Introduction
The treatment of the blood pressure (BP) in diabetic patients has a great relevance due to the high cardiovascular risk (CVR) that they present and to the early develop-
to suffer cardiovascular diseases. These diseases comprise ictus, myocardial infarction and peripheral arteriopathy. Moreover, it has been proved that both entities are closely related, as the hypertensive patients have the double of risk of showing some degree of intolerance to the glucose than the non-diabetic patients. At the same time, the persons with T2D show BHT more frequently than the rest of the population.

From what has been exposed in the previous paragraph it can be supposed that the possibilities that the diabetic patients show cardiovascular events might be limited if we insist definitely in the associated risk factors. In this article, we will investigate the best way to treat the BHT in the population with T2D according to the objectives established by the competent authorities. At the same time, we will develop an algorithm that will facilitate the choice of the most adequate drugs in each case. The interest in this clinical situation should be a priority, considering the scarce data obtained as regards to the early diagnosis and the intensive treatment of the BHT in the T2D, according to the values from several studies performed in Spain. A wide population with moderate-high CVR does not receive an optimized treatment in spite of the available resources. This stresses the importance of an adequate BP control in patients with T2D. We will deepen into this subject along these lines.

**Etiopathogenic relation between BHT and T2D**

The genetic predisposition to suffer BHT and T2D jointly has been described on a polygenic heritance basis, but a concrete alteration and clearly contributing factor has not been stated, unlike what happens with more rare causes of BHT. Several mechanisms have been proposed that both conditions interrelate:

- Expansion of intravascular volume by insulin stimulus on the reabsorption of sodium in the renal proximal tubules.
- Alterations on the vasodilatation by the increase of the vascular walls rigidity, which is manifested by an anomalous response to the local nitric oxide administration. It has been placed in the context of the protein glycosylation of the vascular matrix.
- Over-stimulation of the renin-angiotensin-aldosterone axis with an increase of the insulin resistance and the reabsorption of sodium and water.
- Activation of the sympathetic nervous system and higher resulting insulin resistance.
- Increase of intracellular calcium.
- Reabsorption of the filtered glucose excess.

As it is evident, the mechanisms of the production of BHT in this population are multiple, what makes the BP values control complicated and requires more than one drug in several occasions. Usually, to act on only one factor will be insufficient, and we should resort to combinations that might block the different etiopathogenic processes.

**Diagnosis of BHT**

The establishment of a definite diagnosis of BHT shall be based in the information obtained in different BP mechanisms, and shall be performed during each patient’s visit. In order to confirm the diagnosis, the abnormally high values of the BP have to be determined during at least two different occasions, separated in a month between them as minimum. The technique of BP self-determination shall be correct, with the patient at rest during 5 minutes, placing the pressure cuff near the heart, and having taken the indicated hypertensive medication, if this is the case. Moreover, it is useful to perform measurements in sedation, decubitus and bipedestation if a possible disautonomy is suspected.

In certain occasions, it will be difficult to rule out the “white coat BHT” and determine a diagnosis with certainty if we count exclusively with the values obtained in the specialized care consultation. We might use the information that the self-measurement provides us as regards to the blood pressure and, even, to the outpatient blood pressure monitoring.

**Peculiarities of the BHT in T2D**

The BHT of the diabetic patients has some differential characteristics regarding to the non-diabetic hypertensive population. It is usual to find higher BP values in diabetic patients up to 70 years of age, in the context of the early arteriosclerosis that these patients suffer. These differences tend to disappear in more advanced ages. Another characteristic factor is the higher difference between the systolic BP and the diastolic BP, known as pulse pressure. This phenomenon increases with the age and is associated to a higher CVR than the simultaneous
increase of both values. It is also frequent to find an isolated systolic BHT, caused by the excessive rigidity of the arteries that hinders from expanding in response to the ventricular ejection. It is considered an independent risk factor by cardiovascular death, hypertrophy of left ventricle and microalbuminuria. It can be observed the pattern known as dipper, with a scarce or null reduction of BP during the night (reduction under 10% as regards to the day values).

Whatever has been mentioned previously only ratifies the high CVR of these patients, what makes the BP control a key factor to prevent the onset of complications both macrovascular and microvascular. In fact, it has been determined that the relation risk / benefit is more favorable for the pressure control than for the glycemic control.

Treatment algorithm of BHT in T2D (figure 1)

Blood pressure objectives
Considering the results obtained in several clinical studies, the international organisms have established the value of 130/80 mmHg as objective for diabetic patients. Lower BP objectives have been studied as well, as a diastolic BP lower than 60 mmHg, without demonstration of relevant benefits in the reduction of CVR. In another section of this seminar the BP objectives will be dealt with in depth in several clinical situations.

It has to be pointed out the proved fact that the cardiovascular benefit is only obtained while the BP values are maintained under the mentioned limits. In the diabetic population, unlike it happens with the glycemic control, there is no “bequeathed effect” when the strict pressure control is abandoned. Therefore, the follow-up of the BP should not be overlooked and it should be a constant practice in the follow-up of the patient with T2D and BHT.

Non-pharmacological treatment
The change of lifestyle is accepted as initial therapy before starting a treatment with drugs in diabetic patients with BP up to 139/89 mmHg if there are no other associated CVR factors, microalbuminuria or lesion of target organs. During three months, the patient shall modify the lifestyle in order to: a) reduce his weight, as obesity usually occurs in the same clinical context than the BHT and the T2D, b) improve the lipid profile that is characterized by cholesterol particles bond to low density lipoproteins more atherogenic, low values of cholesterol bound to high density lipoproteins and high triglycerides, and c) increase the insulin sensitivity. It is recommended to perform moderate-intense physical exercise almost every day of the week, though with certain precaution in patients with ischemic cardiopathy suspicion, to whom a previous ergometry shall be performed before starting the exercise. Of course, the patients should be encouraged to abandon the tobacco habit, which is a CVR known factor. The consumption of salt plays a relevant role in this group of patients, due to the already mentioned increase of the renal absorption of sodium and the intravascular volume that is produced in the T2D. The reduction of the salt intake is more useful in these patients than in the population in general, especially in elder patients who show a higher sensitivity to the volume expansion.

