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Expert consensus on management of diabetic patients with impairment of renal function

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Expert consensus on management of diabetic patients with impairment of renal function

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This work has been presented to both societies on 2010

1. Preamble

1.1. Definition of the objective of the recommendation

Following discussions by the organisation committee and approval from the working group, the main objectives of this recommendation are to respond to the following points:

- to help decrease the number of diabetic patients that reach end-stage renal failure;
- to help decrease the morbidity-mortality in diabetic patients presenting with renal impairment;
- to be in line with the previous recommendations;
- to integrate the specific nature of patients with diabetes and renal impairment with regard to each of the already existing recommendations in various areas (chronic renal failure, hypertension, lipids, cardiovascular (CV) risk, etc.);
- to help in the care pathway of the patient and to describe the role of each of the participants and the therapeutic care schedule.

It should be noted that the recommendations from the French National Authority for Health [HAS] for the management of type 2 diabetes (T2DM) excluded the care of complications and thus the very specific nature of chronic renal failure in diabetic patients. The last expert opinion on the subject (diabetic uraemia) dates from 1999.

Of course there are many more patients with T2DM than patients with T1DM concerned by this problem; nevertheless, the therapeutic objectives and the management are the same.

Some points have been the subject of recent recommendations or expert opinions. These data will not be treated again but will be discussed based on these recommendations.

The distinctive characteristics of elderly subjects will not be addressed.

The working group (authors of this article) drew on the guide for analysis of the literature and gradation of the recommendations published by ANAES (January 2000), which was used to evaluate the scientific level of evidence provided by the literature according to different criteria.

The recommendations proposed here were classified as Grade A, B or C according to the following conditions:

- **Grade A recommendation** is based on scientific proof established by studies with a high level of evidence;
- **Grade B recommendation** is based on a scientific presumption provided by studies with an intermediate level of evidence;
- **Grade C recommendation** is based on studies with a low level of evidence;

- in the absence of certainty, the proposed recommendations correspond to **a professional agreement** (emanating from exchanges between members of the working group).

All of these recommendations were developed with funds belonging to both societies, without external funding.

All the members of the working group declared their potential conflicts of interest.

2. Introduction, generalities

The theme "Management of diabetic patients with impairment of renal function" largely evolved since the publication 10 years ago of the expert report from ALFEDIAM and the Society of Nephrology in 1999 [1]. A large amount of scientific data was produced, which changed previous beliefs:

- the means of best estimating the impairment of renal function, which are still being debated;
- the means of slowing the deterioration of renal function;
- the proof that a diabetological intervention (with therapeutic target) is effective;
- new care flowcharts and new compounds for the treatment of diabetes appeared;
- the best approach to cardiovascular risk and its particular nature in case of renal impairment.

Several international authorities provided their contribution (NICE 2002 [2], KDOQI [3], Royal College of Physicians (2006) [4], ADA (2006) [5], Scottish recommendations (2008) [6], etc.).

The present report intends to evaluate the most recent data.

Diabetes has become the main cause for beginning dialysis: the incidence of ESRD (end-stage renal disease) due to diabetic nephropathy doubled between 1991 and 2001 in the USA [7]. In France, diabetic patients accounted for 22.8% of new ESRD patients managed on dialysis in 2006, i.e. as many as those beginning dialysis due to high blood pressure or vascular nephropathy [8].

2.1. Epidemiology, definition of microalbuminuria and diabetic nephropathy

2.1.1. Microalbuminuria

Microalbuminuria is defined as a urinary albumin excretion (UAE) rate between 30-300 mg/24 h; higher rates are categorised as macroalbuminuria.

The existence of microalbuminuria is an important factor for screening diabetic patients that are at high risk of presenting with progressive diabetic nephropathy *(Grade B)* [9,10]. It increases the risk of developing diabetic nephropathy by 21-fold in type 1 diabetes and by 4.4-fold in type 2 diabetes *(Grade A)* [11]. Patients with an increased GFR (glomerular filtration rate) ("hyperfiltration") are at high risk of presenting with progressive diabetic nephropathy *(Grade B)* [12].

The presence of microalbuminuria is also a marker for patients with high risk of cardiovascular complications *(Grade A)* [13].

2.1.2. Full-blown diabetic nephropathy

The diagnosis of full-blown diabetic nephropathy may be suspected clinically on the basis of long-diagnosed diabetes (> 10-15 years) associated with macroalbuminuria > 300 mg/24 h or eGFR < 60 ml/min/1.73 m^2 and the absence of renal signs or extra-renal signs indicating another type of involvement (eGFR = estimated glomerular filtration rate using an appropriate formula; see below).

Non-diabetic nephropathy must be suspected in any diabetic patient presenting with rapid deterioration of renal function (> 10 ml/min/year), sudden onset of nephrotic syndrome (especially if diabetes duration is less than 5 years) and in the absence of diabetic retinopathy; an absence of micro- or microalbuminuria is also suspicious. This glomerulopathy can only be proven with biopsy [14]. Nephropathy other than diabetic glomerulosclerosis may occur, and depending on the series, the frequency varies from 8% to 71% *(Grade B)*. There is no indication for renal biopsy if there are no suspicious factors for another cause of nephropathy. The indications and non-indications for renal biopsy in diabetes were the subject of a consensus conference, which issued guidelines in 1991 that are still valid today [14].

Diabetic nephropathy rarely develops before ten years of hyperglycaemic progression in patients with type 1 diabetes; upon diagnosis of type 2 diabetes however, 3% of patients already present with kidney disease *(Grade B)*. The incidence of diabetic nephropathy is about 3% per year between 10 and 20 years of diabetes progression *(Grade B)*. On the other hand, the development of diabetic nephropathy is exceptional after 30 years of diabetes, which raises suspicion that many subjects are protected from it. The prevalence of diabetic nephropathy in type 2 diabetes is more variable.

There is an 18 to 25% incidence of starting dialysis 10 years after the discovery of proteinuria in type 1 diabetic patients *(Grade B)* [15]. The incidence of diabetic nephropathy in patients starting haemodialysis is 19.7%; the prevalence of diabetes in haemodialysis is 17.9% [16]. In addition, there is an East-West gradient in the incidence of diabetic nephropathy in France (9% in Brittany *versus* 30% in Alsace, according to the 2008 REIN registry).

The rate of renal function deterioration in diabetic nephropathy may vary from 2 to 20 ml/min/year *(Grade B)* [17-20] and is closely interrelated with blood pressure and proteinuria. There is a well-documented close correlation between poor blood pressure control and worsening renal function in type 1 and 2 diabetes *(Grade C)* [17,21,22]. By blocking the renin-angiotensin system, and by controlling blood pressure and other risk factors, deterioration of the GFR can be slowed significantly to around 2 to 3 ml/min/year *(Grade A)* [23-25] (see Chapter 6).

2.2. Risk factors for developing nephropathy in patients with type 1 or 2 diabetes

Some factors have been identified that call for increased monitoring for the risk of developing nephropathy in diabetic patients:

- **1. Microalbuminuria** (see Chapter 3).
- **2. Sex:** Nephropathy is more common in men than women *(Grade B)* [26].
- **3. Family predisposition to developing diabetic nephropathy.** Diabetic nephropathy is more common in families of type 2 diabetics Pima Indians and in certain type 1 diabetic families in the Caucasian population, without an identified cause.
- **4. Arterial hypertension:** Poor blood pressure control is a factor that contributes to deterioration of renal function in all diabetic patients l [18,20,27-29].
- **5. Ethnic origin and social conditions:** The incidence of end-stage renal disease in diabetes is 2.6 times greater in the black population than the white, after adjustment for the greater prevalence of diabetes in the black population [30].
- **6. Age at onset of diabetes:** Onset of type 1 diabetes before the age of 20 years is a risk factor for the occurrence of diabetic nephropathy *(Grade B)* [31].
- **7. Glycaemic control:** Good glycaemic control is a determining factor in the primary prevention of diabetic nephropathy *(Grade B)* (Chapter 5.1) in type 1 and 2 diabetes; its benefit in secondary prevention is less marked.
- **8. Tobacco:** Tobacco smoking is a factor that exacerbates the progression of diabetic nephropathy *(Grade B)* [32,33].
- **9. Hypercholesterolaemia:** Hypercholesterolaemia is an independent factor of progression of renal failure, but statin treatment in type 1 and 2 diabetic patients with microalbuminuria and macroalbuminuria have provided variable results. However no long-term randomised, double-blind study has been done (Chapter 7.4.2).

2.3. Types of nephropathy associated with diabetic nephropathy

It is important to be aware of the possible existence of other types of nephropathy than diabetic nephropathy in nephropathic diabetic patients. The most common types are:

- **1. Nephropathies with associated vascular lesions.**
- **2. Glomerulopathies [34].**
- **3. Renal papillary necrosis [34].**
- **4. Pyelonephritis [35,36].**
- **5. Obstructive nephropathy [37].**

2.4. Renal impairment and cardiovascular risk (see Chapter 7)

Chronic renal failure and a rise in urinary albumin excretion increase the cardiovascular risk and are seen most frequently in elderly subjects with a high absolute cardiovascular risk. Furthermore, diabetes constitutes an independent risk factor. Overall, subjects that present with both diabetes and chronic renal failure have, in virtually all cases, an increased absolute cardiovascular risk and must receive dietary/lifestyle counselling and drugs for cardiovascular prevention that are suitable to this category of patient according to the recommendations of the French National Authority for Health.

In most cases of type 2 diabetes patients who present with chronic renal impairment, the risk of dying from cardiovascular causes is much higher than progressing to end-stage renal disease [38] (Level 4).

These pathological conditions, which are often silent, should therefore be identified early in order to adjust the appropriate preventive measures. To a large degree, these are the same as the preventive measures for progression to renal disease itself.

3. Evaluation of renal impairment in diabetic patients

3.1. Objective

To review and analyse the new formulas recommended for estimating the GFR (eGFR).

3.2. Summary of the previous French recommendations:

- **Urinary albumin excretion (UAE)** should be measured yearly in type 1 diabetics after 5 years of diagnosis and in type 2 diabetics once it is discovered. Microalbuminuria is defined as a UAE between 30-300 mg/24 h (or 30-300 mg/g of urinary creatinine on first morning urine). It is an independent marker of renal and cardiovascular risk and total mortality (*Grade B,* justified by the existence of several cohorts with concordant results) [4,39-41]).
- **The glomerular filtration rate (GFR)** must be measured yearly in type 1 and 2 diabetics and according to the former recommendations. Chronic renal failure is defined as a glomerular filtration rate < 60 ml/min as estimated by the Cockcroft-Gault formula [10]:

$$\text{CG (ml/min)} = \frac{(140\text{-age [years]}) \times \text{mass [kg]} \times \textit{Constant}}{\text{Serum creatinine [in µmol/L]}}$$

where *Constant* = 1.23 for men and 1.04 for women.

3.3. Why new recommendations are being issued for diabetic patients

The recommendation concerning microalbuminuria is recent (2007) [43].

The recommendation concerning renal failure is older, and all the international recommendations issued since 2002 have mentioned the use of other measurement methods for renal function than the Cockcroft-Gault formula (CG); the method cited most often is the simplified MDRD formula (4 parameters: sex, age, serum creatinine, ethnicity) [44].

The CG formula contains sources of error in cases of obesity and in subjects over the age of 75 years. Indeed, weight and age are significant parameters of the CG formula,

and a valid calculation requires that these data remain within a so-called "normal" range.

- **Weight:** The majority of patients followed are type 2, and these patients are overweight or obese: the GFR estimation using the CG formula is then biased (weight is the numerator of the CG formula, and this always leads to overestimation of the GFR in overweight patients) [45]. Yet, overweight and obesity on their own are associated with GFR modifications [46] and an increased risk of renal failure [47,48]. It is therefore important to work with the most precise estimations possible in these patients, with formulas that are bound to be the least biased possible.
- **Hyperglycaemia** increases the glomerular filtration rate. This physiological phenomenon (demonstrated in healthy subjects) [49] is present in type 1 [50] and type 2 [51] diabetics. A case in point: in the same type 1 diabetic patient with nephropathy, the GFR can be estimated at 35 ml/min/1.73 m^2 with hyperglycaemia of 3.3 g/L *versus* 21 ml/min/1.73 m^2 with euglycaemia of 0.93 g/L [52]. Chronic hyperglycaemia is associated with a significant loss of accuracy in the CG formula when the HbA_{1c} is > 8% [53].

3.4. Estimation of renal function in diabetic patients

Since 2002, the international recommendations have integrated these data:

- NICE (2002) [2] concerns type 2 diabetes;
- KDOQI (Levey, 2003) [3];
- Royal College of Physicians (2005) [4] concerns chronic kidney diseases. *The authors advocate the preferential use of the MDRD formula, especially due to the absence of weight in its formula. Depending on the under-estimation of the high values, they propose that a numerical value not be given if the GFR is estimated to be > 90 ml/min/1.73 m^2, and to not consider subjects with GFR between 60 and 89 ml/min/1.73 m^2 as having chronic kidney disease if there is no other evidence (microalbuminuria, etc.);*
- ADA (2006) [5] concerns diabetic patients and has recommendations similar to KDOQI, *with the 2 useable formulas.* The diagnosis of chronic kidney disease is based on pathological levels of urinary albumin excretion or an estimated GFR < 60 ml/min/1.73 m^2.

However, the simplified MDRD formula also presents sources of bias: it is imprecise in subjects with normal renal function. The MDRD equation was established from a population of patients with renal failure and clearly underestimates normal or high GFR values. In the 60 and 90 ml/min/1.73 m^2 bracket, this underestimation is around 20mL/min/1.73 m^2 for T1DM (DCCT- Diabetes Control and Complications Trial) [54] and 10 ml/min/1.73 m^2 for T2DM [55,56]. The eGFR results provided by the MDRD must not be taken into account for values greater than 60 ml/min (although this level is not included in the definition of chronic renal failure). The Scottish recommendations (2008) [6] propose *asking analytical laboratories not to provide the result if it is greater than 60ml/min/1.73 m^2.*

3.5. Several pragmatic aspects

The following describes the current situation in France: biological analytical laboratories are obliged to provide the serum creatinine result with an estimation of the GFR using the de Cockcroft formula, as recommended in 2002, once the patient's weight is known (generally declared) (and theoretically body height as well if a result that is standardised to the body surface is desired). Calculation of the MDRD equation is more difficult, but slide rules, systems of calculation, tables and Internet sites make it easier to obtain a result.

Doctors in private practice are currently very familiar with the Cockcroft-Gault formula but have little knowledge of the simplified MDRD formula. However biological laboratories have begun to provide results from both formulas fairly often; it is therefore important to be well familiar with the previously mentioned biases:

- CG overestimates the GFR in overweight subjects (risk of mistaking the extent of deteriorating renal function);
- CG underestimates the GFR in very elderly subjects;
- MDRD is more accurate than CG for GFR < 60 ml/mn/1.73 m^2, but its performance remains insufficient for normal GFR values, particularly above 90 ml/min/1.73 m^2 (it is recommended that the results not be provided if the value estimated by the MDRD formula is greater than 60 ml/min).

It would probably be difficult and perhaps counterproductive to propose completely changing the formulas used. However the MDRD equation is preferred in most international recommendations, since it is less biased by the weight problem, which is one of the characteristics of T2DM patients. It is therefore important that the reading of the results is understood: **MDRD always gives a more accurate estimation of the GFR when it is pathological;** MDRD is less valid however for correctly quantifying normal values.

