Dietary Proteins, Cholesterol and Thyroxine: A Proposed Mechanism

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Summary The effects of dietary protein sources on plasma cholesterol concentrations are well-documented: animal proteins are hypercholesterolemic relative to plant proteins. While this effect of dietary proteins has been shown in many species, the mechanism is not known. This review will explore the relation between dietary proteins and plasma thyroxine concentrations. Data will be presented showing that feeding dietary animal proteins consistently depresses plasma thyroxine levels. Furthermore, the effects of thyroxine on cholesterol metabolism is consistent with the effects of dietary proteins on cholesterol metabolism. Although evidence is not conclusive, data support the hypothesis that dietary proteins may affect plasma cholesterol levels through changes in plasma thyroxine concentrations. To elucidate the mechanism by which this happens will be the basis for future research.

Key Words soy protein, casein, plasma cholesterol, thyroxine

Different dietary proteins affect plasma cholesterol levels differently. Animal proteins increase plasma cholesterol levels as compared to plant protein sources (1–3). While this effect is clearly documented in many species including man, the mechanism has not been conclusively demonstrated. This review will briefly explore the relation between changes in dietary protein sources, changes in cholesterol metabolism and changes in plasma thyroxine.

My initial research into the effects of dietary proteins on cholesterol metabolism was a study in which pigs were fed either dietary plant protein or animal protein sources (4). The purpose of this experiment was to investigate whether the protein effect occurred in the swine, an animal that metabolizes cholesterol similarly to man, and to investigate whether the protein effect was independent of dietary fat effects on cholesterol metabolism.

Pigs were fed isocaloric diets for twelve weeks containing 0.1% cholesterol. The diets differed in the protein and fat content. The animal protein sources were casein and lactalbumin. The plant protein sources were soy, corn and wheat proteins. The polyunsaturated to saturated fat ratio was either 3.0 or 0.1. The experiment consisted of 4 groups of pigs: Animal Protein/Saturated Fat; Vegetable Protein/Saturated Fat; Animal Protein/Polyunsaturated Fat; and, Vegetable Protein/Polyunsaturated Fat.

The results after 14 weeks of feeding are shown in Table 1. The greatest plasma cholesterol levels occurred in the animal protein/saturated fat group (205mg/dl) whereas the lowest levels were found in the plant protein/polyunsaturated fat group. The result clearly indicated that animal protein sources increase plasma cholesterol levels as compared to plant protein sources, independent of dietary fat saturation.

In this experiment plasma amino acid levels were also determined. The amino acid concentrations found in the blood reflected the amino acid composition of the proteins. Pigs fed animal proteins had significantly greater levels of lysine, arginine, valine, isoleucine and leucine than those fed plant proteins. Plasma tyrosine levels were similar between treatment groups. I hypothesized that the differences in plasma amino acid composition could affect cholesterol metabolism by altering hormone concentrations. Those hormones especially of interest were insulin, glucagon and thyroxine; hormones involved in the metabolism of cholesterol.

A follow up experiment was designed to
investigate the effects of soy protein or casein on plasma lipoprotein cholesterol concentrations and plasma insulin, glucagon and thyroid hormone concentrations in the gerbil (*Meriones unguiculatus*) (5). The gerbil has, in my opinion, several advantages over the rat as an experimental animal model to study cholesterol metabolism. When fed a low-fat, low-cholesterol Chow diet the gerbil's plasma total cholesterol and HDL cholesterol levels is similar to the rat. However, unlike the rat feeding a high-fat, moderate cholesterol diet causes an increase in total cholesterol levels manifested primarily as an increase in LDL cholesterol. The gerbil being a desert rodent conserves fluids meaning that the collections of their feces are easier and less likely to be contaminated with urine. The gerbils is smaller than the rat which is an advantage in determining total body cholesterol. Although less blood is available for analyses in the gerbil, this is usually not a limiting factor.

