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News
In the treatment of persons with T2D, the control of hyperglycemia is one of the main objectives, and an effective way to reduce and delay the onset of either microvascular or macrovascular impairments. At present, we count with several approaches, several drugs and different therapeutic antihyperglycemic guidelines, which we have to adapt in a customized manner to each of the persons with T2D taking into account their age, the hyperglycemia level, the evolution of the disease, the associated comorbidities and the social and personal situation. Though the basis of the initial treatment of the T2D is constituted by the changes in the lifestyle that incorporate a nutritional treatment and the increase of physical activity, together with the oral medication, in certain situations the administration of insulin is required in order to achieve an adequate control.¹

On one hand, the use of insulin is recommended when a metabolic decompensation takes place, if there are clear symptoms of hyperglycemia or if the levels of glycemia or HbA₁c are very high. On the other hand, the insulinization will be necessary when the glycemic control objectives are not achieved with other treatments, the clinical guidelines recommend the starting of insulin therapy adding a single dose of intermediate insulin or slow analogue with later dose adjustment. However, the use of two doses of premixed insulins proved to yield better results regarding the improvement of the HbA₁c and the postprandial glycemias.² For this reason, it is recommended to consider the guideline of two injections of premixed insulin of 8.5-9% in these cases. Premixed analogues should be used rather if injections immediately before the meals are preferred, if the hypoglycemias are an important risk for the patient or if the postprandial fluctuations of the glycemia are very marked.

Moreover, starting insulin administration suggests starting a structured diabetes education that includes frequent self-analysis and self-control for an adequate adjustment of the dose. If after the beginning of the insulin therapy with slow or intermediate insulin and the later increase of the dose, the HbA₁c objectives are

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**List of acronyms quoted in the text:**

NPH: neutral protamine Hagedorn insulin.
Premixed insulins in type 2 diabetes. E. Menéndez Torre

not achieved, there are two options in the insulin therapy intensification: to evolve to a basal bolus guideline, adding a dose of a fast analogue to the considered meals, or to change the guideline to premixed insulins in multi-doses, generally before breakfast and before dinner. This last guideline might be easy to understand and to carry out by the majority of the patients with T2D with which an adequate control is achieved in more than half of the cases, without differences as regards to the number of hypoglycemias or other adverse effects. On the other hand, the guideline with premixed insulins might provide a better life quality compared to the basal bolus guideline.

The usual guideline of two daily doses of premixed insulins before the breakfast and dinner might intensify itself if considered necessary adding a new dose before lunch, achieving an improvement of the HbA1c, increasing the risk of mild hypoglycemias only moderately, which in any case are kept at low levels. The mixtures of insulin have also proved their efficacy in hospitalized patients, achieving a similar glycemic control to the basal bolus guideline without differences in the hypoglycemias’s incidence. At the hospital, they might constitute a very flexible tool to reach an adequate metabolic control in changing situations, as the concomitant treatment with corticoids in variable doses.

To sum up, the premixed insulins are an efficient option, as well as safe and very useful in patients with T2D who require insulin due to a metabolic decompensation, or who need the intensification of the previous treatment guideline with other antidiabetic drugs or with slow or intermediate insulin.

Declaration of potential conflict of interests
E. Menéndez Torre received fees for teaching activities through invitations of Sanofi-Avenits, Novonordisk and Lilly.

References
Abstract
Recent studies have shown that elevated concentrations of plasma lipopolysaccharide (LPS) constitute a metabolic mechanism enough for triggering insulin resistance, obesity and type 2 diabetes in animal models, and that high fat diets lead to increased plasma LPS concentrations through changes in the gut flora. We review here the LPS effects in metabolic processes in vitro. In humans, an altered innate immune system has also been associated with metabolic disorders such as insulin resistance, high endotoxemia markers (LBP, sCD14) and low LPS-neutralizing proteins (adiponectin, bactericidal permeability-increasing protein, αα-defensins and lactoferrin). In fact, insulin resistance is well known to be associated with inflammation, with a decrease in innate immune efficiency and a reduction in the production of antimicrobial proteins. In this revision, we propose a new view according to which buffering efficiency of the innate immune system could prevent LPS-induced metabolic diseases.

Keywords: metabolic endotoxemia, endotoxemia markers, LPS-neutralizing proteins, insulin resistance, obesity.

Introduction
Obesity is well known to be associated with a cluster of metabolic diseases, such as dyslipidemia, hypertension, insulin resistance, type 2 diabetes and atherosclerosis. Adipose tissue has an essential role as energy storage depot and for secreting adipokines influencing diverse tissue targets such as brain, liver, muscle, β cells, gonads, lymphoid organs, and systemic vasculature. Expression analysis of macrophage and non-macrophage cell populations isolated from adipose tissue demonstrates that adipose tissue macrophages are responsible for secretion of almost all of pro-inflammatory cytokines. In recent years, it has become evident that alterations in the function of the innate immune system are intrinsically linked to metabolic pathways in humans. Central to metabolic diseases is insulin resistance associated with a low-grade inflammatory status. The mechanisms through which proinflammatory cytokines, like tumor necrosis factor α (TNF-α), interleukin-6 (IL-6) and interleukin 1-beta (IL-1β) interact with cellular insulin signal transduction cascades have been better understood in the last few years. In vivo, a direct correlation between increased circulating proinflammatory cytokines and insulin resistance has been well-demonstrated.

The origin of this increased inflammatory activity in obesity and type 2 diabetes is virtually unknown. Immune system homeostasis is challenged by continuous external insults, like saturated fatty acid-rich diets, pathogen associated molecular patterns (PAMP) like lipopolysaccharide (LPS) and advanced glycation products (AGEs), burden of infection and oxidative stress. These continuous insults could result in a chronic low level of inflammation associated with insulin resistance.

This revision is focused in the effects of metabolic concentrations of plasma LPS in insulin resistance and other
metabolic disorders associated with obesity, and the possible role of an inefficient innate immune system responding to this challenge.

**Endotoxemia effects on obesity and insulin resistance**

LPS is an important structural component of the outer membrane of Gram-negative bacteria. LPS consists of three parts: a lipid A, an oligosaccharide core, and an O side chain. LPS is one of the best studied and most potent immunostimulatory components of bacteria which induces toxicity through increased signaling, triggering systemic inflammation. LPS leads to a strong stimulatory release of several cytokines that are key inducers of insulin resistance which is a putative factor for the triggering of metabolic disorders. Lipid A is the main pathogen associated molecular pattern of LPS and is acylated with saturated fatty acids. Removal of these fatty acids results in complete loss of endotoxic activity. LPS stimulation of mammalian cells occurs through series of interactions with several proteins including the LPS binding protein (LBP), CD14, MD-2 and TLR4. LBP is a soluble shuttle protein which directly binds to LPS and facilitates the association between LPS and CD14. CD14 is a glycosylphosphatidylinositol-anchored protein, which also exists in a soluble form. CD14 facilitates the transfer of LPS to the TLR4/MD-2 receptor complex and modulates LPS recognition. MD-2 is a soluble protein that associates non-covalently with TLR4 but can directly form a complex with LPS in the absence of CD14. MD-2 is associated with the extracellular domain of TLR4 and augments TLR4-dependent LPS responses in vitro being essential for correct intracellular distribution and LPS-recognition of TLR4. The TLR4 receptor complex, recruits the adapter protein, myeloid differentiation factor-88 (MyD88). MyD88 in turn recruits interleukin-1 receptor–associated kinase (IRAK) and, by activating IKKβ and NF-κB, ultimately induces the expression of numerous inflammatory mediators. Furthermore, TLR4 can be activated with saturated free fatty acids, stimulating NF-κB signaling and expression of inflammatory cytokine genes, such as TNF-α and IL-6 in adipocytes and macrophages.

A recent article has demonstrated that metabolic concentrations of plasma LPS are a sufficient molecular event to trigger insulin resistance, obesity and type 2 diabetes. This process was called metabolic endotoxia, defined as the association between metabolic concentration of circulating endotoxin (LPS) and inflammation- and high fat diet-induced metabolic diseases. Metabolic concentration is the minimum LPS concentration to produce metabolic disorders, but not enough to produce acute endotoxia. Interestingly, metabolic concentrations of plasma LPS were increased by a high fat diet. The same authors reported new interactions between a high fat diet and the microbial gut flora. They found that high fat feeding changes microbial gut flora (decreasing *Bifidobacterium* spp.) and increases intestinal permeability, leading to increased LPS absorption, endotoxia, inflammation and metabolic disorders. Selective increases of *Bifidobacterium* spp. in gut flora improved high fat diet-induced diabetes in mice and this was associated with decreased concentration of circulating LPS.

In vitro, LPS induces nuclear factor-kappaB- and MAPK-dependent proinflammatory cytokine/chemokine expression primarily in preadipocytes. These changes are associated with a decrease in adipogenic gene expression, lower ligand-induced activation of peroxisome proliferator activated receptor (PPAR)-γ and decreased insulin-stimulated glucose uptake in adipocytes. Persistent LPS stimulus impaired adipocyte differentiation and decreased the expression of lipogenic enzymes (FABP4, LPL), of different adipokines (adiponectin, resistin, visfatin, leptin) and of PPAR-γ. Thus, LPS stimulus lead to adipose tissue insulin resistance and to adipocyte dysfunction usually found in the systemic metabolic disorders linked to obesity.

These findings in animal models are mirrored by different observations regarding endotoxia markers and LPS-neutralizing proteins in humans, summarized below (table 1).

<table>
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<th>Table 1. Endotoxia markers and LPS-neutralizing proteins</th>
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<td>• Soluble CD14 (sCD14)</td>
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<td>• Lipopolysaccharide binding protein (LBP)</td>
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<td>• Adiponectin (ADIPOQ)</td>
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<td>• Bactericidal/permeability increasing protein (BPI)</td>
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<td>• Human α-defensins (DEFA1-3)</td>
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<td>• Lactoferrin (LTF)</td>
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Endotoxemia markers and LPS-neutralizing proteins

Endotoxemia markers

Endotoxemia markers are molecules of innate immune system which are produced by leukocytes (macrophages and neutrophils), adipose tissue, liver, kidney, lung, thymus, small intestine and mammary tissue in response to LPS stimuli. This review is focused in the main endotoxemia markers soluble CD14 (sCD14) and lipopolysaccharide binding protein (LBP), two phase acute reactants that are released in response to LPS.

Soluble CD14 (sCD14)

The earliest cell-mediated events following endotoxin release appear to involve the glycosylphosphatidylinositol anchored protein CD14. Different lines of evidence support a central role for CD14 in LPS-mediated responses. Specific monoclonal antibodies (mAb) against CD14 inhibit the ability of LPS to stimulate monocytes. Transfection of CD14 into the 70Z/3 pre-B cell line enhances the responsiveness of these cells to LPS by more than 1000-fold. CD14 also exists in a soluble form (sCD14), and the levels are significantly raised in septic patients. The physiological role of sCD14 is not yet completely understood. sCD14 has been shown to inhibit the LPS-induced TNFα production in whole blood and monocytes, and in a mouse model of endotoxin shock, sCD14 has been shown to inhibit lethality as well. However, contrary to this inhibiting effect of sCD14 on LPS effects, sCD14 facilitates the activation of endothelial cells that do not express membrane CD14. Troelstra et al reported that the effect of sCD14 on neutrophil response to LPS was a balance between activation and inhibition, depending on the concentration of circulating LBP in serum. However, sCD14 could play a key role as intermediate in the neutralization of LPS under physiological conditions. sCD14 accelerates the transfer between LPS micelles and lipoproteins by acting as a carrier. sCD14 also enhances the release of monocyte-bound LPS, transferring LPS into plasma and into lipoproteins and, thus, decreasing cellular responses to LPS, such as induction of TNF-α and interleukin 6 synthesis.

Recently, a direct relationship between sCD14 and endothelial function in type 2 diabetic subjects has been found in opposite to the inverse association of these parameters in non-diabetic subjects. Furthermore, sCD14 was significantly and inversely associated with insulin resistance, waist to hip ratio, systolic and diastolic blood pressure and inflammatory markers (sTNFR1 and sTNFR2), once fasting triglycerides and smoking was controlled. sCD14 could also be a marker of hepatic insulin resistance and dysfunction. In fact, decreased serum sCD14 concentration was associated with higher circulating alanine aminotransferase levels. These apparently protective associations of sCD14 with metabolic parameters (insulin sensitivity, blood pressure, hepatic injury) are supported by the anti-inflammatory activities of sCD14, neutralizing LPS effects in in vitro models.

Interestingly, genetic variations that lead to lower serum concentration of sCD14 were associated with insulin resistance and the presence of increased inflammatory markers.

Lipoplysaccharide Binding Protein (LBP)

Lipoplysaccharide Binding Protein (LBP) is an important LPS marker. LBP is a 65-kDa protein present in blood at high concentrations (approximately 2-20 µg/mL). Although the molecular structure of LBP is not entirely known, LBP clearly binds LPS (and LPS substructures, such as lipid IVa) through the recognition of lipid A. The plasma protein LBP dramatically accelerates binding of LPS monomers from aggregates to CD14, thereby enhancing the sensitivity of cells to LPS. Furthermore LBP acts as a lipid transfer protein, a function in correlation with its sequence homology to lipid transferases (phospholipid transfer protein and cholesterol ester transfer protein). LBP co-purifies with HDL particles and additional studies have shown that LBP can transfer LPS to lipoproteins, neutralizing LPS effects.

Serum LBP reflects the serum endotoxin (LPS) concentration and is negatively associated with insulin sensitivity. Interestingly, serum LBP concentrations are increased in patients with type 2 diabetes.

LPS-neutralizing proteins

Several naturally occurring proteins possess the capacity to bind to bacteria-associated LPS, resulting in reduction of bacterial viability. These LPS-neutralizing proteins are adiponectin, bactericidal/permeability-increasing protein (BPI), human α-defensins and lactoferrin.
Adiponectin (ADIPOQ)

Adiponectin (ADIPOQ) is almost exclusively produced by adipocytes and abundantly present in serum, where it circulates in two higher-order forms: a low-molecular weight dimers or trimers and a larger high-molecular weight complex of 12-18 subunits.60 ADIPOQ is known to affect LPS-mediated inflammatory events. It inhibits LPS-induced NF-κB activation and IL-6 production, and increases PPARγ2 expression in adipocytes, while in macrophages it suppresses both LPS-induced TNFα and IL-6 production. Peake et al suggested that adiponectin may have anti-inflammatory potential by directly binding to LPS.61

It is well known that adiponectin expression is reduced in obesity and insulin resistance states. Plasma levels of adiponectin have also been reported to be significantly reduced in obese/diabetic mice and humans, and in patients with cardiovascular diseases, hypertension or metabolic syndrome.62 A direct insulin-sensitizing effect of adiponectin in vivo has been extensively reported. The main mechanism of action of adiponectin in insulin-sensitizing actions are mediated through a reduction of tissue triglycerides content and activation of PPARα63 and AMP kinase,64,65 leading to the up-regulation of insulin signaling. However, the anti-inflammatory effects of adiponectin and LPS neutralizing action cannot be forgotten, as two indirect ways to improve insulin sensitivity. Single nucleotide polymorphisms studies also support the role of adiponectin as a factor influencing the susceptibility to insulin resistance and type 2 diabetes.66,67

Bactericidal/increasing protein permeability (BPI)

Bactericidal/increasing permeability protein (BPI) is located in the azurophilic granules of neutrophils. BPI is an approximately 55 kDa cationic protein with selectivity towards Gram-negative bacteria, most likely due to its strong affinity for LPS.68 Besides its bactericidal activity, BPI also neutralizes the cytotoxic effects of LPS. Most of the antibacterial and LPS binding activity of hol-BPI is found in 20-25 kDa N-terminal fragments/domains of the protein.69 N-Terminal fragments/domains of BPI also inhibit LPS induced E-selectin expression and reduce NF-κB activation in LPS-stimulated endothelial cells.70 Furthermore, rBPI21, a recombinant 21 kDa protein/peptide corresponding to amino acids 1-193 of N-terminal human BPI in which a cysteine is replaced by an alanine at position 132), is bactericidal and binds to and neutralizes endotoxin.71

Plasma BPI concentration was directly correlated with insulin sensitivity and HDL-cholesterol concentrations, and inversely associated with metabolic parameters (waist-to-hip ratio, fasting triglycerides) and with serum LBP and LPS concentration. Genetic variations that lead to lower serum concentration of BPI were associated with insulin resistance and increased circulating inflammatory markers.59

Human α-defensins (DEFA1-3)

Human α-defensins are arginine-rich peptides, containing 29-35 amino acids. Their three disulfide bridges connect cysteines 1-6, 2-4 and 3-5. Human α-defensins are synthesized as 93-100 amino acid prepropeptides with a 19-amino acid signal peptide and a 41-51 amino acid anionic pro-segment. α-defensins are predominantly found in neutrophils (mainly DEFA1-3) and in small intestine Paneth cells. A stimulus-dependent release of pre-synthesized defense-containing cytoplasmic granules contributes to the local antimicrobial response.72 Recently, significant positive associations among plasma α-defensins (1-3) concentrations and non-atherogenic lipid profile and vascular function in apparently-healthy Caucasian men have been reported.73

Lactoferrin (LTF)

Lactoferrin is a pleiotropic glycoprotein of the innate immune system that is involved in LPS buffering. Lactoferrin is a monomeric, 80 kDa glycoprotein, with a single polypeptide chain of about 690 amino acid residues and two sialic acid molecules, that is produced by neutrophils and several epithelia types. Lactoferrin is folded into homologous N- and C-terminal lobes, each comprising two domains that enclose a conserved iron binding site. This protein is positively charged in N-terminal region (the first 60 aminoacids) of N-lobe at physiological pH because it is rich in arginine.74 Lactoferrin is able to bind and buffer other pathogen associated molecular patterns in addition to LPS, viral DNA and RNA, CpG sequences, and soluble components of the extracellular matrix.75 This ability is associated with lactoferrin anti-inflammatory activity, as demonstrated in several studies,76,77 in which lactoferrin down-regulates pro-inflammatory cytokine production in cell lines acting via NF-κB,78 decreasing the release of TNF-α and IL-6 in mice.

Circulating lactoferrin concentration was inversely associated with body mass index, waist-to-hip ratio, fasting triglycerides and fasting glucose, and directly associated
with HDL-cholesterol. Furthermore, circulating lactoferrin concentration was associated with vascular function in obese subjects with altered glucose tolerance. Two non-synonymous LTF gene polymorphisms that produce two aminoacid changes in the N-terminal region were associated with dyslipidemia according to glucose-tolerance status.

The concentration of all these proteins and peptides with LPS-neutralizing effect were decreased in metabolic disorders associated with insulin resistance and obesity. Thus, the high LBP and endotoxin concentrations could be markers of an unbalance of the innate immune system.

**Buffering Efficiency Hypothesis**

The evidences reviewed here led us to propose the buffering efficiency hypothesis (figure 1). LPS is an important factor that might produce insulin resistance and obesity in humans. Chronic low-grade inflammation and associated insulin resistance might be viewed in the context of an unbalanced innate immune system. A decreased production of anti-LPS proteins and peptides were associated with insulin resistance, obesity, vascular dysfunction, hepatic dysfunction and dyslipidemia. A partial lost in the buffering efficiency of LPS could increase its negative effects on metabolism. Furthermore, insulin resistance might result in a decreased concentration of those proteins that buffer LPS. It is well known that adiponectin production by the adipose tissue is decreased under insulin resistance and inflammatory conditions. Neutrophils also lose antimicrobial efficiency in insulin resistant conditions, decreasing the production of lactoferrin, BPI and other antimicrobial proteins. Neutrophil activity may be restored by controlling hyperglycemia using insulin. Stegenga et al reported that hyperglycemia impaired neutrophil degranulation in humans after intravenous endotoxin administration.

Impairment of neutrophil function was associated with a poor metabolic profile in subjects with type 2 diabetes, including a decreased neutrophil deformability and a high production of reactive oxygen species and proinflammatory cytokines. High PKB (a major downstream PI3K effector) activity was found to promote neutrophil and monocyte development/proliferation. In this sense, insulin resistance and a low grade inflammatory state potentiate each other, producing a vicious cycle, strengthened by an unbalanced innate immune system.

**Conclusions**

There is now strong evidence that type 2 diabetes and the metabolic syndrome are associated with a low-grade inflammatory state associated with an unbalanced innate immune system. This low-grade inflammatory state is triggered by a continuous exposure to external insults such as reactive oxygen species (ROS), fatty acids, AGEs and LPS. Metabolic concentrations of plasma LPS are associated with insulin resistance and obesity in animal models, and this increase in plasma LPS could be caused by intestinal translocation of LPS from Gram-negative bacteria present in gut flora. High fat diet could contribute to this increased LPS translocation from intestine into the bloodstream.