In addition, there is a broad range of heterogeneity of renal impairment in diabetes. **The natural history of increasing microalbuminuria, followed by a decreasing glomerular filtration rate, such as described in the 1980's [57,58], does not explain all the observed clinical situations:**

- around 20% of type 2 diabetic patients with renal failure have normal albumin excretion [59,60,61], which represents a large number of patients [62]. Type 1 diabetics can also have this particular presentation [63].

This concept of renal failure with normal renal excretion of albumin is the origin of the new definition of chronic kidney disease associated with diabetes: pathological urinary albumin excretion (microalbuminuria) or estimated GFR < 60 ml/min/1.73 m^2 [64].

- Conversely, urinary albumin excretion reaches very high "nephrotic" levels (> 2 500 mg/24 h) in a substantial number of patients [65,66]. Significant proteinuria then

also occurs with increased tubular secretion of creatinine, which lowers the value of serum creatinine as a marker of the glomerular filtration rate [67,68].

There must be systematic monitoring for microalbuminuria and estimation of the GFR, regardless of the patient's stage of renal impairment. To facilitate matters, it is possible to consider the result of the urinary albumin excretion measurement relative to that of the urinary creatinine, which is simpler, since it limits the collection of urine upon waking (normal urinary albumin/creatinine ratio < 30 mg/g or 3 mg/mmol).

Recommendations

R 01 – The urinary albumin excretion must be measured at least yearly in type 1 and 2 diabetics (yearly if normal results and more often with pathological values). Microalbuminuria is defined as urinary albumin excretion between 30-300 mg/24 h (or 30-300 mg/g of urinary creatinine in first morning urine). It is an independent marker of renal risk, cardiovascular risk and total mortality.

R 02 – The serum creatinine measurement must be done at least once per year in diabetic patients in order to estimate their glomerular filtration rate (eGFR) in ml/min/1.73 m^2 using an equation of prediction *(Grade C)*. The equations used in 2009 were:

a) the MDRD equation:

MDRD (mL/min/1.73 m^2) = 186 × (serum creatinine [mg/dl])$^{-1.154}$ × (age [years])$^{-0.203}$ × (0.742 if woman)

The result must be multiplied by 1.2 in black subjects.

b) the Cockcroft-Gault formula (Cockcroft, 1976):

$$\text{CG (ml/min)} = \frac{(140\text{-age [years]}) \times \text{weight [kg]} \times \textit{Constant}}{\text{Serum creatinine [µmol/L]}}$$

With *Constant* = 1.23 for men and 1.04 for women.

rq 1: the MDRD equation is more reliable in cases of renal failure (estimated GFR < 60 ml/min/1.73 m^2) and when the weight is abnormal (BMI less than 18.5 or greater than 25 kg/m^2)

rq 2: the Cockcroft-Gault formula must be called into question if the patient is overweight and/or the patient is elderly

R 03 – The diagnosis of chronic kidney disease is based on microalbuminuria in diabetic subjects or eGFR < 60 ml/min/1.73 m^2. The pathological nature and the risk of progression of GFR between 45 and 60 ml/min/1.73 m^2 are uncertain, particularly in elderly persons or in the absence of microalbuminuria.

3.6. Prospects for the decades ahead

Short-term progress is expected with regard to the assessment of renal impairment:

- **a) standardisation of the serum creatinine measurements:** Serum creatinine measured at 90 µmol/L can vary in value by around 10-15 µmol/L due to differences in the calibration of the creatinine assay techniques [69], with subsequent significant consequences for the GFR estimation. The use of standardised creatinine assays ("IDMS-traceable") is recommended [70,71], although serum creatinine is not standardised in the large majority of medical analytical laboratories. It is hoped nevertheless that this will occur in the near future, thus improving the predictive value of the formulas that are used.
- **b) development of new formulas:** There are two fnew ormulas which deserve to be mentioned: The Mayo Clinic Quadratic (MCQ) equation, and especially the new Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (Levey, 2009) [73], which was just established and validated – more accurate and less biased than the MDRD equation – on a very large sample (8254 subjects, 30% of which were diabetics), thus implying that it will be the next reference.

4. Renal presentation that requires consultation with a nephrologist

4.1. Objectives

To define the timeline and indication for a nephrology consultation request and to describe the preliminary work-up for obtaining specialist advice.

4.2. Indications for nephrology management

The diabetic patient that presents with signs of nephropathy must be sent to a nephrologist as soon as one of the following conditions is met:

4.2.1. Proteinuria greater than 300 mg/24 h or creatinine clearance less than 60 ml/min/1.73 m²

Verification of the absence of factors that are bound to raise suspicion as to other causes of nephropathy, and optimisation of protective measures for the kidneys.

4.2.2. Any renal failure with creatinine clearance < 60 ml/min

Metabolic disorders that require correction through supplementation begin to appear with creatinine clearance less than 45 ml/min (1, 25-$(OH)_2$ D3 and EPO deficiencies).

4.2.3. Lack of decrease in microalbuminuria or proteinuria output despite treatment with ARBs or ACE inhibitors at maximum dose

It has been clearly demonstrated that in type 1 and 2 diabetes blockage of the renin-angiotensin system significantly slows the progression of nephropathy through a drop in the urinary protein output *(Grade A)* [24,25]. There is a correlation between urinary protein output and the rate of renal

function deterioration due to glomerular hyperfiltration and tubular nephrotoxicity of the proteins *(Grade B*) (ADVANCE, 2009) [74].

4.2.4. Persistent hypertension (HTN) despite well-conducted hypertensive treatment or the occurrence of unstable blood pressure

Blood pressure control is a major factor in the prevention of diabetic nephropathy (Chapter 6).

Resistance to hypertensive treatment must prompt an investigation for the aetiology of this HTN.

Unstable blood pressure in a patient that was initially controlled must systematically prompt a work-up for superimposed nephropathy, requiring rapid nephrological advice in order to look for (expert opinion):

- renal artery stenosis;
- post-infectious glomerulonephritis, especially in the presence of a chronic foot ulcer and haematuria;
- bladder emptying disorder.

4.2.5. Decrease of GFR > 10 ml/min/year

Decrease of the GFR of more than 10 ml/min/year is suggestive of progressive renal disease, and consultation with a nephrologist is mandatory to optimise the therapeutic plan or to screen for superimposed nephropathy.

4.2.6. Injection of contrast product in a diabetic patient with Stage IV renal failure

4.3. Essential morphological and biological work-up for the nephrologist at the first consultation [75]

When a diabetic patient meets one of the previous conditions, he must be referred to the nephrologist with the following work-up:

- **a kidney + bladder ultrasound with post-void residual testing;**
- **a laboratory work-up with:**
  - plasma creatinine and estimated GFR; plasma urea; serum sodium, potassium, calcium, phosphorous, uric acid; bicarbonate; CRP; HbA1c;
  - CBC;
  - urine protein and microalbumin, urine creatinine;
  - 24 hour urine for urea, Na^+, K^+;
  - urine analysis with culture and sensitivity;
  - electrophoresis of blood proteins;
  - exploration of lipid anomaly of less than one year.

If the patient presents with eGFR < 45 ml/min, the above-stated work-up must be supplemented by the following data:

- iPTH, 25-OH vitamin D test;
- serum ferritin, saturation coefficient (if anaemia);
- anti-Hbs, HbsAg, Anti-Hbc

The issue of Doppler ultrasound for the renal arteries ais regularly confronted: indeed, the prevalence of renal artery stenosis is estimated to be between 0.5 and 3% in a non-selected hypertensive population. It can reach 15% to 30% in a selected population [76], but there is little specific data in the diabetic population. The STAR study [77] and the American College of Cardiology (ACC)/American Heart Association (AHA) 2005 guidelines [9] show that there is no benefit in dilating severe stenosis of the renal artery for blood pressure control and improvement of renal function. It is therefore not relevant to systematically perform this examination, especially as it is a poorly reproducible one.

4.4. Schedule of follow-up and tests [75]

At Stage 3, the monitoring schedule with the attending physician or diabetologist is every 3 to 6 months. The eGFR divided by 10 gives the time interval in months between two medical visits (e.g., eGFR of 40 ml/min = frequency of medical visits every 4 months).

The monitoring schedule with the nephrologist is determined according to the progression of the disease, intercurrent complications and difficulties reaching the therapeutic targets:

- if the eGFR is < 45 ml/min and the renal function remains stable, a yearly medical visit is recommended;
- if the eGFR is < 20 ml/min and the renal function is stable, one medical visit every 6 months;
- if the eGFR is < 15 ml/min, one medical visit every 3 months.

Recommendations

R 04 – The diabetic patient that presents with signs of nephropathy must be referred to a nephrologist if:

- the urine protein is greater than 300 mg/24 h or creatinine clearance is below 60 ml/min/1.73 m²;
- there is no decrease in urine microalbumin or protein levels despite ARB or ACE inhibitor treatment at the maximum dose;
- hypertension persists despite well-conducted antihypertensive treatment or unstable blood pressure occurs;
- there is a drop in GFR > 10 ml/min per year.

R 05 – Any consultation request should be accompanied by the above-described morphological and biological work-up, which the nephrologist requires at the first visit.

R 06 – There is an optimal schedule of follow-ups and testing according to the degree of renal impairment.

5. Management of diabetes with renal impairment

5.1. Primary or secondary prevention of diabetic nephropathy: Effects of diabetic treatment

5.1.1. Effects of glycaemic control on the incidence of micro- or macroalbuminuria

Type 1 diabetes

DCCT study (Grade A): prevention of microvascular complications: After 6.5 years of follow-up, the treatment group showed a significant 39% reduction in the incidence of microalbuminuria and 54% in the incidence of macroalbuminuria [79].

Type 2 diabetes

Kumamoto study (Grade A): after 6 years of follow-up, the risk of microalbuminuria was significantly decreased in the intensive group (incidence of microalbuminuria at 6 years was 7.7% *vs.* 28.0%, $P = 0.03$) [80].

UKPDS study (Grade A): at 9 years, there was a significant decrease in the risk of occurrence of microalbuminuria (- 22%, $P = 0.0006$), proteinuria (- 33%, $P = 0.003$), as well as the risk of doubling of the serum creatinine (- 60%, $P = 0.03$) [5,6,81]

ADVANCE study (Grade A): After a 5-year follow-up, the primary outcome of this study was significantly reduced in the intensive treatment group (hazard ratio (HR): 0.90, $P = 0.01$) due to a reduction in the risk of renal complications: incidence of microalbuminuria (0.79; CI 95%: 0.66-0.93, $P = 0.006$) [the reduction of the risk ratio (RR) of microalbuminuria was therefore 21% [82].

VADT study (Grade A) [83]: An increase was observed in the rate of urinary albumin excretion in the standard group compared to the intensive control group at the limit of statistical significance ($P = 0.05$). There was a non-significant trend of reduced risk of progression of normal albuminuria to the stages of microalbuminuria or macroalbuminuria in the intensive group compared to the standard group (3.9% *vs.* 6.3%, $P = 0.11$). In this study, no difference was noted between the two groups with regard to decline of renal function (estimated glomerular filtration).

5.1.2. Effects of glycaemic control on the incidence of macroalbuminuria and renal failure

Type 1 diabetes

In the DCCT study, there was a significant 54% reduction in the incidence of macroalbuminuria in the intensive group [84].

Type 2 diabetes

Kumamoto study (Grade A): In the patients with microalbuminuria at inclusion, the incidence of macroalbuminuria was significantly reduced (11.5% *vs.* 32.0%, $P = 0.04$) in the intensive arm [80].

UKPDS study: In the group receiving intensive treatment, there was a significant reduction at 9 years in the risk of proteinuria occurrence (- 33%, $P = 0.003$), as well as the risk of doubling of the serum creatinine (- 60%, $P = 0.03$) [81].

ADVANCE study: After a 5-year follow-up, the intensive treatment of glycaemia was associated with a significant reduction in the development of macroalbuminuria (2.9% *vs.* 4.1%; $P < 0.001$). There was a trend of decreased risk of end-stage renal disease or death of renal origin (0.4% *vs.* 0.6%; $P = 0.09$). There were no differences seen with regard to doubling of the serum creatinine [82].

VADT study: An increase was seen in the rate of urinary albumin excretion in the standard group compared to the intensive control group at the limit of statistical significance ($P = 0.05$). There was a non-significant trend of reduced risk of progression of normal urine levels of albumin to the stages of microalbuminuria or microalbuminuria in the intensive group compared to the standard group (3.9% *vs.* 6.3%, $P = 0.11$). In this study, no difference was noted between the two groups with regard to decline of renal function (estimated GFR) [83].

5.1.3. Durability of the benefits of intensive glycaemic control

Type 1 diabetes

After the end of the DCCT study, all the patients then received the same glycaemic management and were followed for 8 additional years (EDIC). The difference in HbA_{1c} between the two initial groups lessened and was no longer statistically different: the benefits of the initial glycaemic control lasted 8 years after the end of the trial. Patients with normal urine albumin at the end of the DCCT trial, 6.8% in the initially intensive group *versus* 15.8% in the conventional group, developed microalbuminuria during the EDIC follow-up; this was a 59% ($P < 0.001$) reduction in the risk of microalbuminuria occurrence compared to the initial conventional group [86] *(Grade A)*. The incidence of proteinuria was also significantly decreased (1.4% *vs.* 9.4%). After adjusting for the variables at inclusion, the initial intensive treatment of the DCCT significantly reduced the risk of proteinuria by 84% at the end of the EDIC (95% CI: 67% - 92%) compared to an only 57% risk reduction at the end of the DCCT (95% CI: - 1% – + 81%). Maintenance of the renal benefit of the initial intensive glycaemic control was also observed in patients with normal urine albumin at the end of the DCCT, with an 87% risk reduction of proteinuria at the end of the EDIC. In the patients with microalbuminuria at the end of the DCCT, there was also a 77% risk reduction of proteinuria at the end of the EDIC.

At the end of the EDIC follow-up, the prevalence of an alteration in renal function (defined by creatinine clearance < 70 ml/min/1.73 m^2) was reduced in the intensive group *versus* the conventional group (< 1% *vs.* 4%, $P < 0.001$), while the GFR (estimated by isotopic method) was similar between both groups at the end of the DCCT. The prevalence of increased plasma creatinine (≥ 20 mg/l) at the end of the EDIC follow-up was also significantly reduced in patients initially treated in the intensive group compared to the conventional group (5 *vs.* 19, $P = 0.004$). Ten subjects in the initial intensive group *versus* 17 in the conventional group ($P = 0.17$) doubled their serum creatinine level between inclusion in the DCCT study and the end of the EDIC follow-up. The number of diabetics requiring dialysis and/or kidney transplantation was lower in the initial intensive group, without reaching however the threshold for statistical significance (4 *vs.* 7, $P = 0.36$).

In summary, the renal benefits of intensive glycaemic control, which were observed after the DCCT intervention,

persist for 8 years with a marked decrease in the risk of occurrence and of progression of diabetic nephropathy.

Type 2 diabetes

The ten-year follow-up of patients from the UPKDS trial after the end of the intervention (final mean follow-up of 17 years, with a mean intervention time of 10 years) demonstrates that early intensive control of hyperglycaemia very significantly reduces the long-term risk of microvascular complications (- 24%, $P = 0.001$); there was not more elaborate data available on the specific risk of nephropathy. This long-term benefit was observed, while at the end of the intervention in 1997, all the patients in the trial had switched to what is known as conventional management, and in the years following, there were no longer any differences with regard to HbA_{1c} or blood pressure between both groups [87]. The concept of a "memory effect" of early intensive glycaemia control with regard to microvascular status has thus been suggested, since it has been demonstrated in the DCCT study for type 1 diabetes.

