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A number of recent clinical trials with HMG CoA reductase inhibitors have clearly demonstrated the efficacy of cholesterol lowering as a risk-reduction strategy for the primary and secondary prevention of coronary artery disease.

The Scandinavian Simvastatin Survival Study (4S), the West of Scotland Coronary Prevention Study (WOSCOPS), the Cholesterol and Recurrent Events (CARE) trial, the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID), as well as numerous other investigations, have established that decreasing elevated levels of LDL-cholesterol will result in a reduction in coronary artery disease risk.

The beneficial effects of LDL-cholesterol reduction occur early and are additive to other risk-reduction therapies. Lipid lowering therapy should be part of the comprehensive treatment of all patients with atherosclerotic vascular disease and patients at high risk.

So far the therapeutic goal of reducing LDL-cholesterol to provide the best benefit in most patients has not been established. Ongoing studies are attempting to obtain an LDL-cholesterol reduction far below 100 mg/dl.

From the results of subgroup analysis, new studies have been started with statins and fibrates in defined patients (those with diabetes, renal insufficiency, etc). Other statin properties, besides their lipid lowering effects, have been documented. These mechanisms might contribute to some positive effects of this group of substances. Side-effects of statins are rare, although drug interactions with statins are still observed.

Other drugs are being tested for their lipid lowering potency. New bile acid binding resins are under study. These compounds have a higher affinity to bile acids and, therefore, lower dosing might be possible.

The observation that the saturated plant stanol sitostanol is more effective in inhibition of intestinal cholesterol asorption than sitosterol and reduces serum LDL-cholesterol between 10 and 30 percent was followed by the introduction of sitostanol oleate in margarine in Finland. Since sitostanol is excreted unchanged with the faeces and its absorbabilty is negligible, this compound seems to be extremely safe. For this reason, sitostanol oleate-enriched margarine will become available soon in several countries. Although the reduction in LDL-cholesterol is much less compared to HMG CoA reductase inhibitors, it will probably help to reduce the incidence of coronary heart disease in the population.

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Our epidemiological studies have shown strong links between indices of poor fetal and early infant growth and loss of glucose tolerance and the insulin resistance syndrome (syndrome X) in adult life. These findings have been reproduced world wide.

We have proposed the thrifty phenotype hypothesis as an explanation of the overall processes involved in these relationships. This postulates that fetuses in a poor nutritional environment due to poor maternal or even grand maternal nutrition or due to poor placentation mount adaptive responses which serve at least two functions. Firstly there is a redistribution of the flow of nutrients within the fetus to prioritise the growth of organs such that, for example, brain growth is relatively protected. Secondly there are permanent structural and functional changes in organs which serve to provide postnatal adaptation to a poor nutritional environment.

However, if the organism becomes obese as an adult the conflict between this and the metabolic programming for poor nutrition leads to a loss of glucose tolerance and the insulin resistance syndrome. It is possible that different types and/or timings of the early nutritional insult(s) determine the exact spectrum of the adult changes in metabolism (Hales *et al.*, 1997).

We have used a rat model in which pregnant and/or lactating dams are fed a reduced protein diet (8%) and compared the *in vivo* and *in vitro* changes in metabolism with controls (20% protein) in order to test and refine this hypothesis (Desai & Hales, 1997). By combining early growth retardation with diet-induced adult obesity we have been able to reproduce the insulin resistance syndrome in the rat (Petry *et al.*, 1997).

We have also shown major changes in insulin-regulated carbohydrate and lipid metabolism. In young adult life there is an increase in insulin receptors in liver, muscle and adipose tissue. There are changes in the insulin signalling cascade in adipose tissue such that there is enhancement of insulin-stimulated glucose uptake, but a reduction in its effect to inhibit lipolysis. These changes may be mediated by quantitative changes in the isoforms of enzymes involved in the signalling cascade. These changes may increase glucose storage as fat and increase fatty acid oxidation to conserve plasma glucose, thereby enhancing survival in conditions of poor and internmittent nutrition.

Most recently we have also shown that longevity is programmed positively or negatively in male rats according to the pattern of early growth (Hales *et al.*, 1996). Evidence has been obtained that these changes are linked to the rate of telomere shortening in the kidney.

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