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Barley & the Prevention of Cardiovascular Disease

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The Pathogenesis of Cardiovascular Disease

Cardiovascular disease (CVD) is a broad classification for diseases of the heart and vasculature, including coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism.[1] CVD has been the number one worldwide cause of death during the past decade.[2] An estimated nine in 10 Canadians have at least one CVD risk factor, with over 40 per cent of individuals aged 20 to 79 having elevated levels of total cholesterol.[3] Without lifestyle changes among Canada's middle-aged population, chronic diseases such as CVD are predicted to cause many individuals to live in sickness, disability and immobility in their latter years.[4] In the United States, CVD accounts for approximately one out of every three deaths with more than 2,150 Americans dying daily.[5] CVD is also becoming more prevalent in developing countries. In the Middle East, CVD accounts for 25 to 31 per cent of deaths and in China, an estimated 230 million people, or one in five adults, have CVD.[6,7]

Many cardiovascular diseases develop through atherosclerosis, a process by which damaged arterial endothelium induces lipid deposition and fibrosis.[8] The major factors that cause endothelial injury and promote atherogenesis include cigarette smoking, hypertension, hyperglycemia and atherogenic lipoproteins, such as low-density lipoprotein cholesterol (LDL-C).[9] Over time, the build-up of arterial plaques causes luminal narrowing and reduced blood flow, or plaques may break off and cause myocardial infarction or stroke.[8]

Arterial inflammation and endothelial dysfunction play key roles in the progression of atherosclerosis and the associated risk of adverse cardiovascular events.[10] An atherosclerotic plaque with substantial inflammation and a thin fibrous cap is typically the underlying cause of an acute cardiovascular event.[10] The endothelium is the single layer of cells that line blood vessels and play an important homeostatic role in the vascular system.[8] Healthy endothelial cells inhibit platelet aggregation, white blood cell adhesion, and smooth muscle cell proliferation.[11] Nitric oxide is produced by the endothelium and is a critical regulatory molecule involved in vasodilation.[8] A decrease in nitric oxide bioavailability and the resulting endothelial dysfunction are believed to be early signs of atherosclerosis.[12,13]

Cereal fibre is strongly associated with reduced risk of myocardial infarction and stroke, as well as a reduced incidence and rate of death from CVD.[17]

Nutrition for Cardiovascular Disease Prevention

Lifestyle plays a key role in the risk of developing CVD. Consuming a heart-healthy diet, adhering to a regular exercise routine, avoiding tobacco products and maintaining a healthy body weight are critical components to preventing atherosclerotic CVD.[14] Calorie-dense, nutrient-deficient, highly processed diets lead to elevated postprandial glucose and lipids, a condition termed "postprandial dysmetabolism."[10] These postprandial metabolic changes may increase free radical production and trigger a cascade of endothelial dysfunction and sympathetic hyperactivity.[10] Diets rich in fruits, vegetables, legumes, fish, poultry and whole grains provide protection against CVD, whereas diets high in red meat, processed meat, refined carbohydrates, and high-fat foods increase disease risk.[15]

The Institute of Medicine has set the Adequate Intake for fibre at 14 grams per 1,000 kcal, or about 25 grams per day for women and 38 grams per day for men.[16] This recommended

level of intake was set based on data that showed a relationship between dietary fibre intake and risk of coronary heart disease.[16] However, it is estimated that 90 per cent of the U.S. population does not consume enough dietary fibre with the average American consuming only 15 grams per day, or even less for those on low carbohydrate diets.[17] In Canada, average intake is only about half the recommended amount.[18] Cereal fibre is strongly associated with reduced risk of myocardial infarction and stroke, as well as a reduced incidence and rate of death from CVD.[17] The metabolic pathways by which these benefits are likely achieved include: reducing weight, waist circumference, body mass index, per cent body fat and per cent trunk fat mass; improving glucose metabolism and insulin sensitivity; and lowering the risk of metabolic syndrome and diabetes.[17]

Barley (Hordeum vulgare) is an ancient cereal grain that has been grown and consumed for thousands of years. Whole grains contain all of the essential parts and naturally occurring nutrients of the entire grain kernel in their original proportions. As a whole grain, barley is a source of important nutrients that are associated with disease prevention including dietary fibre, resistant starch, trace minerals, vitamins, phytoestrogens and antioxidants. Barley has one of the highest fibre contents of the cereal grains (Table 1) and is one of the richest sources of ß-glucan, a non-starch polysaccharide and soluble fibre found primarily in the cell walls of the endosperm and aleurone layer.

