Efficacy of oat bran (Avena sativa L.) in comparison with atorvastatin in treatment of hypercholesterolemia in albino rat liver.

Maisaa M. AL-Rawi
Biology Department, Girls College, Makkah, Saudi Arabia.

Abstract

Introduction: The present study deals with the effect of oat bran (Avena sativa L.) in the treatment of hypercholesterolemia in comparison with a hypocholesterolemic drug, atorvastatin, on hypercholesterolemic liver in male albino rats.

Material and Methods: For this purpose four groups of rats (each containing 6 rats) were used. The first group was used as a control, the second was cholesterol-fed group with cholesterol (0.5% w/w) for 6 weeks. The third group was oats-fed hypercholesterolemic rats on oat supplemented diet (20% w/w) for 4 weeks and the forth group was atorvastatin-treated hypercholesterolemic rats orally at a dose of 0.18 mg/Kg body weight/day for 4 weeks.

Results: The biochemical results revealed a significant increase in serum LDL-C and a significant decrease in HDL-C level. In addition the activity of AST was increased in cholesterol-fed rats. Meanwhile, the treatment with oat soluble fiber or atorvastatin drug improved the above mentioned parameters. The histopathological examination of liver sections of cholesterol-fed group showed accumulation of lipid. Hepatocytes showed ballooning degeneration and manifested clear necrotic signs. Inflammatory cellular infiltration was found around the blood vessels, mild fibrosis near the portal blood vessels. However, liver impairment was reduced markedly in the liver of oat soluble fiber fed rats rather than atorvastatin drug treated rats.

Conclusion: The present study, however, confirms that the cereal grain oat may have potent beneficial health effects in reducing LDL cholesterol and should be included in the prudent diet of individuals with hyperlipidemia.

Keywords: liver, histopathology, oat bran, atorvastatin, hypercholesterolemia

Introduction

The Oat (Avena sativa) is a species of cereal grain, and the seeds of this plant, are used for food for people and animals, especially poultry and horses (Anderson et al., 1990). Oat is the only cereal containing a globulin or legume-like protein, avenalins, as the major (80%) storage protein. Globulins are characterized by water solubility; because of this property, oats may be turned into milk but not into bread. The more typical cereal proteins, such as gluten and prolamines. The minor protein of oat is a prolamine: avenin. Oat protein is nearly equivalent in quality to soy protein which has been shown by the World Health Organization to be the equal to meat, milk, and egg protein. The protein content of the hull-less oat kernel (groat) ranges from 12–24%, the highest among cereals (Asp et al., 1983).

Oats, an important source of water-soluble fibers, have long been recognized as a potential cholesterol-lowering dietary component (Davidson et al., 1991). Indeed, Ripsin et al. (1992) concluded from a meta-analysis of 12 trials that soluble fiber from oat products had a significant effect on total cholesterol concentrations. It was estimated that a daily consumption of ≈3 g soluble fiber lowered total cholesterol by 0.13 mmol/L in normocholesterolemic persons and by 0.41 mmol/L in hypercholesterolemic persons (Brown et al., 1999).

The beneficial effects of oat products on the lipoprotein profile are ascribed to their soluble fiber compound,  β-glucan (Braaten et al., 1994).  β-glucan from oats is a nonstarch polysaccharide that is composed of β-(1→4)-linked glucose units, which are separated every 2–3 units by a
single β-(1→3)-linked glucose unit (Bell et al., 1999), β-glucan from barley (Bourdon et al., 1999) or yeast (Nicolosi et al., 1999) has also been shown to be hypocholesterolemic.

On 21 January 1997, the US Food and Drug Administration (FDA, 1996) approved the printing on food-product packages of a health claim that "a diet high in soluble fiber from whole oats (oat bran, oatmeal and oat flour) and low in saturated fat and cholesterol may reduce the risk of heart disease". In its proposal, the FDA reviewed 37 studies in which oats were consumed as hot and cold cereals or used in a variety of other foods, eg, muffins, breads, shakes, and entrées.

