Effect of Nandrolone Decanoate on the Lipid Profile of Male Peritoneal Dialysis Patients

Atherosclerotic cardiovascular disease is the leading cause of mortality in patients undergoing renal replacement therapy (1,2). Among other risk factors, lipid abnormalities are considered critical for the accelerated atherogenesis in these patients (2–4). A profile of dyslipidemia in continuous ambulatory peritoneal dialysis (CAPD) patients includes near normal or moderately elevated total cholesterol and low-density lipoprotein cholesterol (LDL-C), reduced high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A (ApoA), and often markedly elevated very low-density lipoprotein cholesterol, apolipoprotein B (ApoB), and triglycerides (5,6). In addition to these alterations, an elevated serum lipoprotein (a) [Lp(a)] concentration, a strong independent risk factor for atherosclerotic cardiovascular disease, has also been reported in dialysis populations (7–10).

Anemia is a universal complication of renal disease. Nowadays, recombinant human erythropoietin (rHuEPO) is the standard therapy for the treatment of this disturbance. However, diverse studies in hemodialysis have showed that androgens may be a valid alternative to rHuEPO, especially in elderly patients (11). An excellent response to anemia after nandrolone decanoate (ND) administration has also been reported in CAPD patients, although the evolution of lipids was not evaluated (12). Since androgens may have potentially harmful effects on the lipid profile (13), the aim of this study was to investigate the impact of androgens on the evolution of lipid parameters in CAPD patients receiving ND as therapy for anemia.

METHODS

Thirteen male patients aged above 50 years, on maintenance chronic CAPD, received androgens as therapy for anemia, and were included in this prospective study. All patients were over 50 years because improvement in hematologic parameters shows maximal response in this age group (14). Informed consent was obtained in all cases. The mean age of the patients was 62 ± 9 years (range 51 – 78 years), and the mean time on dialysis was 17 ± 7 months (range 10 – 36 months). The etiology of renal failure was diabetic nephropathy in 7 patients, nephroangiosclerosis in 3, glomerulonephritis in 2, and unknown in 1. All patients were treated with a cycle of ND for 6 months (200 mg per week, intramuscularly). No patient experienced any significant concurrent illness, such as systemic infection, peritonitis, or blood losses, during the study period. Oral iron supplements (ferrous sulfate, 105 mg elemental iron per day) were administered to all patients in order to maintain normal body iron stores (serum ferritin above 100 ng/mL and transferrin saturation higher than 20%). During the study, the CAPD procedure for each patient was not altered and no major alterations to drug regimens were made. No patient received lipid-lowering agents.

Hematologic parameters (hemoglobin and hematocrit levels) were measured monthly. Lipid profile was determined at the start of the study (baseline) and after 6 months of androgen therapy. Blood samples were drawn after an overnight fast of 12 hours. Serum was separated and stored at 4°C for analysis of total cholesterol, LDL-C, HDL-C, triglycerides, ApoA, and ApoB. Total cholesterol, HDL-C, and triglycerides were measured enzymatically (Menarini Diagnostics, Firenze, Italy). LDL-C was calculated with the Friedewald formula. ApoA and ApoB were quantified by kinetic immunonephelometry (Beckman, Palo Alto, California, U.S.A.). Serum for Lp(a) was stored at –70°C. Lipoprotein (a) was assessed by enzyme-linked immunoassay (Biopool AB, Umeå, Sweden).

All data, except Lp(a) levels, are expressed as mean ± standard deviation. Differences in the evolution of parameters were analyzed by Student's t-test or analysis of variance and multiple range analysis (Scheffe's test) when appropriate. Serum Lp(a) concentrations are expressed as median and range, and the Friedman test for repeated measures was used for comparisons. Differences in Lp(a) between groups were assessed by the Mann–Whitney U test. A p value of less than 0.05 was considered statistically significant.

