Effects of Chocolate in the Endothelial Function of Patients with Acute Coronary Syndrome

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Abstract

Introduction: Unsweetened chocolate improves endothelial function, but there are few data on its action in patients with coronary disease.

Objective: To assess the endothelial function in patients with acute coronary syndrome after consumption of unsweetened chocolate and white chocolate.

Methods: This is a randomized crossover clinical trial that evaluated 11 patients admitted with acute coronary syndrome. The patients were selected to receive unsweetened chocolate or white chocolate and crossed over to receive the other intervention after seven days. The primary outcome was the variation in flow-mediated vasodilation of the brachial artery pre and post intervention in both groups. The secondary outcomes were the values of flow-mediated vasodilation and the diameter of the brachial artery after the intervention, the levels of high-sensitivity C-reactive protein (hsCRP) and erythrocyte sedimentation rate (ESR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) and heart rate (HR).

Results: The variation of flow-mediated vasodilation pre and post intervention was higher in the group that received the unsweetened chocolate compared with the group that received white chocolate. Both groups showed a significant increase in flow-mediated vasodilation after intervention. The flow-mediated vasodilation after intervention, however, was higher in the group receiving unsweetened chocolate (0.32±0.10) compared to white chocolate (0.21±0.11) (p=0.001). There were no significant differences in hsCRP, ESR, SBP, DBP or HR values.

Conclusion: The consumption of chocolate improves endothelial function in patients after acute coronary syndrome patients and this effect is more pronounced with the consumption of unsweetened chocolate.

Keywords: Acute coronary syndrome; Cacao; Endothelium, vascular

Introduction

Lipid profile and inflammation have a clear association with atherosclerosis and ischemic heart disease. The vascular endothelium plays an active role in this process, since it is responsible for the release of vasoactive substances such as nitric oxide (NO) and prostacyclin. The effects obtained by the release of NO include anti-atherogenic properties, inhibition of platelet aggregation and adhesion and anti-inflammatory mechanisms1,2. Impaired endothelial function thus represents a greater risk to patients even in the absence of coronary artery disease2. The best-known ways to improve endothelial function are through behavioral measures and pharmacological therapies such as the use of statins. There is evidence, however, that indicate that flavonoids (present in high concentrations in cocoa) also have anti-inflammatory effects: they have antioxidant effects, improve endothelial function by increasing the bioactivity of NO, inhibit oxidation of LDL and seem to reduce the levels of inflammatory...
markers\textsuperscript{2-6}. In addition, chocolate consumption seems to improve the flow-mediated vasodilation in healthy individuals. There seems to be an inverse relationship of the consumption of flavonoids and cardiovascular mortality\textsuperscript{4,7}.

Despite the known effect of flavonoids and chocolate (particularly those with high concentrations of cocoa), there is little evidence of its benefit in patients with established coronary disease or after an acute coronary event.

The objective of this study was to evaluate and compare the acute response of unsweetened chocolate and white chocolate on the endothelial function of patients after acute coronary syndrome by flow-mediated dilation of the brachial artery by ultrasound\textsuperscript{7}.

**Methods**

This is a randomized, crossover, placebo-controlled study that selected patients with ischemic heart disease during hospital stay for acute coronary syndrome, to receive 100 g of unsweetened chocolate containing 85% cocoa or 100 g white chocolate (containing no cocoa).

The inclusion criteria were age > 18 years and the presence of unstable angina or an episode of acute myocardial infarction (evidenced by 2 mm ST segment elevation in two contiguous leads on the electrocardiogram or more than three times elevation on troponin levels). Exclusion criteria were absence of symptoms compatible with unstable angina and/or absence of evidence of ischemic heart disease by complementary test; allergy or intolerance to chocolate components; and presence of diabetes mellitus.

The primary outcome was the difference in the variation of flow-mediated vasodilation of the brachial artery pre and post-intervention between the two groups. Secondary outcomes were the values of flow-mediated vasodilation and the brachial artery diameter after intervention in both groups, change on the levels of high-sensitivity C-reactive protein (hsCRP) and erythrocyte sedimentation rate (ESR), reduced systolic and diastolic pressure and 40-minute heart rate after unsweetened chocolate consumption or placebo.

Randomization was performed using specific software and random allocation was maintained through manila envelopes (with sequence of randomization) made by an independent researcher and were only opened after signing the Informed Consent Form. Two groups were structured: the unsweetened chocolate group received, at first, a 100 g bar of unsweetened chocolate containing 85% cocoa; the white chocolate group received, at first, a 100 g bar of white chocolate.

In both groups, the pharmacological therapy advocated by the corporate guidelines was maintained. The patients involved were transported to the ultrasound sector on wheelchairs to prevent any physical activity from interfering in the evaluations of endothelial function. In the ultrasound sector, the patients had their blood pressure and heart rate measured.

