RRT irrespective of the primary renal diagnosis and of the apparent duration of the diabetic disease.

Conclusions

Available data suggest that a proportion of RRT patients develop diabetes after renal treatment is started. The pathogenesis of the disease is multifactorial. In any case diabetes has a strong impact on survival. I hope that this editorial comment may motivate other nephrologists to review and report their own data concerning the emergence of diabetes in dialysis patients, since currently information in this field is woefully incomplete.

References


**Editor's Note**

Please see also the Brief Report by Catalano and Postorino (pp. 1124–1128 in this issue).

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**Are cardiac troponins reliable serodiagnostic markers of cardiac ischaemia in end-stage renal disease?**

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**Introduction**

In classical cases the effective management of massive acute myocardial infarction can be based exclusively on typical changes in the ECG in order to obtain the maximum benefit from timely reperfusion. In the real world, however, a clear-cut diagnosis from the ECG is often not possible, at least not initially, so that additional diagnostic tests are necessary to arrive at a definite diagnosis early on. In this setting the conventional cardiac enzyme assays have limitations not only because serial measurements over several hours may be required, but also because they lack sufficient...
sensitivity and/or specificity. In recent years new serodiagnostic markers for myocardial ischaemia have been introduced into clinical practice. In particular, the cardiac isoforms of the troponins fulfil the requirements of rapidity and superior diagnostic accuracy. The crucial question arises whether this diagnostic accuracy still is true in patients with end-stage renal disease (ESRD). Although definite answers are not yet in, we shall review in the following the information currently available.

Cardiac troponins as serodiagnostic markers for myocardial ischaemia

The proteins of the troponin complex (Figure 1) regulate muscle contraction by modulating the calcium-dependent interaction of actin and myosin. The three-subunit complex consists of the tropomyosin-binding subunit troponin T (39 kDa), the actomyosin-ATPase-inhibiting subunit troponin I (26.5 kDa) and the calcium-binding subunit troponin C (18 kDa). In contrast to the cardiac enzymes these myofibrillar proteins are undetectable by the available immunoassays (normal values: <0.1 µg/L) in serum under physiological conditions. Following loss of cell membrane integrity during ischaemia these intracellular proteins are released into the bloodstream from injured muscle cells. The troponin assays, in particular the troponin T assay, allow the identification of a subset of patients who have cardiac cell damage undetectable by the conventional enzyme markers. These patients with minor myocardial cell damage are at particularly high risk of subsequent transmural myocardial infarction and death, and may therefore derive the most benefit from therapeutic interventions.

Troponin C is of little value for the specific diagnosis of myocardial ischaemia, because of extracellular expression in slow skeletal muscle fibres. In contrast, troponin T and I are ideally suited as serodiagnostic markers for myocardial injury, since the heart and extracardiac muscles express distinct isoforms, which are encoded by different genes [1,2]. By comparison, the conventional ‘cardiac’ enzymes creatine kinase (CK), including the relatively cardiac-specific CK-MB isoforms, lactate dehydrogenase (LDH) and aspartate aminotransferase (AST) are less specific, as they are expressed in several extracardiac tissues. The cardiac isoforms of troponin I (cTnl) and troponin T (cTnT) can be specifically recognized by monoclonal antibodies which do not cross-react with the skeletal muscle isoforms. The superior specificity of the cTnl and cTnT detection has been demonstrated in the setting of perioperative myocardial infarction where CK-release from surgically damaged skeletal muscle can make the interpretation of the conventional CK/CK-MB-assays difficult.

The cardiac troponins can be detected in the serum for up to 2 weeks and more after an ischaemic event. For cTnT it has been shown that an initial rapid release from a cytoplasmic pool is followed by a prolonged leakage of cTnT from the myofibrillar compartment of damaged cardiac muscle cells [3]. Therefore the determination of cardiac troponins in the serum affords a time-integrated assessment of protein release from damaged cardiomyocytes.

The sensitivity and specificity of cTnT as a diagnostic marker have been demonstrated in a variety of clinical settings including acute myocardial infarction, unstable angina syndromes, assessment of postschaemic myocardial reperfusion, and perioperative myocardial infarction (reviewed in [4]. Adams et al. [5] have reported on the validation of cTnl as a diagnostic marker for myocardial ischaemia.

