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The ability of the wide range CRP assay to classify individuals with low grade inflammation into cardiovascular risk groups

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ABSTRACT

Background: High sensitivity C-reactive protein (hsCRP) has become a routine assessment tool to discriminate between patients at low, intermediate or high risk for cardiovascular events using the threshold values of 1 and 3 mg/L, respectively. Over the past years, several studies have proposed the wide range C-reactive protein (wrCRP) as an alternative to the hsCRP in various clinical scenarios. However, the potential use of wrCRP in assessing the cardiovascular risk has not yet been evaluated.

Methods: Both wrCRP and hsCRP were evaluated in 15,780 apparently healthy individuals who underwent a routine annual checkup in the Tel Aviv Sourasky Medical Center. Individuals with CRP levels > 5 mg/L were excluded. Agreement between the two methods was observed using the Bland-Altman method and the concordance correlation coefficient. Deming regression was used to build a calibration equation. Reclassification of individuals' risk level was observed and Cohen's kappa was used to evaluate risk agreement.

Results: A high correlation (r = 0.98) along with a significant difference ($p < 0.001$) between hsCRP and wrCRP raised the need for calibration. A simple calibration equation (Adjusted wrCRP = 0.3136 + 0.8803 × wrCRP) led to high agreement which enabled 8.4% reclassification of the risk group. A change in the intermediate risk threshold value from 1 to 0.9 mg/L led to an almost perfect agreement (kappa = 0.87, $p < 0.001$) and a low reclassification rate (7.6%), with under 0.05% of the population undergoing a major reclassification (from high to low risk or vice versa).

Conclusions: In the era of limited financial resources, wrCRP assay may be used as a reasonable routine assay to evaluate the cardiovascular risk in patients undergoing a routine annual checkup.

1. Introduction

Microinflammation is believed to contribute significantly to the pathogenesis of atherosclerosis [1–3], as well as to the development of other cardio-vascular risk factors such as arterial hypertension, heart failure, valvular disease and atrial fibrillation [4,5] and even to other non-cardiovascular pathological states such as depression [6] and poor self-rated health perception [7]. C-reactive protein (CRP), a marker of inflammation, has become a part of the routine patient global risk assessment and may provide a comprehensive view of the patient's cardiovascular risk factors [8–10]. Higher CRP levels have been associated with increased risk for vascular events [11–13]. It has been shown that individuals with a hsCRP level of > 3 mg/L have an adjusted 10-year relative risk of 1.45 of coronary heart disease compared to individuals with < 1 mg/L [12]. High sensitivity CRP (hsCRP) has been recommended to discriminate between patients with low, intermediate and high risk for cardiovascular events using the threshold values of 1 and 3 mg/L, respectively [1,11]. Current guidelines recommend using

Abbreviations: hsCRP, high sensitivity C-reactive protein; wrCRP, wide range C-reactive protein