Hypercholesterolemia is an established major risk factor for coronary artery disease. Lifestyle modification is the preferable form of treatment for most types of hyperlipidemia. Cholesterol metabolism is determined by diet, genetics, cholesterol absorption, and sterol synthesis and excretion (Anderson et al., 1990). The synthesis and excretion of bile acids is the major pathway of elimination of cholesterol. Primary bile acids are synthesized from cholesterol in the liver, and considered to catalyze the rate-limiting step in the biosynthesis process (Cohen, 1999). Hepatic bile acid synthesis is controlled in the liver through negative and positive feedback mechanisms. The consequences of increased bile acid excretion are stimulated cholesterol uptake from the circulation (Grundy et al., 1971; Reihner et al., 1990) followed by a decreased serum cholesterol concentration (Miettinen, 1979).

Oat bran has been shown to decrease serum cholesterol (Ripsin et al., 1992; Brown et al., 1999). Consumption of a diet rich in soluble fiber including oat bran (Jenkins et al., 1993) or of a diet supplemented with oat bran (Kirby et al., 1981; Anderson et al., 1984; Marlett et al., 1994) has been shown to increase fecal excretion of bile acids.

Alovastatin is the preferred clinical lipid-regulating drugs (Li et al., 2003), it can effectively regulate blood lipids abnormal delay atherosclerosis progress in reducing clinical cardiovascular events in patients with hyperlipidemia (Chenhanyao, 2006). Alovastatin has been shown not only to significantly lower LDL cholesterol levels (range -41% to -61%) in a dose-dependent manner in hypercholesterolemic patients (Nawrocki et al., 1995) but also to reduce plasma triglyceride levels by up to 46% in hypertriglyceridemic patients in the presence or absence of elevated LDL cholesterol concentrations (Bakker-Arkema et al., 1996; Alaupovic et al., 1997).

Because of the lack of sufficient reports on the histological effects of oat for treating hypercholesterolemia. The aim of this study was to investigate the cholesterol lowering efficacy of the dietary oats in comparison with a hypocholesterolemic drug, alovastatin, on hypercholesterolemic liver in male albino rats.

Material and methods

1-Chemicals
Cholesterol, alovastatin and oats were used in the present study. Cholesterol was supplied from Sigma Chemical Co. (ST. Louis MO). Alovastatin was purchased from the Egyptian International Pharmaceutical Industries Company (10th of Ramadan city, Egypt) in the form of tablets. Oats were obtained from Nahrain Company for food industries Cairo-Egypt, and prepared in powder form and given to rats in their diet.

2-Animals and design of the experiment
Male albino rats (Rattus rattus) weighing about 140-160 g were used in the present study.

Rats were divided into four groups as follows:-

Group 1: Normal untreated control group. This group was fed on standard diet and supplied with water ad libitum.

Group 2: Cholesterol-fed group. The rats were fed on a normal diet supplemented with cholesterol (0.5% w/w) for 2 weeks to induce hypercholesterolemia (Moussavi et al., 1989), then continued to receive the cholesterol-supplemented diet for further 4 weeks.

Group 3: Oats-fed hypercholesterolemic group. Rats were fed on cholesterol-supplemented diet (0.5 % w/w) for 2 weeks to induce hypercholesterolemic
rolemia and given oats-supplemented diet (20% w/w) (Jacobs, 1983) besides the same diet of cholesterol for another 4 weeks.

**Group 4:** Atorvastatin-treated hypercholesterolemic group. Rats were fed on a cholesterol-supplemented diet (0.5% w/w) for 2 weeks to induce hypercholesterolemia and given orally atorvastatin at a dose of 0.18 mg/Kg body weight/day (Guerin et al., 2000) besides the same diet of cholesterol for another 4 weeks

**3- Histological examination**

For histological examinations, small pieces of the liver were immediately fixed in 10% neutral formalin solution, dehydrated in a graded series of alcohol, cleared in xylol and mounted in molten paraplast at 56-60°C and cut at 5µm on rotary microtome. The paraffin sections were stained with haematoxylin and eosin for histological studies and examined under light Leitz microscope.

