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Preliminary Report on the Association of Apolipoprotein E Polymorphisms, with Postoperative Peak Serum Creatinine Concentrations in Cardiac Surgical Patients

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Background: **Renal dysfunction after cardiac surgery occurs in up to 8% of patients and is associated with major increases in morbidity, mortality, and cost. Genetic polymorphisms have been implicated as a factor in the progression of chronic renal disease, but a genetic basis for the development of acute renal impairment has not been investigated. The authors therefore tested the hypothesis that apolipoprotein E alleles are associated with different postoperative changes in serum creatinine after cardiac surgery.**

Methods: **The authors performed a prospective observational study with use of data from 564 coronary bypass surgical patients who were enrolled in an ongoing investigation of apolipoprotein E genotypes and organ dysfunction at a university hospital between 1989–1999. Renal function was assessed among apolipoprotein E genotype groups by comparisons of preoperative (CrPre), peak in-hospital postoperative (CrMax), and perioperative change (DCr) in serum creatinine values.**

Results: **The ϵ4 allele grouping (E2 = 2/2,2/3,2/4; E3 = 3/3; E4 = 3/4,4/4) was associated with a smaller increase in postoperative serum creatinine (perioperative change: E4, +0.17; E3, +0.26; E4, +0.27 mg/dl) and a lower peak postoperative creatinine than the ϵ2 and ϵ3 in univariate and multivariate analysis (peak in-hospital postoperative serum creatinine multivariate: $P = 0.015$ *vs.* ϵ3, $P = 0.038$ *vs.* ϵ2). There was no difference in baseline creatinine among allele groups.**

Conclusions: **Inheritance of the apolipoprotein ϵ4 allele is associated with reduced postoperative increase in serum creatinine after cardiac surgery, compared with the ϵ3 or ϵ2 allele. This is the first report of a possible genetic basis for acute renal impairment. These data may contribute to renal risk stratification for cardiac surgery and raise questions regarding apolipoprotein E and the pathophysiology of acute renal injury. (Key words: Acute renal failure; heart surgery; postoperative complications.)**

OF the 800,000 patients who undergo coronary artery bypass surgery worldwide annually,[1] approximately 8% will experience a significant perioperative acute renal injury, and up to 1% will require dialysis.[2–4] Acute renal injury after cardiac surgery is important because even minor degrees of postoperative renal dysfunction are associated with major in-hospital increases in morbidity, mortality, and cost.[2,3,5] Acute renal failure is independently associated with mortality after cardiac surgery,[6] with rates increasing from less than 1% in unaffected patients to 20% in patients with moderate acute renal injury, exceeding 60% for patients requiring dialysis.[2–4]

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In addition, the likelihood of discharge to an extended-care facility for survivors of a postoperative renal injury are increased two- to threefold compared with those without renal injury.[3] Although many variables have been described that can identify cardiac surgical patients at risk for renal dysfunction,[2–4] significant unexplained variability in renal outcome still exists.

Genetic polymorphism has been identified as a factor in the occurrence and progression of chronic renal disease; allele associations have been made with several genes, including apolipoprotein E (APOE).[7–24] APOE genetic polymorphisms have also been linked to differing risks for other chronic diseases, including late-onset Alzheimer disease and atherosclerosis.[25–27] An association of APOE–ϵ4, with impaired recovery from several acute neurologic disorders, including neurocognitive dysfunction after cardiac surgery, has recently been reported.[28,29] A genetic basis for acute renal impairment, however, has not previously been evaluated. APOE is a lipoprotein involved in numerous functions, including lipid metabolism, tissue repair, and immune response; the gene locus for the three major APOE alleles (ϵ2, ϵ3, and ϵ4) is located on chromosome 19q13.2.[30] We therefore used univariate and multivariate analyses of raw and ranked perioperative serum creatinine data to test the hypothesis that APOE alleles are associated with different postoperative changes in serum creatinine after cardiac surgery.