The DASH dietary pattern was initially developed for the treatment and prevention of hypertension, but has since been utilized in numerous CVD studies. The diet is high in vegetables, fruits, low-fat dairy products, whole grains, poultry, fish and nuts, and low in sweets, sugar-sweetened beverages, and red meats. It is also low in saturated fat, total fat, and cholesterol, but rich in potassium, magnesium, calcium, protein and fibre. The American Heart Association reports that of the various dietary patterns that have been studied to prevent CVD, the DASH diet provides the highest quality evidence for improving blood pressure and lipid profiles.[19] As a high-fibre, whole-grain food, barley fits with the DASH dietary pattern.

Table 1. Fibre content of selected foods[20]

Whole grain (dry)	Total dietary fiber (g/100g)
Barley, pearled	15.6
Rye	15.1
Wheat	12.2
Oats	10.6
Buckwheat	10.0
Corn	7.3
Quinoa	7.0
Wild rice	6.2
Brown rice, long grain	3.5

Barley ß-Glucan: Effect on blood cholesterol concentrations

Elevated serum cholesterol is a major risk factor for CVD.[21] For every 0.0259 mmol/L reduction in LDL-C, total mortality is reduced by one per cent.[10] Diet therapy is an important and complementary treatment for hyperlipidemia.[22] Nutritional factors that are known to increase LDL-C are saturated and trans fatty acids, dietary cholesterol and excess body weight, whereas polyunsaturated and monounsaturated fatty acids, plant sterols/stanols, and viscous fibre can reduce LDL-C.[21]

Increasing consumption of soluble fibres has clinically significant effects by reducing LDL cholesterol an estimated five to 10 per cent.[23] Soluble fibre reduces postprandial lipemia, decreases lipid oxidation, inhibits lipogenic enzymes, and is inversely associated with C-reactive protein (CRP) concentrations.[24,25] High-sensitivity CRP is a nonspecific marker for systemic inflammation and an important predictor of adverse cardiovascular events and the progression of arterial atherosclerosis.[10]

It was first observed by de Groot et al.[26] that the consumption of rolled oats reduced total serum cholesterol concentrations in men. The cholesterol-lowering properties of oats were later discovered to be attributable to their primary soluble fibre, ß-glucan.[27] This led researchers to examine the cholesterol-lowering ability of barley, since barley provides one of the highest levels of heart-healthy ß-glucan at three to 11 per cent on a dry-weight basis.[28]

Three meta-analysis studies have reported the cholesterol-lowering effect of barley ß-glucan.[28-30] The first of these studies reported the combined results from eight trials.[29] The studies were of relatively short duration (four to 12 weeks) and the ß-glucan dosage ranged from three to 10 grams per day (median dose seven grams per day) administered through various forms of barley products. Meta-analysis revealed that compared to controls, barley consumption resulted in significantly greater reductions in total cholesterol (-0.35 mmol/L), LDL-C (-0.26 mmol/L), and triglycerides (-0.13 mmol/L), but not HDL-C (0.026 mmol/L).[29]

A second meta-analysis included results from 11 studies.[28] A significant effect of barley and isolated barley ß-glucan on total cholesterol (-0.30 mmol/L) and LDL-C (-0.27 mmol/L) compared to control was reported.[28] The third and most recent meta-analysis investigated the effect of ß-glucan from both oats and barley on blood cholesterol levels and found that total cholesterol decreased by 0.60 mmol/L and LDL-C was reduced by 0.66 mmol/L.[30] Results from individual randomized controlled trials showing the effects of barley on lipid concentrations are presented in Table 2.