LPS stimulates the release of antimicrobial proteins (by neutrophils and by epithelial cells from the lung, liver and adipose tissue) which also protect from other injuries such as reactive oxygen species and AGEs. A higher efficiency (response and release) in this process could allow a greater neutralizing effect of LPS. On the other hand, insulin action is an important factor in the devel-
opment and maintenance of neutrophil function and efficiency. Thus, a continuous exposure to metabolic concentrations of plasma LPS could begin a vicious cycle, weakening the innate immune system and increasing proinflammatory cytokines and ROS due to a partial inefficiency of the innate immune system. As a consequence, the decreased protection in front of LPS challenge would increase metabolic disturbances. According to the buffering efficiency hypothesis, an increased efficiency of the innate immune system attenuates metabolic endotoxemia, and decreases thereby the negative effects of LPS on insulin sensitivity and metabolism.

Acknowledgements:
CIBEROBN Fisiopatología de la Obesidad y Nutrición. This work was partially supported by research grants from the Ministerio de Educación y Ciencia (SAF2008-0273).

Declaration of potential conflicts of interest
No disclosures.

Practical considerations

- Elevated circulating endotoxemia markers (LBP) and decreased LPS-neutralizing proteins (BPI and LTF) could reflect metabolic endotoxemia associated with insulin resistance.

- These markers may help to predict the development of type 2 diabetes and cardiovascular disorders. Also, an increased efficiency of the innate immune system is associated with an insulin-sensitive profile in healthy subjects.

- External administration of LPS neutralizing peptides (synthetic cationic peptides) may be helpful to stop the inflammation-insulin resistance vicious cycle and to recover the efficiency of the innate immune system.

References


Consensus statement on continuous glucose monitoring*

Consenso sobre el uso de la monitorización continua de glucosa

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Introduction
Taking in account the extraordinary technological development that the continuous sensors of interstitial glucose had during the last years, the New Technologies Group of the Spanish Diabetes Society deemed it necessary to draw up a consensus document as regards to its possible usefulness in the daily clinical practice. The continuous glucose monitoring system (CGMS) are exclusively mentioned in this document, which measure the concentration of the latter in the interstitial fluid of the subcutaneous cell tissue.

Two types of systems are available at the Spanish market at present: a) the micro-dialysis systems with external sensor, as the GlucoDay® (Menarini Diagnostics, Florence, Italy) and b) the subcutaneous in situ sensor systems, as the CGMS (continuous glucose monitoring system), the Guardian®, the Guardian real time® or the Paradigm RT® (Medtronic MiniMed, Northridge, CA); the monitor Navigator® (Abbott Laboratories, Alameda, CA) is pending of commercialization, probably for 2009; finally, the Seven System® (Dex-Com Inc., San Diego, CA) is only available in the United States. All the systems count with amperimetric sensors that quantify the generation of sensors produced after the oxidation of the glucose by the glucose oxidase enzyme. These electrodes have a half-life of only 3-7 days, mainly due to the enzymatic progressive degradation. The sensor is usually inserted in the subcutaneous cell tissue of the abdominal wall, the arms or the thighs and the generated signal is collected and processed in an external monitor. They require several calibrations daily (more than two), that are performed by means of the introduction of the capillary glycemia in the monitor.

None of the available sensors at present have the precision of the usual capillary glucometers. This limitation is due, in part, to the low concentration of glucose in the interstitial fluid, to the own dynamic of the glucose and the inherent delays to the measurement system. For this reason, at present they are approved as a complement to the measurement of the capillary glycemia.

Basically, we can classify them in retrospective reading systems (Holter type) and reading systems in real time.
Continuous glucose monitoring. M. Ruiz de Adana, et al.

- **Retrospective reading systems (Holter type).** The glucose data are downloaded at the end of the record using all the calibration points for its adjustment. The correlation with the capillary glycemia values are in the region of $r=0.8$. The clinical precision estimated by means of the point & rate error grid analysis, offers us perfectly adequate information for the decisions taking, it is placed in the region on 70%.

- **Reading systems in real time.** The data are generated as from an initial latency period and the first calibration. They count with alarm systems for hypoglycemia and hyperglycemia and some models count with predictive alarms. In euglycemia situation, the means of the absolute difference between the differences of each pair of values corresponding to the interstitial capillary-glucose glycemia is in the region of 0.9 mmol/L, suggesting a relative difference of 15%. The clinical precision estimated by means of point & rate error grid analysis is of 75% for the Medtronic and Abbott systems, and between 64 and 88% for the Menarini system.

### Clinical results

Taking in account its recent development, we do not count with sufficient clinical studies that prove the efficiency at mean-long term.

#### Retrospective reading systems

In general, the clinical studies carried out with the CGMS of Medtronic offer different results. Some authors observe relevant reductions of glycosylated hemoglobin (HbA$_{1c}$) and others do not. It has to be taken into account that the studies differ clearly regarding to the design, frequency of use, duration, studied population, etc., which difficult more the obtaining of consistent conclusions. Probably, the most relevant clinical study has been recently published. It shows a clear use benefit each 4 weeks with CGMS in pregnant women with diabetes (T1D and T2D) as regards to the reduction of the HbA$_{1c}$ and a lower incidence of macrosomy. However, its effect on the presence of hypoglycemias did not show a relevant benefit and, moreover, a tendency to a higher number of caesarean sections could be observed as well as newborns of low weight considering the gestational age in the experimental group.

#### Reading systems in real time

Four randomized studies have been published, which have successively provided the following conclusions: a) the glucose sensors in real time might improve the levels of HbA$_{1c}$ in children and adults with inadequate glycemic control, as they achieve a reduction of the HbA$_{1c}$ concentrations when its use is equal or higher than 3–4 days per week; b) they might reduce the hyperglycemia times (23%) and hypoglycemia times (21%), as well as the night hypoglycemias (38%), and c) in the greatest published series performed in patients with a suboptimal metabolic control, a reduction of the HbA$_{1c}$ has been informed of 0.5% in adults (>24 years of age), which however was not observed in children, adolescents or adults under 24 years of age.

### Possible uses of the continuous glucose monitoring (CGMS)

There are clinical situations in which the CGMS might provide valuable information to confirm a suspicion diagnosis, or to be helpful in the therapeutic adjustment. In this paper we have chosen to list the clinical situations in which the use of the CGMS might have a special interest, since that every diabetic patient at some moment of the process might be an assessment subsidiary of continuous monitoring of interstitial glucose (table 1).

Recently, in its annual recommendations, the American Diabetes Association (ADA) stated the following affirmations: a) the continuous glucose monitoring, together with the intensive insulin treatment might be a useful tool to reduce the HbA$_{1c}$ in screened adult patients (>25 years of age) with T1D (evidence A level) b) though the reduction evidence of the HbA$_{1c}$ is lower in children, adolescents and young adults with diabetes, the CGMS might also be useful in these patients, and the benefits are correlated with the level of systems use (evidence C level) and c) the CGMS might suppose a complementary tool in patients with unnoticed hypoglycemias and/or frequent hypoglycemia events (evidence E level).

### Conclusions

The glucose monitoring systems in subcutaneous tissue offer the possibility of a continuous and dynamic assess-
ment of the interstitial glucose levels. Even with less precise systems than the capillary glycemia meters, they have proved certain benefits in the improvement of the glycemic control ($HbA_1c$) and the reduction of the glycemic variability, the exposure time to the hyperglycemias, etc., about the perception of the quality of life that might allow us to carry out approaches to the cost-effectiveness and improve the knowledge about the range of possible clinical indications.

Methodologically well set out clinical studies are still necessary to assess the impact of these systems on the control level ($HbA_1c$) and other metabolic variables, as the frequency of the hypoglycemias, the glycemic variability, the exposure time to the hyperglycemias, etc., about the perception of the quality of life that might allow us to carry out approaches to the cost-effectiveness and improve the knowledge about the range of possible clinical indications.

### Table 1. Clinical and experimental situations in which the continuous glucose monitoring systems present special interest

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<th>1. Diagnosis confirmation and hypoglycemia treatment:</th>
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<th>2. Therapeutic adjustments in patients who do not achieve the glycemic control targets:</th>
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<tr>
<td>• Impact of additional intakes about the glycemic profile</td>
</tr>
<tr>
<td>• Practice of physical exercise</td>
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<tr>
<td>• Intercurrent situations</td>
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</tbody>
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<thead>
<tr>
<th>4. Diabetes and hospitalization:</th>
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<tbody>
<tr>
<td>• Treatment units of critical and/or coronary patients</td>
</tr>
<tr>
<td>• Pancreatic tissue transplant</td>
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<th>5. In clinical investigation:</th>
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<tbody>
<tr>
<td>• Study of the glycemic profile variability</td>
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<tr>
<td>• Comparison of the effect on the glycemia of several therapeutic interventions (drugs, education programs, etc.)</td>
</tr>
<tr>
<td>• Experimentation in closed loop systems</td>
</tr>
</tbody>
</table>

### Declaration of potential conflict of interests
M. Ruiz de Adana received fees for conferences and/or consultancy by Abbott, Lilly, Medtronic, Roche, Novalab, Grupo Ars XXI de Comunicación y Servier, and has taken part in clinical trials totally or partially financed by GSK, Novartis, Pfizer and sanofi-aventis. M. Rigla took part in clinical trials totally or partially financed by Novo Nordisk, Pfizer and sanofi-aventis.

### References
Introduction

Type 2 diabetes mellitus (T2D), has become one of the most serious health problems of our times, and its proportions are already epidemic in most of the world. Therefore, there is an increasing interest in identifying individuals with high risk of diabetes in order to plan prevention strategies, as several studies have demonstrated that with changes in life style and/or medication it is possible to prevent or at least delay the onset of the disease. The progression from the normoglycemia to the diabetes might take several years, which entails interme-

Abstract

This review analyses the prevalence of prediabetes in Spain, based on various epidemiological cross-sectional studies conducted in our country and the prospective data available on the incidence of T2D in these categories. The analysed data show a prevalence of impaired glucose tolerance (IGT) between 10-17% and a prevalence of impaired fasting glucose (IFG) between 6-12% in the Spanish population, comparable as those reported in other European populations or in USA. These prevalences apparently have been stable over the last decade. By applying the revised criteria of the ADA 2003, IFG prevalence triples to 20-30%. Prospective studies have shown the IGT and IFG are both highly predictive of diabetes and its effect is cumulative, being the risk maximum for individuals with combined IGT-IFG. Only a single prospective study in our population has shown that reducing the cut-off point for defining IFG as currently recommended by the ADA optimises the sensitivity-specificity balance in predicting diabetes.

Keywords: prediabetes impaired fasting glucose, impaired glucose tolerance, epidemiology, prevalence, Spain.

Resumen

En esta revisión se analiza la prevalencia de prediabetes en España utilizando varios estudios epidemiológicos transversales realizados en nuestro país, así como los datos prospectivos disponibles de incidencia de diabetes tipo 2 en estas categorías. Los datos analizados muestran unas prevalencias de intolerancia a la glucosa (ITG) de entre el 10 y el 17% y de glucemia basal alterada (GBA) de entre el 6 y el 12% en la población española, comparables a las referidas en otras poblaciones europeas o en Estados Unidos. Estas prevalencias, aparentemente, se han mantenido estables en la última década. Al aplicar los criterios revisados de la American Diabetes Association (ADA) 2003, la prevalencia de GBA se triplica, hasta el 20-30%. Los estudios prospectivos han demostrado que tanto la ITG como la GBA son altamente predictivas de diabetes, y que su efecto es acumulativo, siendo el riesgo máximo en los individuos con GBA e ITG combinadas. Sólo un estudio en nuestra población ha mostrado que reducir el punto de corte para definir la GBA según las recomendaciones actuales de la ADA optimiza el balance sensibilidad-especificidad en la predicción de diabetes.

Palabras clave: prediabetes, glucemia basal alterada, intolerancia a la glucosa, epidemiología, prevalencia, España.
“Prediabetes” is an old term that was coined by the World Health Organization (WHO) as a retrospective diagnosis, that described the condition of a person previous to the diabetes diagnosis. A radically different definition has been recently introduced in the United States to describe jointly the individuals with IFG and/or IGT, stressing their high risk of developing diabetes in the future. Since then, the use of this term has been generalized in the scientific literature.

The prediabetes prevalence, and the associated diabetes risk, might vary widely in different populations, having its particular study a special interest in the Spanish population. In this review, we analyse the prediabetes prevalence found in the different transversal epidemiological studies performed in our country, as well as the available prospective data as regards to the incidence of T2D in these categories.

IFG and IGT. Concept and classification
The IGT, considered a “classic” prognosis factor of T2D, was introduced by the National Diabetes Data Group in 1979 with the objective of defining an enhanced risk phase of progression to diabetes in which, however, the reversion to normality was also possible. The increased risk to develop a cardiovascular disease (CVD) in this intermediate phase was also recognized. Moreover, this category and its definition are incorporated as clinical dysglycemia class in the WHO classification of 1980. The term refers to the glycemia concentrations between 140 and 200 mg/dL, 2 hours after an oral glucose overload (OGO), which are values that are clearly over the normality but below the limit in order to define diabetes.

The concept IFG was introduced in the report of the American Diabetes Association (ADA) in 1997 with the objective of defining the zone between the higher limit for the normal baseline glycemia and the lower limit of the baseline glycemia associated to diabetes, as analogue categories to the IGT for the baseline glycemia, defining it as a fasting glycemia concentration between 110 and 126 mg/dL. This definition was also adopted in the WHO report of 1999.

In the transversal study performed in the province of León through a clinical survey and OGO, in which 572 individuals have been included, the IGT prevalence was of 10.3%. In the study of Lejona (Vizcaya), in which 862 individuals have been studied, older than 30 years and screened randomly, through OGO, the prevalence of IGT was of 10.4%. In another population and transversal study performed in Aragón, with a sample screening of 935 subjects between 10 and 74 years of age and in which OGO was carried out in all of them, except to the

Table 1. Values of plasmatic glycemia for the diabetes mellitus diagnosis and other dysglycemia categories (WHO 1999; ADA 2003)

<table>
<thead>
<tr>
<th>Category</th>
<th>Baseline Glycemia (mg/dL)</th>
<th>Glycemia after 2 hours of the OGO (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>110 WHO, 100 ADA</td>
<td>&lt;140 WHO, ADA</td>
</tr>
<tr>
<td>IFG</td>
<td>110-125 WHO, 100-125 ADA</td>
<td>–</td>
</tr>
<tr>
<td>IGT</td>
<td>–</td>
<td>140-200 WHO, ADA</td>
</tr>
<tr>
<td>DM</td>
<td>&gt;126 WHO, ADA</td>
<td>≥200 WHO, ADA</td>
</tr>
</tbody>
</table>

known diabetic patients, the IGT prevalence was of 7.2%. In the study performed in Catalonia, which included 3839 subjects aged 30-89, 2214 underwent the OGOT, the IGT prevalence was 11.9%. In the Guía study performed in Gran Canaria, one of the highest prevalences of DM and IGT were found in the Caucasian population. A total of 691 subjects older than 30 years were screened through a stratified sampling by age and sex in the town of Guía; a survey was done to all of them, as well as an exploration and an OGTT. The IFG and IGT were of 8.8 and 17.1%, respectively. In the SIRS (Spanish Insulin Resistance Study) 2949 patients were included with ages ranging between 34 and 69, screened from seven Spanish cities (Arévalo, Talavera de la Reina, Guadalajara, A Coruña, Avilés, Vic, Alicante and Mérida), resulting the global prevalences of IFG and IGT of 7.6 and 9.4%, respectively. In the Pizarra study done at (Málaga), after studying 1,226 persons aged from 18 to 65 through surveys, exploration and OGTT in 982 cases, the prevalence of IFG was of 12.4% and 11.5% of IGT. In the Asturias study, carried out on 1034 individuals aged from 30 to 75 who have been screened randomly and underwent a survey, exploration and OGTT, the prevalences of IGT and isolated IFG were of 11.4 and 2.8%, respectively. In this study, the prediabetes prevalences with revised criteria of the ADA 2003 have also been described, being the prevalence of the isolated IFG, isolated IGT and combined IFG and IGT of 14.6, 6.5 and 5.3%, respectively.

In a recent analysis, the effect of the criteria changes for IFG of the ADA 2003 in this population was evaluated, observing that the prevalence of the IFG was trebled becoming 22.5%. In the city of Yecla (Murcia), 286 persons were studied, from which 261 underwent the OGTT, resulting an IGT prevalence of 13.2% while the isolated IFG was of 0.2%. In the province of Girona, a sample of 1748 persons were analysed aged 25 to 74, representative of the general population, through determination of fasting glycemia in venous blood. An IFG prevalence of 8.6% was found. Finally, in the population study performed at Telde (Gran Canaria), which included 1030 individuals aged 30 to 82 who have been screened randomly and underwent a survey, exploration and OGTT, the prevalences of IGT and isolated IFG were of 11.4 and 2.8%, respectively.

In the XIX Congress of the Diabetes Spanish Society (SED), held in February 2008 at Sevilla, preliminary data have been submitted on the diabetes prevalence studies of Valencia and Madrid. The one done in Valencia is a transversal study performed in the twenty-two health centers of the Valencian Community, which included 5724 subjects aged 18-88. The prevalence of IFG was of 10.2% and of IGT of 12.6%.

### Table 2. Global prevalences of glucose intolerance (IGT) and impaired fasting glucemia (IFG) in the Spanish population

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>n</th>
<th>IGT (%)</th>
<th>IFG (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO criteria (110-125 mg/dL)</td>
<td>ADA criteria (100-125 mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Franch Nadal et al. (León 1992)</td>
<td>&gt;18</td>
<td>572</td>
<td>10.3</td>
</tr>
<tr>
<td>Bayo et al. (Lejona 1993)</td>
<td>&gt;30</td>
<td>862</td>
<td>10.4</td>
</tr>
<tr>
<td>Tamayo et al. (Aragón 1997)</td>
<td>10-74</td>
<td>935</td>
<td>7.2</td>
</tr>
<tr>
<td>Castell et al. (Catalonia 1999)</td>
<td>30-89</td>
<td>3,839</td>
<td>11.9</td>
</tr>
<tr>
<td>De Pablos et al. (Guía 2001)</td>
<td>&gt;30</td>
<td>691</td>
<td>17.1</td>
</tr>
<tr>
<td>Lorenzo et al. (SIRS 2001)</td>
<td>34-69</td>
<td>2,949</td>
<td>9.4</td>
</tr>
<tr>
<td>Sorliker et al. (Pizarra 2002)</td>
<td>&gt;18</td>
<td>1,226</td>
<td>11.5</td>
</tr>
<tr>
<td>Botas et al. (Asturias 2003)</td>
<td>30-75</td>
<td>1,034</td>
<td>13.3</td>
</tr>
<tr>
<td>Martínez Candela et al. (Yecla 2004)</td>
<td>&gt;30</td>
<td>286</td>
<td>13.2</td>
</tr>
<tr>
<td>Masiá et al. (Girona 2004)</td>
<td>25-74</td>
<td>1,748</td>
<td>–</td>
</tr>
<tr>
<td>Boronat et al. (Telde 2005)</td>
<td>30-82</td>
<td>1,030</td>
<td>11.4</td>
</tr>
<tr>
<td>Catalá et al. (Valencia 2008)**</td>
<td>18-88</td>
<td>668</td>
<td>10.8</td>
</tr>
<tr>
<td>Zorrilla et al. (Madrid 2008)**</td>
<td>&gt;18</td>
<td>537</td>
<td>–</td>
</tr>
</tbody>
</table>

*Prevalences referred to isolated IFG. **Preliminary data.
departments of the Community of Valencia. Results of
2,092 subjects were presented. Applying the revised cri-
teria of the ADA 2003: a prevalence of isolated IFG of
23.3% is described as well as a prevalence of isolated
IGT of 4.4% and combined IFG and IGT of 6.4%.\(^\text{30}\) In
the diabetes prevalence study of the Community of Ma-
drid which included 2,268 persons aged between 30 to 74
from the databases of the health card of the Community
of Madrid, using a two stage sampling clusters, a IFG
prevalence of 5.9% has been documented from the fast-
ing glycemia only (without OGO).\(^\text{31}\)

**Prospective studies of diabetes and prediabetes incidence**

The study of Lejona (Basque Country) has been during
several years the reference to evaluate the risk of devel-
opping diabetes in subjects with prediabetes in Spain. Ten
years after this prevalence study performed in 1985, the
same population was evaluated again by using new
OGOT (according to WHO criteria, 1985). The inci-
dence of DM in individuals with IGT was 2%/year, be-
ing this the most important diabetes prognostic factor in
this population (odds ratio: 4.17).\(^\text{32}\)

Recently, a re-evaluation of the cohorts of Asturias and
Pizarra was completed (Málaga) (table 3). In the Astu-
rias study, 700 subjects who took part in the prevalence
study of 1998-1999, who were re-as-
sessed in 2004-2005 after a mean follow-up of 6.3 years.
Only 630 subjects who did not have DM in the initial
study had been screened in order to study the diabetes
incidence, and the questionnaire was carried out again as
well as the exploration and the OGO with the obtaining
of baseline venous blood and after 2 hours (WHO crite-
ria 1999).