RESULTS

After 6 months of treatment, androgen administration was followed by a significant increase in hemoglobin concentration and hematocrit with respect to baseline values: from 9.2 ± 2.1 g/dL and 27.9% ± 6%, to 11.8 ± 1.9 g/dL and 35.1% ± 5.1%, respectively ($p < 0.001$). This increase in the hematologic parameters reached statistical significance after the first month of therapy.

Serum lipid changes after the 6 months of ND administration in the whole group of 13 patients are depicted in Table 1. There were no significant variations in serum levels of total cholesterol, LDL-C, or ApoA-I. However, a significant decrease in HDL-C and an increase in triglycerides and ApoB levels were evident. Serum concentration of Lp(a) decreased from 43 (range 19 – 84) to 22 mg/dL (range 6 – 60) ($p < 0.001$). This decrement represents a mean percent reduction of 41% with respect to baseline. The decrease in Lp(a) levels was observed in 10 of the 13 patients (77%). The prevalence of patients with Lp(a) levels above 30 mg/dL was significantly higher at baseline compared to post androgen administration (77% vs 23%).

No correlations were found between the changes in serum lipids and the increase in the hematologic parameters. Additionally, there were no differences in the lipid profile between the groups of patients classified by pri-

mary renal disease (diabetics vs nondiabetics), at both baseline and the end of the study (Table 2). Endogenous creatinine clearance and Kt/V did not undergo significant modifications during the study: basal, 2.39 ± 0.92 mL/min and 2.03 ± 0.18; 6th month, 2.21 ± 1.10 mL/min and 2.13 ± 0.20, respectively.

Liver biochemistry profile and serum levels of prostate-specific antigen (PSA) were also evaluated. There were no elevations in bilirubin and/or hepatic enzymes during androgen therapy. Likewise, serum concentrations of PSA did not change significantly.

DISCUSSION

One of the most important clinical problems in patients receiving renal replacement therapy is the high incidence of cardiovascular disease, which has become the leading cause of mortality in patients with chronic renal failure (1,2). Lipid abnormalities, especially disturbances in lipoprotein metabolism, are a major cause of accelerated atherosclerosis in this population. Patients on CAPD have a more atherogenic lipoprotein profile, including significantly higher Lp(a) levels, than have hemodialysis patients and healthy persons (7). Moreover, Lp(a) has been clearly identified as a further independent risk factor for atherosclerotic cardiovascular disease (7–10).

Erythropoietin is now the standard treatment for the anemia of renal disease. However, rHuEPO has several limitations, related mainly to side effects, high cost, and availability (13). The main adverse effect is the development or aggravation of hypertension, with an incidence ranging between 20% and 30%. With respect to cost, it has been estimated that, for every 10 000 hemodialysis patients treated with rHuEPO, net Medicare expenditures will be US$118,370,000 higher than if androgens are used. Data clearly show that, in several countries, the availability of rHuEPO is very limited or even impossible to obtain. These are evident reasons to take into account the potential use of alternative treatments, such as androgens, for the anemia of renal disease.

Androgens have been showed to be a useful therapy for anemia in dialysis patients. Teruel *et al.* (11) have reported that the evolution of hematologic parameters after androgen administration is similar to that observed with rHuEPO therapy. In a recent study, we also found an excellent response to anemia after ND in CAPD patients (12). However, adverse changes in the lipid profile have been considered a classic side effect of androgens (13). Since data on the potential harmful effect of these agents on lipid parameters in PD patients are scarce, we examined in this prospective study the impact of ND administration on the lipid profile of patients on maintenance CAPD.

