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Inflammatory status modulates plasma lipid and inflammatory marker responses to kiwifruit consumption in hypercholesterolaemic men

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Abstract *Background and aims:* Kiwifruit has the potential to improve markers of metabolic dysfunction, but the response may be influenced by inflammatory state. We aimed to investigate whether inflammatory state would modulate the effect of consuming two green kiwifruit daily on plasma lipids and markers of inflammation.

Methods and results: Eighty-five hypercholesterolaemic men completed a 4-week healthy diet run-in, before randomisation to a controlled cross-over study of two 4-week interventions of two green kiwifruit/day plus healthy diet (intervention) or healthy diet alone (control). Anthropometric measures and fasting blood samples (plasma lipids, serum apolipoproteins A1 and B, high-sensitivity C-reactive protein (hs-CRP) and interleukin (IL)-6, tumour necrosis factor-alpha (TNF-α) and IL-10) were taken at baseline, 4 and 8 weeks. Subjects were divided into low and medium inflammatory groups, using pre-intervention hs-CRP concentrations (hs-CRP <1 and 1–3 mg/L, respectively).

In the medium inflammatory group the kiwifruit intervention resulted in significant improvements in plasma high-density lipoprotein cholesterol (HDL-C) (mean difference 0.08 [95% CI: 0.03, 0.12] mmol/L [$P < 0.001$]), total cholesterol (TC)/HDL-C ratio (−0.29 [−0.45, −0.14] mmol/L [$P = 0.001$]), plasma hs-CRP (−22.1 [−33.6, −4.97]% [$P = 0.01$]) and IL-6 (−43.7 [−63.0, −14.1]% [$P = 0.01$]) compared to control treatment. No effects were seen in the

Abbreviations: apoA1, apolipoprotein A1; apoB, apolipoprotein B; BF, body fat; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; HOMA2, homeostasis model assessment 2 model; IR, insulin resistance; IL, interleukin; LDL-C, low-density lipoprotein cholesterol; NZ, New Zealand; NF-κb, nuclear factor-kappa B; RPAQ, recent physical activity questionnaire; sLDL, small-dense LDL; TC, total cholesterol; TG, triglycerides; TNF-α, tumour necrosis factor-alpha; WC, waist circumference.

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low inflammatory group. There were significant between inflammation group differences for TC/HDL-C ($P = 0.02$), triglyceride (TG)/HDL-C ($P = 0.05$), and plasma IL-6 ($P = 0.04$).
Conclusions: Inflammatory state modulated responses to the kiwifruit intervention by improving inflammatory markers and lipid profiles in subjects with modestly elevated CRP, suggesting this group may particularly benefit from the regular consumption of green kiwifruit.
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Introduction

Obesity, identified by Framingham researchers in 1983 as an independent risk factor for cardiovascular disease (CVD), has been shown to increase the prevalence of a number of other CVD risk factors including dyslipidaemia, type 2 diabetes, impaired glucose tolerance and hypertension [1]. Metabolic syndrome describes the presence of a cluster of these factors: raised blood glucose; blood pressure (BP) and triglycerides (TG); decreased high-density lipoprotein cholesterol (HDL-C); and central obesity [2]. There is now a substantial amount of evidence that central obesity in particular initiates a chronic-low grade inflammatory state that promotes systemic metabolic dysfunction, which leads to the development of these disorders [3]. An intermediate state with mild metabolic dysfunction where there is some increase in inflammation has also been identified [3].

With increasing adiposity, as well as tissue expansion, there is an increasing shift towards a pro-inflammatory environment, with the recruitment of immune cells (such as macrophages and T cells) and the upregulation of pro-inflammatory adipokines, such as tumour necrosis factor-alpha (TNF-α) and interleukin (IL)-6, and a down-regulation of anti-inflammatory cytokines, such as IL-10 [3]. These adipokines can then spill-over into the circulation, leading to modest increases in systemic levels of cytokines or acute-phase reactants, such as C-reactive protein (CRP), which may then promote pro-atherogenic effects [4].

High-sensitivity (hs)-CRP is commonly used as a marker of inflammation, in studies which investigate the effect of dietary modification on inflammation [5]. Various cross-sectional studies have shown an inverse association between plasma CRP and dietary intakes of fibre, fruit and vegetables, carotenoids, flavonoids, vitamin C, vitamin E [5,6] and phylloquinone (vitamin K) [7]. Different fruit intervention studies have shown reductions in plasma CRP [8–11].

Kiwifruit is a good source of many of the dietary components that are associated with a beneficial effect on CRP. These include significant levels of fibre, vitamins E and K, folate, carotenoids, flavonoids and polyphenols, and one of the highest concentrations of vitamin C of any commonly consumed fruit [12].

We recently conducted a randomised controlled trial, which assessed the impact of consuming two green kiwifruit a day alongside a healthy diet on plasma lipids, in a group of hypercholesterolaemic men. The primary results from this study have been published [13], and showed that consuming two green kiwifruit a day for 4 weeks had favourable effects on plasma HDL-C and the total cholesterol (TC)/HDL-C ratio, compared to a healthy control diet, but no effect on CRP was seen. Likewise, no significant change in plasma CRP concentrations was seen in two other kiwifruit interventions [14,15]. Inflammatory status may modulate the responsiveness to dietary manipulation, as has been shown by a small number of studies. All these studies involved some sort of dietary fat manipulation and, although the studies often differed in the manner in which CRP is categorized and most had small group numbers, all found significant differences in response between low and high CRP groups on various plasma lipid components [16–20].

The present study, a predefined secondary analysis of our randomised kiwifruit trial, aimed to determine if there was a difference in plasma lipid and inflammatory response to the kiwifruit intervention, by stratifying subjects based on pre-intervention plasma CRP concentration into low and medium inflammatory groups.

Methods

Subjects and study design

The study protocol, and recruitment and exclusion criteria for subjects for this randomised controlled trial are described in greater detail elsewhere [13]. In brief, 87 men (27–73 y old) with a low-density lipoprotein cholesterol (LDL-C) concentration >3.0 mmol/L and a plasma TG concentration <3.0 mmol/L, but, otherwise healthy (exclusion criteria included diagnosed chronic disease such as coronary heart disease, diabetes and cancer), non-smokers, and not taking any cholesterol lowering medication were recruited from the Auckland region in New Zealand (NZ). The study was conducted between May and September, 2010, according to the guidelines laid down in the Declaration of Helsinki. All procedures involving human subjects were approved by the Massey University Human Ethics Committee (MUHEC): Southern A 09/76. Written informed consent was obtained from all subjects.

Subjects made five visits to the Massey University Human Nutrition Research Unit. During the first visit (Baseline 1) anthropometric measures (height, weight, waist circumference (WC) and percent body fat (% BF)), and a blood sample for lipids were taken, and an appointment for a nutrition consultation with a nutritionist was made to outline the healthy diet (visit 2). The healthy diet which