The diabetes incidences were. Five cases/1,000 inhabit-
ants/year in individuals with normoglycemia. 21 cas-
es/1,000 inhabitants/year in those with isolated IGT,
34.7 cases/1,000 inhabitants/year in individuals with
IFG and 95.2 cases/1,000 inhabitants/year in individuals
with combined IFG and IGT. In the multivariate logistics
regression analysis, the fasting glycemia and the glyc-
emia 2 hours after the OGO were the most important di-
abetes prognosis factors.\(^\text{33}\)

In the Pizarra study, 824 individuals who took part in the
transversal study of 1997-1998, were re-evaluated (in the
period 2003-2004) after 6 years of follow-up. The sam-
ple for the incidence study included 714 subjects with
initial DM. In both studies, an OGO was performed de-
termining basal glycemia and 2 hours after (WHO crite-
ria 1999). The age and the presence of obesity, central
obesity and IFG and/or IGT in the initial study were rel-
levant markers for the onset of T2D during the follow-up.
The diabetes incidences in the different categories were:
10 cases/1,000 inhabitants/year in individuals with nor-
moglycemia; 31.1 cases/1,000 inhabitants/year with iso-
lated IGT, 38.1 cases/1,000 inhabitants/year with isolat-
ed IFG and 66 cases/1,000 inhabitants / years in those
with combined IFG and IGT.\(^\text{34}\)

**Evaluation of criteria change for IFG**

In the Asturias study, the impact of the reduction of the
cut point to define the IFG to 100 mg/dL in the Spanish
population has been evaluated prospectively. The appli-
cation of the ADA criterion for IFG (100-126 mg/dL)
trebled the number of individuals with IFG. The diabetes
incidence were of 3.8, 19.5 and 58.0 cases per 1,000 in-
habits / year in subjects with initial values of fasting
glycemia <100 mg/dL, between 100 and 110 mg/dL and
between 110 and 125 mg/dL, respectively. The inclusion
of individuals with intermediate risk (in the zone 100-
110 mg/dL) in the IFG de/finition changed its prognosis
positive value, as well as its speci/fici ty and its sensitivity
to predict diabetes of 36.5, 94.5 and 43.2% to 19.9, 77.3
and 75%, respectively. The analysis of the ROC curve,
including all the levels of fasting glycemia from 64 to
125 mg/dL, according to its capability to predict the dia-
abetes, showed that the closest point to the ideal one of

<table>
<thead>
<tr>
<th>WHO criteria 1999</th>
<th>Normoglycemia</th>
<th>Isolated IGT</th>
<th>Isolated IFG</th>
<th>IGT + IFG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asturias Study(^\text{33}) n= 630, mean follow-up 6.3 years</td>
<td>5.0 (2.8-8)</td>
<td>21 (10.9-40.4)</td>
<td>34.7 (14-71.5)</td>
<td>95.2 (54.1-167.7)</td>
</tr>
<tr>
<td>Pizarra Study(^\text{34}) N= 714, mean follow-up 6 years</td>
<td>10.0 (7.0-14.7)</td>
<td>31.1 (25.3-57.3)</td>
<td>38.1 (18.4-52.5)</td>
<td>66.0 (39.1-111.5)</td>
</tr>
</tbody>
</table>

IFG: impaired fasting glucemia; IGT: impaired glucose tolerance. WHO: World Health Organization.
100% of sensitivity and 100% of specificity in all the glycemic range was the value 100 mg/dL. Therefore the study concluded that the reduction of the cut point to define the IFG optimized its capability to predict diabetes in this population25 (figure 1).

Conclusions
The different epidemiologic studies performed in our country show prevalences of IGT between 10 and 17% and IFG between 6 and 12%. The values are comparable to those of the prevalence of IGT of 11.9% and IFG of 10% that refer to the European population according to the DECODE study (Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe), and also to the data of IGT prevalence of 14.9% and of 8.3% that refer to the population of the United States according to the national NHANES survey (National Health and Nutrition Examination Survey) III.8 Unlike the T2D prevalence, which seems to have increased in our country during the last decade,35 the prediabetes prevalence was kept stable apparently. This same tendency has been observed in the population of the United States.36

When applying the criteria revised by the ADA 2003, the IFG prevalence trebles up to 20-30%. The available prospective studies show: that both the IGT and the IFG are highly predictive of diabetes and that its effect is cumulative, observing a maximum risk in the individuals with combined IFG and IGT. The inclusion of both measurements allows a better stratification of the diabetes risk. Only a study showed that to reduce the cut point in order to determine the IFG according to the ADA recommendations might optimize its sensitivity-specificity in diabetes prognosis in our population. By means of cohorts of bigger size and with higher representativeness in all the Spanish population, these findings can be determined better.

Declaration of potential conflict of interest
S. Valdés Hernández and E. Delgado Álvarez state that there are no conflicts of interest as regards to the content of this article.

Practical considerations

- Several epidemiologic studies in Spain have demonstrated prevalence to impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) of 10-17% and 6-12%, respectively, comparable to the one published for European and American populations.
- Both the IGT and the IFG are highly predictable as regards to the diabetes development and its effect is cumulative, therefore the presence of both increases the risk in a substantial manner.
- When applying the revised criteria of ADA 2003, the prevalence of IFG trebles up to 20-30%. However, at present there is no consensus if this strategy optimized the sensitivity and the specificity in the diabetes prognosis.

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Main differences between impaired fasting glucemia and impaired glucose tolerance

Introduction

Both the impaired fasting glucemia (IFG) as well as the impaired glucose tolerance (IGT) make up the so-called “prediabetes”. However, in several epidemiologic studies it has been proved that these two impairments correspond to different populations, with only a reduced number of subjects that share both entities. This happens because they have a different pathogenic mechanism, leading to the following differences as regards to its distribution within the population, the risk of develop-
ing type 2 diabetes, the cardiovascular risk, the risk of developing complications and the mortality. In the following paragraphs, we will proceed to analyse these differences.

Pathogenesis

The IFG is characterized by a deficit in the early secretion phase of the insulin and by an increase of the hepatic resistance to the action of such hormone, which can be understood as an increase of the hepatic glycogen. When an oral overload with 75 g of glucose (OGO) is done in these patients, it can be observed from the very beginning that the glycemia values are high, and that they remain high after 30 and 60 minutes, with higher levels than those of the individuals with IGT and those with normal glucose tolerance (NGT). However, after 120 minutes the glycemia is reduced up to practically normal values (figure 1). As regards to the insulin levels during OGO in these same subjects, it can be observed that there is a reduced response at an initial phase, with lower levels than those of the individuals with IGT or NGT, though this secretion is similar than the secretion of subjects with normal glucose tolerance (figure 2) after 60 minutes.

On the other hand, the IGT is characterized by an increase of the peripheral resistance to the insulin action in the muscle, as well as by a deficit of insulin secretion, both in the early and late-phase. When an OGO is performed to these patients, it can be observed that they show normal glycemia levels at the beginning. However, after 60 minutes their levels are raised relevantly and are kept high after 90-120 minutes (figure 1). As regards to the insulin levels in the OGO, it can be observed that they are slightly reduced after 30-60 minutes and from that moment they increase, but not sufficiently to reduce the levels of glycemia that remain high, due to the great muscular resistance to the insulin action (figure 2).

Therefore, in subjects with IFG there is a hepatic resistance to the insulin and a deficit in the early phase of its secretion, whereas in the IGT there is a muscular resistance to the insulin accompanied by a remarked insulin deficit, as the early and late-phase are affected. The individuals with the combination of both impairments (IFG + IGT) shall take part of the physiopathologic impairments of both processes.

Recently, a study has been published that analysed the physiopathologic differences between the IFG and the IGT at other levels, and in this way it has been objectified that they also show a different response in relation to the release of the intestinal peptides after the intake, so the patients with IGT have a reduced GIP (glucose-dependent insulino-tropic polypeptide) response, where-
Impaired fasting glycemia and glucose intolerance.

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as those with IFG show an increase in the GLP-1 (glucagon-like peptide-1). This might explain, at least in part, the higher deficit in the insulin secretion that is shown by the individuals with IGT.

Population distribution

The distribution of the IFG and the IGT is different considering age and sex of the individuals, whereas the IFG is more frequent in men and in young persons, stating their prevalence while the age of the patients rises. Contrary, the IGT is more frequent in women and its prevalence increases while the age rises, so it is more frequent in elderly persons. This fact led to the recommendation, in individuals over 65 years of age, to take into account the use of OGO as systematic diagnosis method for the detection of impairments in the metabolism of carbohydrates.

Risk of developing diabetes

There is no doubt about the higher risk of developing diabetes that both the individuals with IFG and IGT show, being even higher the risk in those who suffer the combination of both impairments. Up to date, in most of the studies aimed to determine the differences between both entities, the diagnosis criteria recommended by the World Health Organization (WHO) in 1999 have been used (IFG: baseline glycemia between 110 and 125 mg/dL; IGT: glycemia after 2 hours from the OGO between 140 and 199 mg/dL). Only a few studies have used the American Diabetes Association (ADA) criteria of 2003, in which the lower diagnosis level of IFG was reduced from 110 to 100 mg/dL, leaving the rest of the criteria the same. This is relevant as the results that have been obtained are substantially different.

The risk of developing T2D in patients with IGT or IFG (WHO 99) is similar (and it is assessed that it is 4-5 times higher than in the subjects with normal tolerance to glucose), with an annual diabetes development rate of 5-10%. In those persons that have IFG + IGT, the risk is approximately the double than with any of them in an isolated manner. Considering the WHO-99 criteria, the prevalence of diabetes in subjects with IGT is almost the double than in those with IFG, the IGT results more sensitive, though slightly less specific, than the IFG in order to identify persons who might develop diabetes.

As we have already mentioned, in 2003 the ADA reduced the diagnosis value of the IFG from 110 up to 100 mg/dL with the intention of improving its sensitivity and equal it to the IGT, and in this way eliminate the need to undergo an OGO. However, in practice, in spite of having equalled the sensitivity of the IFG and the IGT with the new criteria (ADA 2003), the specificity has been remarkably reduced and the positive prognosis value of the IFG to detect subjects in risk, increasing in 4 the number of individuals with IFG. Notwithstanding, it persists the identification of different individuals by the IFG and the IGT, as it happened with the previous criteria (WHO 99).

In view of the above, we can conclude that both entities (IFG and IGT) are useful to identify subjects with high risk to develop diabetes, and the individuals identified with each of the criteria are different, so it has to do with two complementary strategies (and not excluding) with the same aim.

Cardiovascular risk

In several studies, it has been demonstrated that both the IFG and the IGT imply an increased cardiovascular risk (CVR). However, the IGT entails a higher risk and is a better prognosis factor of the CVR than the IFG. These differences might be due, at least in part, to the
### Practical considerations

- The impaired fasting glucemia (IFG) and the impaired glucose tolerance (IGT) imply different physiopathology impairments. The hepatic insulin resistance and the early impairment of the insulin secretion prevail in the IFG, whereas the muscular resistance in the IGT prevails and the insulin secretion is more affected, both in the early and late-phase.

- Both entities are associated to 4-5 high fold risk to develop diabetes than the subjects with normal tolerance to the glucose, though the IGT turns out to be more sensitive and slightly more specific than the IFG.

- Both the IFG and the IGT are also associated to an increase of cardiovascular risk, which is higher in the case of the IGT.

The fact that the IGT is associated mainly to the existence of other factors of CVR, and that the affected patients show higher levels of triglycerides and arterial pressure values than in the IFG. However, it could be stated that these differences in the CVR of both entities persisted after the adjustment, taking into account the remaining CVR factors.

These differences are even more evident as regards to the cardiovascular mortality, as it could be demonstrated in the DECODE study (figure 3). In this study, it could be observed that the increased glycaemia figures after 2 hours of the OGO were associated to an increase of the total mortality and cardiovascular risk, regardless of the fasting glycaemia value, not being the high fasting glycaemia sufficient to predict the mortality by its own. It could also be observed that the higher number of deaths took place in the group of subjects with IGT, but with a normal fasting glycaemia. These same results were obtained in Asiatic population in the DECODE study.

### Conclusions

Therefore, we can conclude that the IGT has a pathogenic mechanism and a population distribution different from the IFG ones, as it implies a risk of cardiovascular and mortality events higher than the one of the IFG. Both entities determine a higher risk of suffering diabetes; however, they detect different groups of individuals, constituting two complementary entities to identify individuals with a high cardiovascular risk.

### Declaration of potential conflicts of interest

F.J. García Soidán states that there are no conflicts of interest as regards to the content of this article.

### References

Impaired fasting glycemia and glucose intolerance. F.J. García Soidán


Prevention of type 2 diabetes based on nutritional therapy and/or increase of physical activity

S. Artola Menéndez
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Abstract
The increasing incidence of type 2 diabetes is associated with the western lifestyle. Intervention programs oriented to increasing exercise combined with an adequate nutrition therapy have a protective effect against the development of type 2 diabetes in people at risk. These results are even better than with the pharmacologic approach. Prevention of diabetes with lifestyle intervention is cost-effective from a health care point of view. It is important to detect people at high risk to develop type 2 diabetes to prevent progression of hyperglycemia. There are not enough data with exercise alone neither on diabetes prevention nor in morbidity and mortality. There is a need for studies exploring the effect of interventions with exercise alone or combined with nutrition therapy on cardiovascular morbidity and mortality.

Keywords: diabetes, prevention, diet, exercise.

Introduction
The diabetes mellitus (DM) is a metabolic disorder characterized by a deficit of insulin secretion or its peripheral action, or both. The T2D affects more than 7% of the population. The incidence is increasing especially in the developing countries and between the young populations. Such increase is very much related to the “western lifestyle”, in other words, with inadequate diet habits and physical inactivity. The impaired glucose tolerance (IGT) and the impaired fasting glucose (IFG) are considered intermediate phases between the normal glucose tolerance (NGT) and the DM. The IGT term1 was introduced in 1979 and reflects a peripheral resistance to the insulin action. The IFG term,2 introduced in 1997, expresses an increase of the glucose hepatic synthesis and a defect in the early insulin secretion.
Can diabetes be prevented?
There are two strategies to reduce the development of diabetes: 1) interventions on the lifestyle, and 2) pharmacological treatment. In this chapter, we will develop the evidences and recommendations about the prevention of T2D based on nutritional therapy and/or the increase of physical activity. Intervention studies have been published during the last years that have evidenced clearly positive results.

The great studies developed in China, Europe and the United States have demonstrated clearly that the conversion of IGT to T2D can be avoided or delayed at least. It is confirmed that the loss of weight is the determining factor in the prevention of diabetes. In table 1, the studies on the prevention of diabetes are depicted with non-pharmacological measures.

**Table 1. Main studies on non-pharmacology intervention for the prevention of diabetes**

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Publication Year</th>
<th>Design</th>
<th>Education Intervention</th>
<th>Size</th>
<th>Mean follow-up</th>
<th>Results* (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malmö Preventive Trial&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Sweden</td>
<td>1991</td>
<td>Non randomized intervention in a cohort group</td>
<td>Diet treatment and/or increase of exercise. Intervention of 6 months with annual follow-up</td>
<td>n= 222 (from a cohort of 6956). Men with incipient T2D (41) or IGT (181)</td>
<td>6 years</td>
<td>&gt;50</td>
<td>After 12 years (in 1998), the group with IGT on which the intervention took place was still without increasing mortality</td>
</tr>
<tr>
<td>China Da Qing IGT and Diabetes Study (CDQPDS)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>China</td>
<td>1997</td>
<td>Clinical trial after screening of IGT in general population</td>
<td>Diet and/or exercise. Individual and group intervention. weekly, 1 month, monthly 3 months, and quarterly follow-up with half-yearly evaluation</td>
<td>n= 530 Men (283) And women (247) with IGT</td>
<td>6 years</td>
<td>31-46</td>
<td>Diet only, exercise only, or diet and exercise have been effective in similar level</td>
</tr>
<tr>
<td>Finnish Diabetes Prevention Study (DPS)&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Finland</td>
<td>2001</td>
<td>Randomized clinical trial and partially blind</td>
<td>Quarterly intensive intervention with customized advice on diet and exercise. Annual medical revision with OGTT</td>
<td>n= 522 Men (172) and women (350) between 40 and 65 years of age with BMI &gt;25 kg/m² and previous diagnosis of IGT</td>
<td>3.2 years</td>
<td>58</td>
<td>The prevention of the diabetes was obtained with modest reductions of weight NNT= 22 (or 5 in 5 years)</td>
</tr>
<tr>
<td>Diabetes Prevention Program (DPP)&lt;sup&gt;8&lt;/sup&gt;</td>
<td>United States</td>
<td>2002</td>
<td>Change of habits</td>
<td>Intensive course of 16 sessions to reduce the weight in 7% by means of diet and exercise. Monthly reinforcement and six months - control</td>
<td>n= 3234 Men (1043) and women (2191) &gt;25 years and with IFG and IGT</td>
<td>2.8 years</td>
<td>58</td>
<td>NNT= 7</td>
</tr>
</tbody>
</table>

*Reduction of the progression towards diabetes mellitus. BMI: body mass index; IFG: impaired fasting glucemia; IGT: impaired glucose tolerance; NNT: number needed to treat; OGTT: oral glucose tolerance test with 75 g of glucose.

**Intervention studies**

**Malmö Study<sup>3</sup>**
It was one of the first intervention studies in which modifications of the lifestyle have been used for the prevention of DM. It was performed on men between 47 and 49 years of age of the population of Malmö (Sweden). Some subjects with IFG and all those who had NGT performed a “usual follow-up”. The patients with T2D and those with IGT have been randomized to a program in
lifestyle change that consisted of exercise and diet during 6 months. At the end of the study it could be proved that the IGT group in which the intervention was done has a lower incidence of T2D. After 12 years of follow-up, the patients with IGT who received an intensive program on lifestyle showed the first mortality rates than those with NGT and less than half of mortality than those with IGT who had performed a “usual follow-up”.

The China Da Qing Diabetes Prevention Study (CDQPDS)\(^4\)

This study analyzed the effect of one intervention of 6 years with diet plus exercise in 577 subjects of Chinese race that showed IGT and had a mean age of 45. The participants were randomized to one of the three groups of active treatment (a: only diet, b: only exercise and c: diet plus exercise) or to the control group. The incidence of T2D after 5 years was of 67.7% (CI 95%, 59.8-75.2) in the control group, versus 43.8% (CI 95%: 35.3-52.3) in the diet group, and 41.1% (CI 95%: 33.4-49.4) in the exercise group and 46% (CI 95%: 37.3-54.7) in the diet plus exercise group (p <0.05). After the adjusted analysis according to the baseline differences in the body mass index (BMI) and the baseline glycemia, the diet, the exercise and the diet plus exercise, showed a respective reduction of 31% (p <0.03), 46% (p <0.0005) and 42% (p <0.005). Surprisingly, the double intervention achieved a lower reduction than the one observed with the isolated exercise.

The Finnish Diabetes Prevention Study (DPS)\(^5,6\)

In this study, 522 subjects with overweight / obesity and IGT, a mean age of 55 years and 66% of women, were randomized to a program of intensive lifestyle modifications (LM) versus a conventional follow-up during 3.2 years. The intensive treatment consisted of 7 sessions with a nutritionist during the first year and, then, four annual sessions together with a physical exercise program. The control group received usual recommendations on diet plus exercise. The reduction of 5% of weight observed in the intervention group reduced the incidence of diabetes from 23 to 11%, with a relative risk reduction (RRR) of 58%. Each of the five intervention components (loss of weight, increase of the physical activity or at least 30 min/day, reduction of 30% of the intake of total fats, reduction of 10% of the saturated fats and increase of the fibre intake) contributed to the risk reduction. It has to be pointed out that the 21% of the participants reached four of the five objectives and that only 6% did not achieve any. From the subjects who reached the five objectives of lifestyle, none of them developed diabetes. Among those who did not achieve any of the objectives, a 35% developed diabetes.