Recommendations

R 07 – Tight glycaemic control ($HbA_{1c} < 7\%$) reduces the incidence of micro- and macroalbuminuria, both in type 1 and type 2 diabetics. *(Grade A).*

R 08 – Early intensive control of glycaemia has a durable renal benefit with a persistent decreased risk of micro- and macroalbuminuria in type 1 diabetic patients. *(Grade A).*

R 09 – Early intensive control of glycaemia is associated with long-term reduce decline in renal function in type 2 diabetes. *(Grade B).*

5.2. Treatment of diabetes associated with nephropathy: adjustment of diabetic treatment according to renal function

The HAS recommends the HbA1c objectives for subjects with type 2 diabetes. The ideal HbA_{1c} objectives however, in case of chronic renal failure (CRF), are not specified in the absence of large trials including patients presenting with known renal failure; all indications show that they must not be modified and are even probably more stringent since it has been shown that the quality of the glycaemic control affects the progression of renal impairment. Furthermore, this latter is an aggravating factor for the progression of degenerative complications, which makes attainment of the glycaemic control objectives even more necessary [88,89]. The HbA_{1c} objectives must therefore be rigorously achieved based on the flowcharts recommended by the different organisations (HAS 2007 [90]), (ADA 2007 [91]). The existence of altered renal function however is likely to modify the metabolism of the different recommended products and therefore alter the recommendations. For several months now, there have been some new additions to the choice of therapeutic products: DPP-4 inhibitors and GLP1 analogues.

In addition, chronic renal failure itself is a source of insulin resistance and modification of the insulin clearance.

5.3. The question is raised as to whether the existence of renal impairment is likely to modify the flowchart or the use of the different classes of medication.

There are no large controlled clinical studies that have been done in the populations of type 2 diabetic patients with renal failure. The series are short and have focused rather on pathophysiology.

5.3.1. Biguanides

Metformin is the first line therapy in all good practice recommendations. However, congestive heart failure and kidney failure are the main contraindications cited in the MA. The fear is based exclusively on lactic acidosis, with its significant severity (general mortality 30%), although the frequency is extremely rare (incidence about 3 per 100,000 patient-years).

The plasma concentrations of biguanides increase in case of renal failure at unchanged daily doses, but most studies do not find increased levels of serum lactic acid [92]. The incidence of lactic acidosis in diabetes without the use of metformin is around 10 per 100,000 patient years [93,94]; it is thus the same as with the use of metformin. A recent study (2008) [95] reviewed all the epidemiological data of the "UK General Practice Research Database"; the incidence of lactic acidosis due to metformin was 3.3 per 100,000 patient-years, while the incidence of lactic acidosis in patients taking sulfonamides was 4.8 per 100,000 patient-years. Considering the small number of cases, no formal analysis was proposed, but this work clearly shows that it is important to remain cautious with regard to the biguanide/lactic acidosis relationship. The number of cases of lactic acidosis has not increased since the introduction of this drug in the United States, despite its use in patients presenting with renal failure [92,96].

The risk incurred by a patient with chronic renal failure taking metformin can be considered minor, especially if the dosage is reduced according to his glomerular filtration rate. A recent literature review [97] recommends the use of metformin at the usual doses in patients with eGFR > 60 ml/min/1.73 m^2, and at half the dosage for eGFR between 60 and 30 ml/min/1.73 m^2. Below 30 ml/min/1.73 m^2, it appears that abstaining from use is recommended by most scientific societies. The MA has not been modified however for the most recent data.

Recommendation

R 10 – Metformin remains the first-line drug for the management of type 2 diabetes, even in cases with renal impairment. Its dosage must be reduced (divided by 2) when creatinine clearance is between 60 and 30 ml/min; it must be withdrawn below 30 ml/min *(Grade B).*

5.3.2. Glitazones

Glitazones have been withdrawn from the French market. The debate on the use of glitazones in diabetic patients presenting with renal impairment focuses on two aspects in

which no large series has provided answers up until now: the potential nephroprotective effect of glitazones and the iatrogenic potential of sodium-water retention.

Many studies have tried to demonstrate a nephroprotective effect of glitazones. In patients with moderate renal failure (40-45 ml/min/1.73 m^2), blood pressure control is easier in patients taking glitazones, and the renal survival is better. This difference in renal survival no longer reaches the significance threshold however when corrected for blood pressure control [98].

Another series [99] studied the effects of one year of treatment with rosiglitazone on the progression of urinary albumin excretion. There was a significant decrease in urinary albumin excretion, and this data was confirmed [100,101]. Nevertheless, a sub-study of the PROACTIVE therapeutic trial suggested an increased risk of GFR alteration in subjects taking pioglitazone compared to placebo, whereas the HbA1c values, blood pressure and lipid levels were more favourable with active treatment [102].

However, a slight difference must be pointed out: glitazones in fact promote sodium-water retention [103].

It therefore seems logical to recommend caution when glitazones are used in the treatment of diabetic patients with chronic renal failure who present with frequent sodium-water retention. No large series have been done on this subject. A second slight difference has been shown: the presently demonstrated risk of fractures [104]; yet, chronic renal failure is in itself a factor of bone fragility.

These two slight differences argue rather against the use of glitazones in case of renal failure associated with T2DM.

Recommendation

R 11 – CRF is not in itself a formal contraindication for the use of glitazones when the eGFR is > 30 ml/min. The risk of sodium-water retention however related to glitazone use and the increased risk of fractures must be largely taken into account *(Grade B).*

5.3.3. Alpha-glucosidase inhibitors

Acarbose is metabolised entirely by the intestinal tract. Less than 2% of active metabolite is found in urine, although these metabolites may be involved in hepatotoxic manifestations. Miglitol, which is absorbed in the intestines, is eliminated via the urine. This therefore suggests that arcabose is preferable in instances of CRF, although no large series has succeeded in establishing this position. The KDOQI 2007 recommendations [105] propose that these products not be used for creatinine levels greater than 2 mg/dl (180 µmol/l). These drugs are used very little in diabetic patients with chronic renal failure and there is no large cohort that has been treated with them. Furthermore, these products are recognised as being prone to inducing gastrointestinal disorders, although this problem is already highly prevalent in patients with chronic renal failure.

5.3.4. Sulfonamides

All the sulfonamides are to varying degrees metabolised by the liver into diverse substances, active and inactive, which are generally excreted by the kidneys. Under these conditions, sulfonamides and their metabolic derivatives, in cases of renal failure, are likely to participate in iatrogenic hypoglycaemia due to their accumulation.

Tolbutamide, glipizide and gliclazide probably result in less hypoglycaemia, insofar as their metabolites are inactive or very weakly active.

The pharmacokinetic data suggest that the hypoglycaemic risk in T2DM patients with CRF is considerably decreased with the use of glipizide compared to glibenclamide or glimepiride [106]. Nevertheless, the risk of hypoglycaemia must be kept in mind with T2DM patients that present with decreased creatinine, and this proportional to the degree of eGFR loss.

Recommendation

R 12 – The use of sulfonamides is possible with CRF, but the predominant renal elimination of some sulfonamides must shift the emphasis to products with short half-lives and inactive metabolites, in addition to a dosage adjustment, in order to limit the hypoglycaemic risk in case of CRF *(Grade B).*

5.3.5. Meglitinides

Meglitinides are insulin-secretors with short half-lives. The iatrogenic risk in cases of renal function impairment is hypoglycaemia, though considerably lower than for the sulfonamides due to the brief half-life. Only repaglinide is used in France. A single, multicentre open-label trial compared 151 patients with normal renal function and 130 with alteration of renal function [107] without increase in hypoglycaemia. Only 8% of the administered dose was eliminated via the urine. This demonstrates why there is no dosage adjustment in cases of renal failure and shows that the prescription remains safe in cases of renal impairment.

Recommendation

R 13 – Meglitinides have a low hypoglycaemic risk and can be used in case of CRF *(Grade C).*

5.3.6. GLP1 analogues

No long series on GLP1 use in diabetic patients with renal failure has been reported until now, and therefore no guidelines can be provided. However, the laboratories that produce exenatide and liraglutide report increased frequency and severity of side effects in patients with an eGFR less than 30 ml/minute/1.73 m^2. Exenatide is in fact eliminated via the renal route, and liraglutide presents two minor metabolites that are eliminated in the urine.

There is not enough data available on these new drugs, therefore holding the prescription in case of severe renal impairment (eGFR < 30ml/min/1.73 m^2) is called for *(Grade C).*

5.3.7. DPP-4 inhibitors

The DPP-4 inhibitors are much too recent for the availability of large series of patients with renal failure. The data are mainly pharmacokinetic and show that there is not real change in the pharmacokinetics for eGFR > 50 ml/min/1.73 m^2. For eGFR between 50 and 30 ml/min/1.73 m^2, a half-dose reduction (50 mg of sitagliptine) is suggested [108] due to the elimination per renal route. Cohort studies would be useful however to confirm this data. In the meantime, it is advisable to avoid their use for eGFR < 50 ml/min/1.73 m^2.

5.3.8. Insulin

The use of insulin forms part of the recommended flowchart in type 2 diabetic patients. Insulin therapy is not contraindicated in the event of renal function impairment. There is a modification in insulin clearance, since 30 to 80% of the circulating insulin is eliminated through the kidneys. However, the consequences of this modified insulin clearance are counterbalanced by the occurrence of insulin resistance. The rapid analogues have better preservation of their pharmacokinetic properties than that of regular insulin in cases of chronic renal failure [109]. There is an increase in the duration of action with a risk of hypoglycaemia between meals. Finally, the 2003 ADA-AHA recommendations emphasise the risk of sodium-water retention with use of the insulin-glitazone combination in these patients.

Recommendation

R 14 – To summarise, the use of insulin in T2DM patients with renal impairment does not pose any difficulty. The rules of use are not modified with regard to the traditional recommendations *(Grade A).* The doses are sometimes reduced, and the kinetics, which are prolonged due to the CRF, need to be taken into account.

5.3.9. Summary

The existence of impairment of renal function does not modify the management flowchart of T2DM patients; nor does it modify the therapeutic objectives or decisional thresholds for intensifying the therapy, i.e., for switching from monotherapy to bitherapy, then tritherapy and insulin therapy.

The slight therapeutic differences engendered by renal impairment depend on the degree of GFR alteration and the products in question. Generally, the following should be emphasised:

- reasonable caution with regard to the biguanides according to the GFR;
- adjustment in the risk of hypoglycaemia according to the sulfonamide used;
- caution with regard to new products such as GLP1 or the DPP-4 inhibitors, in which only the "manufacturers" recommendations are available, even though some preliminary data indicate a half-dose prescription for a majority of DPP-4 inhibitors. This raises questions concerning the combination of DPP-4 inhibitors and biguanides;
- no reluctance with regard to the use of insulin, except for reinforced vigilance and comprehensive therapeutic education in the use and adjustment of doses due to the increased half-life relative to CRF.

6. Multifactorial management of nephroprotection

6.1. Overall objectives

- To reduce the rate of progression and thus the incidence of end-stage renal disease (ESRD).
- To reduce the associated morbidity-mortality, particularly cardiovascular (CV).
- Intermediary objectives:
- to reduce proteinuria (without minimal threshold, to 0 if possible);
- to prevent microalbuminuria and progression to macroalbuminuria.

Proteinuria is the main factor for progression of diabetic nephropathy [110]. Reduction of proteinuria is associated with a proportionate reduction in the renal risk of progression and the CV risk (CV mortality, congestive heart failure) [111].

6.2. Blood pressure objectives

All of the international scientific societies currently recommend blood pressure targets < 140/90 mmHg in hypertensive individuals at low risk, and a lower blood pressure target, < 130/80 mmHg, in diabetic patients, patients with nephropathy [JNC7 2003 [112], WHO 2003 [113], KDOQI 2004 [114], BHS 2004 [115], HAS 2004 [116] et 2005 [117], ESH 2007 [118], ADA 2008 [119], or even in all patients with high risk (coronary history or equivalent) or with a calculated Framingham risk > 10% at 10 years [120].

These recommendations are essentially based on post hoc analyses and the conclusions of the BPLTTC 2003 meta-analysis [121]. However, the positive results of this meta-analysis were largely influenced by those of the UKPDS 38, which compared a "traditional" blood pressure target of 180/85 mmHg to a "lower" target of 150/85 mmHg [122].

The *Cochrane Database of Systematic Review* [123] used this meta-analysis by excluding UKPDS 38 and including the following prospective trials of blood pressure targets: MDRD [124], HOT [125], ABCD [126], AASK [127], and REIN-2 [128]. In these trials, an additional mean blood pressure decrease of 4/3 mmHg did not modify the incidence of any of the following criteria: total mortality, myocardial infarction,

CVA, heart failure, major CV events, end-stage renal disease. Also this study did not show worsening of the risk for lower blood pressure targets.

With regard specifically to the diabetic populations and patients with renal failure, the analysis did not show any benefits for blood pressure targets < 135/85 mmHg, *but in both situations, the arguments for the lack of benefits are less robust.*

In the IDNT study on 1590 patients with diabetic nephropathy, the recommended blood pressure target while on hypertensive treatment was less than or equal to 135/85 mmHg. The post hoc analyses of IDNT showed a linear relationship between systolic BP and rate of progression to nephropathy [129,130]. This relationship continued until a systolic BP of 120 mmHg. Below this threshold, the overall risk of mortality increased and the renal benefits became marginal.

Recommendations

R 15 – Adequate blood pressure control slows the progression of diabetic nephropathy *(Grade A).*

R 16 – The target BP is < 130/80 mmHg when the BP is read at medical visits *(Grade C).*

Treatment with 2 or more hypertensive drugs is usually necessary to achieve this target blood pressure. The systolic BP should not be decreased below 120 mmHg, particularly in patients with high coronary and vascular risk *(Grade C).*

Multiple BP readings enable better assessment of the real BP of patients, thus the benefit of home blood pressure monitoring. It facilitates treatment compliance and the achievement of predefined therapeutic targets. Ideally these devices would be reimbursed as part of the framework of care for severe chronic nephropathies, i.e., complicated CRF or associated with diabetes.

Recommendation

R 17 – Home blood pressure monitoring should be encouraged for assessing the blood pressure before treatment, for obtaining therapeutic targets while taking treatment and preventing hypotension (peer consensus). The blood pressure targets taken at home are < 125/80 mmHg *(Grade C).*

6.3. Which drugs to prescribe

According to the French (HAS 2004 CRF and HAS 2005 HTN) [119,117] and international recommendations, renin-angiotensin system (RAS) blockers are indicated as first-line treatment in diabetic subjects and/or those with nephropathy.

According to these recommendations, angiotensin II receptor blockers (ARBs) are proposed more specifically for nephropathy in patients with T2DM (DN2) on the basis of available trials *(Grade A).* This recommendation needs to be put into perspective however based on the fact that ARBs and ACE inhibitors achieve similar reduction of proteinuria [131], and the common practice of using ACE inhibitors for cardiovascular prevention in diabetic patients that have both renal and cardiovascular impairment.

According to the KDOQI 2006, the renal benefit is a class effect and is common to both ACE inhibitors and ARBs, which are interchangeable. The KDOQI 2006, like the NICE 2008, recognise however possible differences between drugs and stress the benefits of long-acting RAS blockers that can be taken (and be eefective) in a single daily dose. The medico-economic recommendation of HAS 2008 [132] urging the use of ACE inhibitors in place of ARBs was based on the results of the ONTARGET study, which showed the equivalence of these two classes on the prevention of cardiovascular morbidity-mortality, and on the generally lower cost of ACE inhibitors, most of which are generic. These recommendations apply to non-complicated essential hypertension, excluding the preferential indications (diabetes, renal failure) acknowledged in the HAS 2004 (CRF) and 2005 (HTN) recommendations.

