Apolipoprotein E Genetic Polymorphisms and the Development of Nephropathy in Type 2 Diabetes

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Background: Apolipoprotein E (ApoE) polymorphisms have been proposed as the risk factor for the development of diabetic nephropathy (DN). A number of studies have investigated the association between the ApoE isoforms and DN. However, the findings remain inconclusive.

Objective: To determine the association between the ApoE polymorphisms and DN.

Material and Method: Two hundred thirty patients with type 2 diabetes were divided into two groups, patients with clinically diagnosed DN and normoalbuminuric patients. ApoE genotypes were determined by RT-PCR analysis. Student's t-test, ANOVA test, Chi-square test, odds ratio, and logistic regression was performed.

Results: The frequency of ApoE4 genotype was significantly lower in DN patients (8.7%) than in normoalbuminuric patients (21.7%). Logistical regression analysis showed that subjects with ApoE4 genotype (adjusted OR = 0.43; 95% CI: 0.19-0.99) were less likely to have DN than subjects with ApoE3 genotype. Furthermore, when analyzed only in patients with overt DN vs. patients with normoalbuminuria, the frequency of e4 allele was decreased in overt DN (2.8% vs. 21.7%, adjusted OR = 0.13; 95% CI: 0.03-0.57) and the frequency of e2 allele was increased (25.4% vs. 13.0%, adjusted OR = 2.34; 95% CI: 1.02- 5.38).

Conclusion: ApoE4 genotype is associated with protection from type 2 DN, and subjects with e2 allele have increased risk of developing type 2 overt DN.

Keywords: Diabetic nephropathy, Type 2 diabetes, Apolipoprotein E Polymorphisms, ApoE

Diabetic nephropathy (DN) is a major complication in patients with type 2 diabetes and the most commonly recognized cause of end-stage renal disease (ESRD) in the USA, Europe, and Asia[1]. Multiple risk factors have been implicated in DN including hyperglycemia, hypertension, smoking, and dyslipidemia[2]. However, select individuals with diabetes are at differential risk for DN on the basis of a familial inheritance pattern[3,4]. It is believed that specific genetic backgrounds influence DN development. Identification of risk genes could provide a powerful tool for identifying the subset of diabetic patients who are likely to develop DN.

Apolipoprotein E (ApoE) has an important role in lipoprotein metabolism. It binds with high affinity to the LDL receptor and facilitates endocytosis of the associated lipoprotein particle. An ApoE exon 4 gene polymorphism, located on chromosome 19, has three common alleles, e2, e3, and e4, coding for the three isoforms of ApoE proteins: ApoE2 (Arg$^{158}\rightarrow$Cys), ApoE3 (parent isoform) and ApoE4 (Cys$^{112}\rightarrow$Arg), respectively. These isoforms have been shown to alter the affinity of ApoE for its receptors, thereby influencing plasma lipid and apolipoprotein levels[5]. An adverse lipid profile is a risk factor and may be a major promoter of DN[6,7].

Previously studies have shown that the ApoE2 is associated with an increased risk of type 2 DN[8-11]. Furthermore, it has been reported that ApoE4 is associated with protection from DN in both white and Japanese patients[12,13]. In contrast, several studies failed to find any association between ApoE polymorphisms and DN[14-16]. Therefore, the findings remain in conclusive. Emerging evidence suggests that type 2 diabetes patients with nephropathy likely have different causes of disease and different ethnic

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groups may have unique genetic risk profiles. Thus, we conducted a case-control study to investigate the relationship between ApoE polymorphisms and DN in a Thai population.

Material and Method

Two hundred and forty seven of type 2 diabetes patients with/without nephropathy were recruited from Phramongkutklao Hospitals, Bangkok, Thailand. Sample size is based on the ability to detect an association between ApoE polymorphisms and DN. The target sample size for the case control study is 198. Protocols were approved by the local ethical review committee, and all subjects participated in the study after giving informed consent.

