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Adrenocorticotrophic hormone lowers serum Lp(a) and LDL cholesterol concentrations in hemodialysis patients

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Adrenocorticotrophic hormone lowers serum Lp(a) and LDL cholesterol concentrations in hemodialysis patients. Previously, we have shown that short-term administration of adrenocorticotrophic hormone (ACTH) results in reduced concentrations of apolipoprotein B-containing lipoproteins, including lipoprotein(a), and reduced activities of hepatic lipase. These effects were observed in steroid-treated patients suffering from iatrogenic ACTH deficiency and in healthy individuals. The direct nature of the influence of ACTH on hepatic lipoprotein metabolism was confirmed by *in vitro* experiments. The aim of the present investigation was to study the effects of ACTH treatment on uremic patients, who exhibit disturbed lipoprotein pattern due to the slow removal of triglyceride-rich lipoproteins and who probably are ACTH resistant. Eight patients on chronic hemodialysis were studied. After one intramuscular injection of Synacthen Depot (a synthetic $ACTH_{1-24}$ preparation from Ciba Geigy AG, Basel, Switzerland) 1 mg, the only change noted was a significant reduction of 26% in median lipoprotein(a) concentration. After five injections, a further decrease (65%) was found in the lipoprotein(a) concentration. Also, reductions in median concentrations of total cholesterol, low density lipoprotein cholesterol and apolipoprotein B were observed. The magnitude of these changes was 15 to 30%. In contrast to previously studied groups, no changes were observed regarding triglyceride metabolism. Significantly increased median concentration of apolipoprotein CIII was found. However, the excess apolipoprotein CIII was confined to the fraction that was not associated with apolipoprotein B. Thus, administration of ACTH to uremic patients improved their atherogenic lipoprotein profile, a fact that may have future therapeutic implications. In comparison to previously studied groups, the uremic patients responded rather slowly and not at all regarding triglyceride metabolism.

The lipoprotein pattern of uremia is well known [1, 2]. The main features include moderate hypertriglyceridemia, low high density lipoprotein (HDL) cholesterol concentration, and accumulation of remnant particles [3]. In general, the apolipoprotein composition agrees with the lipid profile [4]. This lipoprotein pattern is in accordance with delayed catabolism of triglyceride-rich lipoproteins [5], probably caused by reduced activity of lipoprotein lipase (LPL) in combination with disturbed enzyme substrate and possibly receptor ligand functions of the lipoproteins [5–7]. However, although the general outlines of the pathogenetic process seem clear, there is still a lot to be learned. In spite of the atherogenic features observed in a population at greatly increased risk of death in the complications of atherosclerosis [8], there is as yet no consensus on an appropriate lipid-lowering treatment.

It has recently been shown that, in addition to the classical dyslipoproteinemic features, lipoprotein(a) [Lp(a)] concentration is increased in hemodialysis patients who manifest high molecular weight isotypes of apolipoprotein(a) [9]. The mechanism behind this phenomenon is not known. Increased concentration of lipoprotein(a) is a well established, independent risk factor for the development of atherosclerosis [10], but to date there is no safe and effective treatment, neither in uremia nor in general.

Recently, we reported a lipid-lowering effect of short-term adrenocorticotrophic hormone (ACTH) treatment in healthy individuals [11] as well as in steroid-treated patients [12]. In both groups, total cholesterol and triglyceride concentrations fell markedly, suggesting an enhanced uptake of apolipoprotein B-containing lipoproteins via the low density lipoprotein (LDL) receptor. Moreover, HL activity was decreased after ACTH treatment, a finding that could explain the observed increase in HDL_2 cholesterol concentration. The hypothesis that ACTH exerts direct effects on hepatic lipoprotein metabolism was supported by *in vitro* experiments with HepG2 cells (a human hepatoma cell line) [11] (Berg et al, unpublished observations). The administration of ACTH also resulted in a decrease in Lp(a) concentration [11, 12]. However, Lp(a) concentration responded similarly to dexamethasone treatment, indicating that this otherwise unexplained effect is at least partly steroid-mediated [11]. The increase in LPL activity after ACTH treatment, observed only in the steroid-treated group of patients [12], suggested the involvement of extrahepatic tissues. The aim of the present study was to find out whether ACTH exerts its lipid-lowering effect also on uremic patients, in spite of their complicated disturbances of lipoprotein metabolism and possible ACTH resistance [13, 14]. This was done with future treatment possibilities in mind as well as the hope of gaining additional insights into this recently recognized effect of ACTH and into the uremic dyslipoproteinemia.

