Applied nutritional investigation

Oral resveratrol and calcium fructoborate supplementation in subjects with stable angina pectoris: Effects on lipid profiles, inflammation markers, and quality of life

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Objective: This study aimed to evaluate the effects of short-term (60-d) oral supplementation with calcium fructoborate, resveratrol, and their combination on the clinical and biological statuses of subjects with stable angina pectoris.

Methods: A randomized, double-blinded, active-controlled, parallel clinical trial was conducted in three groups of subjects. Of the total number of subjects included in study (n = 166), 87 completed the 60-d test treatment study period and 29 followed in parallel their usual medical care and treatment. The primary outcomes were inflammation biomarkers (high-sensitivity C-reactive protein), left ventricular function markers (N-terminal prohormone of brain natriuretic peptide), and lipid markers (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triacylglycerols). Quality of life was assessed by the Canadian Cardiovascular Society angina class and the number of angina attacks per week.

Results: There was a significant decrease of high-sensitivity C-reactive protein in all groups at the 30-d and 60-d visits. This decrease was greater (39.7% at 60 d) for group 3 (calcium fructoborate), followed by group 2 (resveratrol plus calcium fructoborate, 30.3% at 60 d). The N-terminal prohormone of brain natriuretic peptide was significantly lowered by resveratrol (group 1, 59.7% at 60 d) and by calcium fructoborate (group 3, 52.6% at 60 d). However, their combination (group 2) was the most effective and induced a decrease of 65.5%. Lipid markers showed slight changes from baseline in all groups. The improvement in the quality of life was best observed for subjects who received the resveratrol and calcium fructoborate mixture (group 2).

Conclusion: The results indicate that the combination of resveratrol and calcium fructoborate has beneficial effects in patients with angina (ClinicalTrials.gov, ISRCTN02337806; March 25, 2010).

Introduction

Atherosclerotic ischemic heart disease is a major health problem worldwide [1]. Inflammation is a main factor in the initiation, progression, and acute complications of an atherosclerotic plaque [2]. Resveratrol has shown significant cardiovascular protective effects [3] in models of myocardial injury [4,5], systemic and pulmonary hypertension [6], and type 2 diabetes [7]. Several cardioprotective mechanisms of resveratrol, including antioxidant, anti-inflammatory, and anti-fibrotic actions, have been identified [8]. The low in vivo bioavailability caused by rapid resveratrol metabolism and elimination, its major disadvantages, limits the results for patient studies [9]. Boron is a bioactive element for humans and boron-containing compounds present different biological activities [10]. Calcium fructoborate (CF) is a complex of calcium, fructose, and boron found naturally in fresh and dried...
fruits, vegetables, herbs, and wine [11,12]. In previous studies, the effect of CF on human polymorphonuclear neutrophils and macrophages, which play a central role in the inflammatory response, has been investigated [13,14]. Two very recent studies have provided important information on the possible molecular anti-inflammatory activity of CF in the treatment of osteoarthritis [15,16].

The purpose of this controlled pilot study was to assess the short-term synergistic effect of resveratrol in combination with CF on the clinical and biological statuses of subjects with stable angina pectoris. The combination of these two substances was based on the fact that CF acts as a stabilizer for resveratrol degradation in the digestive tract [17]. Furthermore, CF might present a positive synergism together with resveratrol, increasing the anti-inflammatory properties of the former and the biological efficacy of the latter as an antioxidant agent.