Diabetes was defined by the following criteria[17]: 1) treatment with oral anti-diabetic agents and/or insulin therapy; 2) a fasting plasma glucose ≥126 mg/dL; or 3) a random plasma glucose ≥200 mg/dL. Exclusion criteria for the diagnosis of type 2 diabetes were: 1) diabetes secondary to known causes such as chronic pancreatitis; or 2) type 1 diabetes defined by presentation with ketoacidosis or requirement of insulin therapy from the disease onset[17]. All patients were reviewed with retrieval of medical and personal data, including baseline demographic characteristics, hypertension, use of antihypertensive or lipid lowering medications, and co-morbidities. All participants received a physical examination including blood pressure and anthropometry. Trained technicians measured blood pressure in the sitting position in the right arm thrice by using a random-zero sphygmomanometer, and the average of the last two readings was used. Body weight, height, and waist circumference were measured according to a standard protocol. BMI was calculated as weight in kilograms divided by height in meters squared.

Laboratory measurement

Blood samples were collected after an overnight fast (10-12 hours). Fasting plasma glucose, lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride), blood urea nitrogen (BUN), and serum creatinine were determined using enzyme-colorimetric methods (Cobas 8000 modular analyzer Series, Roche-Diagnostics, Switzerland). Hemoglobin A1C (HbA1c) was measured by means of high-performance liquid chromatography (Cobas 8000 modular analyzer Series, Roche-Diagnostics, Switzerland). ApoE lipoprotein was measured using

the chemiluminescence immunoassay (Immulite 1000, Siemens Medical Diagnostic Products, USA). Glomerular filtration rate (GFR) was estimated from calibrated serum creatinine with the Cockcroft-Gault equation[18]. A central regional laboratory performed serum creatinine for all of the patients using standardized with isotope dilution mass spectrometry (IDMS) method.

Urinary albumin and creatinine concentrations were measured, and the ratio of urinary albumin and creatinine concentrations was expressed as the urinary albumin excretion index (UAI). DN status was determined on the basis of measurement of UAI in at least two of the last three urine specimens. Patients were divided into three groups according to levels of UAI and urine protein: normoalbuminuria (UAI <30 mg albumin/g creatinine), microalbuminuria (UAI 30-300 mg albumin/g creatinine), and overt nephropathy (UAI >300 mg albumin/g creatinine and/ or persistent proteinuria). Patients were considered DN if they had persistent microalbuminuria/proteinuria or had ESRD caused by DN.

ApoE genotyping

Genomic DNA was extracted from whole blood using a phenol/chloroform method. ApoE genotyping was determined by real time polymerase chain reaction (Taqman SNP genotype assay, ABI PRISM 7900HT Sequence Detection System). E2 allele corresponds to Cys112 Cys158; e3 allele to Cys112 Arg158 and e4 allele to Arg112 Arg158. The e2 allele carriers (e2/e2 and e2/e3; ApoE2) were compared with e3/e3 allele homozygotes (ApoE3) and e4 allele carriers (e3/e4 and e4/e4; ApoE4) to study the effect of ApoE genotypes. Seventeen e2/e4 allele patients were excluded from the analysis, as they could not be classified as ApoE2 or ApoE4.

Statistical analysis

Continuous data were described as means and standard deviations (SD). Categorical variables were described as percentages. Means were compared using the Student's t-test and one-way analysis of variance (ANOVA) followed by Bonferroni post hoc analysis. Categorical variables were compared using the Chi-square test or Fisher's exact test. The odds ratio and logistic regression was performed to correct for HbA1c, fasting plasma glucose, total cholesterol, triglyceride, HDL-cholesterol and ApoE lipoprotein. Analysis was performed to exam using a standard statistical software package SPSS 11.5 (SPSS Inc.,

Chicago, IL, USA). Differences were considered statistically significant at p<0.05.