The dose response to ß-glucan was investigated in two of the meta-analyses. Tiwari and Cummins[30] found a continuous dose response relation of ß-glucan on total cholesterol levels based on 126 doses from 33 studies. A dose of one gram/day ß-glucan from oats and barley resulted in a 0.079 mmol/L decrease in total cholesterol. No statistically significant dose-response relationship was observed for net change in LDL-C.[30] In other research, AbuMweis et al.[28] was unable to quantify a dose-dependent response because a wider dosage range may be required or differences in the molecular weight of the ß-glucan may have affected the response. Talati et al.[29] did not find a dose response analysis due to the limited number of included studies (eight randomized controlled trials).

Together these meta-analyses provide strong support for the cholesterol-lowering effects of ß-glucan. Although not all of the individual studies included reached this conclusion, the majority demonstrated cholesterol reduction. Inconsistencies in study results may be due to differences in the ß-glucan dose, background diet composition, food processing and the initial variation in cholesterol level.[29] Further, genetic attributes of the barley cultivar that affect the solubility, molecular weight and/or viscosity of the ß-glucan may also impact study outcomes.[31]

Table 2. Randomized, controlled studies of barley and lipid concentrations

Study	Study design Duration Sample size (n)	Treatment type Dose (g/day)	Effect of treatment on total cholesterol	Effect of treatment on LDL-C
Behall et al.[32]	Crossover 5 weeks n=16	Barley flakes, flour, pearl barley providing 3 or 6 g/d barley soluble fibre	3 g/d: ↓ 17% 6 g/d: ↓ 20%	3 g/d: ↓ 17% 6 g/d: ↓ 24%
Behall et al.[33]	Crossover 5 weeks n=27	Barley flakes, flour, pearl barley providing 3 or 6 g/d barley soluble fibre	3 g/d: ↓ 9% 6 g/d: ↓ 10%	3 g/d: ↓ 13.8% 6 g/d: ↓ 17.4%
Biorklund et al.[34]	Parallel 5 weeks n=75	ß-glucan 5 or 10 g/d	No significant change	No significant change
Obrigger et al.[35]	Crossover 3 weeks n=13	Barley or barley mutant providing 3.3 g/d ß-glucan	No significant change	No significant change
Keenan et al.[36]	Parallel 6 weeks n=155	ß-glucan HMW 3 or 5 g/d ß-glucan LMW 3 or 5 g/d	HMW 3g/d: ↓ 8% HMW 5 g/d: ↓ 12% LMW 3 g/d: ↓ 7% LMW 5 g/d: ↓ 11%	HMW 3g/d: ↓ 9% HMW 5 g/d: ↓ 15% LMW 3 g/d: ↓ 9% LMW 5 g/d: ↓ 13%
Keogh et al.[37]	Crossover 4 weeks n=18	ß-glucan 9.9 g/d	No significant change	No significant change
Li et al.[38]	Crossover 4 weeks n=10	8.9 g/d barley soluble fibre	↓ 14.5 %	↓ 21.0%
Lupton et al.[39]	Parallel 4 weeks n=79	30 g barley bran flour 3 g barley oil	Flour: ↓ 7.7% Oil: ↓ 7.1%	Flour: ↓ 6.5% Oil: ↓ 9.2%
McIntosh et al.[40]	Crossover 4 weeks n=21	Barley bran and flakes in bread, muesli, spaghetti and biscuits providing 8 g/d ß-glucan	↓ 6%	↓ 7%
Rondanelli et al.[23]	Crossover 4 weeks n=24	ß-glucan-enriched barley flour providing 6.0 g/d ß-glucan	↓ 5.0%	↓ 8.6%
Shimizu et al.[41]	Parallel 12 weeks n=39	Pearl barley providing 7 g/d ß-glucan	↓ 8.0%	↓ 7.4%

