

STATE OF THE ART
REVIEWSMark B. Andon, PhD,
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The Oatmeal-Cholesterol Connection: 10 Years Later

Abstract: *Ten years have passed since the Food and Drug Administration (FDA) completed their review of the literature pertaining to the consumption of whole-oat sources of soluble fiber and a reduction in blood cholesterol concentrations. Since that time, data have continued to accumulate regarding oat-soluble fiber consumption, cholesterol, and other physiologic vectors related to cardiovascular health. The objective of this review was to compare the findings of more contemporary analyses of the oat and cholesterol-reduction literature to determine if newer information is consistent with the original conclusion reached by the FDA. A number of formal assessments have been conducted subsequent to the FDA review, and virtually all have reached the same conclusion, namely, consumption of oats and oat-based products significantly reduces total cholesterol and low-density lipoprotein cholesterol concentrations without adverse effects on high-density lipoprotein cholesterol or triglyceride concentrations. In addition, a number of new insights about the potential benefits of oats have emerged over the past 10 years. These more recent data indicate that including oats and oat-based products as part of a lifestyle management program may confer health benefits that extend beyond total cholesterol*

and low-density lipoprotein cholesterol reduction.

Keywords: cholesterol; oats; heart disease; soluble fiber; CHD; CVD

In 1997, in response to a petition submitted by the Quaker Oats company, the US Food and Drug Administration (FDA) approved the first food-specific health claim for foods containing whole-oat sources of soluble fiber (oats, oat

The intent of this benchmark is to provide a high level of confidence in the validity of the relationship. Although it does not require unanimous and incontrovertible scientific consensus, it is meant to be a strong standard based on the totality of the science, with little likelihood of being reversed by new data.

As is the case for many lifestyle-health-disease relationships, the passing of time brings new information that becomes part of the overall constellation of work defining

Many epidemiologic studies provide evidence that high levels of whole-grain consumption (3 or more servings per day) are associated with reductions in risk for cardiovascular disease, diabetes, and obesity.

bran, and oat flour) and reduced risk of coronary heart disease (CHD).^{1,2} Their decision was based on a review of the evidence demonstrating that consumption of whole-oat sources decreases total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) concentrations. In their assessment, the FDA applied the standard of significant scientific agreement.³

the area. As such, it is prudent for the health professional community to monitor and interpret the science as it continues to evolve. This is particularly the case for those areas that have become authoritative standards of care. There are a number of examples of mainstream lifestyle management standards that have changed as new data

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have come to light. Examples include the recommended dietary allowances, the Dietary Guidelines for Americans, medical nutrition therapy for diabetes, and the amount and type of recommended physical activity.

With the passing of a full decade since the FDA's decision to permit a health claim for oat consumption and reduced risk of CHD, the objective of this review is to determine if subsequent formal analyses, which include more contemporary studies, are in agreement with the FDA's initial conclusion. In addition, new insights into the potential benefits of oat consumption that are of interest to lifestyle medicine practitioners will be explored.

Reaffirmation of the Oat and Blood Cholesterol Reduction Connection

A number of groups have performed formal analyses of the literature pertaining to oats and cholesterol lowering subsequent to the FDA's approval of the oat health claim in 1997. Moreover, much of this work has included data published after the FDA concluded their review. In 1999, Brown et al⁴ reported a meta-analysis of the cholesterol-reducing effects of several soluble fibers, including that from oats, and found a significant impact on TC and LDL-C and no effect on high-density lipoprotein cholesterol (HDL-C) or triglyceride (TG) concentrations. In 2002, as part of their evidence-based report on the detection, evaluation, and treatment of high blood cholesterol in adults, the National Institutes of Health recommended the addition of sources of soluble fiber to the diet, including oats, to enhance LDL-C reduction as part of the Therapeutic Lifestyles Changes (TLC) diet.⁵ The evidence used to make this recommendation was ranked as moderate to very strong based on both randomized controlled trials and meta-analyses. Consumption of plant sterol- or stanol-containing foods is also recommended as part of the TLC diet to enhance LDL-C reduction, and Jenkins et al and others have demonstrated that sources of soluble fiber and plant sterol or stanols can

be combined to increase LDL-C reduction.^{6,7} In 2004, a dossier compiled by Quaker Products Malaysia was submitted to and subsequently approved in 2006 by the Ministry of Health Malaysia to permit a functional claim for the relationship between the consumption of oat-soluble fiber and a reduction in blood cholesterol concentrations.⁸ The Joint Health Claims Initiative (JHCI) was an effort established in the United Kingdom through the collaboration of consumer organizations, enforcement authorities, and industry trade groups to develop a code of practice for food-based health claims. In 2004, the JHCI expert committee concluded, using an evidence-based review of the literature, that the totality of the science substantiates a relationship between the consumption of whole oat sources of soluble fiber and a reduction in blood cholesterol.⁹