Results

Clinical characteristics of type 2 diabetic patients with and without nephropathy are listed in Table 1. The duration of diabetes was significantly longer in patients with nephropathy than those without nephropathy. The frequency of diabetic retinopathy, history of cardiovascular disease, and hypertension were significantly higher in patients with nephropathy than those without nephropathy. No significant differences were noted in gender, age, family history of diabetes, body weight, body mass index (BMI), waist circumference, and blood pressure. As listed in Table 2, DN patients had significantly higher fasting plasma glucose, HbA1c, plasma triglyceride, BUN and plasma creatinine levels, and lower GFR and HDL levels.

Frequencies of ApoE2 genotype (e2/e2, e2/e3), ApoE3 genotype (e3/e3), and ApoE4 genotype (e3/e4, e4/e4) in type 2 diabetes patients are shown in Fig. 1. In the DN group, frequencies of ApoE2, ApoE3, and ApoE4 genotypes were 20.0%, 71.3%, and 8.7%,

Table 1. Characteristics of the subjects with type 2 diabetes according to nephropathy status

Clinical characteristics	DN (n = 115)	Non-DN (n = 115)	p-value
Male (n, [%])	61 (53.1)	50 (43.4)	0.147
Age (yr)	60.54±7.94	60.26±7.11	0.780
Duration of diabetes (yr)	15.08±9.86	9.59±7.34	<0.001
Family history of diabetes (n, [%])	82 (73.9)	81 (72.3)	0.794
History of CVD (n, [%])	22 (19.1)	9 (7.8)	0.012
History of hypertension (n, [%])	89 (84.0)	78 (72.2)	0.038
Smoking (n, [%])	30 (26.1)	19 (16.5)	0.076
Body weight (kg)	69.67±16.13	68.53±15.28	0.581
Waist circumference (inch)	36.06±5.24	35.13±4.73	0.157
BMI (kg/m2)	26.48±4.99	26.59±5.26	0.871
SBP (mmHg)	145.88±18.69	139.79±20.34	0.086
DBP (mmHg)	85.28±11.69	82.32±10.04	0.123
Diabetic retinopathy (n, [%])	53 (46.1)	14 (12.2)	<0.001

BMI = body mass index; CVD = cardiovascular disease; DBP = diastolic blood pressure; DN = diabetic nephropathy; SBP = systolic blood pressure

Table 2. Laboratory profiles of the subjects with type 2 diabetes according to nephropathy status

Laboratory profile	DN (n = 115)	Non-DN (n = 115)	p-value
HbA1c (%)	8.30±1.85	7.87±1.21	0.039
FPG (mg/dL)	170.52±75.00	147.94±45.57	0.006
TC (mg/dL)	171.66±36.00	176.03±41.09	0.391
HDL(mg/dL)	45.54±13.57	49.96±15.86	0.024
LDL (mg/dL)	108.30±38.40	105.95±38.95	0.645
TG (mg/dL)	148.10±65.60	130.28±54.13	0.026
ApoE lipoprotein (mg/dL)	4.73±3.21	4.38±1.33	0.286
BUN (mg/dL)	34.88±21.83	16.80±8.65	<0.001
Serum creatinine (mg/dL)	4.08±3.46	1.10±0.78	<0.001
eGFR (mL/min)	38.59±32.96	75.82±29.60	<0.001

BUN = blood urea nitrogen; DN = diabetic nephropathy; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; HbA1c = hemoglobin A1C; HDL = high density lipoprotein; LDL = low density lipoprotein; TC = total cholesterol; TG = triglyceride
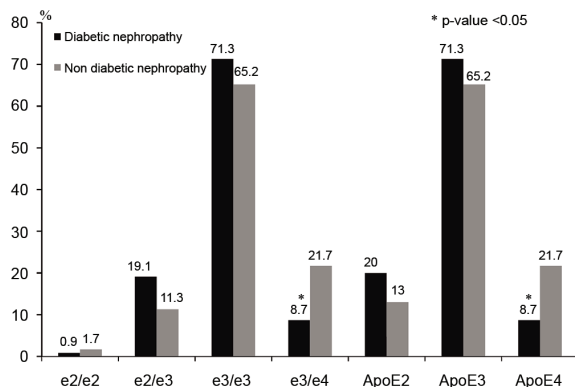
Fig. 1 Frequency of ApoE genotypes according to nephropathy status; ApoE2 = e2/e2, e2/e3; ApoE3 = e3/e3; ApoE4 = e3/ e4, e4/ e4.

