Study and Therapy News

Retinoids, Hyperlipidemia and Atherosclerosis: Where Do We Stand Today?

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Already during the first trials with oral synthetic retinoids in the late 1970s it was noted that a significant proportion of the patients developed hypertriglyceridemia and, to a lesser extent, hypercholesterolemia. This was a major concern because such lipid changes are epidemiologically associated with an increased risk of ischemic heart disease (IHD) and stroke, i.e. diseases which are secondary to atherosclerosis. However, hyperlipidemia is just one of many culprits in the pathogenesis of atherosclerosis. For instance, increased blood pressure, hyper-coagulation, smoking, and chronic or acute inflammations of the blood vessels have also been implicated in this process. Interestingly, recent data indicate that retinoids may actually improve some of these aspects of atherosclerosis.

The aim of this review is to summarize the present knowledge about the negative and positive effects of retinoids in relation to atherosclerosis.

Retinoid-induced hyperlipidemia

Typically, retinoid therapy increases the serum triglycerides (TG) and very low-density lipoprotein (VLDL) levels within 4–6 weeks of commencing treatment and effects a redistribution of serum cholesterol from the high-density lipoprotein lipoprotein (HDL) fraction to the low-density lipoprotein (LDL) fraction. Virtually all retinoids exert this effect when given orally in therapeutic doses, but the magnitude of the changes varies for different drugs and between individuals. For example, in a head-to-head comparison of isotretinoin and etretinate carried out some 15 years ago (1), we found that the former drug was clearly the most potent inducer of serum lipids changes. Thus the average increase in VLDL-TG after 8 weeks of consecutive treatment of psoriasis patients with comparable doses of isotretinoin and etretinate was 37% and 10%, respectively, and the corresponding increments in the LDL/HDL cholesterol ratio were 33% and 14%. Importantly, all the reported lipoprotein changes reverted to pre-treatment values after an 8-week wash-out period.

In general, hypertriglyceridemia (>2 mmol/l) occurs in about 30% of patients treated with oral retinoids, and usually involves a two-fold or less elevation of serum triglycerides (2). Such triglyceride elevations are usually asymptomatic, but could possibly increase the risk of athero-sclerosis if maintained for very long periods of time (3). Slightly elevated total serum cholesterol (>6 mmol/l) is commonly observed in patients treated with retinoids, but overt hypercholesterolemia (>7.5 mmol/l) is only rarely induced (<10% of patients). However, the LDL/HDL-cholesterol ratio is frequently raised during therapy, and this is of major concern during long-term treatment, because in the population at large a high LDL/HDL ratio is strongly correlated to an augmented risk of IHD (4). In a small population of patients that cannot readily be predicted, isotretinoin may cause severe hypertriglyceridemia (>10 mmol/l), which in rare instances pre-cipitates life-threatening pancreatitis (5).

The bulk of evidence suggests that retinoids do *not* increase the intestinal absorption of fat, but they do increase the synthesis of TG and VLDL particles, and inhibit the

elimination of these particles from the circulation (6–9). The molecular and cellular aspects of these effects have only partially been elucidated. For example, retinoids increase the expression of apo C-III, an antagonist of plasma TG catabolism; in one study isotretinoin treatment (80 mg/day; for 5 days) resulted in elevated plasma apo C-III, but not apo E concentrations (10). This increased apo C-III transcription is mediated by the retinoid X receptor (RXR) (10).

A matter of great concern is whether or not the hyperlipidemic response is genetically determined and thus potentially predictable. A clue in this direction comes from a recent study by Rodondi and coworkers (11) who hypothesized that familial combined hyperlipidemia, isolated or as part of the metabolic syndrome, might be the underlying genetic defect and that isotretinoin treatment is able to unmask this familial predisposition. The results of this study suggests that the hyperlipidemic response is indeed genetically determined and that individuals with a family history of hyperlipidemia should only be treated with retinoids on strong indications and under strict surveill-ance with regard to serum lipid elevations. Other types of pre-therapy hyperlipidemia are, how-ever, not necessarily associated with a hyper-response to retinoids, but patients with such conditions should be examined for occult concomitant diseases (diabetes, hypothyreosis, renal disease, etc)

How can retinoid hyperlipid-emia be reversed?

