Spinal Cord (1998) 36, 868–869

http://www.stockton-press.co.uk/sc

Letter to the Editor

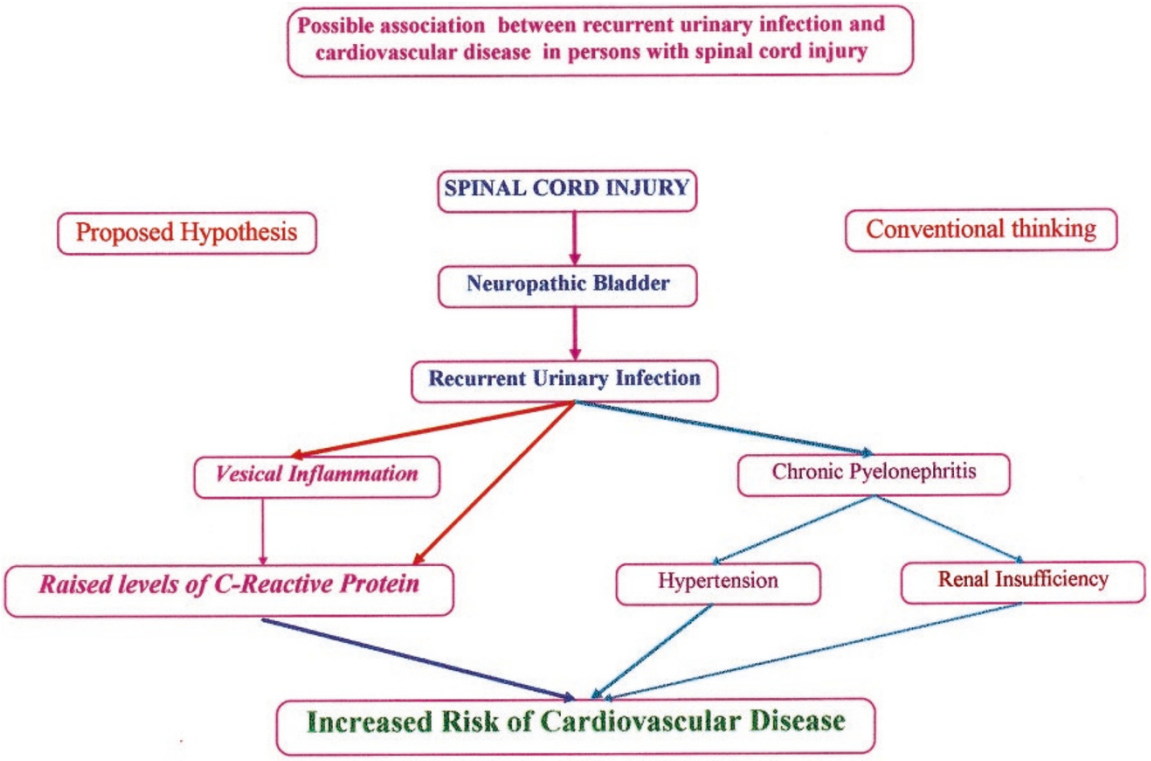
Recurrent urinary infection, raised serum levels of C-reactive protein, and the risk of cardiovascular disease in patients with spinal cord injury: a hypothesis

Frankel and associates[1] observed that heart disease was the second commonest cause of death in patients who sustained spinal cord injury between 1973 and 1990. Cardiovascular morbidity affects patients with spinal cord injury earlier than able-bodied individuals. Subjects with spinal cord injury exhibit decreased glucose tolerance and insulin resistance.[2] Together with increased fat mass and dyslipidaemias,[3] these metabolic derangements may be risk factors for cardiovascular disease.

A significant number of persons with spinal cord injury suffer from recurrent episodes of acute urinary infection; some of them continue to have chronic, low-grade urinary infection. Urinary infection in spinal cord injury patients is associated with raised serum levels of C-reactive protein.[4] We observed varying degrees of inflammatory changes in the bladder biopsies taken from asymptomatic patients with spinal cord injury.