respectively. In the non-DN group, these were 13.0%, 65.2%, and 21.7%, respectively. The frequency of ApoE4 genotype and e3/e4 was significantly lesser in the DN than non DN group (p<0.05). On logistical regression analysis, ApoE4 genotypes (odds ratio = 0.37; 95% CI = 0.17-0.81, p = 0.013) were less likely to have nephropathy than were ApoE3 genotype. After adjustment for potential risk factors (HbA1c, fasting plasma glucose, total cholesterol, triglyceride, HDL-cholesterol and ApoE lipoprotein), the adjusted odds ratio of ApoE4 genotypes were 0.43 (95% CI = 0.19-0.99, p = 0.046) (Table 3).

DN status was determined on the basis of measurement of UAI; all patients were divided into three groups according to levels of UAI and urine protein: normoalbuminuria, microalbuminuria, and overt nephropathy. The frequency of the ApoE4 genotype was significantly different between the three groups, with the ApoE4 genotype being less frequent in overt nephropathy subjects than in microalbuminuria and normoalbuminuria subjects (2.8% vs. 18.2% vs. 21.7%, p = 0.002). The frequency of the ApoE2 genotype had the opposite pattern (25.4% vs. 11.4% vs. 13.0%, p = 0.053), whereas the frequency of the ApoE3 genotype was similar in the three groups. Logistical regression analysis (Table 4) showed that odds ratio of e2 allele and e4 allele were 2.26 (95% CI = 1.06-4.85) and 0.10 (95% CI = 0.02-0.46), respectively when the odds ratio of non-e2 allele and non-e4 allele for the presence of overt nephropathy is presumed to be 1.000, respectively. Furthermore, the odds ratio of e2 allele (2.34; 95% CI = 1.02-5.38) and e4 allele (0.13; 95% CI = 0.03-0.57) for overt nephropathy were changed only slightly by adjustment for HbA1c, fasting plasma glucose, total cholesterol, triglyceride, HDL-cholesterol and ApoE lipoprotein. The ApoE2 and ApoE4 genotypes were also compared with ApoE3 genotype for the presence of overt nephropathy. The ApoE4 genotypes were reduced in overt nephropathy (crude odds ratio 0.12;

Table 3. Logistic regression model examining associations between ApoE genotypes and presence of nephropathy in patients with type 2 diabetes

	Crude OR (95% CI)	p-value	Adjusted[a] OR (95% CI)	p-value
ApoE2	1.40 (0.68-2.89)	0.359	1.54 (0.73-3.25)	0.253
ApoE3	1	1	1	1
ApoE4	0.37 (0.17-0.81)	0.013	0.43 (0.19-0.99)	0.046

[a] Adjusted by HbA1c, fasting plasma glucose, total cholesterol, triglyceride, HDL-cholesterol and ApoE lipoprotein

Table 4. Logistic regression model examining associations between ApoE genotypes and presence of overt nephropathy in patients with type 2 diabetes

	Crude OR (95% CI)	p-value	Adjusted[a] OR (95% CI)	p-value
Alleles				
e2 (ref. non e2 allele)	2.26 (1.06-4.85)	0.036	2.34 (1.02-5.38)	0.045
e3 (ref. non e3 allele)	1.24 (0.11-13.92)	0.862	4.36 (0.23-83.94)	0.329
e4 (ref. non e4 allele)	0.10 (0.02-0.46)	0.003	0.13 (0.03-0.57)	0.007
Genotypes				
ApoE2	1.76 (0.82-3.82)	0.149	2.08 (0.93-4.68)	0.075
ApoE3	1	1	1	1
ApoE4	0.12 (0.03-0.52)	0.005	0.14 (0.03-0.62)	0.010

