

# 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 (HDL), low density lipoprotein cholesterol (LDL), FPG and fasting plasma insulin (equal to fasting immunoreactive insulin, FIRI) were performed by standard methods. HbA1c was determined by high performance liquid chromatography (HPLC). Homeostasis model assessment for beta cell function (HOMA-beta =  $[360 \times \text{FIRI} (\mu\text{U}/\text{mL})] / [\text{FPG} (\text{mg}/\text{dL}) - 63]$ ) 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.