1.1 Cardiovascular Disease - Statistics

There has been a paradigm shift in recent years in the global health profile. The burden of diseases has gradually shifted from communicable to non-communicable diseases. Non Communicable Diseases (NCD) is considered as the major cause of death worldwide. There were 37 million deaths due to NCD in 2008 and Cardiovascular Diseases (CVD) contributed to 48% of these deaths. Cardiovascular diseases include Coronary Heart Disease (CHD), cerebrovascular disease, peripheral artery disease, rheumatic heart disease and congenital heart disease. According to the World Health Report 2002, cardiovascular diseases (CVD) will be the largest cause of death and disability in India by 2020. Incidence of CHD is increasing in alarming proportions and is estimated to cause 61 out of 64 million deaths due to CVD by the year 2015. In India the prevalence of CHD is estimated to be 3-4% in rural areas and 8-10% in urban areas among individuals aged above 20 years.

1.2 Coronary Heart Disease – Role of Inflammation

CHD is a manifestation of atherosclerosis. Laboratory and experimental evidence indicate that atherosclerosis, in addition to being a disease of lipid accumulation, also represents a chronic inflammatory process. Inflammation plays a critical role in all stages of atherosclerosis from a nascent lesion to acute coronary syndromes. Innate immune system interact with other metabolic risk factors at various stages to form the atheromatous plaque. Risk factors that contribute to CHD are age, sex, diabetes, hypertension, Total Cholesterol (TC), Low Density Lipoprotein Cholesterol (LDL-C), High Density Lipoprotein Cholesterol (HDL-C) and smoking. However, 40% of CHD
deaths occur in people who have normal cholesterol, or have levels below the population average and this may be attributed to chronic subclinical inflammation \(^\text{10}\).

### 1.3 Inflammatory Markers of CHD

This subclinical inflammation associated with CHD can be ascertained early using various inflammatory markers. These markers include adhesion molecules, cytokines, fibrinogen, serum amyloid A, high sensitivity C Reactive Protein (hsCRP), leucocyte count, etc.\(^\text{11,12}\) (complete list of inflammatory markers is mentioned in chapter 2).

### 1.4 CRP and high sensitivity CRP (hsCRP)

CRP is a novel inflammatory marker sensitive to systemic inflammation and tissue damage \(^\text{13}\). This acute phase reactant is synthesized by hepatocytes and is transcriptionally driven by Interleukin-6 \(^\text{14}\). High sensitivity CRP assays have a range of measurement below the measurement range of conventional CRP assays. This measurement is an indication in the evaluation of conditions associated with inflammation in otherwise healthy individuals \(^\text{15}\). Compared to all the inflammatory markers that are existent now, hsCRP has the analyte and assay characteristics that are conducive for clinical use \(^\text{12,16}\). An expert panel of the national academy of clinical biochemistry, USA after a thorough review opined that hsCRP is the only marker to fulfill all the criteria to be accepted as a biomarker for risk assessment in primary prevention of CVD \(^\text{11}\). With the plasma half-life of CRP being about 19 hours, the only determinant of its concentration is, the rate of synthesis, which is a reflection of the magnitude of the pathology \(^\text{17}\).
1.5 High Sensitivity CRP as a predictor of risk

The normal range of CRP is 0 – 6mg/L, individuals are categorized as having low risk if the value is less than 1 mg/l, average if the value is between 1.0 to 3.0ml/l and high risk if the value is more than 3.0mg/l12. Several large scale prospective epidemiological studies have shown that plasma levels of hsCRP is an independent predictor of risk of future myocardial infarction, stroke, peripheral artery disease and vascular death among individuals without known cardiovascular diseases18,19. Elevated plasma levels of CRP have been associated with coronary heart disease20-26, ischemic stroke27, peripheral artery disease28, insulin resistance syndrome29 and hypertension30.

Hs CRP value has been proven to significantly improve global cardiovascular risk prediction along with the traditional risk factors31, and thus is included as an integral component of Reynolds risk score. The addition of hs CRP has been reported to have enhanced the sensitivity of prediction of coronary risk by Framingham risk score as well32.

