the RAGE, but also by other scavenger receptors, the expression of which is, at the same time, increased by glycosylated LDL itself.\textsuperscript{72,73} In this way, the lipid accumulation process in the atherosclerotic injury is strengthened in diabetes. On the other hand, it has also been described an atherosclerotic potential in glycosylated lipids, mainly in the glycerol phosphatidylethanolamine, which is the main lipid product of glycosylation. The presence of glycerol phosphatidylethanolamine in the LDL favors the oxidative modification and its uptake through the scavenger receptors.\textsuperscript{77,78}

LDL modified in plasma circulation

Different forms of LDL modified in plasma circulation have been detected.\textsuperscript{79} The oxidized LDL, the glycosylated LDL and the electronegative LDL are the principal modified forms that have been identified in blood.

Oxidized LDL

The ELISA methods are used in most of the studies in order to detect oxidized LDL in plasma.\textsuperscript{80} The differences in the specificity of the used antibodies (that recognize oxidized phospholipids or specific epitopes of the
oxidized ApoB), as well as the great heterogeneity that has oxidized LDL (the extensive oxidized particles are very different from the minimally oxidized), make that the observed values are very different, with concentration ranging between 0.001% of total LDL and 1-2%. In spite of the methodological differences that make its standardization difficult, the results obtained by different authors are quite consistent. Increased concentrations of oxidized LDL have been described in patients with family hypercholesterolemia and combined family hyperlipidemia. In patients with coronary and periphery vascular disease have been related with the thickness of the arterial wall and are considered as a prognosis factor of clinical cardiovascular events and the onset of metabolic syndrome. Regarding to diabetes, several studies have shown that the concentration of oxidized LDL is higher in patients with T2D and in prediabetic condition, and that is related to the glycemic control and the presence of vascular complications. Another related parameter is the susceptibility to the ex vivo oxidation of the total isolated LDL of patients with T2D, that coincides fully with these results and reinforces the idea that the LDL in T2D is more oxidized and is more oxidizable, especially when there is an inadequate glycemic control. This is due to the fact that in this situation there is a higher oxidative stress, more concentration of NEFA in plasma, a higher production of VLDL and predominance of sdLDL.

However, the results in patients with T1D are not so clear, not even in situations of inadequate glycemic control, with results clearly contradictory among different groups. Results have been published that show higher, lower or equal oxididability in LDL in patients with T1D compared to a normoglycemic population. As a whole, it can be asserted that in the T1D the LDL is not more oxidizable than that of the normoglycemic individuals, and only in individuals with a long evolution diabetes time and a scarce metabolic control the LDL has been observed more susceptible to oxidation. Regarding to the presence of oxidized LDL, few studies have been done and they have found differences related to the normoglycemic individuals.

**Glycosylated LDL**

As it is logic, high concentrations of glycosylated LDL have been detected in patients with T1D and T2D and they are related directly to the glycemic control and with the presence of the microalbuminuria. The initial products of glycosylation (Schiff base and Amadori products) are bond to Lys of the proteins altering its physicochemical characteristics, in this case of the ApoB of the LDL. This is the majority form of glycosylated LDL in plasma, as the half-life time of the LDL is relatively short (3-5 days). The glycosylated LDL shows a reduced plasmatic catabolism and a higher susceptibility to the oxidation. Inflammatory properties have also been described as it activates the route of the MAP-kinase and the STAT5 transcription factor, increasing monocytes chemo taxis and the migration of smooth muscular cells. However, these effects have a lower intensity than those presented by the glycosidase LDL and oxidized LDL, leading some authors to set out if the inflammatory effects of the glycosylated LDL is not due to the coexistence of lipoperoxidative processes provided its higher oxididability. In this sense, it has also been described that the sdLDL, besides being more oxidizable, is glycated more easily.

LDL has also been detected in plasma that contains AGE. Since the formation of AGE requires higher formation time than the LDL plasmatic half-life, it has been suggested that these AGE-LDL have been generated in the arterial wall and have come out to plasmatic circulation after the formation. As it has been stated previously, AGE-LDL or glycosylated LDL shows a higher inflammatory potential than the glycosylated LDL; however, it remains to establish its relevance in the plasmatic circulation.

**Electronegative LDL**

The LDL is a set of heterogeneous particles that might differ in the lipid / protein ratio, density, size and electric load. Based on this last characteristic and using ion exchange chromatography, agarose electrophoresis or capillary electrophoresis, several authors have detected a minority form of LDL with a higher negative electric load. A specific ELISA has also been developed. The modifications described previously have in common that they generate an increase of the negative load in the LDL particle. In this way, it can be considered that the electronegative LDL (LDL[-]) comprises several modified LDL, included the oxidized LDL, the glycosylated LDL and the sdLDL. However, the proportion of LDL(-) is of approximately 5% in healthy individuals, but it can exceed the 10-20% in individuals with dislipidemia or diabetes. Considering that the amount of oxidized or glycosylated LDL in
ApoE or ApoC-III, which explains in part its higher density and also some of its atherogenic characteristics. The increase in NEFA might be related to an insulin-resistance situation, which is frequent in diabetes, but also with a content of acetylated lipoproteins (Lp-PLA) in the LDL(-) 5-10 times higher than the non-modified LDL, as lysophosphatidylcholine and NEFA are the degradation products of this enzyme. The observation that the reduction of the content in PAF-AH after the treatment with insulin in patients with T1D is associated to a lower capacity of inducing the release of chemokines in endothelial cells supporting the possible inflammatory role of the PAF-AH associated to LDL(-). Towards the same direction points the observation that the content in lysophosphatidylcholine of LDL in patients with T2D is increased and is related with its contents in PAF-AH.

The proportion of LDL(-) is increased in pathologies that show a high CVR, as familial hypercholesterolemia, hypertriglyceridemia, and renal dysfunction, and insulin-resistance, and the presence of atherosclerosis pathology has been associated. The treatment with statins reduces this proportion in hyperglycemic patients. Moreover, the improvement of the glycemic control with insulin reduces the LDL(-) in patients with T1D, though this might not happen in patients with T2D. This might imply that the non enzymatic glycation processes have a more relative importance in the T1D, while the oxidative modification would play a more relevant role in the T2D. On the other hand, it has also been suggested that the presence of the underlying atherosclerosis can increase the proportion of LDL(-), rising the systematic inflammation level that increases the phospholipase expression that might generate LDL(-). Precisely the PAF-AH is considered a CVR factor and its expression is increased in situations of oxidative stress or inflammation. The fact that the concentration of PAF-AH is increased in patients with diabetes might be directly related to the higher proportion of LDL(-) and, in contrast, it might be one of the causes of the CVR increase in the diabetes. Likewise, other lipolytic enzymes that might intervene in the qualitative modification of the lipoproteins in the diabetic patients.

In vitro studies have demonstrated that the LDL(-) induces the release of cytokines, chemokines and growth factors, and activates the inflammatory transcription factors in endothelial cells and in circulating leukocytes. Moreover, it induces the cytotoxicity and apoptosis, specially potent effects in isolated lipoproteins in diabetic patients. On the other hand, LDL(-) shows a high aggregation degree, which might favor its sub-endothelial retention and its binding to proteoglycans. It binds with a low affinity to the LDL receptor, but it has also a low affinity to scavenger receptors, implying an increased time of permanence in blood. Another important characteristic is an abnormal increase of proteins different from the ApoB, as ApoE or ApoC-III, which explains in part its higher density and also some of its atherogenic characteristics. There is no clear agreement regarding to the mechanism responsible of the inflammatory activity of LDL(-). Some authors indicate that this is due to the presence of oxidized lipids, but others have pointed out increased contents in lysophosphatidylcholine and NEFA as responsible for the inflammatory action. In fact, Gaubatz et al. asserted that most of the part of the negative electric load present in the LDL(-) is due to the content in NEFA, stressing the important role that these compounds have in the LDL(-) atherogenic characteristics. The increase in NEFA might be related to an insulin-resistance situation, which is frequent in diabetes, but also with a content of acetylated lipoproteins (Lp-PLA) in the LDL(-) 5-10 times higher than the non-modified LDL, as lysophosphatidylcholine and NEFA are the degradation products of this enzyme. The observation that the reduction of the content in PAF-AH after the treatment with insulin in patients with T1D is associated to a lower capacity of inducing the release of chemokines in endothelial cells supporting the possible inflammatory role of the PAF-AH associated to LDL(-). Towards the same direction points the observation that the content in lysophosphatidylcholine of LDL in patients with T2D is increased and is related with its contents in PAF-AH.

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proteins have an increased expression in situations of systemic inflammation. Since in patients with diabetes the systemic inflammation level is higher than in the healthy population, such inflammation might have a relevant role in the accelerated development of the atherosclerosis that such patients show.

Conclusions
The qualitative modifications of the LDL that alter its functionality are frequent in diabetic patients. In a pathological situation as the T2D, in which the hyperglycemia, the oxidative stress, the systemic inflammation and the increase of NEFA in plasma appear simultaneously, LDL might suffer multiple modifications that increase its atherogenicity. All these processes are intimately linked among them, so the increase of the NEFA is due to the insulin-resistance that will lead to hyperglycemia, the glycation and lipoperoxidation strengthen mutually and favor an inflammatory condition that stimulates the production of lipolytic enzymes that also modify the lipoproteins and increase its contents in NEFA that increase the oxidability at the same time.

The potential usefulness of the LDL modifications in diabetic patients is stated, first, in its contribution to clarify the physiopathology of the early onset and the aggressive development of atherosclerosis. Second, though there are no epidemiologic studies and clinical trials addressed specifically to demonstrate that the modifications of the LDL might explain the percentage of vascular events that are not detected by the classic risk factors, it is not difficult to consider that the qualitative modification of the LDL plays a relevant role in the high CVR of the diabetic patients. The treatments with antioxidants have not shown to be efficient in the reduction of the atherosclerosis events, but some therapies well determined in the reduction of the CVR as the treatment with statins, besides reducing the LDL cholesterol, reduce the proportion of modified LDL particles in plasma, reinforcing the role of the qualitative modifications of the lipoproteins in the development of the atherosclerosis. However, awaiting new data to confirm the efficiency to avoid or reduce the formation of modified LDL, acting on implied mechanisms, the measures addressed to reduce the atherogenicity of the LDL should be based on the reduction of the cLDL, the non-HDL cholesterol and the ApoB.

