The Effects of Flaxseed Supplementation on Insulin Resistance in Adults With or at Risk for Metabolic Syndrome

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Abstract
Metabolic Syndrome is a significant health problem that is currently on the rise. It is associated with an increased risk of type 2 diabetes, as well as a number of other health conditions. In addition to lifestyle modifications and pharmaceuticals, supplementation with omega 3-fatty acids has shown promise to help with glycemic control. This review looks at the effects of flaxseed supplementation on glycemic control in adults with or at risk for metabolic syndrome.

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Biography

[Redacted for privacy]

Abstract

Background: Metabolic Syndrome is a significant health problem that is currently on the rise. It is associated with an increased risk of type 2 diabetes, as well as a number of other health conditions. In addition to lifestyle modifications and pharmaceuticals, supplementation with omega 3-fatty acids has shown promise to help with glycemic control. This review looks at the effects of flaxseed supplementation on glycemic control in adults with or at risk for metabolic syndrome.

Methods: An exhaustive search of available medical literature was performed using Medline-OVID, CINAHL, and Web of Science. Keywords used included: flaxseed, flaxseed oil, pre-diabetes, pre-diabetic state, metabolic syndrome X, and metabolic syndrome.

Results: Thirteen articles were reviewed for relevancy. Two studies were found, both were RCTs. One of the studies found that supplementing flax with other lifestyle changes decreased participants fasting glucose levels, as well as prevented an increase in hemoglobin A1c. While the other study did not show any change to patients fasting glucose levels. The overall quality of the studies was moderate to low and further studies would need to be done that specifically measure levels of insulin resistance in patients and follow up for a longer period of time.

Conclusion: Flax supplementation cannot be used as a reliable method for glycemic control in patients with or at risk for metabolic syndrome at this time, but research does appear to lean toward the benefits of supplementation.

Keywords: flaxseed, flaxseed oil, pre-diabetes, pre-diabetic state, metabolic syndrome X, metabolic syndrome
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Table I: Characteristics of Reviewed Studies
List of Abbreviations

MetS……………………....Metabolic Syndrome
ATP III…….National Cholesterol Education Program’s Adult Treatment Panel III
CVD…………………….Cardiovascular Disease
Type 2 DM………………Diabetes Mellitus Type 2
Flax…………………….Flaxseed
BMI……………………..Bone Mass Index
Hgb A1C……………….Hemoglobin A1C
TAG……………………..Triacylglycerol
HDL……………………..High Density Lipoprotein
LDL……………………..Low Density Lipoprotein
Il-6………………………Interlukin-6
TNF-a………………….Tumor Necrosis Factor a
ALA……………………..Alpha Linoleic Acid
g/d………………………..grams/day
The Effects of Flaxseed Supplementation on Insulin Resistance in Adults With or at Risk for Metabolic Syndrome

BACKGROUND

Metabolic Syndrome affects more than one in five Americans, according to the national health survey.\(^1\) The risk of developing metabolic syndrome increases with age and more than 40% of people in their sixties and seventies are affected. Individuals with metabolic syndrome are at approximately twice the risk of cardiovascular disease compared to people without this syndrome.\(^2\) Furthermore, the risk of developing type 2 diabetes increases by almost five fold. Since cardiovascular disease (CVD) and diabetes are two of the top ten causes of morbidity and mortality in the United States, this is a major health concern.\(^3\)

Metabolic syndrome is a cluster of metabolic abnormalities which have been defined by the National Cholesterol Education Program’s Adult Treatment Panel III report (ATP III).\(^4\) These abnormalities that make up metabolic syndrome are defined as; waist circumference >102cm in males and >88cm in females, triglycerides ≥150 mg/dl, HDL cholesterol <40mg/dl in males and <50mg/dl in females, blood pressure ≥ 135/85 mmHg, and fasting glucose ≥110mg/dl. A patient with three of these five components can be diagnosed with metabolic syndrome.
Metabolic syndrome is an important focus in medicine today because of its reversible nature. Individuals with metabolic syndrome or at risk of developing metabolic syndrome, can decrease their risk of more serious health complications through lifestyle modifications such as dietary modification and aerobic exercise.\textsuperscript{2-4} Not everyone with metabolic syndrome develops diabetes or CVD.

