**Editorial**

# Health screening packages: the place of measuring C-reactive protein

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C-reactive protein (CRP) was first identified in 1930 by Tillet and Francis, as a substance present in the sera of acutely ill patients, which had the ability to bind the C-polysaccharide on the cell wall of *Streptococcus pneumoniae*[1]. They named the substance CRP because the reaction between the protein and the polysaccharide was very specific. However, the original precipitin test lacked analytical sensitivity, and CRP remained in obscurity until the early 1980s, when analytically sensitive and specific commercial immunoassays became available.

CRP consists of five identical, non-glycosylated polypeptide subunits non-covalently linked to form a disc-shaped cyclic polymer, with a molecular weight of 115,000 to 140,000[2]. CRP binds the polysaccharides present in many bacteria, fungi and protozoal parasites. In the presence of calcium ions, it can bind phosphorylcholine, phosphatidylcholines such as lecithin, and polyanions such as nucleic acids. The protein contains little or no carbohydrates; on cellulose acetate or agarose electrophoresis, the protein migrates anywhere from the slow gamma to the mid-beta region.

CRP is a sensitive, though relatively non-specific, marker of systemic inflammation. It is synthesised rapidly by hepatocytes in response to cytokines released into the circulation by activated leucocytes. Concentrations can rise within 24 to 48 hours, reaching levels 10- to 100-fold higher than basal concentrations in healthy subjects.

In the past decade, the number of clinical applications associated with CRP has increased dramatically. CRP levels have been linked with outcomes in peritoneal dialysis patients[3], stroke[4] and obstetric and gynaecological conditions[5]. The most significant application of CRP, or more specifically, high-sensitivity CRP, has been as a predictor of cardiovascular disease risk[6,7]. High sensitive CRP (hsCRP) refers to values within lower, previously "normal" or "healthy" ranges for CRP.

CRP testing in health screening programmes was discussed and rejected by Koenig, on the basis of several unresolved issues, vis à vis: the uncertain causal relevance of CRP, the additive predictive value of CRP in the context of routine total cholesterol measurements which had not been replicated in many populations, the lack of availability of population-based cut-points for interpretation and risk assessment in primary and secondary care settings, the reliability of analytical measurements, and the existence of potential therapeutic modalities in the event of a raised CRP level in asymptomatic healthy individuals[8].

In 2002, the Centers for Disease Control and Prevention (CDC) and the American Heart Association (AHA) convened a workgroup to address the role of emerging markers of inflammation, including CRP, in cardiovascular disease and published their recommendations in 2003[9]. The workgroup concluded that hsCRP is currently the best inflammatory marker for cardiovascular disease. Over 25 prospective epidemiological studies have shown that CRP is a strong and independent predictor of future myocardial infarction, ischaemic stroke, peripheral arterial disease, and sudden cardiac death in apparently healthy men and women[10-12]. Many studies also show a dose-response relationship between the level of hsCRP and the risk of incident coronary disease. Population cut-offs have been determined, and therapeutic interventions such as aspirin and statins are available to reduce CRP levels.

To assess cardiovascular risk, CRP should ideally be measured by highly sensitive assays capable of reliably measuring concentrations within normal ranges, with low analytical assay variability. The coefficient of variation for hsCRP values is <10% in the 0.3-10 mg/L range[13]. There are currently over 30 methods, many of which have been cleared by the US Food and Drug Administration (FDA)[14-15]. Proficiency-testing programmes for CRP are available. An internationally accepted standard,

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CRM470, enables comparisons among various laboratories[16], and providers of all 28 hsCRP methods evaluated in the CDC standardisation survey claim to use CRM470 to calibrate their methods as stipulated by the FDA[17]. Pre-analytical specimen requirements are minimal – CRP is relatively stable in plasma and serum and shows little seasonal and diurnal rhythm[18].

Thus, perhaps it is now time to revisit the question: Should C-reactive protein measurement be included in health screening packages? The answer is Not Yet.

A single CRP measurement has limitations. Atherosclerosis is an inflammatory process with multiple risk factors such as cigarette smoking, hypertension, atherogenic lipoproteins and hyperglycaemia. High-sensitivity CRP is not specific for atherosclerosis and levels do not appear to correlate well with the extent of angiographically-defined atherosclerosis[19,20]. The inflammatory cascade may have sources other than atherosclerosis. CRP measurements should be performed in a metabolically stable person without obvious inflammation or infections.

CRP exhibits considerable within-subject variability[21] that is often higher than established risk factors such as serum cholesterol. Hence, two separate measurements are required to classify risk level. CRP also has a broad population distribution. Studies have shown that over 95% of subjects in most populations have hsCRP values of <10 mg/dL, but data is limited for some high-risk populations such as South Asians and Africans.

Additional studies are required in examining cardiovascular risk at various hsCRP levels to better redefine the cut-off points used for cardiovascular risk prediction and assign levels of absolute risk to each stratum. Evidence is lacking as to whether reductions in hsCRP levels from interventions are associated with reductions in cardiovascular risk. Cost-effectiveness has yet to be evaluated in clinical studies and should preferably be as an endpoint of clinical trials. There should be continued performance testing for hsCRP assays for application to risk assessment. The FDA recently introduced a new classification called cardiac CRP (cCRP), to harmonise nomenclature but may inadvertently confuse users instead.

Coronary heart disease (CHD) is the second cause of mortality in Singapore and strategies to reduce CHD have also shown to reduce cerebrovascular events. Cardiovascular risk factors are additive in their effect. Both lifestyle modification and pharmacological interventions are essential strategies to reduce cardiovascular risk. A healthy lifestyle reduces serum CRP levels while obesity, physical inactivity and smoking increase levels[22,23]. As CRP levels may be influenced more by lifestyle than by genetics, CRP measurement may prompt public health authorities to focus on health improvement strategies that may ultimately lower national health costs[24].

In this issue of the Singapore Medical Journal, Hawkins and Leong[25] have proposed that for clinicians prepared to consider treatment in patients with elevated hsCRP levels, hsCRP measurement should be included as part of health screening packages to selected patients based on individual cardiac risk. They suggest that hsCRP measurement be done at the end of the first consultation after initial cardiac risk assessment. The risk assessment may be used to rule out the need for hsCRP measurements in those with CHD/CHD equivalent, those on anti-lipid treatment and those with a risk factor of 0. This is in concordance with the recommendations proposed by the AHA/CDC that traditional cardiovascular risk factors be assessed and an absolute risk score calculated before hsCRP is measured.

In conclusion, CRP should presently not be included in routine health screening packages. There is limited data in treating patients with elevated hsCRP on the basis of hsCRP alone, and prospective clinical trials to prove efficacy are needed. Measurement of hsCRP is best employed as an adjunct to major risk factors to further assess absolute risk for CHD primary prevention, so as to permit intensification of intervention and/or motivate patients to improve their lifestyle. This view has recently been endorsed by Lloyd-Jones et al[26] who concluded that there is no definitive evidence that, for most individuals, CRP adds substantial predictive value above that provided by risk estimation using traditional risk factors for CHD. Many questions must be addressed before CRP can be incorporated into risk prediction algorithms and before universal screening with CRP can be recommended.

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