Association between C-reactive protein and Incidence of Type-2 Diabetes in a Japanese Worksite-based Cohort

Chaochen Wang[1], Hiroshi Yatsuya[1], Koji Tamakoshi[1], Hideaki Toyoshima[2], Yuanying Li[3],Kentaro Yamshita[1], Mayu Uemura[1], Atsuko Aoyama[1]

1 Nagoya Univ; 2 Anjo Kosei Hospital; 3 Osaka Univ;

Introduction

- Chronic low grade systemic inflammation is suggested to be involved in the pathogenesis of type-2 diabetes mellitus (T2D).[1]

- High-sensitivity C-reactive protein (CRP)—an acute-phase protein—was proved to be a suitable marker of systemic inflammation and shown to be increased in patients with type-2 diabetes.[2-3]

- The identification of high-risk individuals would be helpful to implement early lifestyle intervention strategies to prevent diabetes. A range of prediction models and rules to predict the onset of T2D have been published so far. [4-6]

Introduction

✓However, it is still unclear whether the association between serum CRP and incident T2D is a causal one or the consequence of other confounders like obesity. *Brunner EJ et al.* reported evidence that systemic CRP levels are not responsible for development of insulin resistance.

✓And, most studies have been conducted in white groups so it is still unknown whether these relationship exists in Eastern Asian populations.

Objective

✓We examined whether CRP is a risk factor to predict T2D incidence in a Japanese worksite-based cohort.

Methods: Subjects and blood test

✓3507 civil servants from Aichi Prefecture were included in our study. Subjects were aged 35-66 at baseline (2002) and without self-reported diabetes.

✓Blood samples were stored at -80 degrees Celsius until biochemical assay. C-reactive protein (CRP) was measured by latex nephelometry (BNII; Dade Behring Co, Ltd).

✓T2D incidence was defined as the year when annually-assessed fasting blood glucose level first exceeded 126mg/dl, or self-reported initiation of medication through follow-up until 2007.

Statistical analysis

- Subjects with CRP value 10 mg/L or higher were excluded from our analysis. And we also divided them into 4 groups according to the CRP level quartiles. (Q1: 0.02-0.18; Q2: 0.18-0.34; Q3: 0.34-0.69; Q4: 0.69-10)

- Cox-proportional hazards regression was used to estimate hazard ratios (HRs) for the incidence of T2D adjusted for sex, age, body mass index (BMI), alcohol intake, smoking status and family history of diabetes.

- Further analysis we stratified the subjects by smoking habits (current smokers and nonsmoker = never and past smoker)

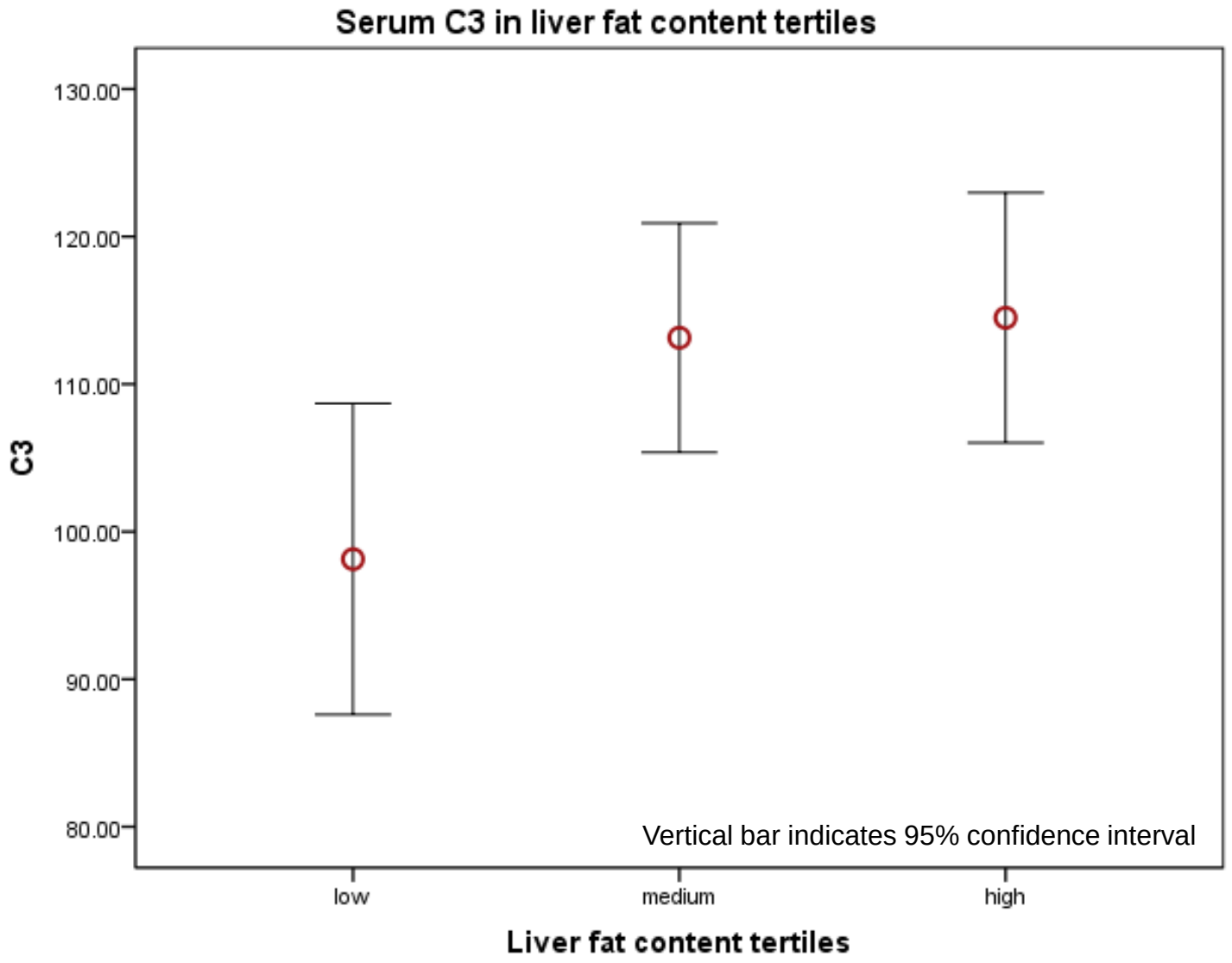
Subject characteristics according to the quartiles of serum CRP level :