Material and Methods

After approval from the Duke University Medical Center Institutional Review Board and patient informed consent, 564 coronary artery bypass surgical patients were enrolled in a study between 1989 and 1999 that examined APOE and perioperative organ dysfunction. Exclusion criteria included history of emergency surgery and severe hepatic, cerebrovascular, or renal (preoperative serum creatinine $>$ 2.0 mg/dl) disease. Anesthesia was managed with use of the attending anesthesiologist's preference; use of agents with renal effects (*e.g.*, intravenous dopamine) was not regulated, and antifibrinolytic agent administration was restricted almost exclusively to ϵ-aminocaproic acid, which went from an uncommon to an almost routine therapy approximately half way through the study period. Cardiopulmonary bypass (CPB) was performed with use of standard methods previously reported.[29]

Apolipoprotein E Analysis

Genomic DNA from a blood sample was analyzed for APOE genotype with use of a method published in the literature,[31] with minor modifications for fluorographic rather than for autoradiographic detection of DNA. Briefly, high-molecular-weight DNA is extracted from prepared, crude leukocyte nuclei *via* Genepure automated nucleic acid extractor (P.E. Applied Biosystems, Foster City, CA). The three major APOE alleles are then identified with use of a polymerase chain reaction-based restriction-enzyme genotyping protocol. Study personnel were blind to the results.

Perioperative Renal Data

Blood samples were obtained preoperatively and daily postoperatively until hospital discharge per institutional routine to assess serum creatinine values. Preoperative serum creatinine (CrPre) was the value obtained closest to surgery, but not within 24 h of the procedure. Peak serum creatinine (CrMax) was the highest in-hospital postoperative value. CrMax and the perioperative difference in serum creatinine (DCr; CrMax $-$ CrPre) were used for analysis of postoperative renal function. Demographic variables included several previously reported risk factors for perioperative renal dysfunction after cardiac surgery, including age, gender, CPB time, weight, hypertension, history of diabetes, and preoperative ejection fraction.[2,3]

Statistical Analysis

Genotype assignment to the most common (*i.e.*, E3 = 3/3) or less common genotype groups (*i.e.*, E2 = 2/2,2/3,2/4; E4 = 3/4,4/4) was determined by the presence of ϵ2 and ϵ4 alleles. An alternate genotype arrangement grouping APOE2/4 subjects with the E4 group was also evaluated. Demographic and perioperative characteristics were compared among APOE genotype groups by use of analysis of variance. The distribution of raw creatinine data was approximately normal; therefore, parametric methods were justified for analysis. However, to ensure robustness of primary results from raw data, these analyses were also performed for ranked data.

An initial, unadjusted analysis compared CrPre, CrMax, and DCr among the APOE genotype groups. The association of the three genotype groups with CrMax was then evaluated with use of multivariate analysis of covariance, adjusting for CrPre and allowing for potential effects of age, gender, CPB time, weight, hypertension, history of diabetes, and preoperative ejection fraction. The two-way interactions between genotype groups and these

potential renal risk factors were also tested. Nonsignificant covariates were removed from the analysis in a stepwise manner. Significant overall genotype effects were followed up by Scheffé adjusted *post hoc* pairwise comparisons between groups. Similar analyses were performed for DCr values to validate the selection of CrMax as the primary outcome variable. Analyses were performed with use of SAS software, version 6.12 (SAS Institute Inc., Cary, NC); significance was judged at $\alpha = 0.05$.

Results

Overall APOE genotype and DCr distributions among the 564 patients were comparable to those previously reported in large populations with similar inclusion criteria (table 1).[3,32] Demographic variables were similar among groups with the exception of the history of diabetes, which occurred more commonly in the APOE2 genotype group (tables 1 and 2). In two patients (3/3, 2/3), postoperative acute renal failure developed (CrMax $>$ 4.0 mg/dl).

Preoperative serum creatinine among APOE genotype groups was not significantly different (Kruskal–Wallis, $P = 0.54$). However, CrMax and DCr values were differentially distributed when assessed by grouped APOE alleles (fig. 1); this was true whether APOE2/4 subjects were grouped with either the $\epsilon 2$ or the $\epsilon 4$ bearers. The APOE2/4 genotype (15 patients, 2.7%) was grouped with the E2 bearers rather than with the E4 bearers because this combination proved to be a stronger predictive model.

