Diabetes mellitus and cardiovascular risk

Recommendations of the Working Group of Diabetes Mellitus and Cardiovascular Disease of the Spanish Diabetes Society, 2009

Diabetes mellitus y riesgo cardiovascular. Recomendaciones del Grupo de Trabajo Diabetes Mellitus y Enfermedad Cardiovascular de la Sociedad Española de Diabetes, 2009

Cardiovascular risk

The subjects with diabetes have a risk of developing cardiovascular disease 2-4 times higher than the one observed in the general population of similar age and sex, risk that is kept after adjusting for other classic cardiovascular risk factors. In this sense, the cardiovascular complications attributable to the atherosclerosis are responsible of the 70-80% of all the causes of death in diabetic subjects, and represent more than 75% of the total of hospitalizations due to diabetic complications. The characteristics of the atherosclerosis lesions in the diabetic subjects are: faster and earlier development, more generalized and early affection, higher frequency of unstable plaques, similar incidence in both sexes and greater presence of silent ischemia-necrosis or with lower clinical expressiveness. The main clinical manifestations of the atherosclerosis are the ischemic cardiopathy, the cerebrovascular accidents, the obliterative atherosclerosis of the lower limbs, the affection of the renal and aortic arteries. The cardiovascular disease risk and the cardiovascular and global mortality are also increasing in patients with metabolic syndrome and in pre-diabetes situation, ranging this risk between 1.5 and 2 times higher than the general population.

The current clinical evidences and the consensus recommendations support that diabetes, in general, has to be considered a high cardiovascular risk situation, mainly the T2D with other cardiovascular risk factors and most of the diabetic patients after 10 years of diagnosis. Moreover, the diabetes has to be considered of high cardiovascular risk in the following situations: clinical or sub-clinical cardiovascular disease, insulin resistance and metabolic syndrome with 4 or 5 components, presence of multiple factors of risk as dyslipidemia, blood hypertension and nicotine poisoning or the existence of renal failure or albuminuria.

Principal cardiovascular risk factors in diabetes (table 1)

Dyslipidemia

The diabetic dyslipidemia is characterized by the association of hypertriglyceri-
ApoB is superior to cholesterol in order to predict the cardiovascular risk and for the follow-up of the efficacy of the hypolipemiant treatment. The blood hypertension (BHT) in subjects with diabetes is more frequent, with a higher prevalence to 60%. The intervention studies about the hypertension in diabetes have evidenced an important reduction (32-44%) of the cardiovascular morbimortality, both for the coronary manifestations and for the cerebrovascular. The values of systolic blood pressure (BP) ≥130 mmHg or ≥80 mmHg of diastolic pressure are considered risk factors in diabetes. In those subjects with proteinuria or renal failure, the recommended values are still lower: systolic <120 mmHg and diastolic ≤75 mmHg. The reduction of the BP has proved clear benefits in the reduction of the cardiovascular risk and of the diabetic nephropathy. The intensive treatment of the BHT in the diabetes reduces significantly the cardiovascular complications: diabetic complications in 24%, death related to the diabetes in 32%, ictus in 44%, heart failure in 56% and micro vascular complications in a 37%.

The thiazide diuretics, the beta-blockers, the ACEI, the ARA II and the calcium-antagonists are useful to reduce the incidence of cardiovascular disease and of cerebrovascular stroke in diabetic patients. The treatments based on the ACEI or on the ARA II have a favorable influence on the progression of the diabetic nephropathy and reduce the albuminuria. The hyperglycemia, per se, is a risk factor of micro and macro vascular disease. The Hyperglycemia, both in fasting condition and postprandial, is responsible of the lipoprotein modifications that result in a higher atherogenic risk. The glycosylation of the Apo proteins is proportional to the concentration of glucose in plasma; there exists a good correlation between glycaemia and glycosylated LDL. The glycosylated hemoglobin (HbA1c) is a good mortality risk marker in patients with diabetes and a continuous risk marker of cardiovascular disease. There is a direct relation between the reduction of the HbA1c and the incidence and evolution of the vascular complications.
hand, the time of duration of the diabetes, time of chronic exposure to hyperglycemia, is related to the cardiovascular risk, considering a situation of high risk after 10 years of clinical diagnosis of diabetes.