The Japanese study

The study of Kosaka et al.\(^7\) included 458 men with IGT who were randomized, with a ration 4:1, to standard intervention (n= 356) or intensive (n= 102). The objective was to keep a BMI <24 kg/m\(^2\) in the control group, and a BMI <22 kg/m\(^2\) in the group of active intervention by means of diet plus exercise. In the intervention group, the recommendations on diet and physical activity on an active basis each 3-4 months was repeated. The accumulated incidence of T2D after 4 years was of 9.3% in the control group and 3% in the intervention group. The loss of weight resulted to be of 0.39 kg in the control group versus 2.18 kg in the intervention group (p <0.001). The intensive treatment was associated with a 67.4% of risk reduction of T2D (p <0.001).

The Diabetes Prevention Project Study (DPP)\(^8\)

This is one of the clinical trials with a higher number of subjects. It included 3234 individuals of the United States with IFG and IGT, from which 68% were women and 45% corresponded to ethnic minorities. The mean age was of 51 and the BMI of 34 kg/m\(^2\). The study compared three intervention branches, a) control group, b) pharmacological intervention (metformin) and c) LM, during almost 3 years of follow-up. The DM incidence was of 11, 7.8 and 4.8 per 100 persons and year, respectively, in each group. The intervention on the lifestyle reached a 7% of reduction in weight and reduced the incidence of DM from 29 to 14% (RRR= 58%, CI 95%: 48-66). The DM incidence in the metformin group was reduced in a 31% (CI 95%: 17-43). The number of subjects that needed to be treated (NNT) for LM was of 6.9 (CI 95%: 5.4-9.5) versus 13.9 (CI 95%: 8.7-33.9) for metformin. A later analysis\(^9\) of the data corresponding to this study concluded that the physical activity helps to keep the weight and to reduce the risk of developing diabetes, even in subjects who do not lose weight.

The Indian Diabetes Prevention Programme Study (IDPP)\(^10\)

This study might be considered a reproduction of the DPP study in the Indian population. The progression to
diabetes of the subjects who showed IGT was even higher than in the European or American studies. The intensive intervention both with LM and metformin reduced relevantly the diabetes incidence (RRR= 28.5 and 26.4%, respectively) without detecting any improvement with the addition of both interventions (28.2%).

**Persistence of the effects of the long-term intervention**

One of the most discussed aspects is if the beneficial effects persist at long-term once the active intervention is discontinued. In the trials with different drug groups, fast risk parity can be proved with the subject who had not received any sort of treatment, whereas in the trials with LM the conclusions are more optimistic after extended follow-ups. Thus, in the DPS follow-up, the effect on the reduction of the diabetes incidence was kept for at least 4 years after the intervention ended. The number of cases with T2D after 7 years of total follow-up (4 years of intervention plus 3 years of follow-up) was of 75 in the intervention group versus 110 in the control group. The incidence rate was of 4.3 (CI 95%: 3.4-5.4) and 7.4 (CI 95%: 6.1-8.9) per 100 persons and year in the intervention and control groups, respectively. The hazard ratio was of 0.57 (CI 95%: 0.43-0.76) with NNT of 22 subjects per year (figure 1). The risk reduction to develop T2D was kept in 43% during the 3 years of follow-up. Though the value is lower than 58%, observed after 4 years of active intervention, this is an important datum from the health public point of view. These findings show that the real benefit as regards to the prevention of the diabetes has to be focused through the LM more than in the pharmacological treatments, whose effects are extinguished when the intervention is interrupted. The high incidence of DM, even in the intervention group, suggests that the strategies on LM should be set out in all the high-risk subjects, even before they develop IGT.

The China Da Qing Diabetes Prevention Outcomes Study (CDQDPOS) carried out a follow-up during 20 years after the intervention of 6 years with LM. The subjects under LM had a 51% less of DM incidence (reduction of the hazard ratio of 0.49; CI 95%: 0.33-0.73) and in this group it was kept a 43% less of DM incidence (reduction of the hazard ratio of 0.57; CI 95%: 0.41-0.81) during the later 20 years of follow-up (figure 2).

In 2005, a systematic revision was published of the Cochrane Library about the structured interventions of encouraging the physical activity and the diet in order to reduce the risk of developing diabetes. The intervention groups with LM reduced the T2D incidence after a year in approximately 50% (risk reduction: 0.55; CI 95%: 0.44-0.69) compared to the control groups.

In 2007 a meta-analysis was published that evaluated the efficacy of the interventions with pharmacological treatments and LM in order to prevent or delay T2D in persons with IGT. The accumulated effects for all the types of intervention in the lifestyles reached a risk reduction of 0.51 (CI 95%: 0.44-0.60: p <0.001), indicating a RRR to develop DM of 49%, without important differences to analyze separately the three groups of diet, exercise and diet plus exercise. For the antidiabetic drugs, the risk reduction was of 0.7 (CI 95%: 0.62-0.79; p <0.001) and for orlistat, a drug for obesity of 0.44 (CI 95%: 0.28-0.69; p <0.001). The authors concluded that both the intervention on the LM and the pharmacological intervention reduce the progression rate to DM in persons with IGT, but the first
ones seem to be more efficacious than the treatment with drugs.

In July 2008, a new revision of the Cochrane Library was published. The screening criteria have been randomly studied with interventions on the diet and/or the exercise for a minimum of 6 months that detected the T2D incidence in subjects at special risk of developing it. Eight studies have been included that performed a joint intervention (diet plus exercise) (n= 2,241) versus a control group (n= 2,509) and two studies with only diet intervention (n= 167) and only exercise (n= 178). The duration of the studies ranged between 1 and 6 years. Globally, the diet plus exercise intervention reduced the risk of developing diabetes in 37% (RR= 0.63; CI 95%: 0.49-0.79). Such intervention showed benefits associated to the reduction of weight, the BMI and the abdominal perimeter. The benefit was modest in blood lipids. However, the intervention on the lifestyle improved indeed the control of the arterial pressure, with a reduction of the systolic pressure of –4 mmHg (CI 95%: [–5]–[–2]) and the diastolic pressure of –2 mmHg (CI 95%: [–3]–[–1])

No relevant effects were observed in the diabetes incidence when the interventions of only exercise versus control were compared or only diet. None of the studies provided relevant data in relation to the diabetes and cardiovascular morbimortality, nor lifestyle.

Should diabetes be prevented?
The epidemic increase of the diabetes and its consequences at long term justify the efforts to prevent its onset. In the two intervention studies with diet and exercise that perform cost-effectiveness analysis (DPP8 and IDPP10), it is pointed out that the prevention of the diabetes through the intervention on the LM is cost-effective from the health public system point of view. It is important to identify the individuals at high risk of developing diabetes in order to prevent the worsening of the hyperglycemia. The recommended screening for the general population would be performed in the form of a validated questionnaire based on parameters such as age, family diabetic history, previous hyperglycemia history, the physical inactivity and the BMI or waist measure. In subjects at special risk, the performance of the oral glucose tolerance test (OGTT) should be considered.

Therefore, it is necessary to make a double effort: on one hand, to identify the patients at higher risk both of developing diabetes and of showing cardiovascular diseases (IGT, metabolic syndrome), and on the other hand, to intervene with programs of exercise, diet and weight control. If in the meta-analysis of Gillies et al. the authors concluded that the intervention on LM was at least as effective than the pharmacological intervention to prevent the onset of T2D, in the Cochrane Library revision of 2008 it is confirmed that the combination of diet and exercise has a favorable effect not only on the prevention of T2D but also in the reduction of weight and waist perimeter and in the reduction of the systolic and diastolic pressure. Any improvement in the cardiovascular risk factors is accompanied by a lower onset of cardiovascular events. On the other hand, the diet and the exercise had a very modest effect in the lipid profile.

Recommendations of the clinical practice guidelines
The American Diabetes Association (ADA), issued a consensus document on the approach of the prediabetes stages. The association between obesity and diabetes
Seminars on diabetes
Prevention of type 2 diabetes with diet plus exercise. S. Artola Menéndez

obliges to determine, as first priority, the control of the overweight with modifications of the lifestyle addressed to losses of 5-10% of the body weight, and a minimum exercise of 30 minutes daily (table 2). The group of experts recommends the performance of OGTT if it is foreseen that the IFT/IGT stages detection in the subject might be benefited from the treatment with metformin. Moreover, it does not indicate the performance of OGTT in those individuals who will only follow recommendations on lifestyle. In its last update of 2009, 17 the ADA asserts that the patients with IGT (evidence A) and IFT (evidence B) should receive advice in order to reduce the risk of developing diabetes and should be referred to a structured program in order to lose 5-10% of body weight, as well as to increase the physical activity up to 150 minutes weekly of moderate exercise, as walking.

The International Diabetes Federation (IDF), 18 proposes, in a recent consensus document, a strategy in order to prevent the diabetes addressed to two groups of subjects: a) the individuals at high risk of developing diabetes and b) the general population.

The Canadian Guideline 19 incorporates the performance of a structured program of LM that includes a moderate loss of weight as well as regular physical activity, in order to reduce the T2D development in subjects with IGT (recommendation of grade A, level 1A) and in those with IFT (recommendation of grade D).

Conclusions
The several discussed studies on intervention suggest that at present it seems possible to prevent diabetes, or at least to delay its onset. The option approach should be the changes of lifestyle, taking in account that any change, regardless of how small it is, provides relevant results. The increase of physical exercise together with a balanced diet reduces the T2D incidence in subjects with IGT or metabolic syndrome. There is not sufficient data about the prevention of diabetes only with exercise, nor about its effect on the morbimortality. It seems to be necessary to develop studies that analyse the exercise and the diet benefits on the morbidity and cardiovascular mortality.

Declaration of potential conflict of interest
S. Artola Menéndez states that there are no conflicts of interest as regards to the content of this article.

References

Table 2. Recommendations for individuals with IFG / IGT16 or both

<table>
<thead>
<tr>
<th>Population</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFG or IGT</td>
<td>Modifications of lifestyle (reduction of 5-10% of weight and moderate activity during 30 min/day)</td>
</tr>
<tr>
<td>IFG and IGT plus at least one of the following:</td>
<td>Modification of lifestyle and/or metformin (850 mg twice daily)</td>
</tr>
<tr>
<td>• &lt;60 years</td>
<td></td>
</tr>
<tr>
<td>• BMI ≥35 kg/m²</td>
<td></td>
</tr>
<tr>
<td>• Family history of first grade of diabetes</td>
<td></td>
</tr>
<tr>
<td>• High triglycerides</td>
<td></td>
</tr>
<tr>
<td>• Low HDL</td>
<td></td>
</tr>
<tr>
<td>• Arterial hypertension</td>
<td></td>
</tr>
<tr>
<td>• HbA1c &gt;6.0%</td>
<td></td>
</tr>
</tbody>
</table>

BMI: body mass index; HbA1c: glycosylated hemoglobin; HDL: high-density lipoproteins; IFG: impaired fasting glucemia; IGT: impaired glucose tolerance.

Practical considerations
• An adequate diet and the increase of physical exercise might delay the T2D development in patients at high risk
• The beneficial effects of the lifestyle modifications seem to extend themselves once the intervention therapy ended, whereas the benefits of the pharmacological treatments are extinguished after their interruption.
• The modifications on the lifestyle are cost-effective; therefore they should be set out in all the patients at high risk, even before they develop glucose intolerance.

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Pharmacological interventions to prevent type 2 diabetes

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Abstract
Considering the results from the largest studies in type 2 diabetes prevention, there’s no doubt that the first treatment option in this subset of patients should be promoting lifestyle changes. However, assuming what the large trials defined as lifestyle changes, the question is if these measures are reliable to be applied in the general population. Nevertheless, lifestyle changes are so effective in diabetes prevention that any change, even modest, could derive in positive results. There’s also no consensus about what drug should be used first, in which patients and how long. Considering that there’s a chance for preventing type 2 diabetes, we are still waiting for the results of upcoming studies which will confirm or complement what is known up-to-date on diabetes prevention.

Keywords: type 2 diabetes, prevention, lifestyle changes, acarbose, metformin.

Introduction
Diabetes mellitus (DM) is a metabolic disorder characterized by the presence of chronic hyperglycemia together, in a greater or lesser extent, with the impairments in carbohydrate, protein and lipid metabolism. Taking into account the statistics that characterize the T2D, this suggests at present a health and socio-economic problem of great magnitude. Moreover, even in the better previsions, these values will obtain an overtone of real epidemic in the near future worldwide. We are facing a potentially serious and asymptomatic disease, that is unknown by the patient in most of the cases, which frequently comes together at the moment of diagnosis by the presence of chronic disorders (micro and macro vas-

Resumen
Si nos basamos en los resultados de los grandes estudios sobre prevención de diabetes, no cabe duda de que la aproximación inicial de elección debería ser efectuar cambios saludables en el estilo de vida. Uno se pregunta si la implementación de los protocolos de estos estudios es extensible a la práctica cotidiana. Sin embargo, la eficacia que han demostrado en cuanto a prevención de diabetes es tan grande, que cualquier pequeño cambio en el estilo de vida podría ofrecer resultados significativos. No existe consenso a la hora de decidir si debemos o no utilizar fármacos cuando estas medidas no son suficientes. Durante los últimos años, han aparecido múltiples estudios que han utilizado fármacos con este propósito. En 2007, se posicionaron por primera vez tres sociedades científicas que contemplaron la utilización de algunos de ellos en personas de alto riesgo en las que los cambios en el estilo de vida se consideran, a priori, ineficaces. Con la certeza inicial de que podemos prevenir la diabetes tipo 2 (DM2), deberemos esperar a la aparición de nuevos estudios en los próximos años que intentarán corroborar y complementar lo que hasta la fecha conocemos.

Palabras clave: diabetes tipo 2, prevención, cambios en el estilo de vida, acarbosa, metformina.
cular. It has not to be forgotten, moreover, that the intermediate situations between normality and DM are not only evident risk situations for the development of this disease. There are a lot of epidemiologic evidences that show that the risk of showing some cardiovascular disease events (CVE) are substantially increased in those situations that undergo glycemies between normality and diabetes.\(^4\) If we take into account that the disorders in the tolerance to glucose are part and appear frequently together with other components of the so-called metabolic syndrome, these findings are easily understandable.

There is no doubt that, when DM prevention studies are evaluated, the initial approach of choice would be the implementation of healthy changes in the lifestyle. It is true that, when it is analysed what is understood and is applied as “intensive changes in the lifestyle” in the great prevention studies, one asks oneself if these protocols are extendible to the daily routine. Nevertheless, if we take into account such considerable efficiency that they have showed, any change, as small as it can be, offers us clinically relevant results. At present, there is no consensus as regards to the use or not of drugs in case that the previously mentioned measures are not sufficient. There is neither consensus about which drug to use first, on which sort of patient and for how long.

**Diabetes prevention studies with pharmacology interventions**

Though there were previous studies directly leading to prevent the T2D and other studies that, in post hoc analysis, have stopped as regards to this subject, it was not until 2001 when, successively, the results of four studies came forth, randomized and controlled, in subjects with reduced oral glucose tolerance (reduced OGT) and impaired fasting-glucemia (IFG), whose primary objective was to evaluate different strategies addressed to prevent T2D. The four studies included the essential number of patients that ensures a high reliability of the obtained results. Moreover, almost simultaneously, the results of other great studies were published in which, though the presence of reduced OGT, which was not a requirement, different strategies for the prevention of the disease were evaluated in individuals with high risk to suffer it. The results of these last studies were the final support to convince that T2D is a disease that can and must be prevented (table 1).

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Intervention</th>
<th>Intervention effect (NNT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP(^5)</td>
<td>3,234</td>
<td>Placebo</td>
<td>-31%/14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metformin</td>
<td>-58%/7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lifestyle changes</td>
<td></td>
</tr>
<tr>
<td>I-DPP-1(^7)</td>
<td>531</td>
<td>Placebo</td>
<td>-26.4%/6.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metformin</td>
<td>-28.5%/6.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lifestyle changes</td>
<td>-28.2%/6.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Combination of both</td>
<td></td>
</tr>
<tr>
<td>STOP-NIDDM(^8)</td>
<td>1,429</td>
<td>Placebo</td>
<td>-25%/11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acarbose</td>
<td></td>
</tr>
<tr>
<td>XENDOS(^9)</td>
<td>3,304</td>
<td>Placebo + lifestyle changes</td>
<td>-37%/36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Orlistat + lifestyle changes</td>
<td></td>
</tr>
<tr>
<td>TRIPOD(^1)</td>
<td>236</td>
<td>Placebo</td>
<td>-58%/6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Troglitazone</td>
<td></td>
</tr>
<tr>
<td>DREAM(^1)</td>
<td>5,269</td>
<td>Placebo</td>
<td>-62%/7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rosiglitazone</td>
<td></td>
</tr>
</tbody>
</table>

NNT: number of individuals needed to be treated in order to prevent a case; reduced OGT: reduced oral glucose tolerance.

Several drugs have been studied in order to evaluate the prevention of new cases of DM in subjects with intermediate stages between normality and T2D. Among these drugs, some stand out that usually is used to treat the DM per se (metformin, ascarbose and glitazones) and others used as drugs for the reduction of weight (orlistat).

**Metformin**

This drug is undoubtedly the most studied one as regards to the prevention of DM. The most numerous cohorts of patients that have been evaluated in intervention studies with this drug are the one included in the Diabetes Prevention Program (DPP)\(^3\) study. The subjects included in the study represented the American population and those of different origins: mean age 50.6, approximately 70% were women, 57% were men and 73% of the women were obese (body mass index [BMI]: >30 kg/m\(^2\), 70% had family history of T2D and 305 of arterial hypertension, and approximately a third part of them had lipid metabolic disorders. Moreover, the fasting glycemia had to be between 95 and 125 mg/dL.
To sum up, these were individuals with high risk of reduced OGT.

The 3234 patients were distributed randomly in three types of intervention: a) a group at intensive lifestyle changes (open study, 1,079 individuals); b) a group at placebo (1,082 subjects) and c) a third group to receive metformin 850 mg/12 h (these two last ones, double blind: 1073 subjects). Considering the obtained results, the follow-up period of the DPP study was interrupted a year before what has been stated in the initial protocol, and ended with a mean follow-up period of 2.8 years. The therapeutic compliance with metformin was excellent during the study and in spite of the foreseeable gastrointestinal effects and the drug dosage; it reduced the relative DM risk in 31% versus placebo.

While the ethnic origin and the sex of the subjects did not have a relevant influence in the results of the interventions performed in the DPP study, the effects of the patients’ age, the BMI and the baseline glycemia value deserve a separate comment. In the youngest individuals (especially in those ≤44 years of age) metformin was as effective as the measures on lifestyle (44 and 48% of reduction, respectively), while the benefits obtained in the subjects over 60 years of age were not so important. Higher benefits with metformin were also observed in those individuals with a level II obesity (51% of reduction compared to placebo). As regards to the influence of the fasting glycemia figures, it has to be pointed out that the highest reduction in the onset of T2D with metformin occurred in those individuals with glycemia between 110 and 125 mg/dL (48%), quite similar to 63% obtained by the lifestyle changes.6 To sum up, metformin is especially useful in young and obese patients and those that have IFG.

Recently, the results of two studies have been published in India and China, in which similar results have been notified using 250 mg of metformin (2 or 3 times a day). The Indian Diabetes Prevention Program 1 (I-DPP-1)7 states, for the first time, that the combination of metformin and lifestyle changes is not more effective than the single use of these last ones. In second place, it shows that, at least in the Indian population, the use of metformin in doses lower than those used in the DPP is as effective as the healthy changes in the lifestyle. And in third and last place, this study suggests that the efficiency in the lifestyle changes in this type of population is lower than the one observed in other studies (reduction of the new cases of T2D in 28%).

**Acarbose**

The alpha-glycosidase inhibitor, acarbose, has also been evaluated in several studies for the prevention of DM. The most outstanding one is the Study to Prevent Non Insulin Dependent Diabetes Mellitus (STOP-NIDDM trial).8 It is an international study (Canada, Spain, Germany, Austria, Israel and Scandinavian), multicenter, randomized and placebo controlled that assessed the usefulness of acarbose when preventing or delaying the conversion of reduced OGT to T2D. For this, 1,429 individuals were included (mean BMI: 31 kg/m2, mean age: 55; 50% women) with reduced OGT and that besides, had fasting glycemia of >100 mg/dL. The use of acarbose reduced the onset of T2D in 25% during a mean follow-up period of 3.3 years. The number of patients to treat during 3 years in order to prevent T2D was of 11. Likewise, it increased the normalization rate of the oral glucose tolerance. It is necessary to point out that the beneficial effects of acarbose have been obtained in all the included age groups (40-70 years of age), in both sexes and in any BMI value. Though the adverse effects (gastrointestinal mainly) were more frequent in the group of patients who received acarbose, no serious adverse effect could be observed in any case.