Acknowledgements
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Declaration of potential conflict of interests
J.L. Sánchez Quesada and A. Pérez Pérez state that there are no conflicts of interest as regards to the content of this article.

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Genetic manipulation of IRS proteins: animal models for understanding the molecular basis of diabetes

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Abstract
The identification of insulin receptor substrate (IRS) proteins in the 1990s represents a key phase of diabetes research as it has enabled our present understanding of the molecular basis of insulin and insulin-like growth factor (IGF) action. The generation of mice with targeted deletions of the four major IRS proteins has revealed invaluable information about the biological functions of these signaling molecules and has provided novel insights into the role of defective insulin signaling in the development of diabetes and metabolic diseases. *Irs*1-deficiency in mice causes reduced body size, beta cell hyperplasia, and increased life-span. Disruption of *Irs*2 has demonstrated that this branch of the insulin/IGF signaling cascade has an important role in peripheral insulin action and pancreatic beta-cell growth and function. Global disruption of IRS2 signaling in mice causes diabetes due to failed beta cell compensation in the presence of peripheral insulin resistance. Gene targeting of *Irs*3 or *Irs*4 did not produce remarkable phenotypes suggesting that either they play very specific roles in limited tissues or that their absence may be compensated for by other signaling mechanisms. A complete understanding of the cellular events mediated by IRS1 and IRS2 will reveal new strategies to prevent or cure diabetes and other metabolic diseases.

Keywords: insulin, signal transduction, beta cell, gene targeting, animal models, insulin resistance, obesity.

Introduction
Data from health organizations and epidemiological studies indicate that the two most common forms of diabetes are increasing at alarming rates in developed countries, including Spain. Type 1 diabetics have partial or complete beta-cell deficiency due to destruction of insulin-producing cells by the immune system. Although peripheral insulin resistance was considered historically to be the principal cause of type 2 diabetes, it has now become evident that early beta cell loss and/or defective insulin secretion also underlie this prevalent form of diabetes. However, the site of the primary defect in insulin action remains unclear as does the relationship between insulin resistance and impaired β-cell function.

The current diabetes epidemic emphasizes the importance of understanding the combined defects that cause type 2 diabetes. Elucidating the molecular basis of diabetes will certainly lead to the implementation of improved therapies for preventing or treating this insipid disease. Generation of mice with targeted mutations of the genes encoding insulin signaling molecules provides a unique approach to assess the contributions of impaired insulin action to the pathogenesis of insulin resistance and diabetes. Thus, in the present article, we will discuss mouse models where IRS proteins have been genetically targeted to generate loss-of-function or gain-of-function tools. Due to space limitations, we can only briefly discuss the phenotypes of these models but we refer the reader to the original articles and prior reviews.

The molecular basis of insulin action
Insulin binds to the alpha subunit of the insulin receptor in the plasma membrane which activates the intrinsic tyrosine kinase activity of the beta subunit. In contrast to most tyrosine kinase receptors which utilize autophosphorylation to create binding sites for SH2-containing signaling molecules, the IR interacts poorly with SH2 domains and therefore, relies on an alternative strategy of phosphorylating adaptor proteins to mediate intracellular signaling (figure 1). The molecular cloning of these
Adaptors, named IRS proteins, in the 1990s provided a mechanistic and evolutionary explanation for the divergence of insulin signaling from oncogene and growth-factor signaling. Upon phosphorylation by activated IRs or IGF-I receptors, IRS proteins are capable of recruiting various signalling molecules including phosphoinositide-3-kinase (PI3K), Fyn kinase and Grb2. Thus, IRS proteins are the principal mediators of cellular responses to insulin and IGF-I. Products of PI3K activate a network of serine-threonine kinases, including AKT, implicated in the action of insulin on glucose transport, glycogen synthesis, cell proliferation and apoptosis (figure 1).

Insulin receptor substrate 1 (IRS1) was the first major substrate of the insulin receptor to be cloned; deletion of this gene in mice provided researchers with an unexpected surprise as it revealed the existence of other IRS proteins. The IRS-protein family contains at least four principal members, IRS1-4. IRS1 appears to be ubiquitously expressed. IRS2 was initially identified as a component of the interleukin-4 signaling pathway, but it is now known to be expressed in nearly all cells and tissues. IRS3 is predominantly expressed in adipose tissue, and was purified and cloned from rat fat cells; IRS4 was purified and cloned from HEK293 cells, where it is the major IRS-protein. IRS4 is expressed predominantly in the pituitary, thymus and brain.

The basic technology of gene targeting

Animal models are indispensable tools for studying the molecular basis of disease as well as the physiological role of a specific gene product. Experimental models can be categorized as natural or induced. Natural models are those in which a condition occurs spontaneously such as the db/db mutation which produces obesity in mice. In 2007, the Nobel Prize in medicine was awarded to Mario R. Capecchi, Martin J. Evans and Oliver Smithies for their discoveries related to embryonic stem cells and DNA recombination in mammals. These discoveries provided the basis for the development of the immensely powerful technology referred to as gene targeting for the production of induced models in mice.

Knockouts are used to study the function of specific genes, detect their protein products, and link them to diseases that arise when their function is inadequate. Gene targeting experiments have elucidated the roles of numerous genes in embryonic development, adult physiology, aging and disease. To date, more than ten thousand mouse genes (approximately half of the genes in the mammalian genome) have been knocked out. Although mice are especially attractive for gene targeting given that their physiology is similar to humans, Drosophila and C. elegans are also useful for producing transgenics to study insulin signaling.

In order to create genetically modified animals, it is necessary to modify the DNA of germ-line cells so that the modified DNA is transmitted from generation to generation. When an investigator wants to accomplish this, the method of choice is homologous recombination. To perform homologous recombination, the DNA sequence of the gene of interest must be known. With this information, it is possible to replace any gene with a DNA construct of your choosing. The first step involves the design and production of the DNA sequence you want to insert into the chromosome in place of the wild-type allele. Regardless of what is inserted, one must include some flanking DNA that is identical in sequence to the targeted locus. In addition to the positive selection marker (e.g. antibiotic resistance), a negative selection marker (e.g. thymidine kinase) is often incorporated in the replacement vector. The DNA construct that has been engineered to contain a mutant copy of the
gene is introduced into special embryonic stem cells (ES cells) that are grown in tissue culture. Cells that take up the foreign DNA are screened to find those in which the mutant copy has replaced one good copy of the gene. ES cells with one mutant copy are introduced into an early embryo (blastocyst) that is subsequently implanted in a foster mother. Mice that are born from this manipulation are mated to each other. One in four mice from this mating will contain two mutant copies of the gene. Now begins the work of establishing a knockout colony and characterizing the phenotypes (if any) produced by targeted deletion of the gene of interest (table 1).

Constitutive deletion of “Irs1” in mice

Irs1 knockout mice are IGF-1 resistant and are growth retarded both prenatally and postnatally.6,15,16 They exhibit birth weights between 40-60% of wild-type mice, and this persists throughout adult life. Disruption of Irs1 also causes insulin resistance, mainly in skeletal muscle, and abnormal glucose tolerance. However, these mice do not develop diabetes due to the presence of β-cell hyperplasia. Irs1-deficiency has also been observed to produce hypertension and hypertryglyceridemia.17 Isolated islets from Irs1 knockout mice manifest a secretory defect and reduced insulin synthesis, suggesting a role for IRS1 in islet function.18 Recently, Selman et al have reported that deletion of Irs1 but not Irs2 extends lifespan in female mice.19 Irs1-deficient females displayed resistance to age-sensitive markers of aging including skin, bone, immune, and motor dysfunction. Thus, these findings reinforce observations from other long-lived mouse models which suggest that longevity is governed by an endocrine-signaling axis involving IGF1, IGF1R, and IRS1.

Complete deletion of “Irs2” reveals its importance for beta cell function

Mice lacking Irs2 develop diabetes due to insulin resistance and pancreatic beta cell dysfunction.16,20,21 As early as 4 weeks of age, these animals have markedly abnormal glucose tolerance. By 8 weeks, male Irs2 knockout mice have reduced insulin-stimulated whole-body glucose disposal and a partial reduction in insulin suppression of hepatic glucose production, suggesting profound insulin resistance in liver and skeletal muscle. By 12-16 weeks, male Irs2-deficient mice exhibit severe hyperglycemia, polydipsia, and polyuria and die from dehydration and
Various lines of evidence suggest that Irs2 null mice do not possess mechanisms to generate new beta-cells nor can they sustain survival of existing insulin-producing cells. Conversely, overexpression of IRS2 specifically in the endocrine pancreas via the rat insulin promoter (RIP) causes beta cell hyperplasia. Additionally, Irs2 null mice display decreased beta cell replication and insufficient beta cell compensation despite a similar degree of insulin resistance as WT controls. Microarray analysis of these islets revealed a significant reduction of IRS2 expression in the high fat diet-fed Gck(+/-) mouse islets compared with WT islets, demonstrating that without intact IRS2 signaling, beta cells are unable to expand to meet the demands imposed by insulin resistance. Increased expression of the pro-apoptotic protein BAD has been detected in islets of Irs2 knockouts. Moreover, isolated islets from these animals display higher levels of active caspase-3 which can be corrected by re-introduction of IRS2 via adenovirus infection. In isolated WT murine islets, IGF1 stimulates phosphorylation of Erk1/2, Akt, and the Akt target Foxo1. By contrast, in islets of Irs2 null mice the phosphorylation of these targets is reduced, and cleaved/activated caspase-3 is insensitive to IGF1 stimulation, which is consistent with decreased growth and survival of Irs2-deficient beta cells.