Most Americans are currently overweight or obese giving them at least one risk factor of metabolic syndrome. When examined by the Framingham cohort,\textsuperscript{4} a study focused on identifying the major cardiovascular disease risk factors, it found the presence of metabolic syndrome was majorly predictive of new onset diabetes. A variety of medications, lifestyle modifications, and supplements have been examined to understand their effect on insulin resistance in patients with and at risk for diabetes. The American Heart Association currently recommends regular exercise, weight loss, and a healthy diet as important elements in prevention and control of diabetes.\textsuperscript{5}

More recent research has begun examining the relationship of dietary fats and how they can modify insulin sensitivity. One type of fat of particular interest has been omega-3 fatty acids which are commonly found in seeds. Among the major seed oils, flax contains the most omega-3 fatty acids, specifically a-linoleic acid.\textsuperscript{6} Inclusion of omega 3-fatty acids in the diet has been associated with improved insulin sensitivity as well as glycemic control.\textsuperscript{7} One study\textsuperscript{8} found that daily flaxseed consumption resulted in statistically significant improvements in glycemic control of type 2 diabetics. Similarly another study\textsuperscript{9} showed that supplementation of flaxseed gum on type 2 diabetics resulted in decreased fasting blood glucose levels.
While flax supplementation shows promise in diagnosed diabetics, few studies have focused on supplementation as a more preventative measure in at risk patients. Prevention is of particular interest as metabolic syndrome is expected to continue to rise worldwide; its prevalence parallels that of obesity. Perhaps supplementing in patients who are on the cusp of diabetes, like those with metabolic syndrome, will benefit from the addition of omega-3 fatty acids to their diet with diet and exercise.

METHODS

An exhaustive search of the literature was performed using Medline- OVID, CINAHL, and Web of Science. Keywords used included: flaxseed, flaxseed oil, prediabetes, prediabetic state, metabolic syndrome X, and metabolic syndrome. Studies were required to use flaxseed supplementation in patients with metabolic syndrome or with at least one risk factor of metabolic syndrome and then measure glucose and/or hemoglobin A1c levels pre and post supplementation. Other relevant articles were searched for further information. Articles were assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).10

RESULTS

A total of 13 articles were reviewed for relevancy. Two articles11,12 fit inclusion criteria, both were randomized controlled trials, in English, and the studies were performed on humans. See Table I. One study13 examined flaxseed consumption on glycemic control in obese adults, but was excluded because it was not a published article, rather an abstract recently presented at a medical conference.
This was a randomized control trial\textsuperscript{11} that looked at the effects of lifestyle counseling, lifestyle counseling with flaxseed supplementation, and lifestyle counseling with walnut supplementation in adults with or at risk of metabolic syndrome for 12 weeks. Participants were recruited through two large universities in Shanghai by reviewing clinical records of physical exams from 2008. Participants were included if they met three of the following criteria: waist circumference $\geq 90$ cm for men and $\geq 80$ cm for women, triglycerides $\geq 1.7$ mmol/L, HDL cholesterol $< 1.03$ mmol/L and for men $< 1.30$ mmol/L for women, blood pressure $> 130/85$ mm Hg, fasting glucose $\geq 5.6$ mmol/L, and LDL $\geq 3.4$ mmol/L. Exclusion criteria included: history of allergy or high consumption of nuts, flaxseed, or sesame seeds ($>120$g/wk), clinically diagnosed renal, liver, heart, pituitary, thyroid, mental disease, or diseases affecting absorption, history of CVD, cancer, or mental disorder, use of antidepressants, estrogen, or steroid therapy, and pregnancy or lactation. Patients who responded to recruitment solicitations were then invited to attend a screening visit, where their eligibility was confirmed.\textsuperscript{11}

