High Dose Flaxseed Oil Supplementation May Affect Fasting Blood Serum Glucose Management in Human Type 2 Diabetics

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Abstract: Type 2 diabetes is characterized partially by elevated fasting blood serum glucose and insulin concentrations and the percentage of hemoglobin as HbA1c. It was hypothesized that each of blood glucose and its co-factors insulin and HbA1c would show a more favorable profile as the result of flaxseed oil supplementation. Patients were recruited at random from a population pool responding to a recruitment advertisement in the local newspaper and 2 area physicians. Completing the trial were 10 flaxseed oil males, 8 flaxseed oil females, 8 safflower (placebo) oil males and 6 safflower oil females. Patients visited on two pre-treatment occasions each three months apart (visits 1 and 2). At visit 2 subjects were randomly assigned in double blind fashion and in equal gender numbers to take flaxseed oil or safflower oil for three further months until visit 3. Oil consumption in both groups was ~ 10 g/d. ALA intake in the intervention group was ~ 5.5 g/d. Power was 0.80 to see a difference of 1 mmol of glucose /L using 12 subjects per group with a p < 0.05. Flaxseed oil had no impact on fasting blood serum glucose, insulin or HbA1c levels. It is concluded that high doses of flaxseed oil have no effect on glycemic control in type 2 diabetics.

Key words: human, flaxseed oil, fasting serum glucose, insulin, HbA1c, type 2 diabetes

1 INTRODUCTION

Type 2 diabetes is partially characterized by elevated fasting blood serum glucose (FSG) and insulin concentrations (in most cases), the percentage of hemoglobin as HbA1c, and decreased insulin sensitivity4–6. Insulin insensitivity is brought on frequently by obesity or being overweight which results in a reduction in insulin receptor and post-insulin binding signaling transduction mechanisms7–9. The response of the pancreas to insulin insensitivity is to increase the blood serum concentration of insulin10–11. However this rise in insulin levels seldom compensates completely for the insulin insensitivity and consequently blood serum glucose concentrations rise12–15. A rise in blood serum glucose concentrations rise causes an increase in glycosylated HbA1c as there is an increased ratio of glucose to hemoglobin concentration thus allowing the glycosylation process to occur at a higher rate16–18. There is an interest in omega 3 fatty acids to control blood glucose levels. However, several studies in the 1980s showed a deterioration of glycemic control in type 2 diabetes consuming high doses of fish oil containing eicosapentaenoic acid (EPA, 20:5 n-3) and docosahexaenoic acid (DHA, 22:6 n-3) or purified EPA or DHA19–22. However, lower doses of fish oil or purified EPA or DHA resulted in no change in glycemic control23–25. Low doses of flaxseed oil containing alpha-linolenic acid (ALA, 18:3 n-3), which is metabolized to EPA and DHA in the body, did not improve glycemic control in type 2 diabetics. McManus et al.26 and Goh et al.27 giving 35 mg ALA / kg body weight in the form of flaxseed oil for three months, failed to note any change in fasting blood plasma glucose. McManus et al. (1996)28 also noted no change in HbA1c. However, higher doses of ALA have never been examined in conjunction with glycemic control in human type 2 diabetics and hence this
paper represents new information. Such information is important to flaxseed oil researchers, physicians and type 2 diabetic patients concerned with the impact of flaxseed oil on glucose management by highest ever reported dose of this oil by type 2 diabetics.

As ALA is, to some extent, desaturated and elongated to EPA and DHA it was reasoned that higher doses of ALA should be examined, given that high doses of flaxseed oil dramatically reduce platelet reactivity28,29) suggesting significant accumulation of EPA and DHA. High dose EPA and DHA deteriorates glycemic control20-22), thus rationalizing the current study on high dose ALA.

2 METHODS AND MATERIALS

Inclusion criteria were: 18 years of age or older, type 2 diabetic and not involved in physical training program, not taking insulin or any omega 3 supplement including fish oil, not pregnant or planning on becoming pregnant and no known sensitivity to flaxseed oil or safflower oil. Subjects (n=20 male, 20 female) were randomly chosen from among 71 Caucasians who met the inclusion criteria and who responded to a Sydney, Nova Scotia newspaper advertisement and two area physicians. Of these patients 18 males (10 flaxseed oil and 8 safflower oil) and 14 females (8 flaxseed oil and 6 safflower oil) completed the three required visits. This study received approval from the Cape Breton University Human Ethics Review Committee.

