NOTE

Effect of Levothyroxine on Total Lipid Profiles as Assessed by Analytical Capillary Isotachophoresis in a Patient with Hypothyroidism

YOSHIHIRO KIYA, SHIN-ICHIRO MIURA, BO ZHANG, HIDENORI URATA* AND KIEJIRO SAKU

Department of Cardiology, Fukuoka University School of Medicine, Fukuoka 814-0180, Japan
*Department of Internal Medicine, Fukuoka University, Chikushi Hospital, Fukuoka 818-0067, Japan

Abstract. The patient was a 51-year-old Japanese female who had been diagnosed with hyperlipidemia. At the first medical examination, her serum levels of total cholesterol (TC) and triglyceride (TG) were 482 and 205 mg/dl, respectively. Since hyperlipidemia was not improved by pravastatin, atorvastatin or nicoestol, and since the levels of thyroid-stimulating hormone (TSH) and free T4 were 730 IU/ml and 0.3 ng/dl, respectively, the patient was diagnosed as secondary hyperlipidemia with hypothyroidism. A method for the charge isolation of lipoproteins using capillary isotachophoresis (cITP) is proposed as a clinical application because it allows us to quantitatively measure electronegative low-density lipoprotein cholesterol (LDL-C), a potent marker of coronary heart disease. After 5 months of treatment with levothyroxine, Serum TC and LDL-C levels drastically decreased without statin treatment and high-density lipoprotein cholesterol (HDL-C) increased. In the lipoprotein profiles as assessed by cITP after treatment with levothyroxin, all HDL-C subfractions were increased and fast-migrating LDL/electronegative LDL appeared to be greatly reduced after treatment, while the area under the non-modified LDL peak was increased. The cITP analysis was able to obtain more information about coronary risk factors and may be clinically useful for evaluating the effect of treatment with levothyroxine in patients with hypothyroidism and secondary hyperlipidemia.

Key words: Hyperlipidemia, Hypothyroidism, Lipid Profiles, Capillary Isotachophoresis

HYPOTHYROIDISM can cause secondary hyperlipidemia. The lipid profile usually exhibits an increase in plasma total and low-density lipoprotein cholesterol (TC and LDL-C) and triglycerides (TG). This profile is likely to increase the risk of coronary heart disease [1]. Effective treatment of the underlying thyroid disorder would be expected to lower cholesterol levels in most patients. Lipoproteins are usually isolated by density, particle size or electric charge, and the particle size of LDL is also associated with the electric charge [2]. Schmitz et al. [3] developed a method for the charge isolation of lipoproteins using capillary isotachophoresis (cITP), and its clinical application is being proposed because it allows us to quantitatively measure electronegative LDL, a potent marker of coronary heart disease [4]. We slightly modified the original method to achieve a better separation of each fraction, and examined the clinical relevance of this technique [5]. In the present case, we found that hyperlipidemia was improved by effective treatment of hypothyroidism, and that cITP was clinically useful for determining the indications for the treatment of hyperlipidemia.

Case Presentation

The patient was a 51-year-old Japanese female. Her clinical course is shown in Fig. 1. At the first medical examination, her serum levels of TC and TG were 482
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The patient was diagnosed with hyperlipidemia. Initially, although the patient was administered pravastatin at 5 mg/day for 30 days, hyperlipidemia did not improve. Although her medication was changed to atorvastatin at 10 mg/day for 1 year, there was still insufficient improvement, and her medication was changed to niceritrol at 750 mg/day for 3 months. Thus, hyperlipidemia did not improve with pravastatin, atorvastatin or niceritrol. At 1 year and 4 months from the diagnosis of hyperlipidemia, the levels of thyroid-stimulating hormone (TSH) and free T4 were 730 IU/ml and 0.3 ng/dl, respectively. Finally, the patient was diagnosed as secondary hyperlipidemia with hypothyroidism.