The most recent systematic consideration of the relationship between oat consumption and cholesterol reduction was published in the form of a review by the Cochrane Collaboration, an international not-for-profit organization that produces systematic reviews of health care interventions.¹⁰ Objectives of the review pertained to the consumption of whole-grain foods and CHD risk. However, because the evidence considered was confined to data from randomized controlled trials and because 8 of 10 studies identified that met the inclusion criteria used oats as the whole grain, this review was a de facto evidence-based evaluation of the effect of oat consumption on cholesterol reduction. Three of the 8 oat-based studies selected in the Cochrane review were included in the FDA's evaluation of the oat-soluble fiber health claim,¹¹⁻¹³ and the remaining 5 studies were published after 1997.¹⁴⁻¹⁸ The authors had concerns regarding the short duration of the studies and the small number of subjects in some studies. However, when all 8 oat studies were pooled in a meta-analysis, a significant effect of oat consumption to lower TC ($P = .0005$) and LDL-C concentrations ($P = .0008$) was observed. The LDL-C value equated to a mean percentage reduction (95% confidence interval) from

baseline of -4.9% (-7.6% to -2.4%). This magnitude of effect could reduce CHD risk within the range of about 5% to 15% because every 1% reduction in LDL-C is associated with a decreased risk for CHD of 1% to 3%.¹⁹⁻²³ HDL-C and TG concentrations were measured in 6 studies, and the weighted treatment differences in the meta-analysis were not significant ($P = .95$ for HDL-C, $P = .83$ for TG).

During the past 10 years, research on the effect of oats on cholesterol lowering has continued. Formal assessments of these data show that the FDA accurately applied the standard of significant scientific agreement and that their initial assessment was correct. That is, additional data collected after the health claim was approved has not changed the understanding of the totality of the evidence. The precise mechanism by which oat consumption reduces cholesterol is not known. However, ample data show that the viscous soluble fiber in oats (β -glucan) increases bile acid excretion, which in turn increases bile acid synthesis and thereby reduces circulating concentrations of cholesterol.²⁴⁻²⁷ Consumption of oat-soluble fiber exhibits a dose-response relationship with cholesterol reduction.^{4,11,28} However, estimates of the magnitude of this relationship have been inconsistent, owing in part to differences in study populations, baseline cholesterol concentrations, and length of treatment periods. In addition, the effect of frequency of consumption of oat products throughout the day is a potential source of variability and has not been systematically examined. Although regular, compared with irregular, meal frequency is associated with improved blood lipid profiles, studies examining the effect of meal frequency per se on blood lipids have produced mixed results.²⁹⁻³¹

New Insights Regarding Oats and Reduced Risk of Heart Disease

Cholesterol Lowering From Oats During Weight Loss

Reduction in body weight per se can result in blood lipid lowering.³² Thus,

the usual course of designing studies to test the effect of oat consumption on cholesterol lowering has been to minimize changes in body weight. However, because of the incidence of overweight and obesity in the population, lifestyle management of cardiovascular disease risk often includes efforts to reduce body weight. Thus, the effect of oat consumption on cholesterol concentration during weight loss has great practical significance. Two randomized controlled trials have evaluated the effect of oat consumption on blood cholesterol concentrations during programmed weight loss.^{33,34} Whole oats or oat bran were incorporated into hypocaloric diets and compared with diets matched for macronutrient content without oats. Body weight loss was significant but equal in the oat and control groups. Although plasma TC and LDL-C concentrations were reduced in both groups, the consumption of oats/oat bran produced an additional increment in mean TC and LDL-C reduction of between 4% and 12% ($P < .05$) beyond that driven by a simultaneous reduction in body weight.

Effect of Oats on LDL Particle Subclass and Number

In addition to serum cholesterol concentrations, it has been suggested that the lipoprotein subclass may provide an additional degree of precision in profiling the risk of cardiovascular disease.³⁵ Small, dense LDL particles may have a greater propensity for oxidation and lower clearance rate than larger, less dense LDL. To determine the effects of consuming oat or wheat-based cereals on LDL subclass and particle size, Davy et al³⁶ studied 36 overweight, sedentary men with a mean age of 59 years. For 12 weeks, the men were instructed to maintain their usual diet, except they were randomly assigned to consume either whole-oat/oat bran or whole-wheat cereals providing a total of 14 g of dietary fiber per day. A significant time-by-treatment effect (baseline to end of treatment) was observed for the LDL-C concentration (oat group decrease of -2.5% compared with a wheat group increase of 8.7%, $P = .02$). Moreover, greater magnitudes of change

were observed between the oat and wheat groups in small, dense LDL concentrations (oat group decrease of 16.2% compared with a wheat group increase of 59.0%, $P = .01$); large, less dense LDL concentration (oat group increase of 13.0% compared with a wheat group decrease of 14.8%, $P = .08$); and LDL particle concentration (oat group decrease of 5.0% compared with a wheat group increase of 14.2%, $P = .01$). These data suggest that simply measuring serum total or LDL-C concentrations may underestimate the overall effect of oat consumption on reducing cardiovascular disease risk because it does not account for more subtle changes in the physical characteristics of the LDL particle.