Achievement of the blood pressure targets in most patients requires a combination of 2 or more hypertensive medications from the thiazide diuretic or calcium channel blocker categories [18].

Few studies however have compared the strategies of adding hypertensive drugs in diabetic nephropathy.

Usually the addition of a thiazide diuretic potentiates the antihypertensive and antiproteinuria effects of the RAS blocker, and these products should be used when renal function is altered due to the early sodium retention that accompanies it [133].

Recommendations

R 18 – RAS blockers are preferentially indicated with diabetic nephropathy due to their antihypertensive and antiproteinuria effect *(Grade A).*

R 19 – Treatment based on 2 or more hypertensive drugs is usually necessary to attain the blood pressure target. Thiazide diuretics or long-acting calcium channel blockers can be used as second-line treatment *(Grade C).*

6.4. When to start

In hypertensive patients with normal urinary albumin, the use of ACE inhibitors reduces the incidence of microalbuminuria (BENEDICT) [134], (ROADMAP) [135].

In hypertensive T2DM patients with microalbuminuria, these drugs should also be used for the prevention of diabetic nephropathy (IRMA-2) [136,137].

The benefits of ARBs were demonstrated in patients with type 2 diabetes and proteinuria > 0.5 g/d (RENAAL, IDNT) *(Grade A).* These patients should thus be treated for the prevention of progression and reduction of the incidence of ESRD.

6.5. Stage up to which CRF can be treated with RAAS blockers

The benefits of RAS blocker treatment persit until the most advanced stages of renal failure, although if the absolute magnitude of this benefit is lower considering the shorter timeframe to ESRD [138,139].

RAS blockers are also recommended as the preferred treatment for hypertension in patients beginning dialysis due to their ability to maintain the longest residual diuresis (KDOQI HTN) *(Grade C).*

Recommendation

R 20 – RAS blockers are indicated as the preferred treatment in hypertensive diabetics *(Grade B);* in diabetics with micro- and microalbuminuria, including those that are normotensive *(Grade B),* provided that the systolic BP on treatment does not drop below 120 mmHg (peer consensus); and finally, in patients with diabetic nephropathy at all functional stages of chronic kidney disease *(Grade A).*

6.6. Optimisation strategies

ARBs (and ACE inhibitors) as monotherapy reduce proteinuria by an average of 35-40% and reduce in proportion the risk of progression of DN2. Many patients have persistent proteinuria and GFR decline despite RAS blocker treatment at the maximum recommended dose (and as used in the trials).

The dietary intake of sodium chloride is the main modifying factor on the antiproteinuric effect of the RAS blockers. Dietary intake of sodium chloride should thus be limited to 6-8 g/d [HAS 2004 [116], HAS 2005 [117], KDOQI 2006 [140,141], NICE 2008 [142,143].

In patients that are unable to limit sodium intake, the effect of RAS blockers can be "rescued" through the use of thiazide diuretics [133].

Recommendations

R 21 – A sodium chloride limited diet (6-8 g/d) is recommended in diabetic patients to promote the antihypertensive and antiproteinuric effect of RAAS blockers *(Grade A).* The dietary intake of sodium should be regularly evaluated (with the 24-hour urine sodium measurement). Dietry counselling for limiting sodium intake should be clearly explained to the patient, ideally with the assistance of a dietician (peer consensus).

R 22 – RAS blockers should be titrated to the maximum authorised dose or until the blood pressure and urine protein targets are reached *(Grade A).* In nonresponding patients, an increase of doses beyond those outlined in the SPC dosages can be considered, provided that there is good tolerability (blood pressure, renal function, serum potassium) and a close monitoring *(Grade C).*

Recommendation

R 23 – ARBs and ACE inhibitors could be combined in patients with significant residual urine protein (> 1/g) or rapid progression of diabetic nephropathy, provided that there is acceptable tolerability (blood pressure, renal function, serum potassium) and a close monitoring *(Grade C).* This combination is not recommended however in any other situations (peer consensus).

6.7. Precautions for use

The antiproteinuric effect of ACE inhibitors and ARBs occurs relatively early after the treatment is introduced. This effect peaks 1 to 3 months after the start of treatment. This effect is dose-dependent with a different dose-response relationship from the low blood pressure relationship.

An increase in plasma creatinine up to 25 to 30%, maximum at 1 to 2 months after the introduction of treatment, can occur in patients, especially those with a glomerular filtration rate below 60 ml/min/1.73 m^2. The initial increase in plasma creatinine is associated with a more significant reduction of urine protein and, in the long-term, better preservation of renal function [144]. Treatment with RAS blockers therefore should not be decreased or discontinued, except if the increase in plasma creatinine exceeds 30% of the baseline value [144]. These products must also be decreased or temporarily discontinued in the event of intercurrent events that promote dehydration (fever, diarrhoea, heatwave).

Increased serum potassium (> 5.5 mmol/L) is a common complication of renin-angiotensin system blockers, particularly in diabetic patients, those with a glomerular filtration rate less than 60 ml/min/1.73 m^2 and those with a high dietary intake of potassium (fruits and vegetables). This rarely results in the definitive discontinuation of RAS blockers but requires closer monitoring and more frequent measurements of serum potassium and eventually dose reduction of the ARB.

Recommendation

R 24 – RAS treatment in diabetic patients with nephropathy may frequently lead to increased plasma creatinine and potassium. Plasma creatinine, eGFR and blood potassium should be measured 1 to 2 weeks after the start of treatment or after any dose increase. An increase of 25% to 30% of creatinine from the baseline and up to 5.5 mmol/l of blood potassium on treatment is acceptable and should not result in the withdrawal of treatment *(Grade C).* An increase beyond these values requires specialised advice (peer consensus).

6.8. Associated measurements

Several measurements may be associated with blood pressure control and the use of RAS blockers.

6.8.1. Limitation of dietary protein intake

The benefit of limited dietary protein intake in the progression of diabetic nephropathy has not been formally demonstrated [145,146]. The 2004 HAS recommendations [116] specify an intake of 0.8-1.0 g/kg/d *(Grade B)*. The KDOQI 2006 [140,141] and the CARI [147-151] guidelines endorse an intake of 0.75 g/kg/d. Protein restriction is theoretically contraindicated in nephrotic patients due to the risk of malnutrition.

The dietary protein intake should be regularly evaluated in patients with CRF using the urine urea measurement according to the Maroni formula [152]: protein intake (g/d) = urine urea (mmol/d)/5.5.

Recommendation

R 25 – The dietary protein intake must be moderately limited (0.8 to 1.0 g/kg/d) in diabetic patients with diabetic nephropathy and an eGFR < 60 ml/min/1.73 m^2, and in the absence of nephrotic syndrome *(Grade B)*. Protein intake should be regularly evaluated using the 24 hour urine urea measurement (peer consensus).

6.8.2. Weight loss

In obese patients, weight loss may constitute an important accessory to hypertensive treatment for restoring sensitivity to insulin and improving lipid profile. These metabolic improvements are likely to slow down the progression of chronic kidney disease.

Recommendation

R 26 – Obese patients with diabetic nephropathy should ideally lose weight (10%) while ensuring adequate nutritional intake *(Grade B)*. The potential cardiovascular and metabolic benefits associated with weight reduction must also be taken into account *(Grade A)* (CARI Guidelines).

6.8.3. Quitting tobacco use

There are no prospective randomised studies on this subject. The concordant data of retrospective studies and small cohort studies have suggested the following conclusions (CARI Guidelines):

- tobacco addiction accelerates the development and progression of diabetic nephropathy;
- quitting tobacco slows the progression of diabetic nephropathy;
- ongoing tobacco addiction confers a greater risk than passive tobacco use.

Recommendation

R 27 – All diabetic patients (T1DM and T2DM) must be strongly encouraged to not smoke or to quit smoking in order to reduce renal risk, as well the cardiovascular risk *(Grade C)*.

6.9. Specificity of nephropathy in type 1 diabetes (DN1)

In hypertensive patients with type 1 diabetes, hypertension should be treated preferentially by an ACE inhibitor.

At the stage of normoalbuminuria and in the absence of hypertension, there is no systematic indication for treatment with ACE inhibitors or other RAS blokers.

At the stage of microalbuminuria, in accordance with the existing recommendations (KDOQI 2005, NICE 2008), treatment with ACE inhibitors should be started, even if blood pressure is normal [153].

Following the Lewis collaborative trial [154], ACE inhibitors have been recommended for the treatment of diabetic nephropathy associated with type 1 diabetes, as these drugs have a demonstrated benefit in the reduction of the combined criteria: doubling of the plasma creatinine + incidence of ESRD + death.

Recommendation

R 28 – Treatment with ACE inhibitors should be started in T1DM with hypertension *(Grade B);* and in diabetics with microalbuminuria, regardless of the blood pressure *(Grade B);* in diabetics with nephropathy (proteinuria > 300 mg/d and/or eGFR < 60 ml/min/1.73 m^2) *(Grade A)*.

7. Cardiovascular risk management in diabetic patients with chronic renal impairment (high risk already established)

7.1. Objectives

To define and raise awareness of the high cardiovascular risk established by the combination of diabetes and renal impairment.

To update the data on the management of each risk factor by considering the effect of the presence of renal impairment relative to the traditional recommendations.

7.2. Introduction

Subjects who present concurrently with diabetes and chronic renal failure have on the whole an increased absolute cardiovascular risk.

In the majority of cases, the risk of a type 2 diabetic patient with chronic renal impairment **dying of cardiovascular causes is much higher than that of progression to end-stage renal disease** [1] (Level 4).

7.3. Cardiovascular risk evaluation

This evaluation does not differ from that of other patients (see the ANAES Clinical Practice Recommendations "Methods of overall cardiovascular risk evaluation" (ANAES 2004: www.has-sante.fr)).

However, there are no risk equations that include renal function or urine albumin in their prediction algorithm; as a result, all of these equations greatly underestimate the cardiovascular risk in patients with chronic renal failure in general and in diabetic patients with chronic kidney disease (CKD) in particular. Recent data from the ADVANCE study highlight the excess cardiovascular risk incurred by both deterioration of the GFR and the increase in urine albumin levels [74].

Some epidemiological data enable an estimation to be made concerning the order of magnitude of the relative risk related to renal impairment, independent of the risk attained by traditional risk factors:

- **microalbuminuria:** cardiovascular risk multiplied by **1.5 to 2;**
- **macroalbuminuria-proteinuria:** risk multiplied by **2 to 3;**
- **eGFR < 60 ml/min:** risk multiplied by **1.5 to 1.8;**
- **eGFR < 30 ml/min:** risk multiplied by **3 to 5.**

Recommendation

R 29 – Diabetic patients with renal impairment have a very high cardiovascular risk; it must be stringently managed with regard to the different known factors [155] *(Grade A).*

7.4. Management of cardiovascular risk factors

7.4.1. Blood pressure reduction

The data from randomised, controlled trials **testing the specific cardiovascular effect of hypertensive drugs** in diabetic patients with renal disease are relatively limited.

A meta-analysis of the sub-groups of studies using a full-dose of ACE inhibitors compared to studies using a dosage less than or equal to half of the maximum dose showed a 22% reduction in mortality from all causes [156,157] *(Grade B).* The meta-analysis by Balamuthusamy (2008) [158] confirmed the benefit of RAAS blockers on mortality and CV events in diabetics with nephropathy.

The ONTARGET trial included 37% of diabetics at high cardiovascular risk, although few had renal impairment [159]. Telmisartan was equivalent to ramipril on the main criterion (a combination of major cardiovascular events). The combination of these two drugs did not provide additional benefit for this criterion but was associated with more adverse effects, particularly renal *(Grade B).* **ONTARGET can thus be considered as demonstrating equivalent results for ACE inhibitors and ARBs with regard to mortality and cardiovascular events, including for CKD diabetic patients.**

In the ASCOT study, the arms including amlodipine and perindopril were associated with fewer cardiovascular events in patients with chronic kidney disease compared to the atenolol and bendroflumethiazide arms [160] *(Grade B).*

In type 2 diabetics with high cardiovascular risk, the ADVANCE study demonstrated the benefits, regardless of the initial blood pressure, of the combination of perindopril and a diuretic at low doses *versus* their placebo on an endpoint combining micro- and macrovascular events [161]; death from cardiovascular origin or any causes was less frequent in the active arm *(Grade B).*

Finally, two combinations were compared in the ACCOMPLISH trial: benazepril ± amlodipine *vs.* benazepril ± hydrochlorothiazide, in 11,506 patients, over 60% of whom were diabetics [162] *(Grade B).* The study was stopped prematurely, after 36 months, after demonstrating a benefit of the amlodipine combination on a combined criterion (death of cardiovascular origin, myocardial infarction, ischaemic CVA, resuscitated cardiac arrest, hospitalisation for angina pectoris, coronary artery revascularization).

Recommendation

R 30 – The recommendations with regard to blood pressure in the management of cardiovascular risk in diabetics with renal impairment are:

- blood pressure < 130 mm Hg systolically and < 80 diastolically (*Grade B* for cardiovascular risk);
- first-line use of either the ACE inhibitors or long-acting ARBs, aiming for the full-dose administration of the selected drug *(Grade B);*
- frequent need for combination with a second class drug: dihydropyridine or thiazide *(Grade B).*

7.4.2. Treatment with lipid-lowering agents:

The indications for the use of hypolipidaemic agents for cardiovascular prevention in diabetics with renal impairment do not differ from the general recommendations. There is a large amount of data available based on analyses of sub-groups in the many cardiovascular trials testing statins (HPS [164], TNT [165]). Statin treatments on the whole reduce the incidence of major coronary events, coronary revascularisation and ischaemic cerebral vascular accident at 5 years by about 20% for each mmol/l reduction of LDL cholesterol. The benefits of hypolipidaemic treatment in the particular population of subjects that present with chronic renal failure was the focus of a trial (SHARP) that compared the combination of simvastatin and ezetimibe [163] and concluded that there was a 17% reduction in major events of atheromatous origin.

The recommendations are to begin treatment with one of the statins that has demonstrated its efficacy (atorvastatin, simvastatin, and to a lesser extent, pravastatin) in diabetic subjects in whom the coronary risk at ten years is estimated to be greater than or equal to 20%, or in whom the risk of cardiovascular death at ten years is estimated to be greater than 10%. And yet, diabetics over the age of 50 years that present with stage 2 or 3 chronic renal failure have a coronary risk at ten years greater than 20%. In diabetic patients with coronary artery disease that present with moderate renal impairment (eGFR < 60 ml/min/1.73m²), only the analysis from a sub-group of the TNT (Treating to New Targets) study

suggested a reduction of cardiovascular events (- 35% over 5 years) in the group taking 80 mg of atorvastatin *vs.* 10 mg of atorvastatin [165] (Level 2). This single post hoc study is not sufficient for systematically recommending high doses of statins in this population (except in cases of documented coronary disease).

The KDOQI 2006 recommendations go further and consider all patients with chronic kidney disease (eGFR < 60 ml/min/1.73 m^2), whether or not they are diabetic, as eligible for secondary prevention and suggest treating them with statins, with an LDL cholesterol target < 1.00 g/l.

A meta-analysis of 50 studies on over 30,000 subjects treated with statins or placebo assessed the cardiovascular benefits of this class of hypolipidaemic agents. This study suggests that, in the population of subjects with renal impairment before the dialysis stage, statins reduce mortality of any origin or from cardiovascular cause, as well as the incidence of non-fatal cardiovascular events [163] (Level 2) (meta-analysis including small studies, which dilute the significance, although the benefit persists).