Key words: uremia, lipoprotein, hypertriglyceridemia, acrenocorticotrophic hormone, triglycerides, hemodialysis.

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Table 1. Serum lipid, lipoprotein and apolipoprotein concentrations as well as postheparin plasma lipase activities in hemodialysis patients

	Day 1	Day 3	Day 8	Day 22
Serum total cholesterol *mmol/liter*	5.34 (4.04–7.89)	5.31 (4.07–7.25)	4.66 (3.66–6.88)[a]	5.24 (4.07–7.36)
Serum HDL cholesterol *mmol/liter*	0.65 (0.56–1.65)	0.72 (0.56–1.54)	0.70 (0.52–1.54)	0.69 (0.56–1.50)
Serum LDL cholesterol *mmol/liter*	3.67 (2.60–5.89)	3.70 (2.34–5.44)	2.55 (2.02–5.01)[a]	3.70 (2.63–5.55)
LDL/HDL	5.3 (3.1–6.8)	4.9 (3.5–6.4)	3.4 (2.9–6.3)[a]	5.0 (3.6–8.1)
Serum triglycerides *mmol/liter*	1.71 (0.78–4.20)	1.69 (0.61–3.24)	2.10 (0.73–5.43)	1.53 (0.69–2.89)
Serum apo AI *g/liter*	1.06 (0.96–1.51)	1.07 (0.96–1.52)	1.11 (0.94–1.47)	1.06 (1.00–1.49)
Serum apo B *g/liter*	1.14 (0.94–1.37)	1.10 (0.92–1.31)	0.93 (0.73–1.20)[a]	1.15 (0.88–1.63)
Serum apo B-associated apo CIII *mg/liter*	20 (7–26)	15 (3–24)	22 (10–27)	14 (7–39)
Serum nonapo B-associated apo CIII *mg/liter*	31 (18–85)	31 (19–84)	48 (23–120)[a]	25 (13–84)
Serum apo B-associated apo E *mg/liter*	15 (11–20)	12 (4–30)	17 (9–120)	16 (9–60)
Serum nonapo B-associated apo E *mg/liter*	35 (15–220)	39 (26–230)	38 (17–300)	37 (19–300)
Serum lipoprotein(a) *mg/liter*	167 (82–703)	122 (52–626)[a]	41 (16–399)[a]	187 (72–826)
Plasma lipoprotein lipase *mU/ml*	38 (17–87)	47 (28–105)	34 (13–71)	40 (18–79)
Plasma hepatic lipase *mU/ml*	147 (57–427)	117 (54–444)	117 (52–342)	136 (64–278)

Day 1, baseline; day 3, after one injection of $ACTH_{1-24}$ 1 mg i.m.; day 8, after five injections of $ACTH_{1-24}$ 1 mg i.m.; day 22, sixteen days after the last injection of $ACTH_{1-24}$. Data are expressed as median (range).

Apo is apolipoprotein.

[a] $P < 0.05$ as compared to day 1

METHODS

Patients

Patients in this study were recruited from the Dialysis Department, National University Hospital, Reykjavik, Iceland. Eight patients on chronic hemodialysis were included in the study; these four males and four females had a median age of 69 years (range 50 to 75 years). The cause of renal failure was chronic glomerulonephritis ($N = 2$), chronic interstitial nephritis ($N = 2$), polycystic kidney disease ($N = 2$), and nephrosclerosis ($N = 2$). Patients with liver disease or endocrine disorders other than those accompanying renal failure, and patients treated with steroids or lipid-lowering drugs were excluded. All were treated with polysulfone dialyzers and bicarbonate dialysate, four to five hours three times a week. In seven patients, dialysis-associated anticoagulation was achieved by unfractionated heparin. One warfarin-treated patient managed without additional anticoagulation. The median duration of dialysis was 18 months (range 4 to 108 months).

As shown by the median baseline values in Table 1, the patients represented the lipoprotein pattern usually observed in uremia. Their serum triglyceride concentration was slightly increased, ranging from normal to moderately increased. Due to a low HDL cholesterol concentration, the LDL cholesterol/HDL cholesterol ratio was unfavorable.

Procedures

The following protocol, outlined in Figure 1, was carried out after the consent of the local ethics committee:

Day 1. At baseline, blood samples (see below) were collected before a hemodialysis session that was performed in the morning. Directly after the treatment, Synacthen Depot, a synthetic N-terminal fragment (1-24) of ACTH (Ciba-Geigy, Basel, Switzerland) was injected intramuscularly at a dose of 1 mg.