Abbreviations: LMW, low molecular weight; HMW, high molecular weight

In its natural state, barley ß-glucan has a high molecular weight (≥1000 kDa).[42] The use of high molecular weight barley ß-glucan in food applications results in products with high viscosity and undesirable sensory properties.[42] Therefore, enzymatic treatment of ß-glucan can be used to achieve the desired properties.[42] One of the concerns with lowering the molecular weight and the viscose properties of ß-glucan is that the cholesterol-lowering effects will be negated. However, the cholesterol-lowering activity of lower molecular weight barley ß-glucan has been demonstrated in an animal model fed a hypercholesterolemic diet.[42] These results were later supported in a clinical study, which demonstrated that compared to control, both low and high molecular weight barley ß-glucan reduced total cholesterol and LDL-C at either three gram or five gram daily doses.[36]

Several mechanisms have been proposed as to how ß-glucan lowers cholesterol levels. The most likely explanation is that ß-glucans increase bile acid excretion by entrapping bile acids in the viscous gastrointestinal contents or by directly binding to bile acids leading to fecal excretion.[43] Since cholesterol is a substrate for bile acid synthesis, increased excretion results in reduced circulating cholesterol levels.[43] Another way by which soluble fibre may lower cholesterol levels is through fermentation of the fibre in the large intestine. Fermentation decreases pH and increases microbial populations, resulting in enhanced production of short-chain fatty acids that inhibit cholesterol synthesis.[17]

Barley Health Claims

In 2012, Health Canada approved the claim that barley-containing foods are a source of fibre shown to help lower cholesterol.[44] An example of the permitted claim is: *"125 ml of cooked pearled barley supplies 60% of the daily amount of the fibre shown to help lower cholesterol."*[44] The "daily amount" referred to in the claim is three grams of barley ß-glucan, and the food must contain at least one gram of ß-glucan per serving size.[44] Included are dehulled or hulless barley, pearled barley, barley flakes, grits, meal, flour, bran as well as ß-glucan enriched milling fractions. The claim does not include extracted barley ß-glucan.[44]

Health Canada permits the following statements in addition to the primary statement:[44]

- Barley fibre helps reduce/lower cholesterol.
- High cholesterol is a risk factor for heart disease.
- Barley fibre helps reduce/lower cholesterol, (which is) a risk factor for heart disease.

The literature review upon which the Canadian health claim is based demonstrated that barley ß-glucan consumption was consistently associated with statistically significant reductions in both total and LDL-C in 78 per cent of trials.[44]

In 2006, the United States Food and Drug Administration indicated that foods containing barley providing at least 0.75 grams of soluble fibre per serving are permitted to claim that they may help to reduce the risk of coronary heart disease.[45]

Effect of Barley on Other Risk Factors for Cardiovascular Disease

Obesity

From 2007 to 2009, the prevalence of obesity in Canada and the United States was 24.1 per cent and 34.4 per cent, respectively.[46] Obesity causes numerous metabolic changes that increase risk for CVD. Adipose tissue is no longer viewed simply as an energy storage organ, but as an active organ that secretes hormones (i.e. adipokines) that regulate energy homeostasis, insulin sensitivity, and lipid and carbohydrate metabolism.[47] Obesity is recognized as a state of chronic, low-grade inflammation that is associated with elevated inflammatory markers such as CRP, interleukin-6 and tumour necrosis factor alpha.[48] It can result

in changes in cardiac fatty acid metabolism that may play a causal role in the development of obesity-related cardiomyopathies due to cardiac lipid accumulation and excessive fatty acid utilization.[49]

Abdominal obesity is a risk factor for CVD and is one of the characteristics of the metabolic syndrome.[50] A study of 44 hypercholesterolemic Japanese men with a BMI > 22 kg/m2 found that compared to the control diet, a diet containing seven grams per day of barley ß-glucan significantly reduced BMI, waist circumference and visceral fat area, but did not reduce subcutaneous fat area.[41] No differences between the barley and control groups were noted in energy intake or pedometer-measured physical activity, suggesting that barley supports weight loss and promotes body fat loss preferentially from visceral adipose tissues.[41]

Fibre is a key nutrient that contributes to satiety and thus weight management.[51] Since fibre is not enzymatically digested and

absorbed, but instead undergoes various degrees of fermentation in the large intestine, it effectively lowers dietary energy density.[52] Soluble fibres, such as the ß-glucan in barley, contribute to satiety by absorbing large amounts of water and forming gels, thereby increasing stomach distension and slowing gastric emptying.[52]

Ad libitum consumption of high-fibre diets in healthy adults result in increased satiety, reduced hunger and energy intake, and weight loss. Epidemiologic studies demonstrate that a daily intake of approximately three servings of whole grains is associated with a lower body mass index and a reduction in central adiposity, a risk factor for CVD.[53] The Academy of Nutrition and Dietetics has concluded that dietary fibre may promote weight loss when intakes are 20 to 27 grams of fibre per day.[54] As a high-fibre food, barley may assist with weight management.