In the final multivariable model, adjusted for CrPre, a significant association of APOE genotype group with CrMax was seen (genotype group $P = 0.032$; partial $R^2 = 0.0123$; total model $F = 56.5$, 6 degrees of freedom; $P < 0.0001$; total $R^2 = 0.378$; see table 3). In the Scheffé-adjusted *post hoc* pairwise comparisons, the E4 group showed significantly lower CrMax than either the E2 or the E3 group ($P = 0.038$ and 0.015, respectively). Figure 1 shows the very similar results seen with raw DCr data. Multivariate predictors of perioperative renal dysfunction are presented in table 2. Age, gender, preoperative ejection fraction, and CPB time were not significant predictors of CrMax in our model. Ranked data analysis showed very similar results to raw data analysis (genotype group, $P = 0.032$).

Discussion

Our study shows a reduced postoperative increase in serum creatinine after cardiac surgery, with the APOE $\epsilon 4$ compared with $\epsilon 3$ and $\epsilon 2$ alleles in patients with normal preoperative renal function (*i.e.*, PreCr $\leq$ 2.0 mg/dl). In addition, in a multivariate analysis controlled for incidence of diabetes, four other previously recognized renal risk factors (increased preoperative serum creatinine, weight, history of diabetes, and history of hypertension) were independently associated with a greater postoperative increase in serum creatinine. Genetic polymorphism has previously been implicated as a factor in the occurrence and progression of chronic renal disease, but we present the first evidence of a possible genetic basis

Table 1. Descriptive Statistics of the Renal Study Population

	Apolipoprotein E Genotype Groups			
	E2 (2/2, 2/3, 2/4)	E3 (3/3)	E4 (3/4, 4/4)	*P* Value*
N (%)	82 (14.5)	339 (60.1)	143 (25.4)	—
By genotype, N (%)	2/2/4 (0.7)	3/3/339 (60.1)	3/4/134 (23.8)	—
	2/3/63 (11.2)		4/4/9 (1.6)	—
	2/4/15 (2.7)			—
Age (yr)	62.5 (10.3)	62.0 (10.4)	60.7 (10.2)	0.35
Gender (N, % male)	54 (65.9)	251 (74.0)	102 (71.3)	0.31
Weight (kg)	85.5 (17.8)	84.3 (15.9)	84.5 (15.8)	0.84
Hypertension (N, %)	50 (61.0)	193 (56.9)	84 (58.7)	0.78
Diabetes (N, %)	32 (39.0)	88 (26.0)	30 (21.0)	0.014
Bypass time (min)	103.1 (34.7)	109.6 (30.6)	109.2 (31.6)	0.79
Mean preop creatinine (mg/dl†)	1.05 (0.25)	1.06 (0.22)	1.01 (0.23)	0.65

Data is represented as N (%) for categoric characteristics and as mean (SD) for numeric characteristics.

* *P* value for overall univariate comparison of three genotype groups.

† To convert mg/dl to μM, multiply mg/dl by 88.4.

N = number of patients; preop = preoperative.

Table 2. Mean Serum Creatinine Measures in the Study Population, Represented by Genotype Group and Presence or Absence of Diabetes

Genotype Group	E2 (2/2, 2/3, 2/4)		E3 (3/3)		E4 (3/4, 4/4)	
Diabetes	Yes	No	Yes	No	Yes	No
No. of patients	32	50	88	251	30	113
Preoperative serum creatinine (mg/dl)	1.01	1.04	1.04	1.05	1.02	1.03
Max postop serum creatinine (mg/dl)	1.30	1.34	1.40	1.27	1.23	1.19
Pre- to postoperative creatinine (mg/dl)	0.24	0.29	0.36	0.22	0.21	0.16

Diabetic patients are unevenly distributed among the three groups ($P = 0.014$) (table 1). Any variability in postoperative serum creatinine values related to diabetes is controlled for in the multivariate analysis (table 3).

