

## IN THIS EDITION

### **Dietary approaches for atherosclerosis prevention: Vegetable protein.**

This sponsored symposium, held as part of the XIV International Symposium on Atherosclerosis in Rome (June 21, 2006) focused on various beneficial aspects of soy consumption.

Prof. C.R. Sirtori (Milan, Italy) and Prof Widhalm (Vienna, Austria) chaired the event. Prof. Sirtori explained in his opening comments that soy protein is effective in reducing cholesterolaemia.

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## DIETARY APPROACHES FOR ATHEROSCLEROSIS PREVENTION: VEGETABLE PROTEIN

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### **Summary of the symposium, held as part of the XIV International Symposium on Atherosclerosis in Rome (June 21, 2006).**

#### **Healthy food choices in the European guidelines on CVD prevention: how about the implementation in clinical practice?**

*Prof. G. De Backer (Ghent, Belgium).*



Dietary Guidelines for CVD prevention, such as those of the Third European Joint Task Force of European and other Societies published in 2003, are an essential part of clinical strategies to prevent CVD. While such recommendations provide a general framework it is important that local cultural needs in different European countries are also taken into account.

Dietary guidelines also need an implementation plan since surveys in daily practice show an unacceptable gap. The EUROASPIRE II survey, conducted in 15 different centres (Lancet 2001, 357: 995-1001), set out to determine whether patients with CHD are being effectively managed by lifestyle and drugs. Of the total survey sample, 59% had reduced their

calorie intake, but there was wide variation between countries. Despite this, 80% of patients were still overweight. Overall 87% said they had reduced fat intake in the diet and 36% had changed the type of fat they eat. However, at the time of the interview the proportion of the sample with total cholesterol >5mmol/L was 58%. The results of the EUROASPIRE III survey will be available at the end of 2006.

EUROACTION is a demonstration project (hospital and primary care) in preventive cardiology in patients with established disease. This project shows that dietary recommendations are not being translated or implemented as healthcare professionals would like.

A further question is how to implement guidelines for the large majority of people at risk of developing heart disease in the general population, which is more difficult to answer.

A more professional and multidisciplinary approach is needed to implementing dietary changes, involving health care professionals and the food industry among others.

## Vegetable proteins: mechanism for cholesterol reduction.

Dr M. Lovati (Milan, Italy)



Soy proteins are an important dietary tool for cholesterol lowering, especially for patients with high

baseline cholesterol levels. The mechanism for this effect is up-regulation of the LDL receptor on liver cells and the  $\alpha^1$  sub-unit of the 7S soy globulin has been shown to positively modulate LDL receptor activity.

The LDL receptor is regulated by a sophisticated system of membrane bound transcriptional factors and studies with cell cultures investigating the effect of soy protein on SREBP-1 (sterol regulatory element binding protein-1) modulation have shown that the  $\alpha^1$  sub-unit of the 7S globulin causes a marked increase in SREBP-1 in membranes and nuclei.

The effect of a synthetic peptide corresponding to a sequence which differs between the  $\alpha$  and  $\alpha^1$  subunits from the 7S soy globulin on cell cholesterol homeostasis was investigated. In cell culture, cells exposed to the synthetic peptide showed an increased uptake of LDL and of LDL degradation compared with non exposed cells.

A dose dependent increase in the SREBP-2 mRNA and LDL-receptor mRNA was also observed. In an in vivo study, feeding the synthetic peptide to casein-cholesterol fed rats for 14 days resulted in lower plasma cholesterol and triglyceride levels, compared with control rats.

These data provide evidence that the  $\alpha^1$  sub-unit from the 7S soy globulin and its

synthetic peptide are responsible for the direct up-regulation of LDL receptors via the SREBP pathway.

In the future it may be possible to select the breeding of novel soy cultivars with high amounts of bioactive peptides for cholesterol lowering.

## Soy and impact on peroxisome proliferator activated receptors (PPARs).

Prof. S. Kersten (Wageningen, The Netherlands)



Peroxisome proliferator-activated receptors (PPARs) are part of the nuclear hormone receptors

family that play an important role in the regulation of metabolic processes. Three different PPARs exist:  $\alpha$ ,  $\beta/\delta$  and  $\gamma$ , each of which is characterized by a distinct tissue expression profile. PPARs bind specific ligands, and regulate gene transcription by binding to DNA.

Both the fatty acids and isoflavones in soy are potential activators of PPARs, and binding to PPARs is one of the proposed mechanisms for the potential therapeutic effect of isoflavones. PPAR- $\gamma$  stimulates anabolic processes such as adipogenesis, lipogenesis and glucose uptake.

Genistein stimulates adipogenesis at high concentrations and it has been shown that at increasing concentrations genistein can activate the PPAR- $\gamma$  receptor. Genistein and daidzein can also activate PPAR- $\alpha$ , which is involved in catabolic processes such as fatty acid oxidation, and daidzein can activate PPAR- $\beta/\delta$ , although the activation

effect is more modest than with PPAR- $\gamma$ . While isoflavones in soy are able to bind and activate PPARs in vitro it is unclear to what extent isoflavones can simulate gene expression via PPAR- $\gamma$  in vivo.

Polyunsaturated fatty acids, present at high concentrations in soy, are able to bind and activate PPARs both in vitro and in vivo. Soy provides linoleic (18:2) and  $\alpha$ -linolenic (18:3) fatty acids, which are connected with numerous health benefits. For example  $\alpha$ -linolenic acid has been shown to improve vascular function and cardiac arrhythmia and to have anti-inflammatory effects.

