A Clinical Feature of Hyperlipidemia in Patients with Central Diabetes Insipidus

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Abstract. In this study, we analyzed plasma lipid and lipoprotein levels before and after treatment with 1-desamino-8-D-arginine vasopressin (DDAVP) in subjects with partial and complete central diabetes insipidus (DI) in order to determine how a shortage and supplement of this hormone affect plasma lipid metabolism. The subjects consisted of 6 patients with partial and 6 with complete central DI. After treatment with DDAVP through nasal cavity, plasma total cholesterol (TC) level did not decrease either in complete or partial form. Plasma triglyceride (TG) levels decreased from 306±175 mg/dl to 198±91 (35% decrease, p=0.027) in complete form, while TG did not change significantly in partial form. A detailed investigation of plasma lipoprotein metabolism during treatment with DDAVP was carried out in 3 of the 6 subjects with complete form of DI. Lipoprotein lipase activity and mass in post-heparin plasma from those three subjects tended to increase after treatment with DDAVP, along with the complete disappearance of an unusual lipoprotein between low density lipoprotein (LDL) and very low density lipoprotein (VLDL) as analyzed by polyacrylamide gel electrophoresis.

These results suggest that the DDAVP treatment has a favorable effect on lipid and lipoprotein metabolism, especially triglyceride-rich lipoproteins, either directly or through modifying factors contributing to lipid metabolism.

Key words: Hyperlipidemia, Diabetes insipidus

VASOPRESSIN (AVP) is a peptide hormone synthesized mainly by the paraventricular nuclei and supraoptic nuclei and secreted by the posterior pituitary gland. One of its main functions is to stimulate the reabsorption of water in the distal tubules of the kidney, leading to filtration of a more concentrated urine. Patients with central diabetes insipidus (DI) are deficient in AVP so they excrete large amounts of urine and are continually thirsty because of this massive fluid loss.

Recently it was clarified that receptors for this hormone exist in various tissues other than the kidney such as smooth muscle cells, hepatocytes, adipocytes and cardiomyocytes [1-5], and that this hormone stimulates several metabolic processes, including glycogenolysis, gluconeogenesis, and fatty acid oxidation, and promotes lipolysis in rabbit and hamster suprarenal adipose tissues [6-8].

In this study, we studied patients with complete or partial form of central DI accompanied by hyperlipidemia. Hyperlipidemia, especially hypertriglyceridemia was found to be significantly improved by replacement therapy with nasal administration of DDAVP.

Patients and Methods

Subjects

Twelve patients (6 with complete, 6 with partial central DI) were involved in this study (Table 1 and
The mean plasma total cholesterol (TC) and triglyceride (TG) levels were significantly higher in subjects with complete than those with partial DI (Table 2), while TC levels did not differ significantly between partial and complete form.

Representative case

The representative case was a 54-year-old female with complete form of central DI who had marked polyuria and polydipsia when she was diagnosed. Clinical and laboratory findings confirmed the diagnosis of central DI (patient 1 in Table 1). She was 152 cm tall and weighed 52 kg (body mass index 22.5 kg/m²).

Diagnosis of DI

Patients constantly showing Uosm less than Posm during dehydration test were diagnosed as complete DI (Table 1).

| Table 1. Dehydration-pitressin test for subjects involved in this study |
|---|---|---|---|---|---|
| patient | sex | Posm* | U/P ratio** | % increase*** | AVP con.**** |
| Complete | 1 | F | 293 | 0.80 | 107 | 0.4 |
| | 2 | F | 300 | 0.66 | 151 | 1.1 |
| | 3 | M | 303 | 0.92 | 55 | 0.7 |
| | 4 | F | 293 | 0.77 | 83 | NA |
| | 5 | F | 298 | 0.89 | 98 | 0.5 |
| | 6 | F | 299 | 0.78 | 123 | 0.3 |
| Partial | 7 | F | 282 | 1.14 | 88 | 2.7 |
| | 8 | M | 288 | 2.10 | 22 | NA |
| | 9 | F | 295 | 1.42 | 35 | 2.9 |
| | 10 | F | 297 | 1.11 | 32 | NA |
| | 11 | M | 292 | 1.36 | 52 | 1.9 |
| | 12 | F | 289 | 1.23 | 38 | 1.5 |

* plasma osmolality after dehydration
** maximal ratio of urinary/plasma osmolality after dehydration
*** % increase in Uosm during administration of pitressin
**** normal range: 2.3–7.4 pg/ml
NA not available

The representative case corresponded to patient 1.