Nandrolone decanoate, a 19-nortestosterone derivate, does not produce significant alterations of lipids in subjects with normal renal function (15). In hemodialysis

TABLE 1
Lipid Profile After Nandrolone Decanoate Administration in 13 CAPD Patients

Parameter	Baseline	6th month	*p* Value
Total cholesterol (mg/dL)	222±48	218±34	NS
LDL-C (mg/dL)	141±47	143±49	NS
HDL-C (mg/dL)	41±12	33±9	<0.05
Triglycerides (mg/dL)	160±58	214±49	<0.01
ApoA-I (mg/dL)	118±28	106±35	NS
ApoB (mg/dL)	119±39	133±32	<0.05
Lipoprotein (a) (mg/dL)	43 (19–84)	22 (6–60)	<0.001

LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; ApoA-I = apolipoprotein A-I; ApoB = apolipoprotein B; NS = not significant.
All variables are expressed as mean ± standard deviation, except lipoprotein (a), which is expressed as median and range.

TABLE 2
Lipid Profile in CAPD Patients With and Without Diabetes Mellitus, at Baseline and After 6 Months of Nandrolone Decanoate Administration

Parameters	Diabetes mellitus (*n*=7) Baseline	6th month	*p* Value	No diabetes mellitus (*n*=6) Baseline	6th month	*p* Value
Total cholesterol (mg/dL)	228±42	223±31	NS	215±58	212±40	NS
LDL-C (mg/dL)	144±28	146±56	NS	137±66	138±44	NS
HDL-C (mg/dL)	39±11	31±9	<0.05	42±13	35±10	<0.05
Triglycerides (mg/dL)	172±52	212±48	<0.01	145±67	217±54	<0.01
ApoA-I (mg/dL)	129±28	113±37	NS	106±26	98±34	NS
ApoB (mg/dL)	103±33	119±22	<0.05	136±41	149±36	<0.05
Lipoprotein (a) (mg/dL)	40 (19–84)	22 (14–58)	<0.001	40 (19–84)	20 (6–60)	<0.01

LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; ApoA-I = apolipoprotein A-I; ApoB = apolipoprotein B; NS = not significant.
All variables are expressed as mean ± standard deviation, except lipoprotein (a), which is expressed as median and range.

patients (16), administration of ND has been associated with an increase in ApoB levels and decrease in both HDL-C, due exclusively to a decline of HDL_2, and Lp(a). A reduction in ApoA-I, as well as an increment in triglycerides, was also detected. The results of the present study of CAPD patients show a negative effect of ND on HDL-C and triglycerides, whereas serum total cholesterol and LDL-C levels did not change significantly. Serum Lp(a) concentration decreased after ND therapy, with a mean reduction of 41% with respect to baseline.

The mechanism by which ND reduces serum Lp(a) is not known. However, since LDL-C levels did not change significantly in our study, the effect of ND on Lp(a) is suggested to be independent of changes in LDL metabolism. Recently, Fourtounas *et al.* (17) hypothesized that Lp(a) concentration might be influenced by iron stores, suggesting androgens do not have any direct effect on Lp(a) but that they act through lowering iron stores. All patients in our study received iron supplements (ferrous sulfate, 105 mg elemental iron per day) during ND administration in order to maintain adequate body iron stores. Thus, serum ferritin concentrations at the end of the study did not show significant variations with respect to basal values (217 ± 92 vs 184 ± 89 mg/L, respectively). Furthermore, the changes in serum lipids, including Lp(a), did not correlate with the improvement in hematologic parameters.

CONCLUSION

Our data for CAPD patients are in agreement with those previously reported on the improvement of hematologic parameters after androgen therapy in hemodialysis patients. Nandrolone may be considered a valid alternative to rHuEPO as therapy for anemia in selected patients on CAPD. Administration of ND has neutral effects on total cholesterol, LDL-C, and ApoA-I. A negative effect was observed on the serum levels of triglycerides and HDL-C, although, based on our previous studies, this adverse effect is transient. Further studies are necessary to investigate the optimal dose of ND, that is, the minimal dose effective to improve hematologic status associated with no significant adverse effects. Finally, serum Lp(a) concentration decreased significantly, with a mean reduction of 41% with respect to baseline. Clarification of the mechanism by which androgens reduce Lp(a) levels may help to determine future therapies to reduce the concentration of this lipoprotein, an independent risk factor for cardiovascular disease in the dialysis population.

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