**Metabolic syndrome**

Defined by the ATP-III,¹ the WHO,¹³ the IDF 2005,¹⁴ or the AHA 2005 criteria (table 2), among others, consists of a wide constellation of impairments among which the visceral-abdominal obesity and the association of dysglycemia (glycemia altered in fasting period or after carbohydrate load) are included as well as T2D, dyslipidemia (hypertriglyceridemia, reduction of c-HDL, presence of small and dense LDL, increase of apoB), blood hypertoners, hyperuricemia, microalbuminuria (≥30 μg of albumin/mg of urinary creatinine), chronic inflammation and other alterations (increase of the plasma cysteine, increase of the oxidative stress, non-alcoholic fat liver), turning it into a risk marker for the early cardiovascular disease and especially, in patients with diabetes mellitus.¹⁶

**Hypercoagulability and pro-inflammatory condition**

The diabetes entails a hypercoagulability condition, with an increase of fibrinogen and haptoglobin, among other factors. There have also been described alterations of the platelet function, with an increase of the aggregability and the adhesiveness related to plasmatic factors, as the increase of the thromboxane A₂. Several studies have proved that the administration of low doses of acetylsalicylic acid (ASA) contributes to reduce the cardiovascular events up to 15%, stating that in diabetic patients, especially in those with an associated risk factor, the preventive treatment is adequate and that the benefits exceed the possible treatment risks.¹⁵,¹⁷

The pro-inflammatory condition is related with the insulin-resistance. In studies with big size samples and long follow-up, it has been proved that the plasma C-reactive protein (CRP) is a risk factor for the diabetes, regardless of the obesity;¹⁸ some authors consider that its correction might avoid, with an important percentage, the diabetes development;¹⁹ other authors find this relation especially in women.²⁰

**Cardiovascular risk control in diabetic subjects**

The diabetes should be considered as a major and independent cardiovascular risk factor. Moreover, the high prevalence of other major factor of cardiovascular risk associated to the diabetes increases the risk and cardiovascular mortality. In view of this, the cardiovascular risk control in the diabetes should be tackled globally, as a high or very high-risk situation.

### Prevention and treatment of the insulin-resistance, the metabolic syndrome and the cardiovascular risk

The situation of insulin-resistance (IR) should be suspected in subjects corresponding to risk groups with overweight, and especially, with abdominal obesity, in women with polycystic ovary syndrome or gestational diabetes history, and in any individual with hyperglycemia, hypertriglyceridemia or hypertension. The IR and the MS are frequent and represent an important morbimortality cause due to macrovascular disease; moreover, they are associated to a high risk of T2D. The obesity, the physical inactivity and the diet rich in fats are modifiable factors that develop and worsen the IR and the MS, so the prevention and treatment should be based on the correction of these factors, being necessary to add pharmacological treatment occasionally.²¹ The “Mediterranean diet” (that will be hypocaloric and low in fats with the loss of weight is required) and the aerobic physical exercise have demonstrated to be important factors in the prevention of the diabetes onset and of the cardiovascular complications in subjects with glucose intolerance.²²,²³