Max = maximum; postop = postoperative.

for the development of acute renal impairment. Our findings explain approximately as much variability in postcoronary bypass surgery serum creatinine values as can be explained by the combined influences of two known renal dysfunction risk factors: diabetes and hypertension. If APOE genotype is confirmed to be a renal dysfunction risk factor in larger patient groups, this data may contribute to future preoperative renal risk evaluation for cardiac surgical patients. Although analysis of serum creatinine values may not be the optimal method to assess changes in perioperative renal filtration, maximum postoperative values consistently and independently have been associated with morbidity and mortality after cardiac surgery.[2,3] In addition, other more accurate tests of renal function, such as 2- or 24-h urine collections for creatinine clearance, have limitations in the perioperative period and have been less studied regarding their relation to outcome after cardiac surgery. Study findings may be related to isoform-specific differences in APOE interactions with lipid metabolism, inflammation, and tissue repair responses.

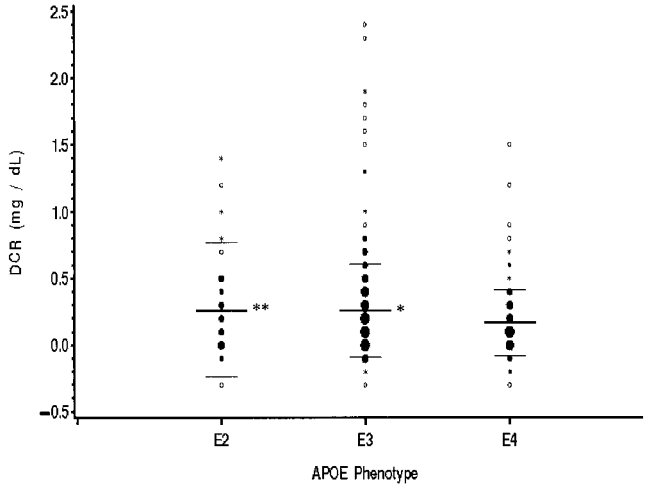

Fig. 1. Postoperative change in serum creatinine values (DCr) after cardiac surgery in the three apolipoprotein E genotype groups (E2: 2/2,2/3,2/4; E3: 3/3; E4: 3/4,4/4/4). Three extreme outliers have been cut off to fit the scale (E2, −1.2; E2, +3.4; and E4, −0.7 mg/dl). Mean DCr for the E4 group is significantly less than for the E2 and E3 genotype groups (Scheffé adjusted $P = 0.038$ and $P = 0.015$,* respectively). Bars represent mean and SD values. Individual data points are shown as open circles, and filled circles of increasing size represent DCr values with greater numbers of datapoints.**

The APOE allele-specific pattern of renal risk after cardiac surgery is similar to that reported for some chronic renal diseases. Although the $\epsilon 3$ allele has been associated with lipoprotein glomerulopathy and progression of diabetic nephropathy,[9,10,16,19] the $\epsilon 2$ allele has been most frequently associated with these and other chronic nephropathies.[7,8,10,13,21,23,24] In contrast, reduced risk of diabetic nephropathy has been attributed to the $\epsilon 4$ allele.[19] The "renal" pattern of APOE allele-associated risk (*i.e.*, $\epsilon 4$ favorable) contrasts with the association observed with atherosclerosis, ischemic heart disease, and numerous acute and chronic neurologic disorders (*i.e.*, $\epsilon 4$ unfavorable).[28,30,31,33,34] However, recent evidence of renal, atherosclerotic, and neurologic disorders that show alternate risk patterns disallows generalization regarding organ-specific APOE allele effects.[20,35,36] An intriguing interpretation of the observations is that APOE allele inheritance influences disease risk through at least two different pathophysiologic mechanisms.

Renal disease has been linked with atherosclerosis and dyslipidemias. Several studies have associated severity of aortic atherosclerosis with postoperative renal injury in cardiac and vascular surgical patients.[37–39] In addition, Kasiske[40] demonstrated an association of intrarenal atherosclerosis with glomerulosclerosis in humans. Conflicting data exists regarding the association of APOE alleles with atherosclerosis.[41] Severe aortic atherosclerosis rapidly develops in APOE-deficient mice. The APOE2/3 genotype has been associated with increased risk of carotid atherosclerosis and microangiopathy-re-

