Dietary Cod Protein Reduces Plasma C-Reactive Protein in Insulin-Resistant Men and Women1–3

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Abstract

Chronic low-grade inflammation has been associated with insulin resistance and type 2 diabetes. Recently, we showed that cod protein (CP) improved insulin sensitivity in insulin-resistant subjects. In this study, we investigated the effects of dietary CP compared with those of other animal proteins on plasma concentrations of inflammatory markers, lipids, and lipoproteins in insulin-resistant subjects. Nineteen Caucasian men and women aged 40–65 y, overweight or obese (BMI > 25 kg/m²), and insulin resistant, rotated in a crossover design and consumed a CP diet and a similar diet containing lean beef, pork, veal, eggs, milk, and milk products (BPVEM) for 4 wk each. Diets differed only in protein source and thus provided equivalent amounts of dietary fibers, monounsaturated fat, PUFA [including (n-3) fatty acids], and SFA. Blood samples were collected before and after each experimental diet. Notably, the CP diet decreased high-sensitivity C-reactive protein (hsCRP; P = 0.021), whereas the BPVEM diet tended to increase it (P = 0.063), leading to a significant difference between diets (P = 0.041). Changes in plasma interleukin-6, tumor necrosis factor-α, and adiponectin concentrations did not differ between diets. Plasma total cholesterol (P = 0.0007), LDL cholesterol (P = 0.014), and apolipoprotein B (P = 0.005) were reduced only by the BPVEM diet. Thus, changes in total cholesterol differed between diets (P = 0.040), whereas changes in LDL cholesterol (P = 0.052) and apolipoprotein B (P = 0.075) tended to differ. Changes in all other lipids and lipoproteins did not differ between diets. Therefore, these results show that CP can lower hsCRP, a marker of inflammation associated with insulin resistance and type 2 diabetes. J. Nutr. 138: 2386–2391, 2008.

Introduction

In recent years, chronic low-grade inflammation has been proposed to be a key factor in the development of insulin resistance and type 2 diabetes (1,2). Indeed several studies have shown that high levels of C-reactive protein (CRP)12 and interleukin (IL)-6 are independent predictors for the development of type 2 diabetes (1,3). In the obese state, adipocytes and macrophages infiltrating adipose tissue secrete cytokines, such as IL-6 and tumor necrosis factor-α (TNFα), which, in turn, stimulate the hepatic production of acute phase proteins such as CRP (2). In support of these concepts, elevated plasma concentrations of TNFα, IL-6, and CRP (2,4) are observed in obese and insulin-resistant individuals. On the contrary, adiponectin is an antiinflammatory adipokine whose circulating levels are reduced in individuals with obesity and type 2 diabetes and are inversely related with magnitude of obesity and insulin resistance (5).

Epidemiological studies have shown that the consumption of fish is associated with a reduced risk of type 2 diabetes (6,7). This beneficial effect could be due at least in part to reduced inflammation. Indeed, fish consumption has been reported to be independently and inversely associated with circulating levels of several inflammatory markers (8,9). This effect has been first attributed to the long-chain (n-3) PUFA eicosapentaenoic acid (EPA; 20:5(n-3)) and docosahexaenoic acid (DHA; 22:6(n-3)). Epidemiological studies have reported an inverse relation between long-chain (n-3) PUFA intake and some inflammatory markers (notably IL-6 and CRP) (10,11). However, intervention studies in humans are less consistent. Whereas some intervention...
studies have observed beneficial effects, others have not (10,11). Interestingly, the possibility that fish protein, particularly its specific amino acid composition, could be implicated in reducing inflammation has emerged from recent studies. Consumption of arginine-rich foods, like nuts and fish, has been associated with a lower likelihood of having high levels of CRP (12). The amino acids taurine, glycine, and glutamine have also been suggested to have antiinflammatory effects (13,14).

We have recently reported in insulin-resistant men and women that the consumption of a cod protein (CP) diet for 4 wk improved insulin sensitivity by ~30% compared with a lean beef, pork, veal, eggs, milk, and milk products (BPVEM) diet (15). Because inflammation and insulin resistance have been linked (1,2), it was thus of particular interest to compare the effects of CP to those of BPVEM on markers of inflammation. We hypothesized that consumption of CP would reduce the circulating levels of IL-6, CRP, and TNFα compared with that of BPVEM. A 2nd issue in this study was to evaluate whether a CP diet could also improve the dyslipidemia, which is observed with insulin resistance (16) and inflammation (17).