Recommendation

R 31 – The recommendations for hypolipidaemic treatment in the management of cardiovascular risk of diabetics with renal impairment are:

- The implementation of treatment with hypolipidaemic agents is based on the concept of very high cardiovascular risk due to the combination of diabetes and chronic kidney disease.
- The introduction of a statin at an effective dose, regardless of the initial LDL-cholesterol, with the objective of LDL cholesterol < 1.00 g/l. *(Grade B).*
- The highest level of evidence in type 2 diabetics is for atorvastatin 10 mg and simvastatin 40 mg *(Grade A).*

Other classes of hypolipidaemic agents (non-recommended):

- fibrates: a secondary sub-group analysis of the international VA-HIT trial assessed the benefits of gemfibrozil *vs.* placebo as secondary prevention in 1046 men with an estimated creatinine clearance less than 75 ml/min/1.73 m^2 and low HDL (less than 0.40 g/l): the incidence of myocardial infarction, whether fatal or not, was decreased [164]. On the other hand, gemfibrozil was associated with an increase in serum creatinine, raising the possibility of an iatrogenic renal risk. Consequently, fibrates are generally not recommended as primary prevention for reducing the cardiovascular risk in diabetic patients with chronic renal impairment. The limited extent of their indications are pointed out in the HAS 2006 recommendations for drug management of type 2 diabetes, and the FIELD and ACCORD Lipids trials results do not modify this recommendation;
- ezetimide: the recent SHARP trial results, which compared the combination of simvastatin and ezetimibe *vs.* placebo [163], suggest it may be beneficial to use ezetimibe in combination with simvastatin in chronic renal failure, a benefit seemingly derived from the decrease in LDL-cholesterol levels.

7.4.3. Treatment with platelet aggregation inhibiting drugs:

The indications for use of platelet aggregation inhibiting drugs as cardiovascular prevention in diabetic subjects with renal impairment do not differ from the general recommendations. The risk of minor haemorrhaging is moderately increased in patients with chronic renal failure.

There is no data from large-scale randomised, controlled trials, specifically on subjects with renal failure, whether diabetic or not. In observational studies *(Grade C),* aspirin at an aggregation inhibiting dose is associated with a reduction in mortality in subjects with a history of myocardial infarction and eGFR < 60 ml/min/1.73m², although with an increased risk of haemorrhage that incorporates only minor hemorrhagic events. The clinical relevance of biological platelet resistance to aggregation inhibition is poorly known in diabetics.

A post hoc analysis of the HOT trial was recently presented (World Congress of Nephrology 2009: Abstract 766. Presented May 25, 2009), which confirmed the benefits of aspirin 75 mg/d in the prevention of mortality and CV events in patients with chronic kidney disease. There was a significant benefit in patients with an eGFR < 45 ml/min/1.73 m^2, and more modest result for eGFR between 45 and 60 ml/min/1.73 m^2. The hemorrhagic risk was greatly increased, although not significantly.

It should be noted that all of these trials with aspirin predate the widespread use of statins, and it is not clear whether the benefits are also significant in patients treated with statins.

Recommendation

R 32 – The recommendations in subjects with renal failure are to introduce platelet aggregation inhibiting drugs at small doses (75 mg/d of aspirin) as soon as the cardiovascular risk becomes very high. The objectives then become secondary prevention. This intervention is therefore relevant for the majority of diabetic patients with renal failure, as mentioned above, with the exception of increased hemorrhagic risk *(Grade B).*

7.5. Lifestyle adjustment: diet, sodium intake, weight control, tobacco use, etc.

- **Dietary adjustment.** The nutritional rules in type 1 and 2 diabetic patients are presented in other recommendations. Protein intake was discussed in the preceding chapter.
- **Sodium intake.** Studies assessing the efficacy of sodium intake reduction with the goal of reducing cardiovascular risk in patients with renal failure resulted in the KDOQI clinical practice recommendations [167]. In the DASH-SODIUM study (Dietary Approaches to Stop Hypertension), the active intervention arm diet was associated with a reduction in blood pressure at all initial levels of sodium intake compared to a typical western diet [168]

(Grade A). Sodium intake is easy to assess in all patients with the 24-hour urine sodium output measurement.

Recommendation

R 33 – For all diabetic patients with renal failure and hypertension, and by extension, for all diabetic patients with chronic kidney disease, a reduction in sodium intake, so as to have a maximum of 2.4 g/d, or 100 mmol/l, or 6 g of dietary salt per day, is recommended in order to lower blood pressure *(Grade A)* and cardiovascular risk.

- **Weight control.** There are no specific trials in the population of diabetics with chronic kidney disease. The extrapolation of data acquired in the general population and in the diabetic population, and the epidemiological data have led to recommendations for weight reduction of around 5% of body weight at one year in overweight subjects (BMI > 27 kg/m^2) *(Grade C)*.
- **Quitting cigarette smoking.** There are no specific trials in patients with chronic kidney disease with regard to the benefits of quitting cigarette smoking on the cardiovascular prognosis. However, trials in the general population and the epidemiological data **demonstrate without ambiguity the benefits of quitting smoking** *(Grade B).*
- **Physical activity.** The benefits of regular physical activity on the cardiovascular prognosis of patients with renal failure, and especially in diabetics, have not been studied in a quality trial. Nevertheless, the cardiovascular benefits conferred by regular physical activity in the general population and in diabetic subjects favour this recommendation for diabetics with renal failure. Physical activity may bring about a transient increase in urinary albumin output. However, there is no factor that could lead to worsening of nephropathy and no contraindication to physical activity due to the nephropathy as such.

7.5.1. Glycaemic control

It appears that the cardiovascular benefits of intensification of hypoglycaemic treatment are real but are probably delayed by several years in both type 1 and 2 diabetes.

7.5.2. Management of anaemia

Monitoring of serum haemoglobin is recommended in patients with an eGFR less than 60 ml/min/1.73 m². Several recent studies and meta-analyses resulted in the revision of indications for erythropoiesis stimulating agents (EPO) by the EMA (European Medicine Agency) in 2007. In a systematic review of 15 studies that evaluated the treatment of anaemia in patients with renal failure before the dialysis stage, no effect on mortality was demonstrated in the small group of three studies that enabled this evaluation to be done [169,170] *(Grade B)*. In a systematic review of 9 studies examining the association between the target level of haemoglobin and mortality in anaemic patients with chronic renal failure, an increased risk of mortality from all causes was demonstrated in the group with the highest objective (from 12.0 to 16.0 g/dl) compared to the low objective (9.0 to 12.0 g/dl); this effect was dominated however by a single large study in dialysed patients presenting with cardiopathy. An analysis limited to the sub-group of pre-dialysis patients did not show a difference in mortality between the two haemoglobin objectives. It should be noted that blood pressure control was more difficult to achieve in the group with the highest haemoglobin target *(Grade B).* Confirming doubts raised by the CREATE and CHOIR studies, the TREAT study (Trial to Reduce Cardiovascular Events with Aranesp Therapy) [171] did not show benefits (combined criteria of mortality and major renal or cardiovascular events) of darbepoetin alpha *versus* placebo (haemoglobin objective of 13 g/dl) in anaemic type 2 diabetics with estimated filtration between 20 and 60 ml/minute/1.73 m^2; it also raised concerns with regard to the safety of this therapeutic intervention: the risk of cerebrovascular accidents was almost doubled in the active arm and the incidence of thromboembolism was increased.

Recommendation

R 34 – The EMA recommendation is to use EPO for the treatment of anaemia only when it is associated with symptoms, with a haemoglobin objective of 10.0 to 12.0 g/l and emphasising the need to not exceed 12.0 g/l.

7.6. Monitoring and course of cardiovascular risk

7.6.1. Monitoring of risk factors

The recommendations for monitoring cardiovascular risk in diabetic patients with chronic renal impairment do not differ from those of other diabetics.

7.6.2. Assessment of renal function and urinary albumin excretion

Preliminary data suggest that:

The normalisation of urinary albumin excretion results in a reduction of cardiovascular risk that is beyond the improvement expected of other risk factors (such as the concurrent reduction of blood pressure).

The reduction of proteinuria is an intermediate marker of reduction of cardiovascular risk.

7.6.3. Assessment of latent vascular injury

The general recommendations for primary prevention in the follow-up of diabetic patients include:

- a yearly, systematic resting electrocardiogram;
- a cardiology work-up for screening of asymptomatic myocardial ischaemia in subjects with increased cardiovascular risk;

- a Doppler ultrasound of the lower limbs with measurement of the systolic pressure index (SPI) for arteriopathy screening of the lower limbs.

This screening should be undertaken in patients over the age of 40 years or who have been diagnosed with diabetes for 20 years, the assessment should be repeated every 5 years or less in case of associated risk factors.

8. Preparation for renal replacement therapy in diabetes

8.1. Some important risk factors for survival in dialysis, which can be identified before dialysis is required

Changes in the demographics and the presence of multiple risk factors and co-morbidities in diabetics who start a programme of dialysis result in a reduction of their life expectancy compared to the general population of the same age [172].

Most of these risk factors can be identified in the pre-dialysis period, allowing a potential window of intervention through risk reduction measures, (see preceding chapters).

One prospective, observational study [173] and the studies from the main registries of patients on dialysis [174-176] were able to describe the influence of the co-morbidities and the factors that traditionally affect survival on dialysis at 1 and 5 years [173,177]:

- **1. Vascular complications** (39%) and **infections** (33%) account for half of the observed cases of mortality in the first year (56%). Limb amputations and infections of dialysis vascular access, in dialysed subjects are mainly observed in diabetic patients.
- 2. A decrease in the **haemoglobin** level of 1 g at the start of dialysis (8.4 *vs.* 9.4 g/dl, $P = 0.01$) is a classic factor of excess mortality, though of complex significance [173,176,178,179]. Studies on the early correction of haemoglobin levels (CHOIR, TREAT) [171] however have not demonstrated the expected cardiovascular protection, with potential excess risk of thromboembolism, especially CVA recurrence in patients that responded poorly to EPO and/or require high doses of erythropoiesis stimulating agents (see preceding chapter).
- 3. Greater frequency of clinical expression of **peripheral vascular disease** (PVD) (39% mortality in patients with PVD *versus* 18.5% in those without PVD, $P = 0.04$), often decompensated by episodes of hypotension during and post-dialysis [172,180,181].

In most studies [178], an increased calcium-phosphorous product [182], age and the presence of vascular co-morbidities, including ischaemic cardiac disease [172] and peripheral vascular disease, were associated with overall mortality at 5 years [176,178,182]. This has been confirmed in type 2 diabeics [173,183]. A lower or haemodiluted haemoglobin level, and an eGFR that is lower at the first dialysis, predict higher early mortality [171,178,184]; this has to do with indirect signs of associated heart failure, which remain underestimated [185-187]. The calculation of the "dry weight" of diabetics [188], the more widespread use of monitoring of markers of ischaemia (troponin T) [187,189], of ventricular remodelling (LVH) [190], and of cardiac distension (BNP) [189] must be the focus of studies of impact and cost/benefit ratio [183,186].

In the cohort study including subjects over the age of 65 years [185], both diabetics and non-diabetics, the course of the patients was the following:

- 1. The diabetic subjects started haemodialysis (HD) with a significantly higher creatinine clearance (MDRD) for serum creatinine levels that were not statistically different. **This confirms the importance, in all patients, and especially in an advanced stage, of estimating the creatinine clearance with the MDRD formula.**
- 2. There was no statistically significant difference in systolic or diastolic blood pressure, but a higher number of hypertensive drugs were required in the group of diabetic patients for the control of blood pressure ($P < 0.01$).
- 3. A high prevalence of vascular disease upon initiation of HD was found but was clearly higher in diabetic patients. Additionally, many more vascular complications were observed in the first and second year in the group of diabetic patients ($P < 0.01$).
- 4. Survival was poor but without significant difference between the two groups (20.0% at 3 years in non-diabetics and 17.0% in diabetic patients).

In conclusion, patients over the age of 65 years with ESRD have a low survival rate, which is not made worse by type 2 diabetes. There is an increased prevalence of vascular co-morbidities in both groups, but the incidence of cardiovascular complications is significantly higher in diabetics immediately after management with dialysis, probably due to greater arterial rigidity and poorer adaptation to the sudden haemodynamic changes of the dialysis session.

All of these concepts reinforce the recommendations in the preceding chapters with regard to management of cardiovascular risk factors, which are sometimes slightly neglected or done in "moderation" due to the chronic renal failure or a "potential risk" of the products used.

8.2. Problem of vascular access

A large consensus maintains that the native arteriovenous fistula is the access of choice for haemodialysis [174,186,191,192]. There is however a low rate of fistula use in the first dialysis session.

The type of access used for the first session is a pragmatic marker of fragility of the managed patients, of maintenance of the patients on dialysis in a specialised centre and of mortality. The lack of transfer to specialised care in a timely manner also seems to limit the early optimisation of vascular access, which could impact directly or indirectly on the medium-term survival [177,191-194].

8.3. Calcium-phosphorus metabolism and arterial calcifications [173,187,195,196]

Calcium-phosphorus anomalies and medial calcific sclerosis are present early in the course of deterioration of renal function in diabetics [195,196]. Monitoring and supplementation appear to be necessary beginning in stage 3 of chronic kidney disease in 30-40% of diabetics. It is recommended that increased parathyroid hormone levels be controlled and maintained within normal values in the pre-dialysis phase and between 100-200 ng/ml during dialysis; the use of native vitamin D is also recommended [195]. Active vitamin D is rarely necessary before the dialysis stage and can cause episodes of hypercalcaemia and acute renal failure in non-dialysed subjects. Besides its musculoskeletal consequences, hyperparathyroidism, like adynamic bone, promotes the transfer of the bone calcium pool to the soft tissues and vessels, with a risk of worsening the diabetic medial calcific sclerosis [195,196]. Arteriopathy of the upper limbs of diabetics is a factor that limits the primary functionality of radiocephalic fistulas, and the need for brachiocephalic access poses a greater risk of cardiac effects [172,194]. Modifications of the serum calcium-phosphorous product, such as hypocalcaemia and hyperphosphoraemia, occur later and often mark the transition to the dialysis stage [173,182]. Early monitoring and suitable interventions, dietary measures and calcium-vitamin supplementation should enable a large number of patients to reach the recommended goals [195] and to improve their cardiovascular and bone status.

8.4. Diabetic treatments

Diabetes is difficult to manage at the end-stage of chronic kidney disease (stage 5 CKD). Uraemia, inflammation and dialysis can complicate glycaemic control, either in synergy and/or opposition, by influencing the secretion of insulin, its metabolism and the sensitivity of peripheral tissues [197] (see preceding chapter).

When the patient is in dialysis, the glycaemic level may fluctuate widely during the day due to the opposed effects of renal failure and the dialysis sessions. Insulin therapy remains the cornerstone of treatment, as most oral treatments have not been evaluated or are contraindicated due to their risk of accumulation (metformin above all). The subsequent dosage adjustments must be individualised according to the glycaemia self-monitoring profiles and by taking into account the cardio- and neurovascular risks.

Pharmacological therapy of diabetic patients with ESRD must be individualised: the treatment objectives are a haemoglobin A_{1c} level close to 7%, fasting blood glucose less than 1.4 g/l and a postprandial blood glucose less than 2 g/l (194). The haemoglobin A_{1c} may be overestimated at the dialysis stage, but it remains a reasonable means of evaluating the glycaemic control in this population [194].

Diabetic patients with ESRD have a **continuous** need for therapeutic education, with the focus on recognising and treating hypoglycaemia (expert advice).

