Original article

Lipid status, inflammatory markers and vascular calcifications in patients on haemodialysis

Yonova D[1] and Dobrev S[2]

Dialysis Clinic[1]; Central Clinical Lab[2]; Med. Univ. Hospital "Alexandrovska", Sofia, Bulgaria

Abstract

The protective role of high density lipoproteins (HDL) on the development of vascular calcifications with atheromatous and medial forms of calcium deposits have been recently suggested. Vascular calcification shares several features with skeletal bone formation at the cellular and molecular levels. Lack or decreasing of serum HDL leads to higher vascular calcification in general population and perhaps even more severely it happens to patients with chronic renal failure where the lipid metabolism is frequently disturbed. Another supposed factor for arterial calcification is the presence of inflammation.

The high rate of cardiovascular morbidity and mortality in haemodialysis (HD) patients and the special importance of presence of vascular calcification in that pathology initiates this study, which has set a goal to establish whether there is a relation between: a). lipid profile and inflammation, accounting C-reactive protein as one of its typical markers, and: b). both lipid profile and inflammation and vascular calcification rate in a group of HD patients, comparing HD group with a group of healthy volunteers. *Hippokratia 2006; 10(1):35-38*

Key words: *High density lipoproteins (HDL), vascular calcification, inflammatory markers, hemodialysis*

Corresponding author: Diana Yonova M.D., Ph.D. Dialysis Clinic, Med. Univ. Hospital "Alexandrovska" "G. Sofijski" Str. No 1, Sofia 1431, Bulgaria. Tel. 35929230463; e-mail: dr_ionova@email.com

Introduction

In recent years debate has appeared about the protective role of high density lipoproteins (HDL) on the development of not only the atherosclerosis, but on the oxidative stress, inflammation and vascular calcification [1, 2, 3, 4, 5, 6]. HDL are responsible for reverse cholesterol transport, i.e., the removal of free cholesterol from blood vessels to the liver [1, 2] They also have antioxidant and antiinflammatory properties[3]. Some studies have demonstrated the ability of HDL to inhibit cytokine-induced responses in endothelial cells [4, 5] and some studies[6, 7] have shown that HDL inhibit low density lipoproteins (LDL) oxidation and production of monocyte chemotactic proteins in artery wall cells. The antiinflammatory effects of HDL appear to be mediated in part by associated proteins, such as apolipoprotein (apo)A-I, which has lipid-binding properties, and the enzymes platelet factor acetyl hydrolase and serum paraoxonase (PON-1), which can eliminate the bioactivity of oxidized lipids [3, 8]. Reports suggest that the protective effects of HDL may encompass an ability to inhibit cytokine-induced inflammatory responses, such as the induction of cell adhesion molecule expression by IL-1ί [9].

HDL may also play an important role in regulating vascular calcification associated with both atheromatous and medial forms of calcification. Some authors have recently demonstrated that human HDL inhibit the spontaneous osteogenic differentiation and mineralization of so called "osteoblast-like" vascular cells (OLVC) in vitro[10, 11]; HDL inhibit this differentiation by suppression of LDL oxidϋtion and of IL-1ί, and IL-6 action. The latters facts suggest that HDL may regulate vascular calcification by directly inhibiting the osteogenic differentiation of vascular cells.

On the other hand increased levels of CRP are significantly associated with the presence of vascular calcification in both aorta and hand arteries (i.e., with both atheromatous and medial forms of calcification), indicating evidence for a relationship between inflammation and vascular calcification [12, 13].The high rate of cardiovascular morbidity and mortality in haemodialysis (HD) patients and the special importance of presence of vascular calcification and inflammation in that population, initiates this study, which tries to establish whether there is a relation between the lipid profile, C-reactive protein and vascular calcification rate in HD patients

Material - methods

Fifty one haemodialysis patients, 23 males and 18 females, (mean age 55 ± 13 years; mean duration of haemodialysis 95.55± 59.96 months) were tested routinely for serum levels of high density lipoproteins (HDL), low density lipoproteins (LDL), total cholesterol (T-chol), triglycerides (Tg) and CRP. Total cholesterol was determined using the cholesterol oxidase DAOS method [17]. Cholesterol fractionations were car-

ried out by agarose gel electrophoresis[18]. Vascular calcification rate (VCR) was registered by sonography of the two carotid and the two femoral arteries in longitudinal and transversal projection (transduser 7 MHz). A control group of 30 healthy volunteers, 15 males and 15 females (mean age 49 ± 15 years), passed the same tests as well.