### Subjects and Methods

#### Subjects.**

These data are part of a study described in detail previously (15). Briefly, 19 Caucasians (10 men and 9 women) aged 40–65 y and overweight or obese (BMI >25 kg/m²) were recruited in the greater Quebec City area by media advertising. To be included in the study, subjects needed a fasting plasma insulin level >90 pmol/L (18), which exceeds the 75th percentile for fasting insulin levels of a sample from the adult Quebec population (19), with fasting plasma glucose <7.0 mmol/L and 2-h plasma glucose <11.1 mmol/L. Exclusion criteria included smoking, major surgery in the 3 mo prior to study onset, significant weight change (±10%) within the 6 mo that preceded the study, and incompatibility with fish consumption (allergy, intolerance, or dislike) and/or calcium supplementation. Individuals who were taking medication that affects lipid or glucose metabolism, or were suffering from a chronic, metabolic, or acute disease were also excluded. Informed consent was obtained after the study protocol was carefully explained to each participant. This study was approved by the Clinical Research Ethical Committee of Laval University Hospital Center.

#### Experimental design.

A crossover design with 2 experimental periods of 4 wk was used to compare the effects of a CP diet to those of a diet containing BPVEM. After the first 2-wk run-in period, subjects were randomly assigned to begin the study with either the CP diet or the BPVEM diet. At the end of the first experimental period, participants returned to their usual diet for a washout period of 4 wk, including a 2nd 2-wk run-in period. Then, the participants crossed over to the other experimental diet for an additional 4 wk.

#### Diets.

A 7-d rotating menu meeting the National Cholesterol Education Program-Adult Treatment Panel (NCEP-ATP) III (20), American Diabetes Association (21), and Dietary Reference Intakes (22) recommendations was formulated. Cod fillets were the only animal protein source for the CP diet and the BPVEM diet consisted of lean beef, lean pork, lean veal, eggs and egg substitutes, and skim milk and milk products. A proportion of 58–68% of daily dietary proteins came from cod or BPVEM proteins, whereas the remaining proteins were of vegetable origin. The 2 experimental diets were formulated to show no differences in macronutrient composition except for the protein sources; thus, the menus were adjusted to provide equivalent amounts of dietary fibers as well as mono-unsaturated fats, PUFA, and SFA (Table 1).

#### Fatty acids in cod fillets and cod liver oil.

To assess whether the fatty acid profile was similar in cod fillets and cod liver oil, the fatty acid composition and content in both dietary sources were determined via lipid extraction based on the method of Bligh and Dyer (23) in the presence of known amounts of added tridecanoin and diheptadecanoyl phosphatidylcholine (NuChek Prep) as internal standards. An aliquot of the total lipid extract (lower phase) was taken for quantitation of the fatty acids following transmethylation (24) and another aliquot was taken for separation of the triglyceride and total phospholipid via TLC (25) prior to transmethylation of these fractions. The FAME were analyzed on a Varian 3400 GLC with a 60-m DB-23 capillary column (100-m
d). Total fatty acid content in cod fillets was 0.54%, whereas in cod liver oil, it was 83.6%. Moreover in the cod liver oil, fatty acids were mainly in the form of triglycerides (91% of total fatty acids), with EPA and DHA not mainly bound to triglycerides (24%) or phospholipids (14%). On the other hand, most of the fatty acids in cod fillets were in the phospholipids fraction (68% of total fatty acids) with most EPA and DHA bound to the phospholipids (53% of total fatty acids).

#### Blood analyses.

Before and after each experimental diet, blood samples were drawn after a 12-h overnight fast in EDTA-containing vacutainer tubes from an antecubital vein for measurement of plasma inflammatory markers, fatty acids, and lipid and lipoprotein concentrations. Blood samples were centrifuged immediately at 1500 × g; 10 min at 4°C to separate plasma, which was thereafter stored at −80°C until analyses.