Additional phenotypes in the Irs2 knockout include that female Irs2 null mice are infertile, hyperphagic, and develop obesity. These were the first clues that IRS2 signaling might also play a critical role in the regulation of appetite and body weight. Irs2 null mice are resistant to the effects of leptin in the hypothalamus, suggesting that IRS2 acts as a point of convergence for leptin and insulin signaling. Detailed analysis of the infertility of Irs1 null females has revealed reduced follicle size, increased numbers of atretic follicles, and impaired oocyte growth and antral cavity development. Granulosa cell proliferation is as well defective in deficient ovaries. These abnormalities were associated with reduced expression of cyclin D2 and increased p27KIP1 levels, indicative of cell-cycle dysregulation. These findings suggest that ovarian rather than central nervous system IRS2 signaling is important in the regulation of female reproductive function. Thus, the Irs2 knockout model may have relevance for the pathophysiology of polycystic ovary disease which is associated with insulin resistance.

**Tissue-specific targeting of “Irs2”**

The multiple phenotypes resulting from the whole-body deletion of Irs2 have complicated studies aimed at defining the relevance of this signaling molecule in specific tissues. Since insulin resistance caused by the absence of IRS2 in peripheral tissues may alter various metabolic pathways and β cell function, conditional deletion of the
Irs2 gene specifically in β cells and the hypothalamus has generated appropriate tools to more precisely determine the roles of IRS2 at these sites. Three different laboratories have produced these tissue-specific transgenes and have all obtained results, though varying to some degree, that support fundamental roles for IRS2 in beta cell compensation and hypothalamic regulation of obesity.

Using the cre-loxP system and the rat insulin promoter, the groups of Morris White and Takashi Kadowaki generated mice with deficiency for Irs2 in the beta cell and the hypothalamus owing to the expression of the RIP promoter in certain neuronal populations. Both studies concur that this form of conditional deletion of Irs2 causes increased appetite, obesity and insulin resistance that progressed to diabetes at around 8-10 weeks of age. Both beta cell mass and proliferation were significantly diminished in young transgenic animals. However, the White group studied these diabetic animals for longer periods of time and made the astute observation that the diabetes in these animals was corrected between 6 and 10 months of age due to the re-population of the endocrine pancreas by functional beta cells. These observations were confirmed by the elegant work published subsequently by the laboratory of Dominic Withers where tissue-specific knockouts of Irs2 were produced not only with the RIP promoter but also using the nestin promoter to delete Irs2 generally in neurons and the proopiomelanocortin (POMC) promoter to restrict the conditional inactivation to a specific population of hypothalamic neurons. This strategy allowed these researchers to address important questions that we were not answered by the former studies which relied solely on the RIP promoter to restrict the deletion of Irs2. Their studies have demonstrated that IRS2 pathways acting in a neuronal population distinct from POMC and neuropeptide-Y (NPY) neurons regulate energy homeostasis and growth. The Withers’s study also concludes that IRS2 in β cells is required for the maintenance of β cell mass, as β cells that escape Cre-mediated recombination are able to repopulate islets with time. Taken all together, these observations clarify the role of IRS2 in β cell function and energy homeostasis and suggest that modulation of IRS2 function is a valid target for the treatment of diabetes and obesity.

Deletion of IRS3 and IRS4
Targeting of Irs3 or Irs4 in mice did not produce remarkable phenotypes. Growth and glucose homeostasis were completely normal in Irs3 knockout mice. However, when Irs1-knockout mice and Irs3-knockout mice were inter-crossed, the resulting double mutants displayed lipo-atrophy with insulin resistance, but without intrahepatic and intramuscular deposits of triglycerides. Male Irs4 knockouts were slightly smaller than WT controls but female null mice were of normal size. Additionally, the breeding of Irs4 knockouts revealed reduced rates of reproduction. Although glucose levels were slightly lower in Irs4 knockout mice, insulin values were normal. Thus, deficiency of Irs4 causes mild defects in growth, reproduction, and glucose homeostasis.

Conclusions: the clinical impact of IRS models
More than a decade has passed since the creation of the first Irs knockout. Clearly, the labor of various laboratories to generate and characterize total and conditional knockouts of IRS proteins has provided many experimental rewards. Although we continue to make new observations in these animals, the IRS knockout models have demonstrated that these proteins exert unique and complementary signals in mediating insulin/IGF-I action.

From the conditional knockouts, we have learned that different tissues contribute uniquely to the pathogenesis of type 2 diabetes. Although peripheral insulin resistance is a well known component of type 2 diabetes, it is clearly not sufficient to provoke diabetes, based on observations from IRS transgenic models. Rather, the Irs2 knockout model emphasizes beta cell insufficiency as a key factor in the development of diabetes. Irs2-deficient mice display peripheral insulin resistance but the real trigger for diabetes in this model seems to be the inability of beta cells to compensate due to a reduction in their number and function. Thus, failure of the IRS-2 branch of insulin/IGF signaling is likely to be an important component of human diabetes. Recently, microarray analysis has revealed that IRS2 expression is significantly reduced in pancreatic islets from humans with type 2 diabetes, consistent with a critical role for IRS2 in maintaining glucose homeostasis in humans. This study coincides with findings from mouse models where hyperglycemia and dislipidemia are correlated with a reduction in the expression levels of IRS2.

Conflict of interest
The authors declare that they have no conflict of interest in relation to the content of this review.
Practical considerations

- The generation of mouse knockouts by gene targeting provides optimal models for studying the physiological function of specific genes and for linking them to human diseases.
- Targeted deletion of the individual IRS genes in mice has provided proof-of-concept that IRS proteins have distinct physiological roles in different tissues.
- These models have demonstrated that the IRS2-branch of the insulin/IGF signaling cascade has an important role in both peripheral insulin action and pancreatic beta-cell growth and function.

References

The behavior of glycemic parameters during the first quarter of pregnancy in women with type 1 diabetes mellitus

Comportamiento de los parámetros glucémicos durante el primer trimestre del embarazo en mujeres con diabetes mellitus tipo 1

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Abstract

Introduction: It is known that there is a higher frequency of hypoglycemia during the first trimester of pregnancy in women with type 1 diabetes mellitus. Patients and methods: We undertook a retrospective longitudinal study of 64 pregnant women with type 1 diabetes mellitus. Four periods were defined: preconception (28 days prior to conception), first, second and third month of pregnancy. Different glycemic parameters between those 4 periods were compared. Results: Mean blood glucose level was similar in the preconception period and in the first month. Afterwards, it progressively decreased during the second and third months. HbA1c showed a similar tendency as the mean blood glucose. Both non-serious hypoglycemia as well as nocturnal hypoglycemia increased throughout the first trimester. There were no significant changes either in the number of daily blood glucose measurements or in the average daily dose of insulin. Conclusion: Together with an improved glycemic control, a tendency towards hypoglycemia –daytime as well as nocturnal– during the first quarter of pregnancy in women with type 1 diabetes is corroborated and does not seem to be attributable to the dose of insulin.

Keywords: type 1 diabetes mellitus, pregnancy, hypoglycemia, glycated hemoglobin.

Resumen

Introducción: Se sabe que las mujeres con diabetes mellitus tipo 1 tienen una frecuencia aumentada de hipoglucemia durante el primer trimestre del embarazo. Pacientes y métodos: Realizamos un estudio longitudinal, retrospectivo, en 64 mujeres embarazadas con DM1. Se delimitaron 4 periodos: preconcepcional (28 días previos a la concepción), primer, segundo y tercer mes de gestación. Se compararon distintos parámetros glucémicos entre estos 4 periodos. Resultados: La glucemia media fue similar en el periodo preconcepcional y en el primer mes. A continuación, disminuyó progresivamente durante el segundo y el tercer mes. La hemoglobina glucosilada tuvo un comportamiento paralelo a éste. Tanto la hipoglucemia no grave como la hipoglucemia nocturna aumentaron durante el primer trimestre. No hubo cambios significativos en el número diario de mediciones de la glucemia ni en la dosis media diaria de insulina. Conclusión: Juntó con un mejor control glucémico, se corrobora una tendencia hacia la hipoglucemia, tanto diurna como nocturna, durante el primer trimestre del embarazo en mujeres con DM1, que no parece atribuible a cambios en la dosis de insulina.

Palabras clave: diabetes mellitus tipo 1, gestación, hipoglucemia, hemoglobina glucosilada.
Important changes occur during pregnancy in the mothers’ metabolism, which adapts itself to ensure an appropriate support of nutrients to the fetus. There is a “physiologic fasting” situation in the pregnant woman, due to the high consumption of nutrients by the fetus (glucose and amino acids), causing the hepatic glycogenesis to be reduced by the lack of substrates. During the pregnancy of a non-diabetic woman a progressive reduction in the fasting glycemia occurs as well as in the mean glycemia. After 28 weeks, the mean fasting glycemia in a group of 66 non-diabetic pregnant women was of 54.8 ± 6.2 mg/dL, and the daily mean glycemia of 71.9 ± 5.7 mg/dL.1

During the first three months a slight increase occurs in insulin sensitivity. In the study Diabetes in Early Pregnancy, it has been proved a reduction in the needs of insulin in the middle of the first quarter of pregnancy in diabetic women.2

It is possible that an alteration in the secretion of contra regulating hormones contributes also to the increased hypoglycemia risk. Several studies performed in pregnant women with T1D have shown a reduced response, or even null, of the adrenalin to the hypoglycemia.3,4 In the study of Rosenn et al.4 it has been detected that the group of pregnant women with T1D did not have any response to cortisol nor glucagon to the hypoglycemia.

The frequent presence of vomit during the first quarter might contribute to the hypoglycemia tendency. However, this factor seems to be of scarce importance.5,6

On the other hand, the adequate glycemic control is fundamental during pregnancy in order to reduce the risk of congenital malformations and other obstetric-neonatal pathologies related to the diabetes. The intensification of the glycemic control contributes to the increase of hypoglycemia’s frequency.7,8

The main risk factors to show serious hypoglycemia during the first quarter of the pregnancy are the previous serious hypoglycemia history, unnoticed hypoglycemias, diabetes duration of 10 years or more, glycosylated hemoglobin (HbA1c) <6.5% and higher dose of insulin (0.1 IU/kg more in the group with serious hypoglycemia than in the group that does not show it).8,9

The hypoglycemia frequency in women with T1D, both serious and not serious, is relevantly higher during pregnancy, especially during the first three months. The values published in the literature are different; they range from 6.1 up to 71% of the women affected by a serious hypoglycemia during pregnancy.