Materials and methods

Study design

The study was randomized, double-blinded, active-controlled, and paralleled with three groups of subjects who received the test drugs and one control group of subjects who were not randomized. This single-center trial was approved by the institutional ethics committee of the Craiova Cardiology Center (Craiova, Romania) according to decision no. 400 in February 2010. The trial also was in accord with the Declaration of Helsinki of 1975, which was last reviewed in 2008. Placebo was not admitted by the hospital bioethics commission owing to ethical considerations. Nevertheless, this trial had a control group with subjects who fulfilled inclusion criteria, but they received only their usual medical care and treatment, without any test materials, during the clinical trial. The number of total enrolled subjects was 166 (Fig. 1). Of 116 subjects who met the inclusion criteria, 87 were included in the intention-to-treat analysis, divided into three groups (29 subjects in each group), and all completed the entire protocol. The remaining 29 were included in the control group and underwent the same analysis as those who received the test materials. The subjects’ ages ranged from 42 to 83 years (mean age 65 y). There were more men (71, 61.2%) than women (45, 38.8%). Most were in Canadian Cardiovascular Society (CCS) angina class III at inclusion (62%), 30% were in class II, and 8% were in class IV. Table 1 presents the baseline demographic characteristics of the subjects who successfully completed the study and the background medication. There were no significant differences among the groups. All subjects continued with their medical therapy as prescribed by their treating physicians. Subjects did not receive any nutritional supplements or other products. They were instructed to follow a diet low in salt or fat if they were hypertensive or dyslipidemic, respectively. Patients with diabetes mellitus were instructed to follow the recommendation of their treating physicians.

Inclusion criteria

Male and female subjects at least 18 y of age were included. All had been diagnosed with angina pectoris (CCS classes II–IV), and they had to be in stable clinical condition for at least 1 mo (angina class, angina frequency). The subjects’ body mass index range was 24 to 27 kg/m² (overweight but not obese). Subjects had to be on standard and stable treatment for angina in the previous month.

Exclusion criteria

Subjects who were unlikely to cooperate in the study, had legal incapacity or limited legal incapacity, and were pregnant or breast-feeding or had child-

![Fig. 1. Flow chart for subject recruitment. CF, calcium fructoborate; ITT, intention to treat; PP, patients; RSV, resveratrol; tx, study treatment.](http://dx.doi.org/10.1016/j.nut.2012.07.006)
boring potential were excluded from the study. Participants in another drug or device trial at the same time or within the previous 30 d or within five drug half-lives of the investigational materials or within the time legally required by the regulatory authorities, whichever was longer, and those with recent (<3 mo) hospitalization for unstable angina, myocardial infarction, or coronary revascula-
tization were also declared non-eligible for this study. In addition, subjects with known alcohol or drug abuse, known moderate or severe liver disease (Child
Pugh score >5), known severe renal disease (serum creatinine >220 μmol/L) or known anemia (blood hemoglobin <11 g/L), and known chronic inflammatory disease did not participate in the study.

The study used a patented, commercially available dietary supplement that was previously shown to be identical to a naturally occurring plant-based boron carbohydrate, i.e., CF [12]. A powdered extract standardized to 50% resveratrol also was used. Subjects were randomized into three groups for treatment. Supplementation for the groups was double-blinded. Group 1 received a single daily capsule of resveratrol 20 mg/d (trans-resveratrol 10.0 mg) combined with CF 112 mg/d (boron 3.0 mg/d) in addition to their usual medical care and treatment. Group 2 received a single daily capsule of resveratrol 20 mg/d (trans-resveratrol 10.0 mg) in addition to their usual medical care and treatment. Group 3 received a single daily capsule of CF 112 mg/d (boron 3.0 mg/d) in addition to their usual medical care and treatment. The non-randomized control group received only their usual medical care and treatment.

The daily serving size of CF was based on the recommended daily levels of boron intake (0.5–7.0 mg/d per person) [18,19]. Using the boron content database of foods commonly consumed by urban and rural Romanians, the boron intake could not have exceeded this determined ratio [17].

The subjects were randomized to receive either the CF and resveratrol combination or the placebo. Subjects were randomized into three groups for treatment. Group 1 received a single daily capsule (100 mg) of the plant-based boron supplement in addition to their usual medical care and treatment. Group 2 received a single daily capsule of resveratrol 20 mg/d (trans-resveratrol 10.0 mg) in addition to their usual medical care and treatment. Group 3 received a single daily capsule of CF 112 mg/d (boron 3.0 mg/d) in addition to their usual medical care and treatment. The non-randomized control group received only their usual medical care and treatment.