Day 3. The same procedure was repeated.

Days 4, 5 and 6. Synacthen Depot 1 mg was injected intramuscularly, always at noon.

Day 8. Blood samples were collected before dialysis.

Day 22. Blood samples were collected before dialysis.

Thus, the blood samples, intended for estimation of treatment effect (days 3 and 8), on both occasions were collected two days after the latest injection. On days 1, 8 and 22, midweek dialysis sessions were performed.

Blood samples

Blood samples were collected after a 12 hour fast for analysis of serum concentrations of total cholesterol, HDL cholesterol, triglycerides, apolipoprotein (apo) AI, apo B, total and nonapo B-associated apos CIII and E, Lp(a), cortisol, and at baseline, plasma concentration of ACTH. Then heparin (Lövens, Ballerup, Denmark) was injected at a of dose of 50 IU/kg body wt. After exactly 15 minutes, a sample was collected in a chilled EDTA-containing test tube for analysis of plasma activities of LPL and hepatic lipase (HL). This sample was placed directly on ice and centrifuged within an hour. All samples were stored frozen at −70°C for analysis in one series.

Analyses

Total cholesterol and triglyceride concentrations were analyzed with enzymatic methods (Boehringer-Mannheim, Mannheim, Germany). HDL cholesterol concentrations were analyzed after precipitation of LDL and very low density lipoprotein (VLDL) cholesterol with dextran sulphate and magnesium chloride. LDL cholesterol concentrations were calculated by the Friedewald formula in seven patients, manifesting serum triglyceride concentrations below 4.0 mmol/liter [15].

Lp(a) concentrations were measured with a radioimmunoassay (Mercodia, Uppsala, Sweden) and apo AI as well as apo B concentrations were measured with immunoturbidimetry with reagents from Roche (Basel, Switzerland). Apo CIII and apo E concentrations, both total and those not associated with apo B, were analyzed with electroimmunodiffusion at Institut Pasteur (Lille, France) [16]. Concentrations of the apo B-associated apos CIII and E were obtained by subtracting those not associated with apo B from the total concentrations. Intra-assay variation of Lp(a) and apolipoprotein analyses was < 3%.