This can be explained in part by the differences in the design of the studies, as not all of them are focused on the same period of pregnancy; some of them study women with pregestational and gestational diabetes and the definition of serious hypoglycemia varies in some of them. These discrepancies also reflect differences among the different sites as regards to the glycemic control targets and education of the patients.7,13

As regards to the possible effects on the fetus, some studies performed in mice detected that the exposure to the hypoglycemia during early stages of the embryogenesis was teratogen.14 However, in the studies performed later in humans, this has not been confirmed.

During the gestation it seems that the indicative parameters of fetal welfare are not affected by mothers’ hypoglycemia. The maintenance of a relative low glucose concentration during pregnancy is associated to an increase of the risk of having a newborn of low weight for the gestational age.15

Objectives
To study the behavior of the glycemic parameters during the preconception period (28 days previous to the conception date, estimated by echography), and the first quarter of pregnancy in women with T1D, taking special interest on hypoglycemia.

Patients and methods
We conducted a longitudinal, retrospective study for which women with T1D have been enrolled who had been assisted at the Diabetes and Pregnancy Unit of Hospital “La Paz” since the preconception period until delivery. The patients who had not undertaken preconception care had been excluded and those who had abortions and multiple pregnancies. The final size of the sample was of 64 patients.

The glycemic control targets have been some pre-prandial and prandial glycemic values of 70-100 and 100-140 mg/dL, respectively. All the patients performed self-
monitoring of the glycemia using the same type of glycometer (One Touch Profile®, LifeScan, Milpitas, CA, United States). The patients were requested to perform self-analysis of the capillary glycemia between 6 and 7 times a day (pre-prandial before breakfast, lunch and dinner, postprandial 2 h after starting breakfast, lunch and dinner, and at dawn between 2 and 5 h). The registered values were downloaded to a computer during each visit (software for the handling of the diabetes: One Touch®, LifeScan, Milpitas, CA, United States). The HbA₁c was measured in the preconception period and each month, using high-resolution liquid chromatography (Bio-Rad, Richmond, RA, United States).

The patients followed a treatment with intensive flexible insulin therapy: 63 of them with bolo-basal therapy (neutral protamine Hagedorn insulin [NPH] and regular), and one of them with continuous subcutaneous insulin infusion (regular). All the patients have been trained as regards to the diabetes self-care, adjusting themselves the doses of insulin in order to achieve the targets. They attended the consultation each 4 weeks during the preconception period and each 1-2 weeks according to the needs, during pregnancy. Both the patient and a member of her family have been trained in the handling of the hypoglycemia, and glucagon was indicated to all of them.

For the definition of serious hypoglycemia we adopt the one included by the American Diabetes Association at present: event that for whose resolution help of a third party was needed.¹⁶ Non-serious hypoglycemia is defined as any event of capillary glycemia ≤50 mg/dL that the patient could solve alone. Night hypoglycemia was considered as any event of capillary glycemia ≤50 mg/dL produced between 00.00 and 05.00 h.

The following variables were compared in the preconception period, the first, second and third month of gestation: a) daily mean number of glycemia measurements; b) mean glycemia; c) HbA₁c; d) frequency of non-serious hypoglycemia; e) frequency of night hypoglycemia and f) daily mean dose of insulin adjusted by weight. The frequency of serious hypoglycemia was very low; therefore it has been compared between the preconception period and the first quarter of the gestation as a whole.

The statistical analysis was done using the SPSS program version 15.0. In order to compare the means among the quantitative variables, analysis of variance was used with the test of Bonferroni as post hoc test, or the t test of Student for dependent samples, as applicable. In order to compare qualitative variables, the χ² test has been used and the Fisher exact test. A value of p <0.05 was considered statistically relevant.

Results
The demographic characteristics of the patients are depicted in table 1.

The mean daily number of glycemia measurements was of 4.9 ± 1.3 in the preconception period, 5.3 ± 1.3 in the second month and 5.6 ± 1.3 in the third month. No statically relevant differences were found.

Five women (7.8%) showed serious hypoglycemia during the preconception period. Likewise, five patients had it during the first quarter. The difference between both data did not reach a statistical significance. Two patients (3.1%) suffered hypoglycemia during both periods.

The mean glycemia of the first month was similar than that of the preconcept ion period (p= 1.000) and decreased progressively throughout the first three months of pregnancy. The most stressed decrease took place between the first and the second month (figure 1).

The HbA₁c was similar during the preconception period and first month (p= 1.000). Afterwards, it decreased progressively until the third month (figure 2).

The frequency of non-serious hypoglycemia was not different in the preconception period than in the first month (p= 1.000). Afterwards, such frequency increased progressively (figure 3).

<table>
<thead>
<tr>
<th>Table 1. Characteristics of the patients</th>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Body mass index (kg/m²)</td>
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<tr>
<td>Duration of the diabetes (years)</td>
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<tr>
<td>Patients with diabetic retinopathy (%)</td>
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<td>Patients with diabetic nephropathy (%)</td>
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<td>Patients with previous serious hypoglycemia (%)</td>
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</table>

The data are expressed as mean ± standard deviation, or number of cases and percentage between brackets.
The night hypoglycemia frequency increased progressively during the first quarter (figure 4).

There have not been relevant changes in the mean daily dose of insulin (preconception 0.62 ± 0.15 IU/kg, first month 0.65 ± 0.16 IU/kg; second month 0.68 ± 0.15 IU/kg, third month 0.64 ± 0.15 IU/kg (p> 0.05).

Discussion
In our study, only the 7.8% of the women have been affected by a serious hypoglycemia during pregnancy. This value is lower than the one usually published in the literature, where the percentage of affected women exceeds the 45% frequently.7-13 It is difficult to define the cause of these differences. We can think that it is due to the pre-
conception care. However, in the study of Evers, et al., also with preconception care, the 41% of the women suffered serious hyperglycemia. In a study in which the evolution of the two groups of patients with or without preconception care has been compared, the serious hypoglycemia frequency was not different between both.\textsuperscript{13}

The finding of a reduction of the mean glycemia and the HbA\textsubscript{1c} during the first quarter is a previously known fact in non-diabetic pregnant patients, that is confirmed in our series of patients with T1D. No differences have been found in the insulin dose adjusted by weight; in other words, the decrease of the mean glycemia is associated to pregnancy by itself. According to this, it increased the hypoglycemia risk during the first quarter.

There are a few studies that assess specifically the night hypoglycemia frequency during pregnancy. In one of them, performed in 43 pregnant women with T1D, it has been found that the 37% of them had hypoglycemia throughout the night, during such time blood samples have been taken from a cannula. Only one of them registered hypoglycemia and the other hypoglycemia remained unnoticed.\textsuperscript{17}

In our study, the night hypoglycemia frequency increases progressively during the first quarter, reaching the 1.1 ± 1.3% of all the measurements in the third month. Taking in account the design, it is impossible to study the quantity of unnoticed night hypoglycemias, as the patients woke up actively to perform the measurement.

Our study was done in a group of patients under treatment with human insulin (regular plus NPH), as the use of insulin analogues during pregnancy was not authorized at that moment. Both the insulin lispro and the insulin aspart have proved to reduce the frequency of serious and non-serious hypoglycemia compared to the regular insulin.\textsuperscript{18-21}

Up to present, only two randomized and controlled studies have been published that compare the therapy with multiple-dose insulin (MDI) and continuous subcutaneous insulin infusion (CSII) during pregnancy. In one of them, the glycemic control level has been compared as well as the development of pregnancy in women with T1D, 30 of them under treatment with CSII and 60 under treatment with MDI. No differences have been found regarding to the frequency or seriousness of the hypoglycemia between both groups (in the group with CSII, the 72% had non serious hypoglycemia and 28% serious hypoglycemia, and in the group with MDI, the 75 and the 25%, respectively).\textsuperscript{22} Recently, a meta-analysis has been published about the topic that includes only two studies (60 women with 61 pregnancies). A relevant increase has been obtained in the mean weight at delivery associated to CSII. The authors do not consider this fact as clinically relevant, as there have not been statistically relevant differences in the macrosomy rate. No differences have been found in any of the analyzed variables, among them the frequency of serious and non-serious hypoglycemia.\textsuperscript{23} This might be due to the small number of adequate trials for the meta-analysis and the low number of participants in the described trials.

**Conclusion**

During the first quarter of pregnancy, in women with T1D we have found a tendency towards the hypoglycemia, which is stated during the second and third month of gestation. This tendency is linked to an improvement of the glycemic control. However, it does not seem attributable to changes in the insulin dose adjusted by weight, parameter in which no statistically relevant differences have been found.

**Declaration of potential conflict of interests**

M. García Domínguez, L. Herranz de la Morena, E. Moya Chimenti and L.F. Pallardo Sánchez state that there are no conflicts of interest as regards to the content of this article.

**References**


Case report discussed by experts

Type 2 diabetes and metformin intolerance

Diabetes tipo 2 e intolerancia a la metformina

Male aged 73, with T2D of 5 years of evolution, who is being treated with glimepiride 6 mg/day and in the last analytic he shows a glycosylated hemoglobin (HbA1c) of 7.7%.

Anamnesis

Personal history
Former truck driver, former smoker and drinker; He ensures that at present he only drinks wine with the meals. He always had good health, except for the several gastritis events after abundant meals that he treats with antacids erratically. He has been operated on herniated disc. He did not tolerate the metformin due to abdominal upsets, reason why he started a glimepiride treatment. He hardly goes to see the physician; he does not perform the glycemic controls and refused to take medication for cholesterol and for arterial pressure (AP). He accepted to be treated on his diabetes because his father died due to this disease. He recognizes that he does less physical exercise every time and since he “left the truck”, he did not do anything but to gain weight.

Data corresponding to the last revision
Weigh 108 kg, height 174 cm, AP 155/95 mmHg, and abdominal waist 112 cm. No peripheral vascular disorder can be observed nor signs of peripheral neuropathy. In the differed analytic the following results appear: creatinine 1.5 mg/dL, basal glycemia 169 mg/dL, HbA1c 7.7, uric acid 8.4 mg/dL, total cholesterol 311 mg/dL, triglycerides 197 mg/dL, cholesterol bound to high density lipoproteins (cHDL) 59 mg/dL, AST 46.7, U/L ALT 44.3 U/L. Though he was requested for a urine sample, he did not submit it.