It is highly recommendated that the monitoring and management of diabetic patients with ESRD be shared between trained endocrinologists competent in the management of ESDR and trained nephrologists competent in diabetology [194] (expert advice)

8.5. Peritoneal dialysis [193,198]

In France, 38% of patients who start dialysis treatment are over the age of 75 years and 36% of those are diabetic. One out of five (18%) begin peritoneal dialysis (PD) [176]. Diabetes is not a determining factor for PD due to visual and motor handicaps, excess abdominal fat, infectious risks, nutritional factors (hypoalbuminaemia related to prior proteinuria), glucose intake of PD bags and insulin management. The survival results [176] however show that only 9.2% of patients who were initially managed with PD had to be transferred to haemodialysis. Of them, 35.8% died, but half (52.7%) continued to maintain the technique at 2 years.

8.6. Kidney transplant

Type 1 diabetics can receive:

- islet cell transplantations within the framework of experimental protocols in France, either isolated or after renal transplantation;
- double kidney-pancreas transplantation;
- more rarely, isolated pancreas transplantations, with the option of kidney transplantation afterwards;
- kidney transplantation alone;
- or much more rarely, pancreas after kidney transplantation.

Kidney-pancreas transplantation, preventive kidney transplantation and living-donor transplantation are the best means of rehabilitation and improvement of life expectancy in these patients (199). Furthermore, these methods result in a significant decrease in treatment costs after the first year [200,201].

Type 2 diabetics can also receive kidney allografts. Access to the transplantation however is rather reduced [176,202] and 2 years after the start of dialysis, type 2 diabetics are transplanted less often than non-diabetics, particularly those that started urgent dialysis in cases of ischaemic cardiopathy and proximal arteriopathy. Nevertheless, the results of kidney transplantation in type 2 diabetics are comparable to those of the general population, even if there is increased morbidity, and frequency and length of hospitalisation in the first year.

8.7. Conclusions

The preparation for renal replacement therapy in diabetic patients prompts several recommendations (expert advice).

Recommendations

R 35 – Preparing the vascular access and proposing dialysis earlier than is presently done.

R 36 – Identifying and stabilising the vascular factors of morbidity-mortality in dialysis.

Recommendations

R 37 – Managing anaemia and calcium-phosphorous metabolism anomalies.

R 38 – Assessing and correcting sodium-water retention.

R 39 – Preventing infectious risks and updating vaccinations.

All of these recommendations are usually carried out by the nephrologist.

9. Diabetic nephropathy and podologic risk

Objective: To respond to the question concerning increased podologic risk in patients with advanced diabetic nephropathy.

There is a large amount of data supporting the fact that both diabetes and renal failure are risk factors for amputation [203-205]. This relationship between renal failure and diabetes runs both ways: in diabetes, end-stage renal disease is a risk factor of amputation [206], and in dialysis, diabetes is a risk factor of amputation [207,208].

Recommendation

R 40 – The combination of diabetes and renal failure is a major risk factor of diabetic foot syndrome and amputation. As a result, particular attention must be given to the feet of patients presenting with this combination of diabetes and nephropathy, especially at the point of end-stage renal disease and in the beginning of dialysis *(Grade B/C)*.

Epidemiological data indicates that amputation in patients with renal failure is a significant risk factor of death from all causes [209-211]. Moreover, end-stage renal disease is a factor for poor post-revascularisation prognosis.

The question of the **revascularisation technique** for "diabetic feet" in patients presenting with end-stage renal disease is important. Some references in the literature side in favour of revascularisation [212], while other studies indicate that the poorer prognosis in patients with end-stage renal disease and the risk of death associated with revascularisation procedures make end-stage renal disease a contraindication for revascularisation [213]. The data in the literature only report on series that are audits of results. There is no study that clearly compares strategies of amputation or of revascularisation [214] through a randomised, controlled approach. In the current literature, the group notes the problem posed by the lack of data that could assist in the decision process between revascularisation or amputation in diabetic subjects that have end-stage renal disease.

Recommendation

R 41 – The group notes the difficulty of caring for trophic problems of the lower limbs in diabetic patients with nephropathy (especially in case of end-stage renal disease), particularly in cases with prior history of amputation or diabetic foot syndrome. The absence of data for therapeutic strategies, notably with regard to revascularisation, justifies specific research in this domain, for instance by specifically consulting the REIN registry.

10. Diabetic nephropathy and care pathways

The relationship between diabetic nephropathy and the management of patients with a care pathway has become an important question. There are several articles on late care by the nephrologist (already addressed in a HAS recommendation on the diagnosis of chronic renal failure [215]), but early care by the diabetologist must be planned for in view of the data suggesting that more frequent visits to a diabetes care centre is a factor in the improvement of metabolic control and reduction of renal complications of type 1 diabetes [216,217]

The care pathway of a patient with diabetic nephropathy has not been clearly identified. The recommendations of the HAS working group on updating drug treatment of type 2 diabetes emphasises *the need for regular renal follow-up, and the recommendation that care of patients with nephropathy be the subject of close collaboration between general practitioners, nephrologists and diabetologists (peer consensus) (the time interval for medical visits was described in the specific chapter on management).*

The specificity of the drugs intended for the treatment of both glycaemia and blood pressure (preceding chapters) seems to justify the systematic consultation of specialists in diabetology and nephrology at this stage of complications. The collaboration of diabetologists and nephrologists, or even the grouping together of nephrology and diabetology services, or at least the presence of a diabetologist in collaboration with the departement of nephrology seems to be preferable when possible. Furthermore, the data in the literature concerning the benefits of an educational programme on the management of the diabetic foot [188] or glycaemic control [219] for patients on dialysis prompts close collaboration, even at the point of end-stage renal disease.

Recommendation

R 42 – The specificity of the management of diabetic subjects with nephropathy justifies the systematic consultation of a specialist in diabetology in collaboration with with the specialist of nephrology (the fine management of diabetes and its specificities can improve patient care) (peer consensus).

11. Conflicts of interests

Authors declare occasional involvements: advisory services and/or clinical trials as investigator and/or medical formation, and/or invitation at congress:

F. Bonnet: Astra-Zeneca, Takeda, MSD, Novartis, Novo-Nordisk, Sanofi-Aventis, Pierre Fabre, Boehringer-Ingelheim, Lilly, Servier.

E. Gauthier: Roche, Amgen, Frésenius, Gemzyne, Baxter.

H. Gin: GSK, Novo-Nordisk, Lilly, Pfizer, Schering-Plough, MSD-Chibret, Sanofi-Aventis, Novartis, Merk-Lipha, Servier, BMS, Astr-Zeneca, Takeda, Pierre-Fabre, Boehringer-Ingelheim.

J.-M. Halimi: Boehringer, Novartis, Sankyo, Menarini, Roche, Astra Zeneca, MSD, BMS-Sanofi-Aventis, Servier, Janssen Cilag, Takeda, Bayer.

S. Hadjadj: Astra Zeneca, Boehringer, Bristol Myers Squibb, Eli Lilly, Glaxo Smithkline Becham, Medtronic, Menarini, Merck/MSD Chibret, NovoNordisk, Novartis, Roche, Sanofi-Aventis, Servier, Siemens, Takeda.

T. Hannedouche: MSD, Novartis, Takeda, Genzyme, Shire, Roche, Amgen.

R. Roussel: MSD-Chibret, Sanofi-Aventis, Roche, Novo Nordisk, Sanofi-Aventis, Servier, Eli Lilly, Takeda, GSK.

V. Rigalleau: Bayer, GSK, Novo-Nordisk, Lilly, Pfizer, Schering-Plough, MSD, Sanofi-Aventis, Novartis, Merk-Lipha, Servier.

P. Zaoui: Novartis, Roche, Amgen, Vofor, Mitsubishi, Genzyme.

Références

[1] La prise en charge des diabétiques urémiques. Règles de bonnes pratiques cliniques. Rapport des experts de l'ALFEDIAM et de la Société de Néphrologie. Diabetes Metab 1999;25:7-72.

[2] The National Institute for health and clinical excellence. Clinical guidelines on Type 2 diabetes 2002;1-258F:Renal disease.

[3] Levey AS, Coresh J, Balk E, Kausz T, Levin A, Steffes MW, *et al.* National Kidney Foundation Practice Guidelines for chronic kidney disease: evaluation, classification and stratification. Ann Intern Med 2003;139:137-47.

[4] Joint specialty comittee on renal Medicine of the Renal Association, and the Royal College of general practitioners. Chronic Kidney disease in adults: UK guidelines for Identification, Management and referral. London, Royal College of Physicians, 2006.

[5] American Diabetes Association. Standards of Medical Care Diabetes Care 2006;29:S4-S42 and 2007;30:S4-41.

[6] Scottish intercollegiate guidelines network. Diagnosis and management of Chronic Kidney Disease. A national clinical guideline 2008. Available on www.sign.ac.uk.

[7] USRDS. Incidence and Prevalence of ESRD. In US Renal Data System 2003. Annual Data Report, Bethesda, MD, National Institute of Health, National Institutes of Diabetes and Digestive and Kidney diseases 2003;47-60.

[8] Rapport Rein. BEH 2008;43.

[9] Parving H-H, Oxenboll B, Svendsen PA, Christiansen JS, Andersen AR. Early detection of patients at risk of developing diabetic nephropathy. Acta Endocrinol 1982;100:550-5.

[10] Mathiesen ER, Oxenboll B, Johansen K, Svendsen PA, Deckert T. Incipient nephropathy in type I (insulin-dependent) diabetes. Diabetologia 1984;26:406-10.

[11] Parving H-H. Chaturvevedi N. Viberti G, Mogensen CE. Does microalbuminuria predict diabetic nephropathy? Diabetes Care 2002;25:406-7.

[12] Magee GM, Bilous RW, Cardwell CR, Hunter SJ, Kee F, Fogarty DG. Is hyperfiltration associated with the future risk of developing diabetic nephropathy? A meta-analysis. Diabetologia 2009;52:691-97.

[13] Dinneen SF, Gerstein HC. The association on microalbuminuria and mortality in non insulin-dependent diabetes mellitus. Arch Intern Med 1997;157:1414-8.

[14] Glassock RJ, Hirschman GH, Striker GE. Workshop on the use of renal biopsy in research on diabetic nephropathy: a summary report. Am J Kidney Dis 1991;18:589-92.

[15] Perkins BA, Krolewski AS. Early nephropathy in type 1 diabetes: the importance of early renal function decline. Curr Opin Nephrol Hypertens 2009;18:233-40.

[16] SIMS REIN 2007.

[17] Preserving renal function in adults with hypertension and diabetes; a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Am J Kidney Dis 2000;36:646-61.

[18] Bakris GL, Williams M, Dworkin L, Elliott WJ, Epstein M, Toto R, *et al.* Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Am J Kidney Dis 2000;36:646-61.

[19] Vora JP, Ibrahim HA, Bakris GL, Hum J. Responding to the challenge of diabetic nephropathy: the historic evolution of detection, prevention and management. Hypertens 2000;14:667-85.

[20] Guidelines de l'ADA. Diabetes Care 01-2004.

[21] Hovind P, Rossing P, Tarnow L, Teerlink T, Stehouwer CD, Emeiss JJ, *et al.* Progression of diabetic nephropathy. Kidney Int 2001;59:702-9.

[22] Carter BL. Implementing the new guidelines for hypertension: JNC 7, ADA, WHO-ISH. J Manag Care Pharm 2004;10:S18-25.

[23] Krolewski AS, Warram JH, Christlieb AR. Hypercholesterolemia - A determinant of renal function loss and deaths in IDDM patients with nephropathy. Kitney Int 1994;45:S125-31.

[24] Hovind P, Tarnow l, Rossing P, Jensen BR, Graae M, Torp I, *et al.* Predictors of the development of microalbuminuria and macroalbuminuria in patients with type 1 diabetes: inception cohort study. BMJ 2004;328:1105-8.

[25] Perkins BA, Ficociello LH, Ostrander BE, Silva KH, Weinberg J, Warram JH, *et al.* Microalbuminuria and the risk for early progressive renal function decline in type 1 diabetes. J Am Soc Nephrol 2007;18:1353-61.

[26] Parving HH, Havind P, Rossing K, Andersen S. Evolving strategies for renoprotection: diabetic nephropathy. Curr Opin Nephrol Hypertens 2001;10:515-22.

[27] Pavlov ME, Knowler WC, Hanson RL, Bennett PH, Nelson RG. Predictive power of sequential measures of albuminuria for progression to ESRD or deadh in Pima Indians with type 2 diabetes. Am J Kidney Dis 2208;51:759-66.

[28] Holman RR, Paul SK, Bethel MA, Neil HA, Matthews DR. Long-term follow-up after tight control of blood pressure in type 2 diabetes. N Eng J Med 2008;359:1565-76.

[29] Knudsen ST, laugesen E, Hansen KW, Beck T, Mogensen CE, Poulsen PL. Ambulatory pulse pressure, decreased nocturnal blood pressure reduction and progression of nephropathy in type 2 diabetic patients. Diabetologia 2009;52:698-704.

[30] Cowie CC, Port FK, Wolfe RA, Savage PJ, Moll PP, Hawthorne VM, *et al.* Disparities in incidence of diabetic end-stage renal disease according to race and type of diabetes. N Engl J Med 1989;321:1074-9.

[31] Mourad JJ, Le Jeune S. Blood pressure control, risk factors and cardiovascular prognosis in patients with diabetes: 30 years of progress. J Hypertens 2008;26:S7-13.

[32] Rossing P, Houaard P, Parving H-H. Risk factors for development of incipient and overt diabetic nephropathy in type 1 diabetic patients. Diabetes Care 2002;25:859-64.

[33] De Cosmo S, Lamachia O, Rauseo A, Viti R, Gesualdo L, Pilotti A, *et al.* Cigarette smoking is associated with low glomerular filtration rate in male patients with type 2 diabetes Diabetes Care 2006;29:2467-70.

[34] Olsen S. Identification of non-diabetic glomerular disease in renal biopsies from diabetics--a dilemma. Nephrol Dial Transplant. 1999;14:1846-9.

[35] Griffin MD, Bergstralhn EJ, Larson LS. Renal papillary necrosis-a sixteen-year clinical experience. J Am Soc Nephrol 1995;6:248-56.

[36] Czaja CA, Rutledge BN, Cleary PA, Chan K, Stapleton AE, Stamm WE; for DCCT/EDIC Research Group. Urinary tract infections in women with type 1 diabetes mellitus: survey of female participants in the epidemiology of diabetes interventions and complications study cohort. J Urol 2009;181:1129-34.

[37] Ponholzer A, Temml C, Obermayr RP, Rauchenwald M, Madersbacher S. The association between lower urinary tract symptoms and renal function in men: a cross-sectional and 5-year longitudinal analysis. J Urol 2006;175:1398-402.

[38] Adler AI, Stevens RJ, Mantey SE, Bilous RW, Cull CA, Holman RR; for UKPDS Group. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int 2003;63:225-32.