**4- Statistical analysis:**

Means and standard deviations were calculated for each group and data were analyzed using Student’s t-test (Snedecor and Cochran, 1967). The conventional level of 5% was taken as the level of significance.

**Results**

Feeding on a diet enriched with cholesterol for 6 weeks caused a significant increase in serum LDL-C level, while a significant decrease in HDL-C was recorded. In addition, the activity of AST was increased in cholesterol-fed rats. Meanwhile, the treatment with oat soluble fiber or atorvastatin drug improved the above mentioned parameters (Table1).

Concerning histological examination of the liver, sections of liver of control rats were formed of hepatic lobules, each lobule is made up of radiating plates. Strands of cells are forming a network around a central vein. The liver strands are altering with narrow sinusoids. These sinusoids have irregular boundaries composed of only a single layer of fenestrated endothelial cells and large irregularly phagocytic cells, which are known as Kupffer cells. Outside the hepatic lobule at certain angles, lie the portal areas of connective tissue each including a hepatic portal vein, a branch of hepatic artery and a bile ductile (Fig.1).

Liver sections of rats of cholesterolfed group showed general impairment of the normal structural organization of hepatic lobules in many areas. Cord-like arrangement of the normal hepatocytes not well distinct (Fig. 2). Appearance of fatty change was manifested by accumulation of lipids in form of large cytoplasmic vacuoles within some hepatocytes displacing the nucleus to one side. Hepatocytes showed hydropic degeneration, swollen and vacuolated cells. The sinusoidal spaces were somewhat dilated, Kupffer cells appeared swollen. Most of the hepatocytes manifested clear necrotic signs, some nuclei revealed clear signs of pyknosis (Fig. 3). Inflammatory cellular infiltration was found around the blood vessels, mild fibrosis near the portal blood vessels (Fig. 4).

Liver sections of rats of group 3 exhibited a normal pattern of liver parenchyma; with marked reduction in fatty droplets and decrease in sinusoidal dilatation (Fig. 5). Less inflammation and less fibrosis in the portal area were noticed (Fig. 6). i.e. reversed towards control sections were considerably higher.

The effect of treatment with atorvastatin in liver sections of rats of group 4 showed less improvement in histological structure comparing with section of rat liver of group 3, pronounced in normalized appearance of liver lobules and hepatocytes. The hepatocytes exhibited reduction in fat accumulation, less inflammation and less fibrosis (Fig. 7), less necrotic cells were also observed (Fig. 8).
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Table (1): Effect of treatment with oat and atorvastatin on serum LDL, HDL and AST of hypercholesterolemic rats.

<table>
<thead>
<tr>
<th>Treatment Pavements</th>
<th>Control cholesterol-fed rats</th>
<th>Oats-fed rats</th>
<th>Atorvastatin-treated rats</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-c (mg/dl)</td>
<td>27.2±2.02</td>
<td>121.3±1.96</td>
<td>33.1±1.6</td>
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<tr>
<td></td>
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<td>S&lt;sup&gt;a&lt;/sup&gt;</td>
<td>S&lt;sup&gt;ab&lt;/sup&gt;</td>
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<tr>
<td>HDL-c (mg/dl)</td>
<td>41.2±1.3</td>
<td>19.4±0.91</td>
<td>38.3±0.62</td>
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<td></td>
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<td>S&lt;sup&gt;a&lt;/sup&gt;</td>
<td>S&lt;sup&gt;ab&lt;/sup&gt;</td>
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<tr>
<td>AST (U/L)</td>
<td>38.6±1.2</td>
<td>50.8±0.89</td>
<td>43.1±0.66</td>
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<td></td>
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<td>S&lt;sup&gt;a&lt;/sup&gt;</td>
<td>S&lt;sup&gt;ab&lt;/sup&gt;</td>
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Values are expressed as means ± SD. of six rats.
(S<sup>a</sup>) Significant at P < 0.05 as compared to control
(S<sup>b</sup>) Significant at P < 0.05 as compared to cholesterol-fed rats group
Fig. 1. Section in the liver of control rat showing hepatic cells (h), Sinusoidal spaces (s) with Kupffer cells (k) and central vein (CV) (X150).