The study included a total of 283 participants randomized into one of three interventions: 1) lifestyle counseling (n=95), 2) lifestyle counseling with 30g/d flaxseed supplementation (n=94), and 3) lifestyle counseling with 30g/d walnut supplementation (n=94). The intervention included all participants receiving counseling and written materials regarding a low-fat diet, limited consumption or red and processed meat, consuming $<5$g/d of salt, increasing consumption of fruits, vegetables, and fish, smoking cessation, and moderate wine consumption. At the beginning of the intervention, all participants had a one hour group session with a registered dietitian. Two isocaloric
breads were provided for each participant every day, breads were similar except 30g flaxseed, 30g of walnut, or neither addition were incorporated into the bread. All breads were prepared in a single bakery under the supervision of two registered dietitians. Adherence was measured by asking participants to return any unused bread that was then weighed. In addition the a-linoleic acid content of the erythrocyte membranes was measured as a marker of compliance. There were no significant differences in baseline characteristics of patients, 90.5% had at least two components of metabolic syndrome.11

The primary outcome of the study was the effect of flaxseed and walnut supplementation as an adjunct intervention to lifestyle counseling on the management of metabolic syndrome. Effects were measured through serum glucose, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, apolipoprotein A-1, B, and E, Hemoglobin A1C, serum insulin, and a-linoleic acid levels in erythrocyte membranes. The secondary outcome included effect on central obesity. At baseline a food frequency questionnaire, a 3-day food record, a 32-general item questionnaire about education, physical activity, lifestyle, health status, and medications was administered. Body weight, height, BMI, waist circumference, blood pressure, and overnight fasting blood samples were obtained at baseline and again at 12 weeks.11

The percentage of patients with metabolic syndrome decreased from baseline by 16.9% in the lifestyle counseling group, 20.2% in the lifestyle and flax group, and 16.0% in the lifestyle and walnut group. Patients in the lifestyle and flax group had significant reversion of hyperglycemia with an odds ratio (95%CI) of 3.01 (1.10-7.54) compared to the lifestyle counseling group. Furthermore, the rate of decrease of central obesity was higher in the lifestyle counseling and flax group (19.2%, P=0.008) and the lifestyle
counseling plus walnut group (16%, P=0.04) compared to the lifestyle counseling group (6.3%).

A post hoc analysis of between group differences in diabetes related traits among participants showed that serum glucose was lower in the flax group compared to the lifestyle only group. The between group mean difference was -0.35 mmol/L (95%, -0.69 to -0.01, P=0.047). Flaxseed supplementation also prevented a rise in participants hemoglobin A1c, with a between group difference of -0.10 (95% CI, -0.20 to 0.00, P=0.05).

Limitations of the study included a relatively short study length. The level of blinding was limited, as flaxseed and walnut breads could be differentiated by participants based on their appearance and taste. This study was composed of participants of Chinese descent only.

**Cornish et al**

This randomized control trial sought to look at the effects of a flaxseed lignan complex (a fiber associated flax and other plant-based compounds) on metabolic composite score and bone mineral in older adults. Participants were recruited through the University of Saskatchewan from the general population of Saskatoon and the surrounding population through a newspaper advertisement. Patients were required to be at least 50 years old, as this age is when patients are at the greatest risk for developing cardiovascular disease due to abnormal blood lipid levels. Patients were excluded from the study if they were taking medications to lower cholesterol levels, were smokers, had type 1 or 2 diabetes, were diagnosed with inflammatory bowel disease, were taking
hormone replacement therapy, had ingested flax oil, flax lignin, or flax fibre within the last two months, or were involved in exercise training ≥ three times per week.

A total of 100 participants were randomized into one of two groups. Fifty participants were randomized into the flaxseed lignan group and fifty were assigned to the placebo group, both groups also completed a six month walking regimen. The intervention was three tablets of flax (543 mg) or placebo which were consumed each day during the six month intervention. All subjects also completed the same exercise intervention, which consisted of walking between 30-60 minutes per day, 6 days a week at 50-65% of their predicted maximal heart rate. Compliance was measured by asking patients to return any unused supplements to the researchers at the end of the study. Overall the groups were balanced prognostically. A total of 6 females and 8 males were defined as having metabolic syndrome, according to the Adult Treatment Panel III guidelines.12

Randomization was computer generated by a research assistant who had no other involvement in the study. Subjects were enrolled by one of the principal investigators, this research assistant in the study assigned participants to the groups. Participants, those administering the intervention and those evaluating the outcomes, were blinded to the group assignment. Allocation sequence was randomized. They were divided by gender.12