In some patients with retinoid hyperlipidemia, adjuvant measures such as weight loss, appropriate dietary modification (restriction of fat and alcohol), physical activity, and retinoid dose reduction are sufficient in reversing the TG eleva-tion while continuing retinoid thera-py. In other patients more vigorous actions have to be undertaken or, in rare cases, the retinoid treatment has to be stopped altogether because of marked hyperlipidemia unrespon-sive to therapy.

A non-pharmacological approach to retinoid hyperlipidemia is to supple-ment the patient with ω-3 fatty acids (from whole fish oil) known to depress the production rate of VLDL (14). Another way of reducing especi-ally TG levels is to prescribe lipid-lowering fibrates, such as gemfibro-zil. The mechanism of action of gemfibrozil involves: *i*) reducing hepatic triglyceride production by inhibiting peripheral lipolysis and decreasing hepatic extraction of free fatty acids, and *ii*) decreasing VLDL production by inhibiting the synthe-sis and increasing the clearance of apolipoprotein B. In a double-blind placebo-controlled study in 14 acitretin-treated psoriasis patients with hypertriglyceridemia, gemfibro-zil (300 mg bid for 8 weeks) was found to significantly reduce the TG concentration from a mean value of 3.7 mmol/l to 1.9 mmol/l (p<0.01) without any concomitant change in

the LDL/HDL-cholesterol ratio (15). It should be noted that neither gemfibrozil nor fish oil appears to interfere with the clinical effective-ness of retinoids.

Other lipid-lowering drugs, such as statins (e.g. simvastatin) and resins (e.g. cholestyramine) are probably more effective than gemfibrozil against retinoid-induced hyper-cholesterolemia, but have not been formally tested for this indication. Theoretically there may be a risk for drug interactions, since both sim-vastatin and retinoids can cause myalgia, and cholestyramine may interfere with the intestinal absorp-tion of retinoids.

Effects of retinoids on blood vessels

In recent years, retinoids have been examined for their influence on vascular smooth muscle cell (SMC) growth and differentiation, inas-much as these processes are thought to be of some relevance in the pathogenesis of vascular occlusive disease. Thus, there is a growing body of in vitro data demonstrating that retinoids antagonize growth factor-stimulated SMC hyperplasia while in some cases promoting a more differentiated SMC phenotype (16). It is hypothesized that these observed effects on SMC phenotype are related to retinoid receptor-mediated changes in the SMC tran-scriptome. Remarkably, all in vivo studies to date have documented desirable changes in vessel wall

geometry with retinoid administration after vascular injury in animals. The changes include attenuation in neointimal mass, an outward re-modeling of the vessel wall, and accelerared re-endothelialization (16). It remains to be investigated if retinoids may in fact be efficacious in the treatment of human vascular disorders.

Effects on endogenous fibrinolysis and hemostasis

The fibrinolytic system is an important protective mechanism against intravascular coagulation and thrombosis. Drugs that enhance endogenous fibrinolytic activity could therefore provide a preventive approach to intravascular thrombosis associated with atherosclerosis and IHD.

The most dramatic example of retinoid-induced changes in the hemostatic systems comes from patients with acute promyelocytic leukemia who are treated with all-trans retinoic acid (ATRA). ATRA induces a complete remission in >90% of patients with acute pro-myelocytic leukemia (APL) and rapidly resolves the life-threatening coagulation/bleeding syndrome, due to intravascular clotting activation typical of this disease (17). In addition, ATRA counteracts the procoagulant action of cytokines on the endothelium and increases the expression of fibrinolysis proteins and the anticoagulant thrombo-modulin by endothelial cells. Prelimi-

nary studies have shown that ATRA also mitigates the hypercoagulable state in breast cancer patients treated with tamioxifen (18). But is there any evidence that retinoids also affect fibrinolysis in for example the ordinary dermatology patient?