Hyperglycemia/Diabetes

The glycemic index (GI) was developed to rank carbohydrate-containing foods based on their effect on postprandial glycemic response.[55] The GI of a food is determined by calculating the area under the blood glucose response curve after ingestion of a food divided by the response to a reference food, typically glucose or white bread.[56] The glycemic load is calculated by multiplying the GI by the carbohydrate content of the food. Consuming a high-GI diet is associated with increased risk of developing type 2 diabetes.[57,58]

Barley has one of the lowest GI of the food grains.[59] The low GI of barley is an attribute that, in addition to its ß-glucan content, may help to promote cardiovascular health. Patients with diabetes are at significantly increased risk of CVD, which accounts for 70 per cent of all deaths among diabetics.[10] An estimated two-thirds of patients with coronary artery disease have abnormal glucose homeostasis.[60] Compared to patients without diabetes, mortality rates one month after an acute myocardial infarction are 50 per cent higher among those with diabetes.[10]

Hyperglycemia is associated with the initiation of pro-inflammatory events and oxidative stress which may adversely affect vascular structure and function by damaging the endothelium.[61] Even in the absence of overt diabetes, postprandial hyperglycemia may exert a negative effect on cardiovascular health.[62] Postprandial glucose concentration may be a better predictor of vascular dysfunction and adverse cardiovascular events than fasting glucose in both healthy and diabetic patients.[63] A meta-analysis of

14 prospective studies found that a high-glycemic-load diet was associated with a 23 per cent increased risk of CVD, while high GI increased risk by 13 per cent.[64] Thus, by preventing postprandial spikes in blood glucose levels, barley may help to protect against the deleterious effects of hyperglycemia.

In addition to being cardioprotective by attenuating blood glucose levels, low-GI diets may modify blood lipid profiles. Although CVD was not the primary focus of a systematic review by Thomas et al.,[65] the study concluded that overweight or obese people on diets that were low GI or low glycemic load had greater improvement in lipid profiles. A meta-analysis that included four studies concluded that low-GI diets had a significant effect on decreasing total cholesterol by 0.27 mmol/L and LDL-C by 0.23 mmol/L, values that are likely to have a positive effect on CVD outcomes.[66] This meta-analysis included a small number of studies due to criteria that excluded studies with insufficiently high GI for the comparator diet or those that used a cross-over design. Another meta-analysis of 28 randomized controlled trials found that low-GI diets significantly reduced total cholesterol by 0.13 mmol/L and LDL-C by 0.16 mmol/L.[67] Lipid improvements were found to be greatest when the low-GI intervention was accompanied by an increase in dietary fibre.[67]

Barley Aligns with Dietary Guidelines for People with Cardiovascular Disease

Barley is a low-fat, high-fibre, whole-grain food that fits with the nutrition guidelines for the prevention of CVD established by leading health promotion organizations:

- The **Heart and Stroke Foundation of Canada** endorses *Eating Well with Canada's Food Guide*,[68] which recommends consuming at least half of grains as whole grains, eating a variety of grains, and choosing grain products that are low in fat, sugar or salt.[69]

- The **American Heart Association** recommends consuming a diet rich in whole grains, with at least half of grain intake as whole grains.[70] Whole grains are recommended as part of the American Heart Association's lifestyle management guidelines for the reduction of both LDL-C and blood pressure.[19]

- The **Academy of Nutrition and Dietetics**—in its position statement on the health implications of dietary fibre—concluded that, with regard to CVD, dietary fibre intake from whole foods may lower blood pressure, improve serum lipid levels and reduce indicators of inflammation.[54]

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