On the other hand, taking into account that the cardiovascular events are the main cause of death of the patients with T2D and that to a great extent these deaths justify the excess of cost that represents for the health systems, it is logic that the possibility of preventing T2D makes us look for the reduction in the incidence of CVD. Most of the studies addressed to prevent the disease have demonstrated that this prevention is associated to an improvement in other cardiovascular risk factors. However, only the STOP-NIDDM proved (in a secondary objective of the study, indeed) a reduction of 49% in the onset of any cardiovascular event and of a heart attack up to 91% associated to the use of acarbose.9

**Agents for the reduction of weight: orlistat**

In Xenical in the Prevention of Diabetes in Obese Subjects Study (XENDOS)10 3305 patients with a BMI ≥30 kg/m2 have been included. Randomly, they have been distributed to an intervention arm with lifestyle changes and orlistat (120 mg/3 times a day) or to the use of such lifestyle changes together with placebo. The 79% of the
included patients had a normal oral glucose tolerance, and 21% had a reduced OGT. After 4 years of treatment, the accumulated incidence of T2D in the patients who received placebo was of 9% while in those who received orlistat was of 6.2%. These data suggest a risk reduction of 37.3%. The use of orlistat was associated to a mean reduction in the weight of 5.8 kg compared to 3 kg obtained in the group that only undertook lifestyle changes. The data of the XENDOS study indicate, once more, the close existing relation between the presence of obesity and the risk of developing T2D.

Glitazones
The insulin sensibilizing properties of glitazones generated a general enthusiasm from the beginning considering a possible role in the prevention of DM. In the Troglitazone in Prevention of Diabetes (TRIPOD) study, the use of troglitazone was assessed for the prevention of DM in 266 patients of Hispanic-American origin with previous gestation diabetes history. Troglitazone or placebo was administered to the patients randomly (400 mg/day). During 30 months of follow-up (mean), the annual incidence of T2D was of 12.1% in the placebo group and 5.4% in the group of women who received troglitazone. In other words, the use of the drug reduced the onset of T2D in 51%. It has to be mentioned that the troglitazone was withdrawn from the market due to its hepatotoxic effects.

Recently, this same group and those patients who ended the TRIPOD study without T2D (89 women) decided to use pioglitazone in an open, observational study, with the aim of assessing its effects in pancreatic beta-cell function, as well as in the sensitiveness to the insulin and in the incidence of T2D. It is the Pioglitazone in the Prevention of Diabetes (PIPOD) study. With the caution with which the results have to be considered as regards to a study of these characteristics, the authors demonstrated beneficial effects on those parameters involved in the pathogeny of the T2D.

Afterwards, the Diabetes Reduction Assessment study with Ramipril and Rosiglitazone Medication (DREAM) study included 5,269 participants (24,872-screened subjects) of origin population of four of the five continents to compare rosiglitazone and ramipril simultaneously. It is a study with a design of $2 \times 2$ factors, placebo controlled, multicenter and of international participation (21 countries), that included patients with reduced oral glucose tolerance and/or fasting altered glycemia. This study assessed the efficiency of ramipril and rosiglitazone in a primary target made up of the T2D onset and death for any reason. As it was expected in a study of these characteristics, a series of secondary objectives were also included, among which the cardiovascular and renal events. The sort of participants was similar to those included in previous studies of this class: patients between 50 and 60 years of age, with overweight or obesity and with the frequent presence of arterial hypertension, dyslipidemia and other features that make up the so-called “metabolic syndrome”.

In the case of the ramipril effectiveness, and in a clear discrepancy with what could be expected by the results of the previous studies, the use of this anti-hypertensive drug did not reduce the onset of new T2D cases. In any case, it has to be pointed out that ramipril had beneficial effects on the carbohydrate metabolism that have to be taken into account. The case of rosiglitazone was completely opposite. The use of this glitazone reduced the T2D onset and the death incidence (primary objective) in 60% and the incidence of new isolated T2D cases in 62%. In other words, a reduction of the same magnitude to the one obtained by the lifestyle changes in previously published studies. It is worth to mention that this effect took place both in men and women in the same way, regardless to the age, the origin continent, the glucose tolerance impairment, the weight and the localization of the adiposity of the subjects. In the conglomerate of cardiovascular events that made up the secondary objective, there were no relevant results. However, it has to be mentioned that in the group that received rosiglitazone 14 cases were observed with congestive heart failure, versus only 2 in the placebo group.

Other drugs
The post hoc analysis of different studies has suggested the possible benefit of the angiotensin-converting enzyme inhibitors in the DM prevention. Ramipril was assessed in the DREAM study with negative results on this regard, as it has already been mentioned. In the same line, a secondary target of the ONTARGET study assessed again the effectiveness of ramipril and telmisartan in patients with vascular disease or high risk of DM. In this sub-study, 5,427 patients were included of the group treated with ramipril, 5,294 of the telmisartan group and 5,280 of the combined treatment group. However, none
of the drugs in neither monotherapy nor the combination of both was associated to a lower incidence of new DM cases during the mean follow-up of 56 months.

Also in a post hoc way, the West of Scotland Coronary Prevention Study\textsuperscript{16} suggested that the use of pravastatin might have a potential benefit in the prevention of DM. However, this hypothesis has not been assessed by any randomized clinical trial.\textsuperscript{17,19}

Finally, preliminary in vitro studies which used new therapies for the treatment of T2D, such as the GLP-1 analogues (exenatide) or the DPP-IV inhibitors, suggest that these therapies do not only improve the insulin secretion, but also boost up the proliferation of the beta cells.\textsuperscript{20} In this way, there is a possibility that these agents might also be useful on this regard, though we have to wait for specifically designed new clinical trials to reply this question.

**Final considerations**

There is no doubt that at present we do not make any mistakes if we assert that we are able to delay the onset of T2D with the combination of health lifestyle habits and some drugs.\textsuperscript{21} Nevertheless, it has to be pointed out that this beneficial effect has been demonstrated in very specific population groups, as subjects with overweight / obesity, approximately of 50 years of age and with intermediate impairments of oral glucose tolerance. The extension of these results to other populations cannot be done without due care.

Though for some persons this is only a “semantic” discussion, it is true that none of the interventions used up to date levels the curve of T2D incidence in the prevention studies performed in individuals with reduced OGT. In other words, the natural history of the disease, though slowed down, progresses inexorably. Moreover, the fact of using drugs used in the treatment of T2D once it has been diagnosed complicates the discussion more. It has to be pointed out that, though it is mentioned repeatedly that the positive effects of the glitazones when preventing the onset of T2D in the group of Hispanic women remain even when the drug is withdrawn (TRIPOD study), the number of individuals included and the minimum number of new T2D cases does not allow to determine a definitive conclusion on this regard.\textsuperscript{11} A total of 1,274 patients of the DPP study randomized to placebo or metformin took part in a “wash-out period” at the end of the study. After two weeks of leaving both treatments, the condition of carbohydrate tolerance was assessed in these subjects. The conversion rate of reduced OGT to T2D after considering the study and wash-out periods was still relevantly lower in the metformin group.\textsuperscript{22} In conclusion; only one part of the “preventive” effect obtained with metformin might be attributed to its purely pharmacological effects on the glycemia. In the STOP-NIDDM and DREAM studies, the results obtained in this sense were quite similar. In other words, once the drug was withdrawn, its effect was reduced and the physiopathologic process that underlies starts again at its usual speed.

**Opinion of the scientific societies**

There is no doubt that the initial approach of choice in the prevention of T2D based on the results of the mentioned studies is to perform healthy changes in lifestyle.\textsuperscript{23} Even so, it is also true when analysing what is understood and is applied as intensive changes of lifestyle in the great prevention studies, one has to ask oneself if these protocols are extendible to the daily practice. However, its effectiveness is such that any change, as small as it might be, might offer us clinically relevant results. In any case, there is no consensus as regards to the use or not of drugs in case that the previously mentioned measures are not sufficient, and to which drug to use first, on whom and during how long.\textsuperscript{24}

In 2007, the International Diabetes Federation published for the first time a consensus document about the prevention of T2D. A proposal of a plan based on the control of modifiable risk factors in persons with high risk to develop T2D and in the general population was stated. Regardless of the risk group, measures of progressive use are stated as well as the use of drugs (metformin and acarbose) in those persons of high risk in which the lifestyle changes are considered inefficient.\textsuperscript{25} For some years, the American Diabetes Association in its general recommendations states in a similar manner and includes the use of metformin as feasible.\textsuperscript{26} Finally, in the consensus of 2008 between the American Association of Clinical Endocrinologist and the American College of Endocrinology, the pharmacological intervention is considered in similar situations by using several drugs, as follows: metformin, acarbose, orlistat or glitazones.\textsuperscript{27}
Practical considerations

- The initial option approach in the prevention of T2D is to undertake healthy lifestyle changes. Provided its efficiency, any small change might offer clinically relevant results.
- At present, some scientific societies as IDF, ADA or the ACE/AACE, consider the use of drugs (metformin, acarbose) in those persons at high risk in which the lifestyle changes are considered inefficient.
- Metformin is especially useful in young patients, obese subjects and those with IFG, though only a part of the obtained “preventive” effect is attributed to the effects on glycemia.

Conclusions

With the initial certainty that we have to and can prevent the T2D, during the following years we will expect the publication of several studies that shall prove and complement what we know up to date about T2D prevention. In most of them there has been a substantial change as regards to the problem approach, specifically, the prevention of the cardiovascular disease included as primary objective. The NAVIGATOR study that uses nateglinide and valsartan, the ORIGIN study, with insulin glargine, the CANOE study that uses rosiglitazone and metformin, and the ACT-ON study that analyses the effects on pioglitazone, are some of them.

Declaration of potential conflict of interest

M. Giménez gave conferences for Glaxo-Smith-Kline and Merck-Sharp-Dhome. I. Conget gave conferences for Glaxo-Smith-Kline, Merck-Sharp-Dhome, Novartis, Sanofi-Aventis and Eli-Lilly and has been part of the Direction Committee of the STOP-NIDDM and DREAM studies.

References

**Prevalence of tobacco use among diabetic patients**

Smoking increases the cardiovascular risk both in the diabetic population and in the non-diabetic. However, considering that the persons with diabetes mellitus (DM) have already an increased cardiovascular risk due to the disease, increasing it more by the consumption of tobacco constitutes a dangerous behavior. The complications risk associated to the consumption of tobacco added to the diabetes is 4 times higher than smoking or having diabetes when it is considered separately.

Besides this increase of cardiovascular risk, there are works that refer that some of the products that are inhaled when smoking, as nicotine, might determine a reduction of the insulin sensitivity, therefore the consumption of tobacco might be related both to an increase of the DM risk in the smoking population and to an increase of the micro/macro vascular complications in this population.

Thus, tobacco and diabetes constitute a “dangerous company”, which is why the measures addressed to reduce the consumption of tobacco are a comprehensive part of the treatment of this disease.
the treatment of the patients with DM. Notwithstanding, there are only a few programs to stop smoking that have been focused on this risk group.

The objective of this work is to register the tobacco habit of the diabetic population assisted in a specialized area consultation, and set out the withdrawal of the tobacco consumption as control objective for the cardiovascular risk factors in the diabetic patient. In order to make out this study, we count with the collaboration of the anti-tobacco unit of our center.

**Material and method**

440 patients have been studied who attended to the endocrinology outpatient consultation during the period comprised between May and December 2007. The following aspects have been assessed: age, type of DM, years since diagnosis, metabolic control, associated cardiovascular risk factors (central distribution obesity, hypertension and hyperlipemia), complications (micro/macro vascular), sleep apnea and chronic obstructive pulmonary disease. The data related to the patient’s tobacco habit have also been collected: if the patient was a smoker, the daily consumption of cigarettes, the level of physical dependence (simplified Fagerström test, a validated survey described in Annex 1) and the level of motivation to stop smoking (Richmond test, a validated survey described in Annex 1); if the patient was not a smoker, since when and the level of tobacco consumption previous to stop smoking.

The smoker patients were informed about the danger that entails the consumption of tobacco for them, and were invited to stop smoking, assessing the abandonment phase at that moment. If the patient had a firm purpose (preparation phase or action phase) and a high motivation (Richmond test equal or higher than 8), the patient was referred to the anti-tobacco unit of the center.

This is a descriptive study in which the absolute and relative frequencies are determined by the qualitative variables and the arithmetic mean, the mean and the standard deviation for the quantitative variables.

**Results**

From the 440 studied patients, 44 were diagnosed with T1D (21 women and 23 men) and 396 had T2D (231 women and 165 men). The gestational diabetes cases were excluded. The characteristics of the study diabetic population are depicted in table 1.

According to the distribution per genders, 252 were women and 188 men; 75 were smokers (17%) and 365 were not smokers (83.0%) and from these, 163 (44.6%) were ex-smokers.

According to the distribution of smokers per ages, 26 (34.7%) were over 61 years old, 18 (24%) were between 51 and 60 years old 20 (26.7%) between 41 and 50, and only 11 (14.7%) were under 40 years old. The details are described in table 2.

Table 3 depicts the distribution per ages corresponding to the ex-smokers group.

Considering the age of the patients with DM, in the group under 40 years old, 44% are smokers and 28% are ex-smokers; in the group of 41-50 years old , 44.4% smoke and 28.9% are ex-smokers; in the group of 51-60 years old , 22.2% smoke and 45.7% are ex-smokers, and in the group over 60 years old , 9% are smokers and 36.3% are ex-smokers.

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Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>Range</th>
</tr>
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<tr>
<td>Age</td>
<td>64.2</td>
<td>13.2</td>
<td>21-90</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77.3</td>
<td>14.8</td>
<td>39-136.9</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>104</td>
<td>14.2</td>
<td>70-146</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>30.2</td>
<td>5.5</td>
<td>16.6-50.6</td>
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<tr>
<td>Years since diagnosis</td>
<td>12.8</td>
<td>9.7</td>
<td>0-50</td>
</tr>
<tr>
<td>Glycosylated hemoglobin (%)</td>
<td>7</td>
<td>1.4</td>
<td>4-12.8</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Total population (n)</th>
<th>Smokers (n)</th>
<th>Women (n)</th>
<th>Men (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>25</td>
<td>11</td>
<td>5</td>
<td>6</td>
</tr>
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<td>41-50</td>
<td>45</td>
<td>20</td>
<td>9</td>
<td>11</td>
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<tr>
<td>51-60</td>
<td>81</td>
<td>18</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>&gt;61</td>
<td>289</td>
<td>26</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>440</td>
<td>75</td>
<td>34</td>
<td>41</td>
</tr>
</tbody>
</table>
Considering the distribution per genders, 45.4% of the women smoke and 42.8% of men under 40 years old; in the group of 41-50 years old, 34.6% of the women smoke and 57.9% of the men; in the group 51-60 years old 21.4% of the women smoke and 23.1% of the men, and in the group over 60 years old, 6.4% of the women smoke and 12.9% of the men. Table 4 depicts this analysis.

Taking into account the type of diabetes, the rate of smokers in patients with T1D is of 45.5%, while in the patients with T2D it is of 13.9%.

Among the smokers, 69 of them consume cigarettes and the other 6 consume cigars. The mean consumption of cigarettes is 24 per day and 5 cigars during a week.

In relation to the tobacco abandonment phase, the 33.3% of the diabetic subjects (25 patients) are under the pre-contemplation phase (they do not have the intention to stop smoking for the next 6 months), 28% (21 patients) under contemplation phase (are thinking of stopping smoking in the next 6 months), 24% (18 patients) under preparation phase (shall try to stop smoking during the next month) and 14.7% (11 patients) under the action phase (withdrawal of less than 6 months).

As regards to the nicotine dependence measured by the Fagerström test, a mean ± standard deviation (SD) of 3.5 ± 2.3 was obtained and in the motivation to stop smoking measured by the Richmond test the mean ± SD was of 5.5 ± 2.5.

**Discussion**

The tobacco constitutes an important modifiable cardiovascular risk factor that increases the micro/macro vascular risk in the diabetic population. The withdrawal of the tobacco consumption shall constitute a target in the treatment of this population, as the different treatment guidelines include for the diabetic patients.

In this work, the tobacco habit prevalence between our diabetic population is of 17%, similar to the one referred by other authors, and lower to the tobacco habit rate in the Spanish population according to the last health national survey, placed at 27%.

Considering the distribution per ages, we find that, this is in relation with the distribution of the diabetics in our population, whose mean age is of approximately 65 years old though the group with higher number of smokers is the one of >50 years old. However, we find the higher rate of tobacco habit in the youngest diabetic subjects; thus, 44.3% smoke among those under 50 years old and 11.9% of the diabetic population among those over such age; similar percentages than those of the general population and of other diabetic series, where the youngsters have higher rates of tobacco habit.

Besides the smokers rate, the exposure to tobacco in diabetic patients in some stage of their life is very high in our population; thus, in the non-smoker population the 44.4% has been in some stage of their life, and this percentage is higher than 80% in men.
It seems that the higher tobacco habit takes place in subjects aged 50 and from that moment the rate of ex-smokers increases, what makes us think that from this age the diabetic patient starts to stop smoking.

We can think that the diabetes diagnosis is a motivation to stop smoking in our population and, therefore, the patients stop smoking as from 50 years old. However, this is unlikely, as we observe that the nicotinism rate in patients with T1D is much higher than in patients with T2D and this is in relation with the mean lower age of the first ones; in other words, the diabetic subjects, as the general population, smoke at early ages.

Considering the gender, a 50% of the women less than 40 years old smoke, while the men smoke more frequently between 40 and 50 years, with a rate of 57.9%. This distribution per gender is also similar than the one reflected in the National Health Survey of 2006, issued by the National Institute of Statistics.12

Transversal and prospective studies show a higher risk of macro/micro vascular disease in the diabetic population, with an increase of the early mortality in the smoker diabetic population,3,4,13 moreover, there are evidences that the nicotine reduces the insulin sensitivity and increases the diabetes risk.4,5 In spite of all these data, the number of diabetic persons is high, and in some series it does not differ from the non diabetic population.14 In our series, the percentage of smokers is lower than the one of the National Health Survey of 2006, but suggests a percentage of 17% with an increase in the younger groups and in women. Moreover, the exposition to the tobacco consumption is very high, with more than 44% of ex-smokers, with the repercussion that it might have on the possible diabetic complications.

The abandonment of tobacco habit implies an evident reduction in the risk of vascular events, with a reduction of the risk in 36% of all the causes of mortality related with diabetes.15 In spite of these evidences, a few strategies performed in order to reduce the consumption of tobacco have been focused in this population and notwithstanding, the tests indicate that the active planning addressed specifically to the diabetic patients resulted in a reduction of the smoker population of this group.10

The nicotinism is a cardiovascular risk factor that has to be controlled in the diabetic population; therefore the record on the tobacco consumption is a datum that cannot be missed in the revisions of these patients. In each revision, the patients have to be reminded about the additional vascular risk that supposes tobacco consumption, recommending them the abandonment of such habit and facilitating them the treatments available in order to get abandon of tobacco habit.

From the 75 smokers of the study, 69 (92%) consume cigarettes, with a mean of 24 per day. The 6 remaining consume cigars in a mean quantity of 5 per week. Moreover, more than 33% of these smokers has not set out the possibility of stop smoking, though all of them refer knowing the risk that this supposes for them, in spite of the fact that the nicotine dependence is light, with a score in the Fagerström test of 3.5 (scores ≤4 indicate a light dependence).18 All this states the need of a procedure addressed to reduce the tobacco consumption in the diabetic population, consistent in motivating the patient who is not predisposed (in this population the motivation is scarce: Richmond test of 5.5; it is considered that in order to include a smoker in a program to get abandon to nicotinism it is necessary that this test shows values between 9 and 10 points),18 to help the motivated patient to perform an attempt to stop smoking and to achieve that those who have tried can keep it and become an ex-smoker.

For this objective, we count with the collaboration of the anti-tobacco unit at our center, where we refer the patients under preparation or action phase with a Richmond test of ≥8. The patients with an abandonment expectation higher than a month, they are offered a customized anti-tobacco advice, proposing them the reduction of 50% in the current consumption of cigarettes and leaving all our help open for the moment in which the patient decides to face the total abandonment of tobacco.

These data allow concluding that the prevalence of tobacco habit in our diabetic population (17%), lower than the general population, is higher in patients less than 50 years old and in patients with T1D. The women smoke more in early ages (<40 years old) and the men between 40 and 50 years old.

