THE INTERLEUKIN-6 PATHWAY AND CARDIOVASCULAR DISEASE IN CKD: A MENDELIAN RANDOMIZATION STUDY

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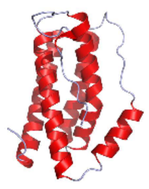
INTRODUCTION



High serum interleukin-6 (IL6) is a strong predictor of cardiovascular (CV) disease in large scale cohort studies in the general population.

This cytokine is substantially increased in chronic kidney disease (CKD) patients but the IL6-CV disease relationship has been investigated just in one relatively small cohort study and it is still unknown whether the link between IL6 and CV disease in CKD is causal in nature.

METHODS

In a cohort of 755 CKD stage 2-5 patients, we studied the relationship of serum IL6 with background CV comorbidities as well as with incident CV events (follow up: 31±10 months) and adopted the functional polymorphism (-174 C/G) in the promoter of the IL6 gene as an unbiased marker (Mendelian randomization) of circulating IL6 to investigate whether the IL6-CV events link is causal in nature.

	GG genotype (n= 52)	CG/CC genotype (n= 703)	P
Age (years)	59±13	62±10	0.09
Males (%)	39 (75)	414 (59)	0.02
Diabetes (%)	21 (40)	242 (34)	0.38
Current Smokers (%)	9 (17)	89 (13)	0.34
CV comorbidities (%)	23 (44)	198 (28)	0.01
BMI (kg/m^2)	27.9±3.8	28.2±4.7	0.54
Systolic BP (mmHg)	132±16	134±18	0.41
Diastolic BP (mmHg)	76±10	78±10	0.15
On anti-hypertensive treatment (%)	44 (98)	647 (97)	0.69
Glucose (mg/dL)	98 (87-127)	99 (88-120)	0.65
Total cholesterol (mg/dL)	173±43	188±45	0.02
Haemoglobin (g/dL)	12±2.0	13±1.8	0.29
Albumin (g/dL)	4.1±0.4	4.2±0.5	0.53
CRP (mg/L)	3.2 (1.2 - 10)	2.3 (1.0 – 5.4)	0.06
Phosphate (mg/dL)	3.71±0.68	3.72±0.78	0.92
eGFR MDRD$_{186}$ (ml/min/1.73m2)	34±12	36±13	0.32
Urinary protein (mg/24h)	0.7 (0.2 - 1.6)	0.6 (0.2 -1.5)	0.53

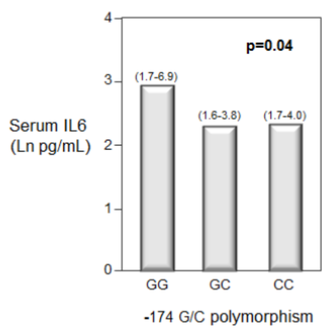


Figure 2

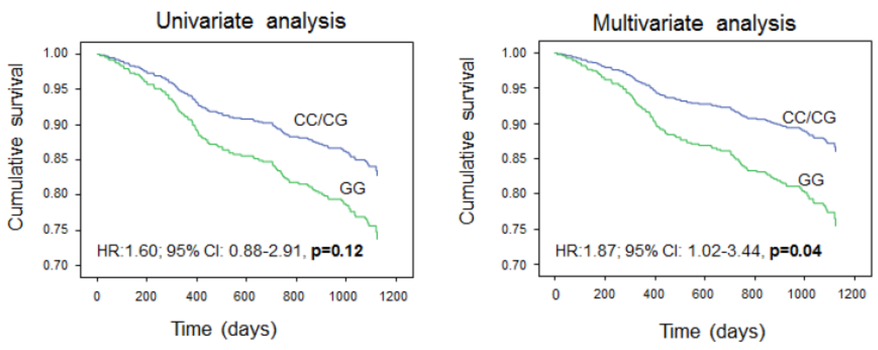


Figure 3

RESULTS 1

Serum IL6 above the median value associated with past CV events both in unadjusted (OR:2.14, 95%CI:1.55-2.95; P<0.001) and multivariate adjusted analyses (OR:1.58, 95%CI:1.12-2.24; P=0.01). Over a 31±10 months (range: 0.3 to 48 months) follow-up, 117 patients had incident CV events and in fully adjusted analyses the incidence rate of these events was by the 67% higher (HR:1.67 95% CI:1.12-2.50; P=0.01) in patients with IL6 above the median as compared with patients with IL6 below this threshold (**Fig. 1**).

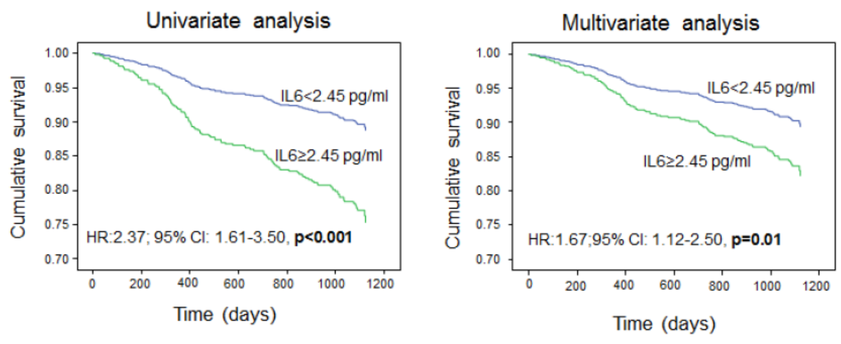


Figure 1

RESULTS 2

Patients homozygous for the risk allele (G) of the -174 C/G polymorphism had higher levels of IL6 than those with other genotypes (GG: 2.90 pg/ml, IQR: 1.7-6.9 pg/ml; CG: 2.40 pg/ml, 1.6-3.8 pg/ml; CC: 2.50 pg/ml, 1.7-4.0 pg/ml, P=0.04) (**Fig. 2**).

Homozygous GG patients had more frequently background CV events as well as a higher rate of incident CV events in unadjusted and fully adjusted (background CV events OR:2.15, 95%CI:1.15-4.0 and incident CV events HR:1.88, 95%CI:1.02-3.44) analyses including a series of risk factors not adequately controlled by Mendelian Randomization (**Fig. 3**).

Because genetic polymorphisms are randomly transmitted at mating, most likely such an association is causal in nature.

CONCLUSION

In stage 2-5 CKD, high serum levels of IL6 associate with background CV events and predict an increased risk of incident CV events. The parallel association with background and incident CV events of the risk allele for high IL6 in the -174 C/G polymorphism supports the contention that the serum IL6-CV events relationship is causal in nature.

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