Table 3. Multivariate Predictors of Postoperative Peak Serum Creatinine Concentration in 564 Patients after Coronary Bypass Surgery

	df	*P* Value	Partial R^2
Apolipoprotein E genotype group	2	0.032	0.0123
Preoperative serum creatinine	1	<0.0001	0.344
Weight	1	0.0003	0.0233
History of hypertension	1	0.056	0.00652
History of diabetes	1	0.049	0.00696

The apolipoprotein E genotype group explains approximately as much variability in postcoronary bypass surgery as can be explained by the combined influences of two known renal dysfunction risk factors, diabetes and hypertension. Genotype assignment to the most common (*i.e.*, E3 = 3/3) or to the less common genotype groups (*i.e.*, E2 = 2/2, 2/3, 2/4; E4 = 3/4, 4/4) is determined by the presence of $\varepsilon 2$ and $\varepsilon 4$ alleles.

df = degrees of freedom.

lated cerebral damage,[35,42] but is also attributed the lowest likelihood of aortic atherosclerosis (*vs.* E3/3 and E3/4) in a study of 720 young men who died of extracardiac causes.[33] However, a majority of studies have linked the $\epsilon 4$ allele to premature atherosclerosis and associated heart disease.[33,34,43] APOE allele–specific lipid abnormalities are well-characterized and associated, in some cases, with progression of chronic renal disease (*e.g.*, type III hyperlipoproteinemia with lipoprotein glomerulopathy). However, the role of dyslipidemias in influencing acute renal injury has not been reported. Despite the significance of atherosclerosis in predicting postoperative acute renal dysfunction, the findings of this study cannot be easily be explained on the basis of APOE isoform–specific atherosclerosis risk alone.

Study findings may reflect isoform-specific differences in the evolution of occult renal impairment relating to known interactions of APOE with inflammation and tissue repair responses. Recent studies have highlighted the significance of inflammation in the pathophysiology of acute renal injury.[44,45] Several stimuli during cardiac surgery (*e.g.*, CPB, endotoxemia, tissue injury) lead to a predictable but highly variable inflammatory response.[46–49] In general, APOE-mediated immunoregulatory effects act to dampen inflammatory responses.[50–53] However, cytokine-mediated alterations in lipid and lipoprotein profiles that potentiate host defenses as part of the "acute phase response," may also be influenced by APOE.[54,55] Renal regeneration after acute injury is critical to structural and functional recovery. The influence of APOE on tissue repair, cell differentiation, and growth has been most studied in neural tissues, in which allele-specific differences have been shown.[54–56] However, APOE allele–specific evaluations of inflammation and healing in the kidney have not been performed.

In summary, we present evidence that the APOE–$\epsilon 4$ allele is associated with a reduced postoperative increase in serum creatinine after cardiac surgery compared with both the $\epsilon 2$ and $\epsilon 3$ alleles. This is the first report of a possible genetic basis for acute renal impairment. These data may contribute to renal risk stratification for cardiac surgery and may raise questions regarding apolipoprotein E and the pathophysiology of acute renal injury.

References

1. Roach GW, Kanchuger M, Mangano CM, Newman M, Nussmeier N, Wolman R, Aggarwal A, Marschall K, Graham SH, Ley C: Adverse cerebral outcomes after coronary bypass surgery. Multicenter Study of Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation Investigators. N Engl J Med 1996; 335:1857–63

2. Conlon PJ, Stafford-Smith M, White WD, Newman MF, King S, Winn MP, Landolfo K: Acute renal failure following cardiac surgery. Nephrol Dial Transplant 1999; 14:1158–62

3. Mangano CM, Diamondstone LS, Ramsay JG, Aggarwal A, Herskowitz A, Mangano DT: Renal dysfunction after myocardial revascularization: Risk factors, adverse outcomes, and hospital resource utilization. The Multicenter Study of Perioperative Ischemia Research Group. Ann Intern Med 1998; 128:194–203

4. Chertow GM, Lazarus JM, Christiansen CL, Cook EF, Hammermeister KE, Grover F, Daley J: Preoperative renal risk stratification. Circulation 1997; 95:878–84

5. Page US, Washburn T: Using tracking data to find complications that physicians miss: The case of renal failure in cardiac surgery. Jt Comm J Qual Improv 1997; 23:511–20