1.6 High Sensitivity CRP – A Risk Marker or Risk Factor

Hs CRP, once considered as an indicator of systemic inflammation has received greater attention as a biomarker of atherosclerosis in the past 12 years. A growing body of evidence suggests, that hsCRP has the potential to mediate atherogenesis independently and by interacting with the traditional risk factors33.

CRP has been reported to precipitate atherosclerosis through several mechanisms:

- Induces the production of inflammatory cytokines and promote monocyte chemotaxis and tissue factor expression
- Increases the expression of cell adhesion molecules, chemokines and endothelin-1
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- Increases monocyte – endothelial cell adhesion\(^{34}\)
- Decreases endothelial nitric oxide synthase expression and activity\(^ {35}\)
- Increases the expression of Plasminogen Activator Inhibitor-1 (PAI-1) in coronary artery endothelial cells and other human endothelial cells\(^ {36}\)

Hs CRP as a therapeutic target has been reinforced by the JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) Trial. JUPITER trial is a large multinational, long-term, double-blind, placebo-controlled, randomized, CRP guided clinical trial designed to assess the effectiveness of statin therapy (rosuvastatin 20 mg/day) on apparently healthy individuals with low LDL cholesterol levels but elevated hs CRP levels (> 2 mg/l)\(^ {37}\). The trial was stopped prematurely as there was a significant reduction (44%) in the cardiovascular events mediated by 37% reduction in hs CRP\(^ {38}\) in the treatment arm.

1.7 Exercise training and High Sensitivity CRP

Aerobic exercise training is one of the core components of primordial, primary and secondary prevention. Aerobic exercise training improves cardio respiratory endurance. Improved cardiorespiratory endurance has been associated with reduction in all-cause and cardiovascular mortality\(^ {39,40}\).

Reviews by Lavie et.al and Plaisance et.al which included numerous trials suggest that higher levels of physical activity and cardio-respiratory endurance have been associated with lower CRP values\(^ {41,42}\). It was envisaged that exercise training exerts its cardio-protective benefits by reducing the subclinical inflammatory process\(^ {43}\).

Longitudinal trials evaluating the effectiveness of exercise training in reducing
inflammation have been conducted since 2002 with a barrage of studies after 2006. Till date there are 12 randomized controlled trials, five non randomized trials and three reviews (one meta-analysis, one systematic review and one narrative review) published on the effect of exercise training on hs CRP.

Although exercise training appears to reduce inflammation, existing trials have reported conflicting results, with some reporting a reduction in CRP and some reporting no improvement. A meta-analysis of five randomized controlled trials by Kelley and Kelley did not find any improvement in CRP with exercise training, although another systematic review of three prospective studies by Kaspis et.al found a reduction in CRP.

1.8 Association between hsCRP and measures of adiposity and aerobic capacity

Association between hsCRP and other established risk factors like adiposity and aerobic capacity, have been studied by many investigators with the intent of understanding the nature and strength of their relationship. Investigators have consistently reported a positive correlation with the measures of adiposity like BMI, waist circumference and fat percentage and a negative correlation with aerobic capacity. However, data pertaining to this investigation in the Indian population, who are at an increased risk of non-communicable diseases, is scant.
1.9 Summary of the need

- Inconsistency in the results of the published trials, very few robust randomized controlled trials, inadequate number of trials in systematic review, to draw evidence, inconsistency in exercise training and limited external validity of the trials necessitates more longitudinal trials to determine the effectiveness of exercise training on CRP.

- It is not known if there is a dose response relationship between exercise intensity and hs CRP and if there is a threshold in exercise intensity for reduction in CRP.

- There is scant data on how Indians, who are genetically susceptible to CHD at a younger age and have higher hs CRP values respond to exercise training.

- Data supporting the association between hs CRP and other risk factors of CHD viz, Body Mass Index (BMI), waist circumference, fat percentage and cardiorespiratory endurance in Indians is scarce.

1.10 Objectives of this Study

- To determine whether a dose response relationship exists between exercise intensity and hs CRP in healthy individuals

- To evaluate the association between percent body fat, waist circumference, peak oxygen uptake and hs CRP concentration in the same population.