[39] Halimi JM, Bonnet F, Lange C, Balkau B, Tichet J, Marre M. DESIR Study Group. Urinary albumin excretion is a risk factor for diabetes mellitus in men, independently of initial metabolic profile and development of insulin resistance. The DESIR Study. J Hypertens 2008;26:2198-206.
[40] Brantsma AH, Bakker SJ, Hillege HL, de Zeeuw D, de Jong PE, Gansevoort RT. PREVEND Study Group. Urinary albumin excretion and its relation with C-reactive protein and the metabolic syndrome in the prediction of type 2 diabetes. Diabetes Care 2005;28:2525-30.
[41] Forman JP, Fisher ND, Schopick EL, Curhan GC. Higher levels of albuminuria within the normal range predict incident hypertension. J Am Soc Nephrol 2008;19:1983-8.
[42] Wang TJ, Evans JC, Meigs JB, Rifai N, Fox CS, D'Agostino RB, *et al.* Low-grade albuminuria and the risks of hypertension and blood pressure progression. Circulation 2005;111:1370-6.
[43] Halimi JM, Hadjadj S, Aboyans V, Allaert FA, Artigou JY, Beaufils M, *et al.* Microalbuminurie et excrétion urinaire d'albumine: recommandations pour la pratique clinique. Société de Néphrologie. Ann Biol Clin 2008;66:277-84.
[44] Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461-70.
[45] Rigalleau V, Lasseur C, Perlemoine C, Barthe N, Raffaitin C, Chauveau P, *et al.* Cockcroft-Gault formula is biased by body weight in diabetic patients with renal impairment. Metabolism 2006;55:108-12.
[46] Bosma RJ, Van der Heide Jj, Oosterop EJ, de Jong PE, Navis G. Body Mass Index is associated with alterd hemodynamics in non-obese healthy subjects. Kidney Int 2004;65:259-65.
[47] Iseki K, Ikemiya Y, Kinjo K, Inoue T, Iseki C, Takishita S. Body mass index and the risk of development of end-stage renal disease in a screened cohort. Kidney Int 2004;65:1870-6.
[48] Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS. Body mass index and risk for end-stage renal disease. Ann Intern Med 2006;144:21-8.
[49] Christiansen JS, Frandsen M, Parving HH. Effect of intravenous glucose infusion on renal function in normal man and in insulin-dependent diabetics. Diabetologia 1981;21:368-73.
[50] Skott P, Vaag A, Hother-Nielsen O, Andersen P, Bruun NE, Giese J, *et al.* Effects of hyperglycaemia on kidney function, atrial natriuretic factor and plasma renin in patients with insulin-dependent diabetes mellitus. Scand J Clin Lab Invest 1991;51:715-27.
[51] Christensen PK, Lund S, Parving HH. The impact of glycaemic control on autoregulation of glomerular filtration rate in patients with non-insulin dependent diabetes. Scand J Clin Lab Invest 2001;61:43-50.
[52] Remuzzi A, Viberti G, Ruggenenti P, Battaglia C, Pagni R, Remuzzi G, *et al.* Glomerular response to hyperglycemia in human diabetic nephropathy. Am J Physiol 1990;259:F545-52.
[53] Rigalleau V, Lasseur C, Raffaitin C, Perlemoine C, Barthe N, Chauveau P, *et al.* Glucose control influences Glomerular Filtration Rate and its prediction in diabetic subjects. Diabetes Care 2006;29:1491-5.
[54] Ibrahim H, Mondress M, Tello A, Fan Y, Koopmeiners J, Thomas W, *et al.* An alternative formula to the Cockcroft-Gault and the modification of diet in renal diseases formulas in predicting GFR in individuals with type 1 diabetes. J Am Soc Nephrol 2005;16:1051-60.
[55] Rossing P, Rossing K, Gaede P, Pedersen O, Parving HH. Monitoring kidney function in type 2 diabetic patients with incipient and overt diabetic nephropathy. Diabetes Care 2006;29:1024-30.
[56] Chudleigh RA, Dunseath G, Evans W, Harvey JN, Evans P, Ollerton R, *et al.* How reliable is estimation of glomerular filtration rate at diagnosis of type 2 diabetes? Diabetes Care 2007;30:300-5.
[57] Mogensen CE, Christensen CK. Predicting diabetic nephropathy in insulin-dependent patients. N Engl J Med 1984;311:89-93.
[58] Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. N Engl J Med 1984;310:356-60.
[59] Tsalamandris C, Allen TJ, Gilbert RE, Sinha A, Panagiotopoulos S, Cooper ME, *et al.* Progressive decline in renal function in diabetic patients with and without albuminuria. Diabetes 1994;43:649-55.
[60] MacIsaac RJ, Tsalamandris C, Panagiotopoulos S, Smith TJ, McNeil KJ, Jerums G. Nonalbuminuric renal insufficiency in type 2 diabetes. Diabetes Care 2004;27:195-200.
[61] Rigalleau V, Lasseur C, Raffaitin C, Beauvieux MC, Barthe N, Chauveau P, *et al.* Normoalbuminuric renal insufficient diabetic patients: A lower risk group. Diabetes Care 2007;30:2034-39.
[62] Kramer HJ, Nguyen QD, Curhan G, Hsu CY. Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. JAMA 2003;289:3273-7.
[63] Caramori ML, Fioretto P, Mauer M. Low glomerular filtration rate in normoalbuminuric type 1 diabetic patients: an indicator of more advanced glomerular lesions. Diabetes 2003;52:1036-40.
[64] Kramer H, Molitch ME. Screening for Kidney disease in Adults with Diabetes. Diabetes Care 2005;28:1813-6.
[65] Hovind P, Rossing P, Tarnow L, Toft H, Parving J, Parving HH. Remission of nephrotic-range albuminuria in type 1 diabetic patients. Diabetes Care 2001;24:1972-7.
[66] Rossing K, Christensen PK, Hovind P, Parving HH. Remission of nephrotic-range albuminuria reduces risk of end-stage renal disease and improves survival in type 2 diabetic patients. Diabetologia 2005;48:2241-7.
[67] Branten AJ, Vervoort G, Wetzels JF. Serum creatinine is a poor marker of GFR in nephrotic syndrome. Nephrol Dial Transplant 2005;20:707-11.
[68] Kemperman FA, Silberbusch J, Slaats EH, Prins AM, Weber JA, Krediet RT, *et al.* Estimation of the glomerular filtration rate in NIDDM patients from plasma creatinine concentration after cimetidine administration. Diabetes Care 1998;21:216-20.
[69] Thomas L, Huber AR. Renal function – estimation of glomerular filtration rate. Clin Chem Lab Med 2006;44:1295-302.
[70] Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, *et al.* Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145:247-54.
[71] Chudleigh RA, Ollerton RL , Dunseath G, Peter R, Harvey JN, Luzio S, *et al.* Performance of the revised « 175 » Modification of diet in Renal Disease equation in paztients with type 2 diabetes. Diabetologia 2008;51:1714-8.
[72] Rule AD, Larson TS, Bergstralh EJ, Slezak JM, Jacobsen SJ, Cosio FG. Using serum creatinine to estimate glomerular filtration rate: Accuracy in good health and in chronic kidney disease. Ann Intern med 2004;141:929-37.
[73] Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, *et al.* for CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate Glomerular filtration rate. Ann Intern Med 2009;150:604-12.
[74] Ninimiya T, Perkovic V, de Galan B, Zoungas S, Pillai A, Jardine M, et al, for ADVANCE collaborative group. Albuminuria and kidney function indepently predict cardiovascular and renal outcomes in diabetes. J Am S Nephrol 2009;20:1813-21.
[75] Recommandation HAS néphropathie chronique grave. Juin 2007: www.has-sante.fr.
[76] HAS Méthode diagnostique des sténosez de l'artère rénale Mai 2004: www.has-sante.fr.
[77] Bax L,Woittiez AJ, Kouwenberg HJ, Mali VP, Buskens E, BraamB, *et al.* Stent Placement in Patients with atherosclerotic Renal Artery Stenosis and impaired renal function: a randomized trial. Ann Intern Med 2009;150:840-8.
[78] Circulation ACC/AHA 2005 Practice Guidelines for the management of patient with peripheral arterial disease.
[79] DCCT. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-86.
[80] Shichiri M, Kishikawa H, ohkubo Y, Wake N. Long termresults of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. Diabetes Care 2000;23:B21-9.
[81] UKPDS 33. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. Lancet 1998;352:837-53.
[82] Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, *et al.* for ADVANCE Collaborative Group, *et al.* Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560-72.

[83] Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, *et al.* for VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129-39.
[84] DCCT. Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications .Kidney Int 1995;47:1703-20.
[85] Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, *et al.* Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract 1995;28:103-17.
[86] EDIC. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. JAMA 2003;290:2159-67.
[87] Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577-89.
[88] So WY, Kong A, Ozaki R, Szeto CC, Chan NN, Ho CS, *et al.* Glomerular filtration rate, cardiorenal end point, and all-cause mortality in type 2 diabetic patients. Diabetes Care 2006;29,2046-52.
[89] Bruno G, Merletti G, Bargero G, Novelli G, Melis D, Soddu A, *et al.* Estimated glomerular filtration rate, albuminuria and mortality in type 2 diabetes: the Casale Monferrato study. Diabetologia 2007;50:941-8.
[90] HAS. Traitement médicamenteux du diabète de type2: recommandation de bonne pratique. Diabetes Metab 2007;33:S1-105.
[91] ADA Statements. Nephropathy in diabetes. Diabetes Care 2004 S79-83 Standards of medical care in diabetes Diabetes Care 2007;S4-41.
[92] Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst. Revu 2006;1:CD002967.
[93] Brown J, Pedula K, Barzilay J, Herson MK, Latare P. Lactic acidosis rate in type 2 diabetes. Diabetes Care 1998;21:1659-63.
[94] Stacpoole P, Wright E, Baumgartner TG, Bersin RM, Buchalter S, Curry SH, *et al.* for DCA-Lactic Acidosis Study Group. Natural history and course of acquired lactic acidosis in adults. Am J Med 1994;97:47-54.
[95] Bodmer M, Meier C, Krahenbuhl S, Jick S, Meier CR. Metformine, sulfonylureas, or other antidietes drug and the risk of lactic acidosis or hypoglycemia. Diabetes Care 2008;31:2086-91.
[96] Selby JV, Ettinger B, Swain BE, Brown JB. First 20 months'experience with use of metformin for type 2 diabetes in a large maintenance organisation. Diabetes Care 1999;22:38-44.
[97] Herrington WG, Levy J. Metformine: effective and safe in renal disease? Intern Urol Nephrol 2008;40:411-7.
[98] Goyal A, Crook ED. Thiazolidinediones and progression of renal disease in patients with diabetes. J Invest Med 2006;54:56-61.
[99] Bakris G, Viberti G, Weston WM, Heise M, Porter LE, Freed MI. Rosiglitazone reduces urinary albumin excretion in type 2 diabetes. J Human Hypertension 2003;17:7-12.
[100] Sarafidis PA, Lasaridis AN, Nilsson PM, Mouslech TF, Hitoglou-Makedou AD, Stafylas PC, *et al.* The effect of rosiglitazone on urine albumin excretion in patients with type 2 diabetes mellitus and hypertension. Am J Hypertens 2005;18:227-34.
[101] Pistrosch F, Herbrig K, Kindel B, Passauer J, Fischer S, Gross P. Rosiglitazone improves glomerular hyperfiltration, renal endothelial dysfunction, and microalbuminuria of incipient diabetic nephropathy in patients Diabetes 2005;54:2206-11.
[102] Schneider C, Ferrannini E, DeFronzo R, Schernthamer G, Yates J, Erdmann E. Effect of Pioglitazone on cardiovascular outcome in diabetes and chronic kidney disease J. Am Soc Nephrol 2008;19:182-7.
[103] Nesto RW, Bell D, Bonow RO, Fonseca V, Grundy SM, Horton ES, *et al.* Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from AHA and ADA. Circulation 2003;108:2941-8.
[104] Home PD, Pocock S, Beck-Nilsen H, Curtis PS, Gomis R, Hanefeld M, *et al.* Rosiglitazone evaluated for cardiovascular outcomes: RECORD. Lancet 2009;373:2125-35.
[105] KDOQI. Clinical Practice Guidelines and clinical practice recommendations for Diabetes in Chronic Kidney Disease 2007:www.kidney.org.
[106] Synder RW, Berns JS. Use of insulin and oral hypoglycaemic medications in patients with diabetes mellitus and advance kidney disease. Semin Dial 2004;17:365-70.
[107] Hasslacher C. Safety and efficacy of repaglinide in type 2 diabetic patients with and without impaired renal function Diabetes Care 2003;26:886-91.
[108] Bergman A, Cote J, Yi B, Marbury T, Swan SK, Smith W, *et al.* Effect of renal insufficiency on the pharmacokinetics of Sitagliptine. Diabetes Care 2007;30:1862-4.
[109] Rave K, Heise T, Pfutzner A, Heinemann L, Sawicki PT. Impact of diabetic nephropathy on pharmacokinetic properties of insulin in type 1 diabetic patients, Diabetes Care 2001;24:886-90.
[110] Keane WF, Brenner BM, de Zeuw D, Grunfeld JP, McGill J, Mitch WE, *et al.* The risk of developing end-stage renal disease in patients with type 2 diabetes and nephropathy: the RENAAL study. Kidney Int 2003;63:1499-507.
[111] de Zeeuw D, Remuzzi, G, Parving, HH, Keane WF, Zhang Z, Shahinfar S, *et al.* Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. Circulation 2004;110:921-7.
[112] Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003;289:2560-72.
[113] World Health Organization, International Society of Hypertension Writing Group. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. J Hypertens 2003;21:1983-92.
[114] Kidney Disease Outcomes Quality Initiative (K/DOQI). K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis 2004;43:S1-290.
[115] Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, *et al.* British Hypertension Society Guidelines for hypertension management 2004 (BHS-IV): summary. BMJ 2004;328:634-40.
[116] Recommandations HAS 2004. Traitement de la progression de l'insuffisance rénale chronique: www.has-sante.fr.
[117] Recommandations HAS 2005. Prise en charge de l'HTA de l'adulte: www.has-sante.fr.
[118] Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, *et al.* Guidelines for the management of arterial hypertension. The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertension 2007;25:1105-87.
[119] American Diabetes Association. Standards of medical care in diabetes - 2008. Diabetes Care 2008;31:S12-54.
[120] Rosendorff C, Black HR, Cannon CP, Gersh BJ, Gore J, Izzo JR, *et al.* Treatment of hypertension in the prevention and management of ischemic heart disease. A scientific statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. Circulation 2007;115:2761-88.
[121] Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet 2003;362:1527-35.
[122] UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998;317:703-13.
[123] Arguedas JA, Perez MI, Wright JM. Treatement blood pressure targets for hypertension. Cochrane Database of Systematic Reviews, Issue 3, 2009.
[124] Sarnak MJ, Greene T, Wang X, Beck G, Kusek JW, Collins AJ, *et al.*The effect of a lower target blood pressure on the progression of kidney disease: long-term follow-up of the Modification of Diet in Renal Disease study. Ann Intern Med 2005;142:342-51.
[125] Zanchetti A, Hansson L, Clement D, Elmfeldt D, Julius S, Rosenthal T, *et al.* for the HOT Study Group. Benefits and risks of more intensive blood pressure lowering in hypertensive patients of the HOT study with different risk profiles: does a J-shaped curve exist in smokers? J Hypertens 2003;21:787-804.