The nicotine dependence is not high, but the motivation to stop smoking is scarce, therefore it is necessary to carry out an active strategy by the professionals in charge
### Annex 1. Fagerström test and Richmond test

#### SIMPLIFIED FAGERSTRÖM TEST

*Physical dependence measurement*

**Assesses the nicotine dependence level in a scale from 0 to 10 points.**

- **How much time passes since you wake up and smoke your first cigarette?**
  - Within 5 minutes ........................................ 3 points
  - 6 to 30 minutes ........................................ 2 points
  - 31-60 minutes ........................................ 1 point
  - After 60 minutes ..................................... 0 points

- **Do you find it difficult not to smoke in places where it is forbidden?**
  - Yes ..................................................... 1 point
  - No ...................................................... 0 points

- **Which cigarette would difficult to give up?**
  - The first one in the morning ....................... 1 point
  - Any other .......................................... 0 points

- **How many cigarettes do you smoke per day?**
  - Less than 10 cigarettes ........................... 0 points
  - Between 11 and 20 cigarettes ................... 1 point
  - More than 30 cigarettes ......................... 3 points

- **Do you smoke more during the first hours after waking up?**
  - Yes ..................................................... 1 point
  - No ...................................................... 0 points

- **Do you smoke if you are so ill that you have to be in bed?**
  - Yes ..................................................... 1 point
  - No ...................................................... 0 points

**TOTAL .................. POINTS**

- Score lower or equal than 4: low nicotine dependence
- Score with values between 5 and 6: mean dependence
- Score equal or higher than 7: high nicotine dependence

#### RICHMOND TEST

*Motivation level measurement to stop smoking*

**Assesses the motivation to stop smoking in a scale from 0 to 10 points.**

- **Would you like to quit smoking if you could do it easily?**
  - No .................................................... 0 points
  - Yes .................................................... 1 point

- **How interested are you to quit smoking?**
  - Not at all .......................................... 0 points
  - A little .............................................. 1 point
  - A lot .................................................. 2 points
  - Very interested ................................... 3 points

- **Will you try to stop smoking in the following two weeks?**
  - Definitely not ..................................... 0 points
  - Perhaps ............................................ 1 point
  - Yes .................................................. 2 points
  - Definitely yes .................................... 3 points

- **How likely are you to be a non-smoker in the following six months?**
  - Definitely not ..................................... 0 points
  - Perhaps ............................................ 1 point
  - Yes .................................................. 2 points
  - Definitely yes .................................... 3 points

**TOTAL .................. POINTS**

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of the treatment of the diabetic population, rendering the same attention to the treatment that to other cardiovascular risk factors that are present in these patients. The objective is to achieve the withdrawal of such consumption. The anti-tobacco advice and the therapeutics available to abandon the consumption are a usual practice in the handling and treatment of the patient with diabetes.

Declaration of potential conflict of interest
M.A. Saavedra Blanco, R. Garrido Martínez, E. León Carralafuente, P. Vaquero Lozano and S. Solano Reina state that there are no conflicts of interest as regards to the content of this article.

References
Aggregation pattern and factorial analysis of cardiovascular risk factors included in the metabolic syndrome in a Spanish non-diabetic population: the VIVA study*

R. Gabriel,1 M. Alonso,1 J. Parra,2 J.M. Fernández-Carreira,3 G. Rojo-Martínez,4 C. Brotons,5 A. Segura,6 J. Cabello,7 J. Muñiz,8 S. Vega,9 J. Gómez-Gerique,10 M. Serrano-Ríos,11 on behalf of the Cooperation Group of VIVA Study

Aims: The aim of this study is to describe the most frequent cardiovascular risk factors (CVRF) clustering related to the metabolic syndrome (MS) in a non-diabetic Spanish population sample. Test by factorial analysis if the CVRF in the MS can be considered manifestations of a unique common factor. Materials and methods: Observational, multicenter, transversal epidemiologic study. 2583 subjects aged 30-65 were randomly assigned from nine population registries. Exclusive aggregations were considered. Correlation among the MS variables was analyzed using factorial analysis. Results: In order of frequency the prevalence of conventional CVRF was: dyslipidemia: 34% (CI95%: 32-35.5); hypertension: 32% (CI95%: 30.2-33.8); obesity: 27% (CI95%: 25.3-28.7); hyperglycaemia: 23% (CI95%: 21.6-25). 22% of the population showed 2 CVRF and 11% 3 CVRF. The most common CVRF aggregations were hypertension-obesity (5.3%; CI95%: 4.4-6.2) and hypertension-obesity-hyperglycaemia (4.1%; CI95%: 3.3-5). MS specific risk variables tended to aggregate in three factors: factor 1 (BMI, waist circumference and basal glycaemia), factor 2 (insulin, glycaemia 2h, and arterial blood pressure), factor 3 (total cholesterol/HDL, triglycerides). Conclusions: There is a high prevalence of CVRF and MS in the population studied. Analysis of the metabolic syndrome does not contribute with additional information to predict cardiovascular risk in susceptible patients, as compared to the clustering of CVRF. Factorial analysis do not confirm the existence of a unifying factor to explain MS.

Keywords: cardiovascular risk factors, metabolic syndrome, factorial analysis.

*Cooperation Group of VIVA Study:
Resumen

Objetivos: Describir las agregaciones más frecuentes de los factores de riesgo cardiovascular (FRCV) que integran con el síndrome metabólico (SM) en una muestra de población española no diabética. Comprobar mediante análisis factorial si los diferentes FRCV considerados en el SM son manifestaciones de un posible único factor común. 

Métodos: Estudio poblacional transversal, multicéntrico, realizado en 2.583 sujetos de 30-65 años elegidos al azar de 9 registros poblacionales. Para el cálculo de la frecuencia de cada uno de los FRCV y de sus agregaciones se utilizaron las definiciones clásicas de cada factor. Las agregaciones de factores se calcularon de forma excluyente. La correlación entre los FRCV se realizó mediante análisis factorial. 

Resultados: De mayor a menor, la prevalencia de los distintos FRCV clásicos considerados en la definición del SM según el NCEP ATP III fue: dislipemia 34% (intervalo de confianza [IC] del 95%: 32-35,5); hipertensión 32% (IC del 95%: 30,2-33,8); obesidad 27% (IC del 95%: 25,3-28,7) e hiperpiglicemia 23% (IC del 95%: 21,6-25). Se observan diferencias significativas entre sexos: predominaba la dislipemia en hombres y la obesidad en mujeres. El 22% de la población mostraba agregación de dos FRCV y el 11% de tres FRCV. Las agregaciones más frecuentes fueron: hipertensión-obesidad, 5,3% (IC del 95%: 4,4-6,2), e hipertensión-obesidad-hiperglicemia, 4,1% (IC del 95%: 3,3-5). Los FRCV considerados tienden en general a formar tres conglomerados: 1) índice de masa corporal, diámetro sagital abdominal y glucemia; 2) insulina, glucemia a las 2 horas y presión arterial, y 3) razón colesterol total/colesterol unido a las lipoproteínas de alta densidad y triglicéridos. En los hombres pueden identificarse hasta cuatro conglomerados de FRCV, mientras que en las mujeres éstos pueden reducirse hasta dos. 

Conclusión: La prevalencia de los distintos FRCV clásicos integrantes del SM según el NCEP ATP III es alta en la población española no diabética. La agregación obesidad-hipertensión arterial es la más frecuente. El análisis factorial no demuestra la existencia de un único factor unificador que permita explicar el conglomerado de factores que define el SM. Se observa una agrupación de FRCV distinta en función del sexo.

Palabras clave: factores de riesgo, síndrome metabólico, análisis factorial.

Introduction

The cardiovascular diseases (CVD) are a public health problem presenting high prevalence and because they constitute cause of death in the adult population in most of the countries. The knowledge of the main modifiable cardiovascular risk factors (CVRF) allow to define and introduce cardiovascular prevention strategies. The determination of the aggregation patterns of the different CVRF among them are every day more important for the evaluation and cardiovascular risk factor. In fact, it has been proved that the different CVRF interact positively, so the cardiovascular risk arisen from the simultaneous exposure to some of them is higher than the one expected from the simple addition of the risk corresponding to each one. At present, the need to treat the subjects intensively who show multiple abnormalities in the CVRF stand out, even in those who show minimally altered values. On the other hand, the contribution of the different CVRF and the way in which they aggregate show a great variability as regards to the different factors, among which the gender has a relevant role, therefore the strategies tend to be more customized every day.

All these facts are related directly to the onset of the metabolic syndrome (MS) entity, which was initially defined as a risk factor in itself for the development of the cardiovascular disease (CVD) and T2D, and in which the insulin resistance or the glucose altered metabolism was a main component. Then, the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) developed a more clinical proposal of the MS, based on the definition of the World Health Organization (WHO), but in which the MS was considered an aggregation of individual factors that constituted a global entity, where the concurrence of three or more abnormalities in the values of its components was a main requirement for the diagnosis. Some later epidemiologic studies validated the existence of this aggregation observing a higher frequency in the association of these abnormalities than the per se random one. Subsequently, other definitions have been developed, on which consensus was achieved regarding to the principal factors that define the MS (glucose intolerance, obesity, hypertension and dyslipidemia) that, when observed thoroughly, they coincide with the classic CVRF but in early phases, therefore the cut points are lower and its assessment form has been improved. In fact, the components of the MS can be assessed easily in the clinical practice, thus, the MS becomes a very efficient tool for the evaluation and prevention of the potential cardiovascular risk. However, it has to be clarified how these components interact among them, and if there is a physiological interrelation that allows considering them as manifestations of a unique entity.

The objectives of this study are to describe the aggregation patterns of the main conventional CVRF that make...

up the definition of the MS in the adult non-diabetic Spanish population and to study if there are differences between men and women. Secondly, to determine, through factorial analysis, the possible correlations among the different CVRF that are considered in the MS, how they interrelate among them and if they can be considered manifestations of a unique common factor.

Material and method
Population
The VIVA Project is an epidemiologic, transversal and multicenter study, performed in 9 geographic zones in Spain: Arévalo (Ávila), Talavera de la Reina (Toledo), Guadalajara, Begonte (Lugo), Vic (Barcelona), Avilés (Asturias), San Vicente del Raspeig (Alicante), Mérida (Badajoz) and Pizarra (Málaga). In 1998, a stratified randomized sample was collected by age and gender of 2,959 subjects aged 35-64, among the population registered at the municipal records of each of the involved sites. Finally, the analysis was done on a total of 2583 patients (87.3%) from the 2,959 polled who had complete information for all the considered variables and who complied with the inclusion criteria: non-diabetic subjects and non-pregnant women (figure 1).

Procedures and determinations
The methods employed for the determination of all considered variables are described widely in another previous work. Briefly, the biochemical parameters (total cholesterol [TC] and cholesterol bound to high density lipoproteins [cHDL], triglycerides, glucose and insulin) have been determined in a standard manner and have been measured in a unique central laboratory (Fundación Jiménez Díaz of Madrid), qualified by the Spanish Society of Clinical Chemistry; the measurements of the anthropometric variables (weight, height and waist circumference [WC]) have been measured with mercury sphygmomanometer in the right arm, with the subject sitting and after 5 minutes of rest. The measures have been validated in a sample of participants and three different persons have compared the obtained results.

Definitions of the cardiovascular risk factors and metabolic syndrome
The CVRF included in the analysis are those that consider the MS definition of the NCEP ATP III. The definitions that have been used to describe its frequency, distribution and aggregation were: hypertension (AHT) ≥140/90 mmHg or anti-hypertensive treatment; impairment of the glucose metabolism (plasmatic fasting glycemia ≥110 mg/dL, and/or 140-199 mg/dL after 2 hours of oral glucose overload); obesity (body mass index (BMI) ≥30) and abdominal obesity (PC >102/88 cm, men/women); dyslipidemia (ratio CT/cHDL ≥ 5 mg/dL or hypoglycemic treatment).

The diagnosis of the MS was done considering the definition of the NCEP ATP III, according to which the subjects shall comply with at least three of the following criteria: 1) WC >102/88 cm (men / women); 2) plasmatic fasting glycemia ≥110 mg/dL; 3) cHDL >40/50 mg/dL (men / women); 4) triglycerides ≥150 mg/dL; 5) systolic arterial pressure (SAP) ≥130 mmHg or diastolic arterial pressure (DAP) ≥85 mmHg.

Statistical analysis
The variables with continuous distribution are summed up through means and confidence intervals (CI) and those of discrete distribution through frequency charts. The statistical comparisons were performed by χ² test for the discrete variables and the Student t test for the continuous variables. For the assessment of the frequency of the different aggregations of the CVRF, the aggregations were considered in an exclusive manner. An exploration factorial analysis was performed in order to determine the correla-
tions and the lowest number of factors that might explain the MS. We used the Kaiser-Meyer-Olkin (KMO) index to determine the sample adequacy level. The mean arterial pressure (MAP) has been used to reduce the co-linearity in the EFA instead of the SAP and DAP. The method of maximum probability has been used for the extraction of a factor that compares the adjustment goodness of the model of a factor with the possible multifactorial model found in the EFA, separately for men and women.13

Results
Socio-demographic characteristics and clinic of the sample
The socio-demographic and clinic characteristics of the entire study population and by genders are depicted in table 1. For all the studied parameters, except for SAP and BMI, the male population showed relevantly higher values compared to women. The women had values relevantly higher regarding to the BMI than men (p <0.05) and there have not been differences between genders as regards to the SAP.

Prevalence of the cardiovascular risk factors
The dyslipidemia was the most frequent risk factor (34%; CI of 95%: 32-35.5) in the entire population, followed by the AHT (32%; CI of 95%: 30.2-33.8), obesity (27%; CI of 95%: 25.3-28.7) and the alteration of the glucose metabolism (23%; CI of 95%: 21.6-25). When we analyzed the differences between genders, we observed that the men showed a relevantly higher prevalence of dyslipidemia (p <0.05) and lower regarding to obesity compared to women (table 2). The prevalence of MS, according to the criterion of NCEP-ATP III, in the sample as a whole was of 15% (CI of 95%: 13.8-16.6), relevantly higher (p <0.01) in men (19.5%) than in women (14.7%). The prevalence of abdominal obesity was of 27.3% (CI of 95%: 22-29) in the sample as a whole and relevantly higher (p <0.01) in women (33.8%) than in men (17.1%).

Table 1. Socio-demographic and clinical characteristics of the sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Men</th>
<th>Women</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>2,583</td>
<td>1,175 (45.5)</td>
<td>1,408 (54.5)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>49 (48-49)</td>
<td>49 (48-49)</td>
<td>49 (48-49)</td>
<td>0.861</td>
</tr>
<tr>
<td>Tobacco consumption (yes/no)</td>
<td>794 (30.7)</td>
<td>533 (45.4)</td>
<td>261 (18.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SAP (mmHg)</td>
<td>126 (125-127)</td>
<td>126 (125-127)</td>
<td>126 (125-127)</td>
<td>0.918</td>
</tr>
<tr>
<td>DAP (mmHg)</td>
<td>79 (78-80)</td>
<td>80 (79-81)</td>
<td>78.5 (77.8-79.1)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.6 (27.5-27.8)</td>
<td>27.4 (27.1-27.6)</td>
<td>27.9 (27.6-28.2)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>94.7 (94.2-95.1)</td>
<td>95.6 (95.1-96.2)</td>
<td>93.8 (93.2-94.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Capillary glycemia (mg/dL)</td>
<td>96.9 (96.4-97.4)</td>
<td>99.3 (98.6-100.1)</td>
<td>94.9 (94.3-95.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA Index</td>
<td>2.8 (2.7-2.9)</td>
<td>2.8 (2.7-3.0)</td>
<td>2.8 (2.6-2.9)</td>
<td>0.405</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>221.4 (219.8-223)</td>
<td>223.9 (221.5-226.3)</td>
<td>219.3 (217.2-221.4)</td>
<td>0.005</td>
</tr>
<tr>
<td>Cholesterol HDL (mg/dL)</td>
<td>51 (50.5-51.6)</td>
<td>46.3 (45.5-47.1)</td>
<td>55 (54.3-55.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>115.4 (112.6-118.2)</td>
<td>134.3 (129.4-139.2)</td>
<td>99.8 (99-102.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BMI: body mass index; DAP: diastolic arterial pressure; HOMA: Homeostasis Model Assessment; SAP: systolic arterial pressure; WC: waist circumference.

Qualitative variables: n and %, quantitative variables: mean and confidence interval, statistical tests: χ² and Student t.
11% of the population showed aggregation of three CVRF: AHT-obesity-hyperglycemia (4.1%; CI of 95%: 3.3-5), which is the most frequent aggregation both in men and women. The aggregation of the four considered factors, hyperglycemia-AHT-obesity-dyslipidemia was only found in 1.9% of the sample (table 4).

### Factorial analysis of the cardiovascular risk factors considered in the metabolic syndrome

In a general manner, the considered CVRF tend to group in three factor clusters that explain up to 61% of the variable. The first cluster is constituted by the basal glycemia and the obesity. The second one includes the glycemia after 2 hours, the insulin and MAP. The MAP is superimposed with the first cluster, therefore it can also be considered as a component. The third cluster comprised blood lipids (CT/cHDL and triglycerides) (table 5).

On this regard, in men, the CVRF tend to group in four clusters that explain up to 70% of the variable (factor 1: basal glycemia and triglycerides, factor 2: BMI and sagittal abdominal diameter; factor 3: glycemia after 2 hours and insulin, CT/cHDL; factor 4: MAP).

In turn, in women, only two factors might explain up to 59.1 of the variable (factor 1: BMI, sagittal abdominal diameter, MAP; basal glycemia and after 2 hours and insulin; factor 2: triglycerides and CT/cHDL). The adjustment goodness of the test showed a value of p <0.001,
both for men and for women, and the null hypothesis of existence is rejected as regards of a unique factor as underlying.

**Discussion**

During the last decades we are considering an increase in the CVRF prevalence, as the hyperglycemia, the dyslipidemia, the AHT or the obesity. In our case, the analysis performed in the general non-diabetic Spanish population places the dyslipidemia as the most prevalent of the considered CVRF (34%), followed by the AHT (32%), the obesity (27%) and the alterations in the glycemia (23%). These results are slightly different than the data described in other epidemiologic studies performed in our field, that reveal that the prevalence of the AHT reaches 40% in mean life ages and the obesity approximately 20%. This can be explained in part because our study is focused on the general population aged 35-64 (does not include elder population, in which the AHT is very high) and non-diabetic population (once excluded from the analysis the cases detected of diabetic patients), in which it is known that the prevalence of AHT is also very high. This can also be related with the differences between sexes as regards to the prevalence and the mean number of CVRF, since the menopausal and post-menopausal female population has an obesity and dyslipidemia pattern that is similar to the men’s pattern than to the young adult woman.

When evaluating the repercussion of the CVRF on the cardiovascular risk, it is important to consider that the different factors interact in a multiplying form among them; therefore the risk derived from the simultaneous exposure to some of them is higher than the one that might be expected from the simple addition of the corresponding risk to each one. However, when analyzing the physiopathology of the different CVRF aggregations, it is more efficient to consider only the excluding aggregations (pure) among the factors. On this regard, the most usual aggregation in the whole of the sample was the AHT-obesity with a global prevalence of 6%. Such aggregation of CVRF was also more frequent in women, but the aggregation AHT-dyslipidemia prevailed on men.

During the last decades, the appearance of the “metabolic syndrome” concept as cluster of several factors is getting more importance in the clinical practice and the identification of the individuals with MS provides opportunities to intervene early in the processes that predispose the development of CVD. The MS is integrated by several abnormalities that in an isolated manner do not constitute a defined disease, but in a concomitant manner they make an associated clinical entity with a high risk of CVD. We have considered the definition of the NCEP-ATP III for our study, which is the most used one in clinical and in epidemiologic studies, and a good operative definition, as it does not affect the involved factors. According to the criteria of NCEP ATP III, the prevalence of MS found in this study (15%) is slightly higher than the one assessed for the active Spanish working population (10.2%) and lower to the one described in the American (25%) and European popula-

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**Table 5. Exploratory factorial analysis of the main CVRF in the population as a whole and per gender**

<table>
<thead>
<tr>
<th>Factors</th>
<th>Total (60.6%)</th>
<th>Men (69.6%)</th>
<th>Women (59.1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Factor 1</td>
<td>Factor 2</td>
<td>Factor 3</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.810</td>
<td>0.226</td>
<td>0.846</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>0.798</td>
<td>0.141</td>
<td>0.219</td>
</tr>
<tr>
<td>Basal glycemia</td>
<td>0.629</td>
<td>0.213</td>
<td>0.118</td>
</tr>
<tr>
<td>Glycemia after 2 h</td>
<td>0.148</td>
<td>0.799</td>
<td>0.503</td>
</tr>
<tr>
<td>Fasting insulin</td>
<td>0.464</td>
<td>-0.194</td>
<td>0.056</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>0.542</td>
<td>0.184</td>
<td>0.127</td>
</tr>
<tr>
<td>Total cholesterol quotient/cHDL</td>
<td>0.856</td>
<td>0.247</td>
<td>0.056</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.314</td>
<td>0.809</td>
<td>0.825</td>
</tr>
</tbody>
</table>

The values in bold represent the correlation quotients that are bound relevantly among them within each factor, making up an independent cluster of factors. The values between brackets show the percentage of the total variable explained by the group of factors identified for the total of the sample (3 factors) for men (4 factors) and for women (3 factors).
This study ensures the results of other studies,\textsuperscript{26,27} that cor
cular risk phenotype aggregations in the population. This study ensures the results of other studies\textsuperscript{26,27} that leave on record that it is frequent to find physiological, metabolic factors in the population as well as strictly cardiovascular and states the inexistence of a common unifier factor.