Fig. 2. Section in the liver of hypercholesterolemic rat showing loss of the normal architecture of the liver with marked lipid infiltration (L), dilated sinusoids (s), central vein (CV) (X150).

Fig. 3. Section in the liver of hypercholesterolemic rat showing marked cloudy swelling hepatocytes with marked cytoplasmic vacuolations. Severe necrosis of hepatocytes, most of nuclei were pyknotic (pn) and lysis (ly) (X 250).

Fig. 4. Section in the liver of hypercholesterolemic rat showing marked proliferation of collagen fibers, inflammatory cellular infiltration, lipid droplets (L) and cytoplasmic vacuolations (X250).
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Fig. 5. Section in the liver of oats-fed rat showed normal architecture of hepatocytes, reduction in fat accumulation, dilated sinusoids (s), reduction in fat accumulation (X150).

Fig. 6. Section in the liver of oats-fed rat showed less inflammation, reduction in collagen content, inflammatory cellular infiltration and fat accumulation. Pyknotic nuclei (pn) (X250).

Fig. 7. Section in the liver of atorvastatin-treated rat showing fat accumulation, less inflammation and less fibrosis (X250).

Fig. 8. Section in the liver of atorvastatin-treated rat showing stages necrotic cells, karyorehxes (kr) (X250).
Discussion

Fatty liver is often linked to an excess of fat mass, and would result from an increase in total energy and carbohydrate intake in humans. There is evidence that food restriction and a lower body weight are accompanied by an improvement of fatty liver in obese adults and children (Eriksson et al., 1986). However, long-term maintenance of a low energy regimen by obese people is difficult; thus the discovery of nutrients that would ameliorate liver hepatic steatosis is of interest (Vajro et al., 1994).

In the present study, atorvastatin treatment in rats induced significant reductions in serum plasma LDL; this finding is consistent with those previously reported by others (Kissebah et al., 1974; Dart et al., 1997; Bertolini et al., 1997; Bakker-Arkema et al., 1997; Durrington et al., 1998; McKenzie et al., 1998). Guerin et al., 2000 reported that atorvastatin therapy (10 mg/d for 6 weeks) in patients displaying a lipid phenotype characteristic of combined hyperlipidemia CHL induced significant reductions in both plasma total cholesterol and triglycerides (31% and 27%, respectively) and equally as in very low density lipoproteins VLDL cholesterol (-43%) and plasma low density lipoproteins LDL cholesterol (-36%). They interpret their data to indicate that 2 independent but complementary mechanisms may be operative in the atorvastatin-induced reduction of atherogenic LDL levels in CHL: first, a significant degree of normalization of both the circulating levels and the quality of their key precursors, ie, VLDL1, and second, enhanced catabolism of the major LDL particle subclasses (ie, light, intermediate, and dense LDL) due to upregulation of hepatic LDL receptors.

Scientific studies support recommendations to increase dietary soluble fiber as part of hyperlipidemia treatment. Fibric acid derivatives act to inhibit the hepatic secretion of VLDL (Kissebah et al., 1974) and to promote triglyceride-rich lipoprotein catabolism through induction of lipoprotein lipase gene expression and stimulation of lipoprotein lipase activity (Heller and Harvengt, 1983).

Including water-soluble fiber in the diet was shown to be an additional, important component of cholesterol reduction efforts (Anderson et al., 1990). Oat gum, guar gum and pectin, all soluble fibers, have hypcholesterolemic effects in animals (Anderson et al., 1984, Matheson et al., 1995; Todd et al., 1990). The addition of beans, oat bran, locust bean gum, guar gum, psyllium or pectin to human diets reduces elevated cholesterol levels by 3-20%, depending on study design (Judd and Truswell 1982; Zavoral et al., 1983; Anderson et al., 1984, 1991; Everson et al., 1992). Water-insoluble fiber does not affect cholesterol levels (Anderson et al., 1990, 1994; Jenkins et al., 1993).

