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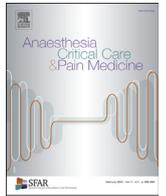
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## Guidelines

## Perioperative management of adult diabetic patients. Preoperative period

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## ABSTRACT

In diabetic patients undergoing surgery, we recommend assessing glycaemic control preoperatively by assessing glycated haemoglobin (HbA1c) levels and recent capillary blood sugar (glucose) levels, and to adjust any treatments accordingly before surgery, paying particular attention to specific complications of diabetes. Gastroparesis creates a risk of stasis and aspiration of gastric content at induction of anaesthesia requiring the use of a rapid sequence induction technique. Cardiac involvement can be divided into several types. Coronary disease is characterised by silent myocardial ischaemia, present in 30–50% of T2D patients. Diabetic cardiomyopathy is a real cause of heart failure. Finally, cardiac autonomic neuropathy (CAN), although rarely symptomatic, should be investigated because it causes an increased risk of cardiovascular events and a risk of sudden death. Several signs are suggestive of CAN, and confirmation calls for close perioperative surveillance. Chronic diabetic kidney disease (diabetic nephropathy) aggravates the risk of perioperative acute renal failure, and we recommend measurement of the glomerular filtration rate preoperatively. The final step of the consultation concerns the management of antidiabetic therapy. Preoperative glucose infusion is not necessary if the patient is not receiving insulin. Non-insulin drugs are not administered on the morning of the intervention except for metformin, which is not administered from the evening before. The insulins are injected at the usual dose the evening before. The insulin pump is maintained until the patient arrives in the surgical unit. It should be remembered that insulin deficiency in a T1D patient leads to ketoacidosis within a few hours. © 2018 The Author. Published by Elsevier Masson SAS on behalf of Société française d'anesthésie et de réanimation (Sfar). This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

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## 1. Evaluation of glycaemic control in a diabetic patient

Practical sheet B summarises the main elements of this text.

Many studies have been carried out in diabetic patients at the time of surgery, but they have mainly been interested in the cardiovascular risk and not in the management of diabetes itself. Glycaemic control is recommended before admission according to objectives adapted to each patient [1] in order to avoid hyperglycaemia and hypoglycaemia. Glycaemic variability should also be monitored during the hospital stay [2]. Glycaemic variability is common due to fasting, stress, development of infection, use of glucocorticoids, etc. Glycaemic control is evaluated during the anaesthesia consultation using two criteria: (i) glycated haemoglobin (HbA1c); and (ii) blood sugar (glucose) levels. Hypoglycaemic and hyperglycaemic episodes should be treated because they may have harmful preoperative consequences and may lead to the intervention being postponed.

Fig. 1 summarises the management that we recommend depending on overall glycaemic control (HbA1c), blood sugar levels before surgery, the recent development of hypo- and hyperglycaemic episodes, particularly those with associated ketosis.

### 1.1. HbA1c

In a treated diabetic patient, HbA1c which reflects mean control over the previous 3 months allows to estimate the quality of glycaemic control before the consultation and adaptation of treatment to fixed objectives [1]. Some studies indicate that raised HbA1c in a diabetic patient is associated with high morbidity/mortality and an increased risk of myocardial infarction and early postoperative infection [3]. For each 1% increase in HbA1c, the risk increases by 40% [4]. The risk of sternal infection is 5-fold higher (OR = 5.3) when HbA1c level is greater than 7.8%. HbA1c > 7% appears to have a negative prognostic value in unrecognised diabetic patients [5]. A correlation exists between HbA1c and mean blood sugar levels (Appendix A). It is wise to postpone surgery (except in an emergency situation) if HbA1c is very high (> 9%) because it demonstrates a lack of glycaemic control and the patient is thus exposed to acute metabolic complications in the perioperative period. Using the same reasoning, HbA1c < 5% indicates probable recurrent severe hypoglycaemic episodes in a patient treated with insulin or hypoglycaemic sulphonamides/glinides and we also recommend postponing surgery in this case (Fig. 1).

Therapeutic adjustments, after advice from a general practitioner (GP) or a diabetologist, should be discussed for HbA1c values between 8% and 9% (chronic, but not threatening, hyperglycaemia requiring therapeutic reinforcement) or between 5% and 6% (repeated hypoglycaemic episodes requiring to reduce the intensity of antidiabetic therapy).

### 1.2. Recent blood and capillary glycaemic values

Some studies have demonstrated a correlation between glycaemia at admission (> 2 g/L or 11 mmol/L) and postoperative morbidity/mortality [6–8], as well as a 10-fold higher risk of complications when glycaemic imbalance exists before surgery [9]. Measurement of blood sugar levels allows, for example, stratification of the risk of sternal infection after cardiac surgery: a blood sugar level < 1.80 g/L (10 mmol/L) before the intervention decreases the risk of death, infection and duration of stay [10].

During the preoperative consultation and in the days immediately preceding the intervention, we recommend monitoring of capillary blood sugar levels. A recent disequilibrium (hyper- or hypo-glycaemia) could have an effect on perioperative management, even if an adequate HbA1c value is observed [11]. In this case, the relation HbA1c/mean blood sugar (Appendix A) is not applicable.

### 1.3. Identification of episodes of hypoglycaemia (sheet B)

Hypoglycaemia is a therapeutic hazard in all treated diabetics, with the risk being particularly high in hospitalised diabetic patients, due to more severe glycaemic variations [12]. Even if the specific role of anaesthesia or surgery has not been established, these situations of instability can contribute to anomalies in glucose regulation, such as hypoglycaemia. Hypoglycaemia is a frequent consequence of treatment with insulin secretors (hypoglycaemic sulphonamides/glinides) or insulin therapy (sheets E and F). It mainly occurs in T1D patients but also in T2D diabetics, at any time.