### Table 2. Metabolic syndrome diagnosis

<table>
<thead>
<tr>
<th>Diagnosis criteria</th>
<th>NCEP-ATP III</th>
<th>WHO</th>
<th>IDF 2005</th>
<th>AHA 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>Three of the below mentioned criteria</td>
<td>Hypoglycemia or IR (HOMA) plus two below mentioned criteria</td>
<td>Abdominal obesity plus two criteria</td>
<td>Three of the below mentioned criteria</td>
</tr>
<tr>
<td></td>
<td>WP &gt;102 M and &gt;88 F</td>
<td>WHR &gt;0.9 M or 0.85 F or BMI ≥30</td>
<td>Major criterion WP ≥94 M or ≥80 F</td>
<td>WP &gt;102 M and &gt;88 F</td>
</tr>
<tr>
<td>Plasma glucose</td>
<td>≥110 mg/dL</td>
<td>≥110 mg/dL or IR</td>
<td>≥100 mg/dL or previous diagnosis of DM</td>
<td>≥100 mg/dL or hypoglycemicant treatment</td>
</tr>
<tr>
<td>TG plasma</td>
<td>≥150 mg/dL</td>
<td>≥150 mg/dL</td>
<td>≥150 mg/dL with specific treatment</td>
<td>≥150 mg/dL with specific treatment</td>
</tr>
<tr>
<td>c-HDL</td>
<td>&lt;40 mg/dL in M or &lt;50 mg/dL in F</td>
<td>&lt;35 mg/dL in M or &lt;39 mg/dL in F</td>
<td>&lt;40 mg/dL in M or &lt;50 mg/dL in F or in specific treatment</td>
<td>&lt;40 mg/dL in M or &lt;50 mg/dL in F or in specific treatment</td>
</tr>
<tr>
<td>BP</td>
<td>≥140/90 mmHg</td>
<td>≥140/90 mmHg or previous treatment</td>
<td>≥130/85 mmHg or hypotensive treatment</td>
<td>≥130 mmHg or ≥85 mmHg or with hypotensive treatment</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>Not included</td>
<td>Albumin/creatinin &gt;30</td>
<td>Not included</td>
<td>Not included</td>
</tr>
</tbody>
</table>

Treatment of cardiovascular risk associated to the metabolic syndrome and diabetes

Treatment of metabolic syndrome and associated cardiovascular risk factors

It consists of the control and customized treatment of all the components of the MS that will depend on the number of factors and their intensity.

- **Dyslipidemia**
  - Objectives: c-HDL <130 mg/dL or c-NO-HDL, <160 mg/dL.; apoB <100 mg/dL.; c-HDL >40 mg/dL in men and >50 in women and triglycerides <150 m/dL.
  - The treatment consists of hygienic-dietetic measures and adding hypolipemiant drugs when necessary, statins, fibrates, nicotinic acid, ezetimibe and associations.
  - **Blood hypertension and microalbuminuria**
  - There are no specific objectives as regards to the control of the BP in these patients; therefore the objectives of the general population have to be considered.
  - Together with the non-pharmacological measures, the most adequate drugs in the MS are the ACEI and the ARA II, which need to be added to other drugs frequently. The beta-blockers should be avoided (unless specific indication), though the new vasodilator beta-blockers (carvedilol and nebivolol) seem to have less unfavorable metabolic effects. The thiazide diuretics in low doses are not recommended either as first line treatment.

Treatment and prevention of cardiovascular disease in diabetes

It is based on the global, strong and early action on all the cardiovascular risk factors.

- **Glycemic control**
  - The main objective is to keep the HbA1c under 7 and 6.5% in most of the subjects with T2D, as well as in diabetic pregnant patients, as far as these values are achieved without risk of hypoglycemia events.
  - Multiple studies24,25 both on T1D and T2D, have demonstrated that an adequate metabolic control represented by low values of HbA1c cause a relevant improvement in the incidence and evolution of the microangiopathic complications, which is a benefit that lasts during years though it might worsen the metabolic control. In relation to the evolution of the macrovascular complications, however, it does not seem to depend on reaching an acceptable level of HbA1c, but the type of treatment that has been used and the onset or not of hypoglycemic events.
  - Since the close relation that there is among some microangiopathies (mainly the nephropathy) and the CVD, it is logical to consider that an adequate metabolic control might have a positive influence in it, but with a lower intensity than the control of other risk factors as the dyslipidemia and the BHT.
  - The therapeutic strategy, according to the consensus between the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD),26 shall consist in starting the intervention from the diagnosis or as early as possible in order to achieve an adequate metabolic control, starting with the adoption of changes in the lifestyle, with a healthy diet in order to reach an adequate loss of weight in case of weight excess, physical exercise and not to smoke, together with the administration of metformin from the beginning of the intervention. If this is not enough, in a maximum term of 3 months the second stage shall start, that will consist of adding sulphonylurea, basal insulin (long-acting: NPH insulin, glargine or detemir), glitazones or incretin mimetics (exenatide) according to the characteristics of each patient. If no HbA1c control is achieved of <7%, the third stage shall start, consisting in adding a third oral drug (sulphonylurea or glitazone) or if the patient was already with insulin, to intensify its administration with two doses of regular insulin, or multiple doses of long-acting insulin, keeping metformin or glitazone. As regards to the use of other oral drugs of more recent appearance, as the dipeptidyl peptidase-4 inhibitors (sitagliptin, vildagliptin), there is no data concerning to the follow-up at long term to assess more definitively its safety and efficiency, but they have the advantage of an effect on the glycemic control, with or without scarce risk of hypoglycemias.
  - Finally, it has to be reminded that in the diabetes associated to the morbid obesity or to the obesity with a body mass index (BMI) >35 and with risk factors associated, the bariatric surgery might have an interesting role in the treatment of the diabetes and the associated cardiovascular risk.