Subjects came fasted (12-14 hours) for visit 1 and 3 months later for visit 2. From visit 1 to visit 2 subjects continued with their normal daily activities. At visit 2 patients were randomized in equal gender numbers to take flaxseed oil (60 mg ALA/kg body weight/day) or safflower oil in the form of 1 gram gelatin capsules for three months until visit 3 (all patients consumed approximately 103 mg of oil/kg body weight/day). On all visits, the age and sex of participants was noted and body weight and height as well as body mass index (BMI) were determined.

The study design allowed for a three month no intervention lead in period to establish stability of FSG, insulin and HbA1c. The three month period was required because HbA1c is a three month record (can only change significantly after three months) of blood serum glucose history. The intervention during the following three months required random intervention with flaxseed oil or placebo (safflower oil). Again the three month period was required for accurate assessment of the impact of flaxseed oil on HbA1c. The extent of changes if any in the control group compared to those in the treatment group allowed a decision on whether the flaxseed oil dose had any impact on FSG, insulin or HbA1c levels.

FSG concentrations were determined by Wako Chemicals (Richmond, VA, USA) Glucose C2 Auto enzymatic method kit and insulin was determined by an ELISA kit (Linco Research, St, Charles, MO, USA) following manufactures’ directions. HbA1c was extracted from fresh blood30) and determined by HPLC using a protein pak 7.5 x 75 mm SP 5PW column (Waters) and the conditions detailed by Ellis et al.31) (Buffer A, pH 6 (phosphate 40 mM/L, NaCl 50 mM/L, NaCN, 5 mM/L, Triton X 0.5 ml/L; Buffer B, pH 7.1, phosphate 40 mM/L NaCl, 200 mM/L , NaCN, 5 mM/L, Triton X 0.5 ml/L). Buffer A was run first for 0.5 minutes, followed by buffer B run for 5.5 minutes, followed by buffer A for 9 minutes, all at 1 ml/minute). All chemicals were from Sigma (St. Louis, MO).

For a given parameter (FSG, insulin or HbA1c) and person, visits 1 and 2 were averaged. This average value was subtracted from the visit 3 value. The values resulting from this subtraction were compared for the flaxseed oil (treatment) group versus the safflower oil (placebo) group using an unpaired t-test with a significance level of p < 0.0531.

3 RESULTS

The composition of the oils is shown in Table 1. Flaxseed oil had 57.2 mg of ALA/100 mg of fatty acid. Safflower oil had only trace amounts of alpha-linolenic acid with linoleic acid (LA, 18:2 n-6) being its single largest component. Both oils had approximately equal amounts of oleic acid (OA). Oil and fatty acid consumption is listed in Table 2. Subjects consumed an average of 60 mg (flaxseed oil) or < 0.1 mg (safflower oil) ALA /kg body weight/day and approximately 103 mg of either oil / kg body weight/ day. Subject baseline characteristics age and BMI (visits 1 and 2) are contained in Table 3. The average BMI at visits 1 and 2 were statistically identical for each of the flaxseed oil and safflower oil subjects. Table 4 contains average values

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>Flaxseed oil</th>
<th>Safflower oil</th>
</tr>
</thead>
<tbody>
<tr>
<td>14:0</td>
<td>-</td>
<td>0.2</td>
</tr>
<tr>
<td>16:0</td>
<td>5.6</td>
<td>6.3</td>
</tr>
<tr>
<td>18:0</td>
<td>-</td>
<td>2.2</td>
</tr>
<tr>
<td>18:1 n-9</td>
<td>15.1</td>
<td>14.1</td>
</tr>
<tr>
<td>18:2 n-6</td>
<td>14.6</td>
<td>74.2</td>
</tr>
<tr>
<td>18:3 n-3</td>
<td>57.2</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>20:4 n-3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>20:5 n-3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>22:6 n-3</td>
<td>-</td>
<td>-</td>
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</tbody>
</table>

Table 1 Fatty Acid Composition (weight percent i.e. mg of an individual fatty acid per 100 mg of fatty acids) in Flaxseed Oil (treatment) and Safflower Oil (placebo).
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for visit 1 and 2 combined and for visit 3 for each of fasting blood serum glucose, insulin and HbA1c levels for each of the flaxseed oil and safflower oil groups. Similar values for each of FSG, insulin and HbA1c were seen between the flaxseed oil and safflower oil groups for the average of visits one and two for each of these parameters. Most importantly, no changes were seen in FSG, insulin or HbA1c levels as the result of flaxseed oil compared to the safflower oil administration. Though visit three values tended to be higher for FSG, insulin and HbA1c in the flaxseed oil group relative to the safflower oil group these values did not reach statistical significance.