The ultrasound evaluations were performed by the same trained and “blinded” examiner for the intervention that the patient was receiving. The methods used to collect the data were based on the latest guideline for noninvasive assessment of endothelial function\textsuperscript{2}: after fasting for 8 hours, Doppler ultrasound was conducted on the patient’s left brachial artery. On the first evaluation, the patient remained at rest and the result of the average of five brachial artery diameter measurements was obtained between 7 cm and 10 cm above the antecubital fossa. In order to promote endothelial stress, the sphygmomanometer cuff was inflated 50 mmHg above the maximum systolic blood pressure and maintained for five minutes above the antecubital fossa. A new assessment was then performed 50 seconds after deflation. The measure considered after endothelial stress resulted from the average of five measurements of the brachial artery diameter, as obtained at rest. The values of flow-mediated pre-intervention vasodilation corresponded to the difference between the average diameters after endothelial stress and rest. After the initial assessment, each patient received 100 g of unsweetened chocolate or white chocolate according to the order of randomization and after 40 minutes the ultrasound evaluation of the brachial artery at rest and endothelial stress was repeated. The values of flow-mediated post-intervention vasodilation corresponded to the difference between the average diameters after endothelial stress and at rest after consumption of the respective chocolate. The groups were crossed over after seven days and the second phase of the study patients who received white chocolate received unsweetened chocolate and vice versa.

After the participation of individuals in each phase of the study, blood samples were collected immediately in order to obtain hsCRP and ESR values.
A sample of 22 cases (11 pairs) was determined to detect a difference of 5.8% in the variation of flow-mediated vasodilation of the brachial artery pre and post-intervention with unsweetened chocolate with a two-tailed alpha of 0.05 and a power of 90%, estimating a loss of 10%, based on the data of Faridi et al. The patients were evaluated according to intention to treat.

Data analysis was conducting using the software SPSS 13.0 for Windows. Continuous variables were analyzed using the Student t test for paired samples or analysis of variance (ANOVA) for repeated measures. Categorical variables were analyzed by the Fisher’s exact test. Continuous variables were expressed as mean±standard deviation and categorical variables were expressed as frequencies. In this study, p values < 0.05 were considered statistically significant.

The study followed the CNS Resolution 466/12 and was approved by the Research Ethics Committee of the institution under No. 20337913.8.0000.0113. All participants signed an Informed Consent Form.

Results

We evaluated 76 patients who were hospitalized at Instituto de Cardiologia de Santa Catarina from October to December 2013, including 11 patients with a mean age of 59.36±9.34 years. The characteristics of the study population are found in Table 1.

The variation of flow-mediated vasodilation pre- and post-intervention (primary endpoint) was higher in the group that received unsweetened chocolate compared to the group that received white chocolate (p=0.008) (Figure 1).

### Table 1
Characteristics of the population studied

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>10 (90.9)</td>
</tr>
<tr>
<td>AH</td>
<td>7 (63.6)</td>
</tr>
<tr>
<td>Smoking</td>
<td>3 (27.27)</td>
</tr>
<tr>
<td>Reason for hospitalization</td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>3 (27.27)</td>
</tr>
<tr>
<td>AMI without ST-segment elevation</td>
<td>7 (63.6)</td>
</tr>
<tr>
<td>AMI with ST-segment elevation</td>
<td>1 (9.09)</td>
</tr>
<tr>
<td>Previous coronary artery bypass grafting</td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>1 (9.09)</td>
</tr>
<tr>
<td>Angioplasty</td>
<td>2 (18.18)</td>
</tr>
</tbody>
</table>

AMI — acute myocardial infarction; AH — arterial hypertension

Figure 1
Changes in flow-mediated vasodilation with unsweetened chocolate (solid line) and white chocolate (dashed line).
Both groups showed a significant increase in flow-mediated vasodilation with intervention (Table 2). The flow-mediated vasodilation post-intervention, however, was higher in the group that received unsweetened chocolate (0.32±0.10) compared to the white chocolate group (0.21±0.11) (p=0.001). The differences in the values of the variables ESR, hsCRP, HR, SBP and DBP were not significant. Other outcomes are presented in Table 2.

One patient had diarrhea after eating unsweetened chocolate. No other adverse effect was reported.