#### Plasma pro- and antiinflammatory markers.

Plasma high-sensitivity CRP (hsCRP), IL-6, and TNFα concentrations were measured as previously described (26). Plasma adiponectin concentration was measured by ELISA (Orsuka Pharmaceuticals).

#### Plasma amino acids.

Individual plasma amino acids were determined by reverse-phase HPLC (Beckman Coulter Canada) with automated precolumn o-phthalaldehyde derivatization.

#### Plasma fatty acids.

The fatty acid composition of the phospholipid fraction was measured as previously described (27) using a HP-88 column (100-m × 0.25-mm i.d. × 0.20-µm thickness, Agilent Technologies). The fatty acid composition of total plasma phospholipids was expressed as the percent of the total area of all fatty acids (C14:0 to C24:1).

#### Plasma lipid and lipoprotein concentrations.

Cholesterol and triglyceride concentrations were determined enzymatically in plasma and lipoprotein fractions with a Technicon RA-500 analyzer (Bayer). Plasma lipoprotein fractions (VLDL, LDL, and HDL) were isolated by sequential ultracentrifugation that have been previously described (28). Apolipoprotein B was measured by nephelometry (BN ProSpec, Dade Behring) with reagents provided by this company (N anti sera to human apolipoprotein B).

### TABLE 1 Nutrient composition of the 2 experimental diets

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>BPVEM</th>
<th>CP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy, MJ</td>
<td>11.0</td>
<td>10.9</td>
</tr>
<tr>
<td>Carbohydrates, % of energy</td>
<td>51</td>
<td>52</td>
</tr>
<tr>
<td>Lipids, % of energy</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Protein, % of energy</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>PUFA, g</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>MUFA, g</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>SFA, g</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>PUFA/MUFA/SFA</td>
<td>1.1:1:1.8:1.0</td>
<td>1.1:1.7:1.0</td>
</tr>
<tr>
<td>n-3PUFA, g</td>
<td>3.5</td>
<td>3.3</td>
</tr>
<tr>
<td>n-6PUFA, g</td>
<td>20.9</td>
<td>21.6</td>
</tr>
<tr>
<td>Cholesterol, mg</td>
<td>228</td>
<td>220</td>
</tr>
<tr>
<td>Total fiber, g</td>
<td>28.0</td>
<td>29.7</td>
</tr>
</tbody>
</table>

1 Mean of the 7-d menu cycle for the 11.0-MJ diets, as determined by using the Canadian Nutrient File database (18). 2 MUFA, mono-unsaturated fatty acids.
Results

Subject characteristics. Except for plasma HDL cholesterol, which was higher ($P = 0.010$), and total cholesterol/HDL cholesterol, which was lower ($P = 0.018$) in women, baseline characteristics for men and women were similar (Table 2). All participants were overweight or obese (BMI 27–41 kg/m$^2$) and had increased abdominal adiposity (waist circumference >100 cm for men and >96 cm for women) (20) and hyperinsulinemia (19). According to the AHA classification for cardiovascular disease risk (29), 6 subjects had baseline hsCRP concentrations <1.0 mg/L (low risk), 9 had concentrations between 1 and 3 mg/L (moderate risk), and 3 had concentrations ≥3.0 mg/L (high risk). Baseline LDL cholesterol concentrations were optimal (<2.6 mmol/L) for 5 subjects, near or above optimal (2.6–3.3 mmol/L) for 3 subjects, borderline high (3.4–4.1 mmol/L) for 4 subjects, high (4.15–4.9 mmol/L) for 6 subjects, and very high (≥4.9 mmol/L) for 1 subject (22).

Anthropometric measures. As previously reported (15), changes in body weight (−1.0 ± 0.2 kg for both diets), BMI (−0.4 ± 0.1 kg/m$^2$ for both diets), and waist circumference (−0.3 ± 0.6 cm for the BPVEM diet and −0.2 ± 0.3 cm for the CP diet) did not differ significantly between the diet periods. Changes in body weight, BMI, or waist circumference and in markers of inflammation, lipids, or lipoproteins were not correlated.

