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Original Article

Novel findings in relation to multiple anti-atherosclerotic effects of XueZhiKang in humans

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Abstract

Background: Previous studies have clearly demonstrated that XueZhiKang (XZK), an extract of cholestin, can decrease low-density lipoprotein cholesterol (LDL-C) and cardiovascular events. However, the mechanism of the effects of XZK on atherosclerosis (AS) in humans has been reported less frequently. In the present study, we investigated the impact of XZK on lipoprotein subfractions, oxidized LDL (oxLDL), and interleukin-6 (IL-6).

Methods: From October 2015 to July 2016, 40 subjects were enrolled in this study. Of them, 20 subjects with dyslipidemia received XZK 1200 mg/day for 8 weeks (XZK group); 20 additional healthy subjects who did not receive therapy acted as controls. The plasma lipoprotein subfractions, oxLDL, and IL-6 were examined at baseline and again at 8 weeks.

Results: Data showed that XZK could significantly decrease not only plasma LDL-C levels (87.26 ± 24.45 *vs.* 123.34 ± 23.99, $P < 0.001$), total cholesterol (4.14 ± 0.87 *vs.* 5.08 ± 1.03, $P < 0.001$), triglycerides (0.95 ± 0.38 *vs.* 1.55 ± 0.61, $P < 0.05$), and apolipoprotein B (1.70 ± 0.35 *vs.* 1.81 ± 0.72, $P < 0.05$), but also oxLDL (36.36 ± 5.31 *vs.* 49.20 ± 15.01, $P < 0.05$) and IL-6 (8.50 ± 7.40 *vs.* 10.40 ± 9.49, $P < 0.05$). At the same time, XZK reduced the concentration of small LDL-C (1.78 ± 2.17 *vs.* 6.33 ± 7.78, $P < 0.05$) and the percentage of the small LDL subfraction (1.09 ± 1.12 *vs.* 3.07 ± 3.09, $P < 0.05$).

Conclusions: Treatment with 1200 mg/day XZK for 8 weeks significantly decreased the atherogenic small LDL subfraction and reduced oxidative stress and inflammatory markers, in addition to affecting the lipid profile, suggesting multiple beneficial effects in coronary artery disease.

Keywords: XueZhiKang; Hyperlipidemia; Low-density lipoprotein cholesterol subfraction; Oxidized LDL; Interleukin-6

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Introduction

Atherosclerotic cardiovascular disease (ASCVD) is a well-known life-threatening multi-factorial disease that has become the primary cause of morbidity and mortality worldwide, including in China.[1] Previous

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studies have confirmed that dyslipidemia, especially increased low-density lipoprotein (LDL) cholesterol (LDL-C) levels, is the most important risk factor for ASCVD, including coronary artery disease (CAD).[2,3] ASCVD is a well-known inflammatory disease that is also related to oxidative stress.[4] Previous data have shown that inflammation is an important feature of atherosclerotic lesions.[5,6] Increased levels of inflammatory markers have been documented in various settings of coronary artery disease.[7,8] Moreover, oxidized LDL (oxLDL) as an oxidized stress biomarker plays a critical role in atherogenesis.[9,10] Ox-LDL can induce endothelial cell apoptosis and reduce antioxidant capabilities through changes in the secretary activities of the endothelium.[11] Hence, the mechanism, which can modify multiple atherosclerotic pathways, may be important for clinical practice.

In fact, LDL and high-density lipoprotein (HDL) both consist of a heterogeneous group of particles differing not only in size and density, but also in chemical composition and physiological function.[12−14] Recent studies have suggested that lipoprotein subfractions or particles may be more promising markers for the prediction of future cardiovascular events (CVE). Our previous observations indicated that the changes in lipoprotein subfractions are associated with inflammatory markers, diabetes, hypertension, and clinical outcomes, suggesting that a drug that can modify the lipoprotein subfractions may be more promising for the prevention and treatment of ASCVD.

XueZhiKang (XZK) is an extract of cholestin, which contains a combination of plant sterols, isoflavones, and lovastatin; each 1200 mg XZK capsule contains approximately 10 mg lovastatin. It has shown lipid-lowering effects comparable to those induced by statins.[15,16] Previous studies have demonstrated that XZK is safe and effective for the prevention and treatment of coronary heart disease in elderly patients.[17,18] However, no data are currently available concerning the impact of XZK on multiple anti-atherosclerotic pathways. The aim of the present study was to investigate the potential effects of XZK on lipoprotein subfractions in humans as a novel lipid marker, on oxLDL as an oxidative stress parameter, and on interleukin-6 (IL-6) as a pro-inflammatory factor.

Methods

Study design and population

The study protocol was reviewed and approved by the Ethics Committee of Fu Wai Hospital and Cardiovascular Institute, Beijing, China, and informed consent was obtained from all patients. This prospective study was conducted from October 2015 to July 2016. The XZK group of 20 patients with dyslipidemia received XZK 1200 mg/day for 8 weeks; 20 healthy subjects who had not received any drug treatment previously were enrolled as the control group. Serum lipid profiles and HDL and LDL subfractions were measured at baseline and again after 8 weeks of treatment.

The inclusion criteria of the present study were as follows: (1) patients with dyslipidemia (fasting total cholesterol (TC) $\geq$ 5.18 mmol/L and/or triglyceride (TG) $\geq$ 1.70 mmol/L), without diagnostic imaging evidence of atherosclerotic lesions detected by arterial ultrasound, coronary chest tomography, or coronary angiography; (2) no history of treatment with statins or other drugs known to affect blood lipids within the previous 4 weeks; and (3) aged 18−70 years. Patients with previous acute coronary syndrome within 1 month, serious heart failure or arrhythmia, infectious disease within 1 month, serious liver or renal dysfunction, autoimmune disease, malignant disease, pregnancy or lactation, or psychiatric disorders, were excluded from this study. In addition, patients with laboratory values >3 times the upper limit of normal (ULN) for aspartate aminotransferase or alanine aminotransferase, or >5 times the ULN for creatine phosphokinase, were also excluded.

Laboratory examinations

Blood samples were obtained from the cubital vein at both baseline and 8 weeks after fasting overnight. All samples were subsequently stored at −80 °C and analyzed immediately after thawing. The concentrations of plasma TC, TG, HDL-C, LDL-C, apolipoprotein A-I (ApoA-I), and apolipoprotein B (ApoB) were measured using an automatic biochemistry analyzer (Hitachi 7150, Tokyo, Japan). TC, TG, HDL-C, and LDL-C levels were measured using enzymatic assays. ApoA-I and ApoB levels were measured using turbidimetric immunoassays. Plasma oxLDL levels were detected by a sandwich enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (Mercodia, Uppsala, Sweden). The detection limit was 0.6 mU/L. Plasma IL-6 concentrations were measured using a high-sensitivity quantitative sandwich ELISA (Quantikine ELISA kit, R&D Systems, Inc., Minneapolis, MN, USA). The mean minimum detectable dose of IL-6 was 0.070 pg/ml.

HDL and LDL subfraction analysis

Blood samples were also used for subfraction analysis. HDL subclass analysis was performed

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