Results

The mean levels (MEAN ± SD) of Tg and LDL (both atherogenic factors) in haemodialysis patients were higher than in the control group, showing a higher risk for atherosclerosis in haemodialysis patients (Table 1; Fig. No 1 and Fig. No 2, respectively).

Table 1

Lipid fraction	HD Group	Controls
Tg (g/l)	1.75 ±0.65	1.45±0.75
LDL(mmol/l)	2.64±1.05	1.96±1.2

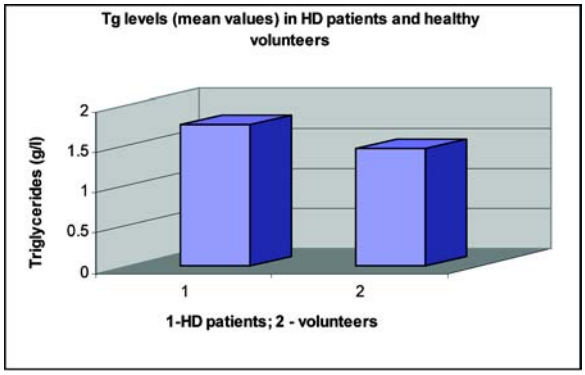

Fig. 1: *Mean levels of triglycerides (Tg) in the investigated HD patients and in the healthy subjects*

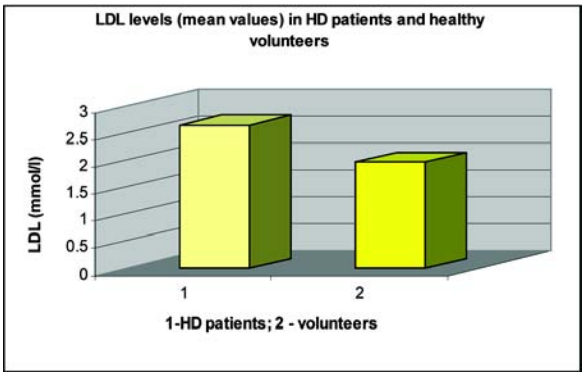

Fig. 2: *Mean levels of low density lipoproteins (LDL) in the investigated HD patients and in the healthy subjects*

There was a significant negative correlation between HDL and VCR in the HD patients group (r = -0.39, π<0.01) (Fig. No 3).

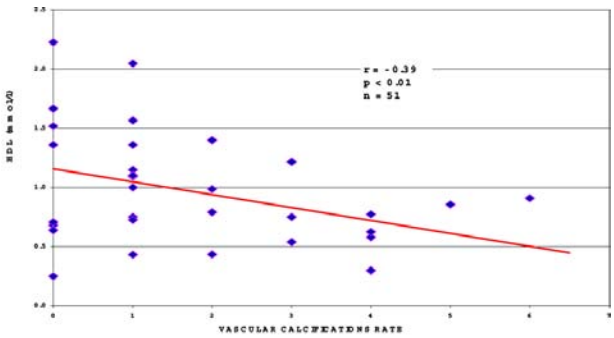

Fig. 3: *Correlation between HDL and vascular calcification rate in the investigated haemodialysis patients*

A negative, but not significant correlation was registered between HDL and CRP and T-chol and VCR (Tabl. No 2).

Table 2

Correlation ratio	r =	p <
HDL/CRP	-0.30	NS
T-chol/VCR	-0.06	NS

A very high positive correlation was registered between CRP and VCR (r = 0.78, p<0.001) (Fig. No 4).