Cara et al. (1992) included that oat bran lowers cholesterol more effectively than rice bran. Rice bran's fiber consists of a relatively low proportion of soluble fiber, 7-13% of its total dietary fiber compared with 40-47% in oat bran. The remainder is insoluble fiber. Other types of insoluble dietary fiber have failed repeatedly to reduce cholesterol levels (Katan 1987; Miettinen and Tarpila 1989; Kestin et al., 1990; Cara et al., 1992; Anderson et al., 1994).

Keenan et al., 1992 have demonstrated that niacin (1500 mg/d) and oat bran (56 g/d [2 oz/day]) have a synergistic effect on improving serum lipid levels, significant reductions (P less than .05) occurred for total cholesterol (-10%) and low-density lipoprotein cholesterol (-16%). High-density lipoprotein cholesterol rose significantly at the end of the oat bran plus niacin phase, but returned to near baseline by the end of the study.

Oat bran contains soluble fibers, such as β-glucan, that increase bile acid excretion and thus decrease serum cholesterol. Significant reductions in serum LDL-cholesterol concentrations when the β-glucan preparation from oat bran was given with a drink (Asp et al., 1983; Reinhner et al., 1990). A possible mechanism of action for the cholesterol-lowering effect of β-glucan is decreased bile acid reabsorption caused by fiber binding or by an increased viscosity of intestinal contents (Axelson et...
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The present study, however, confirms that the cereal grain oat may have potent beneficial health effects in reducing LDL cholesterol and should be included in the prudent diet of individuals with hyperlipidemia.

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تأثير نخالة الشوفان مقارنة بعقار أتورفاستاتين في علاج ارتفاع الكوليسترول على نسيج الكبد في الجرذان البيضاء

ميساء محمد الراوي
قسم الأحياء - كلية التربية الأقسام العلمية للبنات - مكة المكرمة

تناول هذا البحث دراسة تأثير المعالجة بنخالة الشوفان مقارنة بالعقار المخفض للكوليسترول (أتورفاستاتين) على أداء الجرذان البيضاء المصابة عملياً بارتفاع الكوليسترول. سممت الدراسة بتقسيم الجرذان في أربع مجموعات، مجموعة ضابطة ومجموعة ثانية غذيت بالكوليسترول لمدة 4 أسابيع ومجموعة ثالثة غذيت بالشوفران في الجرذان ذات نسبة الكوليسترول المرتفعة لمدة 4 أسابيع. ومجموعة رابعة عولجت بالعقار المخفض للكوليسترول أتورفاستاتين في الجرذان ذات نسبة الكوليسترول المرتفعة لمدة 4 أسابيع.

أظهرت نتائج تحاليل الكيمياء الحيوية ارتفاع تركيز الكوليسترول منخفض الكثافة مع انخفاض تركيز الكوليسترول مرتفع الكثافة في مصل الدم للجرذان المصابة بالكوليسترول وأيضاً ارتفاع نشاط إنزيم الفوسفاتاز الفلوري. وظهر تحسن في تلك النتائج باستخدام كل من الشوفان وعقار أتورفاستاتين في الجرذان.

أوضح نتائج الدراسة التنبؤية في الجرذان المصابة بالكوليسترول، تغيرات في قطاعات الكبد شملت اختلال الشكل لنسيج الكبد كما لوحظ في تجمع الدهون على شكل فجوات سيتوبلازمية في خلايا الكبد وظهور تتكزز بيوي واحتفاظ فتخت لدورة الخلايا الكبدية. ووجد ارتشاح للخلايا الالتهابية، كما أدى استخدام الجربون الكبدية وتشملت خلايا كوفر الالتهابية. أيضاً ظهرت الأوردة البائية محاطة بالخلايا الليفية وخلايا الدم البيضاء. أدت معاملة الجرذان المصابة بالكوليسترول بالشوفران تحسناً ملحوظاً على المستوى النسيجي والخلاوي عند استخدام عقار أتورفاستاتين. وناتج الدراسة فاعلية تأثير الشوفان على خفض تركيز الكوليسترول منخفض الكثافة، وتوصي باستخدام التغذية بالشوفران في المرضى المصابين بارتفاع الكوليسترول.