LIPOPROTEIN AND APOLIPOPROTEIN METABOLISM AMONG PATIENTS UNDER CHRONIC HEMODIALYSIS TREATMENT

ABBAS SAMADI* AND GHOLAMREZA VALI

From the Department of Biochemistry, Kashan Medical University, P.O. Box 87155-111, Kashan, Islamic Republic of Iran.

ABSTRACT

Pathogenic factors that may contribute to hypertriglyceridemia were studied in 55 patients who have been undergoing chronic hemodialysis treatment. Increased levels of triglyceride were observed in the patient group compared to normal controls (190±93 mg/dL vs. 121±45 mg/dL, p<0.05). Similarly, augmented concentrations of VLDL-C were observed among patients compared to the control subjects (36±18 mg/dL vs. 24±8 mg/dL, p<0.05). The major fraction of serum cholesterol was distributed in LDL and lesser amounts were measured in VLDL and HDL. The HDL-C fraction did not display significant variation in the patient group as compared to normal subjects. Apo B levels were higher in the patient group compared to normal subjects (97±26 mg/dL vs. 87±14 mg/dL, p<0.05). In addition, apo A-I levels were significantly lower in the patient group compared to control subjects (84±13 mg/dL vs. 119±14 mg/dL, p<0.05). A reverse relationship was observed between the concentration of plasma albumin and total cholesterol which may explain the reason for overproduction of lipids in renal failure, although other factors may contribute to the increased lipoprotein production observed in patients receiving chronic hemodialysis treatment.


INTRODUCTION

The association between renal dysfunction and cardiovascular disease is observed with greater frequency. Hyperlipidemia is a well recognized complication that occurs in patients undergoing chronic hemodialysis treatment (CHT). The disturbances of lipid metabolism in renal failure are associated with changes in the composition, structure, and metabolic regulation of all circulating molecules responsible for the transport of triglycerides, cholesterol and phospholipids.

*Address for correspondence: Abbas Samadi, University of Paris, Henri Mondor Hospital, Department of Biochemistry and Molecular Genetics, INSERM U. 91, Creteil, 94010, France. Tel No: (1) 49812854, Fax No: (1) 49812895

Increased total triglyceride and enrichment of very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) with triglyceride has been reported previously. The "cardioprotective" high-density lipoprotein (HDL) fraction has variously been reported to be increased, decreased or normal.

This study was designed to examine the changes in the concentration of lipoproteins and apoproteins, and the contribution of liver cells to hyperlipidemia in end stage renal failure.

MATERIALS AND METHODS

Subjects

Fifty-five patients (34 males and 21 females), aged...
between 25 and 45 years were chosen for this study. All patients had been receiving stable CHT for a minimum of one year. They were maintained with five-hour sessions of hemodialysis three times per week. The dialysate used contained 200 mg/dL dextrose and 33 mEq/L acetate. They were taking no medication that might affect serum lipid levels such as steroids, β-blockers, or antihypertensive agents. They were recruited from two outpatient renal units of Tehran (Hashemi-Nejad Hospital) and Kashan (Akhavan Hospital).

Subjects suffering from other diseases or on treatment that might significantly alter serum lipids were excluded. These included neoplastic and untreated endocrine disorders, diabetes mellitus, amyloidosis, systemic lupus erythematosus, or corticosteroid therapy. No patient had a family history of premature vascular disease, and there were no external stigmata of hyperlipidemia. Normal control subjects were chosen from the Hashemi-Nejad hospital personnel. They had no known hypertriglyceridemia, were free of disease and were taking no medication at the time of the study. The normal control group consisted of 69 males and 31 females aged 38±6 years. The patients and normal controls were age and sex-matched. All of the patients who were suffering from type 1IV hyperlipidemia had not been on antihyperlipidemic agents for at least 2 weeks prior to the present study. Informed consent was obtained from all patients and the control subjects.

Protocol

Venous blood specimens were collected in the morning of the dialysis immediately before the start of the session and prior to the administration of heparin. Patients and control individuals had fasted for 12-14 hours just prior to the specimens being collected. Total concentration of albumin was measured by standard autoanalytical techniques. Cholesterol and triglycerides were measured enzymatically with a Technicon RA-1000 analyzer, using reagents from Technicon Instruments Corporation (Tarrytown, NY). Low-density lipoprotein cholesterol was separated from high-density lipoprotein cholesterol by precipitation with phosphotungstate and magnesium chloride according to Phillion et al.* Apo A-I and apo B were determined by monoclonal antibody based fixed-time turbidometric assay (International Diagnostic Laboratories, Chesterfield, MO.). Data are expressed as mean±SD throughout the text. Statistical analysis was performed using Student's t-test to compare differences between CHT patients and normal subjects. P-values of less than 0.05 were considered to indicate statistical significance. Correlation was performed by linear regression analysis.