Dyslipidemia

The primary target is to keep the c-LDL <100 mg/dL or when the triglycerides (TG) are ≥150 mg/dL, the c-NO-HDL <130 mg/dL and the apoB <80 mg/dL.27 The treatment shall be focused in achieving the primary and principal objective. In the cases with very high cardiovascular risk defined by the existence of clinical or sub-clinical cardiovascular disease, nephropathy or association of multiple risk factors, the objective shall be c-LDL <70 mg/dL, or c-NO-HDL <100 mg/dL and apoB<70 mg/dL.
  - If necessary, an inhibitor of the cholesterol intestinal absorption can be associated.
  - The secondary objectives stated by most of the authors and consensus are related to the plasma levels of c-HDL and TG and have a relevant importance in the diabetes characterized by the frequent atherogenic dyslipidemia with reduction of the HDL and an increase in the particles rich in TG and apoB. The target of c-HDL is of >40 mg/dL, though the ideal is >60 mg/dL, which is the level considered as protection factor and related with low risk of disease and cardiovascular mortality for any level of c-LDL,28 and the TG <150 mg/dL. The use of fibrates or nicotinic acid shall be considered when the triglycerides are higher than 200 mg/dL or the c-HDL <40 mg/dL, and will be imperative with TG ≥400 mg/dL. The hypertriglyceridemia have an increase of the
with microalbuminuria or renal failure. we have indicated, if there is nephropathy
Objective: BP <130 mmHg or lower, as
• Arterial hypertension
reduce the rubefaction or the
need of a combined treatment of both hy-
and in cases of elder patients. When to
statin are used or if there is renal failure,
be controlled, especially if high doses of
patic and muscular complications should
brates or nicotinic acid, the possible he-
ovascular risk (table 3).

Table 3. Primary targets in the cardiovascular prevention
in the metabolic syndrome and diabetes mellitus