Gerbils were fed purified diets (0.1% cholesterol) with either soy protein or casein as the protein source for 28 days. Cholesterol concentrations are reported in Table 2. The group fed casein had significantly greater total cholesterol and \(\beta\) cholesterol (LDL + VLDL) levels than the soy protein group. While there was no difference in the absolute HDL cholesterol concentration between treatments, the percent of total cholesterol as HDL cholesterol was much less in the casein fed group (59%) as compared to the soy fed group (73%). The Chow fed group had plasma total cholesterol levels similar to those found in rats (77mg/dl) with 91% of their total cholesterol in the HDL fraction. Thus, this experiment showed that the gerbil responds to dietary protein sources as do other species.

A second objective of this experiment was to examine the relationship between dietary protein sources and plasma hormone concentrations (Table 3). In this experiment insulin was lower and glucagon higher in the casein fed group as compared to the soy protein group. This was unexpected and unexplainable as Sugano et al. (1) and Vahouny et al. (6) have shown the opposite results.

Results that were more intriguing in this study were differences in thyroid hormone concentrations between groups. Gerbils fed casein had reduce thyroxine and TSH concentrations as compared to the gerbils fed soy protein. There was no difference in triiodothyronine between groups. To my knowledge this was the first study to report this specific protein effect, although after a literature search did I find other studies that also reported that dietary protein sources affect plasma thyroxine.

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**Table 1. Total cholesterol levels in swine fed different dietary protein and fat (14 weeks).**

<table>
<thead>
<tr>
<th>Protein Source</th>
<th>Cholesterol (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal protein/saturated fat</td>
<td>205(^{a,b})</td>
</tr>
<tr>
<td>Animal protein/polysaturated fat</td>
<td>169(^{a})</td>
</tr>
<tr>
<td>Plant protein/saturated fat</td>
<td>158(^{a})</td>
</tr>
<tr>
<td>Plant protein/polysaturated fat</td>
<td>111(^{c})</td>
</tr>
</tbody>
</table>

1 From: Forsythe III, W. A. et al. (4). 2 Values followed by different superscripts are significantly different (p<0.05).

**Table 2. Protein source effects on plasma lipids in the gerbil (28 days).**

<table>
<thead>
<tr>
<th>Protein Source</th>
<th>Cholesterol (mg/dl)</th>
<th>(\beta/\alpha) Cholesterol ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (\alpha) (\beta)</td>
<td></td>
</tr>
<tr>
<td>Casein</td>
<td>190(^{a}) 113(^{a}) 76(^{a})</td>
<td>0.70(^{a})</td>
</tr>
<tr>
<td>Soy</td>
<td>159(^{b}) 116(^{a}) 45(^{b})</td>
<td>0.42(^{b})</td>
</tr>
<tr>
<td>Chow</td>
<td>77       70       8</td>
<td>0.12</td>
</tr>
</tbody>
</table>

1 From: Forsythe III, W. A. (5). 2 Values in columns with different superscripts are significantly different (p<0.05).

**Table 3. Protein source effects on plasma hormone concentrations in the gerbil (28 days).**

<table>
<thead>
<tr>
<th>Protein Source</th>
<th>Insulin ((\mu)U/ml)</th>
<th>Glucagon (pg/ml)</th>
<th>Thyroxine ((\mu)g/ml)</th>
<th>T3 (ng/ml)</th>
<th>TSH ((\mu)U/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casein</td>
<td>24.0(^{a})</td>
<td>41.4(^{a})</td>
<td>1.6(^{a})</td>
<td>1.07(^{a})</td>
<td>3.6(^{a})</td>
</tr>
<tr>
<td>Soy</td>
<td>35.8(^{b})</td>
<td>27.7(^{b})</td>
<td>2.6(^{b})</td>
<td>1.02(^{b})</td>
<td>7.5(^{b})</td>
</tr>
<tr>
<td>Chow</td>
<td>22.3</td>
<td>83.0</td>
<td>2.9</td>
<td>1.38</td>
<td>2.4</td>
</tr>
</tbody>
</table>

1 From: Forsythe III, W. A. (5). 2 Values in columns with different superscripts are significantly different (p<0.05).
Akiba et al. (7) reported that laying hens fed a corn-soy protein based diet had greater plasma thyroxine levels than laying hens fed casein as the dietary protein source. In a follow-up study Akiba and Jensen (8) conducted a crossover experiment. Their results clearly show that plasma thyroxine levels respond to the source of dietary protein fed. Laying hens fed fish meal protein had significantly lower plasma thyroxine levels after only 7 days of feeding as compared to those hens fed corn-soy. After 14 days the groups switched diets. Those hens that were switched from the corn-soy to the fish meal had significant falls in their plasma thyroxine concentrations, whereas those switched to the corn-soy from the fish meal had significant increases. In their studies Akiba and Jensen did not report plasma cholesterol levels.