Cardiac troponins in patients with end-stage renal disease

The advantages of the cardiac troponin assays are now widely accepted and the availability of several commercial test systems has permitted their increasing clinical application. However, most of the experience with the troponin assays has been from patients without end-stage renal failure; unfortunately, the diagnostic efficiency in patients with ESRD, who represent a major cardiac risk population [6] has not been established. This is regrettable, because improved diagnosis of cardiac ischaemic syndromes is particularly desirable in the ESRD population, since the evaluation of myocardial ischaemia is limited a priori by the shortcomings of the standard tests: dialysis patients often have abnormal baseline ECGs and may be unable to undergo exercise testing. In addition, atypical chest pain and/or silent myocardial ischaemia are common in this patient population. Furthermore, the interpretation of the standard biochemical tests for the detection of myocardial cell necrosis can be difficult in these patients because of abnormal baseline elevations of cardiac enzymes: it has been reported that patients with chronic renal failure may have an elevated concentration of CK, including CK-MB, in their serum in
the absence of myocardial ischaemia [7]. Therefore the higher specificity and sensitivity of the troponin assays would represent major diagnostic progress in ESRD patients.

The extrapolation of the troponin experience from patients without to patients with ESRD has turned out to be problematic, however. Several recent reports indicated increased cTnT concentrations in ESRD patients on haemodialysis without apparent myocardial ischaemia, e.g. in 15 of 51 (29%) in our experience [8]. Hafner and co-workers [9] and Bhayana et al. [10] reported each on small series of renal failure patients with an unexplained increase of cTnT. McLaurin et al. [11] reported increased concentrations of CK-MB and cTnT in haemodialysis patients without acute myocardial ischaemia and related this to left ventricular hypertrophy.

Why is cTnT increased in ESRD patients? Certainly it is not due to the uraemic state per se, since it is seen only in some haemodialysis patients. We found also no correlation between residual diuresis, serum creatinine, BUN and cTnT (Stevanovich et al., unpublished observations). This is of note in view of the relatively low molecular weight of cTnT (39 kDa). The discordance between standard renal function parameters and cTnT is illustrated by an anecdotal report of a patient with a massively elevated serum concentration of cTnT (13 μg/l, normal: <0.1 μg/l) in the setting of rhabdomyolysis and acute on chronic renal failure [12]. In this 30-year-old patient the cTnT-concentration in the serum normalized within 3 weeks despite persistent renal failure requiring initiation of chronic maintenance haemodialysis. Therefore acute uraemia is unlikely to explain increased cTnT levels.

An alternative explanation could be that cTnT is so sensitive that it detects subclinical myocardial cell injury during the repetitive cardiac stress provoked by haemodialysis sessions or detects myocardial remodeling in the setting of left ventricular hypertrophy. Our haemodialysis population, 29% of whom had increased cTnT levels, was relatively old (mean: 61.3, range 28–86 years) with significant comorbidity (36% diabetes mellitus) and a high prevalence of concentric left ventricular hypertrophy by echocardiography. In contrast, children on haemodialysis without relevant cardiac comorbidity generally have normal cTnT levels (Stevanovich et al., unpublished observations). Thus increased cTnT levels in ESRD patients on haemodialysis may reflect subclinical cardiac injury and/or left ventricular hypertrophy, which is in agreement with the data of McLaurin et al. [11].

It is not even certain that the cTnT in the serum of haemodialysis patients is of cardiac origin. It is known that injured or regenerating skeletal muscle may express different protein isoforms compared with quiescent muscle. For example, the CK/CKMB ratio may be altered in damaged skeletal muscle [13]. Recent work has demonstrated decreased enzymatic activities in important energy-providing metabolic pathways in the skeletal muscle of uraemic patients [14]. At present it is not yet known whether uraemia induces the expression of the cardiac isoform of TnT in skeletal muscle. This possibility must be seriously considered, since the extracardiac expression of cTnT in injured or diseased skeletal muscle has been reported in animals [15] and in humans with polymyositis/dermatomyositis [16]. If extracardiac expression of cTnT does indeed occur in some patients with chronic uraemia, it is intriguing to speculate that cTnT might be an indicator of ill-defined 'uremic myopathy'.