Moreover, it can be observed a different cluster in men and women that state what has been described in other previous works\textsuperscript{28,29} regarding the difference between sexes in the factor involved in the MS. It seems to be a central nucleus bond to glucose metabolism, which in women is closely related with the fat distribution in the body and with the AP, while in men it is related to lipid metabolism and atherogenic index. These results support the tendencies that consider that the clinical approach should be addressed to detect the CVRF in a customized manner.\textsuperscript{30} Therefore, the MS would pass to be a “primary objective” in the prevention of the CVD in the therapeutic plans of patients at risk and not secondary, as other authors set out.\textsuperscript{31,32} So the efforts of future investigations shall be addressed to optimize the prevention strategies and the early detection of the factors that make such MS in the population at risk.

As conclusion, we point out that the prevalence of the CVRF in the general population is high. From them, the dyslipidemia is the most frequent one in the population as a whole, but the AHT is the most common factor present in all the aggregations. There are great differences regarding to the prevalence and the aggregation of the CVRF in men and women. This can be proved by using factorial analysis that indicates a correlation between glucose metabolism and lipid parameters in men and with obesity and AP parameters in women.

Acknowledgements
To Ana Isabel Ortega for her help in the orthographic correction and the manuscript style.

Declaration of potential conflict of interest
R. Gabriel, M. Alonso, J. Parra, J.M. Fernández-Carreia, G. Rojo-Martínez, C. Brotons, A. Segura, J. Cabello, J. Muñiz, S. Vega, J. Gómez-Gerique, and M. Serrano-Ríos state that there are no conflicts of interest as regards to the content of this article.

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Clinical note

Treatment of severe diabetic neuropathy with spinal cord stimulation

Tratamiento de la neuropatía diabética grave mediante estimulación medular

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Abstract

Diabetes mellitus (DM) is a widespread disease among the general population which, because of the damaging effect of hyperglycemia on the nervous or vascular structures, may lead to complications which in many cases are difficult to treat. In general, neurological disorders secondary to DM cause severe, painful processes. A great many clinical practice guidelines are available providing recommendations about different drugs to be used as a monotherapy or in combination, with varying degrees of evidence. Nevertheless, certain clinical situations show no response to pharmacological therapies and, therefore, other resources have to be found and implemented to achieve analgesia. We present a case that was resistant to traditional pharmacological treatments, in which analgesic control was achieved through spinal cord stimulation systems.

Keywords: diabetic neuropathy, spinal cord stimulation, polyneuropathy.

Resumen

La diabetes mellitus (DM) es una patología ampliamente extendida en la población general que, por el efecto perjudicial que ejerce la hiper glucemia sobre estructuras nerviosas o vasculares, puede generar complicaciones, en muchas ocasiones difíciles de tratar. La alteración nerviosa secundaria a la DM ocasiona, por lo general, procesos dolorosos graves. Existen multitud de guías de práctica clínica que realizan recomendaciones sobre el uso de diferentes fármacos en monoterapia o combinados, con distintos grados de evidencia. Sin embargo, hay situaciones clínicas en las que no se produce respuesta a las terapias farmacológicas, por lo que se buscan otros recursos para obtener la analgesia. Presentamos un caso resistente al tratamiento convencional farmacológico, en el que se obtiene el control analgésico mediante sistemas de estimulación medular.

Palabras clave: neuropatía diabética, estimulación medular, polineuropatía.

Case description

The neuropathic pain associated to the diabetes mellitus (DM) is sometimes so serious that the conventional therapies are not sufficient; therefore technical procedures have to be used in order to improve the quality of life.

We present the case report of a male aged 52, with allergy to beta lactamases history, DM over 20 years of evolution under treatment with insulin, temporary hyperparatiroidism, high blood pressure (HBP) under treatment with angiotensin-converting enzyme inhibitors (ACEI), chronic pancreatitis and previous events of nephritic spasms.

The patient was referred due to a serious neuropathic pain in the upper limbs (ULL) and lower limbs (LLLL), described as electric, burning pain with associated feeling disorders in hands and feet bilaterally, of 3 years of evolution. The patient did not show visual or vascular impairments. The pain interfered in the night rest. The patient associated back and cervical osteoarthritic degenerative phenomena and the surgical approach.
The exploration showed a bilateral hypoesthesia in ULL/LLLL, with mild skin excoriations and impairment of the osteotendinous reflex. The patient showed a reduction of touch feeling with monofilament and the vibration with tuning fork. The diagnosis was performed, after ruling out other causes by means of imaging, analytic studies and electromyography (EMG) of the ULL/LLLL, which was informed as diabetic mixed polyneuropathy (sensory-motor), following the recommendations of the Consensus Guideline of the Clínica Mayo.1

The previous treatment for this process indicated by other specialists (traumatology, endocrinology) have been taken into account in the therapeutic proposal, as pregabalin, gabapentin, oxcarbazepine or duloxetine, all of them up to maximum doses, associated to level 2 analgesics of the World Health Organization (tramadol, codeine). Considering the scarce response, a stimulation protocol was started and the indication of a double spinal cord stimulation (SCS), cervical and lumbar.

After the evaluation by the psychologist, the patient was informed accordingly about the complete form technique, and was included in the waiting list. The patient underwent surgery on April 19th 2005 and a cervical and stimulation of posterior spinal cords system was implanted, Synergy Model (Medtronic Neurological Inc., Minneapolis, United States). An electrode Pisces Quad Compact 3890 (Medtronic Neurological Inc, Minneapolis, United States) with electrode point was placed between the spinal body of C4-C5 for ULL, and an electrode Pisces Quad 3890 (Medtronic Neurological Inc, Minneapolis, United States) with electrode point was placed in the spinal body D10-D11 for LLLL.

After 2 months from the implant, the patient recognized an improvement superior to 80%, he perceived paresthesia in the affected zone, and the pain was reduced to baseline levels if he put the stimulator off. In November 2006, he showed a worsening, with an intense pain in the waist, especially on the left side and numbness in the left groin. After revising the stimulation system, a breakage of the lumbar electrode has been determined. The patient underwent surgery on April 26th 2007 in order to withdraw the broken electrode and implantation of a new one with point in T9, with stimulation in LLLL. Since then, the patient keeps pain control, together with adjuvant medication (pregabalin 150 mg/12 h, tramadol 150 mg/day and clonazepam, 3 drops in night doses).

**Discussion**

The DM is the most common cause of neuropathy in occidental countries. It is described in 20-24% of the diabetic patients and affects especially the patients with long evolution DM (15-20 years).1

Antidepressant drugs (duloxetine, amitriptyline) are recommended in most of the clinical practice guidelines as well as anticonvulsants (pregabalin, gabapentin, oxcarbazepine) as first line treatment of the diabetic polyneuropathy, and the opioids as tramadol and oxycodone as second line.1 In general, the pregabalin and the duloxetine are considered a first choice and event the joint use of them.1,2

If the patients do not respond to standard treatment schemes, the invasive measures might be indicated. Thus, the neuro-modulation techniques, as the SCS, used in other pathologies (eg. post-surgical spine pain and syndrome of complex regional pain) or even in advanced therapies in coccygodynia, might be useful in the treatment of these patients.

The SCS is based in the “gate control theory” of Melzack and Wall,3 which states that the painful stimulation might be blocked by an electric or tactile stimulation, mediated by the nervous A-beta, myelinic and fast conduction fibers. From the neuro-chemical point of view, it might act restoring the GABA levels in the posterior spinal horn and probably on the release of adenosine, reducing the neuropathic pain.4

A few studies have been performed with spinal stimulation in patients with diabetic neuropathy. The work of Tesfaye et al.5 has been published in 1996 in which ten diabetic patients were studied and who were implanted with spinal stimulators. Neuro-stimulators were implanted in 5 patients and placebo stimulators in the rest. The tolerability of the exercise on the treadmill after 3 months has been evaluated. At the end of the study it could be observed that both groups improved the pain compared to the baseline pain, but with a greater difference in the patients with active stimulator (1.5-31.3; p= 0.002) compared to the placebo group (15.5-56.3; p= 0.005), which were related with an improvement in the blood flow in the peripheral nerves by a dorsal stimulation of the A-beta fibers an inhibition of the C fibers. The authors recommend the performance of more studies about the diabetic neuropathy, as the safety and efficacy of the
SCS has been determined in the chronic pain of different etiology, though not in diabetic patients.

Petrakis and Sciaccia\(^6\) conducted a study in 60 diabetic patients classified as Fontaine III or IV phases (28 with diabetic neuropathy), who underwent SCS after having received a conservative or non efficacious treatment. The transcutaneous oxygen pressure (TcpO\(_2\)) was measured in patients before and after 2 and 4 weeks of the implant. A pain improvement was found in 35 patients, while 12 showed a partial relief, within 6 months after the implantation. Only 3 from the 28 patients with neuropathy obtained a benefit at long term. As conclusion of this study, it is stated that in patients with a relevant increase of the TcpO\(_2\) post-stimulation, with a relief during a period of 2 weeks, the treatment with SCS might be beneficial at long term, unless the neuropathy is an advanced phase, as it has been observed that it was related inversely to the therapy success.

The SCS\(^7\) is minimal invasive and reversible technique that since it has been used for the first time in 1967 by Shealy, showed a great efficiency and safety in the treatment of the especially neuropathic chronic pain and in other processes, as the ischemic cardiopathy. However, it is not a technique free of possible complications (headache, infection, bruises, hygroma, opening of the surgical wound and displacement or breakage of the electrode).

In conclusion, we believe that the presentation of this case opens an innovative possibility in the therapeutic approach of the serious neuropathic pain in the diabetic patients.

Declaration of potential conflict of interests
V.L. Villanueva Pérez, M. V. Silva Cedeño, L. Vaquer Quiles and J. A. de Andrés Ibáñez state that there are no conflicts of interests as regards to the content of this article.

References
Insulin therapy in type 2 diabetes mellitus

Insulinoterapia en la diabetes mellitus tipo 2

Case report discussed by experts

Male aged 58, with T2D of 14 years of evolution, who showed an HbA1c of 8.2% in the last analytic, he was also controlled with levels that did not exceed 7.5% and does not know what changed, as there have not been recent incidences in his life.

Personal history
Diagnosed of glaucoma, hyperuricemia, mixed hyperlipidemia and diffuse proliferative glomerulonephritis with arteriolar hyalinosis, proteinuria and arterial hypertension since 1993. He underwent a treatment with metformin 2550 mg/day and repaglinide 3 mg, distributed in three daily intakes, night NPH insulin in doses of 14 IU, simvastatin and ezetimibe in doses of 10 mg/day, irbestartan 300 mg/day and acetylsalicylic acid 100 mg/day.

Data corresponding to the last revision
Weight 85 kg, height 174 cm; arterial pressure 143/92 mmHg, abdominal waist 98 cm. No vascular peripheral disorder can be observed nor signs of peripheral neuropathy. In the differed analytic appear the following results: creatinine 1.1 mg/day, basal glycemia 184 mg/dL, glycosylated hemoglobin 8.2%, uric acid 7.4 mg/dL, total cholesterol 229 mg/dL, triglycerides 167 mg/dL, cholesterol bond to high density lipoproteins 37 mg/dL and proteinuria 2.8 g/24 h. There is no other pathologic biochemical datum. As regards to the outpatient control, he carries out a glycemic profile of 4 points per week and a measuring of the AP.

Which modifications would you do to this patient’s hypoglycemiant treatment?
We find ourselves in front of a patient with multiple cardiovascular risk factors. One of them is the T2D, of long evolution, that at present is inadequately controlled due to non-evident reasons, in principle.

We speak about inadequate control as the recommendations of the American Diabetes Association and of the European Association for the Study of Diabetes (ADA-EASD) updated in 2009 are to achieve values of glycosylated hemoglobin (HbA1c) lower than 7% and for this the pre-prandial capillary glycemias shall be kept between 70 and 130 mg/dL, while the postprandial glycemias shall not exceed 180 mg/dL.

List of acronyms quoted in the text:
ABPM: ambulatory blood pressure monitoring; ADA: American Diabetes Association; AP: arterial pressure; BMI: body mass index; cLDL: cholesterol bond to low-density lipoproteins; EASD: European Association for the Study of Diabetes; HbA1c: glycosylated hemoglobin; NPH: neutral protamine Hagedorn insulin.
In this case we do not know the importance of the relative contribution of the pre/postprandial glucose to the HbA1c value, as the patient’s glycemia profiles results are not available. If we based ourselves on the assessments of the fasting glycemia relative contribution and the postprandial glycemia of the HbA1c of Monier et al. in this case for a HbA1c of 8.2 mg/dL, both would range the 50% of relevance, therefore we should treat both the fasting glycemia and the postprandial glycemia with the same effort. Before undertaking any modification to the treatment, it would be convenient to count with several glycemia profiles, with previous values and 2 hours after the three main meals of the day. Basing ourselves on the recommendations of the ADA-EASD consensus, the first modification of the patient’s treatment would be in increasing the doses of the used drugs. We would adjust the night neutral protamine Hagedorn insulin (NPH) increasing it up to 18 IU, with the aim of improving the basal glycemia. We would increase the doses in 2 IU each three days until achieving values of basal glycemia <130 mg/dL. In case of night hypoglycemias, we would assess to replace the NPH insulin for a slow insulin analogue, as the glargine or the detemir.

For the adjustment of postprandial glycemias, we can intensify our treatment of secretagogues doubling the dose of repaglinide previous to the meals that need it, basing ourselves in the patient’s glycemia profiles. In case of not achieving the control targets with these measures, we would have the option to add a third drug by oral route. At present, we could choose the gliptones, as the use of the gliptines (sitagliptine, vildagliptine) in combination with insulin has not been approved yet.

As alternative, or considering the failure of this therapy, we should intensify the insulin treatment. After assessing the patient’s glycemia before lunch, before dinner or when going to bed, a second dose could be added, starting with 4 IU and adjusting 2 IU each 3 days. Should the glycemia before lunch exceed the 150 mg/dL, we would add fast insulin before breakfast. Should the glycemia before dinner exceed the 150 mg/dL, we would add NPH insulin before breakfast or fast insulin before lunch. Should the glycemia before going to bed exceed 150 mg/dL, we would add fast insulin before dinner.

Would you do any change to the treatment of the rest of the cardiovascular risk factors, as the hypertension, the lipids and the uric acid?

The treatment for any patient shall be considered in a comprehensive manner. If our aim is to prevent the morbidity and increase the survival, all the cardiovascular risk factors should be treated as a whole. In this case, there is not only an inadequate control of the glycemia values, but the lipid, arterial pressure (AP) and weight are out of our objectives.

After the evidences showed in studies as the HPS, ASCOT-LLA or CARDS, it is clear the importance of controlling the lipids in the diabetic patient. Our control objective is to achieve a cholesterol bound to low density lipoproteins (cLDL) <100 mg/dL.

Given that this patient has cLDL of 158.6 mg/dL, we would need to pass to atorvastatin 40 mg to achieve a reduction, because if we consider the reduction of 6% doubling the dose of simvastatin, we would reach a cLDL between 134 and 140 mg/dL when achieving the dose limit of this statin.

In the case of the AP control, both the HOT and the UKPDS study showed that an intensive treatment is associated to a lower incidence of cardiovascular complications in the diabetic patients. There is consensus considering that the diabetic patients with hypertension have to keep the AP values below 130/80 mmHg and these values have to be reduced a bit more in patients with nephropathy, as long as they tolerate it. In this case, I consider that the best option might be to add a blocker of the calcium channels. Though the use of a diuretic is also a good option, I would rule it out at first due to the possible increase of the hyperuricemia.

The increase of the uric acid of the patient might be considered mild and asymptomatic, in possible relation with the treatment in low doses of acetylsalicylic acid. I would only intervene advising a protein restriction to 0.8 g/kg of weight/day, as this would improve the value of the uric acid in blood, which is also necessary to improve the renal function of our patient.

The patient’s weight, that shows a body mass index of 28.1, is in the overweight range, therefore he needs a re-
duction of at least 10% of his body weight. In order to achieve this, I would try to introduce a customized balanced diet, together with an increase of regular aerobic exercise that the patient undergoes.

**Which is the number of glycemic and pressure controls you consider appropriate for the patient to undergo?**

Following the recommendations of the ADA-EASD consensus and the International Diabetes Foundation, it is accepted that the self-monitoring of the blood glucose is useful in patients with T2D under insulin treatment. In the case of our patient, and since he is undergoing the dosage change of insulin and the intensification of the oral antidiabetic doses, until achieving the fixed objectives, I would perform a complete profile of six controls each 3 days, and once the glycemia targets are reached, a weekly complete profile.

As regards to the AP control of the patient, I believe it convenient not to give up the weekly control that he was doing, though the recommendations are not so exhaustive, a control during the follow-up visits would be enough. In this case, I consider it convenient to perform an outpatient control of the arterial pressure, in order to rule out the presence of a *non-dipper* pattern, which is more frequent in diabetic hypertensive patients and in hypotensive patients with renal disorder, as the patient herein described. This pattern, besides its prognosis involvement, entails the possibility of customizing the optimal moment of treatment administration in order to restate the physiological circadian profile as much as possible.

**Would you do any complementary test?**

Within the evaluation protocol of the diabetic patient, it is recommended to perform a diabetic retinopathy screening; therefore a funduscopy with pupillary dilatation should be done once a year, or at least each 2-3 years if one or more examinations are normal. Should it be necessary, this can be done more frequently.

An electrocardiogram should be performed in order to rule out any asymptomatic heart disease. It is necessary to perform a thorough examination of the foot of every patient with diabetes, which should include the use of monofilament, turning fork, palpation and visual examination.

**Declaration of potential conflict of interest**

C. Casanova states that there is no conflict of interests as regards to the content of this manuscript.

**References**


Which modifications would you do to this patient’s hypoglycemic treatment?

The patient shows T2D of long evolution, with a recent inadequate control. At present, he receives treatment with metformin in maximum doses, fast acting secretagogues in each meal and night intermediate action insulin in low doses. It is necessary to intensify the current treatment, and for this it would be convenient to undertake self-controls of capillary glycemia in order to obtain information about the glycemic levels during the day (before and 2 h after the meals gradually and on different days). In Guerci et al. study, the group of patients who underwent self-monitoring of the capillary glycemia (six weekly controls on 3 different days, included the pre/postprandial) had a mean glycosylated hemoglobin (HbA₁c) relevantly lower after 5 months as regards to the conventional group.¹

Since the HbA₁c values of our patient, high pre-prandial glycemias can be suspected. In case of fasting hyperglycemias, the NPH insulin should be increased (neutral protamine Hagedorn) 2 IU each 3 days, in order to achieve an optimal glycemic control. On the contrary, if there is a hyperglycemia before dinner, the replacement of NPH insulin should be chosen for 2 doses of premixed insulin during breakfast and dinner (leaving the repaglinide only for lunch), or replace it for a dose of basal insulin (glargine or detemir, 1-2 doses). According to the consensus algorithm of ADA-EASD (American Diabetes Association and European Association for the Study of Diabetes),² it would be added in this case a second dose of NPH at breakfast, though this could increase the hypoglycemia risk with another injection without control of the postprandial glycemias. Both the Treat-to-Target ³ and the Hermansen et al.⁴ confirm a lower incidence of hypoglycemia without differences in the glycemic control with the insulin glargine and detemir, respectively, compared to NPH. Moreover, in this last study a lower weight gain was found with insulin detemir, without differences in the glycemic control. The LANMET study showed also a lower incidence of hypoglycemies with glargine insulin compared to NPH in diabetic patients treated with metformin previously.⁵

In case of using a dose of insulin detemir at night with an adequate control of the fasting glycemia and high pre-prandial glycemias at dinner and/or lunch, a second dose of insulin detemir should be added at breakfast. Both analogues of basal insulin, glargine and detemir, have been compared in a trial performed by Rosenstock et al., who considered that these analogues share a comparable efficiency in the glycemic control (with detemir especially in two injections daily) and that the weight gain is lower with detemir (especially with a daily injection).⁶

If hypoglycemies occur at dawn, the dose of 4 IU NPH insulin could be reduced or a 10% of the dose or change the NPH insulin for glargine or detemir. If the pre-prandial glycemias are controlled and the HbA₁c is ≥7%, the postprandial glycemias could be determined. If they are high, the dose of repaglinide should be increased to a maximum of 4 mg in each meal. In case of no adequate postprandial glycemias are achieved, the repaglinide should be replaced for prandial insulin, preferably analogues of fast insulin (lispro, aspart or glulisine) as part of the basal bolus therapy at breakfast and dinner and, if necessary, analogues of fast insulin at lunch.