The cut-off blood sugar level defining hypoglycaemia has been the subject of debate; nevertheless current consensus suggests a plasma blood sugar level of < 0.7 g/L (3.9 mmol/L) in a diabetic patient. In practice, for healthcare teams, any unexplained malaise in a diabetic patient should be considered as a hypoglycaemic episode until proven otherwise, even if the blood sugar level at the time it is measured (sometimes several minutes after the start of the malaise) appears to be normal. Serious hypoglycaemia is defined by the need for assistance of another person, whatever the blood sugar level. Some hypoglycaemic episodes are not as easily apparent, particularly when hypoglycaemia occurs frequently, diabetes is already a long-lasting disease or when dysautonomia is present. This situation occurs in nearly 40% of T1D patients, 10% of T2D patients on insulin and occasionally in T2D patients on oral antidiabetic drugs [13].

Episodes of hypoglycaemia result from an imbalance between insufficient carbohydrate supply and poorly adapted insulin or insulin-secretor treatment. These situations are particularly frequent in the perioperative period, for example due to prolonged fasting or irregular food intake. It is necessary to be vigilant about the administration of drugs, which have a direct hypoglycaemic

HbA1c	4.0	5.0	6.0	8.0	9.0	10.0	%
Action to take	Postpone	Advice of general practitioner/ diabetologist	Intervention possible	Advice of general practitioner/ diabetologist	Postpone		
Mean blood glucose	0.6	0.9	1.2	1.8	2.1	3	g/l
	3.3	5	6.6	10	11.5	16.5	mmol/l
Hypoglycaemia	> 2 hypoglycaemic episodes (last week)						
Ketosis	Hypoglycaemic coma (in the previous month)						Ketosis ?

Fig. 1. Preoperative strategy according to HbA1c and blood glucose level (Practical sheet B).

effect or those which increase the action of oral antidiabetic drugs (for example quinolones, heparin,  $\beta$ -blockers or trimethoprim-sulfamethoxazole). Deterioration of renal or hepatic function may decrease the clearance of antidiabetic drugs and increase the risk of hypoglycaemia.

#### 1.4. Identification of recent episodes of hyperglycaemia and ketosis (sheet B)

If glycaemic disequilibrium is detected during the anaesthesia consultation (based on HbA1c), therapeutic adjustment should be considered. For example in T2D patients on oral antidiabetic drugs, intensification of treatment should be considered. There are many therapeutic strategies that can be considered, including those established in France by the *Haute Autorité de Santé* [1], and also by international societies [14], validated by the French Society for the study of Diabetes (SFD). Intensification of hypoglycaemic treatment should be personalised and validated on by an expert prescriber.

In T2D and T1D patients treated with insulin, the times at which hyperglycaemia occurs should be assessed using an auto-surveillance booklet and the doses of insulin should be modified accordingly. If necessary, insulin therapy (transient or permanent) may be proposed, particularly if ketosis is detected.

## 2. Specific complications of diabetes (sheet B)

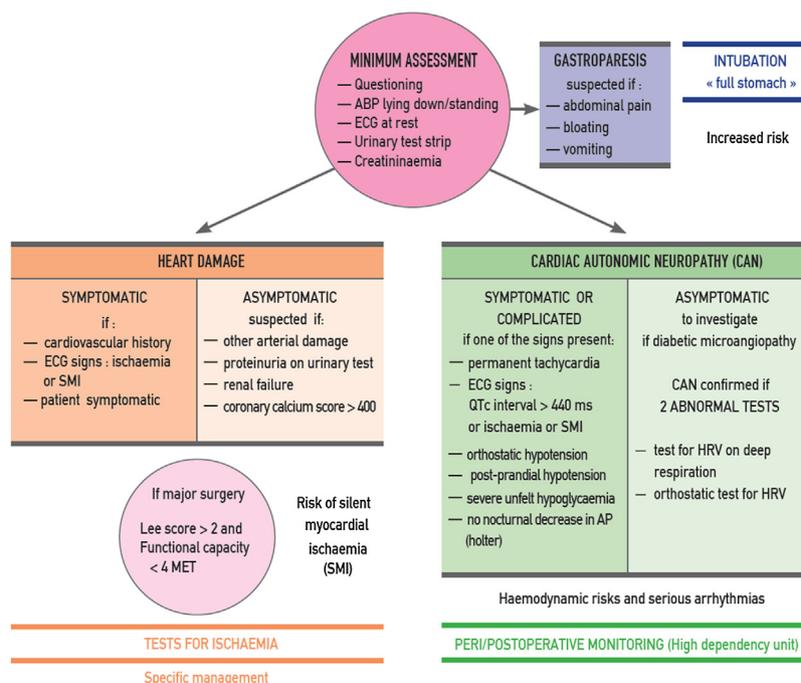
In diabetic patients, the perioperative risk may be increased by gastroparesis and/or heart disease and/or kidney disease.

### 2.1. Gastroparesis

This diabetic complication is the most frequent manifestation of digestive dysautonomia, defined as delayed gastric emptying in the absence of mechanical obstruction. It usually affects diabetic patients with other neuropathic diseases, affecting

30–50% of patients with T1D or T2D. Symptoms classically include anorexia, nausea, vomiting, abdominal pain, sensation of bloating, early satiety or slowing of digestion [15]. It may have adverse repercussions on the absorption of drugs administered by mouth. However, there is a weak correlation between symptoms and the rate of gastric emptying. In many diabetic patients, gastric emptying is even accelerated although patients present with similar symptoms. Finally, some patients have symptoms without abnormal gastric emptying. Gastroparesis may be a factor for post-prandial glycaemic dysregulation. Furthermore, acute hyperglycaemia slows down gastric emptying. There is therefore a reciprocal interrelation between gastric emptying and glycaemia [16]. Clinical examination may reveal abdominal distension with classic 'clapotement' on an empty stomach, a late sign of gastroparesis. Upper gastro-intestinal endoscopy is used as the first-line non-clinical assessment. It helps to eliminate other causes of upper digestive symptoms and to reveal the presence of food remaining in the stomach after night fasting. A barium meal may reveal gastric residue or even phytobezoards. The reference diagnostic examination is gastric scintigraphy carried out using a calibrated meal, preferably solid, labelled with technetium 99 m [15]. Other tests may be proposed such as the respiratory test for carbon 13-labelled octanoic acid.