[a] Adjusted by HbA1c, fasting plasma glucose, total cholesterol, triglyceride, HDL-cholesterol and ApoE lipoprotein

Table 5. Plasma lipid levels by ApoE genotypes in patients type 2 diabetes

Lipid profiles	ApoE2 (n = 38)	ApoE3 (n = 157)	ApoE4 (n = 35)	p-value (ANOVA)	Post Hoc test		
					e2 vs. e3	e2 vs. e4	e3 vs. e4
TC (mg/dL)	167.61±33.43	173.78±40.51	180.94±34.64	0.338	0.386	0.099	0.334
HDL (mg/dL)	50.03±16.44	46.11±13.72	52.63±17.14	0.037	0.131	0.511	0.016
LDL (mg/dL)	101.94±39.22	107.71±39.52	110.13±34.08	0.629	0.420	0.346	0.738
TG (mg/dL)	151.16±68.22	140.71±60.68	119.37±47.55	0.070	0.354	0.023	0.053
ApoE lipoprotein (mg/L)	5.46±1.79	4.46±2.76	4.02±1.09	0.031	0.007	<0.001	0.128

ApoE = apolipoprotein E; HDL = high density lipoprotein; LDL = low density lipoprotein; TC = total cholesterol; TG = triglyceride

95% CI = 0.03-0.52, adjusted odds ratio 0.14; 95% CI = 0.03-0.62). The ApoE2 genotype tended to confer risk for overt nephropathy (crude odds ratio 1.76; 95% CI = 0.82-3.82, adjusted odds ratio 2.08; 95% CI = 0.93-4.68).

As listed in Table 5, plasma levels of lipids were compared by ApoE genotypes. There was significant differences in plasma levels of HDL-cholesterol between three ApoE groups (p = 0.037), but only plasma HDL-cholesterol was significantly higher in the ApoE4 group than ApoE4 group (p = 0.016). Plasma levels of ApoE lipoprotein was greater in the ApoE2 group than the other groups (p = 0.031) and plasma TG levels was greater in the ApoE2 group than the ApoE4 group (p = 0.023). There was no significant difference in plasma levels of total cholesterol and LDL-cholesterol among the three ApoE groups.

Discussion

The major findings of the study are that the ApoE4 genotype is associated with decreased prevalence of diabetic nephropathy, especially overt nephropathy, and the e2 allele is a risk factor for overt nephropathy. The present study provides additional evidence that the ApoE polymorphism is associated with the prevalence of DN, independent of well-described risk factors for developing DN such as hyperglycemia, hypertension, dyslipidemia, and smoking.

Epidemiological studies have suggested that the ApoE2 variant increases and ApoE4 decreases the risk of renal disease in type 2 diabetes[8-13]. The present study is consistent with the results of the previous studies. However, several studies failed to show an association between ApoE polymorphism and DN[14-16]. These different results are poorly understood, but one may consider the following possibilities:

different interactions with dietary habit and environmental factors among various ethnic groups, variable genetic factors, and different diagnostic criteria for DN in each study.

There is evidence that plasma lipid levels are related to the development of renal disease in diabetic patients[19]. ApoE plays a role in the metabolism of lipoproteins and lipid remnants through its ability to bind specific receptor. These changes in binding ability of the various ApoE polymorphisms result in increased plasma triglyceride and remnant-like lipoprotein particle in patients with the ApoE2 genotype and decreased lipoprotein levels in patients with the ApoE4 genotype. The authors found that ApoE2 is associated closely with increases in plasma remnant lipoprotein and triglyceride levels in diabetic patients. One explanation is that the lipid abnormality associated with the ApoE2 genotype may cause renal injury. It is well recognized that high triglyceride-rich lipoproteins from the ApoE2 group have stimulated the accumulation of cholesteryl esters by mesangial cells[11] and enhanced glycosylated LDL deposit in macrophages[20]. There appears to stimulate secretion of inflammatory cytokines (interleukin-6, transforming growth factor-β, monocyte colony-stimulatory factor) that enhance the production of extracellular matrix protein and tubulointerstitium injury[19]. These mechanisms may implicate the ApoE2 polymorphism in the development of glomerulosclerosis and nephropathy[21].