Inflammatory markers. Notably, the CP diet decreased plasma hsCRP by 24% ($P = 0.021$), whereas the BPVEM diet tended to increase it by 13% ($P = 0.063$), leading to a difference between diets ($P = 0.041$) (Table 3). Interestingly, the CP diet led to a reduction in hsCRP in 14 of 18 subjects, whereas the BPVEM diet led to a reduction in only 9 of 18 subjects and to an increase in the other 9 subjects. Changes in plasma IL-6, TNFα, and adiponectin concentrations did not differ with the CP diet compared with the BPVEM diet.

Insulin sensitivity was significantly improved by the CP diet compared with the BPVEM diet as reported in one of our recent publications (15), so we assessed whether this beneficial change was associated with changes in inflammatory markers. The changes in hsCRP, IL-6, TNFα, or adiponectin and insulin sensitivity were not correlated.

Plasma amino acids. Plasma taurine concentration did not change during the CP diet and was 63.73 ± 3.03 μmol/L at the beginning and 66.85 ± 3.17 μmol/L at the end, whereas it decreased from 71.61 ± 6.41 to 56.90 ± 2.99 μmol/L with the BPVEM diet ($P = 0.004$), resulting in a difference between the diets ($P = 0.010$). Modulations in the plasma concentrations of all other amino acids did not differ between the 2 diets (Supplemental Table 1). Diet-induced changes in hsCRP and in plasma amino acids were not correlated.

Fatty acid content in plasma phospholipids. Increases in EPA ($P = 0.014$), DHA ($P < 0.0001$), and total (n-3) fatty acid ($P < 0.0001$) levels in plasma phospholipids were greater when participants consumed the CP diet compared with the BPVEM diet (Table 4). In contrast, total (n-6) fatty acids ($P < 0.0001$) as well as the ratio of (n-6):(n-3) ($P = 0.002$) decreased more after the CP diet period than after the BPVEM diet period. The arachidonic acid [20:4(n-6)] level increased by 9% after the BPVEM diet, whereas it decreased by 11% after the CP diet, leading to a difference between the 2 diets ($P < 0.0001$). Diet-induced changes in hsCRP and variations in EPA, DHA, total (n-3) fatty acid, or arachidonic acid were not correlated.

Plasma lipid and lipoprotein concentrations. The change in plasma total cholesterol differed between the BPVEM and CP diets ($P = 0.040$; Table 5). An 11% reduction ($P = 0.0007$) was observed after the BPVEM diet period but not after the CP diet period. The BPVEM diet induced a 10% decrease in LDL cholesterol ($P = 0.014$) and total apolipoprotein B ($P = 0.005$), whereas it was unchanged by the CP diet. Thus, changes in plasma LDL cholesterol ($P = 0.032$) and total apolipoprotein B ($P = 0.075$) tended to differ between the diets. All other changes in plasma lipids and lipoproteins concentrations did not significantly differ with the CP diet compared with the BPVEM diet.

Discussion

This study is the first controlled dietary intervention, to our knowledge, to investigate the effect of dietary fish protein in modulating systemic markers of inflammation. In the present...
study, CP reduced the plasma hsCRP concentration compared with BPVEM in insulin-resistant human subjects. This result is consistent with recent population-based studies that reported a strong inverse relationship between fish consumption and levels of inflammatory markers, including CRP (8,9). The effect of the CP diet might be of clinical relevance, because the reduction in hsCRP was similar to that observed with thiazolidinediones (30), statin therapy (30–32), or lifestyle interventions (33), all of which have been shown to decrease the risk of type 2 diabetes and/or cardiovascular disease (30–33).

The consumption of both diets resulted in a mean weight loss of 1 kg (1%). However, the changes in body weight were not related with those in inflammatory markers, lipids, or lipoproteins. Also, when weight change and weight change x diet interaction were included in our statistical model to assess whether weight change affected those parameters, no effect was found. Thus, changes in hsCRP, lipid, and lipoprotein concentrations are unlikely attributed to this slight body weight loss.