During the anaesthesia consultation, gastroparesis should be investigated because it creates a risk of stasis (full stomach) and aspiration at anaesthetic induction. At a minimum, questioning of the diabetic during the anaesthesia consultation should focus on the classic clinical manifestations of gastroparesis (sheet B and Fig. 2). If clinical signs suggestive of gastroparesis are present, measurement of the gastric antral area by ultrasound can distinguish whether the stomach is full or not [17]. Echography can also visualise solid residues. In case of doubt, rapid sequence induction should be carried out. Erythromycin and metoclopramide, which can help accelerate gastric motility, may be used [18,19].



**Fig. 2.** Preoperative assessment of the specific complications of diabetes. PH: previous history; UB: urine strip; ECG: electrocardiogram; HR: heart rate; HRV: heart rate variability; MI: myocardial infarction; SMI: silent myocardial infarction; MET: metabolic equivalent; ABP: arterial pressure.

## 2.2. Effects of diabetes on the heart

### 2.2.1. Cardiovascular risk of diabetes

Approximately 75% of diabetic patients die from complications of atherosclerosis. However, the degree of cardiovascular risk is heterogeneous within the diabetic population, linked to co-existing risk factors such as arterial hypertension, lipid abnormalities, smoking, familial history of early cardiovascular problems, and also to specific factors such as glycaemic control, the duration of diabetes and presence of nephropathy in particular. Micro-albuminuria is associated with an increased cardiovascular risk in both T1D and T2D, and the risk is even greater in the presence of macroproteinuria or renal failure [20]. The presence of arterial damage in one area is clearly associated with an increased risk that arteriopathic damage also exists elsewhere.

### 2.2.2. Heart disease

Heart disease has several characteristics in diabetic patients. Myocardial infarction is usually silent and silent myocardial ischaemia (SMI) can be found in 30–50% of asymptomatic T2D patients who have no cardiac history but who present with cardiovascular risk factors [20,21]. Its negative prognostic value has been demonstrated [22–24]. Investigations for SMI are based on provocation tests (exercise tolerance test, myocardial scintigraphy with exercise and/or administration of dipyridamole, stress echography or even stress magnetic resonance imaging). If SMI detection is followed by coronarography, this examination reveals significant coronary stenosis in 30–70% of patients [20]. Detection of heart disease appears logical to prevent cardiac events, but it should be reserved for patients with a very high cardiovascular risk [20]. Measurement of the coronary calcium score by CT scan (without injection of iodinated product) contributes to evaluate the cardiovascular risk; a score of > 400 Agaston units is associated with a worse prognosis and a high prevalence of SMI [25] and should lead to investigations for SMI [20]. However, it should be noted that many rigorous studies have shown that systematic coronary revascularisation before non-cardiac surgery is not useful to reduce the rate of postoperative myocardial ischemic episodes [26]. Conversely, repeated perioperative measurement of troponin, associated with ECG, allows to detect perioperative myocardial damage and helps to initiate cardiovascular treatment [27].

### 2.2.3. Heart failure

The risk of congestive heart failure (CHF) is 2–3-fold higher in diabetic patients. Age, duration of diabetes, heart disease and the presence of albuminuria are all associated with an increased risk of heart failure [28]. Although heart disease and arterial hypertension are the main factors responsible for CHF, diabetic cardiomyopathy is a well-established clinical entity and a proven cause of CHF [29]. Mortality after a first episode of CHF is 10-times higher in T2D patients than in non-diabetic patients. At the preclinical stage, structural and functional alterations of the left ventricle are frequently suspected on the ECG in relation to diabetic cardiomyopathy and might be observed even in the absence of heart disease or hypertension. Left ventricular hypertrophy is often present, but diastolic or systolic dysfunction might also be observed [30]. Measurement of brain natriuretic peptide (BNP) or pro-BNP levels has good sensitivity to detect diastolic or systolic dysfunction at the preclinical stage [31].

### 2.2.4. Cardiac autonomy neuropathy (CAN) (Appendix B)

The dysautonomic cardiac complication of diabetes is rarely expressed by clinical symptoms: permanent tachycardia and orthostatic hypotension in particular (which is often iatrogenic in origin), post-prandial hypotension or severe hypoglycaemias with no effects. These are symptoms of severe CAN. At the infra-clinical

stage, the most frequent complications of CAN include anomalies of heart rate (HR) at baseline and abnormal variability during standardised tests. The prevalence of these abnormalities increases with the duration of diabetes and if glycaemic disequilibrium is long-lasting [32]. In a French multicentre study, confirmed or severe CAN defined by two or three tests assessing variations in HR, was present in 20% of patients and CAN was significantly associated with the presence of microangiopathic complications [33]. The risks linked to CAN include myocardial infarction (MI), which is painless or discovered only on a systematic ECG, an increase in cardiovascular events and an increase in mortality. The risk of sudden death secondary to serious cardiac rhythm disorders should be noted [32,34]. Among mechanisms implicated are the absence of a nocturnal fall in blood pressure (non-dipping type or even reverse dipping) during ambulatory blood pressure measurements, alterations in ventricular repolarisation with lengthening of the QTc interval (> 440 ms) and the co-existence of SMI [32,35].