We propose a hypothesis that raised serum levels of C-reactive protein may provide yet another pathogenic mechanism for the development of cardiovascular disease in patients with spinal cord injury. Different pathogenic mechanisms are likely to require different therapeutic approaches. The conventional thinking on the association between urinary infection and cardiovascular disease, and the proposed additional risk factor of raised serum levels of C-reactive protein linking urinary infection with cardiovascular disease are illustrated in the flow-chart. The proposed mechanism may act as a supplementary risk factor for the pathogenesis of cardiovascular disease in patients with spinal cord injury. This hypothesis is not intended to replace the conventional opinion on the risk factors for the development of cardiovascular disease in patients with spinal cord injury.

The mechanism that relates the level of C-reactive protein to atherothrombosis is unclear. Elevated serum levels of C-reactive protein are non-specific but sensitive markers of the acute phase response to infectious agents, immunologic stimuli, and tissue damage.[5] Raised serum C-reactive protein values are associated with raised serum fibrinogen, plasminogen, factor VIII, white blood cell count, fasting insulin and serum triglyceride values; depressed high density lipoprotein-cholesterol; and raised fasting blood sugar concentrations. These associations are not diminished



by controlling for body mass index.[6] Serum C-reactive protein concentration could be related to the pathogenesis of atherosclerosis via the effects of inflammation on conventional risk factors.[7] A further possibility is that the cytokine and cellular mediators of the acute phase response originating at a distance to the coronary arteries are directly involved in the pathogenesis of atherosclerosis. It is possible that C-reactive protein is a surrogate for interleukin-6, a cellular cytokine associated with recruitment of macrophages and monocytes into atherosclerotic plaques.[8] In addition, C-reactive protein can induce monocytes to express tissue factor, a membrane glycoprotein important in initiating coagulation. Ridker and associates[8] provided convincing evidence that among normal men, base-line serum levels of C-reactive protein are predictive of future myocardial infarction. The risk increased with rising levels of C-reactive protein, even when the values were within the normal range. The increased risk was independent of lipid-related and non-lipid-related cardiovascular risk factors and was reduced by treatment with aspirin in direct proportion to the base-line C-reactive protein value.

If this hypothesis is proved correct, it may be desirable to monitor serum C-reactive protein levels at regular intervals in patients who develop recurrent urinary infection. Randomised aspirin treatment was associated with a large and statistically significant reduction in the risk of myocardial infarction among men with base-line levels of C-reactive protein in the highest quartile (risk reduction, 55.7%; $P = 0.02$).[8] It is possible that the use of aspirin may confer similar benefit to those spinal cord injury patients with raised serum levels of C-reactive protein.

Acknowledgments

Our gratitude to Jacqueline Stevens for the diagram.

S Vaidyanathan, BM Soni,
G Singh, P Mansour, JWH Watt,
P Sett and KR Krishnan
Regional Spinal Injuries Centre
and Department of Histopathology,
District General Hospital,
Southport, Merseyside, UK

References

1 Frankel HL *et al*. Long-term survival in spinal cord injury: a fifty year investigation. *Spinal Cord* 1998; **36:** 266 – 274.
2 Karlsson A-K. Metabolism and sympathetic function in spinal cord injured subjects. Sahlgrenska University Hospital, University of Goteborg, Goteborg, Sweden, 1997, p 4.
3 Tharion G, Prasad KR, Gopalan L, Bhattacharji S. Glucose intolerance and dyslipidaemias in persons with paraplegia and tetraplegia in South India. *Spinal Cord* 1998; **36:** 228 – 230.
4 Galloway A *et al*. Serial concentrations of C-reactive protein as an indicator of urinary tract infection in patients with spinal injury. *Journal of Clinical Pathology* 1986; **39:** 851 – 855.
5 Maseri A. Inflammation, atherosclerosis, and ischemic events — exploring the hidden side of the moon. *The New England Journal of Medicine* 1997; **336:** 1014 – 1016.
6 Mendall MA. Inflammatory responses and coronary heart disease. The 'dirty chicken' hypothesis of cardiovascular risk factors. *British Medical Journal* 1998; **316:** 953 – 954.
7 Mendall MA *et al*. C Reactive protein and its relation to cardiovascular risk factors: a population based cross sectional study. *British Medical Journal* 1996; **312:** 1061 – 1065.
8 Ridker PM *et al*. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *The New England Journal of Medicine* 1997; **336:** 973 – 979.