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ORIGINAL ARTICLE

Alterations of plant sterols, lathosterol, oxidative stress and inflammatory markers after the combination therapy of ezetimibe and statin drugs in type 2 diabetic patients

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Summary The elevation of serum plant sterols in addition to serum LDL-cholesterol (LDL-C) is one of the important risk factors for coronary heart disease. We investigated how to alterations of serum hepatic synthesised cholesterol and plant sterols levels, clinical markers for inflammation and oxidative stress after combination therapy with ezetimibe, an inhibitor of cholesterol transporter in the small intestinal colon, and statin drugs in type 2 diabetic patients. Studies were conducted in 28 patients with type 2 diabetes mellitus complicated with dyslipidemia. Patients were divided into 3 groups as follows: the 1st group is 7 patients treated with 10 mg ezetimibe sequent on pretreatment with mild statin drug (MS + E group), and the 2nd group is 7 patients treated with 10 mg ezetimibe sequent on pretreatment with strong statin drug (SS + E group), and then the 3rd group is 14 patients treated with 10 mg ezetimibe alone without pretreatment with any statin drugs (naïve E group). In addition to various metabolic markers, serum plant sterols such as sitosterol and campesterol, and hepatic synthesised cholesterol such as lathosterol were measured by the gas liquid chromatography. Serum highly sensitive CRP (hsCRP) as an inflammation

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marker, and then malonyldealdehyde (MDA) and carbonyl-modified protein (CMP) as an oxidative stress were assayed by the conventional method, respectively. Fasting plasma glucose and serum glucosylated HbA1c (JDS value) did not show any significant changes after administration of ezetimibe in whole groups. Serum LDL-C was reduced significantly and serum triglyceride exhibited a tendency of reduction in whole groups. Serum sitosterol and campesterol were decreased significantly, while serum lathosterol was increased significantly or markedly in whole patients and also in each group. There were no significant changes in serum hsCRP in whole groups. Both serum MDA and CMP revealed significant or marked reductions in each group.
Conclusions: The present investigation suggests that the combination therapy of the ezetimibe and statin drugs is potential to remarkably reduce serum LDL-C, plant sterols, MDA and CMP, and therefore might lead to prevent atherosclerosis.

Introduction

It has been generally accepted that low density lipoprotein cholesterol (LDL-C) is one of the most powerful risk factors for coronary heart disease (CHD), while plant sterols could be an additional risk factor for CHD [1], ischaemic brain injury [2] and atherosclerotic plaque [3]. Furthermore, hyperglycemia derived from diabetes induces oxidative stress, which leads to atherosclerosis. The overaccumulation of triglyceride-rich lipoproteins (TRLs) seen in patients with type 2 diabetes is attributable to increased production rates of both intestinally derived apoB-48-containing lipoproteins and TRL apoB-100 of hepatic origin [4].

Baseline cholesterol absorption and synthesis were related to glucose, insulin values and insulin resistance syndrome [5]. Statin drugs as 3-hydroxy-3-methylglutaryl (HMG) coenzyme inhibitor is known to inhibit cholesterol synthesis in the liver, which include mild and strong statin drugs [6], and also large dose of statin drug increased fractional and mass absorption of cholesterol [7]. It is well recognised that statin drugs ameliorated atherosclerosis in diabetic patients in order to either improve serum lipid profiles or to show pleiotrophic effect [8]. While, the mechanism of the cholesterol absorption has been unknown in detail for a long time, however Niemann Pick C1 Like 1 (NPC1L1) was cloned as one of the chief mechanisms [9,10]. Furthermore, cholesterol absorption is mainly regulated by the jejunal and ileac adenosine triphosphate-binding cassette transporter G5 (ABCG5) and ABCG8 in mice [11]. In contrast to type 2 diabetes, the findings in type 1 diabetes could be related to low expression of ABCG5 and ABCG8 genes, resulting in high absorption of cholesterol and sterols in general and low synthesis of cholesterol [12].

Ezetimibe, a novel clinically applied drug, affects as a selective blocker of cholesterol absorption in the small intestinal colon through NPC1L1 as a molecular target [13], and also ezetimibe alone reduces postpranial hypertriglyceridemia by blocking both of cholesterol and the intracellular trafficking and metabolism of long-chain fatty acids in enterocytes [14]. Furthermore, ezetimibe could abolish the absorptions of plant sterols as a potential risk factor for coronary heart disease [15], atherosclerosis [16] and also leads to non-alcohol steatohepatitis (NASH) [17].

Therefore, we wondered whether continuously increasing serum plant sterols during long-term statin treatment should be prevented by cholesterol malabsorption including plant sterols or not. Now, we found a novel report that the combination therapy of statin drugs and ezetimibe could be a powerful tool for improving serum lipids profile and for leading to anti-atherosclerosis [18]. We investigated how to alterations of serum hepatic synthesised cholesterol and plant sterols levels, clinical markers for inflammation and oxidative stress after combination therapy with ezetimibe, an inhibitor of cholesterol transporter in the small intestinal colon, and statin drugs in type 2 diabetic patients.

Patients and methods

Studies were conducted in 28 patients with type 2 diabetes mellitus complicated with dyslipidemia. Type 2 diabetes mellitus was defined as either patients with already pretreated diabetes or