The detection of CAN at the infra-clinical stage is based on an analysis of variations in HR during standardised tests for deep respiration, active orthostatism and the Valsalva manoeuvre [32]. These tests are usually carried out with a simple ECG but should be interpreted as a function of age (due to the physiological reduction in HR variability with age). Although these tests are quite easy to perform, they take time and manual calculation is necessary, making their use limited outside a specialised consultation, unless a software programme is used. Variations of HR essentially but non-specifically reveal parasympathetic heart damage. Current recommendations suggest carrying out these tests in T1D patients with known disease for at least 5 years and in all T2D patients, particularly if microangiopathic complications of diabetes exist [36]. CAN is graded according to the result of these tests [32].

If CAN is detected, drugs that may induce orthostatic hypotension should be avoided, ambulatory measurement of blood pressure should be carried out to look for nocturnal non-dipping patterns and the QT interval should be measured on a standard ECG (at minimum). If it is prolonged, problems with paroxysmal ventricular rhythm should be detected by 24-h ECG continuous monitoring [32].

Anaesthesia, whether general (GA) or regional (RA), has pronounced effects on perioperative sympathetic nervous tone [37]. Many clinical investigations have evaluated the influence of IV anaesthetic agents on peripheral autonomic nervous influx. Microneurography allows to assess sympathetic nervous activity in lower limb muscles by placing electrodes in the peroneal nerve [37]. Studies have also assessed the effects of RA on autonomic nervous tone. Whatever the type of neuraxial anaesthesia used, spinal block or epidural, the authors report a significant decrease in sympathetic nervous influx [38,39]. It has also been shown that postoperative epidural administration of morphine after abdominal aortic surgery decreases postoperative hypertension by reducing sympathetic hyperactivity [40]. In the diabetic patient, and in the case of metabolic syndrome, peripheral sympathetic hyperactivity occurs [41]. Interactions between anaesthesia and CAN lead to an increased risk of perioperative haemodynamic instability although mechanisms are unclear. In diabetic patients, a preoperative decrease in respiratory HR variability (respiratory sinus arrhythmia) is associated with a risk of perioperative haemodynamic instability [42,43]. Some authors have reported that perioperative requirement for vasopressor support is correlated with the degree of dysautonomia [44,45]. With regard to its influence on perioperative haemodynamics, it is not surprising to observe that perioperative dysautonomia has a postoperative prognostic impact on the diabetic patient in the long-term [44]. Preoperative evaluation of diabetic patients using simple cardiac autonomy tests (respiratory HR variations) thus

appears useful to identify patients at risk of perioperative haemodynamic instability and of cardiovascular complications despite the absence of clinical symptoms of CAN [32,44]. Diabetic patients suffering from dysautonomia also have a decreased ventilatory response to hypoxaemia and hypercapnia [46] and to perioperative hypothermia [47]. In these patients, more sophisticated haemodynamic monitoring including a continuous measurement of arterial pressure and cardiac index can be recommended [48].

### 2.2.5. Cardiovascular assessment at the anaesthesia consultation

Specific management of a patient with coronary artery disease undergoing non-cardiac surgery have been described in depth in the 2011 SFAR/SFC Guidelines [49]. The present report summarises the minimal cardiovascular assessment and the possible additional assessments that should be done in the diabetic patient.

Questioning the patient will determine:

- if the patient is hypertensive;
- if there is any cardiovascular history, in particular the existence of heart disease, cardiac ischaemia (CI), arrhythmia, cerebrovascular accident or lower limbs arteriopathy;
- if the patient is under the care of a cardiologist;
- if the patient has already undergone coronary, supra-aortic or peripheral vascular revascularisation;
- if there are recent symptoms of angina, these may appear atypical or mild such as dyspnoea or exercise epigastric pain, i.e. symptoms suggesting cardiac ischaemia or of peripheral arteriopathy, symptoms suggesting orthostatic or post-prandial hypotension, episodes of serious unfelt hypoglycaemia;
- current treatments.

The results of earlier investigations are examined: most recent ECG available, echocardiogram, arterial echo-Doppler, investigations made to detect SMI. A meticulous clinical cardiovascular examination is carried out. Orthostatic hypotension is investigated. Critical ischaemia of the lower limbs is ruled out. ECG is done again if the last one had been carried out several months ago and searches for signs of ischaemia or even SMI, tachycardia, arrhythmia, prolonged QTc interval. Measurement of BNP or pro-BNP levels, or an immediate ECG may be prescribed in the case of possible cardiac ischaemia.

Investigations for SMI are therefore recommended in patients scheduled for major surgery if the Lee (revised cardiac risk index) score is  $\geq 2$  and if functional capacity is  $< 4$  metabolic equivalents (METs). The patient will be referred to a cardiologist for specific management and for tests for ischaemia (sheet B and Fig. 2). If the patient has no history nor any coronary symptoms, and in the absence of a specific anomaly on ECG, a silent heart disease should be suspected in patients with a high cardiovascular risk, in particular in the presence of other arterial damage, macro proteinuria, renal failure and when the coronary calcium score is  $> 400$  Agaston units [20].

When CAN is suspected due to the presence of symptoms or complications (permanent tachycardia, QTc  $> 440$  ms, MI or SMI, orthostatic or post-prandial hypotension, serious unfelt hypoglycaemia, absence of nocturnal decrease in blood pressure, unexplained), it should be confirmed by tests analysing HR variations. These tests should also be used to investigate CAN when microangiopathic complications exist. The procedure proposed includes the analysis of HR variations during a deep respiration test and a test for orthostatism (Appendix B). The presence of CAN, when confirmed by two abnormal tests or when symptomatic or complicated, should lead to intra- and post-operative monitoring (in a high dependency unit) (sheet B and Fig. 2).