Another study that found an effect of dietary protein source on plasma thyroid levels was reported by Cree and Schalch (9). They fed rats casein or wheat gluten for 16 days. They reported that the rats fed wheat gluten had greater thyroxine and triiodothyronine concentrations than the rats fed casein. There was no difference in plasma insulin levels between groups. These investigators also did not report plasma cholesterol values.

A final study also showing a protein effect on thyroxine levels is a recent report by Barth and Pfeuffer (10). They reported thyroxine concentrations in pigs fed meals containing either soy protein or casein as the protein source. They found that plasma thyroxine levels were lower in casein fed pigs during the 24h following the meals (See the review by Professor Barth in this workshop proceedings for a fuller explanation of their study).

Thus, there is increasing evidence that dietary proteins sources can affect plasma thyroxine levels. If this is the case, is there evidence that these thyroxine changes are the mechanism by which dietary proteins affect plasma cholesterol metabolism? The answer is that although at present every study that has investigated dietary protein effects on plasma thyroxine levels has found consistent results—that is dietary animal proteins depress plasma thyroxine levels—one cannot conclusively state a cause and effect mechanism exists. At present all that is proved is that an association exists.

Many metabolic changes affecting cholesterol occur when soy protein is fed as the dietary protein source. These changes include (compared to feeding casein) an increased HMG-CoA reductase activity, an increased bile acid synthesis, and an increased fecal bile acid excretion, a decreased hepatic apo B-100 synthesis, and an increased hepatic clearance of LDL and VLDL (10). These same metabolic changes occur when the hypothyroid person is given thyroxine. Again, the effects of protein source and thyroxine are consistent.

That dietary proteins exert their effect through thyroxine can be viewed as the "push" hypothesis. That is, soy protein causes an increase in thyroxine levels. This increased thyroxine level then increases the hepatic clearance of VLDL and LDL, increases the production of bile acids, and increases the excretion of bile acids. Thus, thyroxine "pushes" cholesterol out of the body. This hypothesis is also called the "metabolic" hypothesis.

Beynen et al. (11) and West et al. (12) propose a different hypothesis to account for the hypocholesterolemic effect of soy protein. Their hypothesis can be thought of as the "pull" hypothesis (gastrointestinal hypothesis). They suggest that the initial response to dietary soy protein (relative to casein) is a reduction cholesterol absorption and an increase in bile acid excretion. This change in gut metabolism of cholesterol then precedes plasma cholesterol changes and changes in hepatic clearances (See the review by Professor Beynen in this workshop proceedings for a fuller explanation of their hypothesis).

There is insufficient evidence at the present time to completely accept either hypothesis. They both have inconsistencies. For instance, a deficiency of the metabolic hypothesis is that there is no evidence that thyroxine increases cholesterol absorption as occurs with soy protein feeding. As to the gastrointestinal hypothesis not all dietary protein sources that reduce plasma cholesterol levels do so by increasing the excretion of bile acids. It may be that the both hypotheses contribute to the responses observed when different proteins are fed.

In conclusion, consistent evidence suggests that dietary protein sources affect plasma thyroxine levels. Research needs to be conducted to further elucidate if this is the mechanism by which dietary proteins affect cholesterol metabolism. Still to be explored is the time course of events after feeding protein sources. Does plasma cholesterol change prior to a change in plasma thyroxine? Also, what
is the effect of thyroxine on cholesterol absorption? And finally after these questions are answered, the more important question to be explored is the mechanism by which dietary protein sources modify plasma thyroxine concentrations.

REFERENCES