The present study confirms previous studies[12] that the ApoE4 genotype reduces the risk of DN. ApoE4 was reported to be more effective in modulating direct remnant uptake and converting remnant lipoprotein levels[22]. The authors also found that ApoE4 is associated with higher levels of HDL and lower levels of triglycerides and remnant lipoprotein, a lipid profile that decreases the risk of

CKD including DN[23]. There is strong support for the observation that triglyceride-rich lipoproteins may play an important role in the development of DN. Patients with the ApoE2 polymorphism have higher triglyceride-rich lipoproteins and an increased risk of DN and patients with the ApoE4 polymorphism have lower triglyceride-rich lipoproteins and a decreased risk of DN. Possible explanations for the protective role of the ApoE4 may include the following possibilities: 1) ApoE4 enhances the clearance of triglycerides and remnant lipoprotein, the accumulation of which predominates in overt nephropathy; 2) ApoE4 appears to locate near a renal protective gene within chromosome 19 and these genes are expressed together; or 3) ApoE4 may not be the truly protective gene[12].

The ApoE polymorphisms are associated with lipid levels, especially triglyceride-rich lipoproteins. The authors attempted to assess the independent effects of genetic factors on DN after controlling for lipid profiles and plasma glucose in a multivariate regression model. The ApoE4 genotype and e2 allele remained significantly associated with overt nephropathy. Therefore, the DN risk association with the ApoE polymorphisms may not be directly mediated through lipid levels. The influence of ApoE could extend beyond lipid effects, as with ApoE4 and Alzheimer disease[24]. Interestingly, a high level of ApoE localized to the mesangial area of DN patients, and its isoforms differentially inhibit mesangial cell proliferation through induction of matrix heparan sulfate proteoglycan. Among the three isoforms, ApoE2 was found to be less effective in inhibiting mesangial cell proliferation[25]. Thus, one may hypothesize that ApoE2 influences susceptibility to develop renal pathology. In support of these findings, previous studies also showed that the ApoE2 polymorphism was associated with glomerular damage reflected by impaired filtration capacity of the glomerular basement membrane, extracellular matrix expansion, and increased ApoE protein deposition in the mesangial area and nodular lesions[26-28]. Additionally, mutant forms of ApoE2 could induce a lipoprotein glomerulopathy[29]. Abnormal structure of these ApoE isoforms may cause aggregated deposits in the glomerulus, leading to accumulation of lipoproteins[30].

Whereas the present study confirmed initial impressions of a close association of ApoE polymorphisms with nephropathy in type 2 diabetes, there are several limitations to the present study. First, due to the relatively small sample size after dividing patients into different stages of nephropathy, these risk associations may be weak. Therefore, the authors are in the process of collecting more patients and prospective data on our subjects to exam the associations of genetic factors with disease progression. Second, at the time of examination in the present study, type 2 diabetes patients without nephropathy had diabetes duration of 9.59±7.34 years, which was shorter than the mean duration of patients with nephropathy. Some patients without nephropathy may develop DN in the intervening years.

In summary, the results of present study provide data regarding the ApoE polymorphisms associated with DN, independent of the effect of ApoE genotypes on plasma cholesterol and triglyceride-rich lipoproteins. The ApoE4 genotype is associated with protection from type 2 DN, and e2 allele was associated with increased risk of developing type 2 overt DN. These findings suggest the importance of the ApoE gene in modulating the risk of type 2 DN.