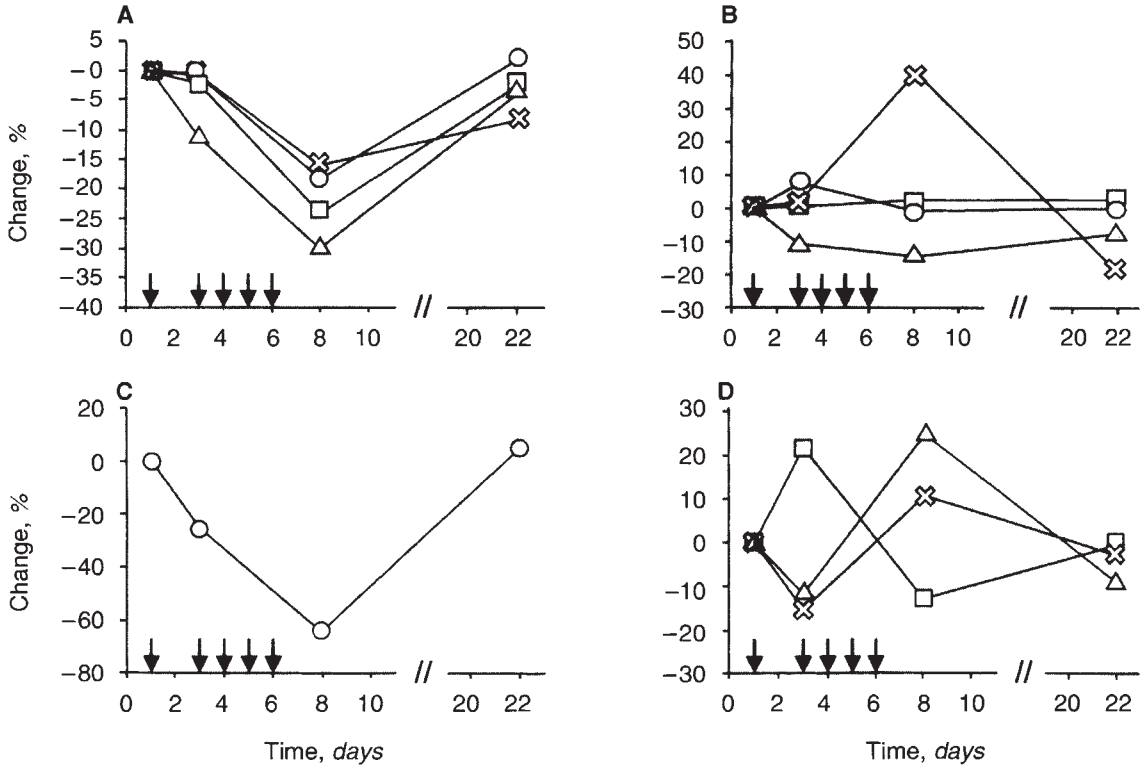

Fig. 1. Percentage changes in study variables on days 3, 8 and 22 as compared to baseline. Arrows indicate injections of $ACTH_{1-24}$ 1 mg i.m. Abbreviations are: Apo B, apolipoprotein B; apo AI; apolipoprotein AI; apo CIII-B, apolipoprotein CIII associated with apolipoprotein B; apo CIII-nonB, apolipoprotein CIII not associated with apolipoprotein B; chol, cholesterol; HDL, high density lipoprotein; HL, hepatic lipase; LDL, low density lipoprotein; LPL, lipoprotein lipase; Lp(a), lipoprotein(a); TG, triglycerides. Symbols in A are: (○) apo B; (□) LDL chol; (△) LDL/HDL; (⊠) chol. Symbols in B are: (□) apo AI; (○) HDL chol; (△) HL; (⊠) apo CIII-nonB. Symbol in C is: (○) Lp(a). Symbols in D are: (□) LPL; (⊠) apo CIII-B; (△) TG.

ACTH concentrations were measured with an immunoradiometric assay (Eurodiagnostics BV, Milab, Malmö, Sweden). This assay does not detect $ACTH_{1-24}$, which is why plasma ACTH concentrations were analyzed only at baseline. Cortisol concentrations were measured by a radioimmunoassay with reagents from Farmos Diagnostica (Turkku, Finland).

Lipase activities were analyzed with direct and selective methods using sonicated [^{3}H]-trioleoylglycerol emulsions, stabilized by phosphatidyl choline, as substrates [17]. As LPL, but not HL, rapidly hydrolyzes a substrate emulsion to which albumin has been added after sonication, specific measurements were achieved at pH 8.0, 0.15 M NaCl, and in the presence of serum. HL activities were selectively determined, using a substrate sonicated in the presence of albumin by assay at pH 9.0 and 0.5 M NaCl.

Statistical methods

Differences in the variance of study variables between test occasions were assessed by the Friedman test. In case of a significant Friedman test, the differences between the variable at baseline and at the other test occasions were estimated by the Wilcoxon rank sum test. Correlations between variables were assessed by the Spearman rank correlation test. Data are expressed as median (range).

RESULTS

All study participants were clinically stable during the study period and no adverse effects were observed. The results are shown in Table 1 and Figure 1. A decrease in serum Lp(a) concentrations was the only significant change observed after one injection of Synacthen. However, after five injections, a further decrease, amounting to 65%, had occurred in the median serum Lp(a) concentration and the median serum concentrations of total cholesterol, LDL cholesterol and apo B as well as the LDL cholesterol/HDL cholesterol ratio were significantly decreased by 15 to 30%. Median serum concentrations of total and nonapo B-associated apo CIII were also significantly increased but not that of apo B-associated apo CIII. All these variables returned to near baseline levels sixteen days after the last injection. There were no significant changes in serum concentrations of triglycerides, HDL cholesterol, apo AI and apo E. The same applied to post-heparin plasma lipase activities.

The relationships between variables agreed with the literature. There was a significant direct correlation between serum concentrations of apo B and those of total cholesterol ($r = 0.92$, $P < 0.0001$) and LDL cholesterol ($r = 0.84$, $P < 0.0001$). Serum concentrations of Lp(a) correlated significantly with those of total cholesterol ($r = 0.31$, $P < 0.05$), LDL cholesterol ($r = 0.37$, $P <$