6. Chertow GM, Levy EM, Hammermeister KE, Grover F, Daley J: Independent association between acute renal failure and mortality following cardiac surgery. Am J Med 1998; 104:343–8

7. Feussner G, Bommer J, Ziegler R: Severe type III hyperlipoproteinemia in two patients maintained on chronic hemodialysis. Klin Wochenschr 1990; 68:65–70

8. Feussner G, Wingen AM, Ziegler R: Type III hyperlipoproteinemia in a child with hemolytic uremic syndrome. Metabolism 1990; 39:1196–9

9. Oikawa S, Suzuki N, Sakuma E, Saito T, Namai K, Kotake H, Fujii Y, Toyota T: Abnormal lipoprotein and apolipoprotein pattern in lipoprotein glomerulopathy. Am J Kidney Dis 1991; 18:553–8

10. Saito T, Sato H, Oikawa S, Kudo K, Kurihara I, Nakayama K, Abe K, Yoshinaga K, Sakaguchi H: Lipoprotein glomerulopathy. Report of a normolipidemic case and review of the literature. Am J Nephrol 1993; 13:64–8

11. Horita K, Eto M, Makino I: Apolipoprotein E2, renal failure and lipid abnormalities in non-insulin-dependent diabetes mellitus. Atherosclerosis 1994; 107:203–11

12. Ellis D, Orchard TJ, Lombardozzi S, Yunis EJ, McCauley J, Agostini R, Diamond JR: Atypical hyperlipidemia and nephropathy associated with apolipoprotein E homozygosity. J Am Soc Nephrol 1995; 6:1170–7

13. Eto M, Horita K, Morikawa A, Nakata H, Okada M, Saito M, Nomura M, Abiko A, Iwashima Y, Ikoda A, Makino I: Increased fre-

quency of apolipoprotein epsilon 2 allele in non-insulin dependent diabetic (NIDDM) patients with nephropathy. Clin Genet 1995; 48: 288–92

14. Yoshida H, Kuriyama S, Atsumi Y, Tomonari H, Mitarai T, Hamaguchi A, Kubo H, Kawaguchi Y, Kon V, Matsuoka K, Ichikawa I, Sakai O: Angiotensin I converting enzyme gene polymorphism in non-insulin dependent diabetes mellitus. Kidney Int 1996; 50:657–64

15. Baboolal K, Ravine D, Daniels J, Williams N, Holmans P, Coles GA, Williams JD: Association of the angiotensin I converting enzyme gene deletion polymorphism with early onset of ESRF in PKD1 adult polycystic kidney disease. Kidney Int 1997; 52:607–13

16. Maruyama K, Arai H, Ogawa T, Tomizawa S, Morikawa A: Lipoprotein glomerulopathy: A pediatric case report. Pediatr Nephrol 1997; 11:213–4

17. Rogus JJ, Moczulski D, Freire MB, Yang Y, Warram JH, Krolewski AS: Diabetic nephropathy is associated with AGT polymorphism T235: results of a family-based study. Hypertension 1998; 31:627–31

18. Yu H, Bowden DW, Spray BJ, Rich SS, Freedman BI: Identification of human plasma kallikrein gene polymorphisms and evaluation of their role in end-stage renal disease. Hypertension 1998; 31:906–11

19. Kimura H, Suzuki Y, Gejyo F, Karasawa R, Miyazaki R, Suzuki S, Arakawa M: Apolipoprotein E4 reduces risk of diabetic nephropathy in patients with NIDDM. Am J Kidney Dis 1998; 31:666–73

20. Boize R, Benhamou PY, Corticelli P, Valenti K, Bosson JL, Halimi S: ApoE polymorphism and albuminuria in diabetes mellitus: A role for LDL in the development of nephropathy in NIDDM? Nephrol Dial Transplant 1998; 13:72–5

21. Werle E, Fiehn W, Hasslacher C: Apolipoprotein E polymorphism and renal function in German type 1 and type 2 diabetic patients. Diabetes Care 1998; 21:994–8

22. Yang AH, Ng YY, Tarng DC, Chen JY, Shiao MS, Kao JT: Association of apolipoprotein E polymorphism with lipoprotein glomerulopathy. Report of 2 cases with a new genotype and comparison of the relative frequencies of apolipoprotein E isoforms in lipoprotein glomerulopathy and in the general population. Nephron 1998; 78:266–70