RESULTS

In order to compare the effect of renal failure in patients receiving CHT, the concentration of albumin, lipids, lipoproteins and apolipoproteins was compared in patient and control subjects (Table I). The concentration of total triglyceride in the patient group was significantly higher (190±93 mg/dL) than the control group (121±45 mg/dL, p<0.05). Overall total concentration of cholesterol was lower in hemodialysis patients (168±40 mg/dL) compared to the control group (191±28 mg/dL). However, the difference was not significant. The VLDL-C levels in hemodialysis patients (37±18 mg/dL) was significantly higher than the control group (24±8 mg/dL, p<0.05) (Table I). Forty-one of the 55 patients had mean VLDL-cholesterol levels that were elevated above the 95th percentile for age and sex and 30 of the 55 patients had a mean LDL-cholesterol concentration in this range. The concentration of HDL-C and LDL-C in hemodialyzed patients was not significantly different from the control group.

The ratio of HDL-C to total cholesterol in patients receiving CHT was significantly lower (0.22±0.10) compared to normal individuals (0.63±0.07, p<0.001). In 48 of the patients (87 percent), the ratio of HDL-C to total cholesterol was lower than the ratio of the mean value for HDL-C to total cholesterol in normal individuals for age and sex.

The serum concentration of apo A-I was significantly lower in the patient group (84±13 mg/dL) compared to...
normal individuals (119±14 mg/dL, p<0.05). On the contrary, the concentration of apo B in hemodialysis patients was higher (97±27 mg/dL) compared to the control group (87±14 mg/dL, p<0.05) (Figure 1). The ratio of apo A-I/apo B which is a risk index for atherosclerosis was significantly lower in hemodialysis patients (0.87±0.5) compared to the normal group (1.4±0.6, p<0.001). The concentration of albumin was lower (4.4±0.8 g/dL) in patients compared to controls (4.6±0.3 g/dL, p<0.05). Moreover, a significant inverse correlation was found between plasma albumin and total cholesterol levels among patients receiving CHT (r=-0.615, p<0.05) (Figure 2).

### DISCUSSION

We measured serum lipid and lipoprotein concentrations in carefully selected patients receiving hemodialysis treatment who had no complicating diseases such as diabetes. In agreement with previous studies, our patients had increased concentrations of serum triglyceride and VLDL-C.\(^1\)\(^2\)\(^3\)\(^4\) Most of the cholesterol was in the LDL fraction, with a smaller proportion in VLDL and HDL. However, a large majority of patients had mean values for HDL-cholesterol either within or below the normal range. Other atherogenic indices such as HDL-C/total cholesterol and apo A-I/apo B were significantly lower in patients receiving CHT. This data may suggest a derangement of both triglyceride and cholesterol metabolism in patients on CHT, i.e. type IIb hypertriglyceridemia rather than type IV as has been generally assumed. This hypothesis may explain the general frequency of athematosus cardiovascular complications in these patients.

Serum concentration of major apoproteins in VLDL such as apo B showed significant elevation in hemodialysis patients. This finding is in agreement with other studies which show a significant rise in the concentration of apo B.\(^3\)\(^1\)

A comparison of the serum lipoprotein levels of patients on CHT with normal controls may make it rather difficult to analyze the pathogenic factors causing hypertriglyceridemia. One reason for this difficulty is that the comparison will inherently include various factors that are related to hemodialysis or high serum urea and uric acid levels. However, it is fair to say that hypertriglyceridemia is the result of either an increased production of or an impaired removal of triglyceride-rich lipoproteins, or a combination of these two mechanisms.

Animal model studies\(^1\)\(^2\)\(^3\) have indicated that increased hepatic lipoprotein synthesis may be the major metabolic abnormality, but considerable differences in lipoprotein metabolism between species make direct comparison with nephrotic syndrome in humans difficult. Some human studies have suggested that oversynthesis is the most important disturbance in the generation of hyperlipidemia.\(^1\)\(^2\)

In the majority of patients in our study suffering from end stage renal failure and receiving CHT, there was a decrease in the level of albumin. There has also been a negative correlation between the plasma levels of albumin with total cholesterol. These findings may reflect that increased hepatic protein and lipid synthesis and secretion may be attributable to the reduced levels of albumin, and liver cells are stimulated to produce more proteins.\(^1\)\(^5\)\(^6\) The cause of hypoalbuminemia in end-stage renal failure is complex and includes: (1) acute phase response of the liver, (2) redistribution of albumin pools, and (3) albumin loss in hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). In addition to hypoalbuminemia, there may be other factors inducing the overproduction of liver cells.

There may be suppressor molecules of protein synthesis that under normal circumstances will regulate the synthesis and secretion of albumin and other proteins by the liver cells to maintain optimal oncotic pressure, whereas in CHT patients such molecules are lost through dialysis. In support of this hypothesis, a recent study was reported by Wanner et al.\(^1\)\(^4\) demonstrating a positive correlation between daily protein and albumin loss into dialysis fluid and increased lipoprotein (a) serum concentration. However, further studies are needed to confirm the influence of various factors on hyperlipidemia in CHT patients. No rational treatment of cardiovascular diseases in patients suffering from renal disease may be provided unless fundamental insight into the effect of various elements on lipoprotein metabolism is gained.

### REFERENCES

1. Shoji T, Nishizawa H, Yamakawa M, Morii H: Role of
Lipoprotein Metabolism Under Hemodialysis


