



The Effects of Estrogens and Phytoestrogens on the Metabolism
and Oxidation of Plasma Lipoproteins

Alice Jane Owen BSc (Hons)

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Department of Physiology,
University of Adelaide,
South Australia

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Abstract

The aim of this thesis was to examine the effects of estrogens and phytoestrogens, on plasma lipoprotein levels and other risk factors for cardiovascular disease, including the oxidisability of low density lipoprotein (LDL).

Hepatic LDL receptor activity plays an important role in the regulation of plasma LDL levels. *In vitro* studies presented here in the human hepatoma cell line HepG2 revealed that of the three major human estrogens, only estradiol was able to upregulate LDL receptor activity at 50 μ M. The phytoestrogens, daidzein, biochanin A, formononetin and coumestrol were all able to upregulate LDL receptor activity *in vitro*. Comparison of the effects of the two lignan phytoestrogens suggested that estrogenicity is an important determinant of their LDL receptor activity regulation.

In an *in vivo* study of hormone replacement therapy (HRT) in postmenopausal women, it was found that estrogen and progestin did not cause significant upregulation of mononuclear cell LDL receptor activity, despite there being noted a reduction in plasma LDL cholesterol. A reduction in the level of the atherogenic lipoprotein(a) was found following three months of HRT, however there was no significant effect of HRT on the parameters of *ex vivo* LDL oxidation.

Ground flaxseed (10g/d), which is rich in phytoestrogenic lignans and α -linolenic acid, was found to increase the levels of Lp(a) in men, while there was no effect noted in

women. This appears unlikely to be due to the fatty acid component of the flaxseed as we found no effect of either n-3 fatty acids or a high polyunsaturated fat diet on Lp(a) in other studies. While statistically significant, the reduction in Lp(a) was small and is unlikely to provide significant cardiovascular benefit. Further dose response studies are required to clarify the role of flaxseed in this reduction and to determine whether the Lp(a) lowering effect is maintained with longer-term supplementation. Further *in vivo* studies with isoflavonoid phytoestrogens found no effect of these compounds on Lp(a). Despite the previously demonstrated ability of daidzein and genistein to protect LDL from oxidation *in vitro*, we found no effect of isoflavone supplementation on *ex vivo* LDL oxidation. Isolated soy-derived isoflavones did not elicit a cholesterol-lowering effect in post-menopausal women, at either moderate (75mg isoflavones/d) or high doses (150mg isoflavones/d). As whole soy protein consumption has been reported to have a cholesterol lowering effect at lower isoflavone levels, this suggests that there may be an additional component of soy which facilitates this effect.

Thus, while estrogen was shown to upregulate LDL receptor activity *in vitro*, it was not possible to demonstrate this effect *in vivo*, suggesting that postmenopausal hormone replacement may be affecting LDL receptor independent catabolism of LDL. Phytoestrogens can upregulate *in vitro* LDL receptor activity, but when isolated soy isoflavones were given to postmenopausal women, no LDL cholesterol-lowering effect was noted. While animal studies suggest phytoestrogenic isoflavones play a role in the cholesterol-lowering effect of soy diets, it appears this effect is not independently mediated by the phytoestrogens.