## 2.3. Diabetic nephropathy

### 2.3.1. Epidemiology

Diabetic nephropathy (DN) is one of the most frequent microvascular complications of diabetes. It occurs in 30% of T1D and approximately 20% of T2D patients [50–52]. However, the frequency of this complication has plateaued or even decreased over the past few years in some countries due to earlier and more appropriate management [53,54]. In the USA, the relative risk of DN has decreased by one-half (13.7 to 6.1%) in 20 years [55]. The risk factors for DN are well known: male sex, South Asian or Afro-Caribbean ethnicity and prolonged evolution of diabetes. DN is the most frequent cause of end-stage renal failure, affecting 45% of individuals with renal failure in the USA. Twenty-four to 50% of patients receiving dialysis are diabetics with end-stage renal failure [52]. The incidence of end-stage renal failure in diabetic patients has greatly increased compared to non-diabetics with renal failure [51,56]. This progression classically occurs more frequently in a patient with advanced T1D; it is often associated with neuropathy and diabetic retinopathy (revealing microvascular complications) [50,51]. However, recent studies show that progression of DN towards end-stage renal failure appears to be comparable for the two types of diabetes and that it has slowed down over the past few years: 4 to 15% in 20 years and 16% in 30 years. The risk factors for progression of DN to end-stage renal failure are the following [57]: raised HbA1c, raised blood pressure, presence of albuminuria, early decrease in glomerular filtration rate (GFR), age, duration of diabetes and raised level of uric acid. DN increases the risk of mortality whatever the type of diabetes (relative risk 40–100-times higher than in non-diabetics) [51]. In the UK, the mortality rate of diabetic patients between 18 and 44-years of age, on dialysis, reaches 30% in 5 years compared to 11% in dialysed non-diabetic patients. It is also a major independent risk factor for cardiovascular complications, atherosclerosis and insulin resistance, fully justifying its prevention [52,58].

### 2.3.2. Physiopathology and diagnosis

The physiopathological concept of DN and its management have evolved greatly over the past few years, explaining the reduction in its incidence and its consequences in terms of morbidity/mortality. Until the start of the last decade, DN was considered to be characterised by lesions of nodular glomerulosclerosis and progressing towards renal failure classified in five stages of increasing severity based on GFR values (Fig. 3) [50,51,59]. The clinical diagnosis depends on the classical trio of micro albuminuria, arterial hypertension and renal dysfunction (of variable severity). Histopathological data have advanced this concept and the term DN has been replaced by diabetic chronic kidney disease (DCKD). Alongside the classic glomerulosclerosis, the renal lesions observed during diabetes may affect the tubules, the renal interstitial tissue and the vessels [60]. Thus, although micro albuminuria is the most frequent biological anomaly, it is not constant (because it only reveals glomerular damage) and does not necessarily reflect the severity of renal dysfunction. There is indeed no correlation between GFR and micro albuminuria, now named moderately increased albuminuria (values between 30 and 300 mg/g).

The pathogenic mechanisms of diabetic kidney lesions are complex and are linked to anomalies other than hyperglycaemia. Glomerulosclerosis is mainly induced by hyperglycaemia, which triggers mesangial expansion and tubular hypertrophy with cellular oedema responsible for initial glomerular hyper filtration. These modifications result in local activation of the renin-angiotensin-aldosterone system with glomerular efferent arteriolar vasoconstriction [51,57,58]. This reaction triggers many pathways of intracellular signalling: inflammation with profibrosing cytokine

Correlation between GFR and albuminuria categories				Categories according to albuminuria		
				A1	A2	A3
				Normal or slightly increased	Moderately increased	Greatly increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
Categories of GFR mL/min/1.73 m <sup>2</sup>	G1	Normal or increased	≥ 90	1 if chronic renal failure	1	2
	G2	Slightly decreased	60-89	1 if chronic renal failure	1	2
	G3a	Slightly to moderately decreased	45-59	1	2	3
	G3b	Moderately decreased	30-44	2	3	3
	G4	Important decrease	15-29	3	3	4+
	G5	End-stage renal failure	< 15	4+	4+	4+

**Fig. 3.** Evaluation of diabetic chronic kidney disease (DCKD) and its severity using two parameters: albumin/creatinine clearance ratio (ACR) and glomerular filtration rate (GFR) [61,62]. In stages A1/G1 and A1/G2, the disease is stable. The other stages, 1–4, indicate an increase in risk of progression to end-stage renal failure.

production, oxidative stress, growth factors, etc. The structural modifications which result include thinning of the basement membrane, alteration of podocytes and mesangial hyperplasia [58].

Measurement of the renal excretion rate of albumin (albuminuria) in a 24-h urine sample has been the “gold standard” for the early diagnosis of DN for many years. However, this parameter is unreliable and is affected by sampling conditions with an appreciable intra-individual variability. Furthermore, this simple measure, revealing tubular lesions, does not reflect the severity of renal dysfunction measured by GFR. There is no relation between the progression of albuminuria and the decrease in GFR. Thus, a positive diagnosis and the severity of DCKD is based on new recommendations [61]. The ratio of albuminuria to urinary creatinine (ACR) and GFR allow the classification of DCKD. There are three stages of increasing severity of ACR: stage A2 (ACR between 30 and 300 mg/g) corresponds to moderately high albuminuria previously termed micro albuminuria. The decrease in GFR is defined by five stages of increasing severity (G1 to G5) (Fig. 3). It is advised to measure the ACR and the estimated GFR on one urine sample rather than on 24-h urines and to perform at least 2 or 3 measurements in 6 months to confirm the diagnosis [62]. Although the estimated GFR is usually based on the MDRD formula, other formulae are also reliable (Cockcroft and Gault, CKD-EPI). Nevertheless, they all underestimate the GFR for subnormal renal function (GFR ≥ 90 mL/min) [62]. The stages A1/G1 and A1/G2 are considered stable and should lead to annual measurements. For all the other stages, the risk of progression toward chronic renal failure increases, as well as the cardiovascular risk. Follow-up with biological control should be carried out 2–4 times a year as a function of severity. The early diagnosis and follow-up of DCKD should be facilitated by the measurement of urinary biomarkers. These are proteins other than albumin such as cystatin C,  $\beta_2$ -microglobulin,  $\alpha$ -1 microglobulin, immunoglobulin G, transferrin, nephrin and metalloproteins, all indicators of tubular or glomerular lesions. Even though some studies have shown that these biomarkers are more sensitive and specific for the diagnosis of DCKD, their usefulness in clinical practice remains to be demonstrated.

