EDITORIAL COMMENT

Autoantibodies to cardiac troponin in patients after renal transplant: A new target for statins?

Autoanticorpos antitroponina cardíaca em doentes após transplante renal. Um novo alvo para a terapêutica com estatinas?

João Morais

Centro Hospitalar de Leiria, Leiria, Portugal

There have been few studies on the immune response to myocardial damage and their findings are of little practical value. Even in myocardial infarction (MI), the classic example of myocardial injury not due to inflammation or infection, the clinical impact of research is limited.

An example of what we would hope for from such research, with potential application to clinical practice, is the recent publication of an interesting study by Savukoski et al., who have developed a new immunoassay for troponin measurement that is free from interference from circulating anti-troponin autoantibodies.

In another study by the same group, the prevalence of troponin-specific autoantibodies in a cohort of 510 patients with suspected MI was 9.2%, but they found no correlation with 12-month outcome.

The practical relevance of this observation is that the presence of these antibodies can lead to false negative readings for serum troponin in patients with MI and thus delay diagnosis.

The presence of these antibodies has also been reported in apparently healthy individuals. Adamczyk et al. reported a 12.7% prevalence of both troponin T and I in healthy blood donors.

This immune response can be partly neutralized by nasal administration of the three troponin isoforms (C, I and T), and such vaccination reduces infarct size when administered prior to or one hour after ischemia/reperfusion injury.

Another area of interest to researchers is the presence of these autoantibodies in patients with dilated cardiomyopathy (DCM), such as those with Emery-Dreifuss muscular dystrophy (EDMD). This rare disease is sometimes diagnosed through the presence of a clinical picture of DCM in which involvement of cardiac muscle precedes that of skeletal muscle. In a study of 10 patients with EDMD and 10 healthy age-matched normal controls, there was no clear relationship between antibody levels and cardiac symptoms, although the authors admit that the detection of anti-troponin I antibodies may be a marker of early stages of DCM in EDMD.

Autoimmunity plays a part in the pathogenesis of several entities, including DCM, myocarditis, rheumatic fever and even atherosclerosis. However, whether it has a causal relationship with DCM is still the subject of debate.

Shmilovich et al. tested three groups, two with DCM (33 ischemic and 32 non-ischemic) and 42 healthy individuals, and found IgG anti-troponin autoantibodies in 18.2% of the ischemic DCM group and 15.5% of the non-ischemic group, as compared to none in the healthy subjects. However, attempts to bind these antibodies to cultured cardiomyo...
ocytess failed and they exhibited no measurable effects on calcium transients, leaving open the question of a possible causal connection.

Daniela Nunes et al. studied patients with Chagas disease and found no correlation with left ventricular ejection fraction; however, when grouped as low and high antibody producers, ejection fraction was lower in the group with higher levels of anti-troponin antibodies ($p=0.042$), and the correlation was even stronger with anti-myosin antibodies ($p=0.013$). The authors concluded that it may one day be possible to use the production of autoantibodies to troponin T and myosin as markers for the early detection of this disease of long-term evolution, which would have considerable clinical impact.

The study by José Nunes et al. published in this issue of the Journal presents a new approach to this subject, focusing on renal transplant patients with end-stage chronic renal disease. In 2013, the same group reported the case of a female patient with DCM and ejection fraction of 30% in which ventricular function improved after renal transplant, although without regaining previous end-diastolic volume. Very high levels of anti-troponin antibodies were found in this patient (IgG 1:640 and IgM 1:80), which presumably prompted the authors to continue their investigation.

In the article published here, a study of 48 renal transplant patients under immunosuppressive therapy, low titers ($<1:40$) of anti-troponin I autoantibodies were detected in most cases ($n=30$); only eight patients had IgG titers $\geq 1:80$, and there was a single value of $1:160$. In only one patient were both anti-troponin I antibody IgG and IgM titers $\geq 1:80$. Clinical cardiac disease was seen in nine patients, but this was not associated with antibody levels. The authors found an interesting correlation between anti-troponin antibodies and statin use, with high levels being detected in only $3/26$ patients under statin therapy as opposed to $10/22$ of those not under statin therapy ($p=0.008$ by the chi-square test), suggesting that the immune response is weakened by statin therapy.

The non-lipid effects of statins have been the subject of much research over the past twenty years, with heated debate between opposing viewpoints. However, statins’ anti-inflammatory effects, for which evidence is accumulating, are more generally accepted.

The long history of investigation into the clinical effects of statins includes their marked reduction of contrast-induced nephropathy, as shown in a meta-analysis published in 2014, with 46% lower relative risk (RR) (RR 0.54, 95% confidence interval 0.38–0.78, $p=0.001$).

Various hypotheses have been put forward concerning the mechanisms behind this effect, but they are merely speculative. The anti-inflammatory effect of statins has been invoked once more, but there are other possibilities, including protection against the cytotoxic effects of contrast agents. A subgroup analysis of the Novel Approaches for Preventing or Limiting Events (NAPLES II) trial showed that a high loading dose of atorvastatin in vitro reduced the activation of the intrinsic apoptotic pathway seen in situations of extreme metabolic or hemodynamic stress.

The authors of the present study consider some of these possibilities from a hypothetical standpoint in the discussion of their results. The idea that renal transplant patients should undergo chronic statin therapy remains controversial. However, while there are clear benefits from statins in patients with chronic renal disease not requiring dialysis, reducing mortality by around 20%, there is less agreement concerning patients on dialysis. A recent meta-analysis of studies in renal transplant recipients was inconclusive due to the heterogeneity in the methodologies used.

Nevertheless, until there is solid evidence either way, the severe vascular disease normally seen in end-stage renal disease, and the attendant higher risk of MI, are in the opinion of this author sufficient reason to consider statin therapy in these patients.

Only further studies can demonstrate whether a reduction in antibody levels is an additional protective factor. We look forward to the results of future studies by the authors of the article published here in their search for answers to these questions.

Conflicts of interest

The author has no conflicts of interest to declare.

References

Autoantibodies to cardiac troponin