## Safety & efficacy of soy in prevention of atherosclerosis in children.

Prof. K. Widhalm (Vienna, Austria).



Professor Widhalm discussed his work to investigate the long-term effects of soy in children

with familial hypercholesterolaemia (FH) (LDL-cholesterol >4 mmol/l, total cholesterol >6.9 mmol/l, and with polygenic hypercholesterolaemia (PH) (LDL >3.4 mmol/l. In phase one of the trial, subjects (n=23) followed a reduced fat diet for 3 months and in phase 2 of the trial (n=20) soy protein was substituted for animal protein.

Saturated fat intake was reduced from 45% of total fat at baseline, to 36.8% after phase 1 and to 30.7% after phase 2 ( $p < 0.0001$ ) and polyunsaturated fat intake increased from 19% at baseline to 25.7% after phase 1 and 33.8% after phase 2 ( $p < 0.001$ ). While the phase 1 diet resulted in a

significant reduction in serum total cholesterol (13%), in LDL-cholesterol (12%) and in apolipoprotein B (10%) the phase 2 soy diet reduced total cholesterol by a further 8%, LDL cholesterol by a further 8% and apolipoprotein-B by a further 21%.

Substituting soy for animal protein is of additional benefit to a low fat diet and may be a useful dietary tool for the prevention of early vascular disease in children and adolescents with FH and PH.

The symposium provided an informative update on some of the more recent work on various aspects of soy, and its potential health benefits.

### **Soy & phytoestrogens: beyond lipid lowering, anti-oxidant, anti-inflammatory effects.**

*Prof. T. Sanders (London, UK)*



Professor Sanders explained that soy protein has anti-atherogenic properties compared

with casein, though research has shown that these effects are reduced with alcohol extracted soy protein.

The anti-atherogenic properties cannot entirely be explained by the effects on serum lipids alone, and other potential mechanisms include anti-inflammatory effects, and antioxidant effects that conserve endothelial function. Both of these effects may occur at lower levels of intake than required for lipid lowering.

The phytoestrogens genistein and daidzein and the metabolite equol can act as antagonists and as partial

agonists for the estrogen receptor- $\alpha$  (ER- $\alpha$ ) and ER- $\beta$ . However, consumption of soy phytoestrogens does not have the undesirable effects seen with oral oestrogens on markers of procoagulant activity (factor VIIc, fibrinogen, von Willebrand factor) on fibrinolytic activity (PAI-I) or on plasma TGF- $\beta$ .

Results from the randomised, double-blind ISOHEART trial in postmenopausal women show that treatment with isoflavone lowered circulating levels of C-reactive protein after 4 weeks of the 8-week study in subjects with initial values  $>1$  mg/L. While endothelium-dependent vasodilation in the forearm vasculature is induced by infused genistein, showing a similar effect to that of 17- $\beta$ -oestradiol, there is no effect with daidzein. Genistein also potentiates the endothelium-dependent vasodilator acetyl choline. Large changes with soy on flow mediation have been observed but the results are very variable – some of these differences are due to dosages and use of different test materials. While real effects can be suspected, more research is needed in this area, and also to determine the influence of the changes on disease risk.

## RECENT PUBLICATIONS

### **Safety and antioxidant effects of a modest soy protein intervention in hemodialysis patients.**

Siefker K, DiSilvestro RA.  
J Med Food 2006;9:368-72.

### **Addressing the soy and breast cancer relationship: review, commentary, and workshop proceedings.**

Messina M, Caskill-Stevens W, Lampe JW.  
J Natl Cancer Inst 6 A.D.;98:1275-84.

### **An overview of the health effects of isoflavones with an emphasis on prostate cancer risk and prostate-specific antigen levels.**

Messina M, Kucuk O, Lampe JW.  
J AOAC Int 2006;89:1121-34.

### **A meta-analysis of the effect of soy supplementation on serum lipids.**

Reynolds K, Chin A, Lees KA, Nguyen A, Bujnowski D, He J.  
Am J Cardiol 2006;98:633-40.

### **Effect of soy protein-containing isoflavones on lipoproteins in postmenopausal women.**

Allen JK, Becker DM, Kwiterovich PO, Lindenstruth KA, Curtis C.  
Menopause 2006. Epub.

### **Isoflavone therapy for menopausal flushes: A systematic review and meta-analysis.**

Howes LG, Howes JB, Knight DC.  
Maturitas 2006. Epub.

### **Effects of isoflavone and exercise on BMD and fat mass in postmenopausal Japanese women: a 1-year randomized placebo-controlled trial.**

Wu J, Oka J, Tabata I et al.  
J Bone Miner Res 2006;21:780-9.

### **Isoflavone supplements containing predominantly genistein reduce hot flash symptoms: a critical review of published studies.**

Williamson-Hughes PS, Flickinger BD, Messina MJ, Empie MW.  
Menopause 2006. Epub.

### **Effect of whey and soy protein supplementation combined with resistance training in young adults.**

Candow DG, Burke NC, Smith-Palmer T, Burke DG.  
Int J Sport Nutr Exerc Metab 2006;16:233-44.

### **Soy protein diet improves endothelial dysfunction in renal transplant patients.**

Cupisti A, Ghiadoni L, D'Alessandro C et al.  
Nephrol Dial Transplant 2006. Epub.

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