Oat Antioxidants and Molecular Atherogenic Events

An emerging area of interest related to oat consumption and cardiovascular disease risk is the potential effect of oat phenolic compounds on the atherogenic process. Through a complex interplay of biochemical events, damage to the vascular endothelium induces inflammation, which leads to the attraction and adherence of immune cells, migration of the immune cells to the subendothelium, proliferation of smooth muscle, and ultimately the formation of atheromatous plaques. Avenanthramides are a group of phenolic compounds unique to oats that have been shown to be absorbed by humans and demonstrated in vitro to have the potential to affect a number of early atherogenic events.³⁷⁻⁴⁰ Liu et al³⁸ measured the effect of an avenanthramide-rich mixture prepared from oats in a human aortic endothelial cell culture model system. Monolayers of aortic cells were exposed to oat avenanthramides then treated with interleukin-1 β to induce an inflammatory state. Pretreatment with the avenanthramide mixture resulted in a significant reduction in the expression of proinflammatory, monocyte attractant, and adhesion molecules. Consistent with this, a dose-response reduction in monocyte adhesion was observed. Additional cell culture studies using a synthetically prepared avenanthramide identical to that isolated from oats have shown that this

polyphenol can inhibit vascular smooth muscle proliferation by arresting the G1 phase of the cell cycle.⁴⁰ Concentrations of avenanthramides achieved using semi-purified and synthetic sources in cell culture models cannot be achieved in vivo via the consumption of oatmeal. Nevertheless, these studies establish a molecular mechanism and raise the possibility that lower concentrations over longer periods of time could have subtle effects on dampening the atherogenic process.

Cardioprotective Benefits of Oats as a Whole Grain

Many epidemiologic studies provide evidence that high levels of whole-grain consumption (3 or more servings per day) are associated with reductions in risk for cardiovascular disease,⁴¹⁻⁵⁰ diabetes,^{42,51-58} and obesity.^{42,59-62} The constituents of whole grains that contribute to a healthier dietary profile and may work in concert to promote reduction of disease risk include complex carbohydrates, fiber, vitamins, minerals, antioxidants, and other phytochemicals.^{63,64} In 1999, the FDA approved a health claim pertaining to the consumption of diets rich in whole-grain foods and a reduced risk of CHD.⁶⁵ Benefits of whole grains that are linked to cardiovascular disease risk but for which no FDA health claim currently exists are discussed below.

Blood Pressure

The dietary approaches to stop hypertension (DASH) diet is a well-accepted and widely recommended eating pattern shown to reduce blood pressure and favorably affect blood lipids and insulin sensitivity.⁶⁶⁻⁶⁸ Although the DASH diet is typically understood as one that emphasizes fruits, vegetables, and low-fat dairy products, it also emphasizes the consumption of whole grains. Using a food group analysis approach, Lin et al⁶⁹ showed that whole grains are a major contributor to the target nutrients of the DASH diet including calcium, magnesium, potassium, fiber, protein, and zinc. The DASH study participants consumed 3-fold more calories from whole grains

Table 1.

Chronology of Formal Literature Reviews for Whole-Oat Products and Cholesterol Lowering

Year and Reference	Type of Review	Group Conducting Review	Was Conclusion Positive?
1992 ²⁸	Meta-analysis	Faculty from the University of Minnesota	Yes
1992 ²⁸	Health claim petition	US Food and Drug Administration	Yes
1999 ⁴	Meta-analysis	Faculty from Harvard University	Yes
2002 ⁵	Evidence-based review	National Cholesterol Education Program Expert Panel, National Institutes of Health	Yes
2004 ⁹	Evidence-based review	Joint Health Claims Initiative Expert Panel, United Kingdom	Yes
2006 ⁸	Functional claim petition	Ministry of Health, Malaysia	Yes
2007 ¹⁰	Systematic review including a meta-analysis	The Cochrane Collaboration	Yes

than refined grains, whereas the control group consumed no whole grains, and typical American diets supply approximately one-tenth of the total grain as whole grain.⁷⁰ In addition to the importance of whole grains as part of the DASH eating pattern, a number of controlled trials have assessed the impact of increased oat product consumption on blood pressure, and most^{16,17,33,71} but not all^{72,73} have shown a favorable affect.