Under normal conditions the availability and activity of plasminogen activators (PAs) are key factors in determining the fibrinolytic capacity of plasma. Two distinct PAs are known, urokinase-type PA(u-PA) and tissue-type PA (t-PA). The local concentration of active (free) PA is determined, in part, by the tissue concentration of PA inhibitor type-1 (PAI-1). Stimulation of endogenous fibrinolysis could therefore be directed at pharmacological up-regulation of t-PA or u-PA synthesis or down-regulation of PAI-1. Recently it was shown that several retinoids enhance fibrinolytic activity in cultured medium of human endo-thelial cells by increasing t-PA synthesis without affecting PAI-1 synthesis (19). The mechanism of this enhanced t-PA synthesis occurs most likely via nuclear receptor proteins (RARs).

In dermatologic patients treated with either isotretinoin or etretinate/acitretin, enhanced baseline t-PA plasma concentrations have been noted, whereas the PAI-1 and von Willebrand factors were unchanged (20). This fits with the clinical observation that retinoid-treated patients often suffer from nose bleedings that are only partially

explainable by mucous membrane toxicity.

Conclusions

The concern about retinoid-induced hyperlipidemia is still valid, especially when very high TG levels are attained or when the patient is on long-term treatment and has other risk factors for atherosclerosis and IHD.

Importantly however, retinoids may also have positive effects on some aspects of atherosclerosis. For example, they may retard smooth muscle cell proliferation in the vessel walls and increase the fibrinolysis via stimulation of plasminogen activity, thus reducing the thromboembolic complications of atherosclerosis during retinoid therapy. In addition, the alleviation of systemic inflammation by retinoids in, for example, cases of severe psoriasis or conglobate acne, probably reduces the stress on the cardiovascular system. Thus, the answer as to whether or not long-term retinoid therapy will ultimately enhance the risk for IHD and stroke probably depends on the patient's intrinsic balance between a negative impact of hyperlipidemia and a positive influence of retinoids on other aspects of atherosclerosis (Fig. 1). Since no prognostic studies have been made to assess the risk for atherosclerosis and IHD in large cohorts of retinoid-treated patients compared to age- and sex-matched controls, it is presently not known how all these effects add up.
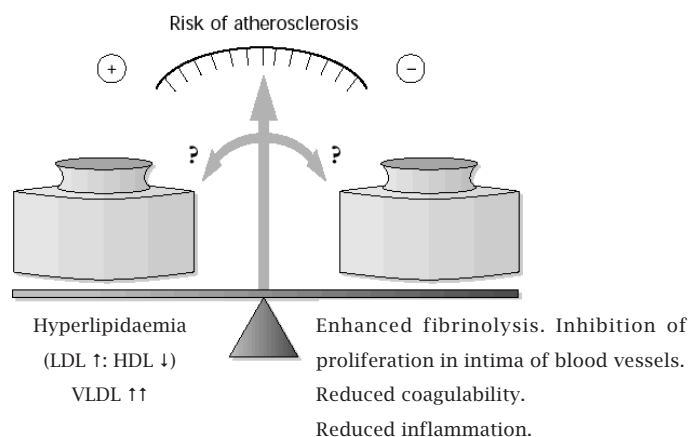
Fig. 1: Summary of putative negative and positive effects of retinoid therapy that might influence the patient's future risk for ischemic heart disease and stroke. The weight of each factor, which is individually variable, will probably determine the balance towards increased or decreased risk of atheroscelerosis (see text for other abbreviations). Reproduced with permission from Retinoids & Lipids Soluble Vitamins in Clinical Practice.

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(a full reference list is provided in the original paper)

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