Analytical cITP of serum lipoprotein was performed on a Beckman P/ACE MDQ system (Beckman-Coulter Inc, Tokyo, Japan) according to the method of Bottcher et al. [6] with some modifications [5]. Briefly, a sample of serum was diluted with leading buffer, prestained with NBD C6-ceramide (Molecular Probes, Inc, OR, USA) for 5 minutes at room temperature, and mixed with a mixture containing leading buffer with hydroxypropylmethylcellulose, spacers and 5-carboxy-fluorescein. The sample was injected into a 30 cm-long capillary, and separation was performed at a constant voltage for 7 minutes. The separated zones were monitored with argon-laser-induced fluorescence detection. Each peak was identified and the peak area in relative fluorescence units was analyzed using 32 Karat Software version 5.0 (Beckman-Coulter Inc).

Fig. 2a shows serum lipoprotein profiles before the administration of levothyroxine. The serum levels of TC, TG, high-density lipoprotein cholesterol (HDL-C) and LDL-C were 418, 254, 59 and 279 mg/dl, respectively. Serum lipoprotein profiles using cITP were characterized by eight peaks: peak 1 was fast (f)-migrating HDL, peak 2 was intermediate (i)-migrating HDL, peak 3 was slow (s)-migrating HDL, peak 4 was chylomicrons and large very LDL (VLDL), peak 5 was small VLDL and intermediate density lipoprotein (IDL), peak 6 was fast (f)-migrating LDL and electronegative LDL, peak 7 was slow (s)-migrating (non-modified) LDL, and peak 8 was a small LDL peak.

The patient was treated with levothyroxine (50 µg/day) and the same dose was maintained for 1 year and 5 months after the diagnosis of hypothyroidism with hyperlipidemia. Serum TC and LDL-C levels drastically decreased to 210 and 101 mg/dl, respectively, without statin treatment, while HDL-C increased to 78 mg/dl. All of the lipoprotein profiles in the patient
after 1 year and 5 months of treatment with levothyroxine are shown in Fig. 2b. HDL subfractions (peaks 1–3) were increased. The chylomicrons and large VLDL, small VLDL/IDL, and fast migrating LDL/electronegative LDL appeared to be greatly reduced after treatment, while the area under the non-modified LDL peak was increased.

Discussion

Patients with hyperlipidemia are at high risk for coronary artery disease (CAD). With advancing age, which is a risk factor for CAD, the percentage of patients with hypothyroidism increases: 21% and 16% of females and males over 75 years of age, respectively [7]. Patients with hypothyroidism are at high risk for acute coronary syndrome (ACS) after adjusting for TC, blood pressure, smoking, and body mass index [8]. The fatality rate for ACS was decreased to 9–31% upon lipid-lowering treatment with levothyroxin [9]. In the comparison of 49 subclinical hypothyroidism (SHT) patients with 33 eutyroid controls, 24 patients who had been treated with levothyroxine showed a significant decrease in TC and LDL-C concentrations [10]. The results of levothyroxine treatment suggest that lipid infiltration of the arterial wall may represent a major mechanism underlying the increase in the intima-media thickness in SHT [11]. In addition, arterial wall stiffness tends to be increased in both overt and subclinical hypothyroid patients, and an appropriate thyroxine treatment could reverse the abnormalities and may reduce the cardiovascular risk [12]. Thus, it is very important that we analyze lipid profiles in detail to help for preventing ACS in patients with hypothyroidism.

The Adult Treatment Panel III of the National Cholesterol Education Program indicated the importance of prevention in subjects with multiple risk factors, and recommended the measurement of complete lipoprotein profiles, rather than screening for only total cholesterol and HDL [13]. Since cITP, which isolates lipoproteins based on electric charge, can be used to separate major LDL, it is a useful technique. In this case, modified LDL, such as chylomicrons, large VLDL, IDL, and small VLDL, were all greatly reduced by treatment with levothyroxin. The fast migrating LDL/electronegative LDL, in particular was greatly reduced. We also found that the area under the non-modified LDL peak increased. Previous studies have shown that electronegative LDL is the most atherogenic component [14] and is associated with insulin resistance [15] and carotid artery atherosclerosis [16] in humans. Therefore, lipid profile analysis with cITP may be clinically useful for evaluating the effect of treatment with levothyroxin for the prevention of ACS in patients with secondary hyperlipidemia and hypothyroidism.

References

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