Primary outcomes for the study included a composite score of metabolic syndrome and bone mineral density. The metabolic composite score was calculated by determining the sex-specific Z scores of each of the following variables: glucose, HDL cholesterol, triacylglycerol, blood pressure, abdominal fat mass, and inflammatory markers. Secondary outcomes were blood lipids, IL-6, TNF-a, blood pressure, and body
composition as assessed by dual x-ray absorptiometry (DXA). Overnight fasting blood samples were obtained at baseline, 2, 4, and 6 months. Height and mass were measured at baseline and 6 months. Body composition was assessed at baseline and after 6 months with DXA. Waist circumference was measured at baseline.\textsuperscript{12}

There were no differences in the metabolic syndrome composite score at baseline between the placebo and flax lignan group. At 6 months, the metabolic syndrome composite $z$ score increased in the male placebo group to a greater extent than in the male flax lignan group. Conversely, there were no differences between women in the placebo group and women in the flax lignan group in their composite score at six months. In the subsample of participants with metabolic syndrome, the males taking the placebo had a greater increase in the composite $z$ score $\pm$ SD (from 0.80 $\pm$ 0.34 to 1.61 $\pm$ 0.39, $p = 0.058$) compared to those taking the flax lignan (from 0.44 $\pm$ 0.27 to 0.78 $\pm$ 0.30, $p = 0.058$).\textsuperscript{12}

Limitations of this study include a high dropout rate of about 19%. Compliance monitoring indicated that that the placebo group ingested 88 $\pm$ 2\% and the flax lignan group ingested 91 $\pm$1\%. The study also included a relatively small cohort. Glucose and or A1c levels were not analyzed individually, rather interpreted as a composite score containing multiple variables. Of the small percentage of participants meeting the metabolic syndrome criteria (14\%), only one female was assigned to the flax lignan group.\textsuperscript{12}
DISCUSSION

The seriousness of metabolic syndrome is that it puts people at an increased risk of many other health complications such as type 2 diabetes. Diabetes is a highly researched area and currently some research with the omega-3 fatty acid supplementation in diabetics suggests this type of fatty acid, commonly found in seeds such as flax, can actually help with insulin and glycemic control.7

Additionally flax supplementation has received significant recognition in recent research6,9 regarding its role in lowering blood pressure and being helpful in the prevention of cardiovascular disease. Flaxseed is also a good source of dietary fiber, contains all the essential amino acids, and is an excellent source of vitamins and minerals.6 It is a readily available supplement found in oil, pills, powdered supplements, enriched grains, and many additional food products.6-9 It is a relatively safe product that can be found in most US grocery stores, pharmacies, and other retail locations.

This systematic review yielded two studies11,12 that evaluated the effect of flaxseed supplementation on patient’s insulin resistance with or at risk of metabolic syndrome. Only one of the two studies11 was able to show that flax supplementation decreased fasting blood glucose levels and prevented an increase in participants HbA1c. This inconsistency can be explained by the fact that the second study12 evaluated insulin resistance as a component of a multivariable composite score making it difficult to quantify and examine the effect of flax on glucose levels individually. The studies were evaluated using the GRADE method and results can be seen in Table 1.
The major limitations of these studies included blinding, cohort size, dropout rates, length of study, baseline characteristics, and evaluation of insulin resistance as a single component versus part of a composite score. Blinding in the Wu et al study\textsuperscript{11} was particularly difficult as participants could distinguish the flax, walnut, and non-supplemented bread based on taste and texture. Furthermore the level of blinding in this study was not explained.

In the Cornish et al study\textsuperscript{12} the cohort consisted of a small number of participants. The study which originally consisted of 100 participants lost 19% to follow-up. Adherence was also low in this study. In the Wu et al study\textsuperscript{11} the intervention lasted only 12 weeks, significant results could have resulted after this study period. The Cornish et al study lasted six months, which was still relatively short. Twelve weeks to six months is not a long enough time frame to understand to what extent flax supplementation may affect glycemic control. Its effects could plateau, increase, or decrease after this amount of time.