Prevention and management of DCKD are currently well codified. Many studies have shown that they depend on multimodal management, which slows down the progression of

DCKD and reduces the cardiovascular complications and mortality of these patients [51,58]. The two main objectives of this management are the administration of antihypertensive treatments and closer control of glycaemia. All antihypertensive treatments have demonstrated efficacy ( $\beta$ -blockers,  $\alpha$ -blockers, diuretics, hydralazine). However, blockers of the renin-angiotensin-aldosterone system have the greatest efficacy. Thus, angiotensin converting enzyme inhibitors (ACE inhibitors) and angiotensin antagonists (sartans) decrease mortality, slow down the progression of DCKD to end-stage renal failure and reduce glomerular hyper filtration and its consequences. It is not currently recommended to combine ACE inhibitors with sartans and there is no proof of superior efficacy of this combination [50,51,62]. The initiation of treatment with ACE inhibitors or sartans is recommended from stage A2 moderate albuminuria and strongly recommended in case of severe albuminuria (A3) and/or estimate GFR < 60 mL/min/1.73m<sup>2</sup> [63,64]. These agents are also recommended in diabetic patients suffering from arterial hypertension. No randomised study has been carried out to determine the optimum arterial pressure cut-off value in these patients. However, experts recommend to maintain arterial pressure at less than 140/85–90 mmHg [20,64–66]. The second-line therapy for DCKD is control of glycaemia and its efficacy on micro vascular complications has been widely established. Thus, the current recommendations advise maintaining HbA1c ≤ 7% [64,67]. Control of hyperlipidaemia is also important, reducing albuminuria and slowing down the decrease in GFR. This is carried out by preferential administration of statins [51]. Early renal transplantation before carrying out dialysis may also contribute to an improvement in morbidity linked to DCKD.

### 2.3.3. Impact of DCKD on anaesthesia

Diabetes is an independent risk factor for the development of acute renal failure in the perioperative period. This may develop in the absence of previous renal dysfunction or in patients with DCKD. Postoperatively, the presence of DCKD increases this risk [68]. The perioperative evaluation of ACR and GFR is essential during major surgery, as a matter of urgency or if the patient presents with diabetic instability or poorly controlled glycaemia. The GFR can be estimated using classic formulae (MDRD, CKD-EPI, Cockcroft and

Gault) if the patient is stable but it should also be measured in other situations. The perioperative management of DCKD is not specific. It is necessary to avoid the administration of nephrotoxic agents or drugs in the perioperative period. Haemodynamic optimisation aims for a mean arterial pressure between 60 and 70 mmHg and > 70 mmHg if the patient is hypertensive, to maintain renal perfusion pressure. To achieve this objective, it is recommended to carry out haemodynamic monitoring in order to evaluate the stroke volume to guide vascular filling and the administration of vasopressors during surgical procedures associated with a risk of haemodynamic instability (haemorrhagic surgery, major surgery or emergency surgery) [68]. All other strategies are non-specific and should follow the recommendations for the management of acute renal failure [68]. Administration of anaesthetic agents should take into account the pharmacokinetic and pharmacodynamic modifications resulting from chronic renal failure without particular specificity in relation to diabetes.

### 3. Treatment management (sheet B)

#### 3.1. Metformin (sheets B and E)

The efficacy of metformin on glycaemic control and reduction of mortality and complications was demonstrated in the UKPDS study [69] and confirmed in the meta-analysis of Selvin et al. [70]. This beneficial effect was also observed in the REACH registry in patients with moderate renal failure (creatinine clearance between 30 and 60 mL/min) or a history of heart failure (HF), which are classic contraindications to its use [71]. In the study of Duncan et al., postoperative complications were identical whatever the treatment used (metformin or not) [72]. These observations have led to the restriction of contraindications and the prescription of metformin as first-line therapy in T2D.

However the risk of lactic acidosis, whose main cause is renal failure, should not be forgotten. The incidence of this complication is 2–9/100,000 patients/year and its mortality rate ranges from 30–50%. In France, the number of cases of lactic acidosis linked to metformin increased from 10 to 72 per year between 2005 and 2010: in most cases, patients were elderly (68% were > 65 years) and took a high dose of metformin (mean of 2600 mg/day). Analysis of cases also showed acute renal failure in almost all patients. Progression toward death was observed in 20% of cases [73].

However, published studies are contradictory: some have found no case [74,75] while others have found it only in the presence of risk factors [76]. Some authors have even reported a better cardiovascular prognosis in patients with HF [77,78]. In contrast, other studies have reported very severe cases, but these were always due to the untimely prescription of metformin (severe renal or heart failure) [79]. It is therefore important to look for risk factors before carrying out surgery:

- renal failure (creatinine clearance < 60 mL/min);
- administration of iodinated contrast agents;
- situations that could alter renal function: dehydration, fasting or medical treatments (ACE inhibitors and sartans, diuretics, non-steroidal anti-inflammatory drugs (NSAIDs));
- severe HF (left ventricular ejection fraction < 30%);

The presence of these risk factors also means that metformin should not be restarted too quickly in the postoperative period.

In practice, we recommend:

- stop metformin the night before;
- do not restart before 48 h for major surgery and after assuring adequate renal function;

- do not stop in case of minor or ambulatory surgery except if there is severe renal failure.