### Table 2

Outcomes found in the pre and post-intervention

<table>
<thead>
<tr>
<th></th>
<th>Unsweetened chocolate</th>
<th>White chocolate</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-intervention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>116.36±15.01</td>
<td>120.00±8.94</td>
<td>0.167</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>78.18±12.50</td>
<td>80.00±7.74</td>
<td>0.441</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>67.09±5.61</td>
<td>68.18±6.35</td>
<td>0.441</td>
</tr>
<tr>
<td>Diameter at rest (mm)</td>
<td>4.47±0.14</td>
<td>4.46±0.16</td>
<td>0.602</td>
</tr>
<tr>
<td>Stress diameter (mm)</td>
<td>4.72±15.13*</td>
<td>4.65±15.13*</td>
<td>0.007</td>
</tr>
<tr>
<td>Vasodilation (mm)</td>
<td>0.24±0.10</td>
<td>0.19±0.11</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Post-intervention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>117.27±14.89</td>
<td>120.90±11.36</td>
<td>0.104</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>80±14.14</td>
<td>82.72±10.09</td>
<td>0.277</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>67.63±4.71</td>
<td>68.54±6.39</td>
<td>0.588</td>
</tr>
<tr>
<td>Diameter at rest (mm)</td>
<td>4.49±0.13</td>
<td>4.45±0.17</td>
<td>0.065</td>
</tr>
<tr>
<td>Stress diameter (mm)</td>
<td>4.81±15.13*</td>
<td>4.66±15.13*</td>
<td>0.001</td>
</tr>
<tr>
<td>Vasodilation (mm)</td>
<td>0.32±0.09**</td>
<td>0.21±0.11**</td>
<td>0.001</td>
</tr>
<tr>
<td>ESR (mm)</td>
<td>23.00±14.44</td>
<td>20.00±12.17</td>
<td>0.258</td>
</tr>
<tr>
<td>HsCRP (mgL)</td>
<td>5.20±4.40</td>
<td>4.00±3.30</td>
<td>0.179</td>
</tr>
</tbody>
</table>

Values expressed as mean±standard deviation
SBP — systolic blood pressure; DBP — diastolic blood pressure; HR — heart rate; ESR — erythrocyte sedimentation rate; HsCRP — high-sensitivity C-reactive protein
*p<0.001 compared to values at rest; **p<0.001 compared to pre-intervention values.

### Discussion

This clinical trial showed that both unsweetened chocolate and white chocolate promote a significant increase in flow-mediated vasodilation. Such increase is significantly greater in response to unsweetened chocolate. The results for unsweetened chocolate are justifiable, but the increase in vasodilation with white chocolate (even smaller than the unsweetened chocolate) was not expected: the effect of unsweetened chocolate can be credited to cocoa, but white chocolate does not contain this flavonoid and the improvement in endothelial function possibly occurred by chance or by factors that cannot be measured.
Different studies have demonstrated that unsweetened chocolate is rich in flavonoids, improves endothelial function in healthy adults7-9. The improvement in endothelial function was also demonstrated in patients with a higher risk profile such as patients with hypertension and smokers10,11. The patients in this study had coronary artery disease and, therefore, endothelial dysfunction, which could compromise the vasodilator response expected in response to the stress caused in the vascular endothelium. Previous data suggest that consumption of unsweetened chocolate in patients with coronary artery disease would not promote any acute or chronic changes12; this study, however, found that the acute effect of chocolate remains significant in this patient profile.

The blood pressure response to the consumption of bitter chocolate is controversial: some data in the literature suggest a potential anti-hypertensive effect3,7,13,14; others, however, do not seem to show the same effect8,9. The results failed to show any changes in SBP, DBP or HR after the consumption of white or unsweetened chocolate. This lack of response could be said to be due to the lack of power of the study and the use of antihypertensive drugs (in particular the use of beta-blockers for all patients).

Despite the known anti-inflammatory effect, with consequent reduction in the values of hsCRP15, we could not prove this benefit in this study, however, we cannot rule out the fact that all patients studied here had recently presented an acute event. It would be logical to expect that the serum levels of hsCRP and ESR could be strongly influenced by the time of collection (higher in the first collection) regardless of the chocolate consumed. This study has some limitations: the sample is small and the outcomes are only substitutive — although there is some evidence that unsweetened chocolate is beneficial in reducing mortality16, for example, this study has no power to exercise any inference about it. There were significant differences between the values of flow-mediated pre-intervention vasodilation (Table 2). This could be a potential bias in assessing outcomes. However, the variation in pre- and post-intervention vasodilation was higher in patients who received unsweetened chocolate, rejecting the influence of baseline measurements in the study findings. Furthermore, the amount of chocolate used in this study, as observed in previous clinical trials3,15, is very large (100 g of unsweetened chocolate correspond to 502 calories) and limits the extrapolation of the data for possible orientations of chronic consumption.

Conclusion
Chocolate consumption improves endothelial function assessed by flow-mediated vasodilation in patients after acute coronary syndrome. This effect is more pronounced with the consumption of unsweetened chocolate (with high cocoa content).

Potential Conflicts of Interest
No relevant potential conflicts of interest.

Sources of Funding
This study had no external funding sources.

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References


