Case report discussed by experts

Insulin therapy in type 2 diabetes mellitus

Insulinoterapia en la diabetes mellitus tipo 2

M ale 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, irbesartan 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.

Anamnesis

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 2009⁴ 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.\(^2\) 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 glitazones, 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,\(^3\) ASCOT-LLA\(^4\) or CARDS,\(^5\) 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\(^6\) and the UKPDS\(^7\) 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 hypoglycemia 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 glycemas 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 glycemas. Both the Treat-to-Target³ and the Hermansen et al.⁴ confirm a lower incidence of hypoglycemia without differences in the glycemic control with the insulin glargine and detemir, respec-tively, 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 glycemas 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 glycemas are controlled and the HbA₁c is ≥7%, the postprandial glycemas 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 glycemas 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-

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List of acronyms quoted in the text:
ABPM: ambulatory blood pressure monitoring; ACEI: angiotensin-converting enzyme inhibitors; ADA: American Diabetes Association; AP: arterial pressure; ARA II: angiotensin II receptor antagonists; cHDL: cholesterol bond to high density lipoproteins, cLDL: cholesterol bond to low density lipoproteins; EASD: European Association for the Study of Diabetes; ESC: European Society of Cardiology; ESH: European Society of Hypertension; GLP-1: glucagon-like peptide 1; HbA₁c: glycosylated hemoglobin; IDF: International Diabetes Federation; NCEP-ATP III: National Cholesterol Education Program-Adult Treatment Panel III; NPH: neutral protamine Hagedorn insulin.

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Case report discussed by experts
Insulin therapy in T2D. C. Casanova García, J.C. Padillo Cuenca

Answer of Dr. José Carlos Padillo Cuenca

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sic insulin aspart 70/30 and with three doses of prandial insulin (aspart) than with detemir, though the incidence of hypoglycemias 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 hypoglycemias 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 glycemia 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 hypoglycemia-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 hypolipemiants 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 triglyceridemia >177 mg/dL., a fibrate or nicotinic acid should be added to the hypolipemiants 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.

**Table 1. Definition of metabolic syndrome according to the IDF criteria**

Central obesity defined as waist circumference >94 cm for men and >80 for Caucasian women (with specific values for other ethnic groups), besides two of the following factors:
- Increase of triglycerides ≥150 mg/dL (1.7 mmol/L), or specific treatment for this lipid impairment
- 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
- High AP: systolic AP ≥130 mmHg or diastolic AP ≥85 mmHg, or previous antihypertensive treatment
- Increase of the plasmatic fasting glucose ≥100 mg/dL (5.6 mmol/L) or previously diagnosed T2D

**Table 2. Definition of metabolic syndrome according to the NCEP-ATO III 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.

**Figure 1. Pharmacological treatment strategies of the arterial hypertension according to the clinical practice guidelines of ESH-ESC (2007)**. 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 transaminasemia 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**

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