Potential conflicts of interest

None.

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ความสัมพันธ์ของรูปแบบความหลากหลายของจีน *apolipoprotein E* กับโรคไตจากเบาหวานชนิดที่ 2

บัญชา สถิระพจน์, อุปถัมภ์ ศุภสินธุ์, รัตนาวรรณ ดินธุป้าน, ดลพรรธ พันธุ์พาณิชย์, ศิริวรรณ ไตรบัญญัติกุล, พรรณบุปผา ชูวิเชียร

ภูมิหลัง: รูปแบบความหลากหลายของจีน *apolipoprotein E (ApoE)* คาดว่าเป็นปัจจัยเสี่ยงหนึ่งของการเกิดโรคไตจากเบาหวาน อย่างไรก็ตามจากการศึกษาที่ผ่านมาไม่สามารถสรุปความสัมพันธ์ของรูปแบบความหลากหลายของจีน *ApoE* กับการเกิดโรคไตจากเบาหวานได้ชัดเจน

วัตถุประสงค์: เพื่อศึกษาความสัมพันธ์ของรูปแบบความหลากหลายของจีน *ApoE* กับการเกิดโรคไตจากเบาหวานชนิดที่ 2

วัสดุและวิธีการ: ทำการศึกษาในผู้ป่วยโรคเบาหวานชนิดที่ 2 จำนวน 230 ราย แบ่งผู้ป่วยออกเป็น 2 กลุ่ม คือ กลุ่มผู้ป่วยเบาหวานที่มีโรคไตและกลุ่มผู้ป่วยเบาหวานไม่มีโรคไต ทำการตรวจวิเคราะห์ความแปรปรวนของจีน *ApoE* ด้วยวิธี *real time polymerase chain reaction* การวิเคราะห์ทางสถิติใช้ *Student's t-test, ANOVA test, Chi-square test, odds ratio* และ *logistic regression*

ผลการศึกษา: กลุ่มผู้ป่วยเบาหวานที่มีโรคไตพบความชุกของ *ApoE4* น้อยกว่ากลุ่มผู้ป่วยเบาหวานที่ไม่มีโรคไตอย่างมีนัยสำคัญทางสถิติ (ร้อยละ 8.7 เทียบกับร้อยละ 21.7 ตามลำดับ) เมื่อวิเคราะห์ความสัมพันธ์แบบ *logistical regression* พบว่าผู้ป่วยที่มีจีน *ApoE4* มีโอกาสในการเกิดโรคไตจากเบาหวานน้อยกว่าผู้ป่วยที่มีจีน *ApoE3* โดยมีค่า *adjusted odds ratio* เท่ากับ 0.43; ช่วงระดับความเชื่อมั่น 95%: 0.19 ถึง 0.99 เมื่อวิเคราะห์แยกเฉพาะกลุ่มผู้ป่วยเบาหวานที่มีโรคไตระยะ *overt nephropathy* กับกลุ่มผู้ป่วยเบาหวานที่ไม่มีโรคไตพบความชุกของ *e4 allele* ร้อยละ 2.8 และ 21.7 ตามลำดับ โดยมีค่า *adjusted odds ratio* เท่ากับ 0.13; ช่วงระดับความเชื่อมั่น 95%: 0.03 ถึง 0.57 และพบความชุกของ *e2 allele* ร้อยละ 25.4 และ 13.0 ตามลำดับ โดยมีค่า *adjusted odds ratio* เท่ากับ 2.34; ช่วงระดับความเชื่อมั่น 95%: 1.02 ถึง 5.38

สรุป: ผู้ป่วยเบาหวานที่มีจีน *ApoE4* สัมพันธ์กับการป้องกันการการเกิดโรคไตจากเบาหวาน และผู้ป่วยเบาหวานที่มี *e2 allele* สัมพันธ์กับการเกิดโรคไตจากเบาหวานระยะ *overt nephropathy*