<table>
<thead>
<tr>
<th>Dyslipidemia</th>
<th>MS</th>
<th>DM</th>
<th>High risk DM*</th>
</tr>
</thead>
<tbody>
<tr>
<td>c-HDL &lt;130 mg/dL</td>
<td>&lt;100 mg/dL</td>
<td>&lt;70 mg/dL</td>
<td></td>
</tr>
<tr>
<td>c-NO-HDL</td>
<td>&lt;160 mg/dL</td>
<td>&lt;130 mg/dL</td>
<td>&lt;100 mg/dL</td>
</tr>
<tr>
<td>Apo B</td>
<td>&lt;100 mg/dL</td>
<td>&lt;80 mg/dL</td>
<td>&lt;70 mg/dL</td>
</tr>
<tr>
<td>TG</td>
<td>&lt;150 mg/dL</td>
<td>&lt;150 mg/dL</td>
<td>&lt;150 mg/dL</td>
</tr>
<tr>
<td>c-HDL &gt;40 in male</td>
<td>&gt;40 in male*</td>
<td>&gt;40 in male*</td>
<td></td>
</tr>
<tr>
<td>&gt;50 in female</td>
<td>&gt;50 in female*</td>
<td>&gt;50 in female*</td>
<td></td>
</tr>
<tr>
<td>CT/c-HDL</td>
<td>&lt;5</td>
<td>&lt;4</td>
<td>&lt;3,5</td>
</tr>
<tr>
<td>Apo B/apo A1</td>
<td>&lt;0.9</td>
<td>&lt;0.7</td>
<td>&lt;0.6</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>&lt;140/90 mmHg</td>
<td>&lt;125/75 mmHg with macroalbuminuria or renal failure</td>
<td></td>
</tr>
<tr>
<td>HbA1c</td>
<td>&lt;7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1D</td>
<td>T2D</td>
<td>&lt;6.5</td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td>Assess according to risk and age</td>
<td>Assess in &gt;40 years of age with one or more risk factors</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Clinical or sub-clinical cardiovascular disease, presence of microalbuminuria, metabolic syndrome characterized by the presence of 4 or 5 of the classic components or association with multiple classic risk factors (hypercholesterolemia, hypertension, nicotine poisoning, etc.). c-HDL when higher better ideal >80 mg/dL. *In diabetes mellitus and in the MS, the c-NO-HDL shall be estimated and used, replacing the c-LDL as far as the triglycerides are >200 mg/dL and as an option when the triglycerides are >150 mg/dL. *The HbA1c targets should be achieved without clinical or sub-clinical hyperglycemia given the risk they have of increasing the cardiovascular morbimortality.

apoB ≥120 mg/dL, represent a high cardio-
vascular risk (table 3).
With the association of statins and fi-
brates or nicotinic acid, the possible he-
patic and muscular complications should
be controlled, especially if high doses of
statin are used or if there is renal failure,
and in cases of elder patients. When to
achieve the therapeutic targets there is a
need of a combined treatment of both hy-
polipemiant drugs, we shall use nicotinic
acid, bond to the laropiprant in order to
reduce the rubefaction or the fibrates, in
this last case the fenofibrate will be the
choice.30,31

• Arterial hypertension
Objective: BP <130 mmHg or lower, as
we have indicated, if there is nephropathy
with microalbuminuria or renal failure.32
Together with the non-pharmacological
measures, the most adequate drugs in
the subject with BHT and diabetes are the
ACEI and the ARA II especially due to
their renal protector effect. Other drugs as
the diuretics, the calcium antagonists
and the beta-blockers have demonstrated their efficiency in the reduction of the car-
diovascular morbimortality. Two or more
drugs are needed frequently in order to
achieve the BP recommended levels.33

Other cardiovascular risk factors
Smoking should be completely forbidden.
On the other hand, in spite of the arisen
controversies and awaiting new studied,
the use in primary prevention of low doses
of acetylsalicylic acid is recommended in
subjects >40 years of age and with other
risk factors.
During the last years, the role of the in-
flammation has been studied (and mainly
the PCR as an inflammation marker) and
the beginning and progression of athero-
sclerosis; most of the prospective studies,
not all, have observed a good correlation be-
 tween PCR and atherosclerosis, regardless
of the classic cardiovascular risk factors.34,35

Regarding to the relation or role of
the inflammatory parameters, especially the
PCR, as markers of cardiovascular risk in
diabetes, the discussion is still open.
While some authors find that these param-
ters have a low statistical weight as a car-
diovascular risk factor,36 others consider,
both in the univariate and multivariate
analysis, that they have an important
weight as markers of the cardiovascular
risk, mainly in subjects with nephropa-
thy37 or in all the subjects with diabetes,
suggesting their use to determine the vas-
cular risk.38

Conclusions
The subjects with diabetes should be con-
sidered as cardiovascular high-risk sub-
jects and, consequently, as tributaries of
a strong intervention for the prevention of
CVD. There are clear evidences that the
correction of all the cardiovascular risk
factors entail an important reduction of
the cardiovascular morbimortality.

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