Which is the approach you would give to the global treatment of this patient?
It has to do with an obese patient (body mass index [BMI] 36), non reliable, with multiple risk factors (arterial hypertension, hypercholesterolemia, abdominal perimeter >102 cm) that complies with metabolic syndrome criteria and mild renal disorder (creatinine 1.5 mg/dL, creatinine clearance 67 mL/min [Cockcroft-Gault], glomerular filtration rate [GFR] 48.49 mL/min, MDRD [Modification of Diet in Renal Disease Study equation]). Moreover, he shows a hypertransaminasemia indicative of non-alcoholic fatty liver disease (NAFLD). He started the treatment with sulphonylureas (glimepiride) due to intolerance to the metformin; in spite of that, the patient keeps an inadequate metabolic control (glycosylated hemoglobin [HbA1c] of 7.7%.

The first impression is that he is a patient who does not help much, with a high cardiovascular risk and a slender control of the risk factors. We shall assess the complica-
Case report discussed by experts

Type 2 diabetes and metformin intolerance. M. Seguí Díaz, M.ª J. Goñi

Assessment of complications risk, both macrovascular and microvascular. On this regard, the use of cardiovascular risk tables would be unnecessary, taken in account his manifested dyslipidemia (total cholesterol of 311 mg/dL), that causes him a marginal risk higher than the ones depicted by them, and obliges us to insist on the treatment with statins and platelet antiaggregants. It should be stressed on the control of his arterial pressure (AP) using, as first intention, an angiotensin-converting enzyme inhibitors (ACEI), an angiotensin II receptor antagonists (ARA II) or a calcium antagonist that does not affect in his metabolic control and improve his renal function, night alpha-blockers and in case of not reaching the target, diuretics and beta-blockers, betting for those who show a poor metabolic activity (for ex. carvedilol).

The microangiopathic complications should be assessed, insisting on carrying out an ophthalmologic evaluation (funduscopy) and assessing the presence of proteins in urine (albumin/creatinine index). The condition of the micro-macro vascular complications provides strong arguments with which to determine therapeutic objectives according to international recommendations (HbA1c <7%) (table 1), and to apply decision trees according to the recent algorithms.

From here, we would assess his ponderal condition that will inform us, to a good extent, the underlying cause of his current condition. Thus, taking into account his obesity, it would be precise to insist on the dietetic measurements, physical exercise of at least 150 minutes per week (30 min/day) and a weekly control of his weight. An hypocaloric diet estimated according to the sex, the age (in persons over 70 years a reduction of 30% should be applied), the estimation of the maximum acceptable weight (height in m² x 25, that is to say, 81 kg) and his current activity (quite limited, in the region of 42 kcal/kg/day) that would recommend to indicate a fractioned diet of not more than 2,400 kcal/day.

Sensu stricto, considering his physiopathology, we should introduce drugs for his metabolic control that shall act on the peripheral insulin resistance, affecting on the real causes of his current condition and on the insulin-resistance signs (arterial hypertension, dyslipidemia, obesity, non-alcoholic fatty liver disease [NAFLD], etc.). Such is the case of the metformin (as regards to the one to which the patient showed intolerance) and, though in a different manner, of the glitazones.

Which is the approach you would give to the diabetologic treatment?

Though it is true that the unique use of the diet and the exercise previous to the treatment with metformin is not collected in all the international consensus, following the reasoning of our team it would be convenient, with the collaboration of the nursing staff, its early introduction to educate and hold the patient responsible of his own disease. The gastric intolerance of the metformin is a matter that unfortunately obliges to withdraw several treatments, though sometimes it is exclusively due to an inadequate introduction of the medication and a final excessive dose. As the last consensus of the ADA/EASD indicates, it has to be started with a low dose of 500 mg (1-2 times a day) and increase it each week until achieving the optimal dose or the tolerated dose by the patient.

Assuming a completely resistant intolerance to the slow and scheduled re-introduction of the metformin, there are several alternatives according to the target of keeping the normoglycemia. All the therapies would be contraindicated with renal dysfunction, except for the strict insulin-therapy. A glomerular filtration (GF) of 48 mL/m would be the limit of them all and would constitute a datum against the use of secretagogues, as the sulphonylureas (glimepiride). Other data against it would the hypoglycemia risk, considering the used doses and taking into account his ponderal condition, as well as the pancreatic exhaustion risk; therefore in my opinion they would not be recommendable, at first. In this sense, the use of glinides (repaglinide), before or after the insulin-therapy, would increase the safety vs. the renal function.

Table 1. Control targets in the diabetic patient

<table>
<thead>
<tr>
<th>Target</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>&lt;7.0</td>
</tr>
<tr>
<td>Basal/pre-prandial glycemia (mg/dL)</td>
<td>70-130</td>
</tr>
<tr>
<td>Postprandial glycemia (mg/dL)</td>
<td>&lt;180</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>&lt;100</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>&lt;150</td>
</tr>
<tr>
<td>AP (mmHg)</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Tobacco</td>
<td>No</td>
</tr>
</tbody>
</table>

Modified of the American Diabetes Association 2009.
and would reduce the hypoglycemia risk with a slight lower weight gain, though its doses (3 tablets), in this case, would not be adequate for a non compliant patient.

In the previous algorithms of the ADA/EASD, that is to say, from 2006, after a first step with modification of the life styles and metformin, the night insulin and the metformin were put in the same level (the cheapest ones) or the glitazones (lower risk of hypoglycemias). In the current algorithm, the new drugs are introduced and the decision is divided according to the highest or lowest evidence degree.

Therefore, in this case, and considering this exclusive objective of glycemic control in a patient with intolerance to the treatment with metformin, it would not be misconceived the use of NPH night insulin or a slow analogue (glargine, detemir) in an obese patient who has not lost the pancreatic beta-cell function, as he would improve his metabolic behavior quickly, and at the same time he would keep pancreatic beta cells and would represent an affordable economic cost. The Treat-to-Target trial showed that the dosage of night insulin associated to the oral therapy was safe and fast in obese patients with a slight increase of weight. However, he is a non-collaborative patient.

The use of some drugs or others, as regards to patients with overweight or not-(metformin in overweight and sulphonylureas in normal weight) has been left aside some years ago. The BMI informs the degree of insulin resistance of the patient. From this point we shall assess the therapies that in their action mechanism do not increase the insulin levels, taking into account its relation with the increase of the body weight (secretagogues). On this regard, the drugs that reduce the insulin resistance in the peripheral system would avoid the early exhaustion of pancreatic beta cells and, therefore, the secondary increase of the circulating insulin. Thus, in general, the possibility of using metformin initially, together with other therapies like glitazones, should be taken into account. In this sense, the ADOPT study showed that the rosiglitazone when used alone in monotherapy, was able to keep the glycemic control during more time in comparison with the glibenclamide and metformin. Consequently, the use of glitazones would be the alternative therapy that in the absence of metformin would be adjusted better to the physiopathology mechanism involved in this patient, and would improve the symptoms that depend of the insulin resistance, as the non-alcoholic steatohepatitis. Its use might delay the starting of the insulin treatment. Certain use contradictions should be ruled out before starting the treatment, as the acute coronary syndrome, the peripheral arteriopathy and the heart disorder. The main side effect that has to be considered with the glitazones in this patient would be the possibility of edema onset and a probable weight increase (3-4 kg mean).

Other therapies that should not induce to an increase of weight and with a few side effects, but with a higher cost, are those based on incretin. The Food and Drug Administration have approved the gliptins, the DPP-4 enzyme inhibitors, in monotherapy. They are able to produce a level of metabolic control similar to other drugs, with fewer side effects (up to present) and absence of hypoglycemia. Other drugs, also based on the strengthening of the incretin effect, are the GLP-1 receptor agonists, like the exenatide, and seem to contribute to the conservation of pancreatic beta cells. The exenatide, of recent introduction in the Spanish market, stimulates the insulin secretion and inhibits the glucagon secretion, and has the beneficial feature of inhibiting the gastric emptiness in obese patients increasing the sensation of satiety and allowing the loss of weight. As counterpoint, its administration route is parenteral, b.i.d, and has frequent gastrointestinal side effects (nausea in 10-20% of the patients).

In conclusion, in this patient it should be insisted on the therapeutic compliance and on the diabetologic education before implementing (or at the same time) any pharmacologic treatment. Among them, the use of drugs with hypoglycemic effect that do not alter pancreatic betacells and that have demonstrated its safety in the mild renal disorder would be a good alternative to the metformin. Thus, the night NPH insulin, or its slow analogues (glargine, detemir), and the glitazones would be good therapeutic options.

Which are the medical controls you would recommend?

The controls would be the usual ones that the international guidelines recommend, among them; it should be ensured the measurement of the HbA1c on a three-month basis until achieving the adequate control and every six months after reaching the objective (table 2). The involvement of the nursing staff by means of scheduled
information and training sessions is relevant to demonstrate the negativism of this patient, to motivate him in order to introduce the necessary changes, and at the same time, to educate him until certain self-responsibility is achieved as regards to the handling of his disease. Thus, after the first information/motivation period, and after reaching the adequate metabolic control, the visits should be spaced out every 3 months, alternating with the visit to the physician, which would take place twice a year.

The self-analysis is controversial in patients under oral treatment with drugs without hypoglycemia risk, considering the limited cost-efficacy that has been found with the measurement. In turn, we would choose this in case of indicating insulin-therapy. In the same way, it is worthwhile encouraging the home controls of his AP.

