Response to Effect of Fenofibrate on Vascular Endothelial Function: Statistical Appraisal and its Validity

We recently published an original research article reporting that short-term fenofibrate improves flow-mediated dilation (FMD) in healthy normolipidemic older adults.¹ By assessing the response to vitamin C infusion before and after fenofibrate treatment, we determined that the mechanism for the improvements in FMD was reduced oxidative stress. We also assessed the influence of changes in clinical characteristics on the improvements in FMD. On the basis of these analyses, we concluded that oxidative stress was the primary mechanism for the improvements in FMD in response to fenofibrate.

In a letter to the editor, Dr Kawada² recently stated concerns about our statistical analyses. Specifically, there was a concern that the distributions for circulating factors may not be normal. In response, we would like to emphasize that bivariate correlations were performed on the change in these factors from baseline to 2 or 7 days of fenofibrate treatment, not with the raw values. Although it is true that the raw values for circulating factors may not be normally distributed, this is not necessarily the case for the changes over time. To address Dr Kawada’s concern, we analyzed the normality of all variables used in correlation analyses, including the change in FMD, blood pressure, and circulating factors. Using the Shapiro–Wilk test, we found that all factors had a normal distribution except the 2-day change in C-reactive protein and the 7-day change in triglycerides. However, after log transformation, these variables were not related to the change in brachial FMD for those respective time periods (2-day C-reactive protein: $r=0.35$, $P=0.14$; 7-day triglycerides: $r=-0.30$, $P=0.19$), consistent with the results in the original publication.

In our original article, we performed a linear regression to examine the effect of treatment and changes in potentially modulating factors on the change in FMD. We only included factors that were likely to have an influence, which for the change at 7 days included those factors that were correlated to the change in FMD (blood pressure) and factors that changed in response to fenofibrate (total and low-density lipoprotein cholesterol). By analyzing the residuals, we determined that the error distribution is normal for this regression. As requested by Dr Kawada,² we present the linear regression results at 7 days here (Table). Although these collinearity statistics in our analysis meet standard criteria,³ we performed individual regression analyses as recommended by Dr Kawada.² In each model for the 7-day change in FMD, the effect of treatment group was significant ($P<0.05$).

On the basis of the results of these new analyses, we confirm our original conclusions that the improvements in FMD with fenofibrate are independent of changes to clinical factors in this study. However, as we previously mentioned, the variability of some measures, particularly circulating triglycerides, may limit our ability to accurately assess their contributions to improvements in FMD. Thus, studies with larger sample sizes may be needed to more definitively determine the influences of changes in clinical characteristics on vascular function with fenofibrate treatment.

Table. Linear Regression Analysis for the Influence of Fenofibrate Treatment, Blood Pressure, and Cholesterol on the Change in Flow-Mediated Dilation After 7 Days

<table>
<thead>
<tr>
<th>Variable</th>
<th>$\beta$</th>
<th>$r^2$</th>
<th>P Value</th>
<th>Tolerance</th>
<th>VIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
<td>0.514</td>
<td>0.130</td>
<td>0.049</td>
<td>0.491</td>
<td>2.037</td>
</tr>
<tr>
<td>Change in SBP</td>
<td>-0.315</td>
<td>0.042</td>
<td>0.245</td>
<td>0.417</td>
<td>2.398</td>
</tr>
<tr>
<td>Change in DBP</td>
<td>-0.159</td>
<td>0.011</td>
<td>0.543</td>
<td>0.436</td>
<td>2.294</td>
</tr>
<tr>
<td>Change in TC</td>
<td>0.194</td>
<td>0.012</td>
<td>0.523</td>
<td>0.322</td>
<td>3.104</td>
</tr>
<tr>
<td>Change in LDL-C</td>
<td>-0.083</td>
<td>0.003</td>
<td>0.766</td>
<td>0.377</td>
<td>2.652</td>
</tr>
</tbody>
</table>

$\beta$ indicates standardized beta coefficient; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; $r^2$, squared part coefficient; SBP, systolic blood pressure; TC, total cholesterol; and VIF, variance inflation factor.

Disclosures

None.

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