The daily serving size of CF was based on the recommended daily levels of boron intake (0.5–7.0 mg/d per person) [18,19]. Using the boron content database of foods commonly consumed by urban and rural Romanians, the boron intake could not have exceeded this determined ratio [17].

The follow-up included three visits: inclusion, at 1 mo (30 d), and at 2 mo (60 d). The study treatments were well tolerated.

Noninvasive two-dimensional echocardiography was performed only at inclusion to exclude left ventricular systolic dysfunction or heart failure.

Coronary angiography was not performed because it is highly unlikely that a regression of atherosclerotic plaques would be observed in such short time (e.g., y 2 in one study [21]). Platelet function was not assessed. Tolerance was evaluated at each visit by asking subjects about the appearance of any adverse events. Compliance was assessed after each subject returned the test material boxes by counting the remaining capsules and calculating the percentage of compliance.
Results

There was a significant decrease of hs-CRP in all groups at the 30-d and 60-d visits (Table 2). This decrease was greater for group 3 (CF), followed by group 2 (resveratrol plus CF). After 30 d, group 3 continued to show the greatest decrease (22%), followed by group 2 (resveratrol plus CF), because the percentages of differences obtained from baseline were the highest compared with the other groups. Thus, the decrease in angina episodes per week was 59%. Nitroglycerin consumption followed a similar trend, with a decrease of 67.6%. For groups 1 and 3, the results were comparable and significant: the decreases in angina episodes per week were 50% for group 1 (resveratrol) and 48.8% for group 3 (CF). For nitroglycerin consumption, the decreases after 60 d were 56.2% for group 1 (resveratrol plus CF), because the percentages of differences obtained from baseline were rather low (9.2% for total cholesterol, and 2.7% for HDL cholesterol). There was an improvement in the subjects’ quality of life in all groups. Tables 4 and 5 present the significant decreases in the number of angina episodes per week and nitroglycerin consumption, increases in SAQ scores, and improvement in angina class in all groups. In Table 4, the improvement in the quality of life was best observed for subjects in group 2 (resveratrol plus CF), because the percentages of differences obtained from baseline were the highest compared with the other groups.

Table 3
Changes in lipid profile

<table>
<thead>
<tr>
<th>Group</th>
<th>Inclusion</th>
<th>Month 1</th>
<th>Month 2</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Group 1</td>
<td>176.5 ± 89</td>
<td>171.1 ± 97</td>
<td>164.3 ± 79 (−6.9%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Group 2</td>
<td>167.5 ± 95</td>
<td>165.2 ± 89</td>
<td>163.7 ± 71 (−2.2%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Group 3</td>
<td>172.5 ± 75</td>
<td>166.8 ± 77</td>
<td>162.2 ± 69 (−5.9%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Control</td>
<td>169.4 ± 85</td>
<td>168.3 ± 91</td>
<td>164.8 ± 82 (−2.7%)</td>
<td>0.04</td>
</tr>
<tr>
<td>LDL Cholesterol (mg/dL)</td>
<td></td>
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<td></td>
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<tr>
<td>Group 1</td>
<td>123.2 ± 63</td>
<td>118.4 ± 59</td>
<td>115.3 ± 57 (−6.4%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Group 2</td>
<td>118.5 ± 57</td>
<td>115.2 ± 54</td>
<td>113.2 ± 56 (−4.4%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Group 3</td>
<td>122.6 ± 46</td>
<td>115.1 ± 49</td>
<td>111.2 ± 55 (−9.2%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Control</td>
<td>121.2 ± 61</td>
<td>118.7 ± 57</td>
<td>116.6 ± 52 (−3.7%)</td>
<td>0.04</td>
</tr>
<tr>
<td>HDL Cholesterol (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Group 1</td>
<td>53.2 ± 25</td>
<td>52.8 ± 27</td>
<td>54.1 ± 33 (1.6%)</td>
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<tr>
<td>Group 2</td>
<td>52.3 ± 45</td>
<td>51.9 ± 27</td>
<td>52.8 ± 35 (0.9%)</td>
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<tr>
<td>Group 3</td>
<td>50.1 ± 20</td>
<td>51.3 ± 23</td>
<td>52.7 ± 26 (5.1%)</td>
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<tr>
<td>Control</td>
<td>51.8 ± 23</td>
<td>51.2 ± 32</td>
<td>51.6 ± 29 (−0.3%)</td>
<td>0.04</td>
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<tr>
<td>Triglycerides (mg/dL)</td>
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<td></td>
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<tr>
<td>Group 1</td>
<td>134.1 ± 64</td>
<td>131.2 ± 72</td>
<td>128.8 ± 58 (−3.9%)</td>
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<tr>
<td>Group 2</td>
<td>127.1 ± 72</td>
<td>127.8 ± 67</td>
<td>125.7 ± 68 (−1.1%)</td>
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<tr>
<td>Group 3</td>
<td>137.6 ± 54</td>
<td>135.8 ± 62</td>
<td>132.7 ± 64 (−3.5%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Control</td>
<td>132.4 ± 69</td>
<td>130.4 ± 81</td>
<td>129.8 ± 72 (−1.9%)</td>
<td>0.04</td>
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</table>