So far for cTnT. As for cTnI, McLaurin et al. [11], Hafner et al. [9], Bhayana et al. [10], and Adams et al. [5] reported that the concentration of cTnI is generally not increased in renal failure patients in the absence of myocardial damage. The cause of the different behaviour of cTnT and cTnI is not clear: it is unlikely that the slightly lower molecular weight of cTnI (26.5 kDa) compared with cTnT (39 kDa) results in dialysance of sufficient magnitude to explain the different steady state levels of the cardiac troponin isoforms in the serum. It is possible that cTnI is less sensitive than cTnT to detect subclinical myocardial injury and/or remodelling of a hypertrophic left ventricle in dialysis patients. On the other hand, cTnI may retain its cardiac-specific expression during uraemia in contrast to the extracardiac expression of cTnT in some patients. Therefore it has been suggested that cTnI may be superior to cTnT for the diagnosis of myocardial ischaemia in patients with renal failure, but in our opinion this conclusion is not sufficiently substantiated. What is clearly needed is the systematic comparison of cTnI and cTnT in a large number of patients with varying degrees of acute and chronic renal failure, including ESRD patients undergoing haemodialysis or peritoneal dialysis.

Clinical recommendations

In patients with intact renal function the new serodiagnostic markers for myocardial ischaemia cTnI and cTnT offer distinct advantages over the standard biochemical assays because of their rapidity and superior diagnostic efficiency. In a subset of patients on chronic maintenance haemodialysis cTnT, but not cTnI levels may be increased without evidence of acute cardiac ischaemia; no data on patients on peritoneal dialysis or other renal replacement therapies are currently available. It remains to be seen whether the increase in cTnT reflects the high sensitivity of this assay to detect cumulative subclinical myocardial cell injury in haemodialysis patients or whether the increase reflects the extracardiac expression of the cardiac isoform of TnT during uraemia. In the absence of sufficiently large comparative studies the relative diagnostic value of the cardiac troponins as new serodiagnostic markers in renal failure patients is uncertain. Therefore we caution clinicians not to overinterpret minor increases of the cardiac troponins in patients with ESRD.
Torsade de pointes in haemodialysis patients

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What is torsade de pointes?

Desertenne et al. [1] were the first to describe torsade de pointes (TDP) as a separate form of ventricular arrhythmia with unique characteristics which they called ‘tachycardie ventriculaire à deux foyers opposés variables’. It is defined as a polymorphic ventricular tachycardia characterized by cycles of alternating electrical polarity with the electrical axis rotating around the isoelectric line. The amplitude of the ventricular complexes varies in a sinusoidal pattern with complexes of low amplitude linking phases of opposite polarity. The rate is in the range of 150–300 beats/minute with varying RR intervals. TDP characteristically is a recurrent, non-sustained arrhythmia over 20–60 s. It tends to self terminate without major haemodynamic compromise, but it may also cause syncope or even precipitate ventricular fibrillation and cardiac death. TDP occurs on the basis of a lengthened QT interval, reflecting prolonged cardiac repolarization.

TDP has to be differentiated from regular monomorphic ventricular tachycardias, from polymorphic ventricular tachycardias not related to QT interval prolongation, and from atrial fibrillation with fast atrioventricular conduction in patients with bundle branch block or WPW syndrome.

Which forms of torsade de pointes exist?

Lengthening of the QT interval as a prerequisite for TDP is the common feature of the hereditary and acquired long QT syndromes, which are distinct entities with supposedly different underlying pathomechanisms (see Table I). While in the hereditary form arrhythmias are triggered by adrenergic activation or enhanced sympathetic nervous system tone (adrenergic-dependent form), in acquired long QT syndromes TDP is typically precipitated by bradycardia or so-called ‘short- long- short’ RR interval sequences (pause-dependent form). The inherited form is a rare disorder which may or may not be associated with deafness (Lange-Jervell-Nielsen, or Romano-Ward syndrome respectively). The acquired long QT syndrome, which is also the subject of the case report by Huynh et al. in this issue, is much more common and of considerable clinical significance. It is produced by different drugs and conditions, which delay repolarization in the ventricular myocardium. Apart from class I and III antiarrhythmic drugs, some antianginal and inotropic

References