The mechanisms by which dietary proteins could regulate hsCRP are not known but are probably related to their specific amino acid composition. Beef and pork proteins contain less taurine than white fish protein (34). In this study, the decreased plasma taurine concentration after the BPVEM diet period could have contributed to the trend for increased plasma hsCRP concentration in subjects fed that diet. Indeed, in vitro studies have consistently demonstrated that taurine can suppress proinflammatory mediator production (TNFα, IL-1β, IL-6, inducible nitric oxide synthase) in macrophage cell lines, activated mouse and rat macrophages, and human peripheral blood mononuclear cells by interfering with some signaling pathways, particularly with nuclear factor κB activation (13). On the other hand, the CP diet used in this study was rich in arginine compared with the BPVEM diet (15). Although the arginine fasting plasma concentration, which derive mostly from its metabolic fate and turnover, did not differ between the 2 diets, it could have been implicated in the reducing effect of CP on hsCRP. Evidence suggests that higher arginine intake can increase NO production (35,36), which might downregulate hsCRP expression in vivo (37,38). Interestingly, a study in rats demonstrated that postprandial (30 and 120 min after test meal) plasma arginine concentrations were higher after CP than casein feeding, whereas fasting concentrations were similar (39). Therefore, it would be of great interest to examine whether postprandial amino acid concentrations, taurine, and arginine in particular, differ after consumption of CP compared with BPVEM and if the differences are related to plasma hsCRP concentration.

Accumulating evidence shows that elevated CRP levels are independently associated with insulin resistance (1,4) and a higher risk of developing type 2 diabetes (1,3). Conversely, interventions improving insulin sensitivity decrease CRP levels (2). In the present study, despite an improvement in insulin sensitivity (15) concomitant with decreased hsCRP following the consumption of the CP diet, changes in these 2 variables were not correlated (n = 32; r = −0.28; P = 0.121). Nevertheless, the number of subjects in our cohort was likely too small to detect a significant correlation.

In this study, we added cod liver oil to the BPVEM diet to match the (n-3) PUFA intakes between both diets. The higher proportion of EPA and DHA in phospholipids and their higher dilution in the cod fillets than in the added oil could have enhanced their digestion and absorption and explain the greater increase of EPA, DHA, and total (n-3) PUFA in plasma phospholipids of subjects fed the CP diet compared with those

### Table 3: Plasma markers of inflammation before (pre) and after (post) consuming BPVEM and CP diets for 4 wk in a crossover design

<table>
<thead>
<tr>
<th></th>
<th>BPVEM diet</th>
<th></th>
<th>CP diet</th>
<th></th>
<th>Δ</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Δ</td>
<td>Pre</td>
<td>Post</td>
<td>Δ</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>3.32 ± 1.13</td>
<td>3.74 ± 1.35</td>
<td>0.43 ± 0.48</td>
<td>4.02 ± 1.28</td>
<td>3.04 ± 1.05^a</td>
<td>−0.98 ± 0.49</td>
</tr>
<tr>
<td>IL-6, ng/L</td>
<td>2.35 ± 0.32</td>
<td>2.50 ± 0.31</td>
<td>0.15 ± 0.19</td>
<td>2.28 ± 0.29</td>
<td>2.09 ± 0.20</td>
<td>−0.19 ± 0.17</td>
</tr>
<tr>
<td>TNF-α, ng/L</td>
<td>1.41 ± 0.12</td>
<td>1.50 ± 0.14</td>
<td>0.09 ± 0.07</td>
<td>1.44 ± 0.12</td>
<td>1.48 ± 0.17</td>
<td>0.04 ± 0.09</td>
</tr>
<tr>
<td>Adiponectin, μg/L</td>
<td>6.54 ± 0.89</td>
<td>5.60 ± 0.75^a</td>
<td>−0.94 ± 0.37</td>
<td>6.47 ± 0.72</td>
<td>5.53 ± 0.71^a</td>
<td>−0.94 ± 0.59</td>
</tr>
</tbody>
</table>

1 Values are means ± SEM, n = 19. Differences within groups when compared with prediet values: ^aP < 0.01; ^bP < 0.05.

2 P-values refer to comparisons between ΔBPVEM and ΔCP (ANOVA for crossover design with 2 periods).

### Table 4: Plasma phospholipid fatty acids before (pre) and after (post) consuming BPVEM and CP diets for 4 wk in a crossover design