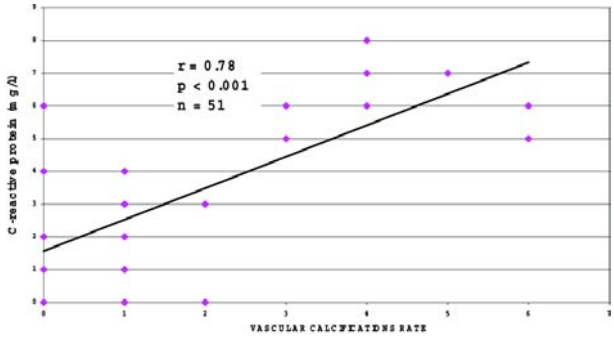

Fig. 4: *Correlation between CRP and vascular calcification rate in the investigated haemodialysis patients*

Only a slight positive relation was found between LDL and VCR; LDL and CRP; Tg and CRP in the group of haemodialysis patients (Table No 3).

Table 3

Correlation ratio	r =	p <
LDL/VCR	0.14	NS
LDL/CRP	0.17	NS
Tg/CRP	0.16	NS

The control healthy volunteers had no abnormal levels of CRP and only a few vascular calcifications - date, showing the importance of the chronic renal failure and

the dialysis treatment on the elevation of some markers of inflammation and on forming of pathological vascular calcifications.

Discussion

The ability of HDL to protect against vascular disease has been a subject of intense research. Epidemiological data suggests a protective effect of HDL against atherosclerotic disease. As a result, HDL-based intervention is considered a potential strategy against cardiovascular disease in humans. HDL may act by mediating reverse cholesterol transport and thereby preventing accumulation and oxidation of lipids and lipoproteins in the artery wall [1, 2, 10, 11]. Enzymes associated with HDL, platelet-activating factor acetyl hydrolase, and PON are able to directly act on oxidized phospholipids and lipoproteins and, hence, destroy their proinflammatory activity [6, 11, 14, 15]. HDL may also exert its antiinflammatory effects by impairing the response of vascular cells to inflammatory cytokines; HDL inhibits IL-1 or TNF-α-induced expression of endothelial cell adhesion molecules E-selectin, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1 [4, 8]. HDL may also facilitate the production of protective molecules such as NO by activating endothelial NO synthase and by preventing the inhibitory effects of oxidized LDL on that enzyme [14, 15, 16]. A number of data also suggest that HDL may prevent calcification of vascular cells and, hence, prevent calcification-induced vascular complications that would impair the proper functioning of the vessel wall [2, 3, 4, 12].

The finding that inflammatory cytokines such as IL-1ć, IL-6, and TNF-αinduce osteogenic differentiation and mineralization of vascular cells suggests that inflammatory cytokines initiate or promote vascular calcification associated or not with atherosclerotic lesions by regulating the differentiation of vascular cells [9, 12]. Hence, strategies that downregulate inflammation or upregulate antiinflammatory agents may prove beneficial in controlling vascular calcification.

In our study the control healthy volunteers had no abnormal levels of CRP, quite less changes in lipid profile than in HD patients, and only a few vascular calcifications - date, showing the importance of the chronic renal failure and the dialysis treatment for the elevation of some markers of inflammation, lipid disturbances and forming of pathological vascular calcifications.

On the basis of our results, cited above, the highly important relation between arterial calcifications and inflammation state in haemodialysis patients is confirmed as well as the presence of reverse dependence between the HDL levels and VCR. Also worth mentioning is the tendency of lowering of HDL in the case of increased CRP. The study did not find an indisputable relation between VCR and the other lipid fractions, although a slight positive tendency of relation was observed between LDL and Tg on one hand and VCR on the other. The conclusion of all this is, that the prevention of vascular calcification in haemodialysis patients requires not only prevention of the renal osteodystrophy as the main and well known reason of the phenomenon, but also prevention of the lipid disturbances and inflammation status – factors surely involved in this pathology.

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