Would you do any complementary test?
In this case, the general condition of the patient has to be assessed as regards to the possible existence of micro-macro vascular complications. Thus, the opthalmologic revision with the inclusion of a funduscopy and the GF determination, the creatinine clearance, the microalbuminuria, albumin/creatinine quotient, creatinine in plasma, and the Electrocardiogram are relevant. Furthermore, the self-analysis is a necessary step in order to motivate the patient and to introduce the necessary changes.
minuria and the albumin/creatinine quotient are relevant to be able to give an idea of the condition of his small vessels. The medication of the AP, the performance of an electrocardiogram, the measurement of the ankle/arm index and the estimation of a cardiovascular irrigation would help in order to obtain an approximate idea of his cardiovascular condition. Likewise, it would be convenient to perform an analytic follow-up of the transaminases (especially if we use glitazones), a study of the hepatic markets and an echographic assessment of his hepatopathy.

Declaration of potential conflict of interest
M. Seguí Díaz states that there are no conflicts of interest as regards to the content of this article.

References

Which is the approach you would give to the global treatment of this patient?
It is presented the case of a patient aged 73 with T2D, who besides gathers the diagnosis criteria of metabolic syndrome, according to the definition of the Third Report of the National Cholesterol Education Program (ATP-III), and the later of the International Diabetes Federation (IDF): obesity of degree 2 (BMI of 35.67), abdominal perimeter of 112 cm, hypertriglyceridemia and hypercholesterolemia with cLDL of 212 mg/dL, estimated with the Friedewald formula. Moreover, the patient shows mild renal disorder (creatinine clearance estimated with the Cockcroft-Gault formula: 67 mL/min/1.73 m², that corresponds to a phase 2 according to the National Kidney Foundation guidelines), hyperuricemia (considered a vascular risk factor) and increase of the transaminases (possible due to an hepatic steatosis).

Before determining concrete therapeutic objectives it is convenient to estimate the patient’s cardiovascular risk (CV). Considering that the European SCORE scales and the American ones of the Framingham study seem to underestimate the risk in diabetic patients, it is advisable to use the UKPDS risk equation. The application of the

List of acronyms quoted in the text:
formula indicates a risk of coronary disease after 10 years of 48.3%, death by coronary disease of 36.8% (high risk) and cerebro-vascular stroke of 22.8% (moderate risk).

Important studies that have been published during the last year demonstrate the importance of the intensive multifactor approach of the patient with T2D in the reduction of vascular events, and not only of hyperglycemia. These results led the American Diabetes Association (ADA), the American Heart Association (AHA) and the American College of Cardiology (ACC) to set out again the recommendations of the glycemic control in T2D. The recently published clinical trials Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease-Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and the Veterans Affair Diabetes Trial (VADT), do not demonstrate a relevant reduction of the serious macrovascular complications in the patients who achieved the target of a HbA1c level <7%. In the ACCORD study, the increase of mortality in the intensive treatment group motivated the interruption of the study before the foreseen termination date. However, it has to be taken into account that in these studies the number of CV events in both treatment groups was lower than the foreseen, given to the intensive treatment of the other risk factors (statins, antihypertensive and platelet antigregants) that was performed in both groups in a similar manner. It has been speculated about the causes of the major mortality of the ACCORD study. Though I could explain the highest number of hypoglycemias, there is only a relation between the serious hypoglycemia and the mortality in the participants of the conventional treatment group of the three trials. For many authors, the major importance falls on in the used therapeutic strategy and the speed of reaching the control.

The characteristics of the patient as regards to his age, HbA1c level and the high vascular risk coincide with the profile of the patients included in these studies; thereby the conclusions are applicable to this special case. In this sense, it is important to consider that in the participants without previous vascular event, with lower time of evolution and HbA1c <8% (characteristics that this patient has), it is indeed stated that a reduction of the risk of having a first CV event is determined. On the other hand, the trials follow-up studies, as the Steno-2 and the UKPDS, show a reduction at long-term of the macrovascular disease when the intensive treatment is implemented as early as possible after the diabetes diagnosis, as it has previously been demonstrated in T1D.

Moreover, it is firmly demonstrated that the intensive treatment with the aim of reaching a HbA1c <7% reduces the onset and/or the evolution of the microangiopathic complications, both in T1D and in T2D. In this particular patient, we do not know the ophthalmologic assessment datum but he shows nephropathy. This datum reinforces the importance of optimizing the glycemic control. The intervention studies, as the ADVANCE study, show a reduction of 21% in nephropathy onset risk or worsening.

Therefore, it should be set out a therapeutic strategy of all the modifiable risk factors, through measurements of life style change and an adequate pharmacological approach.

**Which is the approach you would give to the diabetologic treatment?**

In this particular case, taken in account the characteristics of the patient (lack of motivation and non-compliance of the previously indicated treatments), his inclusion in a continuous program of diabetology education reaches a special importance, with the aim of not only providing knowledge, but also to encourage a change of attitude to help him to assume the determined recommendations.

The specific objectives of these educational interventions should include:

- Diet modifications, with reduction of caloric reduction, restriction of saturated fats (<7%) and limitation of protein intake of 0.8-1.0 g/kg/day.
- Indications addressed to achieve an increase of the physical activity, as walks during 150 min/week.
- Training in the monitoring of the capillary glycemia, provided that, though that there are controversial data about the efficacy in patients who have not been treated with insulin, turns out to be useful in the adjustment of the pharmacologic treatment. In case of having a group education, the patients could have a benefit as regards to this program.

As regards to the modification of the pharmacologic treatment, several practical clinical guidelines (PCG)
have been published recently about T2D, as the one of the Canadian Diabetes Association, the NICE and the Ministry of Health and Consumption, besides the new consensus about the starting and adjustment of the treatment in T2D of the ADA-EASD. Though they might coincide in the need of the frequent monitoring in order to perform the treatment adjustments with the aim of achieving a HbA1c level <7% (≤6.5% in the case of NICE), they differ in the set out strategy in the different handling algorithms.

In this patient, two aspects have to be taken into account. On one hand, the obesity suggests the existence of insulin resistance that might be assessed through the determination of the C-peptide and the HOMA index (homeostasis model assessment). The use of metformin is limited by the previous gastric intolerance and the nephropathy, which advised its use with precaution. The pioglitazone could be the alternative, once the cardiac dysfunction and/or hypertensive cardiopathy is ruled out; with the inconvenience of weight increase that entails its use. However, the HbA1c that the patient shows allows us to suppose that the postprandial hyperglycemia is the main responsible of the inadequate glycemic control. Therefore, the drugs with a higher postprandial effect could be more efficacious in this case (meglitinides, alpha-glucosidase inhibitors, drugs based on the incretin effect, analogues of fast insulin). Recently, the IDF determined the postprandial hyperglycemia as a factor risk regardless of macrovascular disease. The ascorbate has a scarce efficacy and a high incidence of gastrointestinal effects, and the substitution of glimepiride by meglitinides would limit the combination with other drugs without adding higher hypoglycemiant strength. The best option seems to be the association of sulphonylureas with drugs that act through the incretin effect, as the GLP-1 agonists or the DPP-4 inhibitors.

The GLP-1 agonists reproduce the actions of this peptide (to stimulate the insulin secretion and to inhibit the glucagon after the intake), acting in the GLP-1 receptor. Two drugs are known up to date, exenatide and liraglutide (this last one has not been commercialized yet). Exenatide should be administered subcutaneously, starting with 5 µg bid during one month, to continue with 10 µg bid. From its association with glimepiride, a reduction of approximately 1% in the HbA1c can be expected and a loss of weight of 3-5 kg. It has the inconvenience of subcutaneous administration, the incidence of nausea in a 50% of the patients and the possibility of hypoglycemias (would obliged to reduce the dose of glimepiride).

The DPP-4 inhibitors, through the inhibition of the enzyme, also increase the action of the endogenous GLP-1. At present, we count with sitagliptine and vildagliptine. They have the advantage of oral administration, in one dose (100 mg of sitagliptine and 50 mg of vildagliptine in association to sulphonylureas) or 2 bid (vildagliptine 50 mg associated to metformin or glitazones) and the absence of gastrointestinal effects. On the contrary, they have a neutral effect on the weight, and lack of safety studies at long term and efficiency in the reduction of the CV risk. After the association to glimepiride (previously studied), a reduction of the HbA1c of 0.6-0.7% can be expected.

It does not seem necessary at the moment to add basal or pre-prandial insulin but it might be later. To summarize I suggest to combine the actual treatment with glimepiride, exenatide (due to the advantage on the weight) or the DPP-4 inhibitors in case of intolerance or rejection to the subcutaneous administration of exenatide.

Which are the medical controls you would recommend?

Taking in account that the initial approach is addressed to reduce the CV risk, the controls have to be the necessary ones until reaching the set out objectives for each of the risk factors. As regards to the AP control, considering that the values that the patient shows are over 140/90 mmHg, together with the indications about the changes in the lifestyle, the pharmacologic treatment should be started with an ARA II, given its demonstrated effect to reduce CV events in diabetic patients with nephropathy and slow down its progression rate. Once the treatment has been started, controls in each medical visit are recommended. In case the target is not achieved, it is indicated to associate a tiazidic diuretic, as this association is efficient to delay the nephropathy evolution. A control of the creatinine is recommended as well as the control of the plasma potassium 15 days after having started the treatment, and if the patient shows an acute intercurrent process. In case of requiring more drugs, a calcium antagonist or a beta-blocker should be chosen. The association ACEI-ARA II can cause a worsening of the renal function and hyperkalemia.
In the treatment of dyslipidemia it is a priority to achieve a level of cLDL lower than 100 mg/dL, for which a pharmacological treatment is recommended with high doses of statins. If the objective is not achieved, an association with ezetimibe shall be set out. It should be expected to reduce the hypertriglyceridemia (to values <150 mg/dL) with the improvement of the glycemic control and the compliance of the diet recommendations. Once the treatment started, an analytical control should be performed after 3 months in order to determine an assessment and an adjustment of the dose, as well as to rule out the hepatic and muscular toxicity. After reaching the target, controls every six-month shall be determined. An antiaggregant treatment should be recommended with acetylsalicylic acid in primary prevention doses of 75-162 mg/day, once the values of the systolic AP are lower than 145 mmHg.