23. Chowdhury TA, Dyer PH, Kumar S, Gibson SP, Rowe BR, Davies SJ, Marshall SM, Morris PJ, Gill GV, Feeney S, Maxwell P, Savage D, Boulton AJ, Todd JA, Dunger D, Barnett AH, Bain SC: Association of apolipoprotein epsilon2 allele with diabetic nephropathy in Caucasian subjects with IDDM. Diabetes 1998; 47:278–80

24. Matsunaga A, Sasaki J, Komatsu T, Kanatsu K, Tsuji E, Moriyama K, Koga T, Arakawa K, Oikawa S, Saito T, Kita T, Doi T: A novel apolipoprotein E mutation, E2 (Arg25Cys), in lipoprotein glomerulopathy. Kidney Int 1999; 56:421–7

25. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA: Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 1993; 261:921–3

26. Corder EH, Saunders AM, Risch NJ, Strittmatter WJ, Schmechel DE, Gaskell PC Jr, Rimmler JB, Locke PA, Conneally PM, Schmader KE, Small GW, Roses AD: Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. Nat Genet 1994; 7:180–4

27. Eichner J, Kuller L, Orchard T: Relation of apolipoprotein E phenotype to myocardial infarction and mortality from coronary artery disease. Am J Cardiol 1993; 71:160–165

28. Teasdale GM, Nicoll JA, Murray G, Fiddes M: Association of apolipoprotein E polymorphism with outcome after head injury. Lancet 1997; 350:1069–71

29. Tardiff BE, Newman MF, Saunders AM, Strittmatter WJ, Blumenthal JA, White WD, Croughwell ND, Davis RD Jr, Roses AD, Reves JG: Preliminary report of a genetic basis for cognitive decline after cardiac operations. The Neurologic Outcome Research Group of the Duke Heart Center. Ann Thorac Surg 1997; 64:715–20

30. Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, Roses AD: Apolipoprotein E: High-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proc Natl Acad Sci U S A 1993; 90:1977–81

31. Saunders AM, Strittmatter WJ, Schmechel D, George-Hyslop PH, Pericak-Vance MA, Joo SH, Rosi BL, Gusella JF, Crapper-MacLachlan DR, Alberts MJ, Hulette C, Crain B, Goldaber D, Roses AD: Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. Neurology 1993; 43:1467–72

32. Menzel HJ, Kladetzky RG, Assmann G: Apolipoprotein E polymorphism and coronary artery disease. Arteriosclerosis 1983; 3:310–

33. Hixson JE: Apolipoprotein E polymorphisms affect atherosclerosis in young males. Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. Arterioscler Thromb 1991; 11: 1237–44

34. Terry JG, Howard G, Mercuri M, Bond MG, Crouse JR III: Apolipoprotein E polymorphism is associated with segment-specific extracranial carotid artery intima-media thickening. Stroke 1996; 27: 1755–9

35. de Andrade M, Thandi I, Brown S, Gotto A Jr, Patsch W, Boerwinkle E: Relationship of the apolipoprotein E polymorphism with carotid artery atherosclerosis. Am J Hum Genet 1995; 56:1379–90

36. McCarron MO, Muir KW, Weir CJ, Dyker AG, Bone I, Nicoll JA, Lees KR: The apolipoprotein E epsilon4 allele and outcome in cerebrovascular disease. Stroke 1998; 29:1882–7

37. Davila-Roman VG, Kouchoukos NT, Schechtman KB, Barzilai B: Atherosclerosis of the ascending aorta is a predictor of renal dysfunction after cardiac operations. J Thorac Cardiovasc Surg 1999; 117: 111–6

38. Hosaka S, Kamiya K, Akimoto S, Suzuki O, Kobayashi M, Matsukawa T, Tada Y: Atheromatous embolization as a cause of postoperative renal dysfunction in infrarenal aortic reconstructive surgery. Nippon Geka Gakkai Zasshi 1994; 95:109–15

39. Nypaver TJ, Shepard AD, Reddy DJ, Elliott JP Jr, Ernst CB: Supraceliac aortic cross-clamping: Determinants of outcome in elective abdominal aortic reconstruction. J Vasc Surg 1993; 17:868–75