Diabetes

Diabetes is a major cardiovascular risk factor, and a number of prospective epidemiologic studies have shown an inverse relationship between whole-grain consumption and the risk of developing type 2 diabetes.^{42,51-58} This topic was recently reviewed by the Dietary Guidelines for Americans Scientific Advisory Committee, who concluded that consuming at least 3 servings of whole grains per day can reduce the risk of type 2 diabetes.⁷⁴ Similarly, in their recent (2006) set of nutrition recommendations and interventions for diabetes, the American Diabetes Association recommended that primary prevention strategies for those at high risk of type 2 diabetes include meeting the US Department of Agriculture's recommendation of making one-half of all grain choices whole

grains.⁷⁵ Although the precise constituents of and the mechanism through which whole grains affect diabetes risk are not known, emerging research suggests that whole grains may favorably alter insulin sensitivity, which in turn could delay or prevent the onset of type 2 diabetes.^{59,76-78} In addition to the effect of whole grains on type 2 diabetes risk, oat products may favorably affect carbohydrate homeostasis by supplying soluble fiber to the diet. Sufficient quantities of viscous soluble fibers, such as oat β -glucan, can blunt the postprandial raise in blood glucose by delaying stomach emptying and providing a physical barrier to digestive enzymes and absorptive surfaces in the small intestine.⁷⁹

Body Weight

Evidence is beginning to accumulate that diets rich in whole grains are inversely associated with risk of weight gain and obesity.^{42,59-62} This topic was reviewed by the Dietary Guidelines for Americans Scientific Advisory Committee, which concluded that consumption of at least 3 servings of whole grains per day can help with weight maintenance.⁷⁴ Mechanisms potentially responsible for these observations include effects on gut hormones, insulin, and satiety.⁶³ Greater dietary fiber intakes per se may also

be consistent with better maintenance of body weight and could account for the observations regarding whole-grain intake and body weight.^{80,81} According to an evidence-based review by the World Health Organization, there is convincing evidence that diets higher in fiber reduce the risk of obesity.⁸² In addition to the potential effects of whole grains and/or fiber on risk of body weight gain, oats consumed in the form of cooked oatmeal is a high-volume, low-energy-density food. Holt et al⁸³ demonstrated that oatmeal elicited a greater degree of subjective satiety compared with equal caloric amounts of whole grains consumed as cold cereals or bread. These data are concordant with observations by Rolls et al⁸⁴ regarding the effects of incorporating water into a food matrix compared with simply drinking water as part of a meal.

Oat Consumption in the United States

According to the US Department of Agriculture's Economic Research Service, loss-adjusted per capita availability of oats in the US food supply has ranged between 2.0 and 3.4 lb per year during the past 3 decades.⁸⁵ Peak consumption years occurred during the late 1980s and early 1990s, with per capita availability

exceeding 3 lb. This period of time has colloquially been referred to as the “oat bran craze” and was accompanied by the publication of a number of favorable clinical trials regarding oats, oat bran, and the reduction of cholesterol. Currently, the loss-adjusted per capita consumption of oats in the United States is 2.4 lb per year. This is dramatically lower than other common grains (rice = 14.9 lb; corn flour, meal, grits, and hominy = 18.6 lb; and wheat = 94.6 lb per year), most of which are refined before they enter the consumer food supply.⁷⁰ In contrast, all oatmeal, whether it is made with standard, quick, or instant oats, is whole grain.

Summary

During the past 15 years (1992-2007), several formal data analyses of cholesterol reduction from whole oats and oat-based product consumption have been conducted (Table 1). Each of these data analyses has used a different model and a different collection of peer-reviewed literature. Without exception, all have reached the same positive conclusion regarding the ability of oats to lower serum cholesterol. In addition, the more detailed assessments have confirmed that it is primarily the LDL-C fraction that responds, with no adverse effect on HDL-C or TG. Moreover, emerging data suggest that whole oats and whole oat-based product consumption

- reduce LDL-C concentrations during weight loss,
- may favorably alter LDL subclass and particle number,
- supply unique phenolic compounds for which a molecular mechanism has been identified related to reducing early atherogenic events, and
- are consistent with dietary patterns that may favorably alter the risk for elevated blood pressure, type 2 diabetes, and weight gain.

Given the numerous positive evidence-based reviews of oats and cholesterol reduction, as well as the intriguing emerging science, the consumption

of oats and oat-based products should be encouraged as part of an overall lifestyle medicine approach for the prevention of cardiovascular disease. ^{AJLM}

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