Studies have been published that compare the effectiveness on the metabolic control among the analogues of basal insulin and the analogues of biphasic insulin, with different results. In the Holman et al. trial, a better glycemic control was achieved with two injections of bipha-
sic insulin aspart 70/30 and with three doses of prandial insulin (aspart) than with detemir, though the incidence of hypoglycemies and the weight gain were higher. Raskin et al. have also proved a higher effectiveness of the biphasic insulin aspart 70/30 compared to insulin glargine on the reduction of the HbA1c below the control objectives (6.5 and 7%) in patients previously treated with metformin alone or in combination with other drugs and the weight gain and the incidence of hypoglycemies were much higher with premixed insulin. Likewise, the study Robbins et al. obtained similar results comparing two treatment groups, one with biphasic insulin lispro 50/50 and the other with insulin glargine, combined both with metformin, thus the mean HbA1c, the pre-prandial glycemia (except for the fasting glycemia) and the postprandial glycemic were lower in the first treatment group. Malone et al. have also detected a better post-prandial glycemic control (at breakfast and dinner), a lower HbA1c and a discrete increase of the hypoglycemia’s (not at night) in the biphasic lispro 25/75 group, compared to the glargine group, both with metformin. However, in the trial of Janka et al. it was more effective to add insulin glargine in inadequate controlled patients, treated with glimepiride and metformin, than replacing the oral antidiabetics for human premixed insulin 30/70, and the incidence of hypoglycemia was lower in the basal insulinization group. Finally, the basal or premixed insulin dose should be adjusted increasing 2 units each 3 days in order to achieve optimal pre-prandial glycemia without hypoglycemia risk. The metformin should be kept if the patient shows a better tolerance, as this would avoid a ponderal gain increase with the intensification of the insulin therapy. Moreover, the insulin requirements would be lower without an increase of the hypoglycemia incidence. These adjustments would be done each 3 months according to the self-controls and the HbA1c; this is an intensification indicator of the hypoglycemi- ant therapy if it is ≥7%. The benefit on the cardiovascular results of the improvement in the glycemic control of the diabetic patient has not been ratified in the studies ADVANCE, ACCORD and VADT. However, finally the study UKPDS concluded stating the positive effect that causes the intensification of the treatment, either with insulin or with oral antidiabetics (sulphonylureas and metformin), on the cardiovascular events and on mortality.

**Would you do any change to the treatment of the rest of the cardiovascular risk factors, as the hypertension, the lipids and the uric acid?**

The Steno-2 study shows an important benefit of the intensive treatment of the diabetes mellitus, the hypertension and the dyslipidemia on the macro vascular and micro vascular events, through changes in the lifestyle and the pharmacological treatment. Our patient shows, besides diabetes mellitus, an inadequate controlled arterial hypertension, a slightly increased total cholesterol, lower levels of cholesterol bound to high density lipoproteins (cHDL) (<40 mg/dL) and a discrete asymptomatic hyperuricemia, so he complies with all the metabolic syndrome criteria of the International Diabetes Federation (IDF) (table 1) and four of the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) criteria (table 2).

The cholesterol bound to low density lipoproteins (cLDL), assessed though the Friedewald formula (cLDL= total cholesterol – [cHDL + triglycerides/5], gives us a value of 158.6 mg/dL, which is higher than the advised reference value (<100 mg/dL) in the patient with diabetes or with cardiovascular disease as stated by the NCEP-ATP III guideline. The HPS (Heart Protection Study) showed that a reduction of 30 mg/dL of the cLDL reduces the cardiovascular risk in 30%, regardless of the basal level of cLDL. The triglyceridemia is lower than the recommended target in the diabetes, lower than 150 mg/dL.

The intensification of the hypolipemiant treatment, addressed to achieve an optimal lipid profile in our patient, should consist to ensure a diet compliance with a scarce intake of cholesterol (<300 mg/day) and increase the dose of simvastatin to reduce the cLDL up to figures lower than 100 mg/dL. Should this not be like this, atorvastatin 40 mg/day could be changed, which achieves a mean reduction of cLDL of almost 50%. Once the cLDL target has been reached, it is quite probable that our patient might reduce the level of triglycerides below 150 mg/dL. In case of keeping a triglyceridermia >177 mg/dL, a fibrate or nicotinic acid should be added to the hypolipemians treatment in order to achieve the optimal objective of non-HDL cholesterol.
The advisable control targets on the arterial pressure of the diabetic patient match with lower values than 130/80 mmHg, according to the ESH-ESC (European Society of Hypertension and European Society of Cardiology) and ESC-EASD of 2007 guidelines. The control of arterial pressure (AP) should be performed in an outpatient form or with measurements at home following the recommendations of the ESH-ESC guidelines. If values similar to the AP are confirmed in our patient, we are in the presence of grade I arterial hypertension. In order to achieve optimal values lower than 130/80 mmHg, a thiazidic diuretic can be added to irbesartan through the irbesartan 300/hydrochlorothiazide 25 mg daily association, following in this way the recommendations of the ESH-ESC once the “white coat” effect has been ruled out (figure 1). For this, it would be convenient to count with self-monitoring determinations of the AP or the ambulatory blood pressure monitoring (ABPM). Moreover, our patient shows a secondary proteinuria to a double etiology nephropathy, both hypertensive and diabetic. Though the albuminuria is not specified, which we suppose high, the treatment of the renin-angiotensin-aldosterone axis after its determination, adding an angiotensin-converting enzyme inhibitors (ACEI) to the angiotensin II receptor antagonists (ARA II) already indicated as complementary treatment should be reinforced, though there is no sufficient evidence on this therapeutic effect.

The hyperuricemia is asymptomatic and discrete, so it is indicated to adopt measures related to the lifestyle. A diet poor in purines (red meats, entrails, seafood, etc.) might reduce the levels of the uric acid in blood below 7 mg/dL, as a mean reduction of the uricemia is achieved.

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**Table 1. Definition of metabolic syndrome according to the IDF \(^{17}\) criteria**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central obesity defined as waist circumference &gt;94 cm for men and &gt;80 cm for Caucasian women, besides two of the following factors:</td>
<td></td>
</tr>
<tr>
<td>• Increase of triglycerides ≥150 mg/dL (1.7 mmol/L), or specific treatment for this lipid impairment</td>
<td></td>
</tr>
<tr>
<td>• Reduction of cHDL ≤40 mg/dL (1.0 mmol/L) in men and ≤50 mg/dL (1.3 mmol/L) in women, or specific treatment for this lipid impairment</td>
<td></td>
</tr>
<tr>
<td>• High AP: systolic AP ≥130 mmHg or diastolic AP ≥85 mmHg, or previous antihypertensive treatment</td>
<td></td>
</tr>
<tr>
<td>• Increase of the plasmatic fasting glucose ≥100 mg/dL (5.6 mmol/L) or previously diagnosed T2D</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Definition of metabolic syndrome according to the NCEP-ATP III \(^{18}\) criteria**

At least three of the following conditions have to be complied with:

- Abdominal obesity defined as waist circumference ≥102 cm in men and ≥88 cm in women
- Triglycerides ≥150 mg/dL
- cHDL ≤40 mg/dL in men and ≤50 mg/dL in women
- Arterial pressure ≥130/85 mmHg
- Plasmatic fasting glucose ≥110 mg/dL

The American Diabetes Association recommends lowering the limit of plasmatic fasting glucose to 100 mg/dL.

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**Figure 1. Pharmacological treatment strategies of the arterial hypertension according to the clinical practice guidelines of ESH-ESC (2007)\(^{21}\). AP: arterial pressure; CV: cardiovascular**
between 0.6 and 1.4 mg/dL. Moreover, the alcoholic withdrawal would be recommended.

The patient shows a body mass index of 28, with a central distribution of the adiposity according to his waist circumference. This figure matches with a level II overweight, so he would benefit himself with lifestyle modification measures. The modifications would include a balanced diet with scarce intake of saturated fats and rich in fibers, a Mediterranean diet rich in monounsaturated fatty acids (better for the glycemic control) or a diet with a mild reduction in the proportion of carbohydrates (better for the lipid profile), being the latter the most effective for the ponderal weight. The mild and regular aerobic exercise during 30-60 minutes, 5 days per week, would be beneficial, according to the current recommendations of the ADA.

**Which is the number of glycemic and pressure controls you consider appropriate for the patient to undergo?**

When the diabetes pharmacological treatment includes oral antidiabetics that do not cause hypoglycemia, as metformin, glitazones and analogues of the GLP-1 (glucagon-like peptide-1), the monitoring by means of the self-measurement of the capillary glycemia is not necessary. The intensification of the treatment would depend on the HbA1c in these cases. The frequency of the controls depends on the glycemic control level and on the treatment. When the treatment is based on drugs that show hypoglycemia risk (sulphonylureas, glinides and insulin), the monitoring should be more frequent. In case of variable controls and an inadequate metabolic control (HbA1c ≥7) the frequency shall also be higher. Six weekly controls are advised in these cases at least, distributed on two different days and including pre/postprandial levels of capillary glycemia, as the improvement of the glycemic control is achieved in this way. The monitoring frequency of the AP by the patient depends on the control level and the need of intensifying the treatment. If there is an inadequate control of the AP and the treatment has been started, or has been started with combined therapy, a higher number of determinations is necessary to adjust such intervention. This number of determinations can be from once a week or monthly, up to one or more every day, distributed according to the AP rising pattern of each patient, which can be described by the ABPM. This patient, especially, should perform between one or two determinations weekly, and one on alternate days, until reaching the optimal control of the AP after intensifying the treatment; then the frequency of the controls can be spaced to one each 2-4 weeks.

**Would you do any complementary test? Funduscopy or retinography**

This is patient with T2D of long evolution, with diabetic-hypertensive nephropathy; therefore a diabetic retinopathy has to be ruled out as microangiopathic screening protocol through funduscopy or retinography.

**Urinary and hepatic biochemistry**

The determination of the albuminuria of morning sample shall also be appropriate to characterize the nephropathy better, to support the intensification of the treatment and to allow the monitoring of the treatment efficacy with ACEI/ARA II. The determination of the transaminiasemia shall be appropriate to rule out a hepatic steatosis, as the patient complies to metabolic syndrome criteria.

**Electrocardiogram**

An electrocardiogram should be performed in order to rule out asymptomatic repolarization disorders, as ischemia or silent infarction.

**Arterial Doppler of lower limbs**

Since the absence of peripheral vascular and neuropathic symptomatology, it is not indicated to determine “initially” the ankle/arm index by using the Doppler technique to rule out a peripheral vascular pathology, nor an electromyography of the lower limbs to rule out a diabetic polyneuropathy.

**Declaration of potential conflict of interest**

J.C. Padillo Cuenca states that there is no conflict of interests as regards to the content of this manuscript.

**References**

Case report discussed by experts

Insulin therapy in T2D. C. Casanova García, J.C. Padillo Cuenca

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have recently published (December 2008) a “new” consensus for the pharmacological treatment of T2D. A group of experts of both societies proposed a new algorithm that roused certain controversy and that positions itself clearly stating debatable priorities among the available drugs. The most outstanding contributions of this new document, which its intention is to integrate the new data provided by the studies ACCORD, ADVANCE, VADT and UKPDS-PTM, in follow-up phase open 10 years after the study was communicated, might be summarized in two points:

1. A glycemic control objective is kept under 7% of HbA1c.
2. As regards to the new proposed algorithm, it is insisted in starting the treatment with quality life changes and metformin, and to change early to new therapeutic regimes in the patients who can not achieve the mentioned objectives, especially guidelines with sulphonylureas and insulin. Moreover, it states clearly the exclusion of the rosiglitazone and, however, it places the use of pioglitazone in a second therapeutic level (“less well validated therapies”); an extremely careful posture is adopted as regards to the DPP-4 inhibitors (vildagliptin, sitagliptin), seeking protection in the cardiovascular safety lack of knowledge at long term, but the use of exenatide (GLP-1 analogue) is surprisingly prioritized.

The first point, which constitutes the main objective of this consideration, is not excessively controversial, as it is kept within the previous recommendations based on the well-established benefits of reducing the micro and macro-vascular complications (which reduce the quality of life in patients considerably), without trying to go beyond the HbA1c target <7% as other guidelines defend. The data of DCCT (in T1D) and of UKPDS (in T2D) are clear and unquestionable. The new data of ADVANCE also ratify a reduction of renal damage with a reduction of the HbA1c over than 7% though without great achievements in macrovascular events. As the 2008 was a prolific year as regards to the spreading of great studies results (ACCORD, ADVANCE, VADT) that have tried to explain if the intensive control (HbA1c of 6.5% versus standard control of >7%) might reduce the macrovascular complications. The results in this sense, well known at that time, do not reduce the HbA1c excessively as general rule beyond 7%, but admit certain nuances. More than reduction levels of HbA1c, the studies compare different therapeutic strategies among ones and other studies, though the set out HbA1c objective is achieved. Moreover, the general patients evaluated had a very advanced disease.

There is a clear suggestion of benefit in diabetic patients of relative short evolution, of lower risk and/or without
determined cardiovascular disease. On the contrary, it has been noted to the serious hypoglycemia as possible and valid neutralizing cause of the benefit, especially in patients with determined cardiovascular disease.\textsuperscript{9,11} The follow-up data in open phase of the UKPDS study suggest that the macrovascular benefit, the clinic events and the cardiovascular mortality seem to require more time of glycemic control in order to show its beneficial effects. Possibly, the most preventive role of the strict glycemic control is achieved before the clinical cardiovascular disease is developed.\textsuperscript{12}

In view of the above, once more, and as it happens in other fields of the cardiovascular therapeutics, it is a need to individualize the patients, treatment, having to consider the existence of hypoglycemia history and/or risk of showing them as fundamental factors, as well as the years of the evolution of the diabetes and the presence of determined vascular disease. Many patients with a more benign or early profile of the disease might take benefit of a more intensive control, especially the younger patients, without a determined disease and with low risk of hypoglycemia. On the contrary, it is valid that in older patients with determined disease (often advanced atherosclerosis) and who show a greater tendency to serious hypoglycemias with higher lesion risk, the intensive control (HbA\textsubscript{1C} of 6.5\% or less) implies more risks than benefits.\textsuperscript{8,10,11} In any case, the current controversy should not be extrapolated to the patients with an inadequate glycemic control (>8\%), which is the real setting in the usual clinical practice in our environment,\textsuperscript{13} and even in sites of excellence,\textsuperscript{14} as it might be perverse to lead to a greater therapeutic nihilism/inertia and to give up the achievement of glycemic objectives within an integrator approach of the disease.

As regards to the second point object of this comment—the new proposal of algorithm—admits a higher level of controversy and especially it has to be object of a reasoned criticism. First, it is more arguable to provide a new concrete algorithm (displacing the one spread during the last year, with several options in a second step after the metformin);\textsuperscript{15} when there are scarce evidences in results “body to body” among different drugs and even among different therapeutic strategies, at least as regards to the “hard” targets of clinical events or cardiovascular mortality. Secondly, the proposed strategy after metformin in the first step does not seem to take into account the capital importance of minimizing hypoglycemias, the higher value of the DPP4 inhibitors and the worse adverse effect of the sulphonylureas, not even the convenience of avoiding the weight increase, the constant adverse effect of the glitazones, the sulphonylureas and insulin, when all of them are elements that have to be present when determining a therapeutic strategy. In this sense, it cannot be clearly stated why the pioglitazone can be in a second therapeutic step (“Less well validated therapies”) if it has known adverse effects (bone fractures),\textsuperscript{16} or because it can be especially prioritized as regards to other therapeutic groups. Likewise, neither the frequent digestive effects nor the necessary parenteral administration of the GLP-1, introduced in the United States in 2005 and recently in our environment, seem to be object of unfavorable consideration in spite of the doubtful tolerability and difficulty of acceptance of this treatment modality in our environment.

Therefore, the criteria that have led to this new therapeutic algorithm proposed for the treatment of the patient with T2D by a group of experts deserve an open discussion. As the authors state, the therapeutic individualization has always to prevail. The proposal presents, probably, a certain load of subjectivity and a focused view in the economic considerations and in the clinical experience obtained with some hypoglycemic drugs on the other side of the Atlantic Ocean.

**Declaration of potential conflict of interests**

P. Conthe stated that there are no conflicts of interest as regards to the content of this article.

**References**


Comment
Male aged 58, with metabolic syndrome history, as well as level 2 obesity of abdominal predominance (BMI 37 kg/cm², abdominal circumference 101 cm), arterial hypertension, mixed dyslipidemia and T2D of more than 10 years of evolution, under combined treatment with premixed insulin aspart/aspart protamine 30/70 (0.69 IU/kg/day distributed in 2 doses) and oral agents (vildagliptine-metformin, 500/1.000 mg, 2 tablets per day). The metabolic control was usually inadequate (HbA1c of 10.5%) due to the lack of diet compliance. As known micro vascular complications of his diabetes, he showed diabetic nephropathy, non-proliferative retinopathy and erectile dysfunction, which have been treated finally with the implant of a penile prosthesis. As concomitant diseases, he showed a Barrett’s esophagus secondary to gastroesophageal reflux disease (GERD) and a sleep apnea-hypopnea syndrome (SAHS) under CPAP night treatment.

Clinically, the patient referred a progressive edematization of foot and left ankle of 6 months of evolution, with pain, dysesthesias like tingling with numbness and paresthesia of night predominance. He had no fever, or general condition affection. He did not refer previous traumatic lesions in the foot, or apparent tetanus as injuries or excoriations. He did not show either previous clinic of intermittent lameness or other symptomatology. In the clinical exploration, a hard edema could be observed in the foot and left ankle, up to the third part of the leg, with erythema and a discrete increase of local temperature, associated to a great deformity with loss of arch of the foot. He showed interdigital and bilateral nail mycosis, without any other lesions. The proprioceptive sensitivity explored with monofilament and calibrated tuning fork was clearly reduced bilaterally, with distribution “in sock”, though it was more intense in the left lower limb. Moreover, a reduction of the kneecap osteotendinous reflex and Achilles heel in both legs could be observed. The peripheral pulses, back extensor digitorum brevis and tibial posterior muscles were palpable in the right foot, but were reduced in the left foot. The right ankle-arm index was normal (1.1) and it was not able to explore in the left lower limb due to the presence of edematization. The indicative biological parameters of inflammation were within normality (leukocytes 7.2 × 10³/µL with normal formula; hemoglobin 12.2 mg/dL; platelets 202 × 10³/µL, C-reactive protein 4.9 mg/dL; fibrinogen 4.1 mg/dL, ferritin 49 mg/dL).

In the x-ray of the left foot (figure 1), it could be stated the destruction of the joints between the wedges and the basis of the metatarsians, together with impairments in the head of the second and third metatarsians; findings that are compatible with the Charcot arthropathy, with predominance in the Lisfranc joint. Taking in account the symptomatology persistence, it was decided to perform a magnetic resonance imaging (MRI) of the foot in order to proceed with the differential diagnosis with osteomyelitis, notwithstanding that the clinical and biological data were not indicative of an infectious process.

The MRI showed a collapse of the foot vault with desestructuration of the mesofoot, inflammatory
changes with bone edema in the back foot and meso-foot bones and affection of the soft parts, compatible with the presence of osteomyelitis (figure 2). Considering the acute osteomyelitis diagnosis in diabetic foot, intravenous combined antibiotherapy was started with ciprofloxacin and clindamycin, together with foot discharge. The patient showed a favorable evolution with reduction of pain at rest and progressive reduction of the external inflammatory signs. After 3 months of treatment, the patient is asymptomatic, though a deformity in the back part of the foot still persists and certain difficulty for the flexo-extension of the ankle.

Figure 1. Simple x-ray of left foot

Figure 2. Uppermost part: sagittal T1 sequence of the foot for the anatomic assessment of its structures. Lower part: sagittal STIR sequence in the same level than the previous one, which allows assessing the presence of inflammatory changes, as cellulitis, myositis and bone edema.