40. Kasiske BL: Relationship between vascular disease and age-associated changes in the human kidney. Kidney Int 1987; 31:1153–

41. Kashyap VS, Santamarina-Fojo S, Brown DR, Parrott CL, Applebaum-Bowden D, Meyn S, Talley G, Paigen B, Maeda N, Brewer HB Jr: Apolipoprotein E deficiency in mice: Gene replacement and prevention of atherosclerosis using adenovirus vectors. J Clin Invest 1995; 96:1612–20

42. Schmidt R, Schmidt H, Fazekas F, Schumacher M, Niederkorn K, Kapeller P, Weinrauch V, Kostner GM: Apolipoprotein E polymorphism and silent microangiopathy-related cerebral damage. Results of the Austrian Stroke Prevention Study. Stroke 1997; 28:951–6

43. Luc G, Bard JM, Arveiler D, Evans A, Cambou JP, Bingham A, Amouyel P, Schaffer P, Ruidavets JB, Cambien F, Fruchart J-C, Ducimetiere P: Impact of apolipoprotein E polymorphism on lipoproteins and risk of myocardial infarction. The ECTIM Study. Arterioscler Thromb 1994; 14:1412–9

44. Johnson JP, Rokaw MD: Sepsis or ischemia in experimental acute renal failure: What have we learned? New Horiz 1995; 3:608–14

45. Camussi G, Tetta C, Bussolino F, Andres G, Turello E, Baglioni C: Involvement of cytokines and platelet-activating factor in renal pathology. J Lipid Mediat 1990; 2(suppl):S203–13

46. Tonnesen E, Christensen VB, Toft P: The role of cytokines in cardiac surgery. Int J Cardiol 1996; 53(suppl):S1–10

47. Misoph M, Babin-Ebell J: Interindividual variations in cytokine levels following cardiopulmonary bypass. Heart Vessels 1997; 12:119–27

48. Martinez-Pellus AE, Merino P, Bru M, Canovas J, Seller G, Sapina J, Fuentes T, Moro J: Endogenous endotoxemia of intestinal origin during cardiopulmonary bypass. Role of type of flow and protective effect of selective digestive decontamination. Intensive Care Med 1997; 23:1251–7

49. Brix-Christensen V, Tonnesen E, Sorensen IJ, Bilfinger TV, Sanchez RG, Stefano GB: Effects of anaesthesia based on high versus low doses of opioids on the cytokine and acute-phase protein responses in patients undergoing cardiac surgery. Acta Anaesthesiol Scand 1998; 42:63–70

50. Hui DY, Harmony JA, Innerarity TL, Mahley RW: Immunoregulatory plasma lipoproteins. Role of apoprotein E and apoprotein B. J Biol Chem 1980; 255:11775–81

51. Laskowitz DT, Goel S, Bennett ER, Matthew WD: Apolipoprotein E suppresses glial cell secretion of TNF alpha. J Neuroimmunol 1997; 76:70–4

52. Laskowitz DT, Matthew WD, Bennett ER, Schmechel D, Herbstreith MH, Goel S, McMillian MK: Endogenous apolipoprotein E suppresses LPS-stimulated microglial nitric oxide production. Neuroreport 1998; 9:615–8

53. Hill GE, Pohorecki R, Whitten CW: Plasma lipid concentrations correlate inversely with CPB-induced interleukin-6 release. Can J Anaesth 1998; 45:509–14

54. Mouchel Y, Lefrancois T, Fages C, Tardy M: Apolipoprotein E gene expression in astrocytes: Developmental pattern and regulation. Neuroreport 1995; 7:205–8

55. Feingold KR, Hardardottir I, Grunfeld C: Beneficial effects of cytokine induced hyperlipidemia. Z Ernahrungswiss 1998; 37:66–74

56. Arendt T, Schindler C, Bruckner MK, Eschrich K, Bigl V, Zedlick D, Marcova L: Plastic neuronal remodeling is impaired in patients with Alzheimer's disease carrying apolipoprotein epsilon 4 allele. J Neurosci 1997; 17:516–29