Pharmacological treatment
At present, we count with a wide range of antihypertensive drugs based on different action mechanisms that might be useful in diabetic patients with BHT.
The renin-angiotensin-aldosterone system blockers (RAASB) are considered as first choice, which comprise the angiotensin-converting enzyme inhibitors (ACEI) and the angiotensin II receptor antagonists type I (ARA II). It has previously been mentioned about the hyperactivity of this axis in the group of hypertensive diabetic patients, being the inhibition under study during the last years. These drugs have proved to be able to achieve an adequate BHT control, but they have a relevant renal protection effect in T2D than any other pharmacological group, taking into account that they revert the microalbuminuria, stop the progression of the microalbuminuria and prevent the progression of the renal disorder.

Moreover, in some studies its use has been associated to a lower incidence of DM in prediabetic subjects and to a lower rate of ischemic cardiopathy and heart disorder in the diabetic population. The most frequent side effect of the ACEI is the dry cough, as consequence of the bradicin in accumulation. A follow-up should be performed on the renal function in order to rule out its worsening or the onset of hyperpotassemia, especially in patients with previous nephropathy and bilateral stenosis of the renal artery or unilateral in monorenals.

When the pressure control is not sufficient by means of the RAASB, the association of drugs that insist in the volume expansion has to be considered. The thiazides play an important role here, as the hydrochlorothiazide in low doses, of 6.25-12.5 mg. These drugs are considered as effective as the ACEI or the calcium antagonists to reduce the CVR. The reduction in the incidence of heart disorder in patients who receive this medication has been considered as an added benefit. In case of advanced renal failure, loop diuretics should be used as the thiazides loose their efficacy. The most usual adverse effect is the hypopotassemia that might compensate the effect on the potassium of the ACEI or ARA II when used concomitantly. On the other hand, some data indicate that these drugs favor the inset of T2D as regards to other treatments, which has to be assessed in each clinical context.

The commercialized drug within the RAASB is the aliskiren, which the renal protector effect in diabetic patients seems to go beyond the mere reduction of the pressure values and is additive to the ACEI.

There are two groups within the calcium antagonists: the dihydropyridine (DHP) and the non dihydropyridine (non-DHP). The first ones have a predominant peripheral vasodilatation effect while the second ones are mainly cronotropes and negative inotropes. At first a renal protector effect has been described for the non-DHP group but the recent commercialization of DHP of new generation DHP have demonstrated to have a higher clinical efficiency with lower onset of edemas, its most frequent adverse effect. As they lack of a negative metabolic profile, taking into account its antihypertensive potential, the calcium antagonists are an important group for the treatment of the BHT.

The beta blockers have a good antihypertensive effect and the experience in its handling is wide. They can be cardioselective or not, which has raised a certain interest.
as regards to the disappearance of adrenergic symptoms during the hypoglycemia. It is a relevant datum in the diabetic patients, especially in those who receive insulin therapy. They are associated to a negative metabolic profile taking into account the increase of the triglycerides and early evolution of T2D. However, they are a first option in the ischemic cardiopathy and improve the clinical evolution of heart failure.  

The alpha-blockers are another group of antihypertensive drugs to resort to. In spite of the hypotensor effect, they have certain side effects. One of them is the “phenomenon of the first administration”, a sudden reduction of the BP that takes place at the beginning of the therapy, therefore they should be administered preferably before the patient goes to sleep. Most worrying is the higher incidence of heart failure described in some studies, which limited its use. They are a good resource in patients who show prostatic hypertrophy.

In a last stage we can consider the antihypertensive drugs of central action, as clonidine or hidralazine. They might play a role in diabetic patients with BHT of difficult control and on which the antihypertensive drugs of other pharmacological groups have failed.  

In not a few occasions we would need to use combinations to control the BHT in T2D. They can be indicated initially when the values of BP are over the objective and it will be usual to resort to them at some moment of the evolution of the disease. Combinations of fixed doses of several antihypertensive drugs have been commercialized, as ACEI or ARA II with thiazides or calcium antagonists, which increase their antihypertensive strength, and at the same time reduce the incidence of side effects. The numbers of patients who show edemas and ionic disorders have been reduced and the clinical efficiency is preserved.

Conclusions

The treatment of the BHT in patients with T2D is a key factor but complicated and in most of the occasions this treatment will need several drugs to achieve the determined BP. We can start the treatment with only one drug
Practical considerations

- El tratamiento de la presión arterial en pacientes con T2D tiene una gran importancia ya que el alto riesgo cardiovascular es el objetivo de mantener valores de <130/80 mmHg.
- El sistema renina-angiotensina-aldosterona bloqueadores beta son considerados como la primera opción que comprome el sistema angiotensina-conversor-enzima inhibidores (ACEI) y los bloqueadores alfa de tipo 1 (ARA II).

Sin embargo, la adición de otros fármacos debe considerarse si el control es insuficiente en una mono-terapia (diuréticos, calcio antagonistas, bloqueadores, alfa-blockers, aliskiren), según el perfil del paciente.

Declaración de conflicto de intereses

P. Pedriñeres y P.L. de Pablos afirman que no hay conflicto de intereses en este artículo.

Referencias