学 位 論 文 の 要 旨

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学 位 論 文 名　Effect of Serum Cholesterol on Insulin Secretory Capacity: Shimane CoHRE Study

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論 文 内 容 の 要 旨

INTRODUCTION

It has been believed that increased insulin resistance and decreased insulin secretion are both important in the pathogenesis of diabetes mellitus. Previous studies indicate that, in addition to the blood glucose level, the lipid level in the blood may affect functions of pancreatic beta cells. Furthermore, a loss-of-function mutation in the gene encoding the ATP-binding cassette transporter A1 (*ABCA1*), an outward transporter of cholesterol on the cell membrane, reduced insulin secretory capacity without affecting insulin resistance in mice and humans. Since the serum cholesterol level was shown to correlate with the intracellular cholesterol level, it was suggested that apoptotic loss of pancreatic beta cells induced by the accumulation of intracellular cholesterol resulted in reduced insulin secretory capacity.

However, there are limited number of reports that examined whether serum lipid affected the insulin secretion and the glucose metabolism in humans. In this study, we aimed to examine whether there was a relationship between the serum level of total cholesterol (TC) and the insulin secretory capacity in healthy subjects.

SUBJECTS AND METHODS

This cross-sectional study is a part of the cohort study conducted by the Center for the Community-based Health research and Education (CoHRE), Shimane University, which is performed in collaboration with counties located in rural areas of Shimane Prefecture, Japan. Written informed consent was obtained from each participant, and the study protocol was approved by the Ethics Committee of Shimane University.

In health examinations performed between 2006 and 2010, all individuals without severe diseases such as advanced cancer were invited to the study. Most of them were over 50 years of age. A total of 3,306 subjects were assigned to this study. Disease histories, medication and information about lifestyle such as smoking, alcohol consumption and regular exercise were obtained by a questionnaire. According to the information obtained, we excluded subjects who took medicine for dyslipidemia, diabetes and thyroid diseases, and subjects with hemoglobin A1c (HbA1c) $\geq$ 6.5%, or fasting plasma glucose (FPG) $\geq$ 126 mg/dL. Consequently, 2,499 subjects (1,057 men and 1,442 women) were included in the following analyses.

Serum samples were taken after one night fasting, separated within 30 min and biochemical measurements of TC, triglycerides (TG), high density lipoprotein cholesterol (HDLC), low density lipoprotein cholesterol (LDLC), FPG and fasting plasma insulin (equal to fasting immunoreactive insulin, FIRI) were performed by standard methods. HbA1c was determined by high performance liquid chromatography (HLPC). Homeostasis model assessment for beta cell function (HOMA-beta = [360×FIRI (μU/mL)] / [FPG (mg/dL) − 63]) was utilized as a model representing the pancreatic beta cell function. All data were analyzed with statistical software R 3.0.3.

RESULTS AND DISCUSSION

Although the serum TC level had a positive correlation with HOMA-beta in a univariate correlation analysis, after adjustment by confounding factors in a multiple regression analysis,

HOMA-beta had a negative correlation with the TC level. This was further confirmed in a multiple logistic regression analysis, showing that higher TC level was an independent risk factor for decreased insulin secretory capacity (defined as HOMA-beta $\leq$ 30%) together with higher age, lower BMI, lower TG level, male sex and regular alcohol intake. After the participants were stratified by BMI into three groups, the effect of TC level on HOMA-beta increased along with the increase in BMI, and it was highly significant in the highest tertile. These findings indicate that a high concentration of the serum TC level was an independent risk factor of the impaired insulin secretion. The effect was likely to be more potent in obese men than in lean women.

A recent epidemiological study showed that TC or LDLC level was inversely associated with the insulin secretory capacity in over 2,000 subjects (mean age: 43) with normal glucose tolerance. We found the similar association even in aged population (mean age: 66) after adjustment with the confounding factors such as BMI and TG level, suggesting that the inverse association of serum TC level with the capacity of insulin secretion would be a universal phenomenon. In addition, the similar trend was observed in our study, when the analysis was performed with LDLC or non-HDLC instead of TC.

Interestingly, in the present study, HOMA-beta was positively correlated with BMI and TG level. As we excluded diabetic subjects from the studied population, the participants were expected to have reserved ability of insulin secretion. Accordingly, increase in the insulin resistance due to increase in BMI or TG level might be compensated by additional insulin secretion without elevation of the blood glucose level.

CONCLUSION

This cross-sectional study indicated that increased serum TC level might be related to the decrease of insulin secretory capacity in aged healthy population and that reduction of TC level is more necessary in obese subjects to prevent diabetes.

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論文審査の結果の要旨

糖尿病の成因に、インスリン分泌不全は重要な役割を担っている。近年、血中脂質が膵β細胞のインスリン分泌低下に影響を与えるという結果が実験研究により報告されている。しかし、この観点の疫学的な検討はほとんどみられない。申請者は島根大学疾病予知予防プロジェクトセンターが実施した健診受診者において、血中脂質と糖代謝、特にインスリン分泌能との関連を明らかにすることを目的として研究を行った。研究デザインは横断研究とした。2006年から2010年に島根県の離島・中山間地域（隠岐、雲南、邑南）の健診受診者3306名のうち、糖尿病、脂質異常症、甲状腺機能異常に対する薬剤を服用している者、または、空腹時血糖126mg/dl以上、HbA1c6.5%以上の者を除いた2249名を対象とし、ベースラインデータを解析した。インスリン分泌能の指標にはHomeostasis model assessment for beta cell function (HOMA-beta)を用いた。結果、重回帰分析にて、血清総コレステロール(以下TC)はHOMA-betaと負の相関関係を認め、さらに、インスリン分泌不全（定義：HOMA-beta≦30%）を目的変数としたロジスティック回帰分析にて、TC高値はインスリン分泌不全の独立した危険因子であることが示された。また、Body Mass Index（BMI）の三分位で分割し同様の検討を行ったところ、BMIが高い群で前述の関連がより顕著であった。本研究は、地域住民において血清コレステロールを適正に管理することが糖尿病予防につながる可能性を示唆したものである。糖尿病予防に新しい示唆を与える研究であり、博士（医学）の学位授与に値すると判断した。