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>Pre</th>
<th>Post</th>
<th>Δ</th>
<th>Pre</th>
<th>Post</th>
<th>Δ</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>18:2(n-6)</td>
<td>19.80 ± 0.57</td>
<td>18.64 ± 0.48^b</td>
<td>−1.16 ± 0.27</td>
<td>19.39 ± 0.51</td>
<td>19.03 ± 0.57</td>
<td>−0.36 ± 0.33</td>
<td>0.078</td>
</tr>
<tr>
<td>18:3(n-3)</td>
<td>0.22 ± 0.03</td>
<td>0.12 ± 0.03^a</td>
<td>−0.11 ± 0.03</td>
<td>0.17 ± 0.03</td>
<td>0.13 ± 0.03</td>
<td>−0.04 ± 0.04</td>
<td>0.119</td>
</tr>
<tr>
<td>20:4(n-6)</td>
<td>10.57 ± 0.39</td>
<td>11.49 ± 0.41^a</td>
<td>0.92 ± 0.24</td>
<td>11.21 ± 0.58</td>
<td>9.93 ± 0.48^b</td>
<td>−1.28 ± 0.31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>20:5(n-3)</td>
<td>1.08 ± 0.08</td>
<td>1.50 ± 0.07^a</td>
<td>0.42 ± 0.07</td>
<td>1.07 ± 0.08</td>
<td>1.75 ± 0.09^a</td>
<td>0.67 ± 0.07</td>
<td>0.014</td>
</tr>
<tr>
<td>22:6(n-3)</td>
<td>3.41 ± 0.17</td>
<td>4.48 ± 0.14^a</td>
<td>1.07 ± 0.15</td>
<td>3.47 ± 0.22</td>
<td>5.96 ± 0.14^a</td>
<td>2.49 ± 0.16</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total (n-3)</td>
<td>5.73 ± 0.72</td>
<td>7.20 ± 0.21^b</td>
<td>1.47 ± 0.19</td>
<td>5.74 ± 0.29</td>
<td>8.62 ± 0.21^b</td>
<td>2.88 ± 0.20</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total (n-6)</td>
<td>35.44 ± 0.39</td>
<td>34.68 ± 0.29^a</td>
<td>−0.76 ± 0.29</td>
<td>35.62 ± 0.42</td>
<td>32.81 ± 0.31^a</td>
<td>−2.81 ± 0.39</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

1 Values are means ± SEM, n = 17. Differences within groups when compared with prediet values: ^aP < 0.0001; ^bP < 0.01; ^cP < 0.05.

2 P-values refer to comparisons between ΔBPVEM and ΔCP (ANOVA for crossover design with 2 periods).

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TABLE 5  Plasma lipid, lipoprotein, and apolipoprotein concentrations before (pre) and after (post) consuming BPVEM and CP diets for 4 wk in a crossover design

<table>
<thead>
<tr>
<th></th>
<th>BPVEM diet</th>
<th>CP diet</th>
<th>P&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Δ</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.44 ± 0.22</td>
<td>4.83 ± 0.20&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.61 ± 0.12</td>
</tr>
<tr>
<td>Total triglycerides, mmol/L</td>
<td>1.86 ± 0.16</td>
<td>1.38 ± 0.08&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.48 ± 0.14</td>
</tr>
<tr>
<td>VLDL cholesterol, mmol/L</td>
<td>0.72 ± 0.07</td>
<td>0.50 ± 0.04&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.22 ± 0.06</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.49 ± 0.24</td>
<td>3.13 ± 0.21&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.36 ± 0.13</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.24 ± 0.08</td>
<td>1.21 ± 0.08</td>
<td>-0.03 ± 0.04</td>
</tr>
<tr>
<td>HDL&lt;sub&gt;S&lt;/sub&gt; cholesterol, mmol/L</td>
<td>0.47 ± 0.06</td>
<td>0.47 ± 0.05</td>
<td>0.00 ± 0.04</td>
</tr>
<tr>
<td>VLDL triglycerides, mmol/L</td>
<td>0.77 ± 0.03</td>
<td>0.74 ± 0.04</td>
<td>-0.03 ± 0.03</td>
</tr>
<tr>
<td>Apo-B&lt;sub&gt;1,2&lt;/sub&gt;, g/l</td>
<td>1.31 ± 0.15</td>
<td>0.88 ± 0.04&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.43 ± 0.13</td>
</tr>
<tr>
<td>Apo-B, g/l</td>
<td>1.08 ± 0.06</td>
<td>0.97 ± 0.05&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.11 ± 0.03</td>
</tr>
<tr>
<td>LDL apo-B, g/l</td>
<td>0.93 ± 0.06</td>
<td>0.85 ± 0.05&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.09 ± 0.03</td>
</tr>
<tr>
<td>Total cholesterol/HDL cholesterol</td>
<td>4.64 ± 0.30</td>
<td>4.29 ± 0.32</td>
<td>-0.35 ± 0.2</td>
</tr>
</tbody>
</table>