HDLC, high-density lipoprotein; LDLC, low-density lipoprotein

Data are presented as mean ± SD (percentage of differences from baseline)

Table 4
Angina episodes and weekly nitroglycerin consumption

<table>
<thead>
<tr>
<th>Nitroglycerin consumption (tablets or puffs/wk)</th>
<th>Inclusion</th>
<th>Month 1</th>
<th>Month 2</th>
<th>P*</th>
</tr>
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<tbody>
<tr>
<td>Group 1</td>
<td>3.2</td>
<td>3.2</td>
<td>3.2</td>
<td>0.006</td>
</tr>
<tr>
<td>Group 2</td>
<td>3.4</td>
<td>2.1</td>
<td>1.1</td>
<td>0.003</td>
</tr>
<tr>
<td>Group 3</td>
<td>3.1</td>
<td>2.4</td>
<td>1.4</td>
<td>0.007</td>
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<tr>
<td>Control</td>
<td>3.4</td>
<td>2.8</td>
<td>2.4</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Data are presented as number (percentage of differences from baseline)

Discussion

All subjects in this study had been diagnosed with stable angina pectoris. Coronary artery disease, the main cause of angina, is caused by atherosclerosis of the coronary arteries. Atherosclerosis is an inflammatory disease and not merely the passive accumulation of lipids within the artery walls. The literature provides information that oxidized LDL is one risk factor for atherosclerotic inflammation. HDL has a protective effect against the development of atherosclerosis, which results partly from its anti-inflammatory and antioxidant properties [24–26]. Studies of the mechanisms of atherosclerosis have suggested that anti-inflammatory and antioxidant agents might be protective [24,27].

The two substances being tested in this trial, CF and resveratrol, were well tolerated. From the literature, the highest dose of CF administered was 37.5 mg/kg. No toxicity was noted at this dosage [28]. Resveratrol presents a low toxicity [29].

Orally ingested boron has been observed to be well absorbed (>90%) from the gastrointestinal tract in humans, rats, and rabbits. Boron as borate is readily and almost completely absorbed (>90%) from the human gut [30,31]. About 70% of the resveratrol dose given orally as a pill is absorbed; nevertheless, the oral bioavailability of resveratrol is low because it is rapidly metabolized in the intestines and liver into conjugated forms, i.e., glucuronate and sulfonate. Only trace amounts (<5 ng/mL) of...
unchanged resveratrol have been detected in the blood after a 25-mg oral dose [9].

Boron supplements have been reported to lower the platelet count and potentially decrease the risk of thrombosis [32], and experimental evidence has been obtained for the likely usefulness of boron-containing thrombin inhibitors in the treatment of cardiovascular disorders [33]. Recent studies in animal models have suggested that boron deprivation increases the concentrations of plasma homocysteine [34] and insulin [35], which have been suggested as risk factors for heart disease.