The Cornish et al study\textsuperscript{12} had only 14% of its patients meeting the definition of metabolic syndrome. The majority or patients had one or more risk factors. Whereas in the Wu et al study\textsuperscript{11} the majority of patients had at least two components of metabolic syndrome and 63.3% met the criteria for metabolic syndrome. The Wu et al study was also made up of only Chinese participants in China. These participants could have very different lifestyles and diets compared to the US population.

The Cornish et al study\textsuperscript{12} did not evaluate insulin resistance as a primary outcome. Participants fasting blood glucose was interpreted as part of a composite z score which
was made up of 6 variables. A composite score makes it difficult to evaluate the effects of each individual variable. One variable could vary significantly causing the composite score to change and thus reflecting different results than the variables alone.

The two studies regarding flax supplementation yielded two different results. The Cornish et al\textsuperscript{12} found that the metabolic composite z score for the male placebo group increased to a greater extent than that of the flax group. There were no differences between the women in the placebo and flax group. The study suggested that this may be related to the decreased number of estrogen receptors in the post-menopausal participants, which decreased the flax metabolites ability to bind. Thus the study concluded that flax lignan had no effect on glucose levels. Although it did show decrease in the metabolic composite score for males taking the flax supplement. In the Wu et al study\textsuperscript{11} flaxseed supplementation was shown to decrease fasting glucose levels and prevent the increase in hemoglobin A1c levels of participants. This study also found that flax played a role in decreasing central obesity to a greater extent in patients compared to the lifestyle and walnut groups.

Further studies would need to be done on this topic in order to accurately evaluate flax supplementation’s effectiveness in improving glycemic control in patients with or at risk for metabolic syndrome. Since there are only two studies that evaluated this topic and they were of moderate to low quality, the results are not reliable. However, a very recent abstract by Hutchins et al\textsuperscript{13} in February 2013 found that supplementation of 13g of ground flaxseed for 12 weeks decreased glucose levels and increased insulin sensitivity in patients who were overweight or obese with pre-diabetes. These results along with the higher GRADE rating of the Wu et al study\textsuperscript{11} suggests that flax supplementation is more
likely to help improve insulin resistance. A larger, longer lasting randomized control trial, comparing flax supplementation with lifestyle modifications in patients with impaired fasting glucose levels or elevated hemoglobin A1c levels to placebo and lifestyle modifications alone could yield better results.

CONCLUSION

The level of the effects of flaxseed supplementation on insulin resistance in patients with or at risk of metabolic syndrome is still unclear. There are very few studies that currently examine this specific topic. Of the few existing studies, there are inconsistent results. The studies have also been of moderate to low quality making it even more difficult to determine the effects of flaxseed. However, based on the studies thus far, results do suggest that flax supplementation does improve insulin resistance. Further studies are needed to determine the effects and get clearer results on this topic.

Nonetheless, flaxseed supplementation does hold a lot of promise in improving insulin resistance. To what extent it helps and what best way to supplement is still evolving as this is a very new area of research. Still this is a relatively safe therapy that does have proven benefits in decreasing blood pressure and lowering risk of CVD. Due to these benefits, as well as possible benefits in glycemic control, it should be considered in patients with or at risk of metabolic syndrome.
References


13. Hutchins, Andrea M., Blakely D. Brown, Stephen C. Cunnane, Stephanie G. Domitrovich, Earle R. Adams, and Courtney E. Boboweic. "Daily Flaxseed Consumption Improves Glycemic Control in Obese Men and Women with Pre-
Table I. Characteristics of Reviewed Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Inconsistency</th>
<th>Publication bias likely</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cornish et al¹²</td>
<td>RCT</td>
<td>Seriousᵃ</td>
<td>Not serious</td>
<td>Seriousᵇ</td>
<td>Not serious</td>
<td>No</td>
<td>Low</td>
</tr>
<tr>
<td>Wu et al¹¹</td>
<td>RCT</td>
<td>Seriousᶜ</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>No</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

ᵃ Metabolic syndrome was present in a small percentage of the sample population. Variables were not analyzed individually but represented as a composite score.

ᵇ Low compliance rate, small sample size, and large loss to follow up.

ᶜ Lack of allocation concealment