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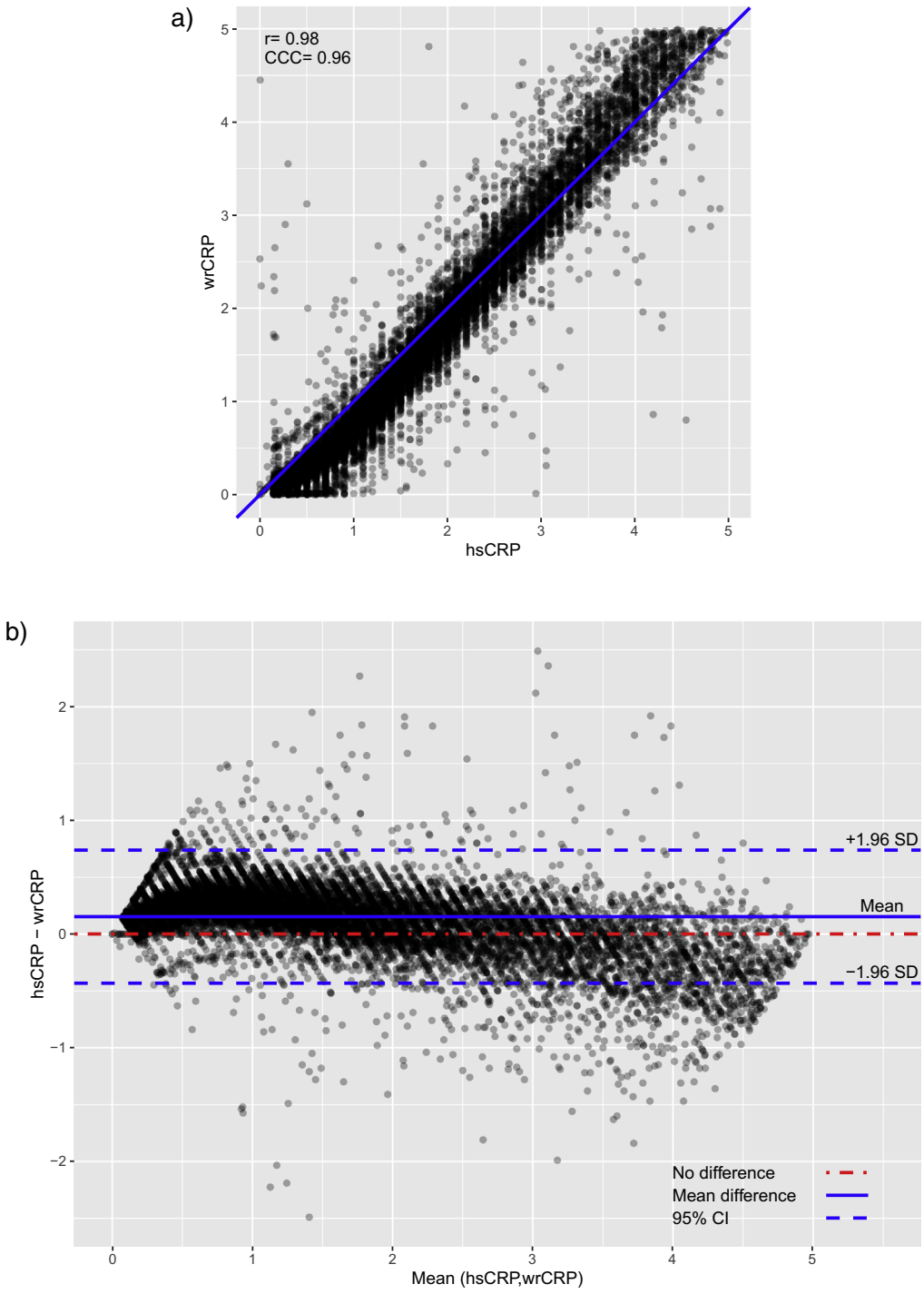

Fig. 1. A Scatter plot (a) demonstrating the correlation between the individuals' hsCRP and wrCRP values and a Bland-Altman plot (b) demonstrating the agreement between the two assays. It is clear that there is a good correlation between the two assays but an underestimation in the lower range and an over estimation in the higher range which raise the need for calibration.

hsCRP levels to aid in selection of patients who would benefit from statin therapy and thus reduce their risk of adverse cardiovascular events [14].

The Dade Behring hsCRP assay and the wide range CRP (wrCRP) assay measure human CRP, albeit using different methods for measuring turbidity. The main difference between the two assays is that the high sensitivity assay is based on polystyrene particles coated with monoclonal antibodies specific for human CRP, the complex is measured nephelometricaly, while the wide range assay is based on latex particles of different sizes coated with Anti-human CRP monoclonal antibody, the complex is measured by immunoturbidity. Immunoturbidimetry measures the absorbance of the light by the sample, nephelometry measures the light scattered at a fixed angle. The level of analyte is determined by comparison with a calibrator of known concentration [15].

Both methods enable measurement of CRP values < 5 mg/L, while the wrCRP offers real time assessment and lower costs [16]. Several studies have compared the wrCRP assay to the hsCRP assay in various clinical scenarios, and have concluded that wrCRP is a reasonable alternative to hsCRP [16–18]. However, these studies did not test the reliability of wrCRP in evaluating the risk of cardiovascular disease. It is therefore important to evaluate the potential use of wrCRP in assessing the cardiovascular risk of patients with CRP levels < 5 mg/L.