	ALL	Q1: 0.02–0.18	Q2: 0.18–0.34	Q3: 0.34–0.69	Q4: 0.69–10	P value
Total(n)	3507	963	890	843	811	
Age(year)						< 0.001
mean(SD)	47.9 (7.1)	46.7 (7)	47.4 (7)	48.8 (6.8)	48.8 (7.3)	
missing = 0						
Sex [n(%)]						< 0.001
male	2677 (76.3%)	636 (66)	683 (76.8)	681 (80.9)	677 (83.7)	
premenopausal female	589 (16.8%)	251 (26.1)	154 (17.3)	101 (12)	83 (10.3)	
postmenopausal female	237 (6.8%)	76 (7.9)	52 (5.8)	60 (7.1)	49 (6.1)	
missing	4 (0.1)					
BMI(kg/m^2)						< 0.001
mean(SD)	22.8 (2.7)	21.7 (2.3)	22.7 (2.6)	23.3 (2.6)	23.9 (2.8)	
missing	20					
alcohol(g/d)						0.06
mean(SD)	13.9 (20.6)	12.5 (18.7)	14.2 (20.4)	15 (22.7)	14.5 (20.6)	
missing	58					
smoking status [n(%)]						< 0.001
current	983	192 (20.5)	236 (27)	242 (29.5)	313 (39.7)	
past	755	193 (20.6)	193 (22.1)	203 (24.8)	166 (21.1)	
never	1682	553 (59)	445 (50.9)	375 (45.7)	309 (39.2)	
missing	87					
regular exercise or not [n(%)]						0.56
yes	1893	512 (54.8)	499 (57.4)	456 (56.2)	426 (54.3)	
no	1570	422 (45.2)	370 (42.6)	356 (43.8)	359 (45.7)	
missing	107					
family history of diabetes or not [n(%)]						0.86
yes	517	138 (14.3)	126 (14.2)	129 (15.3)	124 (15.3)	
no	2990	825 (85.7)	764 (85.8)	714 (84.7)	687 (84.7)	
missing	0					

Results: Multivariate-adjusted means of C3 according to liver fat content tertile

	liver fat content groups				
	low	medium	high	p	linear p
logC3	4.57±0.04	4.71±0.04	4.72±0.05	0.024*	0.029*
logCRP	5.81±0.35	6.45±0.31	6.08±0.37	0.371	0.623
logTNF-α	0.09±0.23	0.19±0.20	0.13±0.24	0.951	0.913
logIL-6	0.01±0.12	0.21±0.11	0.34±0.13	0.233	0.106
logAST	3.10±0.08	3.12±0.08	3.20±0.09	0.747	0.464
logALT	3.09±0.15	3.10±0.14	3.16±0.16	0.950	0.769
logInsulin	1.13±0.18	1.71±0.16	1.64±0.19	0.048*	0.079

Figure 3: Serum level of C3 increases with the accumulation of liver fat content



Discussion

✓Because C3 indicates clearance of apoptotic cells and promotion of liver regeneration, it is possible to speculate that there exists tissue injury inside the liver.

✓Accumulation of triglycerides (TG) in the liver, independently of the initial cause, leads to lipotoxicity, generation of oxidative stress and inflammation. Our study may suggests that liver injury may begin as long as the lipid inside liver tissue increases, even without diagnosis of fatty liver disease.

Discussion

✓One of the breakdown products of C3, termed acylation-stimulating protein (ASP) possibly plays a key role that since it promotes triglycerides accumulation in hepatocytes, thereby creating a vicious cycle that complement activation promotes hepatosteatosis, and that further increases complement activation.[3]

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Discussion

✓Although the evolutionary purpose of immunity is to defend against pathogens and foreign substances, in the setting of obesity, dietary fatty acids, especially oxidized fatty acids may be perceived as foreign substances that modulate inflammation. And the activation of immune pathways can adversely affect hepatic lipid metabolism leading to hepatic injury, steatohepatitis, and fibrosis.

Conclusion

- ✓ The complement system and especially its component C3 appear to be associated with the accumulation of lipid content within the liver tissue.
- ✓ Clarifying the mechanisms whereby C3 contributes to hepatosteatosis may ultimately help in understanding the pathogenesis of fatty liver disease.

References

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