0.05) and apo B ($r = 0.44$, $P < 0.05$), but not with those of triglycerides. There were significant correlations between serum triglyceride concentrations and serum concentrations of HDL cholesterol ($r = -0.56$, $P < 0.01$), apo AI ($r = -0.34$, $P < 0.05$) and apo B-associated apo CIII ($r = 0.81$, $P < 0.0001$) as well as post-heparin plasma activities of LPL ($r = -0.73$, $P < 0.0001$) and HL ($r = 0.37$, $P < 0.05$). Serum concentrations of HDL cholesterol correlated significantly with those of apo AI ($r = 0.90$, $P < 0.0001$), nonapo B-associated apo CIII ($r = 0.49$, $P < 0.01$) and nonapo B-associated apo E ($r = 0.41$, $P < 0.05$), as well as post-heparin plasma activities of LPL ($r = 0.40$, $P < 0.5$) and HL ($r = -0.38$, $P < 0.05$). The relationships between the data of each test occasion were analyzed separately, with results consistent with those above.

There were significant direct correlations between the relative changes in serum concentrations of total apo CIII and total cholesterol ($r = 0.91$, $P < 0.05$) and LDL cholesterol ($r = 1.0$, $P < 0.05$). However, there were no significant correlations between the absolute changes in the same variables. The absolute changes in serum concentrations of Lp(a) correlated directly with baseline concentrations ($r = 0.92$, $P < 0.05$) whereas the relative changes did not. There were no significant correlations between baseline and absolute or relative changes in serum concentrations of total cholesterol, LDL cholesterol, apo B or total apo CIII.

At baseline, the median plasma ACTH concentration [18 pmol/liter (8 to 36 pmol/liter)] was roughly twice as high as the upper reference level. Plasma ACTH concentrations at baseline neither correlated with baseline levels nor with relative changes of any of the study variables. The median serum cortisol concentration was 747 nmol/liter (393 to 857 nmol/liter) at baseline, rising to 1453 nmol/liter (825 to 2000 nmol/liter) after one ACTH injection and 1321 nmol/liter (501 to 1896 nmol/liter) after five injections and again returning to baseline levels, 600 nmol/liter (393 to 1002 nmol/liter). Baseline serum cortisol concentrations were within the normal range. Serum cortisol concentrations did not correlate with other study variables.

DISCUSSION

The aim of the present study was to investigate the effect of short-term ACTH treatment on lipid metabolism in uremic patients. After five injections of ACTH, serum concentrations of total cholesterol, LDL cholesterol, apo B and Lp(a) decreased by 15 to 65%, a response similar to that previously found in healthy individuals and steroid-treated patients [11, 12]. In contrast to these groups, there was apparently no effect on triglyceride and HDL metabolism in the uremic patients, in spite of increased serum apo CIII concentrations.

It has generally been assumed that, apart from stimulating cholesterol uptake in the adrenal gland, ACTH exerts its effect on lipoprotein metabolism through corticosteroids. However, we have recently shown that administration of ACTH induces changes in the serum lipoprotein pattern that are partly different from those observed after steroid treatment [11]. In healthy individuals, short-term ACTH treatment resulted in a decrease in serum concentrations of LDL cholesterol, VLDL cholesterol, VLDL triglycerides as well as Lp(a), and an increase in serum HDL cholesterol concentrations [11]. These changes in serum concentrations of HDL cholesterol and Lp(a), also observed after short-term treatment with dexamethasone, were probably, at least partly, steroid-mediated. However, as the decrease in LDL and VLDL lipids could not be attributed to steroidal influence, the findings were assumed to represent a direct ACTH effect, most easily explained by an increased receptor-mediated uptake of apo B-containing lipoproteins. This hypothesis was supported by *in vitro* experiments showing that ACTH, added to the culture media of HepG2 cells, stimulated the LDL receptor activity [11]. The reduction in HL activity observed after administration of ACTH but not that of dexamethasone also seemed to be the result of a direct hepatic effect; the addition of ACTH to the culture media of HepG2 cells led to a reduced HL secretion (Berg et al, unpublished results). In long-term steroid-treated patients with iatrogenic ACTH deficiency, short-term ACTH treatment induced the same changes as in healthy individuals, except for a more marked reduction in serum triglyceride concentrations and an increase in the previously low LPL activities [12]. The lipid-lowering effect of ACTH has been shown to last for at least eight months (Berg et al, unpublished observations). The future implications of the above findings most obviously include treatment possibilities for steroid-induced hyperlipidemia and perhaps also for other types of hyperlipidemia. The more extended application of ACTH treatment depends on whether it will be possible to separate the hepatic effects from the adrenal actions, possibly residing in different peptide fragments.