[126] Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. Kidney Int 2002;61:1086-97.
[127] Wright JT, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, *et al.* for the African American Study of Kidney Disease and Hypertension Study Group. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease. JAMA 2002;288:2421-31.
[128] Ruggenenti P, Perna A, Loriga G, Ganeva M, Ene-Iordache B, Turturro M, *et al.* for the REIN-2 Study Group. Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised, controlled trial. Lancet 2005;365:939-46.
[129] Pohl MA, Blumenthal S, Cordonnier DJ, De Alvaro F, Deferrari G, Eisner G, *et al.* Independent and additive impact of blood pressure control and angiotensin II receptor blockade on renal outcomes in the irbesartan diabetic nephropathy trial: clinical implications and limitations. J Am Soc Nephrol 2005;16:3027-37.
[130] Pohl MA, Blumenthal S, Cordonnier DJ, De Alvaro F, Deferrari G, Eisner G, *et al.* Independent and additive impact of blood pressure control and angiotensin II receptor blockade on renal outcomes in the irbesartan diabetic nephropathy trial: Clinical implications and limitations. J Am Soc Nephrol 2005;16:3027-37.
[131] Kunz R, Friedreich C, Wolbers M, Mann JF. Meta-analysis: Effect of monotherapy and combination therapy with inhbitors of the renin-angiotensin system on proteinuria in renal diseas. Ann Intern Med 2008;148:30-48.
[132] Guide presciption de l'HAS 2008: www.has-sante.fr.
[133] Vogt L, Waanders F, Boomsma F, de Zeeuw D, Navis G. Effects of dietary sodium and hydrochlorothiazide on the antiproteinuric efficacy of losartan. J Am Soc Nephrol. 2008;19:999-1007.
[134] Ruggenenti P, Fassi A, Ilieva AP, Bruno S, Iliev IP, Brusegan V, *et al.* Preventing microalbuminuria in type 2 diabetes (BENEDICT). N Engl J Med 2004;351:1941-51.
[135] Ritz E, Viberti C, Ruilope M, Rabelink AJ, Izzo JL Jr, Katayama S, *et al.* Determinants of urinary albumin excretion within the normal range in patients with type 2 diabetes: the Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study Diabetologia 2010;53:49-57.
[136] Parving HH, Lehnert H, Bröchner-Mortensen J, Gomis R, Andersen S, Arner P. Effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001;345:870-8.
[137] Viberti G, Wheeldn NM. MARVAL study invest. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect Circulation 2002;106:672-8.
[138] Remuzzi G, Ruggenenti P, Perna A, Dimitrov BD, de Zeeuw D, Hille DA, *et al.* Continuum of renoprotection with losartan at all stages of type 2 diabetic nephropathy: a post hoc analysis of the RENAAL trial results. J Am Soc Nephrol. 2004;15:3117-25.
[139] Hou FF, Zhang X, Zhang GH, Xie D, Chen PY, Zhang WR, *et al.* Efficacy and safety of benazepril for advanced chronic renal insufficiency. New Engl J Med 2006;354:131-40.
[140] KDOQI Clinical Practice Guidelines and clinical practice recommendations for Diabetes in Chronic Kidney Disease July 2006. Guideline 3: Management of hypertension in diabetes and CKD.
[141] KDOQI. Clinical Practice Guidelines and clinical practice recommendations for Diabetes in Chronic Kidney Disease July 2006. Clinical Practice Recommandation 1: Management of albuminuria in normotensive diabetic patients and albuminuria as a surrogate marker.
[142] NICE Guidelines 2008. Chapter 16: Kidney damage: www.nice.org.uk.
[143] NICE Guidelines 2008. Chapter 12: Blood pressure therapy: www.nice.org.uk.
[144] Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? Arch Intern Med 2000;160:685-93.
[145] Pan Y, Guo LL, Jin HM. Low-protein diet for diabetic nephropathy: a meta-analysis of randomized controlled trials. Am J Clin Nutr 2008;88:660-6.
[146] Menon V, Kopple JD, Wang X Beck GJ, Collins AJ, Kusek JW, Greene A, *et al.* Effect of a very low-protein diet on outcomes: Long-term follow-up of the Modification of Diet in Renal Disease (MDRD) study. Am J Kidney Dis 2009;53:208-17.
[147] The CARI Guidelines April 2006. ACE Inhibitor treatment in diabetic nephropathy: www.cari.org.au.
[148] The CARI Guidelines April 2006. Antihypertensive therapy in diabetic nephropathy: www.cari.org.au.
[149] The CARI Guidelines April 2006. Smoking and the progression of diabetic nephropathy: www.cari.org.au.
[150] The CARI Guidelines April 2006. Protein restriction to prevent progression of diabetic nephropathy: www.cari.org.au.
[151] The CARI Guidelines. Weight reduction in obese patients with chronic kidney disease. Nephrology 2007;12:S49-51.
[152] Maroni BJ, Steinman TI, Mitch WE. A method for estimating nitrogen intake of patients with chronic renal failure. Kidney Int 1985;27:58-65.
[153] The EUCLID study group. Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria. The EUCLID Study Group. Lancet 1997;349:1787-92.
[154] Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med 1993;329:1456-60.
[155] Gaede, P., Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003;348:383-93.
[156] Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet 2000;355:253-9.
[157] Strippoli GF, Craig M, Deeks JJ, Schena FP, Craig JC. Effects of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists on mortality and renal outcomes in diabetic nephropathy: systematic review. BMJ 2004;329:828-32.
[158] Balamuthusamy S, Srinivasan L, Adigopula S, Jalandara N, Hathiwala S, Smith E. Renin angiotensin system blockade and cardiovascular outcomes in patients with chronic kidney disease and proteinuria: a meta-analysis. Am Heart J 2008;155:791-5.
[159] Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, *et al.* ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358:1547-59.
[160] Dahlöf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, *et al.* ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required *versus* atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet 2005;366:895-906.
[161] ADVANCE Collaborative Group. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, *et al.* Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560-72.
[162] Jamerson K, Weber MA, Bakris GL, Dahlöf B, Pitt B, Shi V, *et al.* ACCOMPLISH Trial Investigators. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med 2008;359:2417-28.
[163] Baigent C, Landry M. Study of Heart and Renal Protection (SHARP). Kidney Int Suppl 2003;84:S207-10.
[164] Tonelli M, Robins S Bloomfield H, Curhan GC. (VA-HIT). Gemfibrozil for secondary prevention of cardiovascular event in mild to moderate chronic renal insufficiency. Kidney Int 2004;66:1123-30.
[165] Shepherd J, Kastelein JP, Bittner VA, Carmena R, Deedwania PC, Breazna A, *et al.* Treating to New Targets Steering Committee and Investigators. Intensive lipid lowering with atorvastatin in patients with coronary artery disease, diabetes, and chronic kidney disease. Mayo Clin Proc 2008;8:870-9.
[166] Strippoli GF, Navaneethan SD, Johnson DW, Perkovic V, Pellegrini F, Nicolucci A, *et al.* Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomised controlled trials. BMJ 2008;336:645-51.
[167] Kopple JD. National kidney foundation K/DOQI clinical practice guidelines for nutrition in chronic renal failure. Am J Kidney Dis 2001;37:S66-70.

[168] Harsha DW, Sacks FM, Obarzanek E, Svetkey LP, Lin PH, Bray GA, *et al.* Effect of dietary sodium intake on blood lipids: results from the DASH-sodium trial. Hypertension 2004;43:393-8.
[169] Cody J, Daly C, Campbell M, Donaldson C, Khan I, Rabindranath K, *et al.* Recombinant human erythropoietin for chronic renal failure anaemia in pre-dialysis patients. Cochrane Database Syst Rev 2005;3:CD003266.
[170] Phrommintikul A, Haas SJ, Elsik M, Krum H. Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis. Lancet 2007;369:381-8.
[171] Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU, *et al.* TREAT Investigators. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med. 2009;361:2019-32.
[172] Baigent C., Burbury K., Wheeler D. Premature cardiovascular disease in chronic renal failure. Lancet 2000;356:147-51.
[173] Cherukuri A, Bhandari S. Analysis of risk factors for mortality of incident patients commencing dialysis in East Yorkshire. QJM 2010;103:41-7.
[174] Liu J, Louis TA, Pan W, Ma JZ, Collins AJ. State-level adjusted ESRD incident rates: use of observed vs model-predicted category-specific rates. Kidney Int 2006;69:1459-63.
[175] Couchoud C, Stengel B, Landais P, Aldigier JC, de Cornelissen F, Dabot C, *et al.* The renal epidemiology and information network (REIN): a new registry for end-stage renal disease in France. Nephrol Dial Transplant 2006;21:411-8.
[176] Couchoud C, Moranne O, Frimat L, Labeeuw M, Allot V, Stengel B. Associations between comorbidities, treatment choice and outcome in the elderly with end-stage renal disease. Nephrol Dial Transplant 2007;22:3246-54.
[177] Chantrel F, Enache I, Bouiller M, Kolb I, Kunz K, Petitjean P, *et al.* Abysmal prognosis of patients with type 2 diabetes entering dialysis. Nephrol Dial Transplant 1999;14:129-36.
[178] Goodkin DA, Bragg-Gresham JL, Koenig KG, Wolfe RA, Akiba T, Andreucci VE, *et al.* Association of comorbid conditions and mortality in hemodialysis patients in Europe, Japan, and the united state: the dialysis outcome and practice patterns study (DOPPS). J Am Soc Nephrol 2003;14:3270-7.
[179] Keane WF, Brenner BM, de Zeeuw D, Grunfeld JP, McGill J, Mitch WE, *et al.* RENAAL Study Investigators. The risk of developing end-stage renal disease in patients with type 2 diabetes and nephropathy: the RENAAL study. Kidney Int 2003;63:1499-507.
[180] Locatelli F, Canaud B, Eckardt KU, Stenvinkel P, Wanner C, Zoccali C. Oxidative stress in end-stage renal disease: an emerging threat to patient outcome. Nephrol Dial Transplant 2003;18:1272-80.
[181] Ndip A, Lavery LA, Lafontaine J, Rutter MK, Vardhan A, Vileikyte L, *et al.* High levels of foot ulceration and amputation risk in a multiracial cohort of diabetic patients on dialysis therapy. Diabetes Care 2010;33:878-80.
[182] Chonchol M, Dale R, Schrier RW, Estacio R. Serum phosphorus and cardiovascular mortality in type 2 diabetes. Am J Med 2009;122:380-6.
[183] Jungers P, Qualim Z, Nguyen-Khoa T, Massy Z, London G. Cardioprotection: an essential component for predialysis chronic renal failure treatment. Néphrology 2003;24:79-88.
[184] Burrowes JD, Larive B, Cockram DB, Dwyer J, Kusek JW, McLeroy S, *et al.* for the hemodialysis (HEMO)Study Group. Effects of dietary intake, appetite, and eating habits on dialysis and non-dialysis treatment days in hemodialysis patients. J. Ren. Nutr 2003;13:191-8.
[185] Pieringer H, Biesenbach G. Hemodialysis in patients older than 65 years with end-stage renal failure-comparison of outcome in patients with and without diabetes. Z Gerontol Geriatr 2008;41:139-45.
[186] Trespalacios FC, Taylor AJ, Agodoa LY, Bakris GL, Abbott KC. Heart Failure as a cause for hospitalization in chronic dialysis patients. Am J Kidney Dis 2003;41:1267-77.
[187] Zoccali C, Mallamaci F, Tripepi G. Traditional and emerging cardiovascular risk factors in end-stage renal disease. Kidney Int Suppl 2003;85:105-10.
[188] Fleischmann E, Teal N, Dudley J, May W, Bower JD, Salahudeen K. Influence of excess weight on mortality and hospital stay in 1346 hemodialysis patients. Kidney Int 1999;55:1560-7.
[189] Jacobs LH, van de Kerkhof JJ, Mingels AM, Passos VL, Kleijnen VW, Mazairac AH, *et al.* Inflammation, overhydration and cardiac biomarkers in haemodialysis patients: a longitudinal study. Nephrol Dial Transplant 2010;25:243-8.
[190] Sato A, Tarnow L, Parving HH. Prevalence of left ventricular hypertrophy in type I diabetic patients with diabetic nephropathy. Diabetologia 1999;42:76-80.
[191] Nishimura R, Dorman JS, Bosnyak Z, Tajima N, Becker DJ, Orchard TJ. Incidence of ESRD and survival after renal replacement therapy in patients with type 1 diabetes: A report from the Allegheny county registry. Am J Kidney Dis 2003;42:117-24.
[192] Stein G, Fünfstück R, Schiel R. Diabetes mellitus and dialysis. Minerva Urol Nefrol 2004;56:289-303.
[193] Lin CL, Wu MS, Hsu PY, Huang CC. Improvement of clinical outcome by early nephrology referral in type II diabetics on hemodialysis. Ren Fail 2003;25:455-64.
[194] Shrishrimal K, Hart P, Michota F. Managing diabetes in hemodialysis patients: observations and recommendations. Cleve Clin J Med 2009;76:649-55.
[195] Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl 2009;113:S1-130.
[196] Tanaka H, Hamano T, Fujii N, Tomida K, Matsui I, Mikami S, *et al.* The impact of diabetes mellitus on vitamin D metabolism in predialysis patients Bone 2009;45:949-55.
[197] Biesenbach G, Raml A, Schmekal B, Eichbauer-Sturm G. Decreased insulin requirement in relation to GFR in nephropathic type 1 and insulin-treated type 2 diabetic patients. Diabet Med 2003;20:642-5.
[198] Prichard S. Cardiovascular risk in peritoneal dialysis. Contrib Nephrol 2003;140:82-90.
[199] Brunkhorst R, Lufft V, Dannenberg B, Kliem V, Tusch G, Pichlmayr R. Improved survival in patients with type 1 diabetes mellitus after renal transplantation compared with hemodialysis: a case-control study. Transplantation 2003;76:115-9.
[200] Brandle M, Zhou H, Smith BR, Marriott D, Burke R, Tabaei BP, *et al.* The direct medical cost of type 2 diabetes. Diabetes Care 2003;26:2300-4.
[201] Stidley CA, Shah VO, Scavini M, Narva AS, Kessler D, Bobelu A, *et al.* The Zuni kidney project: a collaborative approach to an epidemic of kidney disease. J Am Soc Nephrol 2003;14:S139-43.
[202] Hergesell O, Zeier M. Underdiagnosis of diabetes mellitus in chronic dialysis patients on the renal transplant waiting list. Transplant Proc 2003;45:1287-9.
[203] Markowitz JS, Gutterman EM, Magee G, Margolis DJ. Risk of amputation in patients with diabetic foot ulcers: a claims-based study. Wound Repair Regen 2006;14:11-7.
[204] Wolf G, Muller N, Busch M, Eidner G, Kloos C, Hunger-Battefeld W, *et al.* Diabetic foot syndrome and renal function in type 1 and 2 diabetes mellitus show close association. Nephrol Dial Transplant 2009;24:1896-901.
[205] Ghanassia E, Villon L, Thuan Dit Dieudonne JF, Boegner C, Avignon A, *et al.* Long-term outcome and disability of diabetic patients hospitalized for diabetic foot ulcers: a 6.5-year follow-up study. Diabetes Care 2008;31:1288-92.
[206] Virkkunen J, Heikkinen M, Lepantalo M, Metsanoja R, Salenius JP. Diabetes as an independent risk factor for early postoperative complications in critical limb ischemia. J Vasc Surg 2004;40:761-7.
[207] Graziani L, Silvestro A, Bertone V, Manara E, Alicandri A, Parrinello G, *et al.* Percutaneous transluminal angioplasty is feasible and effective in patients on chronic dialysis with severe peripheral artery disease. Nephrol Dial Transplant 2007;22:1144-9.
[208] Speckman RA, Frankenfield DL, Roman SH, Eggers PW, Bedinger MR, Rocco MV, *et al.* Diabetes is the strongest risk factor for lower-extremity amputation in new hemodialysis patients. Diabetes Care 2004;27:2198-203.
[209] Pliakogiannis T, Bailey S, Cherukuri S, Taskapan H, Ahmad M, Oliver T, *et al.* Vascular complications of the lower extremities in diabetic patients on peritoneal dialysis. Clin Nephrol 2008;69:361-7.