<sup>1</sup> Values are means ± SEM, n = 18. Differences within groups when compared with prediet values: *P < 0.01; **P < 0.05.

<sup>2</sup> P values refer to comparisons between ΔBPVEM and ΔCP (ANOVA for crossover design with 2 periods).

<sup>3</sup> apo-B, apolipoprotein-B.

fed the BPVEM diet. However, this increase does not seem to be of biological significance in this study. Indeed, in the subjects fed the CP diet, there was a 50% increase in plasma total (n-3) fatty acids concomitant with a beneficial 24% decrease in hsCRP, whereas in the subjects fed the BPVEM diet, we observed a 26% increase in plasma total (n-3) fatty acids associated with an unexpected trend (P = 0.06) for an increased hsCRP. Moreover, diet-induced changes in hsCRP were not associated with variations in EPA, DHA, and total (n-3) fatty acids. These results support previously published controversial effects of (n-3) PUFA on this marker of inflammation (10,11) and suggest that the effects on hsCRP mainly arise from dietary proteins. However, because it has been previously reported that fish oil supplementation may decrease ex vivo synthesis of TNFα, IL-1β, and IL-6 by stimulated peripheral mononuclear cells in healthy volunteers (10) and that a consumption of 1.3 g/d of (n-3) PUFA for 5 wk may reduce serum CRP and plasma IL-6 levels in postmenopausal women receiving hormone replacement therapy (40), a contribution of (n-3) PUFA to the improvement in hsCRP following the CP diet in the present study cannot be completely ruled out.

The lipid-lowering response to the BPVEM diet was in accordance with the 5–10% cholesterol reduction expected from the NCEP-ATP III step I diet intervention (20). SFA have deleterious effects, whereas PUFA, mono- and polyunsaturated fatty acids, and dietary fibers have beneficial effects on lipid profile (20). However, the reductions in plasma total cholesterol, LDL cholesterol, and total apolipoprotein B were blunted with the inclusion of CP instead of BPVEM in the NCEP-ATP III diet. In light of the literature, 2 hypotheses can be proposed to explain this phenomenon. First, (n-6) PUFA are the most potent dietary fatty acids in the diet to lower plasma total and LDL cholesterol (41). However, a study in rabbits showed that the beneficial cholesterol-lowering effect of (n-6) PUFA was counteracted when combined with dietary fish protein (42). Second, recent studies have suggested that the inflammatory state of an individual could influence his response to a cholesterol-lowering diet (43–45). Indeed, Zhao et al. (43) observed that individuals with initial higher CRP (>2 mg/L) were less responsive to diets low in saturated fat and cholesterol and high in PUFA (either high in linoleic acid or α-linolenic acid), exhibiting smaller decreases in LDL cholesterol. In our study, the median initial hsCRP concentrations were lower before the BPVEM diet (1.85 mg/L) than the CP diet (2.15 mg/L).

In conclusion, the results from this study suggest that insulin-resistant individuals could benefit from including dietary CP in their diet. Indeed, the acute short-term consumption of CP induced a decrease in hsCRP, a marker of inflammation independently associated with type 2 diabetes and cardiovascular disease risk. Additional studies are, however, required to determine whether proteins from other fish could induce a similar beneficial effect on hsCRP. The optimal number of weekly cod/fish servings needed to obtain this benefit also has to be determined.

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