4 DISCUSSION
There is consistency in the BMI going from visit one to

Table 3 Pretreatment Characteristics of Subjects (all Caucasian). Data (n=32) is reported as mean+standard error of the mean for the subjects who completed the trial.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Flaxseed oil</th>
<th>Safflower oil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.5 ± 1.7</td>
<td>60.7 ± 2.9</td>
</tr>
<tr>
<td>N</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>Body mass index (BMI) kg/m²</td>
<td>32.4 ± 0.9</td>
<td>30.3 ± 0.7</td>
</tr>
<tr>
<td>visit 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index (BMI) kg/m²</td>
<td>32.2 ± 1.0</td>
<td>30.3 ± 0.8</td>
</tr>
<tr>
<td>visit 2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4 Comparison the Effect of Flaxseed (mean 60 mg ALA/kg body weight/day) and Safflower Oil Consumption for Three Months on Fasting Blood Serum Glucose and Insulin Concentrations and HbA1c Levels in Type 2 Diabetics.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All flaxseed oil subjects</th>
<th>All flaxseed oil subjects</th>
<th>All safflower oil subjects</th>
<th>All safflower oil subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean of visits 1 and 2</td>
<td>Mean of visits 1 and 2</td>
<td>Mean of visits 1 and 2</td>
<td>Mean of visits 1 and 2</td>
</tr>
<tr>
<td>Number</td>
<td>18</td>
<td>18</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>8.2 (0.8)</td>
<td>9.0 (0.9)</td>
<td>7.9 (0.7)</td>
<td>8.5 (1.2)</td>
</tr>
<tr>
<td>Insulin concentrations (mU/mL)</td>
<td>12.8 (3.1)</td>
<td>17.7 (5.2)</td>
<td>8.2 (1.0)</td>
<td>7.0 (1.8)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.1 (0.6)</td>
<td>8.0 (0.4)</td>
<td>7.0 (0.4)</td>
<td>8.0 (0.4)</td>
</tr>
</tbody>
</table>

*Visits one and two (lead in period of three months with no intervention) were averaged and subtracted from the corresponding visit three to yield values for each of flaxseed oil and safflower oil interventions. The values of the subtraction were subjected to an unpaired t-test with p<0.05 for statistical significance. Data is reported as mean (standard error of the mean) for the subjects who completed the trial.
two suggesting a stable weight. (Table 3). The data in Table 4 show no change in fasting blood serum glucose among all subjects taking the flaxseed oil supplement. Certainly, the levels of EPA and DHA seen in the blood would have been far less than those seen in fish oil studies and purified EPA and/or DHA20-22 delivering high amounts of EPA and DHA that apparently resulted in glycemic control deterioration in those studies. However as Klein-Platat et al.23, and Phinney32 have indicated it may be that blood levels of EPA and DHA may be inconsistent with tissues targeted by insulin for glucose uptake.

Interestingly, there was a tendency toward increased FSG, HbA1c and insulin levels. In short, one might speculate that the levels of EPA and/or DHA achieved in the insulin targeted tissues did not reach levels sufficient to cause further disruption of glucose homeostasis. After all, the percentage conversion of ALA to EPA and DHA is relatively small. Unfortunately there is no data to confirm the pharmacokinetics of the blood glucose responsiveness to ALA administration in relation to insulin and HbA1c levels.

Diet and medications had no effects on the study as they were consistent throughout the study and between the treatment and placebo groups. None of subjects took flaxseed, fish oil or omega 3 supplements for three months before the study or during the study, thus such supplementation could not affect the results.

In conclusion, the consumption of high dose flaxseed oil may have no effect on glycemic control in type 2 diabetes, though, in light of the trend toward deterioration of glycemic control in the flaxseed oil group, this is subject to longer term studies using high dose flaxseed oil. Thus, type 2 diabetics may benefit from high doses of ALA in terms of reduced platelet reactivity without changing glycemic control. Confirmation of this glycemic control data or establishment of its statistical significance by others where only trends now appear would support such a recommendation.

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References

11. Taniguchi, A.; Fukushima, M.; Sakai, M.; Kataoka, K.; Nagata, I.; Doi, K.; Arakawa, H.; Nagasaka, S.; Tokuyama, K.; Yoshikatsu, N. The role of body mass index and triglyceride levels in identifying insulin-sensitive and
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