As it has already been mentioned, in this case there is a special importance on the consultations on diabetologic education, both initial and follow-up. The frequency of the consultations shall depend on the evolution and attitude of the patient. The last recommendations of the ADA include the glycemic self-control as part of the therapeutic intervention, agreeing with each patient the self-analysis frequency. The other main parameter in the follow-up of the glycemic control is the determination of the HbA1c. As it is collected in the CPG, controls on a three-month basis is recommended, in order to indicate the changes in the therapy, until reaching the control objective, with subsequent six-months determinations.

Would you do any complementary test?
For a correct assessment of the patient, it would be necessary to complete the study through tests that allow the determination of possible vascular complications of the diabetes, that probably might have an evolution time longer that the one known:

- Ophthalmology assessment. If there is not a previous assessment, it is recommended that the first examination, with pupil dilatation be performed by an ophthalmologist (funduscopy, ocular pressure and campimetry). In case no injuries are detected, an assessment will be done each 1-2 years by the ophthalmologist, or a non mydriatic retinography.

- Renal function. The determination of the microalbuminuria through the albumin/creatinine index in a sample of urine. Considering the level of the patient’s creatinine, it is probable that he has microalbuminuria, though it should be pointed out that an important percentage of patients have diabetic nephropathy without detectable albuminuria. Then, periodical controls should be determined in order to assess the response to the treatment.

- For the study of peripheral neuropathy, the vibratory exploration has to be registered with the tuning fork of 128 Hz, the sensitivity to the pressure with monofilament and the osteotendinous reflexes. The combination of more than one test has a diagnostic sensitivity >87%. The electrophysiological study should be indicated only if there are diagnosis doubts. The anamnesis should be completed with a questionnaire in order to detect the symptoms of autonomous dysfunction, and a basic exploration to rule out an autonomous cardiac neuropathy (tachycardia at rest, ortostatism, etc.).

- To assess the subclinical arterial ischemia of the lower limbs with the inspection of possible trophic signs, palpation of peripheral pulses and determination of the ankle-arm index. In case of a pathological result, an arterial echo-Doppler should be indicated.

- As regards to the ischemic cardiopathy screening, it is still controversial if other diagnosis tests are necessary besides the performance of an electrocardiogram (ECG). In the last studies, it has not been stated the usefulness of other tests in asymptomatic patients with a normal ECG.

- Finally, the performance of an abdominal echography will enhance the suspicion of hepatic steatosis and assess the need of ruling out other hypertransaminase causes.

In conclusion, in this patient, after completing the diagnostic study, a multifactor approach should be set out as well as intensive of this last multiple risk factors, with the aim of reducing the high CV risk that he shows.

Declaration of potential conflict of interest
M.J. Goñi states that there is no conflict of interests as regards to the content of this paper.

References


**Therapeutic education in diabetes**

**The importance of adherence to the treatment in diabetes mellitus**

*Importancia del cumplimiento terapéutico en la diabetes mellitus*

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**Abstract**

Even the best treatment loses its efficacy if the patient does not follow it properly. That explains the importance of therapeutic adherence in chronic diseases from different disciplines. This article reviews adherence to the treatment in diabetes as a chronic disease. A description of the most common barriers found in patients with diabetes, different methods for the analysis of therapeutic adherence, as well as control strategies that have proven to be most efficient are in this review. Between them, a therapeutic education of patients and their family members is underlined. Finally, this article emphasizes the position of the World Health Organization on therapeutic adherence.

**Keywords:** diabetes, adherence to treatment, chronic diseases.

**Introduction**

The therapeutic adherence in chronic diseases has an interest from the point of view of several disciplines, as the best treatment loses its efficacy if the patient does not follow it properly. Especially in the diabetes mellitus, such adherence turns out to be crucial and is a measurement variable of the interventions on the therapeutic education. This explains the interest of all the diabetes educators.

**Therapeutic adherence in the chronic diseases context**

The adherence of the treatments of the chronic diseases is a problem of great magnitude given the increase observed in its prevalence during the last years. Different studies have demonstrated that the therapeutic adherence in chronic patients ranges between 50 and 75% in the developed countries. But the magnitude of this problem is even more noticeable in the developing countries, provided their shortage of sanitary resources and the lack of equity as regards to the health care access by the users.

The World Health Organization (WHO), defines the therapeutic adherence as the degree in which the behavior of a person corresponds to the recommendations agreed between a health professional and a patient: as regards to the medication taken, the follow-up of a diet regime and the execution of the changes in the agreed
The therapeutic adherence is not the exclusive responsibility of the patient, as the WHO defines well, but a multidimensional phenomenon determined by the mutual action of a set of factors related to the patient: the treatment/s, the disease/s, the socio-demographic factors and the health system. The patient-professional communication and the therapeutic education are determining factors in this process (figure 1). The lack of adherence is associated to a higher morbimortality, with the increase of direct costs considering the hospitalizations due to acute complications, indirect costs related especially to the sick leave, as well as intangible costs associated to a reduction of the life quality.

The conclusions of the DiMatteo meta-analysis, about 569 studies published between the years 1948 and 1998, in which the psychiatric diseases have been excluded, have been the following ones:

- The lack of therapeutic adherence is always present, though in the last 50 years an improvement on this aspect took place, with a mean lack of adherence of 24.8%.
- The studies about therapeutic adherence that use systems of target measurements, as the accounting of tablets or the physical measures, point out worse rates than the studies based on indirect measurements, as the self-administered questionnaires.
- The continuity of the drugs taking tends to be higher than the adherence to a healthy lifestyle.
- The therapeutic adherence varies as regards to the type of disease. It is higher in HIV, arthritis, gastrointestinal diseases and cancer. The lowest adherences detected in other diseases, such as diabetes and sleeping disorders.
- In most of the studies, the correlation between the therapeutic adherence and the socio-demographic factors is statistically relevant, but modest in magnitude (r >0.15 in all the cases).
- There is a special emphasis in the need of evaluating the therapeutic adherence in a multifactor manner and through several methods, two as minimum.

It is important to tinge that a 75% of therapeutic adherence does not mean that the patients ignore the 25% of the recommendations, or that the 25% do not adhere at all. Moreover, the lack of adherence in a clinical context depends also on the relation between the continuity and the results. In the case of HIV, for example, the therapeutic adherence has to be higher in order to achieve clinical benefits; in turn, in other diseases it could be lower, as the case of the acetylsalicylic acid as a drug for the prevention of the acute myocardial infarction. Paradoxically, in some occasions the lack of therapeutic adherence has been beneficial for the patient, as in the treatment with estrogens in menopausal women, given the later relation that it established with the breast cancer.

**Therapeutic adherence in the diabetes mellitus**

As Golay defends well, the treatment adherence is also a measurement variable of interventions in the therapeutic education, together with the life quality and the prevention of complications. This explains the interest of all the diabetes educators. The problems of the therapeutic adherence are always noticed when the treatment requires self-administration, regardless of the type, the seriousness of the disease and the accessibility to the health resources. The treatment complexity is a variable associated to a worse adherence, and the diabetes is the paradigmatic example of a complex self-administered treatment. Pharmacology treatment with tablets or insulin is required, and not pharmacological with nutritional therapy, physical exercise, tobacco abandonment, prophylactic care of the lesions in the feet, and self-analysis and self-control techniques, among others. On the other
Therapeutic education in diabetes


hand, most of the patients have to add other drugs, as hypolipemians, antihypertensive and platelet antiaggregants, for the prevention and/or treatment of the cardiovascular risk factors. In the presence of chronic complications or other non-related diseases, the “plurimedication” is still higher in patients, associating this to a worse pharmacological adherence.10

Linked to this complexity, the persons with type 1 diabetes mellitus (T1D) (or their parents in case of children) have a great responsibility because they have to take decisions in real time about the treatment guideline that has to be implemented several times a day.3 That is to say not only they have to inject themselves insulin, but they have to decide about which dose of insulin to inject themselves in each meal considering the capillary glycemia of the moment carry out the estimation of the carbohydrates they will consume and foresee the physical activity they will do later. At the same time, they have to assess the tendency of the controls in order to adjust the basic guideline (self-control). This explains the importance of the therapeutic education in the treatment of all the diabetic persons.6

It is important to evaluate the adherence of the different components of the treatment independently: capillary glycemia, insulin administration, oral hypoglycemiant, diet, physical activity, care of the feet, self-analysis, self-control, revisions, etc. For example, a person can be strict in the insulin self-administration, but not in the taking of the tablets, and partially strict in the performance of the glycemic controls. This example demonstrates that the adherence is not a one-dimensional fact. Therefore, it has to be considered the therapeutic adherence in the diabetes either it is T1D or T2D and the different aspects of the treatment, pharmacological or non-pharmacological, as well as the self-analysis and self-control techniques.

It has to pointed out, by its magnitude, the results related to the therapeutic adherence of the transversal, multicenter and international macro-study, Diabetes Attitudes Wishes and Needs (DAWN),7 in which 5,426 adult patients (50% with T1D and 50% with T2D) took part, 2,194 general physicians, 556 endocrinologists and 1,122 nurses. The study was performed in 13 countries: Australia, Germany, Denmark, Spain, United States, France, Great Britain, Holland, India, Japan, Norway, Poland and Sweden. As the table 1 depicts, the therapeutic adherence in the diabetes is not optimal, and a better pharmacological treatment adherence is confirmed than of the nutritional therapy and the physical exercise. The health professionals refer to a better adherence of the clinical guidelines in the T1D than in the T2D.

Several studies8-13 have demonstrated that the most common barriers related to the lack of therapeutic adherence in the diabetes are multi-dimensional and common to most complex chronic treatments. Some of these barriers are referred in table 2.

### Table 1. Therapeutic adherence in diabetes, according to the DAWN study7

<table>
<thead>
<tr>
<th>Adherence (%)</th>
<th>Persons with T1D (n)</th>
<th>Persons with T2D (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacological treatment</td>
<td>83</td>
<td>78</td>
</tr>
<tr>
<td>Diet</td>
<td>39</td>
<td>37</td>
</tr>
<tr>
<td>Physical exercise</td>
<td>37</td>
<td>35</td>
</tr>
<tr>
<td>Self-analysis</td>
<td>70</td>
<td>68</td>
</tr>
<tr>
<td>Medical visits</td>
<td>71</td>
<td>72</td>
</tr>
</tbody>
</table>

T1D: type 1 diabetes mellitus; T2D: type 2 diabetes mellitus.