#### 3.2. Other non-insulin drugs (sheets B and E)

The other non-insulin treatments for diabetes are not taken on the morning of minor or major surgery and are continued in the case of ambulatory surgery. Hypoglycaemic sulphonamides and glinides may cause hypoglycaemia. Taking these medications before emergency surgery means that a glucose infusion should be set up if the patient remains with an empty stomach. This is not the case with the other non-insulin drugs.

#### 3.3. Insulins (sheets B and F)

##### 3.3.1. Subcutaneous (SC) injections

In T1D, basal insulin should never be stopped, whether administered as one or two injections, due to the risk of ketoacidosis.

##### 3.3.2. Particular case of insulin pump (sheet H)

The main risk during the perioperative period is ketoacidosis in T1D patients if continuation of insulin is not immediate after stopping the pump (SC injection by the basal-bolus scheme or continuous intravenous insulin infusion).

In the preoperative period, and with patient questioning, it is necessary to gain an understanding of “total basal delivery”, allowing the prescription of an analogue of long-acting (slow) insulin if the pump is stopped; or to note the replacement scheme, which should be known by the patient (dose of long-acting (slow) insulin if the pump is stopped).

In the case of ambulatory surgery or surgery of short duration, it is necessary to retain the pump which will continue to administer the basal delivery (for example, patients on long-acting (slow) insulin who do not stop their insulin during these types of surgery). Correction of hyperglycaemia during the procedure will be carried out using a corrective bolus administered by SC injection of an ultra-rapid analogue following a basal-bolus protocol (sheets L and Q).

### 4. Fasting

If the patient needs to be left with an empty stomach while he/she is treated with insulin, we recommend setting up a glucose infusion (from 7.00 a.m.) which is stopped if blood glucose is > 16.5 mmol/L (sheets G, H, K, L). Taking sulphonamides or glinides before emergency surgery also requires a glucose infusion if the patient remains with an empty stomach. If the patient does not use insulin, it is not necessary to administer a glucose solution.

### 5. Choice of agents and anaesthesia techniques

#### 5.1. Agents

To date, there is no proof that any anaesthetic agent is associated a better outcome in diabetic patients.

#### 5.2. Techniques

In particular, there is no proof that GA provides better results than RA in diabetic patients, even if RA is associated with a slight increase in glycaemia preoperatively. Spinal and epidural anaesthesia reduce hyperglycaemic injury, but expose the patient

to a haemodynamic risk. The choice between GA and RA will be made as for any other patient. Peripheral nerve blocks are not contraindicated in diabetic patients [80–82] but they should be carried out after taking and recording in the patient’s records several precautions, which are more important than in a non-diabetic patient: preoperative clinical examination with investigations for signs of dysautonomia and pre-existing polyneuropathy.

5.3. Investigations for difficult intubation

Preoperative assessment of risks at intubation should be clearly specified because tracheal intubation may be difficult due to densification of the periarticular collagen structures of the temporomandibular and atlanto-occipital joints. As these metabolic collagen disorders (non-enzymatic glycosylation and anomalies of metabolism) simultaneously affect the interphalangeal joints, it is usually advised to evaluate the difficulties in tracheal intubation using the palm print test in patients with long-term diabetes.

Disclosure of interest

The authors declare that they have no competing interest.

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The values in brackets [] are the corresponding 95% confidence intervals.

Appendix B

Investigations and grading of cardiac autonomy neuropathy in the anaesthesia consultation.

1. Investigations for orthostatic hypotension:

Measure blood pressure after 10 min of decubitus and then 1, 2 and 3 min after changing to orthostatism. Orthostatic hypotension is defined by a decrease in systolic blood pressure of at least 20 mmHg (30 mmHg in hypertensive patients) and/or of diastolic blood pressure of at least 10 mmHg in orthostatism. In the absence of any iatrogenic factor, hypovolaemia and anaemia, its presence is indicative of serious sympathetic dysautonomic damage.

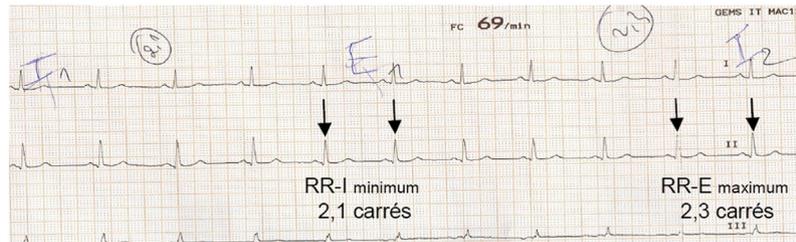
2. Tests exploring the cardio-vagal changes in heart rate (HR):

These tests should be performed at rest and long after coffee or tobacco consumption.

Deep respiration tests: the patient is placed in decubitus position and should train beforehand to this type of respiration. The patient is asked to perform six cycles of deep respiration in 1 min: during each cycle, the patient is stimulated to inspire (for 5 sec) and then expire (for 5 sec) deeply. ECG is recorded continuously during the test and the beginning of both inspiration (I) and expiration (E) are marked on the tracing.

Physiologically, HR increases on inspiration (i.e. RR decreases) and decreases on expiration (i.e. RR increases). The RR-E maximum and RR-I minimum are measured for each cycle. The ratio RR-E / RR-I is calculated for each cycle.

For example: 2.3 / 2.1 for the first cycle (1.0952 = 1.10).



Appendix A

Equivalence between blood glucose levels and HbA1c

There is a direct correlation between HbA1c level in % and mean glycaemia over the previous 3 months [11], according to the formula:

$$\text{Mean glycaemia g/L} = [(28.7 \times \text{HbA1c \%}) - 46.7] / 100, \text{ or}$$

$$\text{Mean glycaemia mmol/L} = (1.5944 \times \text{HbA1c \%}) - 2.5944$$

The table below shows the corresponding values for the standard values of HbA1c.