LPL and HL analysis and midband lipoprotein analysis were conducted for patients 1, 2 and 6.

| Table 2. Clinical profile in patients with central diabetes insipidus |
|---|---|---|---|---|---|---|
| | normal control | complete DI | partial DI | P (complete vs. normal) | P (complete vs. partial) |
| age (y) | 51 ± 4 | 51 ± 8 | 52 ± 12 | ns | ns |
| sex (M : F) | 12 : 10 | 1 : 5 | 2 : 4 | — | — |
| BMI (kg/m²) | 22.6 ± 1.8 | 23.8 ± 2.6 | 22.1 ± 3.8 | ns | ns |
| TC (mg/dl) | 179 ± 18 | 274 ± 82 | 204 ± 45 | 0.037 | ns |
| TG (mg/dl) | 93 ± 38 | 306 ± 175 | 134 ± 45 | 0.031 | 0.042 |

Values are shown as mean ± SD.
BMI, body mass index; TC, total cholesterol; TG, triglycerides
Assay of plasma lipid and lipoproteins

Blood samples were obtained for all subjects involved in this study early in the morning after 12-hour fast unless otherwise described. Plasma TC and TG levels were analyzed by enzymatic methods [9, 10].

Analysis of plasma lipoprotein profile

Disc polyacrylamide gel electrophoresis was performed with 3% polyacrylamide gel according to Narayan et al. [11].

Measurement of lipoprotein lipase (LPL) and hepatic lipase (HL) activities in post-heparin plasma (PHP)

Blood samples were collected from the patients after an overnight fast. An intravenous injection of heparin was given (30 U/kg body mass) and the post-heparin blood samples were obtained 15 min after the heparin injection. Total lipolytic activity was measured using Triton X-100-emulsified triolein

Fig. 1. Comparison of plasma lipids (TG in Fig. 1A or TC in Fig. 1B) before and after treatment with 1-desamino-8-D-arginine vasopressin (DDAVP).

○ denotes triglyceride
● denotes total cholesterol
Circles and bars are mean ± SD. Dark area in each panel shows the normal range for each value in Japanese population.
as previously reported [12]. LPL activity was calculated as the activity in the whole plasma inhibited by the 5D2 monoclonal antibody for LPL [13]. HL activity was calculated as the remaining activity in the presence of the 5D2 monoclonal antibody for LPL.

**Measurement of lipoprotein lipase mass in PHP**

LPL mass was determined by a sandwich enzyme immunoassay we previously reported [14].

**Assay of plasma AVP**

Plasma AVP levels were measured using the highly sensitive radioimmunoassay method employing a reversed-phase silica column by Sakurai et al. [15] after dehydration test.

**Statistical analysis**

Stat View-J 4.11 software was used for all statistical analysis. Statistical significance was accepted at P < 0.05. Mann-Whitney test was used to detect differences between the groups. Comparison within a given group was tested by the non-parametric Wilcoxon signed-ranks test.

**Results**

We investigated plasma lipid profiles of 6 partial and 6 complete diabetes insipidus patients (Table 1) before and after treatment with DDAVP. Fig. 1 shows the changes in plasma lipid levels in all patients with complete or partial DI after treatment with DDAVP. It is notable that the plasma TG levels decreased after treatment (306 ± 175 to 198 ± 91 mg/dl) (-35%) (p = 0.027) in the complete form, whereas these levels did not change significantly in partial form. To clarify the potential mechanism of the TG-lowering during the treatment of DI, we carried out a detailed investigation of lipid and lipoprotein metabolism in 3 out of 6 complete DI subjects. LPL mass and activity in post-heparin plasma before and after treatment were measured in these 3 complete DI subjects (Table 3). Both LPL mass and activity showed a tendency toward increase after treatment. We also analyzed plasma lipoprotein profile by polyacrylamide gel electrophoresis (PAGE) before and after treatment in the three subjects. Fig. 2 shows the result of this analysis for the representative case (patient 1 in Table 1). An unusual lipoprotein peak was detected between the VLDL and LDL peaks before treatment. This abnormal lipoprotein (indicated by arrow), presumably a 'midband' lipoprotein [16-19], completely disappeared after treatment with DDAVP, along with the remarkable decrease in plasma TG (Fig. 3). The disappearance of this lipoprotein was shown in 2 other patients with complete form of DI (patients 2 and 6 in Table 1) (data not shown).