**Methods to analyze the therapeutic adherence**

To measure the therapeutic adherence presents difficulties because an exclusive method for this purpose does not exist. This fact, together with the multiple factors that condition it, explains the differences observed among the several studies. The therapeutic adherence is a behavior of the person and, therefore, a patient might be compliant, not compliant or partially compliant of a part or the entire treatment. The partially methodical behavior is quite frequent, above all in the asymptomatic chronic pathologies, as the T2D, the hypertension, the dyslipidemia, etc., and in a special manner during the weekends and/or vacations. On the other hand, the lack of therapeutic adherence might be intentional or non-intentional. A clear example of intentional adherence would be the omissions of insulin doses in women with T1D to control the weight, and non intentional, associated to determined barriers, as the lack of therapeutic education, technical mistakes, depression, and several cognitive aspects and memory failure in elderly persons, among other factors.
In the diabetes, it is important to measure the adherence of the different components of the treatment in each particular patient. The measurement systems, which have been described in the references, are several. They differentiate among them as regards to direct and indirect methods to measure, the pharmacological treatment adherence (table 3) and non-pharmacological one (table 4). Many of them are only used in investigation studies, while others can be used both in investigation and the usual clinical practice.3,14,15

Table 2. Most common barriers related to the lack of therapeutic adherence in diabetes

- Lack of access to the drugs and to the health assistance
- Complexity in the treatments
- Perception that it is not necessary to take medication when one feels good
- Use of invasive systems and technical mistakes in the performance of the capillary glycemia and in the administration of insulin
- Family or personal conflicts
- Lack of school, work, or social support
- Lack of knowledge or skills about the treatment
- Lack of motivation
- Lack of treatment schemes easy to understand
- Non customized treatment to the needs of each patient
- Cognitive or memory difficulties (especially the association to depression)
- Fear to hypoglycemias (preferable to keep high levels)
- Fear to weight increase (especially in women)
- Inadequate communication with the health team
- Non agreed interventions
- Lack of access to assistance when the patients needs it
- Poor coordination among tests, follow-up tests and coordination among the assistance levels
- Differences of criteria among the different health professionals

Table 3. Systems to measure the pharmacological treatment adherence in diabetes

<table>
<thead>
<tr>
<th>Pharmacological treatment. Direct Methods.</th>
<th>Target methods used preferably in the investigation studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pharmacy records. Consists in contrasting the indicated medication with the one provided by the pharmacy during a determined period</td>
<td></td>
</tr>
<tr>
<td>• Tablets accounting. In each visit the patient has to take the bottles and he is asked about the medication taken during a determined period</td>
<td></td>
</tr>
<tr>
<td>• Drugs counter. Type MEMS electronic monitoring systems: microprocessor incorporated to a drug container that records the day and hour it has been opened</td>
<td></td>
</tr>
<tr>
<td>• Biological indexes. To analyze the levels of drug in blood or the biological markers</td>
<td></td>
</tr>
<tr>
<td>• Supervised doses. Supervision by a relation or professional in the cases in which the effects of the lack of therapeutic adherence might be serious (children with diabetes or elderly persons)</td>
<td></td>
</tr>
<tr>
<td>• Technical observation of the insulin and volume of insulin of the vials and/or pens. Method to assess the adherence of an adequate injection and rotation technique, as well as an approximate method to contrast the volume of the consumed insulin with the indicated volume. It might detect the lack of involuntary therapeutic adherence by mistakes in the technique</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmacological treatment. Indirect methods. Subjective methods used both in the investigation and in the clinical practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Assessment of the professional. The patient is asked about the adherence of the different parts of the treatment. Its value increases when it is contrasted with other members of the team</td>
</tr>
<tr>
<td>Questionnaires. The questionnaires are simple and economic methods, though they underestimate the therapeutic adherence in approximately 20%. The reliability increases when the patient says that he does not take the medication. The most used questionnaires are the Morinsky Green and Haynes Sackett ones14</td>
</tr>
</tbody>
</table>

In spite of the fact that they are not validated in Spanish language, there are questionnaires in English language to measure the adherence of the different treatment components, as the Self Care Inventory Revised Version (SCI-R),16 that might be used in children and adults with T1D or T2D. They are useful to assess the impact of the educational interventions on the therapeutic adherence and its relation with the metabolic control, and can be used individually or in groups of patients. Likewise, there are other similar questionnaires addressed exclusively to persons with T1D.17

Strategies to improve the therapeutic adherence

Besides the basic principle of ensuring the access to health assistance and to the drugs (aspects that the health systems themselves have to afford in each country), different studies, authors and organizations propose multifactor interventions with new assistance models for the chronic patients that include interventions that have demonstrated to be efficient for the improvement of the therapeutic adherence. The proposed strategies are depicted in table 5.3,13,5,16,28
Positioning of the WHO about the therapeutic adherence

Taking into account the relevance and applicability, both in diabetes and in the set of chronic diseases, the main messages about the therapeutic adherence are exposed as summary according to the report issued by the WHO:

1. The deficient adherence of the treatment in chronic diseases is a major problem. The therapeutic adherence in developed countries is estimated in a 50%. This value is lower in underdeveloped countries.

2. The repercussion of the therapeutic adherence grows proportionally to the increase of the chronic disease burden in the world. AIDS, tuberculosis and mental disorders represented the 54% of the world burden of all the diseases in the year 2001, and shall exceed the 65% in 2020 all over the world. The countries with a higher level of poverty are disproportionately affected.

3. The consequences of a deficient therapeutic adherence at long term are translated in low health results and in an increase of the health costs.

4. The improvement of the therapeutic adherence also increases the patients’ safety.

5. To increase the efficiency of the interventions regarding to the therapeutic adherence might have a greater repercussion on the population health than any other improvement of the specific medical treatments. The advances in the biomedical technology cannot be applied in all its potential without a health system that takes into account the determining factors of therapeutic adherence. The access to the drugs is necessary, but insufficient in itself, in order to treat the diseases efficiently.

6. The health systems have to improve the therapeutic adherence in order to face new challenges. The increase of the chronic diseases during the last 50 years makes the acute assistance models of the health assistance services be insufficient to tackle the needs of the population.

7. The patients need support, not to feel guilty. In spite of the evidences that prove the contrary, there is still a tendency to focus the non-adherence factors on the
patient, and they forget the factors related to the professionals and the health system.
8. The therapeutic adherence is influenced by several social and economic factors: team or health assistance system, characteristics of the disease, treatment, and factors related to the patient, etc.
9. Interventions adapted to the patients are needed. No strategy or set of intervention strategies has been stated that had been efficient for all the patients, disorders and environments. Therefore, the interventions have to be adapted to the particular requirements related to the patient and the disease.
10. The therapeutic adherence is a dynamic process that requires strictness because the factors that determine it vary throughout the time and the social changes.
11. The health professionals have to train the patients and relatives as regards to the therapeutic adherence.
12. The family, the community and the organizations of patients are key factors for the success in the improvement of the therapeutic adherence.
13. The therapeutic adherence requires a multi-disciplinary approach. In order to be able to advance on this regards, a higher commitment level is needed among the different involved agents as well as a multi-disciplinary approach. This implies the coordinated action of health professionals, the investigators, the health planners and the responsible parties of the health policies.

Conclusions
The therapeutic adherence is a very important factor that might modify the efficiency of the health system. To increase the efficiency of the interventions on the therapeutic adherence might have a major repercussion on the health of the persons in some cases than any improvement of the specific treatments. The health systems and the involved professionals have to evolve in order to face these new challenges.

Declaration of potential conflict of interests
M. Jansà and M. Vidal state that there is no conflict of interests as regards to the content of this article.

References
Therapeutic education in diabetes


Grinspan’s syndrome in a diabetic woman

Síndrome de Grinspan en una mujer con diabetes

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Case report

50 years old woman, with type 2 diabetes mellitus of 23 years of evolution and an adequate metabolic control during the last 9 years (glycosylated hemoglobin of 6.3-6.6%). She did not show any complication of her diabetes, but suffered from a diffuse proliferative glomerulonephritis with arteriolar hyalanosis, proteinuria and arterial hypertension since 1992. Moreover, the patient was also diagnosed with glaucoma, hyperuricemia and mixed hyperlipemia. According to the treatment with metformin, repaglinide, NPH insulin, simvastatin, ezetimibe, irbesartan 800 mg/day and acetylsalicylic acid.

The patient started with lesions in the oral cavity that caused her discomfort when having her meals. She has been previously treated with antifungal wash and by systemic route, but considering the inefficiency of said treatment she attended an odontology site. After a complete exploration of the oral mucosa, some lesions were observed that had a hyperkeratosic aspect in reticulated pattern, with the basis slightly erythematous of approximately 4 cm of surface, localized on both jugal mucosa. The patient also showed similar lesions in the lateral borders of the tongue. In this localization, the lesions alternated the reticular pattern with an erosive pattern. The presumption diagnosis was of oral lichen planus. This diagnosis was confirmed through an incisional biopsy in the left jugal mucosa. Considering the diabetes triad, arterial hypertension and lichen planus that the patient showed, the case report was classified as Grinspan’s syndrome. She has been treated with triamcinolone acetonide 0.1% in aqueous solution, three times daily during one month, achieving an evident improvement.

Though Grinspan described the syndrome, several authors point out that this association is merely casual and suggest that the main frequency of lichen planus in patients with diabetes and arterial hypertension might be due to the use of several of drugs used in these entities. In this case, it has to do with lichenoid reactions and not lesions of the lichen planus in itself. However, in the diabetic patients, especially those with T1D, a higher frequency of some clinical forms of lichen planus can be observed, mainly the atrophic and erosive forms with a higher tendency to be localized on the tongue. The most usual localizations are the jugal mucosa, the gum and the tongue. It is generally asymptomatic, though there is a chronic form, named erosive bullous lichen, which presents very painful lesions. The treatment includes topic and systemic corticoids (in the serious and mucocutaneous forms), retinoids, cyclosporine and phototherapy. Notwithstanding the controversy as regards to its premalignant nature, the follow-up of the lesions is considered essential.

References