The lipoprotein profile of uremic patients, characterized by hypertriglyceridemia, an elevated LDL/HDL ratio, and increased Lp(a) concentration, clearly constitutes a cardiovascular risk pattern. There is evidence that fibrates [18] as well as statins [19] have favorable effects on this lipoprotein pattern without an unreasonably high incidence of side effects. However, neither of these drug types influences Lp(a) concentration. The present study confirmed the lowering effect of ACTH on the LDL/HDL ratio and the even more marked lowering effect on serum Lp(a) concentration in patients on hemodialysis. However, the hypertriglyceridemia, which may add to the cardiovascular risk pattern in uremic patients, did not respond to ACTH. The Lp(a)-lowering effect, in particular, renders a possible future ACTH-derived medication an attractive treatment option for uremic patients.

No persistent or significant changes were noted regarding triglyceride metabolism, an observation that differs from previous studies. It is possible that the LPL-lowering mechanisms, specific for renal failure, were resistant to the influence of ACTH. The patients studied were on hemodialysis, receiving unfractionated heparin three times a week. Conceivably, the tissue depots of LPL, depleted by heparin [20], did not have the time for an ACTH-induced recovery during the present short-term experiment. It is also noteworthy that post-heparin plasma HL activities did not decrease significantly, in contrast to the HL response to ACTH in healthy controls and steroid-treated patients.

Apo CIII is synthesized by the liver. As a structural part of triglyceride-rich lipoproteins, its main function is believed to be the inhibition of premature hepatic uptake of these lipoproteins [21]. During the lipolytic process, the excess apo CIII is transported from the partially degraded triglyceride-rich lipoproteins to HDL. In fact, most of the circulating apo CIII is carried by HDL. However, slow removal of triglyceride-rich lipoproteins is accompanied by an increase in the apo CIII fraction that is associated with apo B. The present observation of significantly increased serum apo CIII concentrations, in spite of unchanged serum triglyceride concentrations, is of theoretical interest. This is probably caused by increased hepatic synthesis of apo CIII. If it

had been caused by the accumulation of triglyceride-rich lipoproteins, this should have been reflected by increased serum concentrations of triglycerides and apo B-associated apo CIII. It can be speculated that the excess of hepatic apo CIII was channeled towards the nascent HDL or, less likely, into the circulation. Confined to the nonapo B-associated fraction, the excess apo CIII did not seem to disturb triglyceride or HDL metabolism, such as by inhibiting LPL activity [22] or by preventing the uptake of partially metabolized triglyceride-rich particles [21]. It is also possible that the increased availability of apo CIII did indeed inhibit the removal of triglyceride-rich lipoproteins and thereby prevented the expected decrease in serum triglyceride concentration. The effect of ACTH on apo CIII concentration in healthy individuals is not documented. Further studies on the effects of ACTH on triglyceride metabolism in healthy as well as in uremic individuals are called for; possibly ACTH treatment can function as a model for studies on the effect of increased hepatic apo CIII synthesis.

In addition to the resistance of triglyceride metabolism, there was another difference between the uremic response to ACTH treatment as compared to previously studied groups. In the uremic patients, only serum concentrations of Lp(a) were significantly influenced after the first injection, indicating a more sluggish response or a need for a higher dose than in nonuremic individuals. This can probably be explained by a general but compensated resistance to the effects of ACTH in uremia, reflected by increased ACTH concentrations in combination with normal diurnal variation in cortisol concentrations [13, 14]. The high plasma ACTH concentrations found in our patients at baseline support this concept.

From previous studies, we learned that the lipoprotein metabolism of individuals who were either normal or deficient regarding ACTH responded rapidly to short-term ACTH treatment. The present study results demonstrate that ACTH resistant patients also respond, though comparatively slowly. The uremic patients exhibited significant decreases in serum Lp(a) concentrations and LDL cholesterol/HDL cholesterol ratios in response to short-term ACTH treatment, changes that improve their cardiovascular risk profile. Interestingly, serum triglyceride concentrations manifested no significant change.

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APPENDIX

Abbreviations are: Apo B, apolipoprotein B; apo AI; apolipoprotein AI; apo CIII-B, apolipoprotein CIII associated with apolipoprotein B; apo CIII-nonB, apolipoprotein CIII not associated with apolipoprotein B; HDL, high density lipoprotein; HL, hepatic lipase; LDL, low density lipoprotein; LPL, lipoprotein lipase; Lp(a), lipoprotein(a); TG, triglycerides.

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