**Discussion**

In the present study most patients with the complete form of DI had hypertriglyceridemia. Since DI

![Graph showing changes in plasma lipid levels before and after treatment](image)

| Table 3. Lipoprotein lipase and hepatic lipase before and after treatment |
|---------------------------------|-----------------|-----------------|-----------------|
|                                | before          | after           | p               |
| number of subjects             | 3               | 3               | 0.11            |
| LPL mass*                      | 170 ± 29        | 196 ± 11        | 0.11            |
| LPL activity**                 | 6.9 ± 1.3       | 8.2 ± 1.1       | 0.11            |
| HL activity**                  | 9.1 ± 1.1       | 9.6 ± 0.3       | 0.42            |

* shown in ng/ml
** shown in μmoles/ml/h

TC (mg/dl) 388 → 338 (-12.9 %)
TG (mg/dl) 323 → 158 (-51.1 %)
HDL-C (mg/dl) 59 → 56 (-5.1 %)
is a disease caused by a lack of vasopressin, we suspected the mechanism of hypertriglyceridemia in this disease was somehow related to the function of this hormone. Three kinds of AVP receptors have been identified, namely V1a [2], V1b [3] and V2 [4, 5]. V1a receptors, located in the liver, smooth muscle cells and kidney, mediate vasoconstrictor action. V1b receptors, located in the anterior pituitary gland, mediate AVP-induced increase in ACTH action. V2 receptors, located on the kidney, mediate the antidiuretic effect of AVP.

Several reports suggest that this hormone may contribute to lipolysis or TG metabolism [6, 8]. Palazzo et al. [6] reported that AVP promotes triacylglycerol mobilization and utilization in rabbit heart through the V1 receptor. Recently, Al-Barazanjii et al. [20] have reported that in vasopressin-replete rats, improved insulin sensitivity is associated with significant falls in plasma glucagon, triglycerides and total cholesterol. However, the effects of this hormone on the plasma lipid metabolism in human have yet to be clarified.

The fact that the plasma TG level remarkably decreased in most cases after treatment with DDAVP suggests that the function of this polypeptide is related to plasma TG-rich lipoprotein metabolism either directly or through other unknown factors. The mechanism of lowering plasma TG is considered to be either lowering production of TG-rich lipoproteins by the liver or increasing the hydrolysis by LPL of those lipoproteins in the plasma. In the present study, LPL mass and activity from postheparin plasma in 3 complete DI subjects tended to increase after nasal replacement with DDAVP, although not significantly so, suggesting that the TG-lowering may have been caused by the increase in lipolysis of TG-rich lipoproteins in complete DI subjects. Whether this tendency toward increase in LPL after the therapy is directly related to the function of DDAVP or through other metabolic factors remains to be seen.

Interestingly, the abnormal lipoprotein detected by PAGE analysis between VLDL and LDL, presumably 'midband lipoprotein' completely disappeared after the treatment with DDAVP, along with a marked decrease of plasma TG level (Fig. 2), which was observed in 2 other complete DI subjects. Since the 'midband' lipoprotein is believed to be closely related to the incidence of coronary artery disease [16-19], the change of lipoprotein profile caused by the treatment for DI is also a favorable one from the aspect of preventing atherosclerosis.
Taken together, we propose that treatment of DI with DDAVP causes a favorable change in the TG-rich lipoprotein metabolism, which apparently is not relevant to the function of this hormone.

References


