Cardiac autonomic dysfunction and inflammation in type 1 diabetic patients

We read the article by Lanza et al. dealing with the association between cardiac autonomic dysfunction and inflammation in type 1 diabetic patients with great interest. The authors revealed an inverse correlation between C-reactive protein levels and heart rate variability (HRV) parameters, especially with low-frequency (LF) power. Authors have also revealed significantly higher C-reactive protein serum levels in patients with bottom quartile values of LF power that improved significantly with atenolol parallel to improvement in LF power. In our opinion, some points of this work are not sufficiently clear.

Authors reported significant difference ($P = 0.04$) in the alterations of serum high-sensitive C-reactive protein level over the study period between atenolol and no atenolol groups by using two-way ANOVA test (Table 5, Figure 3). The difference between the two groups, with regard to change in serum-high sensitive C-reactive protein level, is partly due to a decrease in atenolol group (from 3.02 $\pm$ 2.9 to 2.01 $\pm$ 1.9 mg/L) and is partly due to a comparable increase in no atenolol group (from 2.89 $\pm$ 2.9 to 3.88 $\pm$ 3.8 mg/L) over study period. If serum high-sensitive C-reactive protein level was not changed over the study period in no atenolol group, then the difference of alterations in serum high-sensitive C-reactive protein level between the two groups would probably not reach statistical significance. Therefore, the statistically significant difference in the alterations in serum high-sensitive C-reactive protein level over the study period between the two groups may not be attributed to atenolol use with the findings of this study.

Authors revealed improved HRV parameters and decreased serum high-sensitive C-reactive protein level in atenolol group without assessing the correlation between the changes in HRV parameters and serum high-sensitive C-reactive protein level. Consequently, they discussed the relationship between autonomic nervous system and inflammatory reactions. However, in order to report such a relationship with data of this study, correlation analysis should have been performed for evaluation of the association between the alterations in HRV parameters and the alterations in serum high-sensitive C-reactive protein levels over the study period.

As stated in the limitations of the study, serum high-sensitive C-reactive protein is a reliable marker of inflammation, but also is a multivariate, non-specific marker of inflammation. Without controlling the influencing factors over time, linking the change in serum high-sensitive C-reactive protein level with atenolol use or autonomic nervous system functions is not appropriate. Evaluation of body mass index, serum triglyceride levels, and microalbuminuria during the follow-up concomitantly with serum high-sensitive C-reactive protein level would add value of this article since these factors were correlated with serum high-sensitive C-reactive protein level at baseline.

Reference


Yildiz et al. raise three major issues about our study on the relation between cardiac autonomic dysfunction and inflammation in type 1 diabetic patients: (i) the difference in the changes of C-reactive protein (CRP) serum levels over the study period between atenolol and no-atenolol groups achieved statistical significance ($P = 0.04$) likely only because, together with the reduction in the atenolol group, there was a comparable increase in CRP in the no-atenolol group; (ii) as no correlation analyses between the changes in heart rate variability (HRV) parameters and in CRP serum levels were done, it cannot be concluded that there was a relation between HRV improvement and reduction of CRP levels in the atenolol group; (iii) without controlling for factors potentially influencing changes in CRP over time, it is inappropriate to link the CRP changes to those in autonomic nervous system or atenolol use.

With regard to the first point, it should be noticed that the true effect of atenolol on CRP levels is not only supported by the significant group-CRP interaction on Z-way analysis of variance, but also by the fact that CRP levels decreased significantly in the atenolol group ($P = 0.025$), whereas they did not show any significant change (specifically, they did not decrease) in the control group ($P = 0.14$).

With regard to the second point, Spearman test, performed to address the issue raised by Yildiz et al., shows a significant correlation between the changes in low-frequency (LF) power and in CRP serum levels in the whole group of 21 patients enrolled in the drug trial ($r = -0.47; P = 0.029$); importantly, the correlation coefficient between the changes in LF power and CRP levels was even higher when considering only the 11 patients treated by atenolol, with $P$-value being just above statistical significance due to the small number of patients ($r = -0.57; P = 0.066$; only 54% statistical power to detect a significant correlation at $P < 0.05$).

Finally, as far as the last observation is concerned, clinical conditions (including diabetic status and body mass index) and medical treatment remained unchanged throughout the whole short study period in the two groups of patients randomized in the drug trial. Thus, there are no reasons to believe that the reduction in CRP levels...