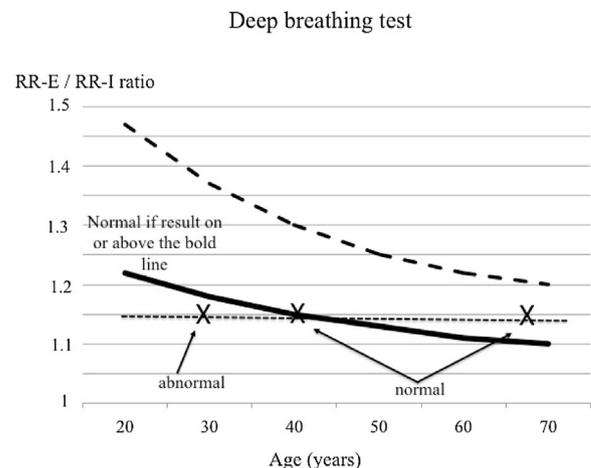
HbA1c	Mean blood glucose level	
%	g/L	mmol/L
5	0.97 [0.76–1.20]	5.4 [4.2–6.7]
6	1.26 [1.00–1.52]	7.0 [5.5–8.5]
7	1.54 [1.23–1.85]	8.6 [6.8–10.3]
8	1.83 [1.47–2.17]	10.2 [8.1–12.1]
9	2.12 [1.70–2.49]	11.8 [9.4–13.9]
10	2.40 [1.93–2.82]	13.4 [10.7–15.7]
11	2.69 [2.17–3.14]	14.9 [12.0–17.5]
12	2.98 [2.40–3.47]	16.5 [13.3–19.3]

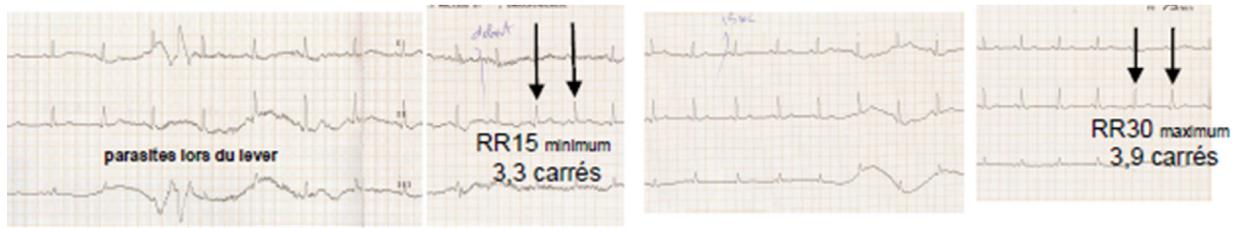
Replace 2.1 or 2.3 squares by 21 mm or 23 mm

The mean of the ratios for 6 respiratory cycles can be calculated.

For example: (1.10 + 1.21 + 1.11 + 1.09 + 1.26 + 1.15)/6 = 1.15

The result is then depicted on the graph below as a function of age.





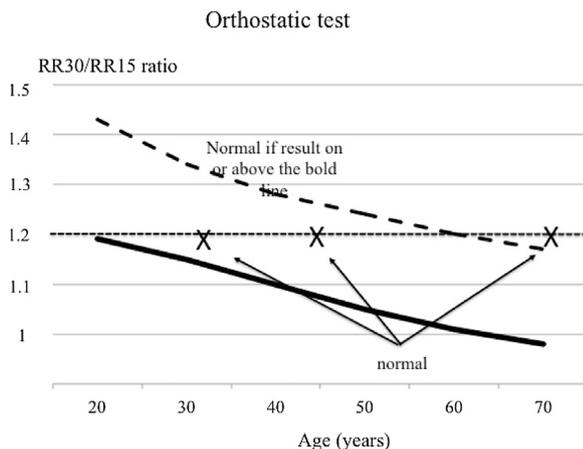
### Correlations (discontinuous line) between the RR ratio during the deep respiration test and age for healthy subjects.

Results for the patient are analysed by positioning them on the graph. They are abnormal if below the line for the 5th percentile (continuous line) [83]. The result is normal if it is on or below the thick line. For example, the test is normal for a patient  $\geq 40$  year of age but not for a younger patient.

#### Orthostatic test:

After 10 min of decubitus, the patient stands up quickly. The ECG is recorded continuously before rising and during the minute following change to the standing position. The HR normally increases in the first seconds following passage to orthostatism to reach its maximum towards the 15<sup>th</sup> second, then slows down and reaches its minimal value towards the 30<sup>th</sup> second. The result is expressed by the ratio  $RR_{30}/RR_{15}$ .

### Correlations (discontinuous line) between the RR ratio during the orthostatic test and age in healthy subjects.



The results for the patient are analysed by positioning them on the graph. They are abnormal if below the line for the 5<sup>th</sup> percentile (continuous bold line) [83]. In our example,  $RR_{30} / RR_{15} = 3.9 / 3.3 = 1.18$ . This result is then projected on the curve as a function of age, for interpretation.

#### 3. Practical procedure proposed

The patient places him/herself in decubitus position  
A standard ECG is recorded  
After 10 min of rest, a deep respiration test is carried out  
Measure arterial pressure and leave the blood pressure monitor in place

Restart the ECG

The patient stands quickly

The ECG is recorded for 1 min

Arterial pressure is measured again at 1, 2 and 3 min.

#### 4. Grading of CAN

From these tests, it is possible to grade the CAN:

- an altered cardio-vagal test identifies possible or early CAN
- definite or confirmed CAN corresponds to two altered cardio-vagal tests
- complicated CAN is identified by the presence of orthostatic hypotension or anomalies in the heart rate tests

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