For this trial, we chose this combination of CF and resveratrol because previous research has suggested that CF stabilizes resveratrol degradation in the digestive tract [17], CF has been shown to be an important anti-inflammatory agent [11,15], and resveratrol has been found to have antioxidant properties [36]. CF also is an antioxidant [11]. The objective was to assess their synergistic effect on the markers under investigation: inflammation, left ventricular function, and lipids.

The increase in CRP levels in the blood is recognized as a marker of cardiac disease risk, and it has a prognostic value in coronary artery disease [37]. Regarding the systemic inflammation measured by hs-CRP, the obtained results showed that resveratrol and especially CF (after 60 d, the decrease was 39.7%) have the beneficial effects of significantly decreasing the hs-CRP level. The CF results are consistent with previous studies in which CF in similar serving sizes caused significant decreases in hs-CRP [15,16]. This is further confirmation of the strong anti-inflammatory effects of CF.

The 76-amino acid NT-proBNP fragment is the most frequently used plasma marker of congestive heart failure [38]. According to the obtained results, the observed decrease was rather high (65.5% in group 2).

According to data from the literature, hs-CRP and NT-proBNP were monitored. Levels of NT-proBNP have been reported to be significantly higher (182.8 pg/mL) in ischemic patients compared with those without ischemia (88.4 pg/mL), with a median hs-CRP level of 2.2 mg/mL [39]. Moreover, in a study of different antianginal therapies, after 12 mo of treatment with valsartan and acetylsalicylic acid, significant improvements in the parameters under investigation in the CF group (group 3), whereas the resveratrol group (group 1) showed the best results for total cholesterol and triacylglycerols, although the values were rather close to those in group 3. The observed changes seem small (<10%) but are nonetheless important because any statistically significant changes in these important cardiovascular markers may decrease the risk of heart disease.

Furthermore, this study showed that the combination of resveratrol and CF (group 2) elicited significant improvements in the number of angina episodes and nitroglycerin consumption per week and in the quality of life for subjects with stable angina pectoris.

In the three experimental groups, CF, resveratrol, and their combination presented positive effects, with the marker values being significantly different from baseline. For the control group, some changes were noticed, but these were of little significance. Thus, the addition of this control group to the trial highlights the improvements in the parameters under investigation in the presence of CF, resveratrol, or their combination in the other groups.

Although the study would have been improved by a larger number of subjects and a longer duration, to our knowledge this is the first clinical study that has evaluated the synergistic effects of resveratrol and CF in patients with ischemic cardiac disease from a clinical point of view (symptoms) and the beneficial effects (anti-inflammatory and antioxidant) of their combination on lipid profiles and inflammation markers. The obtained data are promising and represent an important base for further trials (the next trial has been registered in the international database at http://www.controlled-trials.com/ISRCTN90543844).

**Conclusion**

The combination of resveratrol and CF has beneficial effects in subjects with stable angina pectoris and the outcome of this study supports the use of these products as dietary supplements for improving quality of life. This trial is a starting point for studying the action of a resveratrol and CF mixture in patients with stable angina.

**References**


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**Table 5**

<table>
<thead>
<tr>
<th></th>
<th>Group 1 Baseline</th>
<th>Group 1 Month 2</th>
<th>Group 2 Baseline</th>
<th>Group 2 Month 2</th>
<th>Group 3 Baseline</th>
<th>Group 3 Month 2</th>
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<td>Physical limitations</td>
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<td>55.3</td>
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<td>Angina stability</td>
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<td>81.2</td>
<td>44.2</td>
<td>86.5</td>
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<td>82.6</td>
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<td>Angina frequency</td>
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<td>78.3</td>
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<td>73.2</td>
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<td>Disease perception</td>
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<td>55.6</td>
<td>34.1</td>
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<td>Visual scale score</td>
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<td>2</td>
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<td>1</td>
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</table>

CCS, Canadian Cardiovascular Society; SAQ, Seattle Angina Questionnaire

* P < 0.001 (Wilcoxon signed-rank test).


[26] EFSA. Opinion of the scientific panel on dietary products, nutrition and allergies on a request from the commission related to the tolerable upper intake level of boron (sodium borate and boric acid). EFSA J 2004;80–94.


